THE NEW ARMENIAN MEDICAL JOURNAL
Vol.9 (2015), No 4, p.46-55

MODELING OF ORGANIZED OR CALCIFIED THROMBOEMBOLI: NOVEL ANIMAL MODEL USING ETHYLENE ALCOHOL CO-POLYMER AND THE EFFICACY OF THE LEGACY™ STENT RETRIEVAL DEVICE COMPARED TO SOLITAIRE FR®

Ulm A.J.[1]*, Grigorian A.A.[2], Franklin R.L.[1], Mericle R.A.[1]

[1] Nashville Neurosurgery Group, Nashville Tennessee, USA
[2] Georgia Neurosurgical Institute, Macon Georgia, USA

Received 06/28/2014; accepted for printing 08/22/2015

Abstract

Introduction: A potential source of recanalization failure with stent retrieval devices is the consistency of the occlusive material during mechanical thrombectomy/embolectomy for ultra-acute stroke. The devices that are currently in use, have been evaluated pre-clinically using an autologous blood clot model of stroke, which may not accurately reflect the subset of organized and/or calcified emboli such as carotid plaque and ultra-hard cardiac thrombus or cardiac vegetations. The purpose of the study was to develop a porcine model of stroke using ethylene alcohol mixed with powder (Onyx® embolic agent) to model organized/calcified emboli.

Materials and methods: Twenty five total vascular occlusions were created in three pigs using Onyx® 18 and 500, as well as autologous clot preparations. Onyx emboli with a diameter of 3mm ranging in length of 5-12 mm were created. The non-deformable emboli were delivered to the target vasculature using a novel carotid cutdown technique. The Solitaire FR® device and a novel stent retrieval device were evaluated for efficacy.

Results: Onyx® 18 and 500 were reliably used to produce thrombolysis in cerebral infarction 0 occlusions in a variety of vascular locations. Onyx®-device interaction was easily visualized because of tantalum within the ethylene-alcohol co-polymer. A clear difference in efficacy was seen while comparing the devices with the hard occlusions. The Solitaire FR® failed to remove Onyx® obstructions in five occlusions.

Conclusion: The use of Onyx® to model organized or calcified hard vascular occlusions provides a method to evaluate current and emerging technology regarding their ability to remove these types of ultra-hard obstructions.

Keywords: *thrombectomy, embolectomy, ischemic stroke, clot retrieval, thrombectomy device.*

Introduction

Multiple recent clinical trials have proven the safety and efficacy of stent retriever thrombectomy devices in the treatment of acute stroke [*Berkhemer O et al., 2015; Campbell B et al., 2015; Goyal M et al., 2015*]. The Multicenter Randomized Clinical trial of Endovascular treatment for acute ischemic stroke in the Netherlands study, with broad inclusion criteria, closely resembles real world experience in the use of these devices. It can be revealed from the outcome data of the above-mentioned study that there are existing areas of potential improvement with the currently available devices. Thrombolysis in cerebral infarction 2b and 3 (TICI) recanalization rate was 58.7% and the rate of embolic events in new vascular territories – 9% [*Berkhemer O et al., 2015*]. One possible explanation for the treatment failures is the consistency of the embolus with difficulty retrieving organized or calcified ultra-hard thromboemboli. The efficacy of the commercially available devices to remove autologous blood clots in the animal models of stroke has been conclusively proven [*Brekenfeld C et al.,*

Address for Correspondence:
Arthur J. Ulm M.D.
330 22nd Avenue North, Nashville, TN 37203, USA
Tel.: (615-970-0091)
Fax: (615-320-0009)
E-mail: arthur.ulm@gmail.com

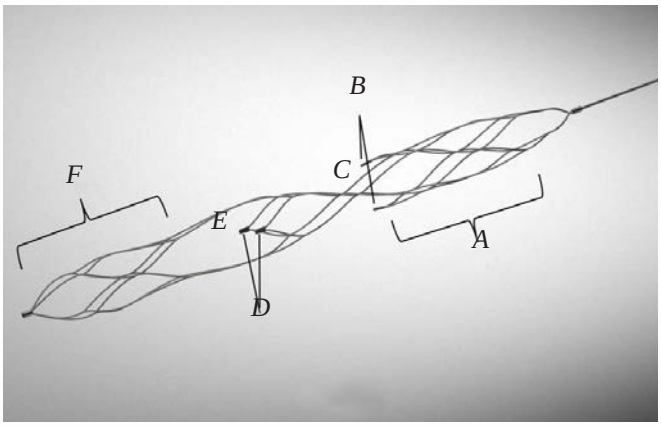
2008; Liebig T et al., 2008; Jahan R, 2010; Mordasini P et al., 2010; Mordasini P et al., 2011; Nogueira R et al., 2012; Roth C et al., 2012; Yuki I et al., 2012]. However, a not well described model for organized or calcified emboli that would mimic the embolization of ulcerated carotid plaque or densely organized cardiac thrombus or vegetations exists there. A method has been developed for the modeling of organized or calcified emboli using ethylene alcohol co-polymer mixed with tantalum powder (Onyx® liquid embolic system, Medtronic, Minneapolis, MN) in the standard pig model of stroke. Using the new model and a standard clot preparation model we report on the safety and efficacy of a novel stent retrieval device designed to remove standard and ultra-hard thromboemboli and compare the FDA approved device most widely used today, the Solitaire FR® stent retriever (Medtronic, Minneapolis MN).

Materials and methods

Animal Care: All procedures were conducted according to the Translational, Testing and Training Laboratories, Inc. – T3 Labs Standard Operating Procedures (SOPs) and ethical guidelines of the Institutional Animal Care and Use Committee. Three swine (weighing between 28-36 *kg*) were used in present study. Animals were housed and quarantined as per T3 labs SOP and given free access to food and water until the night before the endovascular procedure was performed, when food was withheld. The animals received preoperatively Atropine (Med-Pharmex Inc., Pomona, CA) 0.04 *mg/kg* IM, to reduce vagal effect, Telazol (Zoetis Inc., Kalamazoo, MI) 4 *mg/kg* IM in combination with Xylazine (Akorn Inc., Marietta, GA) 0.5 *mg/kg* IM for anesthesia induction and Buprenorphine (Patterson Inc., Phoenix, AZ) 0.01 *mg/kg* IM, for preoperative analgesia.

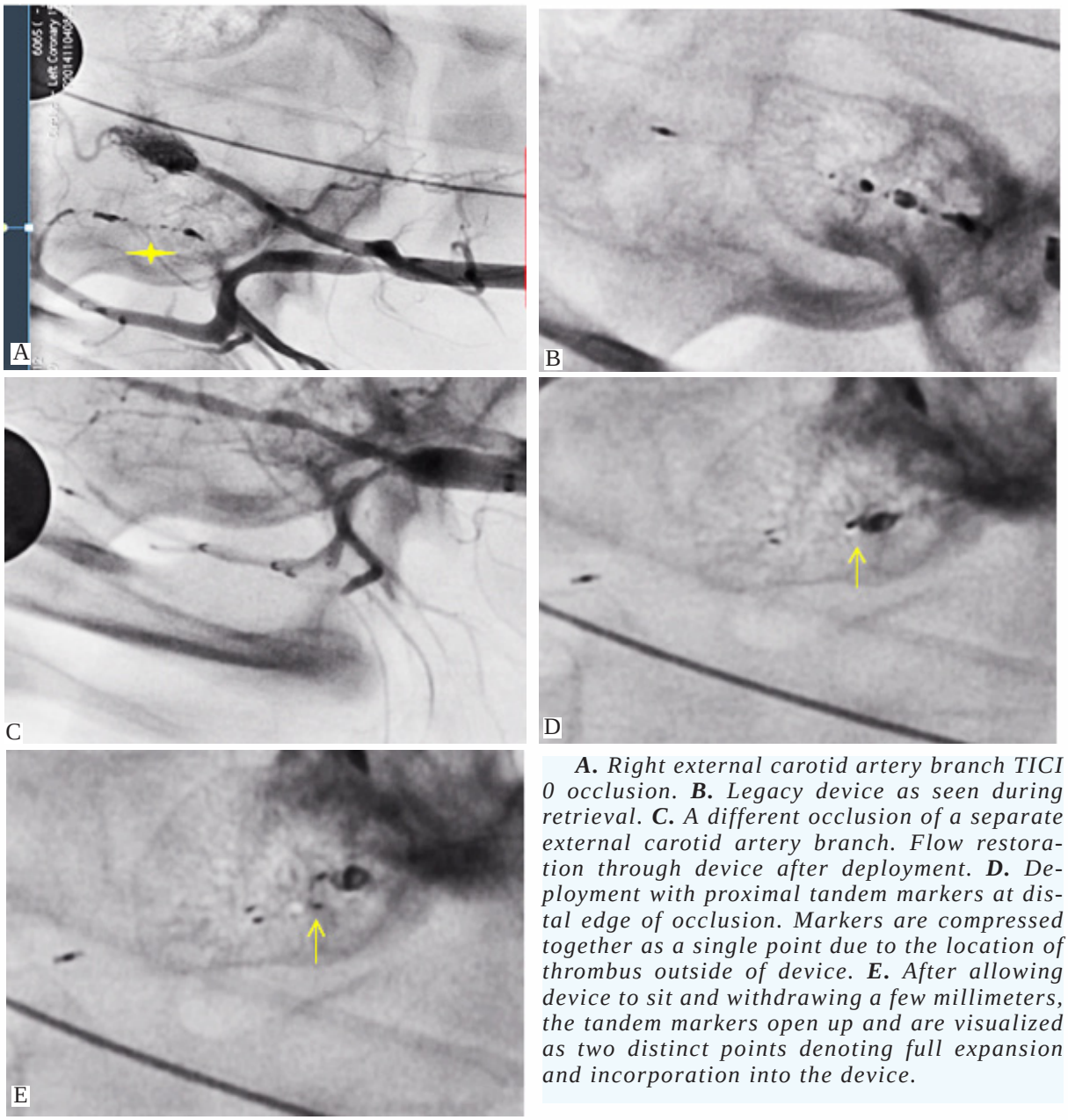
After endotracheal intubation, anesthesia was maintained with 2% to 2.5% Isoflurane (Abbott Labs, Chicago, IL) in Oxygen throughout all procedures. After procedure was completed and still under anesthesia, euthanasia was induced with KCl (Hospira Inc. Lake Forest IL) 1 *mEq/kg* IV. The procedures were completed over three non-contiguous days. The procedures were performed on a fixed single plane angiography system (Siemens, Munich Germany) and a second mobile C-arm (GE, Fairfield, CT) with road mapping and angiographic capabilities to provide bi-plane visualization when necessary.

Legacy™ Thrombectomy Device: The Legacy™ (Nashville, TN) thrombectomy device was designed for the removal of occlusive thrombus in the setting of acute stroke. The device occurs in two sizes designed for site specific deployment. The Carotid T device has a total length of 56 *mm* with a 40 *mm* working distance and a proximal and distal taper. The device is designed to be used for carotid T occlusions, proximal M1 main carotid artery (MCA) occlusions and mid basilar occlusions where the distal landing zone is either the M1 MCA or basilar artery. The expanded outer diameter (OD) is 4.5 *mm* and the device can be deployed in vessels ranging in diameter of 2.5-4.5 *mm*. The M1 device variation has a total length of 46 *mm* with a working distance of 34 *mm*. The M1 device is intended for more distal deployments or smaller proximal anatomy. The OD of the M1 device is 4 *mm* and is intended for the use in vessels ranging in size of 2-4 *mm*. There are three distinct areas of thrombus engagement moving proximal to distal along the device (Fig. 1). Proximally the device functions as a standard stent retriever, expanding and compressing the thrombus against the vessel wall and re-establishing flow across the occlusion (Fig. 2C, 6C). The flow restoration area measures 9.5 and 12 *mm* in length for the M1 and Carotid T devices, respectively. The second area is comprised of drop zones, which are oriented 90 degrees, offset relative to each other. The offset drop zones provide 360 degree vessel coverage and are designed to facilitate thrombus incorporation and as a means to capture ultra-hard emboli within the device (Fig. 1, 6D, F). The enlarged drop zones measure 12 x 4.5 *mm* and 10 x 4 *mm* in the Carotid T and M1 devices. In addition, due to their configuration, the drop zones have a third dimension of depth which further encourages clot integration (Fig. 1C). Tandem x-ray markers are oriented on either side of the device and at the leading edge of both drop zones providing enhanced feedback to the operator (Fig. 1 B and D). The drop zone markers dictate the optimal site of deployment relative to the distal site of the occlusion and give real-time feedback regarding device interaction with thrombus as the device is being withdrawn (Fig. 1, 2D



***A.** Proximal landing zone, flow restoration area. This portion functions as a typical stent retrieval device. Optimal deployment is when the distal edge of the occlusion is just proximal to the first set of tandem markers. **B.** Proximal tandem markers designate the leading edge of the first drop zone. **C.** First drop zone. The third dimension of depth. **D.** Second set of tandem markers at the leading edge of the second drop zone. The ninety degree offset compared with first set of tandem markers. The offset tandem markers provide feedback during retrieval with regard to clot location and orientation to device. **E.** Second drop zone. **F.** Closed ended distal capture basket.*

***Figure 1.** Legacy™ Thrombectomy Device.*



***A.** Right external carotid artery branch TICI 0 occlusion. **B.** Legacy device as seen during retrieval. **C.** A different occlusion of a separate external carotid artery branch. Flow restoration through device after deployment. **D.** Deployment with proximal tandem markers at distal edge of occlusion. Markers are compressed together as a single point due to the location of thrombus outside of device. **E.** After allowing device to sit and withdrawing a few millimeters, the tandem markers open up and are visualized as two distinct points denoting full expansion and incorporation into the device.*

***Figure 2.** Autologous blood clot model.*

and E). The third component is a distal capture basket which is closed ended and is designed to reduce distal embolization during retrieval (Fig. 6 D and F). The distal tip has an incorporated X-ray marker. The devices are mounted on a 180 *cm* nitinol core wire which is .018 proximally and tapers to a distal 23 *cm* long hyper flexible core-coil wire.

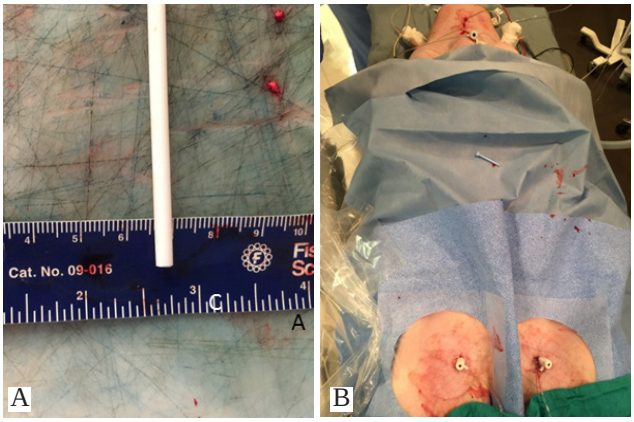
Standard Thrombus Model: Standard autologous whole blood was used to create two consistencies of thrombus. A "soft" clot version was created by combining 1 gram of Barium sulfate, 25 *IU* of bovine thrombin and 10 *ml* of autologous whole blood and incubated at room temperature for 60 *min* in silicone tubing (Clinico Medical, Miekinia, Poland) with an ID of 4 *mm* [*Gralla J et al., 2006*]. A "firm" clot preparation was performed by combining 20 *ml* of whole blood with 2 grams of barium sulfate and incubating at room temperature for 120 minutes in 4 *mm* silicone tubing [*Kan I et al., 2010*]. The placement of the whole blood into silicone tubing is a modification of the standard clot preparation which was performed to standardize clot burden by precisely controlling the diameter of thrombus (Fig. 3).

Organized and/or Calcified Thromboembolic Model: Ultra-hard emboli were modeled using Onyx® 18 and Onyx® 500. Onyx® is an ethylene vinyl alcohol copolymer dissolved in dimethyl sulfoxide that was approved by the US FDA in July 2005 as an embolic agent for brain arteriovenous malformations. The viscosity units are compared to water, where the Onyx® 18 is 18 times more viscous than water and the 500 variety is 500 times more than the viscosity of water [*Ayad M et al., 2006*]. Onyx® emboli were prepared as follows; Onyx® 18 and 500 were agitated on a shaker per manufacturer's guidelines for 30-45 minutes prior to preparation of the emboli. Using an 18 gauge needle the Onyx® was aspirated into a one *cc* syringe. Silicone tubing with an inner diameter of 4 *mm* was prepared by cutting to a length of 10 *cm*, filling with saline, placing a cap tightly on one end and attaching 3 *cc* syringe of saline via a connector to the other end. The Onyx® was then injected into the midpoint of the tubing through an 18 gauge needle while maintaining turgor pressure through the attached syringe. The Onyx® was allowed to set at room temperature within the silicone tubing with physiologic saline for 60 minutes prior to extraction. The Onyx® casts were then removed from the tubing by removing the cap and injecting saline through the syringe. The Onyx® emboli were then prepared by cutting the cast using an 11 blade scalpel (Fig. 3).

Thrombus delivery: Two methods were used for the delivery of clot or Onyx® to the distal vasculature. The first method is the previously described method of clot delivery through a guide. The autologous clots were cut into sections ranging from 10-15 *mm* in length with a diameter of 4 *mm*, aspirated into a syringe and injected through the guide catheter with 2-3 *cc* of saline and allowed to embolize distally [*Brekenfeld C et al., 2008; Liebig T et al., 2008; Jahan R, 2010; Mordasini P et al., 2010; Mordasini P et al., 2011; Nogueira R et al., 2012; Roth C et al., 2012; Yuki I et al., 2012*]. A second method for embolus delivery was developed to accommodate the non-compressible Onyx® emboli. A carotid cutdown was performed to expose the common carotid artery and direct access was used to place a 12 French sheath into the common carotid artery (Fig. 4). A ten French introducer sheath with an ID of 3.3 *mm* (Cook Medical, Bloomington, IN) was trimmed distally and used to inject Onyx® casts and clot directly into the sheath and native blood flow then carried the embolus distally (Fig. 4A). The Onyx® casts were cut into lengths of 5, 7 and 12 *mm*, trimmed externally until they fit into the distal end of the 10 French introducer and injected

Standard autologous clot embedded with Barium for visualization (white streak) and Onyx® casts (dark grey) were used to produce vascular occlusions in the study. The relative uniformity of both the Onyx® and autologous clot due to their formation in silicone tubing.

Figure 3. *Clot Preparation.*



To accommodate the hard non-deformable Onyx® clots a new method of clot delivery was developed. A. A ten French introducer sheath was used to load the Onyx® clots into a 12 French common carotid sheath. The inner diameter of the introducer is 3.3 mm. B. Access via a combined femoral and direct carotid access allowed for standard clot delivery, delivery of ultra-hard emboli as well as proximal and distal angiography.

Figure 4. *Clot injection technique.*

into the 12 French carotid sheath with 2-3 *cc* of saline. Twenty and 40 *mm* long autologous emboli were likewise injected through the 12 French carotid sheath using the 10 French introducer sheath.

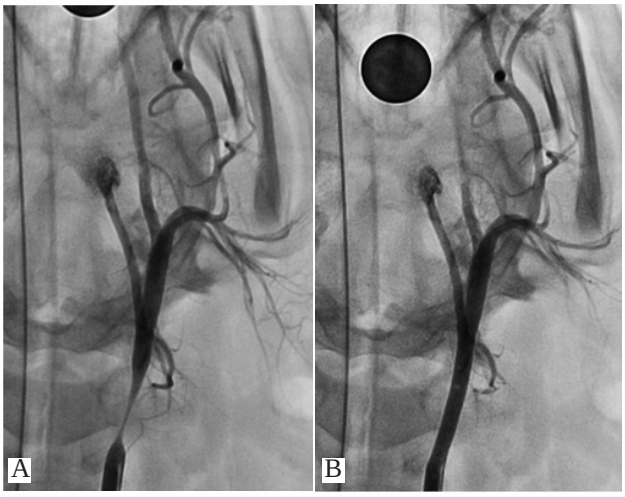
Thrombectomy Technique: Technique for the Solitaire FR® device followed manufacturer's indications for use and an identical technique was used for the Legacy™ device. A Cello™ 8 French balloon guide catheter (Medtronic, Minneapolis MN) was positioned distally in the common carotid artery. A Marksman™ .027 microcatheter (Medtronic, Minneapolis MN) was delivered across the occlusion using a Transcend™ floppy .014 microwire (Stryker Kalamazoo, MI) and a microcatheter angiogram was performed. After deployment, an angiogram was performed through the balloon guide catheter to evaluate for the flow restoration. The device was left in a place for seven minutes at which time the balloon guide catheter was inflated to occlude proximal flow. At this point, aspiration was performed through the balloon guide catheter using a 60 *cc* syringe and the device and microcatheter were removed in tandem through the guide catheter. Immediately following removal, an additional 10-20 *cc* of blood was aspirated through the balloon guide catheter prior to reconnecting to heparinized flush and performing a follow up angiogram to evaluate reperfusion, vasospasm and to identify complications.

Selection criteria, grading scales, device selection, study endpoints: Selection criteria for device evaluation included a treatable vessel diameter (>2*mm*), complete vessel occlusion (TICI 0) and distal vasculature beyond the occlusion which allowed ideal deployment of either the Solitaire FR® or Legacy™ device. Recanalization was graded using a modified thrombolysis in cerebral ischemia (TICI) grading scale as follows; TICI 0 = no flow; TICI 2a = less than fifty percent filling; TICI 2b= >50% filling or complete filling, slow flow and TICI 3 = complete filling, normal flow [*Higashida R et al., 2003; Noser E et al., 2005*]. Vasospasm was graded as mild (≤ 25%), moderate (25-50%) or severe (>50%) [*Grandin C et al., 2000*]. Solitaire FR® device selection was per manufacturer's recommendation. The Solitaire FR® retrievals were performed by an interventionist (RLF) without financial ties to the Legacy device who has extensive clinical experience using the device to treat patients in the clinical setting of acute stroke. Study endpoints included final TICI score, number of attempts, presence and degree of vasospasm, presence of angiographic complications (dissection, perforation) and distal embolization.

Results

Onyx® ultra-hard clot model: Onyx® 18 and 500 were successfully used to produce ultra-hard emboli. There were no difficulties in producing relatively uniform Onyx® casts of 4 *mm* diameter silicone tubing (Fig. 3). The Onyx® was easily removed from the tubing with the injection of saline and the extruded casts were easily cut into sections using an 11 blade scalpel. The Onyx® 18 casts were softer and more pliable than the HD 500 casts. The presence of the tantalum powder within the Onyx® provided excellent visualization of the entire Onyx® embolus throughout the thrombectomy procedure (Fig. 6B and D).

Direct carotid access embolus delivery: There were no complications related to the direct carotid cutdown and access with a 12 French sheath. Immediately after the placement of sheath in both



A. *Just distal to the 12 French sheath, immediately after placement of the sheath into the left common carotid artery, significant vasospasm occurred in both instances of access.* ***B.*** *The vasospasm was rapidly dissipated and normal distal blood flow was observed after the application of topical "Papaverine" (in this case) and spontaneously in another case.*

Figure 5. *Onyx® embolization via direct carotid access.*

animals, there was significant near occlusive localized vasospasm that rapidly cleared with no treatment in one instance and with topical application of dilute "Papaverine" in the second (Fig. 5A and B). The technique was allowed for the delivery of ultra-hard, non-deformable obstructions (Onyx® 500) as well as intact, non-deformed autologous clots. The placement into the distal common carotid artery provided a variety of distal occlusion sites which were localized to internal and external carotid artery branches (Fig. 5B). A total of eight and seven occlusions were performed on each of the sides using this technique.

Efficacy and safety of Legacy™ device and comparison to Solitaire® FR

Standard clot preparation: A total of 15 autologous blood clot vascular occlusions were created, 14 were treated with the new Legacy™ device and 1 was treated with the Solitaire FR® device (Table 1).

From the 14 occlusions treated with the Legacy™ device 5 were "soft" autologous clots and 9 were "firm" autologous clot preparations. The Legacy™ Device achieved complete revascularization from TICI 0 to TICI 3 in one pass in 5/5 "soft" clots in both 10 *mm* length and 15 *mm* length. The Legacy™ Device achieved complete revascularization (TICI 0 to TICI 3) in 7 out of 9 "firm" clots (78%) and near complete revascularization (TICI 0 to TICI 2b) in the remaining 2 out of 9 "firm" clots (22%). The two TICI 2b outcomes with near complete revascularization were extra-long clots (40 *mm*), and these very long clots were prone to break apart during the embolization/injection of clots and tended to occlude side branches and embolized to branch points even before mechanical thrombectomy was attempted. The single treatment with the Solitaire FR® device was using a "firm" 20 *mm* clot and it achieved complete revascularization (TICI 0 to TICI 3). There were no instances of angiographic complications such as dissection or perforation. These results suggest that the Legacy™ Device is similar to Solitaire FR® while treating "soft" and "firm" autologous clots.

Onyx® ultra-hard emboli: Ten total vascular occlusions were produced using either Onyx® 18 or 500 through a direct common carotid artery access technique (Table 2). All occlusive emboli were approximately 3 *mm* in diameter and varied in length between 5, 7 and 12 *mm*. The Legacy™ device was tested in 7 vascular occlusions. In three occlusions using 5 *mm* long Onyx® casts the Legacy™ device produced a TICI 3 recanalization result after a single pass. In three occlusions produced with 7 *mm* long Onyx® casts a TICI 3 result was obtain after a single pass in one case, after four passes in a second case and a TICI 2b result was obtained after a single pass in a third occlusion. In the case of a single 12 *mm* long Onyx® embolus a TICI one result was obtained after three passes. The drop zones and tandem markers along the length of the device functioned as intended. The Onyx® emboli were visualized dragging along the external surface of the landing zone, compressing the tandem markers at the leading edge of the drop zone and falling into the device through the drop zones (Fig. 6D, E, F). Mild vasospasm was noted in four of seven treated vessels. There were no observed angiographic complications such as dye extravasation, perforation or dissection. Overall a TICI 3 result was accomplished in 5 of 7 Onyx® occlu-

Table 1.

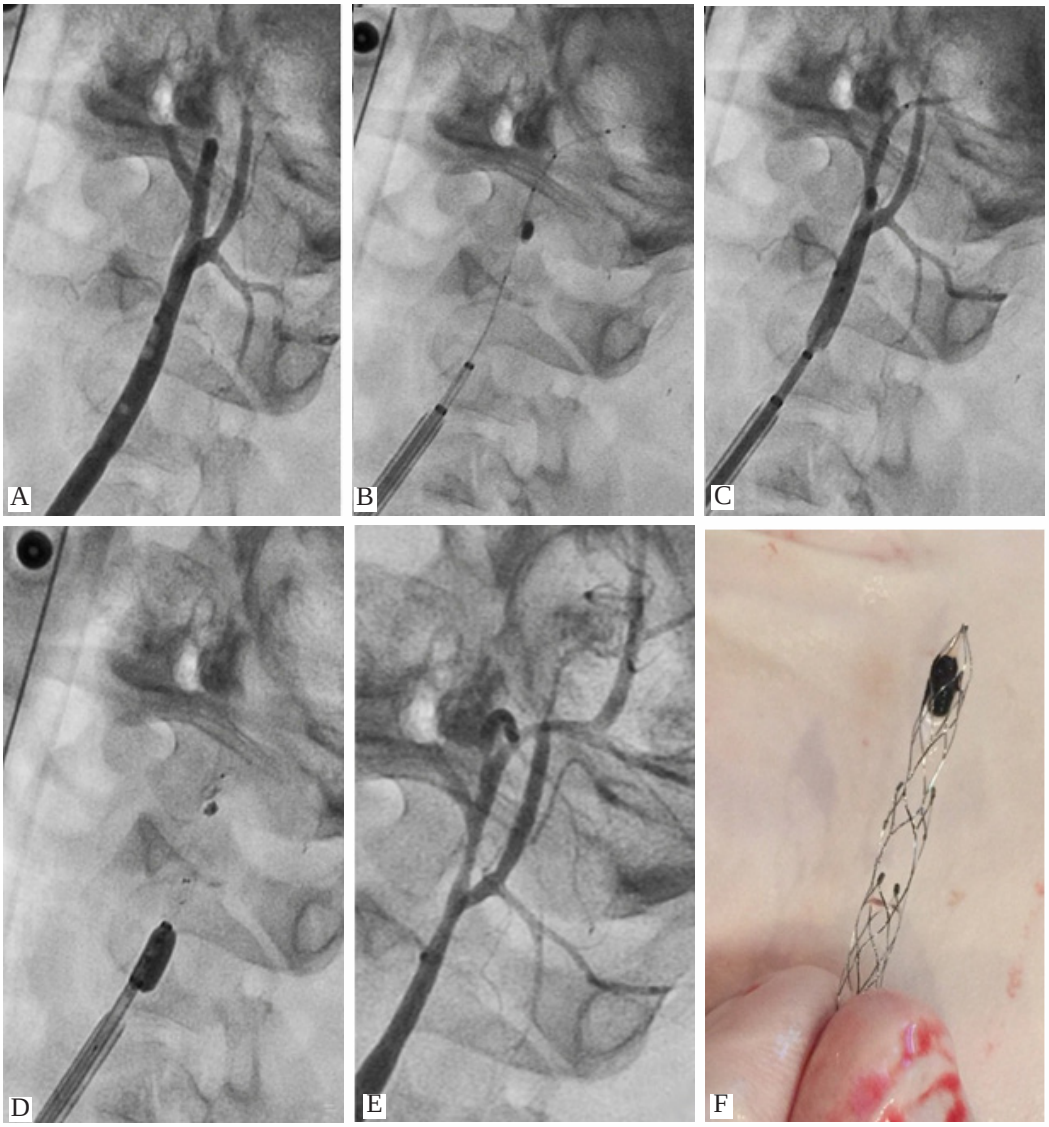
The summary of results: Autologous clot preparation

Device	Injection Method	Clot Type	Size (mm)	TICI pre	TICI final	No. passes	Vasospasm	Distal emboli	Complications
Legacy	Standard	Soft	10x4	0	3	1	Mild	No	None
Legacy	Standard	Soft	10x4	0	3	1	None	No	None
Legacy	Standard	Soft	10x4	0	3	1	None	No	None
Legacy	Standard	Soft	15x4	0	3	1	Moderate	No	None
Legacy	Standard	Soft	15x4	0	3	1	None	No	None
Legacy	Standard	Firm	15x4	0	3	1	None	No	None
Legacy	Standard	Firm	15x4	0	3	2	Mild	No	None
Legacy	Standard	Firm	10x4	0	3	1	None	No	None
Legacy	Standard	Firm	10x4	0	3	1	Mild	No	None
Legacy	Standard	Firm	10x4	0	3	1	None	No	None
Legacy	Carotid sheath	Firm	20x4	0	3	1	Mild	No	None
Legacy	Carotid sheath	Firm	20x4	0	3	1	None	No	None
Legacy	Carotid sheath	Firm	40x4	0	2b	1	Moderate	Yes	None
Legacy	Carotid sheath	Firm	40x4	0	2b	1	Mild	Yes	None
Solitaire FR	Carotid sheath	Firm	20x4	0	3	1	Moderate	Yes	None

Table 2.

The summary of results: Onyx emboli

Device	Injection method	Type of Onyx	Size (mm)	TICI pre	TICI final	No. passes	Vasospasm	Distal emboli	Complications
Legacy	Carotid sheath	18	5x3	0	3	1	None	No	None
Legacy	Carotid sheath	18	7x3	0	3	1	Mild	No	None
Legacy	Carotid sheath	18	12x3	0	1	3	Moderate	No	None
Legacy	Carotid sheath	500	5x3	0	3	1	None	No	None
Legacy	Carotid sheath	500	5x3	0	3	1	None	No	None
Legacy	Carotid sheath	500	7x3	0	3	4	Mild	No	None
Legacy	Carotid sheath	500	7x3	0	2b	1	Mild	Yes	None
Solitaire FR	Carotid sheath	18	5x3	0	0	1	Mild	Yes	None
Solitaire FR	Carotid sheath	18	7x3	0	0	1	Mild	Yes	None
Solitaire FR	Carotid sheath	500	7x3	0	0	3	Moderate	Yes	None



***A.** TICI 0 occlusion of a left sided external carotid artery branch. **B.** Deployment of the Legacy device with offset drop zones (denoted by internal markers) distal to the occlusion. **C.** Flow restoration after the deployment of the device. **D.** Onyx® cast captured within the device and at this point located within the distal capture basket. **E.** Follow up angiogram demonstrating a TICI 3 result. **F.** Onyx® captured within the device after the removal from the balloon guide catheter.*

***Figure 6.** Onyx® retrieval by the Legacy™ thrombectomy device.*

sions, a TICI 2b – in one of 7 and a TICI 1 – in one of 7. The average number of passes per occlusion was 1.7 to achieve the result (Table 2).

As a comparison, the Solitaire FR® device was used in three Onyx® occlusions (Table 2). The Solitaire FR® device failed to remove any of the three occlusions. In two occlusions a single pass was attempted and in one occlusion three passes were completed. The Solitaire FR® was able to "drag" the Onyx® along the vessel wall on three of five occasions, even down to the level of the guide catheter in one instance, but could not incorporate or deliver the Onyx® embolus into the guide catheter resulting in re-embolization and re-occlusion of the vessel (Table 2).

Discussion

Multiple randomized clinical trials have proven the efficacy and safety of mechanical thrombectomy using stent retrieval devices [*Berkhemer O et al., 2015, Campbell B et al., 2015; Goyal M et al., 2015*]. Two devices are currently approved for the use in the United States and several more are approved in the European Union. All devices pass through animal model testing during the development and approval process. The pig model of vascular occlusion is widely used [*Gralla J et al., 2006; Brekenfeld C et al., 2009*]. The models described to date primarily consist of autologous clot preparation and the consistency, size of clot burden, and preparation affect the efficacy of the devices [*Grandin C et al., 2000; Higashida R et al., 2003; Ringer A et al., 2004; Ayad M et al., 2006; Kan I et al., 2010*]. Thrombectomy success is generally defined as a TICI 2b or 3 revascularization [*Berkhemer O et al., 2015; Campbell B et al.,*

2015; Goyal M et al., 2015]. Recanalization failures seen in recent trials, greater than 40% in the Multicenter Randomized Clinical trial of Endovascular treatment for acute ischemic stroke in the Netherlands trial are possibly related to the consistency of the thrombus [*Berkhemer O et al., 2015*]. All currently approved devices have demonstrated a high degree of success in pre-clinical animal trials using various methods of autologous clot generation [*Brekenfeld C et al., 2008; Liebig T et al., 2008; Jahan R , 2010; Mordasini P et al., 2010; Mordasini P et al., 2011; Nogueira R et al., 2012; Roth C et al., 2012; Yuki I et al., 2012*]. A novel stent retrieval device was designed based on the assumption that device failures were related to the presence of hard, cohesive, non-deformable obstructions such as organized and/or calcified thromboemboli. The Legacy™ thrombectomy device has two large offset drop zones oriented ninety degrees relative to each other which are designed to allow hard occlusions to fall within the device as the device is withdrawn along the obstruction (Fig. 1C, 1E, 2, 6D and F). The distal portion of the device has a closed end to capture the obstruction once inside the device (Fig. 6D and F). A new clot model was developed in order to evaluate the efficacy of the Legacy™ device to remove ultra-hard obstructions. The aim was to develop a clot model in which the obstruction is hard and cohesive to simulate the embolization of cholesterol plaque and densely organized cardiac thrombus. Onyx® was chosen due to the inherent radio-opacity provided by the embedded tantalum powder, the ubiquitous presence and familiarity within the interventional community and the ability to adjust the consistency based on the viscosity of the Onyx® used. A novel method of direct carotid access using a 12 French sheath and a 10 French embolus injector was developed in order to deliver the non-deformable Onyx® emboli which allowed for the repeated delivery of uniform 3 *mm* diameter Onyx® emboli of varying length (Fig. 4, 5, 6). Autologous clot was also delivered using this method. In the previously described models for clot delivery, the clot is introduced through a guide catheter into the target vessel. In effect, a thrombus with a 4 *mm* diameter prior to injection is compressed to the inner diameter of the delivery catheter prior to reaching the distal vasculature. This compression during delivery has the potential to deform the thrombus and does not match the in vivo mechanism in which emboli travel from larger diameter vessels to smaller diameter vessels and become lodged due to native blood flow.

The recanalization rates obtained using the Legacy™ device for autologous clot mirror the excellent results obtained previously with the use of multiple other thrombectomy devices (4-15) in present study. A TICI 2b/3 result was obtained in14 of 14 autologous occlusion. However, a clear difference in efficacy was seen while using the Legacy™ device to treat hard Onyx® emboli as compared to autologous clot occlusions. Although the ultimate TICI 2b/3 results were similar (12/14 TICI 3 autologous versus 5/7 TICI 3 Onyx®), the removal of the Onyx® emboli required on average 1.7 passes versus 1.1 passes for the autologous clot (Table 1 and 2). In addition, the 12 *mm* Onyx® obstruction could not be removed. The drop zones on the Legacy™ device were functioned as intended, allowing the hard onyx emboli to enter the inside of the device (Fig. 6F). However, the failure to deliver the 12 *mm* onyx obstruction was likely due to the size limitations of the drop zones relative to the size of the hard obstruction. An even larger difference in efficacy was identified while comparing the Legacy™ device and the Solitaire FR® device using Onyx® emboli. In contrast to the Legacy™ device, the Solitaire FR® failed to capture and remove any of Onyx® obstructions.

The inability of current stent-retriever devices to efficiently capture and remove the subset of ultra-hard emboli might be the reason behind a significant number of revascularization failures seen in the recently published trials. The Onyx® model of vascular occlusion in the swine model of stroke provides a method to evaluate emerging technology for the ability to remove these types of obstructions.

Thus, a model of organized and/or calcified hard thromboemboli is described for the first time in literature. This model clearly differentiated the ability of two different devices to remove hard, organized and/or calcified thrombemboli. The Legacy™ device achieved TICI 2B/3 recanalization in 6 out of 7 hard occlusions (86%), and the only not revascularized case was a very long 12 *mm* hard onyx mass. The Solitaire FR® device achieved TICI 2B/3 recanalization in 0 out of 3 occlusions, even though none of longer more difficult occlusions were attempted with Solitaire FR®.

REFERENCES

1. *Ayad M, Eskioglu E, Mericle RA.* Onyx: a unique neuroembolic agent. Expert Rev Med Devices. 2006; 3(6): 705-715.
2. *Berkhemer OA, Fransen PS, Beumer D, van den Berg LA., et al.* A randomized trial of intra-arterial treatment for acute Ischemic stroke. N Engl J Med. 2015; 372(1): 11-20.
3. *Brekenfeld C, Schroth G, El-Koussy M, Nedeltchev K., et al.* Mechanical thromboembolectomy for acute ischemic stroke: comparison of the catch thrombectomy device and the Merci Retriever in vivo. Stroke. 2008; 39(4): 1213-1219.
4. *Brekenfeld C, Tinguely P, Schroth G, Arnold M., et al.* Percutaneous transluminal angioplasty and stent placement in acute vessel occlusion: evaluation of new methods for interventional stroke treatment. AJNR Am J Neuroradiol. 2009; 30(6): 1165-1172.
5. *Campbell BC, Mitchell PJ, Kleinig TJ, Dewey HM., et al.* Endovascular therapy for ischemic stroke with perfusion-imaging selection. N Engl J Med. 2015; 372(11): 1009-1018.
6. *Goyal M, Demchuk AM, Menon BK, Eesa M., et al.* Randomized assessment of rapid endovascular treatment of ischemic stroke. N Engl J Med. 2015; 372(11): 1019-1030.
7. *Gralla J, Schroth G, Remonda L, Fleischmann A., et al.* A dedicated animal model for mechanical thrombectomy in acute stroke. AJNR Am J Neuroradiol. 2006; 27(6): 1357-1361.
8. *Grandin CB, Cosnard G, Hammer F, Duprez TP., et al.* Vasospasm after subarachnoid hemorrhage: diagnosis with MR angiography. AJNR Am J Neuroradiol. 2000; 21(9): 1611-1617.
9. *Higashida RT, Furlan AJ, Roberts H, Tomsick T., et al.* Trial design and reporting standards for intraarterial cerebral thrombolysis for acute ischemic stroke. Stroke. 2003; 34(8): e109-137.
10. *Jahan R.* Solitaire flow-restoration device for treatment of acute ischemic stroke: safety and recanalization efficacy study in a swine vessel occlusion model. AJNR Am J Neuroradiol. 2010; 31(10): 1938-1943.
11. *Kan I, Yuki I, Murayama Y, Viñuela FA., et al.* A novel method of thrombus preparation for use in a swine model for evaluation of thrombectomy devices. AJNR Am J Neuroradiol. 2010; 31(9): 1741-1743.
12. *Liebig T, Reinartz J, Hannes R, Miloslavski E, Henkes H.* Comparative in vitro study of five mechanical embolectomy systems: effectiveness of clot removal and risk of distal embolization. Neuroradiology. 2008; 50(1): 43-52.
13. *Mordasini P, Frabetti N, Gralla J, Schroth G., et al.* In vivo evaluation of the first dedicated combined flow-restoration and mechanical thrombectomy device in a swine model of acute vessel occlusion. AJNR Am J Neuroradiol. 2011; 32(2): 294-300.
14. *Mordasini P, Hiller M, Brekenfeld C, Schroth G., et al.* In vivo evaluation of the Phenox CRC mechanical thrombectomy device in a swine model of acute vessel occlusion. AJNR Am J Neuroradiol. 2010; 31(5): 972-978.
15. *Nogueira RG, Levy EI, Gounis M, Siddiqui AH.* The Trevo device: preclinical data of a novel stroke thrombectomy device in two different animal models of arterial thrombo-occlusive disease. J Neurointerv Surg. 2012; 4(4): 295-300.
16. *Noser EA, Shaltoni HM, Hall CE, Alexandrov AV., et al.* Aggressive mechanical clot disruption: a safe adjunct to thrombolytic therapy in acute stroke? Stroke. 2005; 36(2): 292-296.
17. *Ringer AJ, Guterman LR, Hopkins LN.* Site-specific thromboembolism: a novel animal model for stroke. AJNR Am J Neuroradiol. 2004; 25(2): 329-332.
18. *Roth C, Junk D, Papanagiotou P, Keuler A., et al.* A comparison of 2 stroke devices: the new Aperio clot-removal device and the solitaire AB/FR. AJNR Am J Neuroradiol. 2012; 33(7): 1317-1320.
19. *Yuki I, Kan I, Vinters HV, Kim RH., et al.* The Impact of thromboembolia histology on the performance of a mechanical thrombectomy device. AJNR Am J Neuroradiol. 2012; 33(4): 643-648.