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Original Paper

Preclinical Evaluation of the NeVa™ Stent Retriever: Safety and Efficacy in the Swine Thrombectomy Model

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Keywords
Animal model · NeVa™ stent retriever · Thrombectomy

Abstract
Background: A novel stent retriever device with an enhanced radial force profile, enlarged offset openings, and a closed distal end has been developed. ***Objective:*** Evaluate the safety and effectiveness of the NeVa™ thrombectomy device in animal model of thrombo-occlusive disease. ***Materials and Methods:*** Seven swine were used in safety and efficacy studies. Thrombo-occlusive disease was modeled using 4 emboli morphologies; 2 distinct models of autologous whole blood thrombi, plasma-enriched thrombi, and Onyx® emboli. A total of 35 vascular occlusions and retrievals were performed using emboli of variable sizes. Pre- and post-modified thrombolysis in cerebral ischemia (mTICI) scores, number of retrievals, and the presence of angiographic complications were recorded. In the safety study, a total of 6 clot retrievals were completed and the vascular territory examined grossly and harvested for histopathological evaluation. A semiquantitative vasospasm study was performed. Radial force testing was performed on NeVa™ and control devices for comparison. ***Results:*** Near-full or full reperfusion (mTICI 2b/3) was achieved in 34/35 occlusions after a mean of 1.2 passes. Full reperfusion (TICI 3) was achieved in 17/17 of whole blood clot occlusions (ranging between 10 and 20 mm) after a mean of 1.06 passes. The rate of mTICI 2b/3 reperfusion was 10/11 (mean, 1.6 passes) and 5/5 (mean, 1.0 passes) for Onyx® and plasma-enriched clot emboli, respectively. Histopathological vessel injury and vasospasm scores were comparable to predicate studies. Radial force curves demonstrated increased expansive radial force and similar compressive radial force compared to predicate devices. ***Conclusions:*** Our preclinical results support the use of the NeVa™ device in a clinical trial to determine if this novel design improves upon current stent retriever outcomes.

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Introduction

Several recent randomized clinical trials have proven the safety and efficacy of stent retriever thrombectomy devices in the treatment of acute stroke due to large vessel occlusion [1–6]. Successful recanalization rates (modified thrombolysis in cerebral ischemia [mTICI] 2b/3) in these studies range between 58 and 88% [1–6]. Multiple passes are often required in order to achieve the desired result and distal embolization to the same and/or previously uninvolved territories are common [6]. The NeVa™ thrombectomy device is a novel stent retriever manufactured by Vesalio™ (Nashville, TN, USA) with an enhanced radial force profile, hybrid cell design with enlarged offset openings, and a closed distal end. The enlarged openings were designed to allow organized, soft and hard emboli to enter the inside of the device and become captured in the closed distal end. We present preclinical safety and efficacy data on the NeVa™ device on a swine model of thrombo-occlusive disease.

Materials and Methods

Animal Care

All procedures were conducted according to the Translational, Testing and Training Laboratories, Inc. – T3 Labs standard operating procedures and ethical guidelines of the Institutional Animal Care and Use Committee. Seven swine (weighing between 28 and 42 kg) were used in our study on noncontiguous days. Animals were housed at T3 Labs Animal Facility quarantined as per T3 Labs standard operating procedures and given free access to food and water until the night before the endovascular procedure was performed, when food was withheld. The animals preoperatively received atropine (Med-Pharmex Inc., Pomona, CA, USA) 0.04 mg/kg i.m., to reduce vagal effect, telazol (Zoetis Inc., Kalamazoo, MI, USA) 4 mg/kg i.m. in combination with xylazine (Akorn Inc., Marietta, GA, USA) 0.5 mg/kg i.m. for anesthesia induction, and buprenorphine (Patterson Inc., Phoenix, AZ, USA) 0.01 mg/kg i.m., for preoperative analgesia.

After endotracheal intubation, anesthesia was maintained with 2–2.5% isoflurane (Abbot Labs, Chicago, IL, USA) in oxygen throughout all procedures. After the procedure was completed and still under anesthesia, euthanasia was induced with KCl (Hospira Inc., Lake Forest, IL, USA) 1 mEq/kg i.v. The procedures were performed on a fixed single plane angiography system (Siemens) and a second mobile C-arm (GE) with road mapping and angiographic capabilities was used to provide bi-plane visualization when necessary.

NeVa™ Thrombectomy Device

The NeVa™ thrombectomy device was designed for the removal of occlusive thrombus in the setting of acute stroke. The device comes in 4 configurations designed for site-specific deployment (Fig. 1). There are 3 distinct areas of thrombus engagement moving proximal to distal along the device (Fig. 2). 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. 2A). The second area is comprised of "drop zones," which are oriented 90° offset relative to each other (Fig. 2C, F). The offset drop zones provide a 360-degree entry area along the device to facilitate thrombus incorporation (Fig. 2, 3). The M1 and T have two drop zones while the $M1^3$ and T^3 have 3 drop zones with the middle drop zone offset (Fig. 1). The enlarged drop zones measure 56 mm^2 in the NeVa™ T and T^3 and 43 mm^2 in the NeVa™ M1 and $M1^3$. As opposed to the proximal flow restoration zone, the drop zones have a third dimension of depth to optimize clot integration (Fig. 2C). Tandem radiopaque markers oriented on either side of the device and at the leading edge of the drop zones provide enhanced feedback to the operator (Fig. 2, 4). 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 the thrombus as the device is being withdrawn (Fig. 4, 5). The third component is a distal capture basket, which is closed ended and is designed to capture a thrombus that becomes incorporated into the device (Fig. 1–3).

Animal Studies

Whole Blood Autologous "Red" Thrombus Model

Autologous blood was used to create two versions of whole blood thrombus [7, 8]. One version was created by combining 1 g of barium sulfate, 25 IU of bovine thrombin, and 10 mL of autologous whole blood

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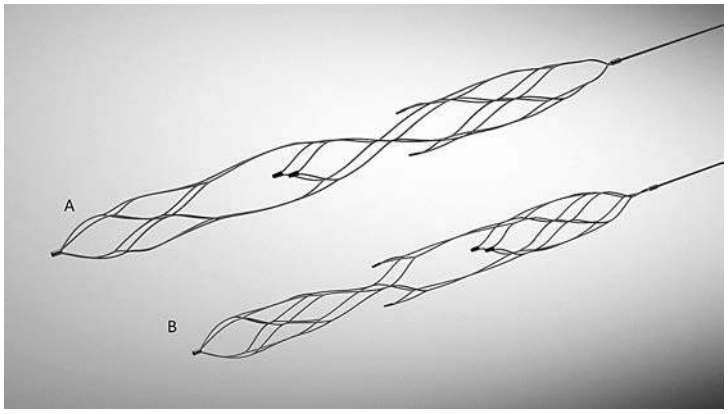

Fig. 1. NeVa™ device. Four variations of the NeVa™ stent retriever were evaluated in the study. The NeVa™ T and M1 differ in working length (37 and 30 mm) and diameter (4.5 and 4.0 mm). The NeVa T[3] and M1[3] have a third "drop zone" and corresponding longer working lengths (47 and 38 mm). All four devices are 0.021 microcatheter compatible. A, NeVa™ T; B, NeVa™ M1.

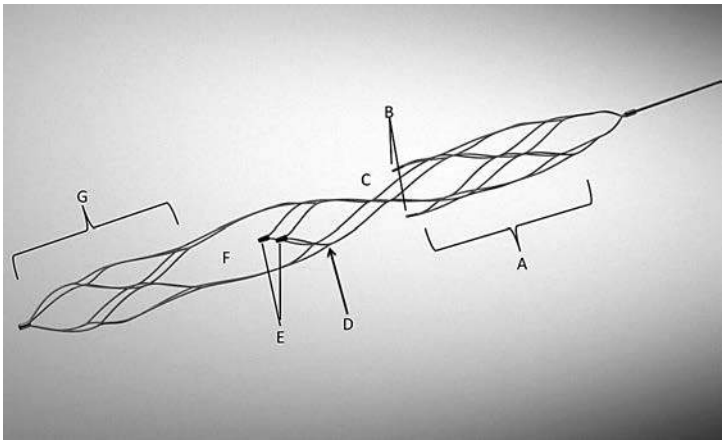

Fig. 2. Device functional zones. A, flow restoration zone, analogous to a typical stent retriever measures 13 and 17 mm in length for the M1 and T; B, offset markers at the leading edge of first "drop zone;" C, first "drop zone;" D, stent retriever zone between "drop zones;" E, offset markers at proximal portion of second "drop zone;" F, second "drop zone" 90° offset relative to first; G, distal capture basket.

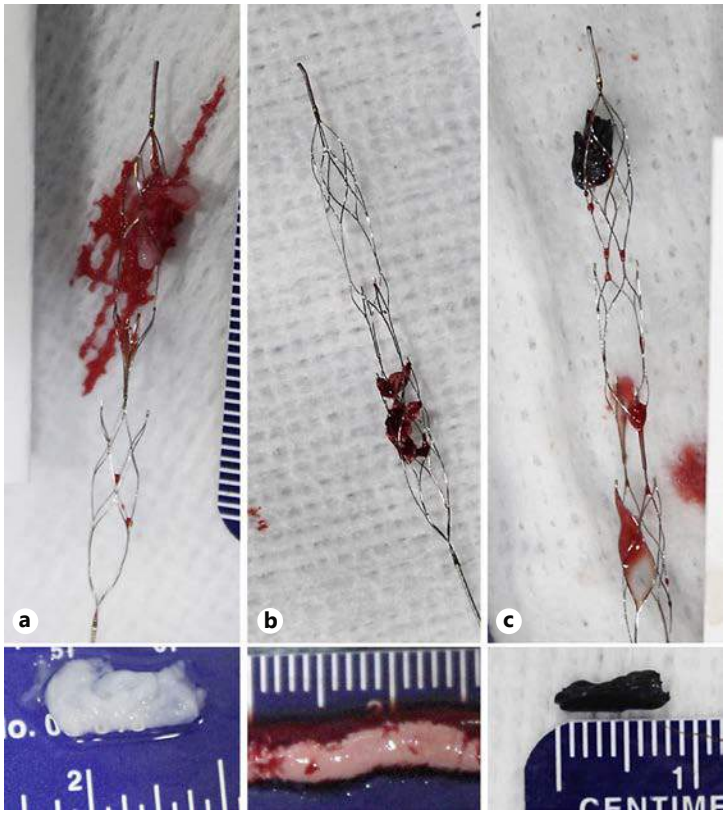

Fig. 3. Clot integration. Three different types of clot were used in the study. **a** Plasma rich white blood clots simulating organized, cohesive thrombi (NeVa™ M1). **b** Autologous whole blood clots simulating fresh thrombi (NeVa™ T). **c** EVAC emboli simulating calcified plaque emboli (NeVa™ M1[3]). In most instances, all 3 types of clot were partially or completely integrated within the device and trapped in the distal basket.

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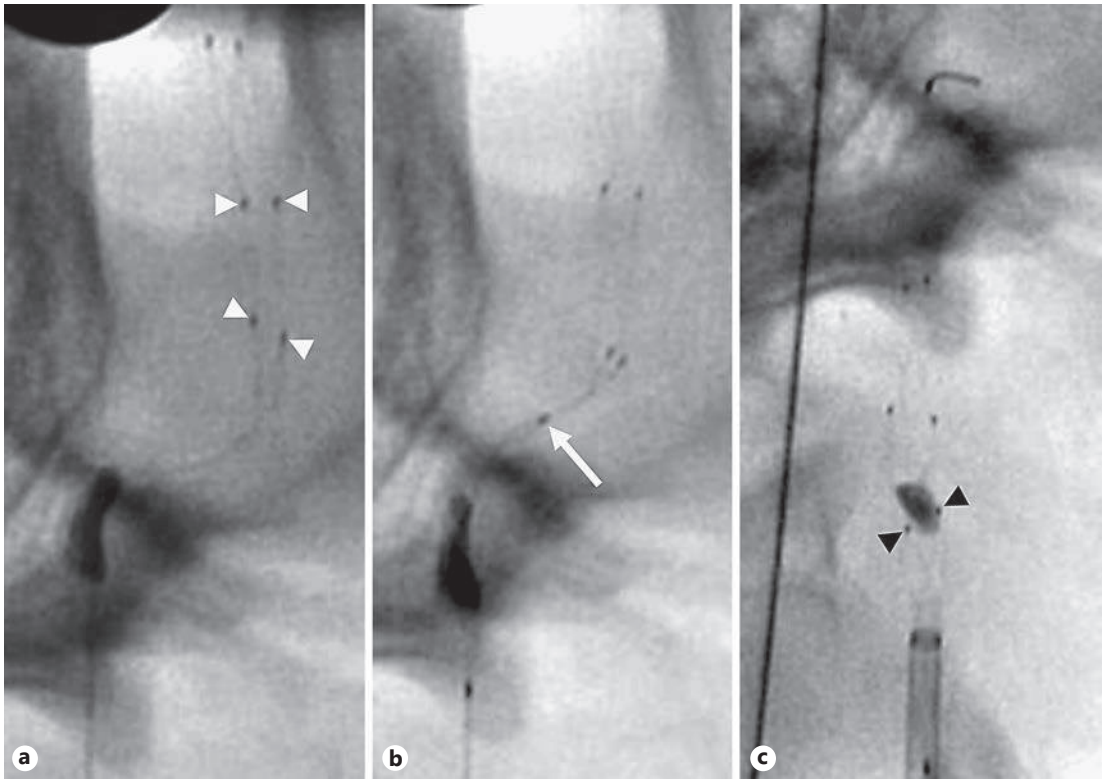

Fig. 4. Drop zone markers. **a** As the device is deployed and initially expands and compresses the thrombus, the two offset markers can be identified as two radiopaque points (white arrowheads) and mark the proximal edge of each drop zone. Both markers can be visualized on single-plane fluoroscopy by optimizing the view. **b** As the device is withdrawn, the thrombus is noted to compress the drop zone markers into a single point (white arrow) as the thrombus approaches the "drop zone." At this point, the operator knows that the clot is external to the device and is aligned to enter through the opening, allowing the operator to slow down the retrieval to maximize clot integration. **c** Successful entry of the thrombus through the "drop zone" is apparent when the markers re-expand to original position on either side of the device (black arrowheads).

and incubating at room temperature for 60 min in silicone tubing (clinicomedical) with an inner diameter (ID) of 4 mm [7]. A second preparation was performed by combining 10 mL of whole blood with 2 g of barium sulfate and incubating at room temperature for 120 min in silicone tubing with an ID of 4 mm [8] (Fig. 3b).

Plasma Rich Autologous "White" Thrombus Model

Plasma rich thrombi were prepared according to a previously published protocol [9]. Whole blood was collected into Vacutainer™ blood tubes containing 3.2% sodium citrate (1:9 volume) which were then placed into a centrifuge at 350 *g* for 10 min at 22 °C. The plasma layer was then collected and $CaCl_2$ was added to the platelet-rich plasma layer at a ratio of 1/10 mL of plasma to reverse the sodium citrate. The recalcified plasma was then incubated at 37 °C for 2.5 h after which the white thrombi were extracted (Fig. 3a).

Ethylene Alcohol Copolymer Embolus Model

Ultra-hard emboli were modeled using Onyx® 18 and Onyx® 500. Onyx is an ethylene vinyl alcohol copolymer (EVAC) dissolved in dimethyl sulfoxide approved by the US FDA for brain arteriovenous malformations [10]. The viscosity units are compared to water, where the Onyx® 18 is 18 times more viscous than water [10]. EVAC emboli were prepared as follows: Onyx® 18 or 500 was agitated in a shaker as per the manufacturer's guidelines for 30–45 min prior to the preparation of the emboli. Onyx 500 was heated to 70 °C prior to agitation. Using an 18-G needle the EVAC was aspirated into a 1-mL syringe. Silicone tubing with an ID of 4 mm was prepared by cutting to a length of 10 cm, filling with saline, placing a cap tightly on one end

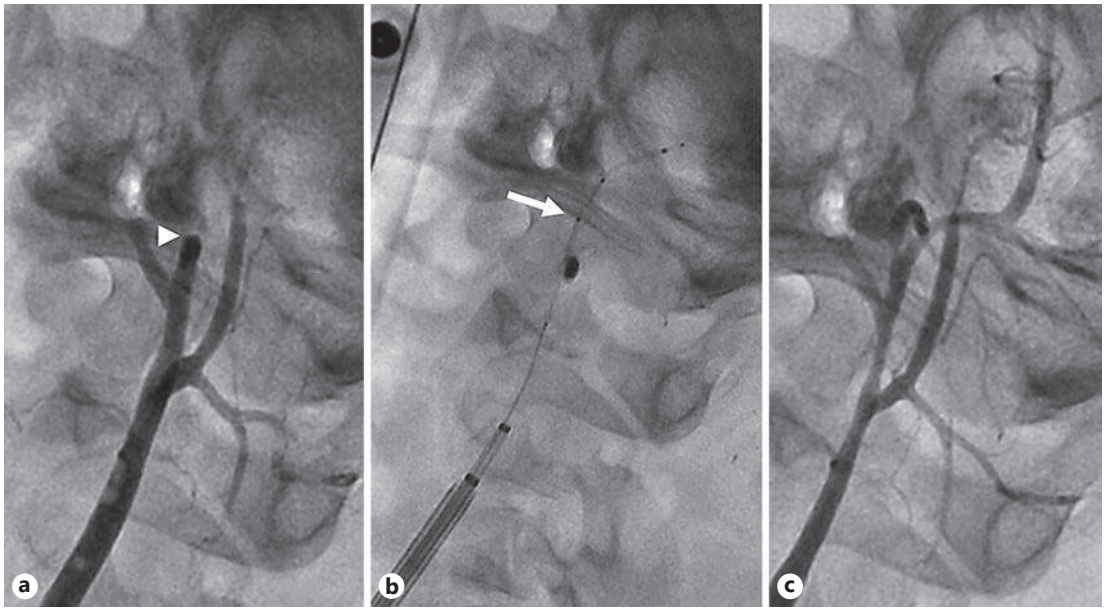

Fig. 5. Simulated thrombectomies. Left carotid artery territory. **a** TICI 0 occlusion of the main trunk of external carotid artery (white arrowhead). **b** NeVa™ T device in microcatheter demonstrating the ideal position for deployment with the first drop zone marker (white arrow) past the distal edge of the occlusion. **c** Immediate follow-up angiogram with TICI 3 reperfusion result after retrieval.

and attaching a 3-mL syringe of saline via a connector to the other end. The EVAC was then injected into the midpoint of the tubing through an 18-G needle while maintaining turgor pressure through the attached syringe. The EVAC was allowed to set at room temperature within the silicone tubing with physiologic saline for 60–120 min prior to extraction. The EVAC casts were then removed from the tubing by removing the cap and injecting saline through the syringe. The EVAC emboli were then prepared by cutting the cast using an 11-blade scalpel (Fig. 3c).

Thrombus Delivery

Two methods were used for delivery of autologous clot or EVAC into the distal vasculature. The first method is the standard, previously described method of clot delivery through a guide catheter, balloon guide catheter or shuttle sheath [7, 11–20]. A second method for embolus delivery was developed to accommodate the ultra-hard, noncompressible EVAC emboli. A carotid cutdown with direct access was used to place a short 10- or 12-Fr sheath into the proximal common carotid artery just distal to the sternum. A 10-Fr introducer sheath with an ID of 3.3 mm (Cook medical) was used to inject EVAC emboli and autologous clot directly into the 12-Fr sheath and native blood flow then carried the emboli distally. The EVAC casts were cut into lengths of 4, 5, 7, and 12 mm, trimmed externally until they just fit into the distal end of the 10-Fr introducer (ID 3.3 mm) and were injected into the 12-Fr carotid sheath with 2- to 3-mL of saline (Fig. 3c). Autologous emboli were likewise injected through the 12-Fr carotid sheath using the 10-Fr introducer sheath. All target vessels were between 1.5 and 4 mm in diameter and all occlusions were performed in the distal carotid territory involving the internal pharyngeal, lingual artery and other external carotid artery branches (Fig. 5).

Thrombectomy Technique

A Cello™ 7- or 8-Fr balloon guide catheter (Medtronic) or a 6-Fr shuttle sheath (Cook Medical) was positioned in the common carotid artery (not in the occluded branch and at a distance from the occlusion to simulate placement in the human cervical internal carotid) through either the 12-Fr direct access sheath or through an 9-Fr common femoral artery sheath. A Marksman™ 0.027 microcatheter (Medtronic) or a Trevo-18 0.021 (Stryker) microcatheter was delivered across the arterial occlusion using a 0.014 microwire and a distal angiogram was performed through the microcatheter. The NeVa™ device was deployed with the proximal tandem markers distal to the leading edge of the obstruction (Fig. 5b). After deployment, an

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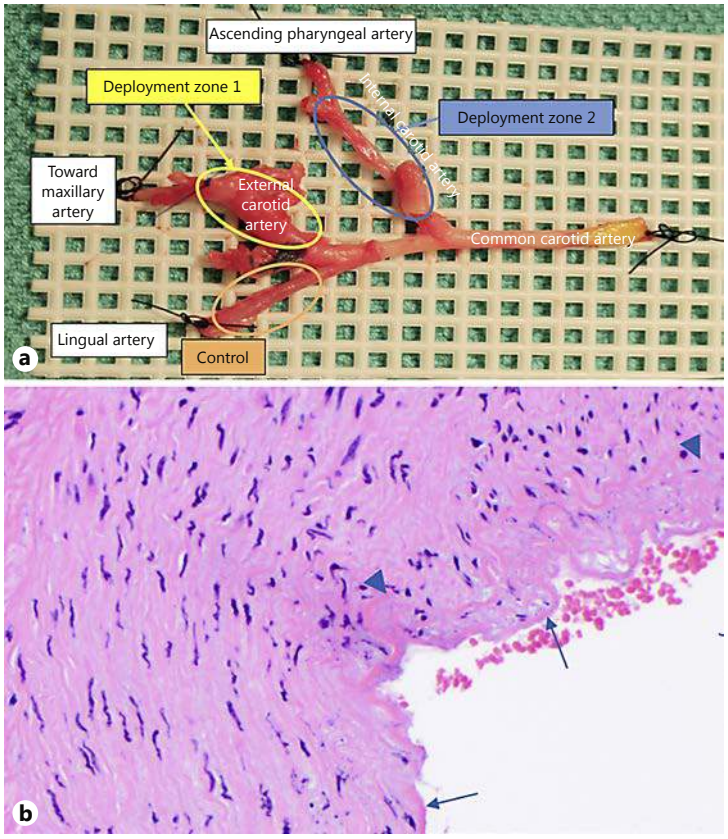


Fig. 6. Histopathological examination following thrombectomy. **a** Gross dissection of distal right common carotid artery after 6 clot retrievals with 3 different morphologies. Five retrievals and 2 occlusions involved the external carotid artery and 1 occlusion and retrieval involved the internal pharyngeal (carotid) artery. **b** Hematoxylin and eosin staining for evaluation of target vessels. The major feature was endothelial cell loss (arrows) with occasional, focal internal elastic lamina disruption (arrow head).

angiogram was performed through the guide catheter to evaluate flow restoration. The device was left in place for 1–7 min prior to retrieval. Retrievals were performed with and without balloon occlusion. When the thrombectomy device approached the distal end of the guide catheter, aspiration was performed through the guide catheter using a large syringe and the device and microcatheter were removed as a unit through the guide catheter. Negative controls were performed to demonstrate that aspiration alone through the guide catheter had no ability to remove the distally placed emboli and in no instance was the guide catheter advanced into the occluded branch vessel during any retrieval. Immediately following removal, follow-up angiograms to grade revascularization, vasospasm and to identify complications were performed [21]. Reperfusion was graded using an mTICI grading scale [22]. Endpoints included final mTICI score, number of attempts, presence of angiographic complications (dissection, perforation, extravasation of contrast), and distal embolization during retrieval (Fig. 5; Table 1).

Safety Study

Four vascular occlusions and 6 retrievals were performed in the distal left carotid artery territory of one of the animals through a proximal carotid artery sheath. Five of the retrievals (3 NeVa™ T and 2 NeVa™ M1[3]) were performed in the main trunk of the external carotid (average diameter 3.1 mm) and one was performed in the internal pharyngeal artery (average diameter 2.7 mm) using NeVa™ M1. Two occlusions were red clot (one pass each), one white clot (one pass) and the fourth was a 7-mm EVAC occlusion (3 passes). A final mTICI 3 result was obtained for the overall territory. At the conclusion of the last retrieval, the pig was euthanized and the internal pharyngeal, external carotid artery branches as well as a control vessel (lingual artery) were examined in situ for evidence of gross injury and then harvested and sent to an independent lab for histopathological examination (Fig. 6). A standardized 20-point semiquantitative injury score was reported for each experimental vessel and the control vessel [11]. In a separate animal, a semiquantitative vasospasm evaluation was performed on 4 vessels under good laboratory practice guidelines using NeVa™ M1 and T. The device was deployed and resheathed three times into a microcatheter with a final deployment and retrieval into a proximal guide catheter to simulate thrombectomy. No calcium channel blocking medica-

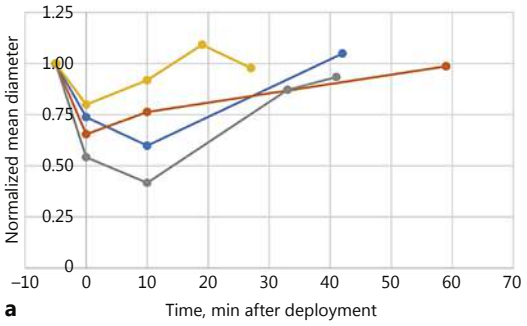
Table 1. Summary of laboratory testing of the NeVa™ thrombectomy device by type, clot morphology, revascularization results, number of attempts, and complications

Device	Embolus	Size	TICI pre	TICI post	Attempts	Complication
T	Red	4×10	0	3	1	–
T	Red	4×10	0	3	1	–
T	Red	4×10	0	3	1	–
M1	Red	4×10	0	3	1	–
M1	Red	4×10	0	3	1	–
M1	Red	4×10	0	3	1	–
M1	Red	4×10	0	3	1	–
M1	Red	4×10	0	3	1	–
M1	Red	4×10	0	3	1	–
T	Red	4×15	0	3	1	–
T	Red	4×15	0	3	2	–
T	Red	4×15	0	3	1	–
M1	Red	4×15	0	3	1	–
T	Red	4×20	0	3	1	–
T	Red	4×20	0	3	1	–
M1	Red	4×20	0	3	1	–
M1	Red	4×20	0	3	1	–
T	Red	4×40	0	2b	1	–
T	Red	4×40	0	2b	1	–
T[3]	White	6×6	0	3	1	–
T	White	6×6	0	2b	1	–
M1	White	14×6	0	3	1	–
T	White	10×10	0	3	1	–
T[3]	White	10×12	0	2b	1	–
T	EVAC	3×4	1	3	1	–
T[3]	EVAC	3×4	0	3	1	–
M1	EVAC	3×4	0	3	1	–
T	EVAC	3×5	0	3	1	–
M1	EVAC	3×5	0	3	1	–
M1	EVAC	3×5	0	3	1	–
M1[3]	EVAC	3×7	0	3	3	–
T	EVAC	3×7	0	3	1	–
T	EVAC	3×7	0	3	4	–
T	EVAC	3×7	0	2b	1	–
T	EVAC	3×12	0	1	3	–

tions, including nimodipine, were given during the semiquantitative vasospasm evaluation. NeVa™ M1 was deployed into the right and left internal pharyngeal while NeVa™ T was deployed into the external carotid maxillary branch on each side. Predeployment mean vessel diameters as well as serial angiographic diameters obtained at time points spanning up to 60 min following retrieval were recorded. The Siemens single-plane vessel segment analysis software was used to determine vessel diameter with calibration based on guide catheter size. An independent good laboratory practice study coordinator determined the vasospasm score at each time point using the measured diameters and a standard scale [21] (Fig. 7).

Radial Force Testing

Radial force testing was performed on 32 NeVa™ T and M1 devices, 4 Solitaire™ 6 × 30, 2 Solitaire™ 4 × 20, and 3 Trevo™ 4 × 20 retrievers. Testing was performed at Machine Solutions (Flagstaff, AZ, USA) on a RX 550 machine and on a Blockwise (Tempe, AZ, USA) TTRT machine within a radial compression chamber at 37 °C by independent contractors. Radial force curves were generated over the diameter range of 0.8–6 mm and cycled 5–10 times for each device. Maximum, minimum, average and standard deviation of the expansive and compressive radial force at 2.0, 2.5, 3.0, and 3.5 mm was recorded for each individual device (Fig. 8).



a

b

	Time point, min	Mean vessel diameter, mm	Mean normal diameter, mm	Spasm score
NeVa M1	pre	2.44	1.00	–
	0	1.8	0.74	2
	10	1.46	0.60	2
	42	2.56	1.05	0
NeVa T	pre	3.76	1.00	–
	0	2.46	0.65	2
	10	2.87	0.76	1
	59	3.71	0.99	0
NeVa M1	pre	2.88	1.00	–
	0	1.56	0.54	2
	10	1.2	0.42	3
	33	2.51	0.87	1
	41	2.69	0.93	1
NeVa T	pre	3.69	1.00	–
	0	2.95	0.80	1
	10	3.39	0.92	1
	19	4.03	1.09	0
	27	3.61	0.98	0

Fig. 7. Semiquantitative vasospasm evaluation. Pre-deployment, immediate postretrieval and vessel diameters obtained through follow-up angiography were used to plot the severity and time course of vasospasm for NeVa™ M1 and T. **a** Graph demonstrating normalized mean diameters over time. **b** Pre- and postretrieval vessel diameters over time with corresponding vasospasm score.

Results

Autologous "Red" Clot Preparation

A total of 19 whole blood autologous clot vascular occlusions were treated using the NeVa™ thrombectomy device. Clot lengths ranged from 10 to 40 mm. A single-pass mTICI 3 result occurred in 16/19 retrievals. A single 15-mm-long clot required 2 passes to achieve an mTICI 3 result due to distal embolization of a piece of clot upon retrieval into the guide catheter on the first attempt. Two 40-mm-long clots fragmented upon injection into separate vessels and the result was an mTICI 2b after a single pass in both instances. The average number of retrievals across the spectrum of sizes was 1.05 to achieve the final result (Table 1).

Autologous "White" Clot Preparation

Five occlusions were performed using plasma-enriched white thrombi to mimic organized clot. An mTICI 2b/3 result was obtained after a single pass in all 5 occlusions (Table 1).

EVAC Ultra-Hard Emboli

Eleven occlusions were performed using EVAC emboli. In 6/6 occlusions with 4- to 5-mm-long emboli, an mTICI 3 result was obtained after a single pass. In 4/4 occlusions produced with 7-mm-long emboli, an mTICI 2b/3 result was obtained with an average of 2.25 retrievals. No significant recanalization was obtained after three retrieval attempts of a single 12-mm-long EVAC embolus (Table 1).

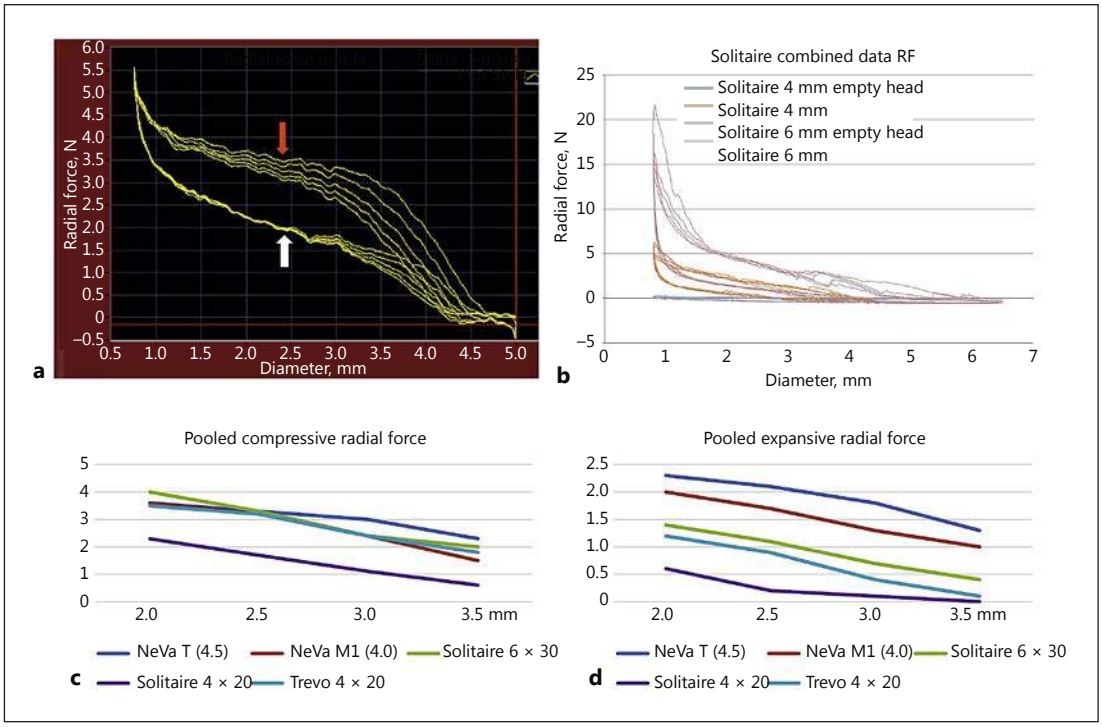


Fig. 8. Radial force. Individual devices were cycled 5–10 times between diameters of 0.8 and 6 mm to produce radial force curves for each device. **a** NeVa™ T representative radial force graph showing 5 cycles. The force curve has a compressive force (red arrow) and an expansive force (white arrow) at each diameter. **b** Radial force curves generated over 5 cycles on a 6 × 30 and a 4 × 20 Solitaire™ device. The mean expansive and compressive radial force at the measured diameters for each device tested were then pooled and an average obtained for 4 diameters ranging between 2.0 and 3.5 mm. **c** Pooled compressive mean radial force in newton at 2.0, 2.5, 3.0, and 3.5 mm. **d** Pooled expansive radial force in newton at 2.0, 2,5, 3.0, and 3.5 mm.

Use of Drop Zone Markers during Thrombectomy

The paired tandem drop zone markers were visualized throughout the retrieval of the NeVa™ devices; from the time of deployment, engagement of embolus and withdrawal into the guide catheter. In retrievals using "red," soft thrombi, in most instances the paired drop zone markers remained separated during the entire retrieval. In these cases, most of the clot was adherent to the outer surface of the device, often along the length of the flow restoration zone (Fig. 3b). In the case of EVAC, these ultra-hard emboli could be identified compressing the paired drop zone markers into a single point as the emboli approached the drop zone during retrieval. When the markers were visualized as a single point, the retrieval speed was slowed or halted and tension released on the delivery wire to provide an opportunity for the EVAC to enter the device from lateral to medial (Fig. 4b). The cycle of applying pull tension and release of tension was repeated until the markers separated into two points or the device was withdrawn proximal to the embolus. In successful attempts, the drop zone markers were visualized to separate into two points when the embolus was captured (Fig. 4c). At this point, the radiopaque EVAC emboli were visualized within the center of the device (Fig. 4c). In most instances, the EVAC emboli were visualized to translate along the inside of the device until being captured within the distal basket during final retrieval into the guide catheter (Fig. 3c). In "white" clot retrievals, the clot was not radiopaque and could not be visualized during thrombectomy. In most instances, the drop zone markers were seen to compress into a single

point and a similar technique as for the EVAC emboli was utilized; the retrieval was slowed or halted and tension released on the pull wire to provide the opportunity for the emboli to enter the inside of the device. Once the markers were identified as two distinct points, the retrieval was completed. In the majority of instances where the drop zone markers were visualized being compressed into a single point followed by immediate expansion into two points upon further retrieval, the embolus was visualized within the device and most often within the distal basket portion after removal from the guide catheter (Fig. 3a, c).

Thrombectomy-Associated Vasospasm, Angiographic Complications, and Histopathology

The majority of vessels showed some degree of angiographic vasospasm within the first 10 min from the device pass but this recovered fully or to less than 10% narrowing on serial angiography performed for 30–60 min after final retrieval. There were no angiographic complications such as perforation, extravasation or dissection observed on follow-up angiography. Gross pathology observed no swelling, bruising or perforation in the target vessels, and all downstream organs were grossly within normal limits (Fig. 6). The major feature found on histology was endothelial loss. Occasional fibrin deposition and focal disruption of the internal elastic lamina were identified. There was no evidence of significant medial injury and no evidence of extensive vessel injury (tear or perforation). A 20-point histological score modeled after the Trevo™ (Stryker) preclinical study was used to quantitate the vessel injury [11]. The injury scores were 4.5 for the internal pharyngeal and 4.75 for the external carotid (Fig. 6).

Semiquantitative Vasospasm Evaluation

Vasospasm was identified in all 4 vessels after 3 deployments, microcatheter resheathing and a simulated thrombectomy into a proximal guide catheter. At T = 0, immediately after simulated thrombectomy, the vasospasm score in 3 vessels was 2 (25–50%) and 1 in the fourth vessel (0–25%). The highest recorded vasospasm score at any time point was 3 (58% narrowing) in one of the internal pharyngeal arteries 10 min after retrieval. By 20 min, the degree of vasospasm was less than 50% in all vessels and by final angiographic evaluation (30–60 min), less than 8% vessel narrowing was noted in all 4 arteries (Fig. 7).

Discussion

Stent retriever mechanical thrombectomy has become widely accepted as the standard of care in the treatment of acute stroke [1–6]. A wide range of successful recanalization rates has been reported from prospective trials [1–6]. In spite of their widespread acceptance and success in improving acute stroke outcome, areas for improvement exist. The ASTER trial, a recently published prospective, multicenter randomized trial of 381 patients, is the most recent randomized trial providing insight into the success rate of current thrombectomy techniques and technology [6]. The study quantified and compared success after three thrombectomy attempts with either contact aspiration alone or stent retriever thrombectomy used with proximal balloon occlusion. In the stent retriever arm of the ASTER trial an mTICI 2b/3 result after 3 passes was obtained in only 67.7% of cases, meaning that a full one third of patients required more than 3 passes to achieve an mTICI 2b or better result. The overall mTICI 2c or 3 result was 56.6% after an unlimited number of retrievals and techniques. Similar results were seen in the contact aspiration arm of the trial. For stent retrievers, efficacy of clot removal has been postulated to be dependent on the degree of migration of clot into the stent struts and it has been postulated that most failures are related to the presence of a large organized clot [9, 19, 23, 24]. A mechanism of failure regarding organized

thrombus has been described as the stent retriever remaining compressed against the vessel wall and sliding between the stent and the wall without retrieving [9]. Multiple retrieval attempts lead to increased time to reperfusion, which would be expected to reduce the chance for meaningful clinical outcomes.

The NeVa™ thrombectomy device was designed to treat all subsets of emboli, including organized and ultra-hard varieties. The device combines a proximal flow restoration segment analogous to current stent retrievers with a middle section containing 2–3 very large offset openings and a final closed-ended segment for clot capture (Fig. 2, 3). The enlarged offset drop zones are areas of minimal metal coverage where clot can fall into the inside of the device. In addition to the offset enlarged openings, the device has enhanced expansive radial force, which is thought to play a role in initial clot integration after deployment [23, 24]. We report on preclinical testing of the NeVa™ thrombectomy device.

Animal Model Thrombectomy

Most previously published animal data on stent retriever thrombectomy devices have utilized autologous "red" whole blood clots ranging in length between 10 and 15 mm [7, 11–18]. All of these studies reported excellent success rates with all devices tested [7, 11–18]. The length of the "red" clot has been reported as a determining factor in success in previous animal studies [25]. The NeVa™ device platform was tested in 19 "red" clot occlusions ranging in length between 10 and 40 mm (Fig. 3b). A high rate of successful recanalization was observed with an mTICI 3 result in all but two instances where 40-mm-long emboli were used. These 40-mm-long clots fragmented and occluded multiple distal branches resulting in an mTICI 2b result (Table 1).

Recent reports have demonstrated a reduced efficacy of stent retrievers in simulated use when using platelet-enriched clots which mimic organized thrombi [9]. Five occlusions with large plasma-enriched "white" clots were performed (Fig. 3a). The NeVa™ device obtained an mTICI 2b/3 result in 5/5 with a single attempt. The "white" clots were formed without radiopaque material and were therefore more visually representative of what is encountered in a real-life procedure as compared to the barium containing clots and EVAC emboli. When removing the "white" resistant clots, deflection of the drop zone markers was identified during retrieval and provided feedback regarding the timing and distance of the pull (Fig. 4).

A novel "clot" model using ultra-hard EVAC emboli was developed in order to determine the limitations of the enlarged drop zones to incorporate resistant thrombi. Eleven occlusions were produced using emboli ranging from 4 to 12 mm. The 7-mm emboli required more than two retrievals in 2/4 occlusions and represent the upper limit of size for removal of these "worst case scenario" emboli. The tandem drop zone markers were clearly identified and observed to become compressed together immediately prior to the EVAC embolus entering through the drop zone and facilitated capture by providing feedback regarding the rate and distance of retrieval (Fig. 3c, 4).

Regardless of clot morphology, in most instances after retrieval, the clot was partially or wholly incorporated into the inside of the device and trapped at the distal closed end of the device (Fig. 3a, c). This finding supports that the drop zones and distal capture basket functioned as intended.

Safety Study

Histopathological evaluation after 6 device retrievals with thrombectomy was performed and demonstrated an injury score comparable to currently approved devices [11]. In the preclinical study for the TrevoI (Stryker) stent retriever, the injury scores ranged between 4.2 and 4.5 after 6 device retrievals without thrombectomy [11]. In both studies, the injury was largely confined to the endothelium with focal and minor damage to the internal elastic

lamina, findings seen with other stent retrievers and balloon angioplasty [11, 26, 27]. Based on these histological findings, the novel features of a hybrid cell design and increased expansive radial force did not lead to unexpected vessel injury (Fig. 6). A semiquantitative vasospasm study was performed and demonstrated findings comparable with predicate devices [7, 11–18]. Stent retrievers induce vasospasm in the pig model of thrombo-occlusive disease, which spontaneously resolves (Fig. 7).

Radial Force

The NeVa™ radial force curve demonstrated increased expansive radial force at all diameters across the indicated range compared to Solitaire™ and Trevo™ (Fig. 8). Interestingly, the difference was greatest at the largest diameter tested and smallest at the 2.0-mm lower limit. At a diameter of 3.5 mm, the expansive radial force of the NeVa™ T was equivalent to the expansive radial force of the 6-mm Solitaire™ and the 4-mm Trevo™ at 2 mm. At a diameter of 2 mm, the NeVa™ T was roughly 40% higher than Solitaire™ 6 × 30 and the Trevo™ 4 × 20. The NeVa™ M1 demonstrated a similar although slightly reduced expansive force at the recorded diameters which was higher than both predicate devices. The significantly higher relative expansive force at the 3.5-mm diameter and above would be expected to help maintain contact with the embolus as the device is withdrawn into larger proximal vessels during retrieval. Combined with large openings, particularly at the drop zones, the increased expansive radial force should facilitate clot integration. In contrast to the expansive force, the compressive force for the NeVa™ T and M1 was comparable to the 6-mm Solitaire™ and 4-mm Trevo™ devices at each diameter examined.

Conclusion

The NeVa™ thrombectomy device has a novel hybrid cell design, which combines features of a typical stent retriever with enhanced expansive radial force, distal offset enlarged openings, and a closed end. In addition, there are offset, mobile markers at the leading edge of the drop zones, which visually guided the capture of resistant emboli. These unique properties and positive preclinical results support the use of the NeVa™ device in a clinical trial to determine if the design features improve stent retriever outcomes in acute stroke.

Disclosure Statement

Vesalio™ provided funding for the study. Arthur Ulm and Arthur Grigorian are shareholders in Vesalio™. Raul G. Nogueira is a clinical trial consultant for Vesalio™.

References

1 Berkhemer OA, Fransen PS, Beumer D, van den Berg LA, Lingsma HF, et al; MR CLEAN Investigators: A randomized trial of intraarterial treatment for acute ischemic stroke. N Engl J Med 2015;372:11–20.
2 Jovin TG, Chamorro A, Cobo E, de Miquel MA, Molina CA, Rovira A, San Román L, Serena J, Abilleira S, Ribó M, Millán M, Urra X, Cardona P, López-Cancio E, Tomasello A, Castaño C, Blasco J, Aja L, Dorado L, Quesada H, Rubiera M, Hernandez-Pérez M, Goyal M, Demchuk AM, von Kummer R, Gallofré M, Dávalos A: Thrombectomy within 8 h after symptom onset in ischemic stroke. N Engl J Med 2015;372:2296–2306.
3 Saver JL, Goyal M, Bonafe A, Diener HC, Levy EI, Pereira VM, Albers GW, Cognard C, Cohen DJ, Hacke W, Jansen O, Jovin TG, Mattle HP, Nogueira RG, Siddiqui AH, Yavagal DR, Baxter BW, Devlin TG, Lopes DK, Reddy VK, du Mesnil de Rochemont R, Singer OC, Jahan R; SWIFT PRIME Investigators: Stent-retriever thrombectomy after intravenous t-PA vs. t-PA alone in stroke. N Engl J Med 2015;372:2285–2295.
4 Goyal M, Demchuk AM, Menon BK, Eesa M, Rempel JL, et al; ESCAPE Trial Investigators: Randomized assessment of rapid endovascular treatment of ischemic stroke. N Engl J Med 2015;372:1019–1030.

5 Campbell BC, Mitchell PJ, Kleinig TJ, Dewey HM, Churilov L, Yassi N, Yan B, Dowling RJ, Parsons MW, Oxley TJ, Wu TY, Brooks M, Simpson MA, Miteff F, Levi CR, Krause M, Harrington TJ, Faulder KC, Steinfort BS, Priglinger M, Ang T, Scroop R, Barber PA, McGuinness B, Wijeratne T, Phan TG, Chong W, Chandra RV, Bladin CF, Badve M, Rice H, de Villiers L, Ma H, Desmond PM, Donnan GA, Davis SM; EXTEND-IA Investigators: Endovascular therapy for ischemic stroke with perfusion-imaging selection. N Engl J Med 2015;372:1009–1018.

6 Lapergue B, Blanc R, Gory B, Labreuche J, Duhamel A, Marnat G, Saleme S, Costalat V, Bracard S, Desal H, Mazighi M, Consoli A, Piotin M; ASTER Trial Investigators: Effect of Endovascular Contact Aspiration vs Stent Retriever on Revascularization in Patients With Acute Ischemic Stroke and Large Vessel Occlusion: the ASTER Randomized Clinical Trial. JAMA 2017;318:443–452.

7 Gralla J, Schroth G, Remonda L, Fleischmann A, Fandino J, Slotboom J, Brekenfeld C: A dedicated animal model for mechanical thrombectomy in acute stroke. AJNR Am J Neuroradiol 2006;27:1357–1361.

8 Kan I, Yuki I, Murayama Y, Viñuela FA, Kim RH, Vinters HV, Viñuela F: A novel method of thrombus preparation for use in a swine model for evaluation of thrombectomy devices. Am J Neuroradiol 2010;31:1741.

9 Machi P, Jourdan F, Ambard D, Reynaud C, Lobotesis K, Sanchez M, Bonafe A, Costalat V: Experimental evaluation of stent retrievers' mechanical properties and effectiveness. J Neurointerv Surg 2017;9:257–263.

10 Ayad M, Eskioglu E, Mericle RA: Onyx: a unique neuroembolic agent. Expert Rev Med Devices 2006;3:705–715.

11 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;4:295–300.

12 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;31:1938.

13 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;50:43–52.

14 Roth C, Junk D, Papanagiotou P, Keuler A, Korner H, Schumacher M, Reith W: A comparison of 2 stroke devices: the new Aperio clot-removal device and the solitaire AB/FR. AJNR Am J Neuroradiol 2012;33:1317–1320.

15 Mordasini P, Frabetti N, Gralla J, Schroth G, Fischer U, Arnold M, Brekenfeld C: 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;32:294–300.

16 Mordasini P, Brekenfeld C, Byrne JV, Fischer U, Arnold M, Jung S, Schroth G, Gralla J: Experimental evaluation of immediate recanalization effect and recanalization efficacy of a new thrombus retriever for acute stroke treatment in vivo. AJNR Am J Neuroradiol 2013;34:153–158.

17 Brekenfeld C, Schroth G, El-Koussy M, Nedeltchev K, Reinert M, Slotboom J, Gralla J: Mechanical thromboembolectomy for acute ischemic stroke: comparison of the catch thrombectomy device and the Merci Retriever in vivo. Stroke 2008;39:1213–1219.

18 Mordasini P, Hiller M, Brekenfeld C, Schroth G, Fischer U, Slotboom J, Arnold M, Gralla J: In vivo evaluation of the Phenox CRC mechanical thrombectomy device in a swine model of acute vessel occlusion. AJNR Am J Neuroradiol 2010;31:972–978.

19 Yuki I, Kan I, Vinters HV, Kim RH, Golshan A, Vinuela FA, Sayre JW, Murayama Y, Vinuela F: The impact of thromboemboli histology on the performance of a mechanical thrombectomy device. AJNR Am J Neuroradiol 2012;33:643–648.

20 Ringer AJ, Guterman LR, Hopkins LN: Site-specific thromboembolism: a novel animal model for stroke. AJNR Am J Neuroradiol 2004;25:329–332.

21 Grandin CB, Cosnard G, Hammer F, Duprez TP, Stroobandt G, Mathurin P: Vasospasm after subarachnoid hemorrhage: diagnosis with MR angiography. AJNR Am J Neuroradiol 2000;21:1611–1617.

22 Higashida RT, Furlan AJ, Roberts H, Tomsick T, Connors B, Barr J, Dillon W, Warach S, Broderick J, Tilley B, Sacks D; Technology Assessment Committee of the American Society of Interventional and Therapeutic Neuroradiology; Technology Assessment Committee of the Society of Interventional Radiology: Trial design and reporting standards for intra-arterial cerebral thrombolysis for acute ischemic stroke. Stroke 2003;34:e109–e137.

23 Haussen D, Rebello L, Nogueira R: Optimizating clot retrieval in acute stroke: the push and fluff technique for closed-cell stentrievers. Stroke 2015;46:2838–2842.

24 Wenger K, Berkefeld J, Wagner M: Flat panel detector computed tomography for the interaction between contrast-enhanced thrombi and stent retrievers in stroke therapy: a pilot study. Clin Neuroradiol 2014;24:251–254.

25 Gralla J, Burkhardt M, Schroth G, El-Koussy M, Reinert M, Nedeltchev K, Slotboom J, Brekenfeld C: Occlusion Length Is a Crucial Determinant of Efficiency and Complication Rate in Thrombectomy for Acute Ischemic Stroke. AJNR Am J Neuroradiol 2008;29:247–252.

26 Brekenfeld C, Tinguely P, Schroth G, Arnold M, El-Koussy M, Nedeltchev K, Byrne JV, Gralla J: Percutaneous transluminal angioplasty and stent placement in acute vessel occlusion: evaluation of new methods for interventional stroke treatment. AJNR Am J Neuroradiol 2009;30:1165–1172.

27 Chan PD, Findlay JM, Vollrath B, Cook DA, Grace M, Chen MH, Ashforth RA: Pharmacological and morphological effects of in vitro transluminal balloon angioplasty on normal and vasospastic canine basilar arteries. J Neurosurg 1995;83:522–530.