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In vitro testing of a funnel-tip catheter with different clot types to decrease clot migration in mechanical thrombectomy

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Abstract

Background: Mechanical thrombectomy is the standard treatment for acute ischemic stroke in patients with large vessel occlusion and can be performed up to 24h after symptom onset. Despite high recanalization rates, embolism in new territories has been reported in 8.6% of the cases. Causes for this could be clot abruption during stent retrieval into the smaller opening of a standard distal access catheter, and antegrade blood flow via collaterals despite proximal balloon protection. A funnel-shaped tip with a larger internal diameter was developed to increase the rate of first-pass recanalization and to improve the safety and efficacy of mechanical thrombectomy.

Methods: This in vitro study compared the efficacy of a funnel-shaped tip with a standard tip in combination with different clot compositions. Mechanical thrombectomy was performed 80 times for each tip, using two stent retrievers (Trevo XP ProVue 3/20 mm, 4/20 mm) and four different clot types (hard vs. soft clots, 0–24h vs. 72h aged clots).

Results: Significantly higher first-pass recanalization rates (mTICI 3) were observed for the funnel-shaped tip, 70.0% versus 30.0% for the standard tip (absolute difference, 32; relative difference 57.1%; $P < .001$), regardless of the clot type and stent retriever. Recanalization could be increased using harder Chandler loop clots versus softer statically generated clots, as well as 0–24h versus 72h aged clots, respectively.

Conclusion: The funnel-shaped tip achieved higher first-pass recanalization rates than the smaller standard tip and lower rates of clot abruption at the tip. Clot compositions and aging times impacted recanalization rates.

Keywords

Ischemic stroke, embolectomy, catheters, blood coagulation

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Background

Mechanical thrombectomy (MT), in combination with best medical management and intravenous thrombolysis, has become the standard treatment for acute ischemic stroke (AIS) in patients with large vessel occlusions.[1,2] Recanalization rates of 83.2% (modified Thrombolysis in Cerebral Infarction (mTICI) reperfusion score $\geq$ 2b) and improved functional outcome of 52% (modified Rankin Scale (mRS) $\leq$ 2 after 90 days) have been achieved for aspiration devices.[1,3] Complete recanalization (mTICI 3), which is associated with the best long-term functional outcome,[4] can be restored in 38.7% of cases for stent retrievers versus 29.2% for aspiration devices.[1] Incomplete recanalization is caused by clot abruption at the tip of aspiration devices, as well as failed interaction of the stent retriever with the thrombus before reaching the tip. Due to the overall 10% incidence of embolism in new territories (ENT) for aspiration devices, endovascular treatment can be further improved.[3,5–7] Although proximal balloon protection can significantly reduce the rate of distal embolization,[8] the risk of antegrade blood flow via collaterals remains. One disadvantage of standard distal access catheters (DACs) is the smaller opening diameter in relation to the larger-sized thrombus and vessel diameters. During stent retrieval into the narrow standard tip the thrombus can

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become compressed and deformed, thus increasing the risk of fragmentation at the tip, also referred to as "decaptive shear".[9–11] Our goal is to improve the safety and efficacy of mechanical thrombectomy by reducing the rate of ENT. This study investigates whether a funnel-shaped tip with a larger diameter (ID 2.5 mm) can achieve higher first-pass recanalization rates and reduce the risk of clot abruption, compared to a standard tip with a smaller diameter (ID 1.5 mm). Our secondary research objective is to examine how different clot compositions and aging times may affect MT success.

Methods

Catheter tip setup

Two introducer sheaths were modified to create the funnel-shaped and standard tips (4 French (F) Radifocus® Introducer II Standard Kit; TERUMO International Systems, Leuven, Belgium). For this purpose, the tapered tip of each introducer was removed. To develop the funnel-shaped tip, one introducer tip was manually dilated to a diameter of 2.5 mm. For the standard tip, the other introducer was cut to a diameter of 1.5 mm, comparable with commercially available DACs. For standardization, both catheters provided the same internal luminal diameter, only the tip was modified.[2] (Figure 1).

MCA model

MT was performed in vitro using a Middle Cerebral Artery (MCA) vasculature model of the M1-segment (inner tube diameter 3.0 mm, length 16 cm). The MCA model was constructed from an IV line blood transfusion kit (CODAN, Medizinische Geräte GmbH & Co KG, Lensahn, Germany) and attached to the shortened 3 cm end of a 9 French introducer sheath for gaining access. Prior to each MT experiment, the model was flushed with 40% aqua-glycerol solution (Glycerin 85%; Caesar & Lorenz GmbH, Hilden, Germany) to simulate blood-like viscosity.[2] (Figures 2 and 3).

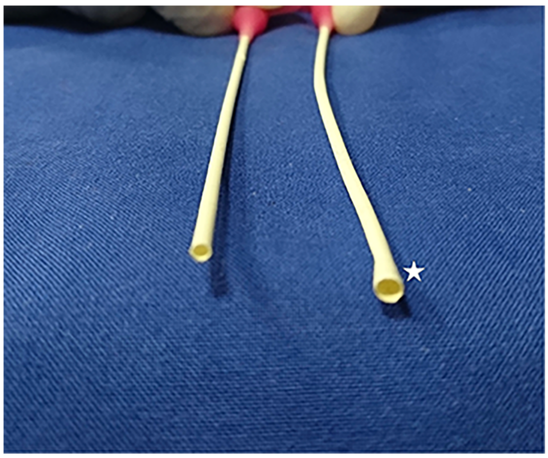

Figure 1. The funnel-shaped tip (asterisk) features a larger opening diameter (ID 2.5 mm), compared to the standard tip (ID 1.5 mm).

Generating blood clots

Blood from five pigs was used to generate clots for the MT experiments and histopathological analyzes. Research was conducted in accordance with all applicable international, national and/or institutional guidelines for the care and use of animals. A statement confirming the study was carried out in compliance with the ARRIVE guidelines. Specifically, the research project was examined by an ethical committee and approved (IRB approval number 23 177-07/G 14-1-094) by the responsible local government authority (Landesuntersuchungsamt Rheinland-Pfalz, Germany), in accordance with the German Animal Welfare Act (Tierschutzgesetz).[2]

Venous whole blood was extracted before sacrificing the pigs, in accordance with the above mentioned animal welfare regulations and procedures. Polyvinyl chloride (PVC) tubes (clear PVC tubing, inner diameter 8.0 mm, outer diameter 12.0 mm; Thermo Scientific Fischer, Waltham, Massachusetts, USA) were half filled with blood, and the ends of the tubes were connected using a silicone cuff.[2]

Two methods were employed for generating blood clots: (I) mechanical preparation using a Chandler loop device (Chandler loop System, Neuffen, Germany), and (II) clot preparation under static conditions. We used untreated non-anticoagulated whole blood to simulate in vivo thrombi as realistically as possible, without coagulation stimulating agents (e.g., sodium citrate solution). The Chandler loop simulated physiological blood circulation under dynamic conditions in a standardized setting. A temperature-controlled water basin was preheated to 38.5 °C. The PVC tubes containing porcine blood were placed in the loop cradle and rotated at 15 rpm.[2] The "moving column of blood"[12] coagulated after 20 to 30 min. Simultaneously, the clots processed under static conditions were prepared by hanging the PVC tubes vertically from a rod for 20 to 30 min at room temperature. After blood coagulation within the PVC tubes, the clots from both preparation methods were removed from the tubes and refrigerated in saline solution at 10 °C. MT was performed either 0 to 24h or 72h after clot preparation. Prior to each experiment, the clots were cut equally into 20 mm segments.[2]

MT procedure

Mechanical thrombetomy (MT) was conducted using the primary combined approach (PCA). One of the four clot types was placed into the MCA model under aspiration for each MT experiment. A stent retriever was released (Trevo XP Pro Vue 3/20 mm; Trevo XP Pro Vue 4/20 mm; Stryker, Kalamazoo, Michigan, USA) over the clot for 3 min. The clot was retracted into one of the catheter tips (funnel tip; standard tip) under aspiration, using a vacuum pressure syringe (60 ml, VacLok, Vacuum pressure syringes; Merit Medical System) set in advance to a

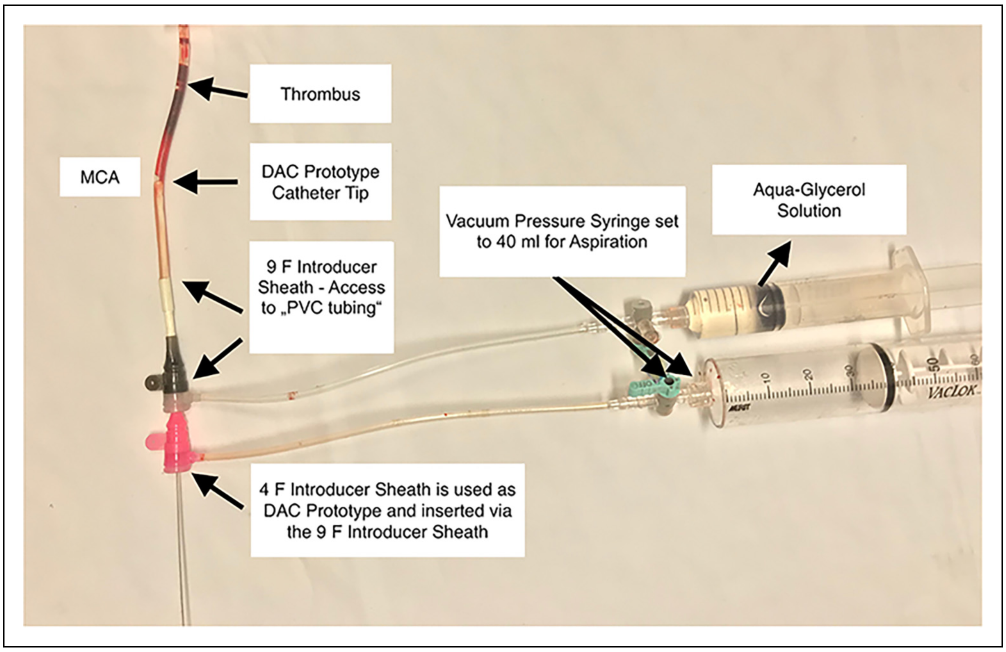

Figure 2. Experimental setup.

negative pressure at a volume of 40 ml. Experiments were performed under visual control using fluoroscopy and video monitoring.[2] Only first-pass recanalization and complete removal of the blood clot into the catheter tip (mTICI 3) was considered as MT success. Second or third-pass recanalization attempts were not included in the analysis. (Figures 2 and 3).

Histopathological analyzes

Histopathological analyzes of fresh (0h) and matured (72h) blood clots, prepared with and without the use of a Chandler loop system, were performed after fixation of clots in 4% buffered formalin (10% neutral buffered formaldehyde solution (PH 6.9); Merck KGaA, Darmstadt, Germany). The clots were cut at 3 mm intervals, arranged into liquid agar for proper orientation and placed into a standard tissue cassette after solidification. (PrintMate, embedding cassette, Thermo Fisher Scientific, Waltham, Massachusetts, USA). The cassettes were then processed overnight in an automated tissue processor and embedded in paraffin. The tissue blocks were sliced into 2 µm thick sections onto microscopic slides using a microtome, and stained with Masson trichrome. For enhanced visualization, the microscopic slides were scanned with Nanozoomer 2.0 HT (Hamamatsu), magnified 200-fold, and exported as TIFF files. To differentiate the exact fibrin distribution, pixel-by-pixel analysis was performed using Trainable Weka Segmentation Fiji plugin v3.2.27.[2,13] Each of the different clot types was graduated according to three different categories: fibrin pattern, distribution and outer circumference.

Statistical analyzes

For the MT experimental series, statistical analyzes were performed with GraphPad Prism 9.2 (GraphPad Software, Inc., San Diego, CA). The Pearson chi-square-test (X^2-test) was used to determine the statistical significance of categorial variables (MT success; failure) involving an independent pair sample (funnel-shaped tip; standard tip). For histopathological analyzes, SPSS Software (23.0 IBM; New York, USA) was utilized for statistical analyzes. Multinomial logistic regression was used to assess the effect of independent variables (thrombus preparation and aging time) and their prediction of nominal outcome parameters (fibrin pattern, distribution and outer circumference). The p value threshold was set to $\alpha < 0.05$ for all analyzes.

Results

MT was conducted 80 times for each tip (funnel-shaped tip; standard tip) using two stent retrievers (Trevo XP ProVue 3/20 mm; 4/20 mm) and four clot types (hard 0-24h; hard 72h; soft 0-24h; soft 72h), resulting in 10 procedures for each combination. The effects of two clot compositions (hard vs. soft) and two clot aging times (0-24h vs. 72h) on MT success were evaluated, resulting in 80 experiments for each clot composition and aging time. A total of 120 experiments were carried out. The results from the preliminary study [2] using 0h hard clots (N = 40) were included in the analyzes (total N = 160). MT was successful, if complete recanalization (mTICI 3) was achieved at first pass for all experiments.

MT results

The funnel-shaped tip achieved successful first-pass recanalization (mTICI 3) in 56/80 MTs (70.0%), compared to the standard tip with only 24/80 MTs (30.0%), (absolute difference, 32; relative difference 57.1%; $P < .001$), regardless of the clot type and stent retriever. (Table 1).

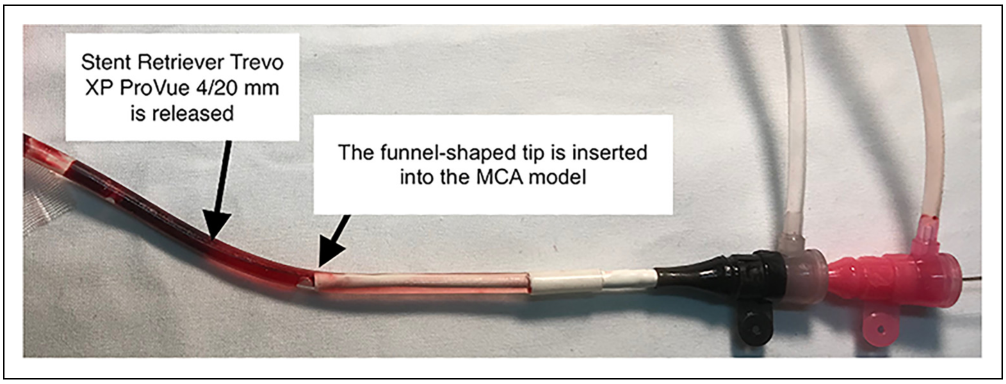

Figure 3. Close-up of the experimental setup.

Table 1. Mechanical thrombectomy results.

	Catheter tip		Clot aging time		Clot composition	
MT success rate	Funnel	Standard	0–24h	72h	hard	soft
N (success) / N (total = 80)	56/80 (70.0%)	24/80 (30.0%)	47/80 (58.8%)	33/80 (41.3%)	46/80 (57.5%)	34/80 (42.5%)
	P < .001		*P* = .027		P = .058	

Comparing two catheter models (funnel-shaped tip; standard tip); two clot aging times (0–24h vs. 72h) and two clot compositions (hard vs. soft) individually with the corresponding p values. MT success rate (in %). MT was considered successful, if complete recanalization (mTICI 3) was achieved at first pass for all experiments.

Failure causes for the funnel-shaped tip

During stent retriever retraction, thrombus loss was responsible for 11/24 MT failures (45.8%), prior to reaching the wall of the funnel-shaped tip. Clot abruption at the wall of the tip caused 13/24 failures (54.2%). (Figure 4).

Failure causes for the standard tip

Clot abruption along the standard tip wall led to 45/56 MT failures (80.4%). The remaining 11/56 failures (19.6%) occurred after the stent retriever failed to interact with the thrombus during retraction, before reaching the tip. (Figure 4).

MT results for the preparation methods

MT performed with hard clots (Chandler loop preparation) was successful in 31/40 (77.5%) cases for the funnel-shaped tip and 15/40 cases (37.5%) for the standard tip (absolute difference, 16; relative difference, 51.6%; P < 0.05). (Table 2) Soft clots prepared under static conditions registered 25/40 (62.5%) successful MTs for the funnel-shaped tip, and 9/40 (22.5%) for the standard tip (absolute difference, 16; relative difference, 64.0%; P < 0.05). Regardless of the catheter tip, MT was successful in 46/80 cases (57.5%) for the harder clots and 34/80 cases (42.5%) for the softer clots (absolute difference 13; relative difference 28.3%; p = 0.06). (Table 2 and Table 3; Figure 5).

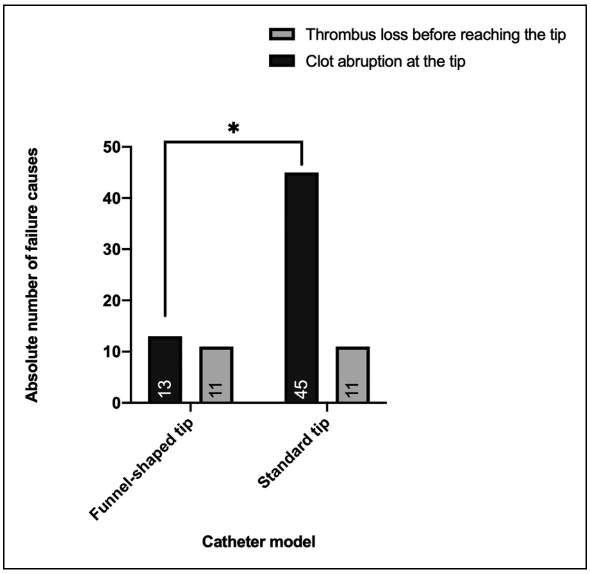

Figure 4. Causes for MT failure for both catheter models (funnel-shaped tip vs. standard tip). The asterisk symbols represent the level of significance. (* P < 0.05; ** P < 0.01).

MT results for the clot aging times

The funnel-shaped tip achieved 31/40 (77.5%) MT successes using 0 to 24h aged clots, in contrast to 25/40 (62.5%) for the 72h aged clots (absolute difference, 6; relative difference, 19.4%; P = .14). The standard tip attained 16/40 (40.0%) MT successes for the 0 to 24h aged clots, versus 8/40 (20.0%) for the 72h aged clots (absolute difference, 8; relative difference, 50.0%;

Table 2. Mechanical thrombectomy results for both catheter tips (funnel vs. standard) using hard clots at different aging times.

Hard clots N (success) / N (total)	Funnel	Standard	Funnel + Standard	
0–24h	18/20 (90.0%)	11/20 (55.0%)	29/40 (72.5%)	P = .132
72h	13/20 (65.0%)	4/20 (20.0%)	17/40 (42.5%)	*P* < .001
	P = .058	P = .022	P = .007	
Hard clots total *N (success) / N (total) = 46/80 (57.5%)*				

MT success rate (in %), defined as mTICI 3. The p values at the end of each row refer to the funnel-shaped vs. standard tips. The p values at the bottom of each column refer to the 0–24 vs. 72h hard clots. Example Row: The funnel-shaped tip achieved a first-pass recanalization rate of 18/20 (90%), compared to 11/20 (55.0%) for the standard tip, when using the 0–24h aged clots (P = .132). Column: MT was successful 18/20 times (90%) for the 0–24h clots, compared to 13/20 (65%) times for the 72h aged hard clots when using the funnel-shaped tip (P = .058).

Table 3. Mechanical thrombectomy results for both catheter tips (funnel vs. standard) using soft clots at different aging times.

Soft clots N (success) / N (total)	Funnel	Standard	Funnel + Standard	
0–24h	13/20 (65.0%)	5/20 (25.0%)	18/40 (45.0%)	P = .032
72h	12/20 (60.0%)	4/20 (20.0%)	16/40 (40.0%)	*P* < .001
	P = .744	P = .705	P = .651	
Soft clots total *N (success) / N (total) = 34/80 (42.5%)*				

MT success rate (in %), defined as mTICI 3. The p values at the end of each row refer to the funnel-shaped vs. standard tips. The p values at the bottom of each column refer to the 0–24 vs. 72h soft clots.

P = .05). Regardless of the clot preparation group and tip, 0 to 24h aged clots achieved a greater MT success rate, totaling 47/80 (58.8%) compared to 33/80 (41.3%) for the 72h aged clots (absolute difference, 14; relative difference, 29.8%; P < .05). (Table 4; Figure 5).

MT results for the stent retrievers

There was no significant difference in terms of improved first-pass recanalization for both stent retrievers. (Table 5).

Histopathological analyzes

A total of 280 clot sections were included in the histopathological analyzes. Harder clots displayed a higher proportion and regular distribution of fibrin than softer clots, (distribution: 56/107 vs. 20/173, respectively; odds ratio (OR), 8.4; 95% CI, 4.606 to 15.320; P < .001), and a reticular or insular fibrin pattern (pattern: 83/107 vs. 32/173, respectively; odds ratio, 15.24; 95% CI, 8.4 to 27.6; P < .001). Comparing both aging times, an outer fibrin circumference was observed more frequently in the 72h aged clots than the 0h clots (circumference: 74/155 vs. 21/125, respectively; odds ratio, 4.524; 95% CI, 2.572 to 7.960; P < .001). (Table 6; Figure 6).

Discussion

Mechanical thrombectomy has advanced the treatment of acute ischemic stroke.[1] However, ENT and clot abruption at the tip of standard DACs can still occur in up to 10% of cases.[5,14] To improve procedural outcome and reduce the rate of distal embolization, we compared a funnel-shaped tip featuring a larger opening diameter (ID = 2.5 mm) to a standard-sized tip (ID = 1.5 mm) in combination with different clot types. The opening diameter of the funnel-shaped tip corresponds to the anatomical diameter of the M1-MCA segment, measuring 2.7 ± 0.23 mm (mean ± 1 SD).[2,15] The smaller opening diameter of the standard tip relates to the inner diameter of customary DACs. One example of a DAC is the SOFIA (MicroVention, Tustin, CA, USA), which is available in different sizes: e.g., 5F (ID 1.39 mm, 0.055 inch).[2,16] For standardization, both catheters in our experiments provided the same internal luminal diameter, only the opening tip diameter was considered the object of comparison.

A significantly higher first-pass recanalization rate of 70.0% was observed for the funnel-shaped tip versus 30.0% for the standard tip, regardless of the clot type and stent retriever (P < .001). In addition, the rate of clot abruption at the funnel-shaped tip was reduced (P < .05). We hypothesize that the funnel-shaped tip provides the following key advantages to facilitate mechanical thrombectomy compared to the standard tip: (Figure 7).

1. Local antegrade blood flow is arrested by "sealing" the vessel lumen with the larger funnel-shaped tip, thereby decreasing the risk of clot overlap and abruption at the tip. The larger opening of the funnel-shaped tip allows better stent retriever retraction and interlock during aspiration.[9]

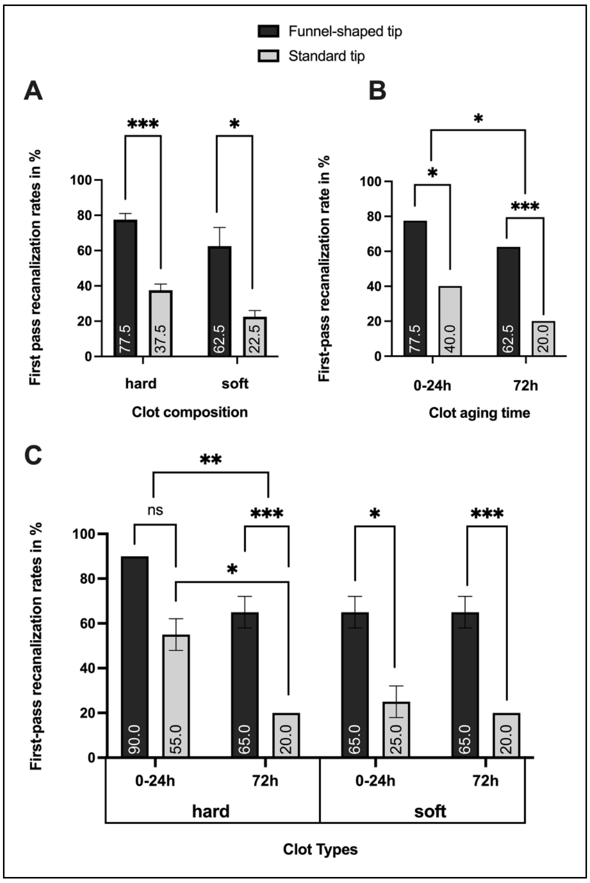

Figure 5. First-pass recanalization rates (mTICI 3) A: First-pass recanalization rates for both clot compositions (hard vs. soft). B: First-pass recanalization for both clot aging times (0–24h vs. 72h) C: First-pass recanalization for four different clot types (hard 0–24h; hard 72h; soft 0–24h; soft 72h). The asterisk symbols represent the levels of significance (ns = non-significant; * P < .05; ** P < .01; *** P < .001). ** First-pass recanalization showed a statistically significant difference for the 0–24h vs. 72h hard clots, 29/40 (72.5%) vs. 17/40 (42.5%), regardless of the tip.

Table 4. Mechanical thrombectomy results for two clot aging times.

Clot aging time N (success) / N (total = 40)	Funnel	Standard	
0–24h	31/40 (77.5%)	16/40 (40.0%)	P = .016
72h	25/40 (62.5%)	8/40 (20.0%)	*P* < .001
	P = .143	P = .051	

MT success rate (in %), defined as mTICI 3. The p values at the end of each row refer to the funnel-shaped vs. standard tips. The p values at the bottom of each column refer to the different clot aging times.

2. Since a catheter has a cylindrical shape, the cross-sectional area of the catheter must be circular. Therefore, the cross-sectional area of a catheter is proportional to the square of the radius → $a = \pi r^2 = \frac{\pi d^2}{4} (a = area,\ r = radius,\ d = diameter)$ → $a \propto r^2$. By increasing the opening diameter of the funnel-shaped tip (ID = 2.5 mm) compared to the standard tip (ID = 1.5 mm), the cross-sectional area of the tip is increased by a factor of 2.78-fold. Assuming that the pressure remains constant, higher aspiration forces ($x \sim 2.78$) can be applied along the cross-sectional area of the thrombus ($F \uparrow = a \uparrow \cdot p = \pi r^2 \uparrow \cdot p$). Thus, the relationship between aspiration force and radius is exponential.[17,18]
3. The self-expanding stent retriever and the thrombus are disproportionally larger in relation to the smaller opening of standard-sized tips. During stent retrieval into the narrow standard tip, the stent retriever and thrombus are compressed and deformed, which ultimately increases the risk of stripping and fragmentation. The funnel-shaped tip mitigates the risk of thrombus deformation at the tip by lowering the resistance and shear forces during stent retrieval.[9]

Table 5. Mechanical thrombectomy results for two stent retrievers.

Stent retrievers N (success) / N (total = 40)	Funnel	Standard	
Trevo XP ProVue Retriever 3 × 20 mm (Stryker)	30/40 (75.0%)	12/40 (30.0%)	*P* < .001
Trevo XP ProVue Retriever 4 × 20 mm (Stryker)	26/40 (65.0%)	12/40 (30.0%)	*P* = .002
	P = .329	P = 1.000	P = .527

MT success rate (in %), defined as mTICI 3. The p values at the end of each row refer to the funnel-shaped vs. standard tips. The p values at the bottom of each column refer to the two stent retrievers. The Trevo XP ProVue Retriever 3 × 20 mm achieved an overall recanalization rate of 42/80 (52.5%) at first pass compared to 38/80 (47.5%) for the Trevo XP ProVue Retriever 4 × 20 mm, regardless of the tip (absolute difference, 4; relative difference, 9.5%; P = .527).

Endovascular device technology is rapidly advancing. New endovascular devices, procedures and techniques are being developed to increase the safety and efficacy of mechanical thrombectomy.[19–23] Enhancements to DACs are focused on improving navigability and trackability, greater tip flexibility and proximal stability.[20,22] Aspiration devices are trending towards larger internal luminal diameters. Examples of large-bore DACs include the AXS Vecta (ID 0.071 inch) and the SOFIA 6F plus (ID 0.070 inch).[19,24,25] If advancing an 8F catheter tip such as our funnel-tip into distal vessels is feasible, then arguably an interventionalist could also consider using a large-bore DAC instead. To the best of our knowledge, there are no studies that compare catheters with funneled tips to large-bore catheters without funneled tips (same distal ID). Further experiments are required to address this question. The important advantages of funneled DACs, compared to large-bore DACs in the clinical setting, are A) an overall larger luminal opening diameter for funneled tips and B) facilitated navigation into distal vessels. Only the tip provides a larger ID. Consequently, funneled DACs would be able to reach distal occlusion sites more effectively. Since large-bore DACs continue

Table 6. Histopathological analyzes.

Clot types	Hard (Chandler loop)			Soft (static)			Aging times	
	0h	*72h*	*0h + 72h*	*0h*	*72h*	*0h + 72h*	*0h*	*72h*
	57	50	107	68	105	173	*125*	*155*
Fibrin pattern absolute number of thrombus segments and amount (in %)								
Insular (a)	29 (50.9)	24 (48.0)	53 (49.5)	4 (5.9)	23 (21.9)	27 (15.6)	33 (26.4)	47 (30.3)
Reticular (b)	14 (24.6)	16 (32.0)	30 (28.0)	2 (2.9)	3 (2.9)	5 (2.9)	16 (12.8)	19 (12.3)
Pattern (a + b)	43 (75.4)	40 (80.0)	83 (77.6)	6 (8.8)	26 (24.8)	32 (18.5)	49 (39.2)	66 (42.6)
No Pattern (c)	14 (24.6)	10 (20.0)	24 (22.4)	62 (91.2)	79 (75.2)	141 (81.5)	76 (60.8)	89 (57.4)
Fibrin distribution absolute number of thrombus segments and amount (in %)								
Peripheral (d)	7 (12.3)	15 (30.0)	22 (20.6)	2 (2.9)	5 (4.8)	7 (4.0)	9 (7.2)	20 (12.9)
Central (e)	5 (8.8)	3 (6.0)	8 (7.5)	1 (1.5)	11 (10.5)	12 (6.9)	6 (4.8)	14 (9.0)
Central + Peripheral (f)	14 (24.6)	12 (24.0)	26 (24.3)	0 (0.0)	1 (1.0)	1 (0.6)	14 (11.2)	13 (8.4)
Regular (d + e + f)	26 (45.6)	30 (60.0)	56 (52.3)	3 (4.4)	17 (16.2)	20 (11.6)	29 (23.2)	47 (30.3)
Irregular (g)	31 (54.4)	20 (40.0)	51 (47.7)	65 (95.6)	88 (83.8)	153 (88.4)	96 (76.8)	108 (69.7)
Outer circumference absolute number of thrombus segments and amount (in %)								
Complete (h)	9 (15.8)	10 (20.0)	19 (17.8)	1 (1.5)	49 (46.6)	50 (28.9)	10 (8.0)	59 (38.1)
Focal (i)	10 (17.5)	7 (14.0)	17 (15.9)	1 (1.5)	8 (7.6)	9 (5.2)	11 (8.8)	15 (9.7)
Rim (h + i)	19 (33.3)	17 (34.0)	36 (33.6)	2 (2.9)	57 (54.3)	59 (34.1)	21 (16.8)	74 (47.7)
No rim (j)	38 (66.6)	33 (66.0)	71 (66.4)	66 (97.1)	48 (45.7)	114 (65.9)	104 (83.2)	81 (52.3)

Absolute number (and relative number) of thrombus segments in reference to fibrin pattern, distribution and outer circumference. The category "fibrin pattern" was further specified as insular, reticular or no pattern. The distribution of fibrin was classified as peripheral, central, both peripheral and central (regular), or irregular distribution, depending on the localization. The outer rim of fibrin (defined as circumferential layer of fibrin surrounding the thrombus) was divided into the subcategories total circumference of fibrin, focal or no rim.

over a greater length, they would be more difficult to maneuver into tortuous vessels.[26] This limitation justifies further development of funneled tips. While large-bore DACs may also reduce antegrade blood flow and transmit higher aspiration forces compared to standard DACs, they would provide local flow arrest similar to "inflexible" or "fixed" funneled tips used in this study.[23,27] Limitations of inflexible funneled tips can be reduced by using funnels with self-expanding Nitinol meshes, such as our newly developed prototype that has properties similar to a stent retriever and is able to fully expand to the vessel diameter at the target site. Ideally, the cross-sectional contact area between the funnel-shaped tip and thrombus would be maximal. Thus, the retraction force, acting on the thrombus during stent retrieval into the tip, would be equally distributed to a larger area. This decreases the "strain σ " on the thrombus ($\sigma \downarrow = \frac{F}{a\uparrow}$), reducing the risk of clot fragmentation at the tip.[9,28] Consequently, the risk of ENT would be estimated to be lower for funneled tips, compared to large-bore DACs. This is highlighted by the fact that large-bore DACs still reach ENT rates of up to 5% (e.g., 5.4%, 4.7% for the Sofia 6F, Sofia Plus, respectively),[29,30] compared to 2.9% for funneled tips.[31] Overall, these results underline the growing importance of funnel-shaped tips.

Scientific literature indicates that other funnel-shaped catheters, such as the Advanced Thrombectomy System (ANCD; R&D, Anaconda Biomed, Barcelona, Sant Cugat del Vallès, Spain),[10] which bares technical resemblance to our funnel-shaped tip, has also shown promising results. In a recently published clinical cohort (N = 32), the ANCD achieved an overall recanalization rate of 91.4% (mTICI $\geq$ 2b) and a complete recanalization rate of 65.7% (mTICI $\geq$ 2c), as well as high functional outcome of 60% (mRS $\leq$ 2).[31] Since funneled catheters have only recently been developed, more research on this topic is required.

Evaluating the causes of MT failure is one advantage of an in vitro setting. Clot abruption at the tip was the leading cause of failure for the standard tip (80.4%), regardless of the clot type. This would imply that MT failure for the standard tip was primarily affected by the smaller diameter of the tip, not the clot type. In contrast, in nearly half of the failures (45.8%) for the funnel-shaped tip the stent retriever failed to interact with the clot. This occurred mainly when using harder clots. The other failures (54.2%) were caused by stripping of clot material at the funnel-shaped tip, especially when using softer clots, which were found to be more susceptible to fragmentation.[9,10,32] These results indicate that MT success relies on the viscosity and composition of different clot types, which may influence the thrombus-vessel and thrombus-device interactions.[9] Successful MT is associated with reduced friction and adhesion during retraction. Certain clot types may be more prone to fragmentation and may increase the risk of ENT.[9,32,33] Fibrin determines the structural integrity of blood clots forming a three-dimensional scaffold. Mechanical forces as well as thrombolysis may cause fibrin fibers to break. Thus, clot composition and geometry play a pivotal role in the pathogenesis of ENT.[34] Evaluating the effect of clot compositions in our study, harder clots (Chandler loop preparation), showed a tendency towards improved recanalization compared to softer clots (prepared under static conditions). Histopathologically, harder clots enclosed a reticular or insular fibrin pattern and a higher regularity of

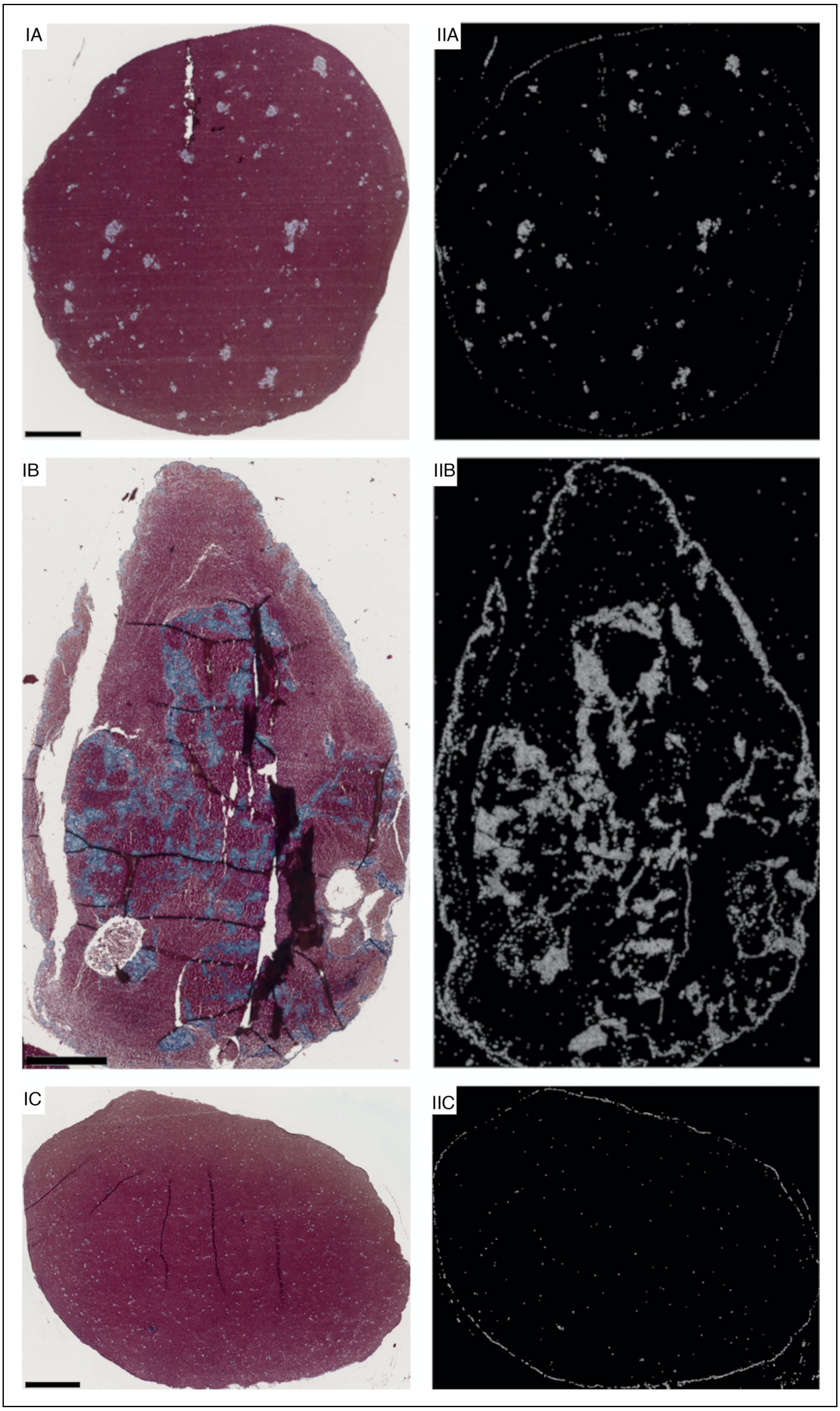

Figure 6. Thrombus graduation before (i) and after (ii) segmentation calculation, grayscale image (IA, IB, IC. Masson-Goldner staining). All scale bars are set to 0.5 mm. a. An example of a Chandler loop 0h thrombus with an insular pattern (i, ii), a peripheral and central distribution of fibrin is demonstrated. b. An example of a Chandler loop 72h thrombus with a reticulated pattern (i, ii), a peripheral and central distribution of fibrin, and a total circumference of fibrin is demonstrated. c. An example of a 0h thrombus prepared under static conditions with the absence of a fibrin pattern (i, ii) and a total fibrin circumference is demonstrated. This thrombus type was predominant for the thrombi prepared under static conditions.

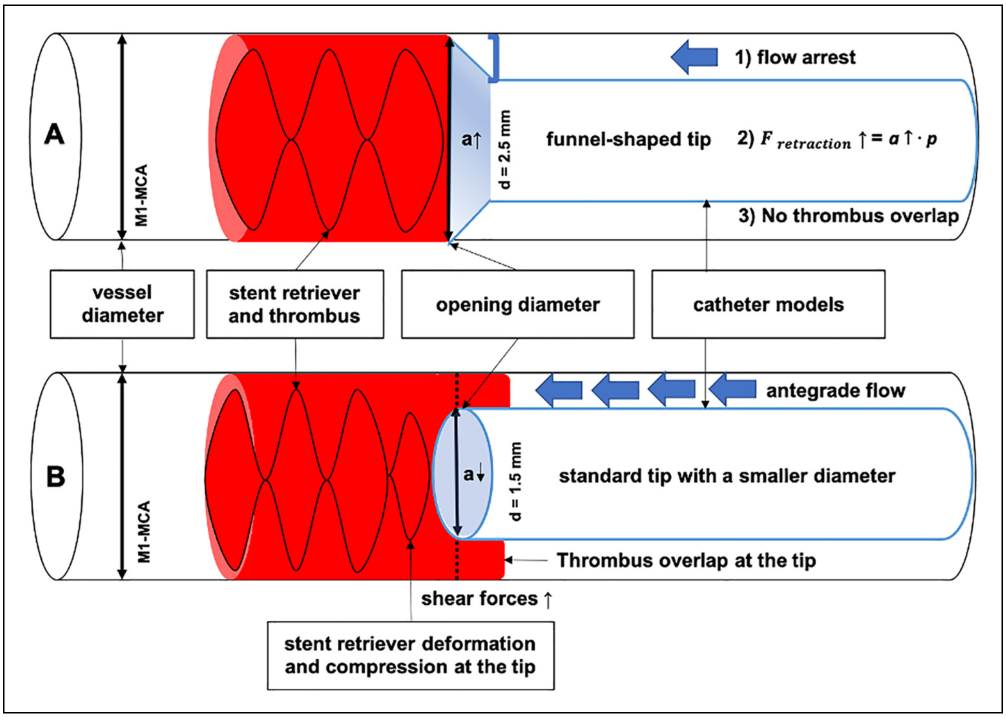

Figure 7. Physical properties of the funnel-shaped tip (A) compared to the standard tip (B) during stent retriever retraction into the tip. p = pressure, F = force, a = area, d = diameter. The dimensions of the diagram are schematic and not to scale. By increasing the opening diameter of the funnel-shaped tip (d = 2.5 mm) compared to the standard tip (d = 1.5 mm), the cross-sectional area of the tip is increased by factor 2.78-fold.

fibrin with intermingled clusters of erythrocytes.[35] Since a Chandler loop simulates blood flow under dynamic conditions, we would expect blood cells and fibrin to be distributed more regularly in harder clots.[35]

Numerous studies indicated that softer erythrocyte-rich blood clots were related to higher recanalization rates, but showed a greater tendency of fragmentation than harder fibrin-rich clots.[9,32,36] Accordingly, softer clots from this study were found to be more susceptible to fragmentation, resulting in higher rates of clot abruption at the tip. Histopathological findings of this study demonstrated significantly lower levels of fibrin, an absence of fibrin pattern, and an irregular fibrin distribution for softer clots ($P < .05$), which may explain a lack of structural integrity.[9,10,32] Although this research project registered higher recanalization rates for the harder “fibrin-rich” clots compared to the softer “fibrin-low” clots ($P = .06$), the results remained at the verge of statistical significance. One explanation could be that harder clots contained enough erythrocytes to exceed the erythrocyte threshold of 20%. This is associated with a reduced force of friction and improved recanalization.[9,10,32,36] Although the quantification of the erythrocyte concentration was beyond the scope of our study, other studies have shown that Chandler loop generated clots reach the erythrocyte threshold of 20%.[35] For future in vitro MT procedure and clot analyzes, we recommend using fixed concentrations of erythrocytes.[9,10,32,36] According to Madjidyar *et al.*, 2020,[37] MT success not only depends on the “right” clot type, but also on the “correct” technique.[37] Mechanical thrombectomy of erythrocyte-rich clots was found to be more successful using the ADAPT technique, while MT of fibrin-rich clots could be improved by stent retriever thrombectomy in conjunction with balloon guide catheters.[37] Since our research project relied on the primary combined approach involving both aspiration and stent retriever thrombectomy, different MT techniques should also be investigated in future studies.[11,37]

Evaluating the effects of clot aging time on MT success, our study demonstrated that the 0 to 24h clots achieved significantly higher recanalization rates than 72h aged clots. ($P < .05$). Histopathologically, the difference between aging times could be explained by an outer fibrin circumference, particularly observed in softer 72h aged clots, which showed the lowest recanalization rates. Aged thrombus material may restructure and degrade, becoming more condensed due to fluid loss. This could increase friction and impede stent retrieval.[32,38] The difference in recanalization rates between the clot aging times was greater for the harder fibrin-rich clots than the softer erythrocyte-rich clots in this study. Since fibrin may dissolve over time, harder fibrin-rich clots could be more susceptible to the aging time.[38]

Limitations

Using homogenous clots under standardized laboratory conditions can be considered a limitation of this study since clinical clots have irregular heterogeneous compositions.[38] According to the Stroke Thromboembolism Registry of Imaging and Pathology (STRIP),[39] it is still difficult to distinguish stroke etiology by determining the clot composition.

However, clots from patients with hypercoagulable conditions showed an overall tendency towards a higher fibrin density; compared to atherosclerotic clots which contained a higher erythrocyte density.[39] Another limitation of this study is the simplified in vitro setup, which was deemed necessary to investigate the proof-of-concept of the modified funnel-shaped tip under standardized conditions. The M1-MCA model was built from a single PVC tube. Therefore, collateral flow conditions and the tortuosity of the MCA-vasculature were not considered. Another limitation is that the diameters of the stent retriever and MCA model (ID 3 mm) both exceeded the diameter of the funnel-shaped tip (ID 2.5 mm). Since the funneled tip did not fully expand to the "vessel" diameter, the risk of clot fragmentation and antegrade blood flow remains. This may have led to an underestimation of the results. Despite this limitation, the funneled tip showed significantly lower rates of clot abruption than the standard tip. In our experiments, we utilized an "inflexible" funneled tip with a length of 2 mm. Longer funneled segments may have the advantage of providing a larger surface area, which may "guide" the thrombus into the opening, forming a protective sheath.[27] Our "actual" funnel-shaped prototype, which was recently patented and was not available at the time of our experiments, features a self-expanding flexible Nitinol tip with a length of 2 to 3 cm, which is able to adapt to the vessel diameter. A guiding catheter prevents the funnel-shaped prototype from expanding before reaching the target vessel. Thus, the prototype combines properties of large-bore DACs with properties of self-expanding stent retrievers. Therefore, this last-mentioned limitation will be mitigated. Further in vitro and in vivo testing of our prototype is currently running and has already indicated promising results.

Conclusion

Overall, this study highlights the importance of funnel-shaped tips for MT. The larger internal diameter of the opening tip enables higher aspiration forces and reduces antegrade blood flow by inducing local flow arrest The larger opening area can also improve clot-device interaction. In this study, funnel-shaped tips achieve higher recanalization rates than standard DACs and reduce the rate of clot abruption at the tip. Furthermore, different clot compositions and aging times influence the success of mechanical thrombectomy.

Author contributions

All authors reviewed the manuscript and have approved the submitted version. Design and conception of the study: E.S.P.; Y.T.; S.K.; MAB.; Data acquisition: E.S.P.; Y.T.; S.K.; S.K-R.; T.G.; L.S.; A.H.; N.K.; J.M.-B.; Analysis and interpretation of data: E.S.P.; T.G.; L.S.; MAB.; Wrote the manuscript: E.S.P.; Prepared Figures 1–2: E.S.P.; Prepared Figure 3: T.G.; L.S.; Prepared Tables 1–5: E.S.P.; Prepared Supplements: E.S.P.; Revised and Edited the manuscript: E.S.P.; Y.T.; MAB.; J.M.-B; S.K.; T.G.

Declaration of conflicting interests

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Data availability

Supplementary information is available for this paper at https://doi.org/10.1038/s41598-019-57315-9. For further information please contact epayne@gmx.de

Ethical approval statement

The work was examined by an ethical committee and approved (IRB approval number 23 177-07/G 14-1-094) by the responsible local government authority (Landesuntersuchungsamt Rheinland-Pfalz, Germany), in accordance with the German Animal Welfare Act (Tierschutzgesetz).

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References

1. Fiehler J. New ESO/ESMINT thrombectomy guidelines: after guideline writing is before guideline writing. *Clin Neuroradiol* 2019; 29: 189–190.
2. Tanyildizi Y, Payne E, Gerber T, et al. In vitro testing of a funnel-shaped tip catheter model to decrease clot migration during mechanical thrombectomy. *Sci Rep* 2020; 10: 633.
3. Turk AS3rd, Siddiqui A, Fifi JT, et al. Aspiration thrombectomy versus stent retriever thrombectomy as first-line approach for large vessel occlusion (COMPASS): a multicentre, randomised, open label, blinded outcome, non-inferiority trial. *Lancet* 2019; 393: 998–1008.
4. Dargazanli C, Consoli A, Barral M, et al. Impact of modified TICI 3 versus modified TICI 2b reperfusion score to predict good outcome following endovascular therapy. *AJNR Am J Neuroradiol* 2017; 38: 90–96.
5. Turk AS, Frei D, Fiorella D, et al. ADAPT FAST study: a direct aspiration first pass technique for acute stroke thrombectomy. *J Neurointerv Surg* 2014; 6: 260–264.
6. Pierot L, Gawlitza M and Soize S. Techniques for endovascular treatment of acute ischemic stroke. *Rev Neurol (Paris)* 2017; 173: 594–599.
7. Goyal M, Menon BK, van Zwam WH, et al. Endovascular thrombectomy after large-vessel ischaemic stroke: a meta-analysis of individual patient data from five randomised trials. *Lancet* 2016; 387: 1723–1731.

8. Brinjikji W, Starke RM, Murad MH, et al. Impact of balloon guide catheter on technical and clinical outcomes: a systematic review and meta-analysis. *J Neurointerv Surg* 2018; 10: 335–339.
9. Yoo AJ and Andersson T. Thrombectomy in acute ischemic stroke: challenges to procedural success. *J Stroke* 2017; 19: 121–130.
10. Sanchez S, Cortiñas I, Villanova H, et al. ANCD Thrombectomy device: in vitro evaluation. *J Neurointerv Surg* 2020; 12: 77–81.
11. McTaggart RA, Holodinsky JK, Ospel JM, et al. Leaving no large vessel occlusion stroke behind: reorganizing stroke systems of care to improve timely access to endovascular therapy. *Stroke* 2020; 51: 1951–1960.
12. Vogel HG, Vogel WH, Schölkens BA, et al. Activity on blood constituents1. In: Vogel HG, Vogel WH, Schölkens BA, et al. (eds) *Drug discovery and evaluation: pharmacological assays second completely revised, updated, and enlarged edition*. Berlin, Heidelberg: Springer Berlin Heidelberg, 2002, pp.277–309.
13. Arganda-Carreras I, Kaynig V, Rueden C, et al. Trainable weka segmentation: a machine learning tool for microscopy pixel classification. *Bioinformatics* 2017; 33: 2424–2426.
14. Balami JS, White PM, McMeekin PJ, et al. Complications of endovascular treatment for acute ischemic stroke: prevention and management. *Int J Stroke* 2018; 13: 348–361.
15. Schreiber SJ, Gottschalk S, Weih M, et al. Assessment of blood flow velocity and diameter of the middle cerebral artery during the Acetazolamide provocation test by use of transcranial Doppler sonography and MR imaging. *AJNR Am J Neuroradiol* 2000; 21: 1207–1211.
16. Kang DH and Park J. Endovascular stroke therapy focused on stent retriever thrombectomy and direct clot aspiration : historical review and modern application. *J Korean Neurosurg Soc* 2017; 60: 335–347.
17. Shi Y, Cheshire D, Lally F, et al. Suction force-suction distance relation during aspiration thrombectomy for ischemic stroke: A computational fluid dynamics study. *Physics in Medicine* 2017; 3: 1–8.
18. Froehler MT. Comparison of vacuum pressures and forces generated by different catheters and pumps for aspiration thrombectomy in acute ischemic stroke. *Interv Neurol* 2017; 6: 199–206.
19. Chartrain AG, Awad AJ, Mascitelli JR, et al. Novel and emerging technologies for endovascular thrombectomy. *Neurosurg Focus* 2017; 42: E12.
20. Spiotta AM, Chaudry MI, Hui FK, et al. Evolution of thrombectomy approaches and devices for acute stroke: a technical review. *J Neurointerv Surg* 2015; 7: 2–7.
21. Bhaskar S, Stanwell P, Cordato D, et al. Reperfusion therapy in acute ischemic stroke: dawn of a new era? *BMC Neurol* 2018; 18: 8.
22. Reymond P, Brina O, Girdhar G, et al. Experimental evaluation of the performance of large bore aspiration catheters. *J Neuroradiol* 2022. DOI: 10.1016/j.neurad.2022.02.007.
23. Espinosa de Rueda M, Ballenilla Marco F, Garmendia Lopetegui E, et al. Thrombectomy aspiration post-market study in acute stroke with the Q aspiration catheter: the TAPAS study. *J Neurointerv Surg* 2022. DOI: 10.1136/neurintsurg-2022-018649.
24. Wessell AP, Cannarsa G, Carvalho H, et al. Thrombectomy for acute ischemic stroke with the new Sofia 6-French PLUS distal access reperfusion catheter: a single-center experience. *Neuroradiol J* 2020; 33: 17–23. 2019/11/14.
25. Almallouhi E, Anadani M, Al Kasab S, et al. Initial experience in direct aspiration thrombectomy using a novel 0.071-inch aspiration catheter. *World Neurosurg* 2019; 126: 272–275.
26. Kyselyova AA, Fiehler J, Leischner H, et al. Vessel diameter and catheter-to-vessel ratio affect the success rate of clot aspiration. *J Neurointerv Surg* 2021; 13: 605–608.
27. Bernava G, Rosi A, Boto J, et al. Direct thromboaspiration efficacy for mechanical thrombectomy is related to the angle of interaction between the aspiration catheter and the clot. *J Neurointerv Surg* 2020; 12: 396–400.
28. Harten U. Mechanik deformierbarer Körper. In: Harten U (ed) *Physik für Mediziner*. 16th ed. Heidelberg: Springer, 2020: 79-115.
29. Bilgin C, Durmus Y, Haki C, et al. Direct aspiration thrombectomy experience with the SOFIA 6F catheter in acute ischemic stroke. *Jpn J Radiol* 2021; 39: 605–610.
30. Möhlenbruch MA, Kabbasch C, Kowoll A, et al. Multicenter experience with the new SOFIA plus catheter as a primary local aspiration catheter for acute stroke thrombectomy. *J Neurointerv Surg* 2017; 9: 1223–1227.
31. Tomasello A, Hernandez D, Piñana C, et al. Mechanical thrombectomy with a novel device: initial clinical experience with the ANA thrombectomy device. *J Neuroradiol* 2022; 49: 324–328.
32. Gunning GM, McArdle K, Mirza M, et al. Clot friction variation with fibrin content; implications for resistance to thrombectomy. *J Neurointerv Surg* 2018; 10: 34–38.
33. Kang DH and Hwang YH. Frontline contact aspiration treatment for emergent large vessel occlusion: a review focused on practical techniques. *J Stroke* 2019; 21: 10–22.
34. Tutwiler V, Singh J, Litvinov RI, et al. Rupture of blood clots: mechanics and pathophysiology. *Sci Adv* 2020; 6: eabc0496.
35. Duffy S, Farrell M, McArdle K, et al. Novel methodology to replicate clot analogs with diverse composition in acute ischemic stroke. *J Neurointerv Surg* 2017; 9: 486–491.
36. Chueh JY, Marosfoi MG, Anagnostakou V, et al. Quantitative characterization of recanalization and distal emboli with a novel thrombectomy device. *Cardiovasc Intervent Radiol* 2021; 44: 318–324.
37. Madjidyar J, Pineda Vidal L, Larsen N, et al. Influence of thrombus composition on thrombectomy: ADAPT vs. Balloon guide catheter and stent retriever in a flow model. *Rofo* 2020; 192: 257–263.
38. Heo JH, Nam HS, Kim YD, et al. Pathophysiologic and therapeutic perspectives based on thrombus histology in stroke. *J Stroke* 2020; 22: 64–75.
39. Brinjikji W, Nogueira RG, Kvamme P, et al. Association between clot composition and stroke origin in mechanical thrombectomy patients: analysis of the stroke thromboembolism registry of imaging and pathology. *J Neurointerv Surg* 2021; 13: 594–598.