Double stent-retriever as the first-line approach in mechanical thrombectomy - a randomized *in vitro* evaluation

Jiahui Li[1], Riccardo Tiberi[1], Pere Canals[1], Daniel Vargas[2], Marc Molina[1], Oscar Castaño[3,4], Alejandro Tomasello[2], Marc Ribo[1]

1. Stroke Unit, Neurology, Vall d'Hebron University Hospital, Barcelona, Spain
2. Neuroradiology, Vall d'Hebron University Hospital, Barcelona, Spain
3. Electronics and Biomedical Engineering, University of Barcelona, Barcelona, Spain
4. Biomaterials for Regenerative Therapies, Institute for Bioengineering in Catalonia, Barcelona, Spain

Corresponding author:

Marc Ribo

Stroke Unit, Neurology, Vall d'Hebron University Hospital, Barcelona, Spain

Hospital Vall d'Hebron, Passeig de la Vall d'Hebron Barcelona 119-129, Spain

E-mail: marcriboj@hotmail.com

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ABSTRACT

Background Repeated number of passes during mechanical thrombectomy (MT) leads to worse clinical outcomes in acute ischemic stroke. Initial experiences with the simultaneous double stent-retriever technique (double-SR) as the first-line treatment showed promising safety and efficacy results. We aim to characterize the potential benefits of using the double-SR as first-line technique as compared to the traditional single-SR approach.

Methods Three types of clot analogs (soft, moderately stiff, and stiff) were used to create terminal internal carotid artery (T-ICA=44) and middle cerebral artery (MCA=88) occlusions in an *in vitro* neurovascular model. Sixty-six cases were randomized into each treatment arm: single-SR or double-SR, in combination with a 0.071'' distal aspiration catheter. A total of 132 *in vitro* thrombectomies were performed. Primary endpoints were the rate of first-pass recanalization (%FPR) and procedural-related distal emboli.

Results FPR was achieved in 42% of the cases. Overall, double-SR achieved a significantly higher %FPR than single-SR (52% vs. 33%). Both techniques showed similar %FPR in T-ICA occlusions (23% vs. 27%). Double-SR significantly outperformed single-SR in MCA occlusions (63% vs. 38%), most notably in saddle occlusions (64% vs. 14%). Double-SR reduced the maximal size of the clot fragments migrating distally (Feret diameter=1.08±0.65mm vs. 2.05±1.14mm).Normalement

Conclusions This randomized *in vitro* evaluation demonstrates that the front-line double-SR technique is more effective than single-SR in achieving FPR when treating bifurcation occlusions that present saddle thrombus.

KEY MESSAGES

- **What is already known on this topic**

The simultaneous double stent-retriever technique (double-SR) provides promising safety and efficacy results. The benefits of using the double stent-retriever technique as first-line approach as compared to the conventional single-SR in combination with a distal access catheter technique have not been investigated.

- **What this study adds**

The double-SR does not imply higher risk of periprocedural distal embolization and is more effective than the combined technique in achieving first-pass recanalization when treating bifurcation occlusions that present saddle clots.

- **How this study might affect research, practice or policy**

We explored the circumstances where the double-SR may increase the chances of first-pass recanalization, which may be helpful to treatment decision-making.

INTRODUCTION

Mechanical thrombectomy (MT) is a widely performed procedure for acute ischemic stroke (AIS) due to large vessel occlusion (1–3). Recent studies determined that achieving complete recanalization (mTICI 2c-3) in the first attempt (First Pass Recanalization [FPR]) is a strong predictor of functional independence (mRS 90-days 0-2) (4) and each additional attempt progressively decreases the probability of favorable outcome (5). Moreover, achieving a sudden recanalization, meaning complete clot retrieval with no clot fragmentation in a single pass has also been associated with improved functional outcomes. Unfortunately, commercially available thrombectomy devices to date can achieve FPR rates ranging only from 30 to 60% (6,7).

The simultaneous double stent-retriever (double-SR) technique was first proposed as a rescue therapy after multiple failed attempts to retrieve a refractory thrombus with a single-SR, especially in vessel bifurcation occlusions when saddle clots are switched from one branch to the other with each additional single-SR pass (8–11). To maximize the rates of FPR, the double-SR technique has been proposed as the first-line treatment and initial experiences showed promising safety and efficacy results (12).

In this randomized *in vitro* evaluation, we aim to characterize the potential benefits of using the double-SR as first-line technique as compared to the traditional single-SR approach.

METHODS

Neurovascular model

The *in vitro* neurovascular model featuring a complete circle of Willis (Flowcat, Barcelona. Spain) was developed based on the vascular anatomies extracted from anonymized CTA images (**Figure 1A**). The manufacturing procedure comprises the following steps: image segmentation to generate the preliminary 3D geometry of the vascular anatomy (13,14), mesh modeling to simplify the anatomy and prepare a printable model (Meshmixer, Autodesk, Inc., CA), 3D printing (Form 3 SLA Printer, Formlabs, Inc., MA), post-printing processing, and manual assembly. The model includes the aortic arch, bilateral carotid arteries, middle cerebral arteries (up to 2 distal M2-MCA branches), anterior cerebral arteries (up to proximal A2), anterior communicating artery, posterior communicating arteries, and posterior cerebral arteries (up to proximal P2-PCA segments).

Clot analogs

Three types of hydrogel clot analogs —namely soft, moderately stiff, and stiff— were fabricated to create occlusions in the neurovascular model. The synthesis procedure has been described previously (15). Briefly, acrylamide and bis-acrylamide solutions of various proportions were prepared: 5%/0.1% for the soft thrombus, 10%/0.1% for the moderately stiff type, and 10%/0.15% for the stiff clot. Ammonium persulphate (0.1mL at 10%) and N.N-methylenebisacrylamide (0.01mL) were added to the initial mixtures as the photoinitiator and crosslinker, respectively. The hydrogels were cast in silicone tubings with inner diameters of 3mm (to induce distal M1-MCA occlusions) or 5mm (to induce terminal ICA occlusions). Once polymerized, clot analogs were stained with Congo red dye to enhance optical visualization. The stained cylinders were cut into 5-12mm long segments to generate the final clot analogs. The length and diameter of each clot were recorded before embolization into de model.

Experimental setup

The neurovascular model was connected in a flow-loop setup with a water reservoir at 37±1°C and a pump supplying approximately 800mL/min (**Figure 1B**). To simulate the transfemoral access, an 8F sheath attached to a silicone tubing was connected to the descending aorta.

To collect the periprocedural distal emboli after each retrieval attempt, a 100-μm pore size filter was placed at the outflow of the model. Similarly, an identical filter was placed at the inflow to prevent foreign particles from recirculating into the model.

***In vitro* MT procedure**

Clot analogs were injected from the carotid artery to embolize the distal M1-MCA or terminal internal carotid artery (T-ICA). Two occlusion patterns were observed at MCA bifurcations (**Figure 1A**): single-branch occlusions —thrombus in the main M1 stem extending into one M2 branch— and saddle occlusions —thrombus extending from M1 into both M2 branches—.

After initial embolization, experiments were 1:1 randomized into primary single or double-SR treatment. Through the transfemoral access, a 6F long sheath (NeuronMAX, Penumbra, Inc., CA) was positioned in the ICA. The triaxial system was completed with the introduction of an 0.071” aspiration catheter (REACT 71, Medtronic, MN) and an 0.021” microcatheter (Headway 21, MicroVention, CA) tracked over an 0.014” microwire (Synchro 14, Stryker, MI).

In the single-SR approach, the microcatheter was advanced through the occlusion site and placed in the dominant vessel branch, i.e., the M1 segment in T-ICA occlusions or the inferior M2 segment in distal M1-MCA occlusions. In the double-SR technique, a second 0.021” microcatheter was placed distally in another branch of the main artery, i.e., the A1 segment in T-ICA occlusions or the superior M2 segment in distal M1-MCA occlusions.

After placing both microcatheters in the target vessels, the microwires were exchanged for the SRs (Catchview 5 x 35 mm, Balt, France), which were then unsheathed across the clot by withdrawing the microcatheters. The aspiration catheter was then navigated to the proximal interface of the thrombus, and the SRs were retrieved simultaneously into the 0.071” catheter under continuous distal aspiration using a 60-cc syringe.

Only one clot retrieval attempt was performed per case. FPR was then defined as complete retrieval of the thrombus in the absence of any large distal embolus (Feret diameter>1mm) (16) remaining in the model (partial recanalization) or in the filter (distal embolization).

Distal emboli sub-analysis

The distal segments of the neurovascular model have vessels as narrow as 1 mm. Thus, most clot fragments would end up in the emboli filter placed at the outflow of the model. To analyze the periprocedural emboli, images of the filter were acquired with a high-resolution digital camera (IPEVO, Inc., CA). The images were then analyzed by an image processing algorithm developed on MATLAB R2020a (MathWorks, Inc., MA). The algorithm works in three main steps **(Figure 2A)**: first, binarization and segmentation of the RGB images, which involves highlighting the emboli ("1") and removing the background ("0"); second, measurement of the Feret diameter and area of each particle, using a circle of known dimensions as the reference; and lastly, generation of the output data: the Feret diameter of the largest embolus (largest-E), the total count of emboli (total-E), the total count of emboli larger than 1mm (total-E>1mm), and the total area of the filter covered by emboli (area-E).

Statistical analysis

Shapiro-Wilk test was used to check the normality of continuous variables (presented as mean±SD). To confirm that the embolized clot analogs were initially not significantly different between treatment arms, statistical tests were conducted to compare clot dimensions (diameters and lengths: Mann-Whitney U) and types (soft, moderately stiff, and stiff: Chi-Square), according to allocated treatments.

Chi-Square tests were used to examine the relationship between the primary treatment approach and the %FPR. Sub-analysis of distal emboli parameters (largest-E, total-E, total-E>1mm, and area-E) was conducted using *t*-tests.

A p-value<0.05 was considered statistically significant. All statistical analyses were performed using SPSS V.23.0 software (IBM Corp., NY).

RESULTS

A total of 132 clots were embolized: 44 into the distal ICA (right 28, left 16) and 88 into the distal M1-MCA segment (right 38, left 50). A single *in vitro* MT procedure was performed for each embolized clot. FPR was achieved in 42.4% (56/132) of the cases. MT outcomes according to thrombus type, occlusion location, and occlusion pattern are summarized in **Table 1**.

Sixty-six cases were randomized into each treatment arm. The embolized clot analogs were comparable between single-SR and double-SR techniques in terms of type (soft=16 cases/arm; moderately stiff=30 cases/arm; stiff=20 cases/arm) and dimensions (diameter=3.53±0.93mm vs. 3.48±0.92mm; length=8.95±3.43mm vs. 9.20±3.01mm). Initial occlusion location and occlusion pattern were also comparable between both treatment groups. Overall, double-SR achieved a significantly higher %FPR than single-SR (51.5% [34/66] vs. 33.3% [22/66]; p=0.035).

Clot stiffness

Overall, there were no differences in the %FPR according to clot stiffness (46.9% [15/32] vs. 33.3% [20/60] vs. 52.5% [21/40], p=0.139). Although not statistically significant, double-SR achieved higher %FPR with all clot types (**soft:** 56.2% [9/16] vs. 37.5% [6/16], p=0.288; **moderately stiff:** 43.3% [13/30] vs. 23.3% [7/30], p=0.100; **stiff:** 60.0% [12/20] vs. 45.0% [9/20], p=0.342).

Occlusion location

Clots embolized to T-ICA presented a significantly larger diameter, but similar length to clots that embolized the MCA territory (diameter=4.52±0.73mm vs. 3.00±0.48mm; length=9.43±4.64mm vs. 8.90±2.20mm).

Overall, FPR was more achievable in MCA occlusions rather than in T-ICA occlusions (51.1% [45/88] vs. 25.0% [11/44]; p=0.004). When treating T-ICA occlusions, single-SR and double-SR showed similar %FPR (22.7% [5/22] vs. 27.3% [6/22]; p=0.728). However, double-SR significantly outperformed single-SR in MCA occlusions (%FPR=62.8% [28/44] vs. 37.8% [17/44]; p=0.019).

Occlusion pattern

Single-branch occlusions represented 71.6% (63/88) of the embolizations in the MCA territory, while saddle occlusions accounted for 28.4% of the cases (25/88, all 25 cases in the left MCA).

Overall, FPR occurred more often in single-branch occlusions than in saddle occlusions (57.1% [36/63] vs. 36.0% [9/25]; p=0.074). In single-branch occlusions, single-SR and double-SR exhibited similar effectiveness in recanalization (50.0% [15/30] vs. 63.5% [21/33]; p=0.275). On the other hand, double-SR showed higher %FPR in saddle occlusions (63.6% [7/11] vs. 14.3% [2/14]; p=0.011).

Distal emboli

The sub-analysis of periprocedural distal emboli included 20 cases of MCA occlusions (10 experiments per treatment arm). Saddle occlusions represented 50% [10/20] of the cases. Thrombus type and dimensions did not differ significantly between single-SR and double-SR arms (diameter=3.10±0.32mm vs. 3.30±0.48mm; length=8.80±0.92mm vs. 9.30±0.95mm). In this subset of data, double-SR achieved a higher %FPR than single-SR (50% [5/10] vs. 10% [1/10]; p=0.051).

The distal emboli analysis by technique is summarized in **Figure 2B**. There were no significant differences in total-E (single-SR=16.6±8.34, double-SR=18.1±13.3; p=0.765), total-E>1mm (single-SR=2.40±1.90, double-SR=1.30±2.21; p=0.248), or area-E (single-SR=4.28±4.06 mm^2, double-SR=2.44±3.76 mm^2; p=0.397). However, the average largest-E detected in the double-SR arm was smaller than that observed in the single-SR arm (1.08±0.65mm vs. 2.05±1.14mm, p=0.038).

DISCUSSION

This randomized *in vitro* study demonstrates that the primary double-SR technique is more effective than single-SR in achieving FPR when treating bifurcation occlusions that present saddle thrombus. According to a recent study (17), saddle occlusion is the most common pattern in occlusions located in the MCA bifurcation (49% [502/1023] of stroke patients). In our thrombectomy model, while the right MCA presented a dominant bifurcation (inferior M2 branch diameter=2.53mm vs. superior branch diameter=1.92mm), the M2 branches in the left MCA were co-dominant (2.6mm vs. 2.7mm) —in terms of vessel diameter and ease of access—. These anatomical differences are probably at the origin of the differences observed in the distribution of the occlusion pattern between both sides (occurrence rate of saddle occlusions: left MCA 28% vs. right MCA 0%). In the setting of an acute stroke, neuroimaging techniques allow visualization of the artery up to the occlusion site and it is not possible to anticipate either the anatomical dominance beyond the occlusion or the occlusion pattern. However, our study suggests that in front of bifurcation occlusions in which there is a relatively high probability of codominance, i.e. top of the basilar or distal M1-MCA as opposed to terminal ICA, it might be reasonable to use double-SR as the first-line approach to increase the chances of first pass recanalization.

As compared to the single-SR approach, the use of double-SR in Y-configuration did not increase the frequency of periprocedural emboli, which could have been a concern due to the repeated crossing of the clot with the microcatheter (18). In fact, double-SR reduced the maximal size of the clot fragments migrating distally, which may mitigate the deleterious effect of distal embolization and improve the angiographic and clinical outcomes.

Although the clinical implications of SR mediated endothelial damage are still unclear, the histological impact of the double-SR on the endothelial surface might be a concern. The cumulative injury on the arterial wall after multiple device passes has been recently assessed in a swine model (19) and the results suggest that, in vessels of similar diameter to human ICA and MCA, the damage induced by two or more retrieval attempts with a single-SR exceeds the trauma caused by a single attempt with double-SR. Therefore, achieving FPR with double-SR as first-line approach may be less traumatic than multiple attempts with single-SR. However, further confirmation in clinical practice is needed since the vessel wall injury may be underestimated in swine models (20). Ongoing randomized trials will determine the safety and efficacy of double-SR in different intracranial locations as the front-line approach in MT in clinical practice.

Several studies suggest that the biomechanical behavior of the thrombus can be a determinant factor of MT procedural success (21). Erythrocyte-rich soft clots are fragment-prone (22) and fibrin/platelet-rich clots present higher stiffness and adhesion/friction against vessel walls (23,24). To date, it is still not possible to accurately predict the clot composition before retrieval of the clot. However, our study suggests that the double-SR approach improves %FPR independently of clot composition. The benefit may come on one hand from reducing the distal embolization in fragment-prone clots, and on the other from an increased traction force while retrieving clots with high adhesion/friction.

In our experiments we used two microcatheters to simultaneously deliver the two SR, ensuring parallel deployment of the SR and maximizing the chances to grab the clot by "sandwiching" it between the SR in their full length (**Supplemental Figure 1A**). The SR could also be sequentially delivered: after deploying the first SR, the microcatheter would be retracted and withdrawn to be navigated again with a microwire to the second branch. At this point, the microcatheter most probably would navigate inside the first SR in the pre-bifurcation segment to cross it at some point and reach the second branch. Sequential SR deployment reduces therefore the SR-clot interaction surface and only ensures adequate “sandwiching” in the distal part of the

SR (**Supplemental Figure 1B**). However, the optimal dual-SR technique should be validated in future bench and clinical studies.

Regarding the clinical relevance of our *in vitro* thrombectomy model, the %FPR achieved for MCA occlusions in our experiments matches the rates reported by clinical data in the literature (25,26)—approximately 50%—, demonstrating that our experimental setup including the hydrogel clot analogs might be a fair representation of clinical cases.

The double-SR as a front-line approach may increase the procedural complexity and treatment cost compared to other commonly used techniques (single-SR assisted by a balloon guide catheter, direct contact aspiration, or combined single-SR and direct contact aspiration). However, under specific anatomical conditions, it can decrease the number of device passes required to achieve revascularization, improving clinical outcomes and reducing the economic burden of post-stroke care (27).

Limitations

There are several inherent limitations of *in vitro* thrombectomy models. The device-clot-vessel wall interactions, the clot heterogeneity, the non-Newtonian behavior of the blood, and the biomechanical responses are not fully replicated. Nevertheless, the reported clinical data on %FPR suggest that our experimental setup can provide a reasonable simulation of clinical cases. The results may vary slightly if other techniques had been used instead of full retrieval of the SR inside the distal access catheter (28).

Concerning the emboli analysis, our methodology only allows for 2D assessment of the clot fragments collected in the filter; therefore, the third dimension is neglected in the analysis. Also, the Feret diameters determined by the image processing algorithm are unconfined measurements, meaning that they are not subjected to compression due to flow pressure and vessel walls. Thus, the reported data are only applicable for comparative analysis purposes and should be interpreted with caution. Lastly, clot fragments remaining in the model after the first retrieval attempt were not collected and thus, not characterized. Although given the higher %FPR in the double-SR arm, analyzing the clot fragments in partially recanalized cases would probably further favor the double-SR technique.

CONCLUSION

Double-SR technique as the front-line approach in MT leads to improved rates of first-pass recanalization. The perks of using double-SR are highlighted when treating bifurcation occlusions with saddle thrombi. The safety and efficacy of double-SR should be confirmed in clinical studies.

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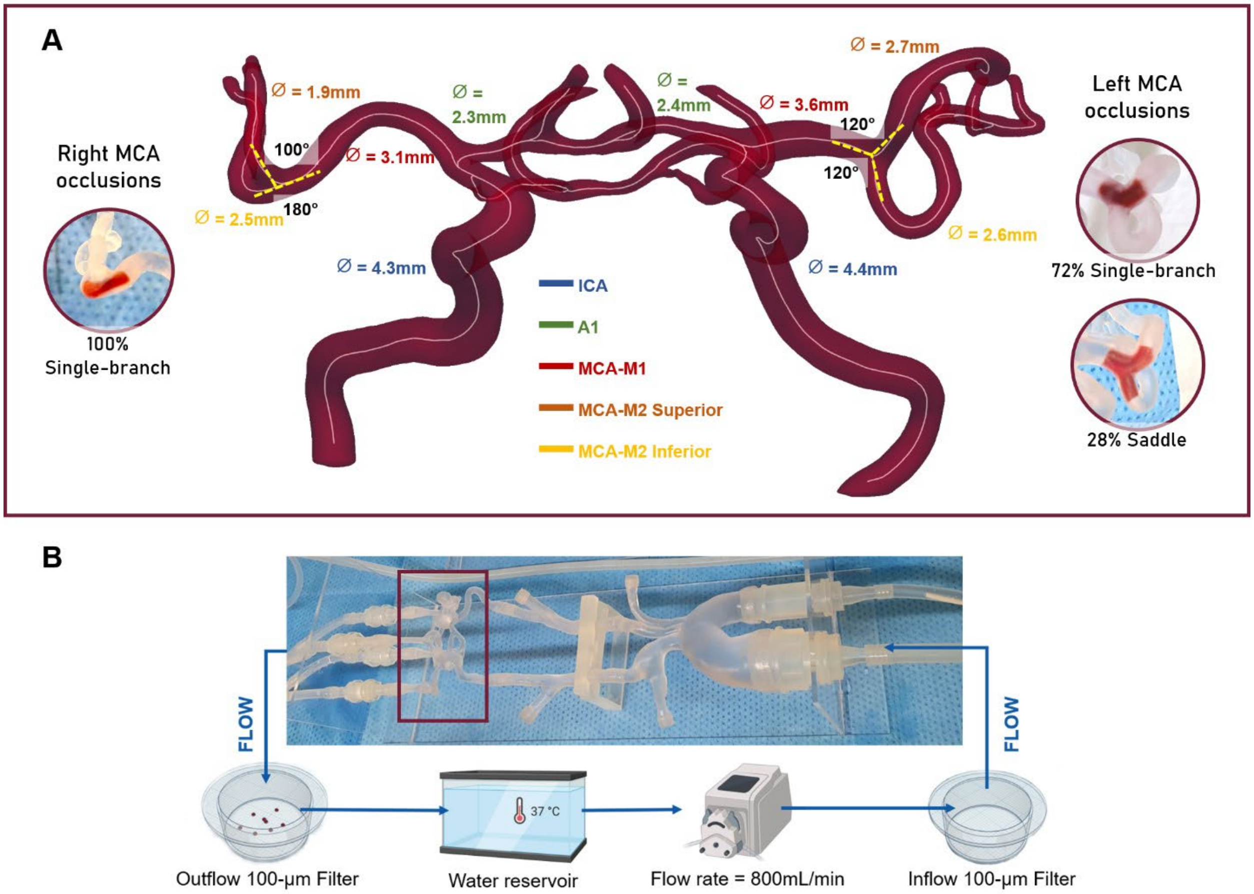

Figure 1. A) Experimental setup to perform *in vitro* MT and collect distal emboli for subsequent analysis. **B)** Diameters and access angles of the main vessel segments in the flow model. MCA occlusion patterns and distribution according to occlusion side.

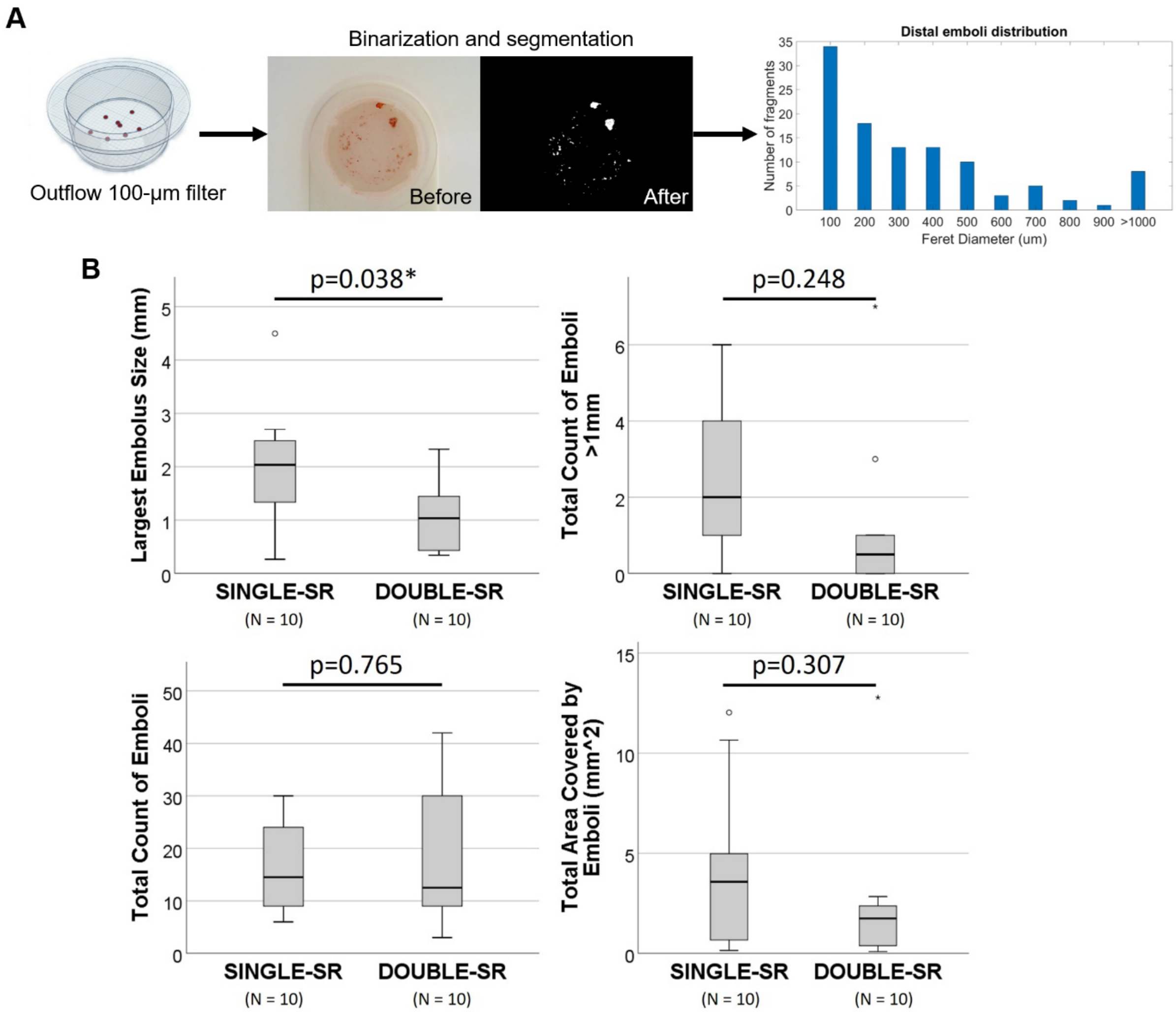

Figure 2. A) Emboli analysis workflow: image acquisition, binarization and segmentation, and image processing output. **B)** Distal emboli parameters —largest embolus' Feret diameter, total count of distal emboli larger than 1mm, total count of distal emboli, and total area of the outflow filter covered by clot fragment— according to the treatment arm.

Table 1. Rates of First Pass Recanalization achieved by the single and double stent-retriever technical approaches.

		First Pass Recanalization (%)		
		Single-SR	**Double-SR**	**p-value**
Clot length (mm)		8.95±3.43	9.20±3.01	
Clot diameter (mm)		3.53±0.93	3.48±0.92	
Overall		33.3% [22/66]	51.5% [34/66]	0.035*
Clot type				
	Soft	37.5% [6/16]	56.2% [9/16]	0.288
	Moderately stiff	23.3% [7/30]	43.3% [13/30]	0.100
	Stiff	45.0% [9/20]	60.0% [12/20]	0.342
Occlusion location				
	M1/M2-MCA	37.8% [17/44]	62.8% [28/44]	0.019*
	T-ICA	22.7% [5/22]	27.3% [6/22]	0.728
Occlusion pattern				
	Single-branch	50.0% [15/30]	63.5% [21/33]	0.275
	Saddle	14.3% [2/14]	63.6% [7/11]	0.011*