

**OPTIMIZATION OF THE USE OF NEW DEVICES
FOR MECHANICAL THROMBECTOMY:
FIRST STEPS TOWARDS THE DEVELOPMENT OF TELEROBOTICS**

Alejandro Tomasello Weitz

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DOCTORAL THESIS

**OPTIMIZATION OF THE USE OF NEW
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TOWARDS THE DEVELOPMENT OF
TELEROBOTICS.**

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I dedicate this thesis, with deep emotion, to the memory of my father, Leslie Tomasello Hart. He taught me the value of hard work and the dignity of one's word. His presence continues to guide and inspire me.

Keep your spirits up; don't lose faith in the goodness of humanity.

Tomasello

ACRONYMS AND ABBREVIATION

aOR – Adjusted Odds Ratio

BGC – Balloon Guide Catheter

CI – Confidence Interval

DSMB – Data Safety Monitoring Board

eTICI – Expanded Thrombolysis in Cerebral Infarction

EVT – Endovascular Treatment

FPR – First Pass Recanalization

ICA – Internal Carotid Artery

ICAD – Intracranial Atherosclerotic Disease

IQR – Interquartile Range

ITT – Intention-To-Treat

LVO – Large Vessel Occlusion

mRS – Modified Rankin Scale

mTICI – Modified Thrombolysis in Cerebral Infarction

MT – Mechanical Thrombectomy

NIHSS – National Institutes of Health Stroke Scale

PP – Per Protocol

SADE – Serious Adverse Device Event

sICH – Symptomatic Intracerebral Hemorrhage

SR – Stent Retriever

TICI – Thrombolysis in Cerebral Infarction

3D – Three Dimensional

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Abstract

Introduction

Acute ischemic stroke, primarily caused by large vessel occlusion (LVO), remains a leading cause of death and disability worldwide. Historically, the treatment of ischemic stroke evolved from intra-arterial fibrinolysis in the 1980s to the development of dedicated mechanical thrombectomy devices such as the stent retriever, which revolutionized stroke intervention. High-level evidence from randomized trials in 2015 established mechanical thrombectomy (MT) as the standard of care for LVO.

Two main strategies emerged: Stent retriever thrombectomy, enhanced by the use of balloon guide catheters to reduce distal embolization and aspiration techniques, which faced integration challenges with balloon guide catheters due to inner lumen constraints.

To overcome navigation and flow control limitations, distal flow restriction devices like the ANA5 Catheter were developed. This device allows simultaneous stent retriever use and aspiration at a more distal site, reducing thrombus fragmentation.

Another strategy is the double stent retriever technique, used in refractory cases or bifurcation occlusions. It improves clot capture by trapping the thrombus between two devices, especially effective against hard or compacted clots that resist single-device retrieval.

Looking forward, robotics in neurointervention offers promising solutions. Systems like CorPath GRX enable remote-controlled, precise manipulation of endovascular tools, enhancing procedural safety, reducing radiation exposure, and potentially enabling remote treatment (telerobotics). Robotics may help standardize complex procedures and expand access to advanced care in underserved regions.

Main Objective

To demonstrate how optimizing the use of emerging devices and technologies can improve clinical outcomes in mechanical thrombectomy for acute ischemic stroke.

Secondary Objectives

1. **To evaluate the safety and efficacy of the ANA5 catheter** in anterior circulation strokes treated within 24 hours of onset, through a single-arm trial. This includes analyzing the impact of device positioning (Bouthillier classification) and aspiration strategies on angiographic success.
2. **To compare the effectiveness of double versus single stent retrievers** in achieving successful recanalization in mechanical thrombectomy, through a randomized clinical trial.
3. **To assess the performance of robotic-assisted versus manual mechanical thrombectomy**, focusing on procedural time, radiological outcomes, embolic events, and the learning curve associated with robotic systems.

Results

In the ANAIS Study, the ANA5 funnel catheter achieved successful reperfusion (eTICI $\geq$ 2b50 within three passes) in 70% of patients in the intention-to-treat population, with first-pass eTICI

2c–3 rates of 44%. No serious adverse device events or symptomatic intracranial hemorrhages were observed at 24 hours. Subgroup analyses revealed higher success rates when the funnel was deployed at or above the intracranial segment of the internal carotid artery. Additionally, continuous aspiration—initiated with the stent retriever withdrawal and maintained throughout the procedure—was associated with better reperfusion outcomes compared to aspiration started only after the retriever entered the funnel.

The **TWIN2WIN Study** enrolled 108 patients, with 50 treated using a single stent retriever (SR) and 58 using the double-SR technique. First-pass reperfusion was significantly higher in the double-SR group (46%) compared to the single-SR group (24%), with an adjusted odds ratio (aOR) of 2.72. Substantial reperfusion within three passes was slightly higher in the double-SR group (89%) versus the single-SR group (84%), though this difference did not reach statistical significance. On average, fewer passes were needed in the double-SR group (1.7 compared to 2.0). Symptomatic intracranial hemorrhage occurred in 6% of single-SR cases and 10% of double-SR cases, with no significant difference between groups.

In the **Core Flow Study**, no significant difference was observed in recanalization rates (defined as achieving TICI $\geq 2b$) between robot-assisted and manual mechanical thrombectomy. The number of distal emboli generated was similar between both approaches, although those produced during robotic procedures were generally smaller in size. Interestingly, the performance metrics did not differ between interventionalists with prior robotic experience and those without.

Conclusions

The use of the ANA funnel catheter in combination with a stent retriever demonstrated high rates of successful and first-pass recanalization, with a favorable safety profile and good clinical outcomes. Optimal results were observed when the funnel was placed above the C1 segment and continuous aspiration was applied.

The double stent retriever technique proved superior to the single device in achieving first-pass recanalization, though final reperfusion rates were similar. Further studies are needed to assess its safety and clinical impact.

Robotic-assisted thrombectomy in a 3D neurovascular model achieved recanalization outcomes comparable to manual procedures, with encouraging results even among physicians with limited robotic experience, suggesting a short learning curve and broad potential for implementation.

Resumen

Introducción

El ictus isquémico agudo, causado principalmente por la oclusión de grande vaso (LVO), sigue siendo una de las principales causas de muerte y discapacidad en todo el mundo. Históricamente, el tratamiento del ictus isquémico evolucionó desde la fibrinólisis intraarterial en los años 80 hasta el desarrollo de dispositivos específicos para trombectomía mecánica, como el stent retriever, que revolucionaron la intervención en estos casos. La evidencia sólida de ensayos aleatorizados en 2015 estableció la trombectomía mecánica (MT) como el tratamiento estándar para la LVO.

Surgieron dos estrategias principales: la trombectomía con stent retriever, mejorada por el uso de catéteres guía con balón para reducir la embolización distal, y las técnicas de aspiración, que enfrentaron desafíos de integración con los catéteres guía con balón debido a limitaciones del lumen interno.

Para superar las limitaciones de navegación y control del flujo, se desarrollaron dispositivos de restricción del flujo distal como el catéter ANA5. Este dispositivo permite el uso simultáneo de un stent retriever y aspiración en un sitio más distal, reduciendo la fragmentación del trombo.

Otra estrategia es la técnica de doble stent retriever, utilizada en casos refractarios o en oclusiones en bifurcación. Mejora la captura del coágulo al atraparlo entre dos dispositivos, siendo especialmente eficaz contra trombos duros o compactos que resisten la extracción con un solo dispositivo.

De cara al futuro, la robótica en neurointervención ofrece soluciones prometedoras. Sistemas como el CorPath GRX permiten la manipulación remota y precisa de herramientas endovasculares, mejorando la seguridad del procedimiento, reduciendo la exposición a la radiación y posibilitando el tratamiento remoto (telerobótica). La robótica podría ayudar a estandarizar procedimientos complejos y ampliar el acceso a atención avanzada en regiones con escasa cobertura.

Objetivo principal

Demostrar cómo la optimización en el uso de dispositivos y tecnologías emergentes puede mejorar los resultados clínicos en la trombectomía mecánica del ictus isquémico agudo.

Objetivos secundarios

1. Evaluar la seguridad y eficacia del catéter ANA5 en ictus de circulación anterior tratados dentro de las 24 horas desde el inicio, mediante un ensayo de un solo brazo. Esto incluye analizar el impacto de la posición del dispositivo (clasificación de Bouthillier) y las estrategias de aspiración en el éxito angiográfico.
2. Comparar la eficacia de la técnica de doble stent retriever frente a un único dispositivo en la recanalización exitosa en trombectomía mecánica, mediante un ensayo clínico aleatorizado.
3. Evaluar el rendimiento de la trombectomía mecánica asistida por robot frente a la manual, centrándose en el tiempo de procedimiento, resultados radiológicos, eventos embólicos y curva de aprendizaje asociada al uso del sistema robótico.

Resultados

En el estudio ANAIS, el catéter ANA5 tipo funnel logró una reperfusión exitosa ($eTICI \geq 2b50$ en tres pases o menos) en el 70% de los pacientes de la población por intención de tratar, con tasas de reperfusión $eTICI 2c-3$ en el primer pase del 44%. No se observaron eventos adversos graves relacionados con el dispositivo ni hemorragias intracraneales sintomáticas a las 24 horas. Los análisis por subgrupos revelaron mayores tasas de éxito cuando el funnel se desplegó a nivel o por encima del segmento intracraneal de la arteria carótida interna. Además, la aspiración continua —iniciada al retirar el stent retriever y mantenida durante todo el procedimiento— se asoció con mejores resultados de reperfusión en comparación con la aspiración iniciada solo después de que el recuperador entrara en el funnel.

El estudio TWIN2WIN incluyó a 108 pacientes: 50 tratados con un único stent retriever (SR) y 58 con la técnica de doble SR. La reperfusión en el primer pase fue significativamente mayor en el grupo de doble SR (46%) frente al grupo de SR único (24%), con una razón de probabilidades ajustada (aOR) de 2,72. La reperfusión sustancial en tres pases fue ligeramente superior en el grupo de doble SR (89%) frente al grupo de SR único (84%), aunque esta diferencia no fue estadísticamente significativa. En promedio, se necesitaron menos pases en el grupo de doble SR (1,7 frente a 2,0). La hemorragia intracraneal sintomática ocurrió en el 6% de los casos con SR único y en el 10% de los casos con doble SR, sin diferencias significativas entre grupos.

En el estudio Core Flow, no se observaron diferencias significativas en las tasas de recanalización (definidas como alcanzar $TICI \geq 2b$) entre la trombectomía mecánica asistida por robot y la manual. El número de émbolos distales generados fue similar entre ambos enfoques, aunque los producidos durante los procedimientos robóticos fueron generalmente de menor tamaño. Curiosamente, los parámetros de rendimiento no difirieron entre los intervencionistas con experiencia previa en robótica y aquellos sin ella.

Conclusiones

El uso del catéter tipo funnel ANA en combinación con un stent retriever demostró altas tasas de recanalización exitosa y en primer pase, con un perfil de seguridad favorable y buenos resultados clínicos. Se observaron resultados óptimos cuando el funnel se colocó por encima del segmento C1 y se aplicó aspiración continua.

La técnica de doble stent retriever resultó superior al dispositivo único para lograr la recanalización en el primer pase, aunque las tasas finales de reperfusión fueron similares. Se requieren más estudios para evaluar su seguridad e impacto clínico.

La trombectomía asistida por robot en un modelo neurovascular 3D logró resultados de recanalización comparables a los procedimientos manuales, con resultados prometedores incluso entre médicos con limitada experiencia robótica.

INTRODUCTION

1. Introduction

1.1. Acute ischemic stroke

Ischemic stroke refers to an acute neurological event characterized by the sudden loss of blood supply to a region of the brain due to arterial occlusion, most commonly from thrombosis or embolism. Ischemic strokes account for approximately 85% of all stroke cases and pose a significant challenge to healthcare systems due to their substantial morbidity and mortality (1).

The brain receives its blood supply from the anterior (carotid) and posterior (vertebrobasilar) circulations, which are interconnected via the Circle of Willis. Ischemic stroke results from the occlusion of a cerebral artery, mostly by the presence of a thrombus, which disrupts cerebral blood flow and leads to oxygen deprivation in brain tissue. This triggers rapid and extensive neuronal loss within minutes (2).

Ischemic stroke is a leading cause of mortality and long-term disability worldwide, affecting millions of individuals annually (3). Arterial occlusions that can be responsible for a Stroke are typically classified based on the size of the affected vessel—large, medium, or small. Among these, large vessel occlusions (LVOs) are associated with the highest clinical burden and mortality rates (4).

Globally, stroke is the second leading cause of death, following ischemic heart disease (3). In Spain, it accounts for the second leading cause of mortality (5.3%), ranking third among men—after ischemic heart disease and cancer—and second among women, following dementia (5).

Mechanical thrombectomy (MT) is currently the primary—and only—endovascular treatment for acute ischemic stroke caused by large vessel occlusion. Given the significant impact of this condition on the general population, substantial efforts are continuously being made to improve the performance and outcomes of mechanical thrombectomy. Importantly, ongoing innovation in MT focuses not only on developing new devices but also on optimizing how they are used, with the ultimate goal of improving clinical outcomes and expanding treatment access.

1.2. Mechanical Thrombectomy

1.2.1. A historical perspective

In 1982, the first successful case of intra-arterial therapy was published, describing the recanalization of a large-caliber intracranial vessel using local fibrinolysis with streptokinase in the basilar trunk (6). More than 20 years would pass before technology enabled the development and market release of the first thrombectomy devices with a reasonable guarantee of success. Among these, the first device specifically designed for mechanical clot removal was the "Mechanical Embolus Removal in Cerebral Ischemia" or MERCI device (7). It consisted of a nitinol wire with a 3D “loop” or corkscrew configuration, designed to be deployed around the thrombus to entrap it within the device structure.

A major Advance in thrombectomy safety and effectiveness came with the introduction of a stent originally designed for intracranial aneurysm treatment via stent-assisted remodeling: the Solitaire (ev3). This laser-cut, closed-cell, “peak-to-peak” configured stent was retrievable, with a relatively low metal surface area (approximately 5%). Its design proved to be a key factor in its success as a thrombectomy device, allowing the thrombus to be incorporated into the stent’s structure and facilitating its removal.

The use of the Solitaire device for thrombectomy was first described by Dr. Castaño in 2009, marking the beginning of modern mechanical thrombectomy — an effective and safe technique (8, 9). It wasn’t until six years later that the tremendous impact of thrombectomy

for large intracranial vessel occlusions in the anterior circulation was confirmed through high-quality scientific evidence from five landmark randomized clinical trials (10, 11, 12, 13, 14, 15). These studies were conducted mostly using stent retriever techniques.

Meanwhile, balloon guide catheters—positioned in the cervical segment of the internal carotid artery—were incorporated into the procedure to achieve proximal flow arrest. These catheters are equipped with an inflatable balloon near the cervical segment of the internal carotid artery, which can be temporarily inflated to occlude the artery and halt antegrade blood flow during thrombectomy. By arresting flow, the balloon minimizes the risk of clot fragmentation and distal embolization.

A parallel line of research and technological development emerged: direct thrombus aspiration, developed by Penumbra. Aspiration catheters connected to suction pumps began to be used, along with a separator device designed to fragment the thrombi (16). The first major study involving this device, The Penumbra Pivotal Trial, demonstrated its effectiveness (17). This study led to changes in the technique, excluding the separator from the system and relying instead on direct contact aspiration for thrombectomy effectiveness.

Technical limitations in developing balloon guide catheters with a sufficiently large inner lumen to accommodate aspiration catheters made it unfeasible to integrate the classical Penumbra system with balloon guide catheters, and therefore prevented the possibility of performing aspiration under proximal flow restriction.

1.2.2. Innovative concepts and approaches

Innovation in medicine involves introducing novel techniques, technologies, and methodologies to ultimately enhance clinical outcomes and the quality of patient care. This concept is particularly important in the field of stroke, where small improvements in technique can have a major impact on the clinical outcome of the procedure.

This process includes not only the development of more advanced medical devices but also identifying the correct ways to use them in order to optimize clinical procedures. Such advancements are crucial, as they allow more patients to benefit from effective treatments, broadening the scope and positive impact of medical interventions.

The renowned explorer and scientist Sir Ernest Shackleton once said, “Superhuman effort is not worth a damn unless it achieves results.” This perspective underscores the importance of working methodically but also always keeping patient needs in mind, in order to focus our efforts on achieving significant clinical breakthroughs.

1.2.3. Flow control and flow restriction

Historically, mechanical thrombectomy procedures faced significant challenges due to the risk of clot fragmentation and distal embolization, which could lead to further ischemic damage (18, 19).

As new thrombectomy techniques were being developed and clinical indicators improved, it became increasingly clear that avoiding fragmentation of the clot during the procedure was crucial, and that the intervention needed to be performed in the shortest possible time.

Initially, this goal was pursued using traditional balloon guide catheters, which allow inflation of a balloon in the internal carotid artery at the level of the neck (19) to achieve flow control.

However, the use of balloon guide catheters has been subject to criticism in clinical practice due to the potential risk of vasospasm when the balloon is inflated in the cervical carotid artery, as well as the challenges related to navigation up to the site of occlusion (20).

For these reasons, efforts began to develop devices capable of reducing flow at a more distal level, thereby allowing improved navigability. The ANA Funnel Catheter device (Anaconda Biomed S.L., Barcelona, Spain) is an innovative stroke thrombectomy tool designed to promote distal flow restriction during the procedure via a deployable distal funnel. This configuration enables simultaneous aspiration, helping to limit clot fragmentation.

The ANA Funnel Catheter is engineered to facilitate the delivery of stent retrievers during mechanical thrombectomy and to create flow restriction during clot retrieval. The device's funnel, once deployed, allows for continuous aspiration and may enhance clot ingestion, thereby reducing the risk of thrombus fragmentation. Once the clot is captured within the funnel, both the stent retriever and the ANA Funnel Catheter are withdrawn together into the guiding catheter to complete the extraction.

Recently, the device has been redesigned for direct deployment at the level of the intracranial internal carotid artery, thus allowing for a more distal flow restriction.

1.2.4. Double stent retriever technique

The double stent retriever technique was originally developed as a rescue strategy for cases in which recanalization failed after the use of a single stent retriever or aspiration alone. It has been employed for several years in situations where standard mechanical thrombectomy techniques were unsuccessful in achieving vessel reopening.

This approach involves the simultaneous deployment of two stent retrievers within the occluded vessel. They can be placed longitudinally (one after the other) or, in the case of thrombi located at arterial bifurcations, deployed in parallel, with one stent retriever introduced into each branch of the bifurcation.

The double device configuration enables the thrombus to be trapped between the mesh structures of both stent retrievers, enhancing the likelihood of complete clot capture and removal. This setup increases the contact surface area between the devices and the clot, thereby improving the chances of achieving successful recanalization in a single pass.

It is well established that hard or compacted thrombi are less responsive to treatment with a single stent retriever. The effectiveness of a single device relies on the thrombus integrating into the device's mesh, allowing it to be ensnared. This integration often fails with hard thrombi, as the clot remains outside the stent's mesh and cannot be effectively captured. The double stent retriever approach shifts the strategy from attempting to trap the thrombus within the mesh of a single stent to compressing and capturing it between two stents (21, 22, 23, 24).

1.2.5. Development of Telerobotics

Currently, robotics in the neuroendovascular field is undergoing phases of preclinical and clinical studies to perform remote treatments for neurovascular patients through telerobotics.

Integrating robotics in medicine has marked a transformative shift in surgical practices, offering enhanced precision, consistency, and reproducibility, and the ability to perform minimally invasive procedures. Robotics have been successfully implemented in various medical fields, such as urology, gynecology, and cardiology, where robotic-assisted surgeries have demonstrated significant benefits, including reduced recovery times, decreased risk of

infection, and improved surgical outcomes. For instance, the da Vinci Surgical System, widely used in laparoscopic surgeries, has set a precedent for using robotic systems in medical practice.

In interventional medicine, a robot refers to a computer-assisted electromechanical system that allows for precise, remote manipulation of procedural tools—such as guidewires, microcatheters, and devices like stent retrievers. The robot acts as a mechanical extension of the physician's hands, enabling fine motor control with high reproducibility and minimal human tremor. These systems often include programmable movements, force feedback, and integrated imaging guidance.

The possibility of performing mechanical thrombectomy through a robotic system may not only improve the precision and efficiency of the procedure but also facilitate interventions in remote areas, where access to specialized care is often limited. The potential of robotics to revolutionize neurointervention lies in its ability to provide stable, controlled movements, reduce human error, and enable complex procedures that may be challenging to perform manually.

HYPOTHESIS

2. Hypothesis

The hypothesis of this thesis is that optimizing the use of newly developed devices and methods in mechanical thrombectomy may lead to improved angiographic outcomes and, potentially, better clinical results.

Moreover, the appropriate use of technology may support the development of telemedicine and robotic-assisted treatments for acute ischemic stroke, particularly in remote areas that are not always accessible to interventional specialists.

OBJECTIVES

3. Objectives

3.1. Main Objective

The general objective of this thesis is to demonstrate how the optimization of the use of new devices and technologies can improve clinical outcomes of mechanical thrombectomy in patients with acute ischemic stroke.

3.2. Secondary Objectives

- To evaluate the efficacy and safety of the newly developed ANA5 catheter through a single-arm trial conducted at our center in patients with anterior circulation stroke within 24 hours of onset. The primary endpoints were successful recanalization (defined as mTICI $\geq 2b$ within three passes) and safety (symptomatic intracranial hemorrhage or device-related serious adverse events). A secondary pre-specified analysis assessed the impact of funnel positioning (based on Bouthillier classification) and aspiration strategy (continuous, initiation-only, or end-only) on angiographic outcomes, to determine the influence of optimal device utilization on procedural success.
- To conduct a randomized clinical trial to compare the efficacy of the double stent retriever technique with that of a single stent retriever in achieving successful mechanical thrombectomy.
- The study explored the feasibility and implementation of an experimental setup for performing robotic-assisted mechanical thrombectomy using a corticoid path and a robotic system. Once the setup was defined, the study aimed to compare the effectiveness of robotic-assisted versus manual thrombectomy by evaluating parameters such as procedure duration, radiological outcomes, and distal emboli formation. Additionally, it investigated the learning curve associated with robotic systems, taking into account the initial adaptation required by operators.

COMPENDIUM OF PUBLICATIONS

4. Compendium of publications

4.1. Article 1

Clinical Results of the ANAIS Study: Mechanical Thrombectomy Using the ANA Device in Combination with a Stent Retriever in Subjects with Acute Ischemic Stroke

Tomasello A, Zamarro J, Terceño M, Diaz-Perez J, Bashir S, Gramegna LL, Requena M, Diana F, Rivera E, Dios M, Hernández D, Sánchez S, Galve I, Ribo M.

AJNR Am J Neuroradiol. 2025 Mar 4;46(3):502-509. doi: 10.3174/ajnr.A8556. PMID: 40037699; PMCID: PMC11979815.

The ANAIS Study

The Advanced Neurovascular Access device (ANA5, Anaconda Biomed) is a unique thrombectomy catheter featuring a distal self-expanding funnel designed to temporarily restrict blood flow in the Internal Carotid Artery (ICA) and capture the clot. When combined with a stent retriever, this design aims to minimize clot fragmentation during retrieval. The ANAIS study evaluated the safety and efficacy of the ANA5 device under various deployment positions and aspiration conditions.

We performed a prospective, single arm, clinical trial, called ANAIS multicenter study assessing ANA5 combined with a stent retriever in patients with anterior circulation acute ischemic stroke, treated within 24 hours of symptom onset. An independent core lab and clinical events committee adjudicated predefined endpoints. The primary efficacy outcome was successful recanalization (mTICI $\geq 2b$) within three passes. The primary safety endpoint included symptomatic intracranial hemorrhage within 24 hours or any device-related serious adverse event.

Interestingly, we preplanned a secondary analysis using data collected through a questionnaire administered to the interventionalists at the end of the procedure. They were asked to indicate the exact location of funnel deployment within the carotid artery, according to the Bouthillier classification. Additionally, they reported whether aspiration was applied continuously, only at the initiation of the retrieval maneuver, or only at the end. The interventionalists were instructed to position the distal end of the funnel and apply aspiration according to their own preference and clinical judgment.

The results were analyzed in both the intention-to-treat (ITT) population—which included all 43 patients enrolled with the intention to be treated with the device—and the per-protocol (PP) population, which excluded patients with protocol deviations. Specifically, 11 patients were excluded from the PP analysis: four due to findings of intracranial atherosclerotic disease (ICAD), two due to unstable guide catheter positioning, and five for multiple minor deviations or insufficient ANA funnel catheter passes, resulting in a PP cohort of 32 patients.

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4.2. Article 2

Randomized Study Comparing First-Line Dual Versus Single-Stent Retriever Technique: TWIN2WIN

Tomasello A, Moreu M, Terceño M, Dinia L, Barrena Caballo MR, Requena M, Jablonska M, Cendrero J, Flores A, Ortega-Gutierrez S, Diana F, Henandez D, de Dios M, Rubiera M, Garcia-Tornel A, Rizzo F, Olivé M, Pérez-García C, Trejo Gallego C, Carmona T, Rodrigo-Gisbert M, Molina C, Ribo M.

Stroke. 2025 Feb;56(2):326-334. doi: 10.1161/STROKEAHA.124.048496. Epub 2024 Dec 20. Erratum in: Stroke. 2025 Apr;56(4):e129. doi: 10.1161/STR.0000000000000489. PMID: 39704055.

The TWIN2WIN study

The primary aim of mechanical thrombectomy is to rapidly restore cerebral blood flow by removing the occlusive clot from the affected artery. Within this context, achieving the First Pass Effect — defined as complete clot retrieval without fragmentation in a single attempt — has emerged as a key procedural goal. This angiographical outcome has been consistently associated with improved clinical and functional recovery in patients with acute ischemic stroke (25).

Unfortunately, currently available thrombectomy devices to date can only achieve FPR rates ranging from 30 to 60% (26, 27, 28). 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 (29, 30). The rationale behind the TWIN2WIN study is that if recanalization at first pass leads to better outcomes and the double stent-retriever technique seems to be effective as a bailout technique in cases where single stent retriever failed, using double stent retriever as frontline strategy may lead to better angiographic and clinical outcomes.

TWIN2WIN is a randomized, multicenter, Phase II clinical trial evaluating the safety and efficacy of first-line double-SR versus single-SR in patients with LVO undergoing EVT. The study followed CONSORT guidelines and was conducted across five comprehensive stroke centers in Spain, with ethics approval at each site and informed consent obtained.

Designed and led by independent academic investigators without industry sponsorship, the trial included blinded adjudication of imaging endpoints by two independent experts via a centralized core lab. A data safety monitoring board (DSMB) oversaw study conduct. All procedures adhered to Good Clinical Practice.

Eligible patients were functionally independent adults (pre-stroke mRS 0–2) with disabling ischemic stroke (NIHSS ≥ 6), in whom EVT could begin within 24 hours of symptom onset or last known well. Inclusion required a single LVO in the terminal ICA, M1-MCA segment, or basilar tip confirmed by initial angiography.

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4.3. Article 3

Modeling Robotic-Assisted Mechanical Thrombectomy Procedures with the CorPath GRX Robot: The Core-Flow Study

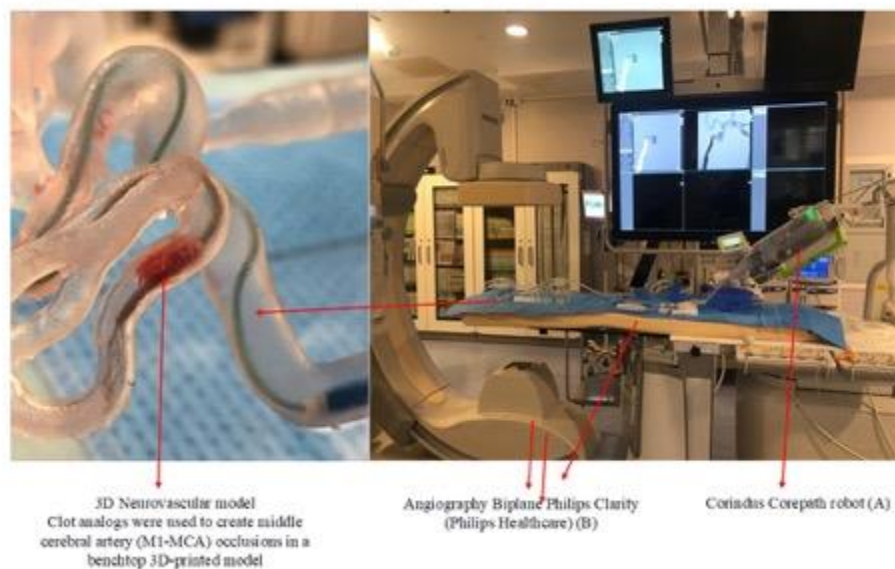
Tomasello A, Hernández D, Li J, Tiberi R, Rivera E, Vargas JD, Losada C, Jablonska M, Esteves M, Diaz ML, Cendrero J, Requena M, Diana F, De Dios M, Singh T, Gramegna LL, Ribo M.

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The Core-Flow Study

Experimental model of the Core-Flow Study

To evaluate the Corindus CorPath robotic system for performing mechanical thrombectomy, we developed an experimental setup within the angiographic suite of the Interventional Unit at Vall d'Hebron Institute of Research. The Corindus CorPath GRX robot (A) was mounted on the angiographic table of the biplane angiography system, which was connected to a 3D-printed model of the Circle of Willis, allowing us to simulate mechanical thrombectomy procedures. Using this setup, we were able to perform mechanical thrombectomies both manually—by directly inserting the catheters into the neurovascular model—and robotically using the Corindus system.



All thrombectomy were performed under fluoroscopic guidance as performed in clinical practice.



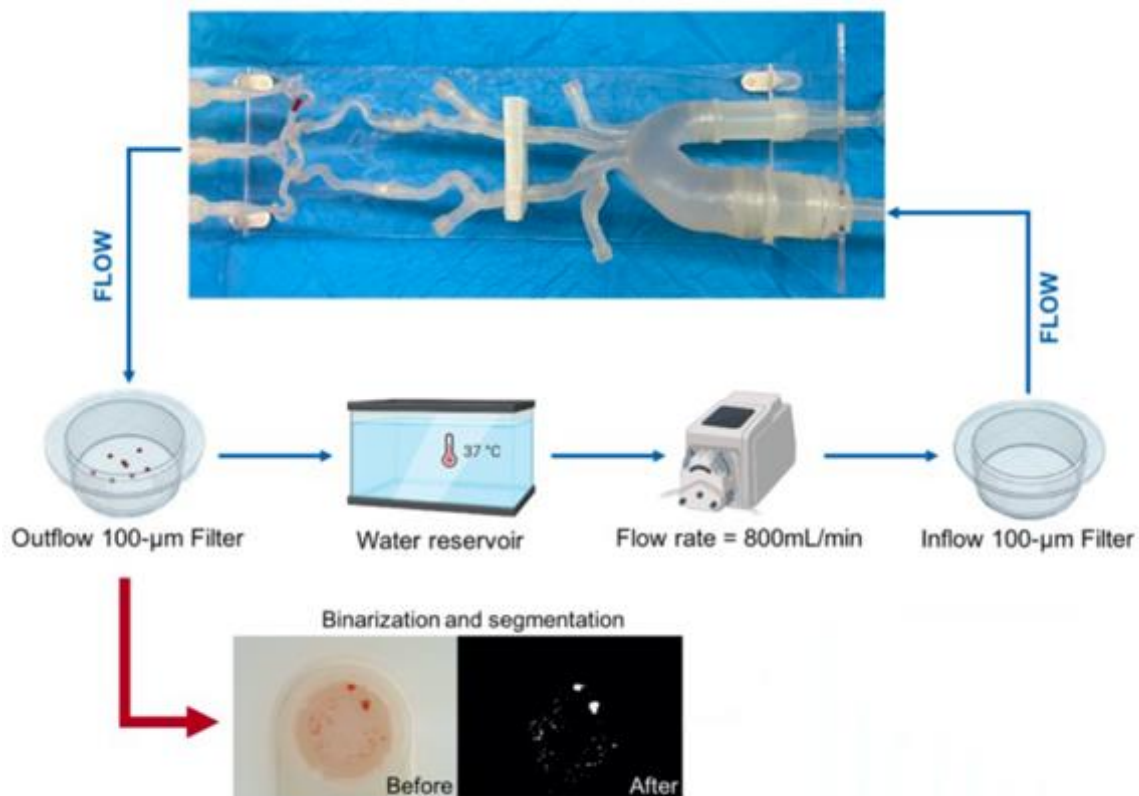
All mechanical thrombectomies were performed under X-ray guidance and evaluated using oblique and anteroposterior angiographic views, employing devices routinely used in clinical practice.

Iterative development of the experimental setup

The optimization of our experimental protocol required multiple iterative cycles of refinement before the final methodology could be established. Our initial challenge was the development of an appropriate clot analog that would reliably produce consistent occlusions while maintaining visibility under fluoroscopy. After testing various compositions with different concentrations of fibrin and erythrocytes, we selected a 2×4 mm radiopaque clot analog fabricated from porcine blood. This specific formulation exhibited the optimal balance of mechanical stability, adhesive properties, and radiographic visibility required for our assessment metrics. Concurrent with clot development, we systematically evaluated potential occlusion sites throughout the cerebrovascular tree, including various segments of the internal carotid artery (ICA), the M1 segment, and proximal M2 branches of the middle cerebral artery (MCA). These preliminary investigations revealed critical limitations in the CorPath GRX robot's range of motion, specifically its restricted advancement capability of 20 cm. Consequently, we determined that M1-MCA occlusions represented the most suitable target for our evaluation, as this location maximized clinical relevance while remaining technically accessible within the constraints of the robotic system.

The refinement of our neurovascular model constituted another critical aspect of our experimental setup development. Beginning with anonymized computed tomography angiography (CTA) images, we employed advanced segmentation techniques using 3D Slicer software to extract preliminary vascular geometries. These initial models underwent substantial refinement through multiple iterations, with each version evaluated for anatomical fidelity, mechanical performance, and compatibility with our thrombectomy devices. The final model architecture incorporated the aortic arch, bilateral carotid arteries, complete middle cerebral artery branches (extending to the distal M2 segments), anterior cerebral arteries with the anterior communicating complex, and the posterior circulation including communicating arteries and proximal posterior cerebral artery segments. After extensive material testing, we selected Elastic 50A photopolymer resin printed at 100µm resolution using a Form 3 SLA printer (Formlabs), which provided the optimal combination of vessel compliance, durability through multiple experimental cycles, and friction coefficients that most closely approximated physiological conditions. This methodical development process was instrumental in establishing a standardized testing environment capable of generating reproducible and clinically meaningful comparative data between manual and robot-assisted thrombectomy approaches.

Emboli assessment performed with the neurovascular model.



The neurovascular model was integrated into a closed-loop flow system to mimic physiological blood circulation. The circuit included a hydraulic pump recirculating water at a flow rate of 800 mL/min, the 3D-printed vascular model, and silicone tubing. An 8F introducer sheath connected to a silicone tube was used to simulate transfemoral arterial access and was inserted into the descending aorta of the model. A 100 μm filter was placed at the outflow of the system to capture distal emboli generated during the procedure. Additionally, a pre-filter was positioned between the pump and the model to eliminate residual particles introduced by reused devices.

To characterize all periprocedural distal emboli, the system included a high-resolution imaging chamber placed downstream. Captured emboli were visualized using bright-field imaging and converted into binary images for further quantification and analysis.

Modeling Robotic-Assisted Mechanical Thrombectomy Procedures with the CorPath GRX Robot: The Core-Flow Study

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ABSTRACT

BACKGROUND AND PURPOSE: Endovascular robotic devices may enable experienced neurointerventionalists to remotely perform endovascular thrombectomy. This study aimed to assess the feasibility, safety, and efficacy of robot-assisted endovascular thrombectomy compared with manual procedures by operators with varying levels of experience, using a 3D printed neurovascular model.

MATERIALS AND METHODS: M1 MCA occlusions were simulated in a 3D printed neurovascular model, linked to a CorPath GRX robot in a biplane angiography suite. Four interventionalists performed manual endovascular thrombectomy ($n = 45$) and robot-assisted endovascular thrombectomy ($n = 37$) procedures. The outcomes included first-pass recanalization (TICI 2c–3), the number and size of generated distal emboli, and procedural length.

RESULTS: A total of 82 experimental endovascular thrombectomies were conducted. A nonsignificant trend favoring the robot-assisted endovascular thrombectomy was observed in terms of final recanalization (89.2% versus manual endovascular thrombectomy, 71.1%; $P = .083$). There were no differences in total mean emboli count (16.54 [SD, 15.15] versus 15.16 [SD, 16.43]; $P = .303$). However, a higher mean count of emboli of >1 mm was observed in the robot-assisted endovascular thrombectomy group (1.08 [SD, 1.00] versus 0.49 [SD, 0.84]; $P = .001$) compared with manual endovascular thrombectomy. The mean procedural length was longer in robot-assisted endovascular thrombectomy (6.43 [SD, 1.71] minutes versus 3.98 [SD, 1.84] minutes; $P < .001$). Among established neurointerventionalists, previous experience with robotic procedures did not influence recanalization (95.8% were considered experienced; 76.9% were considered novices; $P = .225$).

CONCLUSIONS: In a 3D printed neurovascular model, robot-assisted endovascular thrombectomy has the potential to achieve recanalization rates comparable with those of manual endovascular thrombectomy within competitive procedural times. Optimization of the procedural setup is still required before implementation in clinical practice.

ABBREVIATIONS: BGC = balloon guide catheter; EVT = endovascular thrombectomy; MA = manual; MT = mechanical thrombectomy; RA = robot-assisted; SR = stent retriever

Mechanical thrombectomy (MT) is the most effective treatment for acute ischemic stroke due to large-vessel occlusion when combined with IV-tPA, unless contraindicated, and is currently strongly recommended by all therapeutic guidelines.^{1,2}

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However, logistic and geographic limitations in the availability of rapid performance of the thrombectomy procedure create geographic inequities among territories due to the procedure being more accessible in urban areas than in remote rural locations distant from major cities.^{2–4} Appropriate MT programs require not only modern angiography suites but also certified physicians who are well-trained in neurointerventional procedures and remain in continual contact with the neuroscientific society; this scenario ensures the highest-quality standards. In recent years, endovascular robotic devices have emerged as a revolutionary technology that may transform the field of neurointerventional treatment.

The CorPath GRX System (Corindus) is the first FDA-cleared and CE Marked medical device for percutaneous coronary and vascular procedures. It uses articulated robotic arms with multiple degrees of freedom to handle microguidewires and microcatheters, enabling submillimeter movements of both devices to

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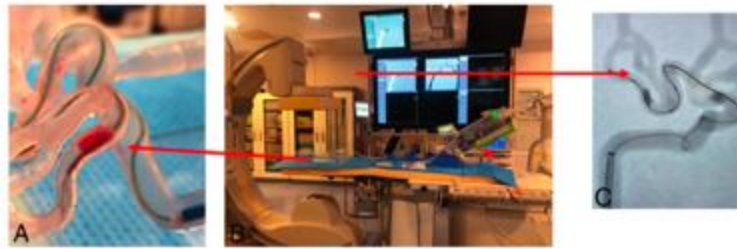


FIG 1. A benchtop 3D printed vascular model with a thrombus inside (A) was connected to a Corindus CorPath GRX robot (B, arrowhead), and MT was performed using SRs (C).

perform precise neurovascular interventions. Physicians can control it remotely, reducing radiation exposure and providing a comfortable and more precise working distance.⁵⁻⁷

Studies focusing on the embolization of intracranial aneurysms have been published dating back to the first-in-human experience reported in 2018, in which a transradial diagnostic coronary angiography was performed.^{6,7}

The potential use of robotic treatment in stroke thrombectomy procedures could represent a substantial advancement in stroke treatment, providing an alternative solution for patients in nonurban areas. Robot-assisted endovascular thrombectomy (RA-EVT) could save time by avoiding long transfers; it also offers patients the possibility of being treated remotely by highly-skilled neurointerventionalists, ultimately improving patient outcomes and quality of life. Although the CorPath GRX, which is capable of performing biaxial procedures, is not fully optimized for thrombectomy procedures, it allows multiple catheter maneuvers and yields an accuracy comparable—or superior—to manual procedures.

The present study aims to describe a potential setup and explore the feasibility (reaching the occlusion), safety (distal embolization), and efficacy (recanalization) of RA-EVT compared with manual procedures performed by operators with varying levels of experience in robotics, using a 3D printed neurovascular model.

MATERIALS AND METHODS

Study Design

Two neurointerventionalists with >3 years of clinical experience in robotic-assisted neuroendovascular embolizations (ie, robot-experienced) performed both manual EVT (MA-EVT, $n=18$) and RA-EVT ($n=24$). One experienced neurointerventionalist in training for the robotic procedure (ie, robot-novice) performed both MA-EVT ($n=6$) and RA-EVT ($n=13$) procedures. Due to the exploratory nature of this pilot feasibility study, the total number of experiments performed by each interventionalist was not predefined on the basis of efficacy assumption; a total number between 19 and 21 experiments per operator was decided.

Neurovascular Flow Loop Model

The neurovascular model was based on the vascular anatomies extracted from anonymized CTA images. The manufacturing procedure comprises the following steps: medical image segmentation to generate the preliminary 3D geometry of the vascular anatomy; mesh modeling to simplify the anatomy and prepare a

printable model; 3D printing setting; postprinting processing and assembly.

Data in the DICOM format was imported and loaded in 3D Slicer (<http://www.slicer.org>),^{8,9} where opacity threshold segmentation was performed to obtain the preliminary 3D geometry of the model. The preliminary 3D geometry was exported to Autodesk Meshmixer (<https://meshmixer.com/>)¹⁰ for the modeling stage and exported to PreForm (Formlabs) to configure the printing material, resolution, optimal geometry orientation, and support structure for 3D printing. The model was printed with commercially available photopolymer resin Elastic 50A at a resolution of 100 μm with a Form 3 SLA printer (Formlabs). The postprinting process consisted of removing support structures from the model, a 10-minute dip in isopropyl alcohol, and exposure to 305-nm ultraviolet light at a temperature of 60°C for 10 minutes. After the postprocessing, the model parts were assembled to constitute the final version of the neurovascular model, which includes the aortic arch, bilateral carotid arteries, MCAs (up to 2 distal M2 MCA branches), anterior cerebral arteries (up to the proximal A2), anterior communicating artery, posterior communicating arteries, and posterior cerebral arteries (up to the proximal P2 posterior cerebral artery segments).

The neurovascular model was connected in a flow-loop setup to mimic blood circulation. The experimental setup comprised a hydraulic pump recirculating saline solution at 800 mL/min, a 3D printed model, and a 100- μm filter at the outflow of the model to collect the periprocedural emboli. All elements were connected through a silicone tubing system. To simulate the transfemoral access, we connected an 8F sheath attached to a silicone tube to the descending aorta. An inflow filter was added between the hydraulic pump and the neurovascular model to filter out the undesired particles introduced into the system by reused devices.

Experimental Thrombectomy Setup

The study was performed using biplane angiography (Clarity, Philips Healthcare): As previously described,¹¹ 2 $\times$ 4 mm (radioopaque) clot analogs were made from porcine blood and used to create arterial occlusions in a benchtop 3D printed model (Fig 1A).¹²

The CorPath CRX robot, consisting of a control console and a robotic unit equipped with an extension arm that can hold a single-use cassette, was installed in the interventional neuroradiology section. The control console, enabling the operator to perform procedures comfortably while seated, was placed in the RX control

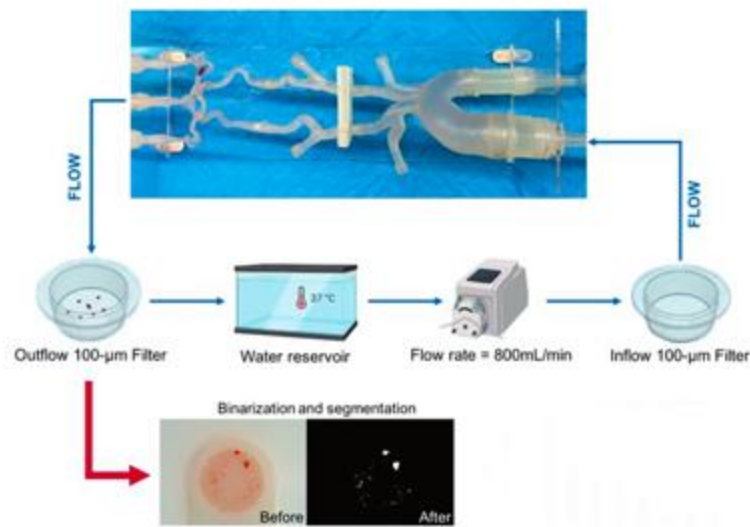


FIG 2. Experimental setup for robot-assisted and manual EVTs.

room. The extension arm and robotic unit were positioned on the lateral side of the table in the angiosuite. A single-use cassette was loaded with a microcatheter and a balloon guide catheter (BGC) (Gateway; Stryker), both of which were connected to the neurovascular model.

The robotic system is currently unable to perform catheterization of the aortic arch because it is limited to an advancement movement of 20 cm. An initial assessment of the optimal positioning of the different devices was performed. Due to the above-mentioned limited range of movement of the microcatheter when using the robot, the limiting factor to reach and cross the clot with the microcatheter is the initial position of the BGC in the ICA. We identified the lowest point in the ICA in which the tip of the BGC should be manually positioned before initiating the RA-EVT for different occlusion locations (Fig 2) and decided to place it in the vertical part of the petrous segment of the ICA. Given this limitation, RA-EVT was considered optimal for occlusions located in the ICA and in the M1 segment of the MCA and in any case beyond the proximal M2 branches.

After clot embolization, experiments were allocated into one of the following treatment arms: 1) robot-experienced/MA-EVT; 2) robot-experienced/RA-EVT; 3) robot-novice/MA-EVT; 4) robot-novice/RA-EVT. A 6F BGC was manually advanced by an experienced specialist nurse to the level of the distal ICA, then a 0.021-inch microcatheter (Phenom 21; Medtronic) was manually advanced to the level of the tip of the BGC. For RA-EVT procedures, the microcatheter and a 0.014-inch microguidewire (Synchro 2; Stryker) were then connected to the CorPath GRX robot by a trained assistant nurse; the neurointerventionalist could take control of the system from the console located in the control room outside the angiosuite (Fig 1).

The thrombectomy technique, manual and robot-assisted, consisted of navigating the microcatheter under fluoroscopy to the

MCA to cross the clot and then deploy a 4 × 40 mm stent retriever (SR; Solitaire X; Medtronic) from the M2 to the M1 segment of the MCA. After an embedding time of 1–2 minutes, the BGC was inflated and the SR was retrieved into the BGC under proximal flow arrest and continuous pump aspiration (Penumbra) (Fig 1C). For RA-EVT device exchanges in the robotic system, balloon inflation/deflation and aspiration were performed at the neurointerventionalist's indication, executed by an assistant nurse.

Each experiment consisted of a single pass per embolized clot. The primary outcome was first-pass recanalization (TICI 2c–3); the secondary outcome was the characterization of the collected distal emboli after each experiment.¹³ The duration of the MT procedure was defined as the moment when the neurointerventionalist first initiated control of the console and began maneuvering the microcatheter, until completion of the first pass.

Characterization of Distal Emboli

Characterization of generated distal emboli has been performed as previously described.¹² The distal segments of the neurovascular model have vessels as narrow as 1 mm. Thus, most embolized particles would end up in the filter located at the outflow of the model. An RGB image of the particles in the filter was captured with a high-resolution digital camera (IPEVO, Inc., Sunnyvale, California) to analyze the emboli generated after each pass. Then, the RGB images were processed by an image-processing algorithm developed on Matlab R2020a (MathWorks). The algorithm comprises 2 primary stages: 1) RGB image binarization, which involves highlighting the emboli ("1") and removing the background ("0") (Fig 2); and 2) quantification of the major-axis length of each particle, using a circle of known dimensions as a reference. Additionally, the algorithm provides output such as the overall particle count as well as the number of emboli of > 1 mm.

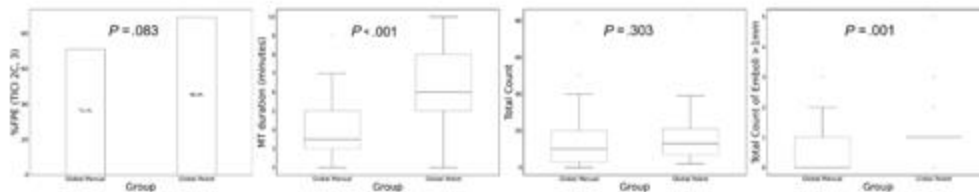


FIG 3. Boxplot analysis shows the difference in median values of various outcomes of thrombectomy (such as recanalization rate, procedural length, and distal emboli generation) when comparing all RA-EVTs and all MA-EVTs. FPE indicates first-pass effect.

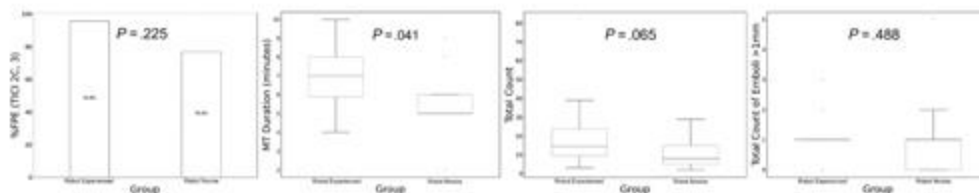


FIG 4. Boxplot analysis shows the difference in median values of various outcomes of thrombectomy (such as recanalization rate, procedural length, and distal emboli generation) when comparing robotic-EVT performed by a robotic-experienced interventional neuroradiologist and robotic-EVT performed by a robot-novice interventional neuroradiologist. FPE indicates first-pass effect.

Statistical Analysis

Results were expressed as mean (SD). Data were analyzed using the SciPy library from Python (<https://scipy.org/>). Normality was tested with Shapiro-Wilk test, and the Mann-Whitney *U* test was used to evaluate differences between RA-EVTs and MA-EVTs. Multiple subgroup analyses were performed to assess the safety and efficacy of the procedure among the 4 treatment arms using a χ^2 test.

As a subgroup analysis, differences in different outcomes (ie, final recanalization rate, number and dimension of emboli, and duration of the MT procedure) were compared between RA-EVT performed by a robot-experienced interventionalist and RA-EVT performed by a robot-novice neurointerventionalist who all had the same levels of experience in MT procedures (>10 years).

Statistical significance was $P < .05$.

RESULTS

We conducted a total of 82 experimental EVT: 37 RA-EVTs and 45 MA-EVTs. Each interventionalist performed between 19 and 21 experiments. There were no robotic system failures or incidents that required the technician to step in during the thrombectomy attempts.

Robot-Assisted EVT versus Manual EVT

Overall, when comparing all RA-EVTs ($n = 37$) versus all MA-EVTs ($n = 45$), nonsignificant trends were observed in terms of the final recanalization rate in favor of RA-EVT: 89.2% versus MA-EVT: 71.1%; $P = .083$. The distal emboli analysis revealed a similar mean total count of particles (RA-EVT: 16.54 [SD, 15.15] versus MA-EVT: 15.16 [SD, 16.43]; $P = .303$); however, a significantly mean higher number of emboli of >1 mm in diameter were observed in the RA-EVT (1.08 [SD, 1] versus 0.49 [SD, 0.84]; $P = .001$). In addition, the mean RA-EVT procedural length was

significantly longer (RA-EVT: 6.43 [SD, 1.71] minutes versus MA-EVT: 3.98 [SD, 1.84] minutes; $P < .001$) (Fig 3).

Robot-Experienced versus Robot-Novice Interventionalists

To assess the impact of the operator's prior experience in the use of the robot, we compared outcomes in experiments performed by robot-experienced ($n = 24$) and robot-novice ($n = 13$) interventionalists (Online Supplemental Data). The observed recanalization rates were 95.8% among the robot-experienced interventionalist and 76.9% among the robot-novice interventionalist ($P = .225$). No significant differences were observed in terms of total emboli count ($P = .065$) or number of emboli of >1 mm ($P = .488$). However, the mean procedural length was found to be slightly-but-significantly longer for robot-experienced (6.85 [SD, 1.54] minutes) compared with robot-novice neurointerventionalists (5.65 [SD, 1.80] minutes; $P = .041$) (Fig 4).

DISCUSSION

In this pilot study, we aimed to characterize the procedural setup and feasibility of performing MT with a robotic-assisted device using a 3D vascular model. We determined that the current robotic features allow an adequate setup to perform RA-EVT in intracranial occlusions located up to the proximal segments on the M2 MCA branches using BGCs and an SR. Thus, patient anatomy should allow navigation of the BGC up to the C2-C3 segments of the ICA. In these conditions, intracranial RA-EVTs performed by physicians with different levels of expertise in the use of the robot were able to achieve similar recanalization rates compared with MA-EVT. RA-EVT may not appear to provide a substantial advantage on its own; however, the current results present opportunities for future scenarios in which skilled neurointerventionalists could potentially perform the intracranial part

of a MT remotely on patients located in distant centers without specialized interventionalists.

In our study, the mean procedural time was slightly higher in the robotic arm compared with the manual procedure, particularly among physicians with experience in robotic procedures. However, in a potential scenario of remote RA-EVT, the absolute increase in the RA procedural time could be neglected if compared with the delays associated with transferring a patient to a comprehensive stroke center to receive EVT.

Furthermore, we aimed to test the safety of the procedure in terms of generation of distal emboli. Overall, our study showed that the total count of generated distal emboli is similar between RA-EVT and MA-EVT. However, we observed a significantly higher number of emboli of >1 mm in the RA-EVT group, which deserves special attention. These results may have been influenced by the use of a 3D plastic model because the friction coefficients between the clot/devices and the vessels are higher than those in human arteries. However, we cannot exclude the possibility that this high rate of clots of >1 cm may be due to the operator's lack of experience with the robot, including performing a procedure in the absence of haptic feedback. Nevertheless, we believe that in the preliminary phases of developing a device, it is important to collect data on the physician's performance with the device, because the data may provide insight into characteristics of the device and help identify areas for improvement. We anticipate that both operator experience and device performance can be improved in the future.

A possible explanation may lie in the relative absence of compliance with the current version of the robotic system when pushing the microcatheters across the thrombus. During manual procedures, the interventionalist can modulate the applied force to gradually advance the microcatheter, avoiding sudden tension releases of the system; however, this step may be more challenging with RA-EVT. Sudden tension releases of the system may also be exacerbated by the increased vessel wall friction of the 3D models compared to a patient's arteries. However, robotic systems have the potential to include automatic compensation and adjustment systems with the ability to optimize microcatheter navigation through the occluding clots.

Most interesting, expert physicians in robot handling achieved results similar to those of physicians with limited robotic exposure (Fig 4), suggesting that spreading this new technology with short learning curves among neurointerventionalists may be relatively straightforward.

Future developments of regional networks will likely consider performing a local MT by an interventionalist not dedicated to neuroendovascular procedures or opting for a remote RA-EVT performed by skilled neurointerventionalists to ensure universal and timely endovascular treatment of patients with stroke with large-vessel occlusions.

To our knowledge, this is the first study that explores the feasibility of robotic assistance in the intracranial part of the MT. Our results suggest that further adjustments will make implementation of this technology possible in assisting acute ischemic procedures in rural areas, thus massively reducing workflow times.

The current CorPath GRX technology still presents limitations that prevent the immediate application of the studied model in clinical practice: It is currently unable to perform the catheterization of

the supra-aortic trunks and deliver the microcatheter up to the clot occlusion. Moreover, the main limitation is the limited range of motion and the impossibility of controlling triaxial catheter systems, preventing the use of intermediate distal-access catheters that provide support during microcatheter navigation and allow distal aspiration.

Our pilot study aimed to provide a preliminary assessment of the feasibility of technology to assist in performing intracranial MT and to generate initial efficacy data. Our results are promising and represent a necessary step toward the implementation of robotics in MT procedures. In the future, integration of acquired vessel imaging, such as CTA or angiography, with the robotic system may enable the robot to recognize the anatomy and offer an assisted navigation in cases of challenging anatomy. Such development allowing a faster, more precise, and safer procedure may facilitate the expansion of an adoption of robotic procedures among less experienced operators or for remote assistance in rural regions.

Limitations

Our study has several limitations. A limited number of operators participated in the study, which may have affected the comparability of the observed outcomes among the various study groups. However, the operators—each having a varying level of experience—conducted multiple experiments to simulate multiple scenarios. Another important limitation is the use of a single 3D printed model, which is a significant constraint due to its limited comparability with real patients. Despite the neurovascular model being internally coated with hydrophilic agents, the friction coefficients between the clot/devices and the vessels are generally higher than those observed in human arteries. This difference may partially explain the increased number and size of distal emboli observed in the RA-EVT arm. Additionally, the model exhibits higher resistance to perforation than in vivo conditions, which hinders the assessment of such complications. Furthermore, a single 3D model was used precluding the wider evaluation according to anatomic variations. We concur with the importance of further exploring the use of robotics to support the catheterization of challenging anatomies in future studies with new iterations of the robotic devices.

CONCLUSIONS

In a 3D printed neurovascular model, RA-EVT has the potential to achieve recanalization rates comparable with MA-EVT within competitive procedural times. Optimization of the procedural setup is still required before implementation in clinical practice.

Disclosure forms provided by the authors are available with the full text and PDF of this article at www.ajnr.org.

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SUMMARY OF RESULTS

5. Summary of results

5.1. The ANAIS Study

The results of the trial are consistent with findings reported in the literature for similar devices. The primary endpoint—successful reperfusion, defined as eTICI ≥ 2 within three passes—was achieved in 70% (30/43) of patients in the ITT population and 81% (26/32) in the PP population. First-pass eTICI 2–3 rates were 44% (19/43) in the ITT group and 56% (18/32) in the PP group. No serious adverse device events (SADE) or symptomatic intracranial hemorrhages (sICH) were observed at 24 hours (0/43).

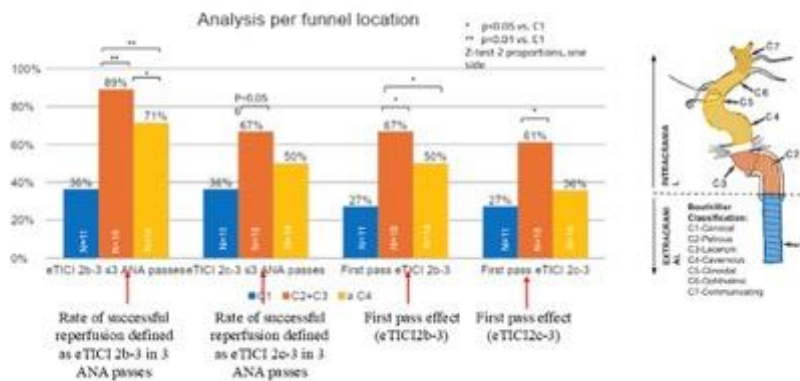
Subgroup analysis per funnel location

In this graph, we illustrate the rate of successful reperfusion according to different definitions (e.g., eTICI $\geq 2b50$ within three passes, or eTICI 2c–3), as well as the rate of first-pass eTICI 2b–3 and eTICI 2c–3. Across all metrics, higher success rates were observed when the funnel was deployed in segments proximal to or above the C2 level of the internal carotid artery.

A) ITT population (n=43): analysis per funnel location⁵

ITT population (n=43): analysis per funnel location⁵

⁵ based on performance questionnaires data

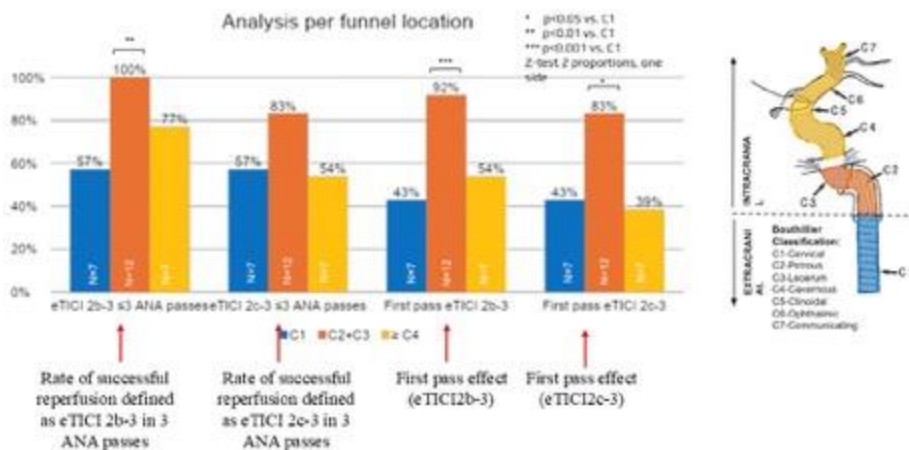


Similar results were observed in the PP population, further supporting that C2 was the optimal position for funnel deployment as identified by the interventionalists.

B) PP population (n=32): analysis per funnel location⁵

PP population (n=32): analysis per funnel location⁵

⁵ based on performance questionnaires data

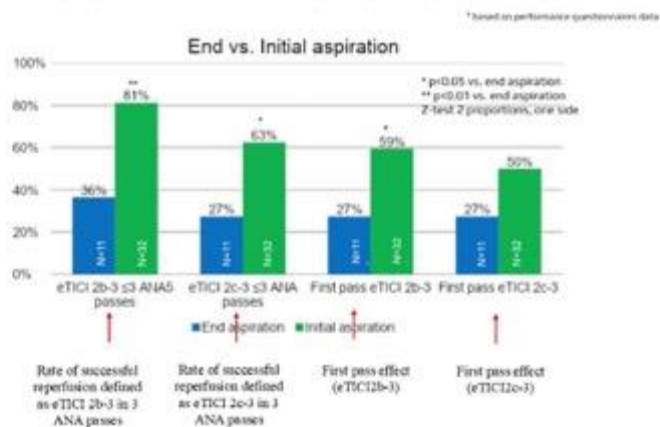


Subgroup analysis per aspiration type

A comparative analysis was conducted as well to evaluate continuous aspiration (initiated with stent retriever withdrawal and maintained throughout, N=32) versus end aspiration (initiated only once the retriever entered the funnel, N=11)

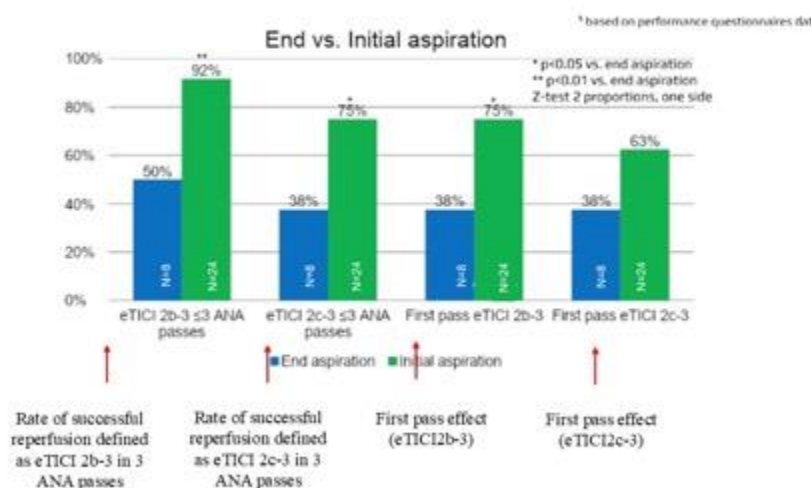
This graph shows the rate of successful reperfusion according to various definitions (e.g., eTICI $\geq 2b50$ within three passes, or eTICI 2c–3), as well as first-pass eTICI 2b–3 and eTICI 2c–3 rates. Across all metrics, higher success rates were observed when aspiration was applied from the beginning of the retrieval maneuver—i.e., from the moment the stent retriever was first pulled back and maintained throughout the entire process.

A) ITT population (n=43): analysis per aspiration type⁶



The results were confirmed in the PP population, thus suggesting that when performing a mechanical thrombectomy with the ANA System the aspiration should start when the stent retriever is first pulled back and maintained throughout the entire process

B) PP population (n=32): analysis per aspiration type⁶



5.2. The TWIN2WIN Study

Between April 2022 and October 2023, a total of 108 patients were enrolled in the study—50 assigned to the single stent retriever (SR) group and 58 to the double-SR group. First-pass reperfusion (FPR) was achieved in 24% of patients treated with the single-SR approach, compared to 46% in those treated with the double-SR technique. This represents a statistically significant difference, with an adjusted odds ratio (aOR) of 2.72 (95% CI, 1.19–6.46), favoring the double-SR strategy.

When looking at substantial reperfusion within three passes, rates were slightly higher in the double-SR group (89%) compared to the single-SR group (84%), although this difference did not reach statistical significance (aOR 1.74; 95% CI, 0.55–5.76). On average, fewer passes were needed in the double-SR group (1.7 ± 1.0) versus the single-SR group (2.0 ± 1.3), with a mean difference of -0.37 passes (95% CI, -0.79 to 0.06).

Regarding safety, symptomatic intracranial hemorrhage (sICH) occurred in 6% of patients in the single-SR group and in 10% of those in the double-SR group (aOR 1.66; 95% CI, 0.40–8.35), with no significant difference between the groups.

Table 1 - Efficacy and safety outcomes of TWIN2WIN Study.

	Single-SR (N=50)	Dual-SR (N=58)	Treatment effect [IC - 95%]	P value	Effect measure
Primary efficacy outcome First-pass complete recanalization (eTICI 2C-3)	12 (24%)	27 (47%)	2.72 (1.19 to 6.46)	0.02	Odds ratio
Secondary efficacy outcome Successful reperfusion within 3 passes (eTICI 2B-3)	42 (84%)	52 (89%)	1.74 (0.55 to 5.75)	0.34	Odds ratio
Time from groin puncture to reperfusion Median (IQR)	36 (27-57)	39 (27-63)	6 (-4 to 16)	0.26	Mean difference
Number of passes Median (IQR)	3 (2-3)	2 (2-3)	-0.37 (-0.79 to 0.06)	0.09	Mean difference
NIHSS at 24 hours Median(IQR)	13 (4-20)	10 (3-20)	-1.1 (-4.9 to 2.6)	0.54	Mean difference
mRs 0-1 at 5 days or discharge	9 (18%)	12 (20%)	1.18 (0.45 to 3.20)	0.74	Odds ratio
mRs 0-1 at 90 days	7 (14%)	16 (28%)	2.31 (0.88 to 6.69)	0.1	Odds ratio
Primary safety outcome Symptomatic intracerebral haemorrhage (SICHs)	3 (6%)	6 (10%)	1.66 (0.40 to 8.35)	0.5	Odds ratio
Secondary safety outcome Intracerebral haemorrhage	10 (20%)	18 (31%)	1.78 (0.73 to 4.51)	0.21	Odds ratio

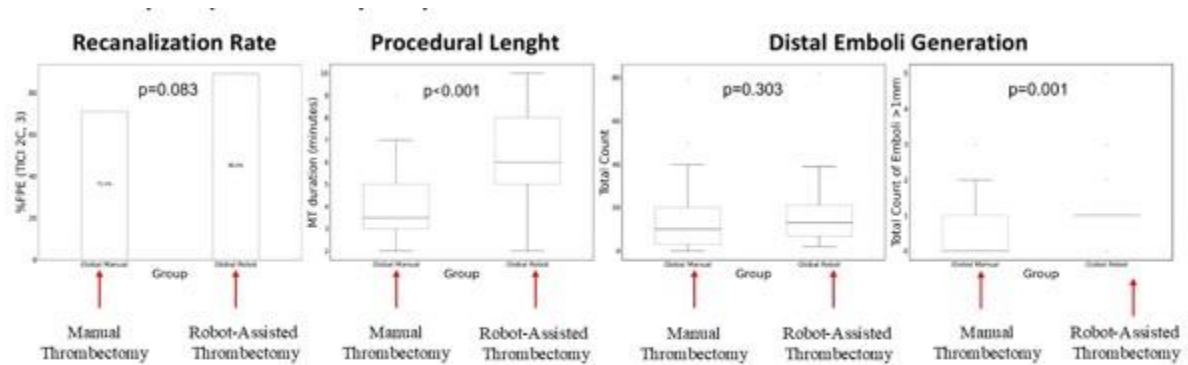
Neurological deterioration (≥ 4 points on NIHSS) at 24h	6 (12%)	9 (16%)	1.15 (0.37 to 3.76)	0.81	Odds ratio
Embolization in a previously uninvolved territory	1 (2%)	1 (2%)	0.96 (0.03 to 25.38)	0.98	Odds ratio
Procedure-related mortality at 5 days or discharge	1 (2%)	2 (3%)	1.78 (0.16 to 39.73)	0.64	Odds ratio
Procedure complications	3 (6%)	5 (9%)	1.38 (0.32 to 7.15)	0.6687	Odds ratio

Table 1: Efficacy and safety outcomes (SR: Stent Retriever, eTICI: expanded Thrombolysis in Cerebral Ischemia, NIHSS: National Institutes of Health Stroke Scale, mRS: modified Rankin Scale, sICH: symptomatic Intracerebral Hemorrhage).

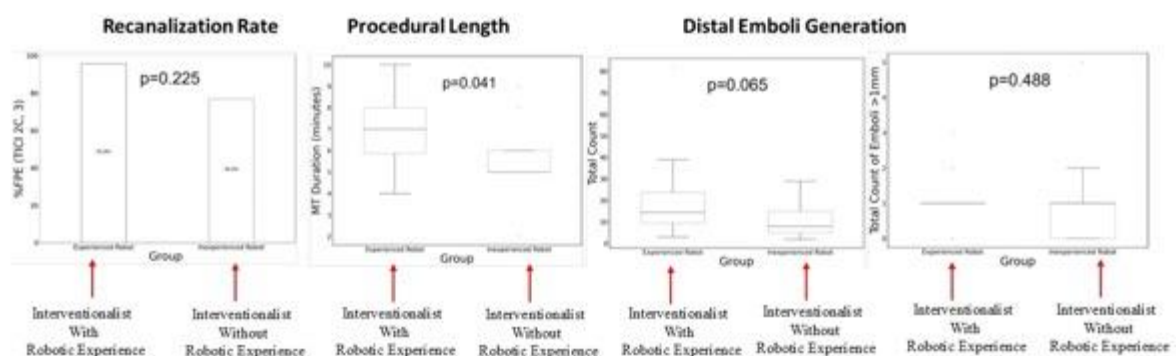
5.3. The Core Flow Study

We observed no significant difference in the recanalization rate (measured as the prevalence of TICI 2b/c) between mechanical thrombectomy performed manually and robot-assisted mechanical thrombectomy. The only difference observed was a slight increase in procedural duration in the robot-assisted group.

Moreover, the number of emboli generated was similar between the manual and robotic thrombectomy procedures. However, the emboli produced during robot-assisted procedures were generally smaller in size.



Interestingly, there was no difference in the metrics achieved by the interventionalists with and without prior experience.



SUMMARY OF THE DISCUSSION

6. Summary of the discussion

The studies presented in this thesis demonstrate that advancements in various technical aspects can significantly enhance the angiographic outcomes of mechanical thrombectomy procedures, with the potential to positively impact clinical results.

Moreover, this research poses the basis for the future implementation of mechanical procedures through telerobotic systems in remote or underserved areas.

Key findings of this thesis include the improved performance achieved by positioning devices in more distal segments of the carotid artery—likely due to increased catheter stability in the intracranial arterial segments—as well as the enhanced efficacy associated with the use of dual stent retrievers, which may increase the rate of successful reperfusion on the first pass, likely through the reduction of thrombus fragmentation.

These innovations allow for more precise adaptation of the endovascular therapeutic approach, contributing to improved clinical outcomes.

In the first study, the ANAIS study, (Mechanical thrombectomy using the ANAconda device in combination with a stent retriever in subjects with Acute Ischemic Stroke) we evaluated the clinical performance of a newly developed mechanical thrombectomy device and compared the results according to different technical approaches, such as the positioning of type of the catheter (called funnel) and the timing of the use of aspiration.

An analysis of the impact of funnel location on radiological outcomes revealed significantly better recanalization rates when the funnel was positioned in the higher intracranial petrous-lacerum segments of the ICA, compared to lower performance when placed at the lower cervical (extracranial) segment. Interestingly, similar findings have been observed with other types of balloon guiding catheters, where efficacy is maximized when positioned more distally in the cervical ICA during thrombectomy (31, 32, 33, 34, 35, 36).

Potential reasons might be that the cervical extracranial ICA (33), since surrounded by the neck's soft tissue, may be prone to collapse during forced aspiration if a BGC or a funnel is positioned too proximal. In contrast, the intracranial petrous ICA is likely more resistant to collapse due to a thick periosteal layer attached to both the vessel and the petrous bone³⁴. The collapse of the cervical ICA can reduce suction force and increase the risk of dissection. Additionally, it may cause shearing of the trapped clot during stent retrieval, potentially resulting in distal emboli.

Furthermore, the study demonstrates a distinct benefit of using continuous aspiration, compared to aspiration applied only at the end of the process, in achieving successful recanalization and high first-pass success rates. These results are interesting but not surprising. In contrast to end-aspiration, continuous aspiration from the initiation of the retrieval maneuver, combined with the antegrade flow restriction created by the deployed funnel, might create a flow reversal that facilitates the ingestion of the main clot and potential fragments into the funnel. This suggests the advantage of initiating aspiration from the beginning of the stent retrieval procedure, likely due to reduction of fragmentation.

Broadly speaking, the findings of the ANAIS study are particularly significant, as they emphasize the critical need for newly developed devices or materials to be thoroughly

understood and effectively adopted by the clinical community— in this case by neurointerventional radiologists. Absent this integration, even the most promising technologies may fail to achieve their intended clinical impact. As results of this ANAIS study, the results were used to correctly design the ATHENA trial, a regulatory study that is currently ongoing that that should lead to approval by the US and European agencies.

In the second study, our findings suggest that the first-line use of the double stent retriever technique is not only safe but also significantly more effective in achieving first-pass reperfusion compared to the single stent retriever approach. Although the study was not powered to assess clinical outcomes associated with this improvement, the observed enhancement in early reperfusion may nonetheless hold clinical relevance.

Our results indicate that the double stent retriever as a first-line strategy in cases with challenging vascular anatomies, particularly at the carotid terminus (23), the M1 segment of the middle cerebral artery, and the basilar tip, where thrombi tend to be more resistant to removal. The use of two stent retrievers provides increased metallic coverage and stabilization, potentially improving clot engagement and reducing the risk of thrombus fragmentation or distal embolization during retrieval.

However, it is important to consider preclinical evidence suggesting a potential increase in vascular wall injury associated with the use of dual stents (24), even if this did not compromise vessel patency, as well as the in vitro study in which we demonstrated the improved efficacy of double stent retrievers in occlusions near arterial bifurcations (37).

Therefore, an optimal balance must be achieved—minimizing the number of passes required while tailoring the technique to the patient's specific anatomical and clinical characteristics.

Interestingly, the positive results of the TWIN2WIN study have encouraged the design of a subsequent randomized clinical trial, TWIN2WIN2, which is currently ongoing. In this trial, we aim to evaluate whether the technique not only improves angiographic outcomes but also has a clinical impact by reducing disability at 3 months.

In the last study, we demonstrated the feasibility of performing mechanical thrombectomy using the Corindus robotic system in a 3D-printed neurovascular model.

Our results suggest that robot-assisted thrombectomy has the potential to achieve recanalization rates comparable to manual procedures, with competitive procedural times and without requiring a steep learning curve. This study is particularly relevant for remote areas in various regions where no centers capable of performing mechanical thrombectomy are available.

The current results present opportunities for future scenarios where skilled neurointerventionalists could potentially perform the intracranial part of a mechanical thrombectomy remotely on patients located in distant centers without specialized interventionalists.

Improving the performance of mechanical thrombectomy is a critical priority in stroke care, given that stroke remains a leading cause of death and long-term disability worldwide. Timely

and effective intervention is essential for optimizing patient outcomes. Technical advances in thrombectomy techniques have a direct impact on survival rates and post-stroke quality of life. By continuously refining and innovating approaches—such as the use of flow restriction catheters, double stent retriever strategies, and robotics in neurointervention—we can significantly enhance the efficacy, safety, and accessibility of acute stroke treatments. These technological developments hold the potential to reduce time to reperfusion, increase the success rates of procedures, and minimize periprocedural complications. Collectively, such improvements contribute to better patient prognoses and more efficient utilization of healthcare resources.

CONCLUSIONS

7. Conclusions

In conclusion:

- 1) In our clinical experience, the ANA funnel catheter in combination with a stent retriever achieved a high rate of complete recanalization and a high first pass success, with a good safety profile and favorable 90-day clinical outcomes. The successful reperfusion rate was significantly higher when the funnel was located above the C1 cervical segment of the ICA and when continuous aspiration was applied during the retrieval procedure.
- 2) In stroke patients undergoing mechanical thrombectomy, first-line double-stent retriever is superior to single-stent retriever in achieving first pass but not final recanalization. Implications on safety and clinical outcomes should be further studied in specifically designed trials.
- 3) Robotic-assisted mechanical thrombectomy has shown the potential to achieve recanalization rates comparable to manual mechanical thrombectomy within competitive procedural times, as demonstrated in a 3D printed neurovascular model. Interestingly, expert physicians in robot handling achieved results similar to those of physicians with limited robotic exposure, suggesting that spreading this new technology with short learning curves among neurointerventionalists may be relatively straightforward.

FUTURE RESEARCH LINES

8. Future research lines

While we observed in the ANAIS study that all the measures taken to improve catheter stability led to better angiographic outcomes, further technological improvements are necessary to enhance catheter navigability. Increased navigability could potentially reduce the duration of mechanical thrombectomy procedures. Moreover, additional multicenter studies are required to confirm the clinical impact of these improvements.

Our double stent retriever technique has proven to be effective in increasing the likelihood of achieving a first-pass effect, even in the absence of an improvement in final reperfusion. However, new studies with adequate statistical power are needed to confirm whether this approach truly results in improved clinical outcomes.

The potential impact of robotics on medical practice extends beyond procedural improvements. It represents a paradigm shift in how we understand and execute medical treatments. Robotics can facilitate remote mechanical thrombectomy allowing experts to perform interventions on patients in remote areas where no interventional neuroradiologist can always be present on call. This capability addresses geographical barriers and ensures that patients receive the best possible care regardless of their location.

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