The Influence of Vessel Curvature and Thrombus Composition on the Effectiveness and Outcomes of Thrombectomy in the Case of Acute Ischemic Stroke

Pedro Lylryk1, Andrii Netliukh2,3, Oleh Kobyletskyi1,3, Oleksander Holub3, Andrii Sukhanov2,3

1Clinica La Sagrada Familia in Buenos Aires, Argentina
2Danylo Halytskyi Lviv National Medical University, Lviv, Ukraine
3Municipal Non-profit Enterprise “Multidisciplinary clinical hospital of intensive care and emergency medical care” (MNE “First Territorial Medical Association of Lviv”), Lviv, Ukraine

Introduction. It is believed that vascular anatomy has a direct influence on the complexity and course of mechanical thrombectomy, and its outcome determines the degree of reperfusion and clinical effect.

Aim. To analyze the influence of the curvature of the intracranial arteries and the composition of the thrombus on the results of thrombectomy.

Materials and methods. 64 patients who underwent mechanical thrombectomy for acute proximal occlusion of the ICA or MCA were prospectively examined. (44 men/20 women among them, the age of the patients ranged from 47-89 years (67.2±1.2). The study was performed by measuring the ICA-M1 angle on angiograms in direct projection. Angles were compared between patients with successful (mTICI group 2b/3) and unsuccessful (mTICI group 0-2a) reperfusion. The functional result was evaluated according to the mRS scale as positive (0-3) and negative (4-5). Removed thrombi were examined by light microscopy with hematoxylin-eosin and orange-red-blue staining.

Results. Among patients of the mTICI 2b/3 group, a larger angle of the ICA-M1 was measured (126.4±2.8°) compared to patients in the mTICI 0-2a group - 107.1±4.9° (p=0.05). Among patients with 1-2 passages, statistically significantly larger ICA-M1 angles were recorded (129.8±3.3°) than among patients with a number of passages >2 (109.2±5.7°), p<0.02. The duration of mechanical thrombectomy was <60 min among patients with larger angles of the ICA-M1 (127.6±4.4° vs. 119.6±4.5°) than in patients with long interventions (>60 min) (p=0.05). Successful reperfusion (group mTICI 2b/3) was achieved in 47 (73.4%) patients. A clinically positive result (mRS 0-3) was observed among 37 (57.8%) patients.

During microscopic examination of thrombi among patients groups mTICI 0/2a, fibrin threads with signs of aging with purple and blue color were present on the periphery (24-48 hours). With a favorable outcome of the operation, the coagulated fibrin fibers were stained red (<16 hours).

Conclusions. With a smaller curvature of the ICA and its branches, and in the presence of “fresh” thrombi, the efficiency of operations increases, and the number of passages and the duration of mechanical thrombectomy decrease. The neurological status of patients at admission correlates with the functional outcome at the time of discharge.

Keywords: Large vessel occlusion, acute ischemic stroke, mechanical thrombectomy, thrombus composition.
Introduction

Stroke is the second leading cause of death and the third leading cause of disability worldwide [1]. Acute cerebrovascular event is a typical neurological emergency, especially in low- and middle-income countries, where a 100% increase in stroke incidence has been observed over the past four decades [2]. Acute ischemic stroke (AIS) (one of two main stroke subtypes) results from brain ischemia caused by cerebral vascular thrombosis [3].

Before the introduction of mechanical thrombectomy (MTE) as an endovascular treatment, thrombolysis using intravenous tissue plasminogen activator (tPA) was the only approved reperfusion therapy in the case of AIS. However, due to the narrow therapeutic window, it could only be used in a small percentage of patients with AIS [4]. In addition, studies show that intravenous thrombolysis is ineffective in large vessel occlusions [5]. A meta-analysis of MTE clinical trials showed that the probability of recovery for patients who underwent MTE is twice as high as for patients who only received systemic thrombolysis [6]. However, several other meta-analyses showed that mechanical thrombectomy is clinically ineffective in 30–40% of patients [7].

From a clinical perspective, it is essential to identify significant clinical, hematologic, and immunologic predictors of success or failure of mechanical thrombectomy, as well as components of the eliminated thrombus, and to assess the clinical outcome three months after treatment [8].

The introduction of MTE significantly improved reperfusion, which, in turn, contributed to the better restoration of neurological functions. At the same time, some patients with AIS still fail to achieve complete blood flow restoration (TICI 2b/3) – approx. in 10–25% of patients [9].

It has been suggested that several factors influence this. It is believed that the reperfusion results can be affected by the type and age of the removed thrombi, particularly the MTE time and the number of passages, as well as the connection with the probable clot dispersion in the distal parts of vessels. Studies show that fibrin-rich thrombi (white) are associated with an increased number of reperfusion maneuvers during the thrombectomy procedure and increased resistance to thrombolysis compared to red blood cell-rich thrombi (red) [10]. The acquired knowledge about the composition and properties of stroke clots can help develop new approaches for better detection and elimination of cerebral vascular occlusions.

There is currently no evidence that vessel anatomy affects the success of reperfusion in MTE. In the MTE study using the pREset retriever (Phenox, Bochum, Germany), successful reperfusion was significantly less likely in patients with a considerably curved middle cerebral artery (MCA) [11]. In patients with AIS after the MCA occlusion, Zhu et al. evaluated the thrombus configuration using gradient-echo MR images in axial cross-section and thus the vessel anatomy at the occlusion site. However, this method provides only indirect information about the vessel curvature, while the vessel anatomy proximal to the occlusion site cannot be analyzed [12].

The aim is to conduct an analysis of prognostic factors and the development of treatment tactics and the selection of optimal technical methods of operation by the method of mechanical thrombectomy in patients with acute ischemic stroke.

Materials and methods

We prospectively examined 64 patients who underwent mechanical thrombectomy due to acute occlusion by the ICA or MCA thrombus during acute ischemic stroke in the period from January 2021 to August 2022. All patients who started thrombolytic therapy were included in the study. They included 44 men and 20 women aged 47 to 89 (67.2±1.2 on average) with one of the following types of occlusion:

- Cervical ICA
- Terminal ICA bifurcation
- Proximal M1
- Distal M1 & Proximal M2
- Isolated M2

Upon admission, after collecting anamnestic data and assessing stroke severity according to the NIHSS scale under the protocol of the Ministry of Health, patients with AIS were evaluated using native and contrast-enhanced CT. Thereafter, depending on the therapeutic window, thrombolytic therapy was started, followed by the transition to
thrombectomy or immediate MTE. Three types of aspiration catheters were used during the study: React 5Fr and 6Fr, Navien 5Fr, SOFIA 5Fr and 6Fr; and two types of stents: Solitaire X 6 and 4x40mm and Solitaire Platinum 4x40mm and 4x20mm. The catheter and stent types used were selected on a case-by-case basis depending on the situation, toolkit, and operator requirements. Femoral approach was performed in all of the cases. The surgical catheter was placed proximally in the corresponding internal carotid artery, and the aspiration catheter was brought as close to the proximal edge of the thrombus as possible. A triaxial system was used to approach the corresponding ICA, and an aspiration catheter was placed adjacent to the thrombus.

We conducted a prospective review of radiological records and measured vessel curvature based on the DSA images: the angles between the terminal ICA and the M1 segment of the MCA (ICA-M1 angle), their diameter at the thrombus location, mainly in the M1 segment. Geometric details of the MCA segment change the direction up and down. Therefore, MCA angles are best visualized and evaluated in the anterior-posterior projection. This study also aimed to evaluate the information about prognostic cut-off values and the prevalence of unfavorable MCA anatomy. The radiological and clinical picture of successful reperfusion of occluded vessels was evaluated. Angiograms before and after MTE were evaluated according to the modified scale of thrombolysis in the case of cerebral ischemia (mTICI). Angles were compared in patients with successful (mTICI group 2b/3) and unsuccessful (mTICI group 0-2a) reperfusion. Any reperfusion was defined as TICI 2a, 2b or 3 score, and successful reperfusion – as TICI 2b-3. Major catheter-related complications were defined as catheter breakage, vessel perforation, arterial dissection, or embolization of previously unaffected distal branches. Vessel curvature and diameter were measured using the RadiAnt DICOM Viewer software and a special tool for angle measuring (Fig. 1). We also analyzed working projections made before and after vessel reperfusion.

The surgery was completed if 1) complete reperfusion was achieved; 2) partial reperfusion was achieved, but, the risk of further manipulations outweighed the potential benefit, or if the vessel was not opened after six passages with the stent retriever.

We also examined the histological composition and age of the removed thrombi.

We fixed the removed thrombi in formalin and examined them using light microscopy with hematoxylin-eosin and orange-red-blue (ORB) staining as modified by Zerbino D. D., Lukasevich L. L. The clinical result was analyzed depending on the effectiveness of the per-formed thrombectomy.

Follow-up scans (CT or MRI) were performed for all patients after 24 hours to assess hemorrhagic transformation. In the case of increasing neurological deterioration, additional MRI or CT scans were performed. Hemorrhages were evaluated as subarachnoid hemorrhage, remote cerebral hematoma, or ECASS (European Cooperative Acute Stroke Study) hemorrhagic infarction type 1 or 2, or parenchymal hematoma type 1 or 2. Symptomatic intracranial hemorrhage was defined as any intracranial hemorrhage associated with an increased ≥4 NIHSS score [13]. In the presence of early vascular signs of AIS on CT and MRI, including hyperdense middle cerebral artery (HMCAS) visualized on CT and the blooming artifact (BA) seen on MRI [10], thrombi are classified as rich in erythrocytes [14].

![Figure 1. The technique for measuring vessel curvature on angiograms in antero-posterior view](image-url)
Patients with HMCAS may respond to stent retrievers better compared to contact aspiration for higher first-pass efficiency [15].

Functional outcome was assessed at discharge from the ward and ~90 days after the stroke. The score was established using the NIHSS and Modified Rankin Scale (mRS). The mRS ranges from 0 to 6, where 0 means no symptoms, and 6 means death. The score of 4 to 6 mRS points was interpreted as a poor clinical result, while 0–3 was deemed a good clinical result.

**Results and Discussion**

Angles were measured on the final control angiograms of all selected patients, including those with T-occlusions of the carotid artery, and in cases where reperfusion was not achieved.

As the stent retriever is retracted toward the catheter through a highly tortuous vessel segment, the stent retriever may reduce its full spatial expansion, resulting in reduced thrombus capture and engagement strength (an effect described as “tapering”). Considerably curved vessels can increase friction between the walls of vessels, catheters, and the conductor, which prevents the thrombus passage and removal. During thrombus removal, a change in vessel anatomy may be observed. When traction is applied to the unfolded stent retriever, the latter transmits this tension to the vessels, causing vessel segments to shorten proximally and lengthen distally to the stent deployment site. This effect is more pronounced in highly curved vessels and can further increase the angles and friction between the thrombus and the vessel wall [16]. Tortuous vessels are not associated with a significantly increased number of post-procedural complications, such as thrombus dispersion, vessel perforation, or intracranial hemorrhage [17]. There is no significant advantage of any of the stent retrievers used over other designs in patients with curved vessels, even though recently developed stent retrievers have been designed to provide greater stability during thrombus removal from considerably curved vessels and, therefore, the phenomenon of “tapering" should be avoided [16].

Alternative techniques, such as forced aspiration, should be evaluated in patients with curved vessels, as reperfusion rates of up to 95% have been reported for this technique [18]. Several studies on forced aspiration have shown conflicting results; however, none of these studies analyzed vascular anatomy as a factor influencing reperfusion success [19].

In patients of the mTICI 2b/3 group, a larger ICA-M1 angle was noted (on average, 126.4±2.8°) compared to patients in the mTICI 0-2a group – 107.1±4.9° (p=0.05) (Fig. 2).

![Figure 2. Angiograms in antero-posterior projection. a – mTICI group 2b/3; b – mTICI group 0-2a](image)

In patients with AIS, two angiographically similar occluded vessels may respond differently to mechanical thrombectomy for not angiographically apparent reasons [14]. A study examining whether the speed of removal affected the effectiveness of clot removal found that rapid extraction gave a stronger advantage to fibrin-rich clots. Fast extraction quickly mobilizes the clot, allowing a higher pulling force [14]. Vessels occluded by fibrin-rich thrombi also require more passages during MTE to achieve reperfusion compared to vessels occluded by erythrocyte-rich thrombi [20].
In our patients, when a small number of passages with a catheter or stent (1–2) were required during MTE, statistically significantly larger ICA-M1 angles were recorded (on average 129.8±3.3°) than in patients with several passages >2 (109.2±5.7°, p<0.02).

The duration of mechanical thrombectomy was <60 min in patients with larger angles of ICA-M1 vessels (on average 127.6±4.4° vs 119.6±4.5°) than in patients with long interventions (≥60 min). The difference was statistically significant (p<0.05) (Tab. 1).

**Table 1. The results and course of surgical interventions in patients with MTE depend on the size of the ICA-M1 angle (in °)**

<table>
<thead>
<tr>
<th>mTICI 2b/3</th>
<th>mTICI 0-2a</th>
<th>&gt;2</th>
<th>&lt;60 m</th>
<th>≥60 m</th>
</tr>
</thead>
<tbody>
<tr>
<td>126.4±2.8°</td>
<td>107.1±4.9°</td>
<td>109.2±5.7°,</td>
<td>127.6±4.4°</td>
<td>119.6±4.5°</td>
</tr>
</tbody>
</table>

The study conducted by Girdar et al. (2020) demonstrated that using a new-generation stent retriever that is longer and/or bigger in diameter improves the success of the first-pass fibrin clot retrieval while not increasing the risk of vascular damage [21]. Another study indicated that the thrombus length does not significantly affect the success rate of MTE reperfusion [22].

We measured the diameter of blood vessels in the thrombus projection in the M1 segment of the middle cerebral artery, and it was 1.82 mm on average. There was no statistically significant difference in the diameter of blood vessels in patients from the studied groups.

The functional result was evaluated using the mRS scale as positive (group mRS: 0–3 points) and observed in 57.8% of patients and negative (group mRS: 4–6 points) in 42.2%, respectively. Of them, hemorrhagic transformation on CT performed after 24 hours was noted in 27.0% of patients from the group with a clinically positive result and 55.6% of patients from the group with a negative functional result. The neurological deficit, assessed at the time of admission according to the NIHSS scale, averaged 13.6±0.8 points in the mRS 0–3 group and 17.5±1.2 points in the mRS 4–6 group (p<0.05). The level of glycemia at admission in these groups averaged 6.3 and 7.5 mmol/L, respectively. INR was 1.14 and 1.25, respectively, at the time of admission. Blood pressure and blood tests, taken at admission and during the patient’s stay in the hospital, did not play a statistically significant role when comparing groups with neurological characteristics.

**Histological study of extracted thrombi**

Typical thrombi consist of a variable share of fibrin, platelets, red blood cells, white blood cells, von Willebrand factor (vWF), and extracellular DNA [23]. The analysis of the resulting thrombus performed in a recent study showed two main types of sites with different compositions: (I) rich in erythrocytes and poor in fibrin; (II) rich in platelets and fibrin [24].
The relationship between fibrin and two other components suggests that fibrin interacts differently with erythrocytes and platelets. Staining showed the presence of dense fibrin throughout the platelet-rich thrombus, in marked contrast to the thin fibrin mesh that surrounded RBC-filled areas [24]. Another study of the stroke thrombi structure revealed a common feature – an inner core of the erythrocyte-rich clot surrounded by an outer shell composed of tightly packed components, including a fibrin sheath and aggregated platelets [23]. It can be assumed that since the removed thrombi differ in their composition and structure, the response to the AIS treatment will vary too.

Histological characteristics of thromboembolism can affect reperfusion results. The histopathological composition of the thrombi to be extracted correlates with difficulties during clot removal [14]. Removing thrombi using thrombectomy means made it possible to conduct a detailed analysis of the morphology and histological composition of the latter. Cardioembolic thrombi have a higher percentage of fibrin-platelet conglomerates compared to non-cardioembolic thrombi [25].

Cardioembolic thrombi consist of platelets clustered in fibrin-rich areas, unlike non-cardioembolic thrombi, where masses of erythrocytes are the dominant and most common cell type. The comparison of these two histopathological characteristics using clinical parameters showed significant differences in the Modified Rankin Scale (mRS), Stroke Scale (NIHSS), the number of retraction maneuvers, and reperfusion time after MTE, with cardioembolic thrombi leading to a worse outcome [25].

Over time, the thrombus’s biochemical composition changes from the moment of the stroke [26]. First, a fresh thrombus is formed with a porous fibrin framework. At this stage, thrombolysis is effective. The clot is easily dissolved by tPA since cross-linking of fibrin and fibrinolysis inhibitors under the action of activated factor XIII has not yet occurred [27]. In the initial phases, the clot consists mainly of activated platelets, fibrin, and erythrocytes. As fibrin deposition grows, the thrombus becomes more compact with smaller pores, leading to less tPA infiltration and decreased thrombolytic therapy effectiveness [27]. The contraction of platelets of cross-linked clots leads to retraction and stabilization of the thrombus, as well as to the compression of disc-shaped erythrocytes into polyhedral, which further increases the density of the thrombus and increases resistance to thrombolysis [28].

Over time, clot formation causes inflammatory reactions leading to the development of a cytokine cascade, which further prolongs clotting. Activated platelets contribute to the penetration of leukocytes. When leukocytes penetrate and activate, the thrombus becomes even more resistant to thrombolysis [29]. Infiltrated neutrophils release anti-inflammatory mediators, forming neutrophil extracellular traps (NETs), which serve as frameworks for erythrocytes, platelets, and prothrombotic molecules, thus contributing to thrombus stability and reconstruction [30]. Clots extracted from patients undergoing mechanical thrombectomy also contain variable amounts of vWF, responsible for the clot binding platelets to collagen and fibrin. High plasma vWF is a strong predictor of ischemic stroke [31].

Our microscopic study of thrombi obtained after MTE at a magnification of x200 in patients from the group with unsuccessful reperfusion (mTICI 1/2a) showed small areas in the center of thrombi stained red (6–24 hours before) or red-purple (16–24 hours) with fibrin threads, and on the periphery – fibrin threads with signs of aging with purple and blue color (24–48 hours) (Fig. 3).
With a favorable surgery outcome (mTICI group 2b/3), coagulated fibrin fibers in the central part of the thrombus were stained red (the thrombus was up to 16 hours old) (Fig. 4).

The mechanical properties and composition of the thrombus can significantly impact the intervention’s effectiveness and risk [23]. The higher reperfusion efficiency of the “red” thrombus can be explained by its physical characteristics, which show reduced stiffness and increased deformability compared to the “white” thrombus [21].

In turn, the increased amount of fibrin in the thrombus makes the clot harder and more elastic, thus reducing the probability of successful linkage and interaction with the thrombus extractor [13]. Moreover, “white” thrombi have a higher friction coefficient than red blood cell-rich thrombus, which makes it more difficult to extract the clot. During MTE, the fibrin-rich thrombus offers increased resistance to sliding along the interior of the vessel or catheter when it is aspirated, which is assumed to be the result of its reduced ability to retain moisture and increased susceptibility to compression with each thrombectomy attempt [9].

The mechanical stability of the thrombus, i.e. its viscosity, elasticity, and stiffness, is primarily determined by fibrin. The stiff and frictional nature of a fibrin-rich thrombus reduces the likelihood of its fragmentation compared to erythrocyte-rich thrombi [32].

In this study, we analyzed the effect of vessel anatomy, assessed by antero-posterior angiogram, on reperfusion outcomes, surgery time, and the number of passages with stent retrievers in patients with acute ischemic stroke after large-vessel occlusion. Patients with failed reperfusion (TICI 0–2a) were shown to have significantly more curved distal carotid segments, proximal M1 segments, distal M1 segments, and/or proximal M2 segments than patients with successful reperfusion outcomes (TICI 2b/3).

A curved clot shape indicates that the latter was formed in a tortuous segment of the M1 MCA, where some of the mechanical force applied during retriever retraction would be distributed radially. In contrast, a straight shape indicates a straight segment of the M1 MCA where mechanical forces can act on a target thrombus with lower impedance.

Thrombi entering more distal segments of the arterial branch from the MCA stem 1) are in the smaller artery, access to which is more complex; 2) increase the curvature to the segment of the MCA stem, dispersing the efforts used to extract the thrombus across the line of the main stem; 3) potentially more tightly packed into the vasculature and resistant to extraction; 4) may require multiple passes to retrieve thrombus fragments from different end-segment branches.

Early and erythrocyte-enriched thrombi are usually associated with favorable outcomes, such as higher reperfusion success, shorter intervention times, and fewer passages. On the other hand, fibrin-enriched thrombi have a less favorable outcome, mainly due to their stiffness and resistance to mechanical thrombectomy.
Worsening of the prognosis is associated with increased thrombus adhesion to the vessel wall and the prothrombotic effect of the local vascular inflammatory response to the recently occluded embolic thrombus [33].

In patients with heart rhythm disorders leading to cerebral thromboembolism, prothrombotic changes, and hemostasis disorders are observed in 50–60% of cases, and arrhythmias lead to thrombus formation and thromboembolic occlusion of cerebral arteries [34].

Although these advances have changed the paradigm of acute stroke management and can be considered part of routine medical care, questions remain regarding the best hemodynamic management of patients with AIS. Although elevated blood pressure is a common phenomenon in the case of AIS, its prognostic value has not been sufficiently studied [35]. Some studies have found a correlation between hypertension and poor outcomes, while others have reported inverse relationships [36]. Other studies have identified elevated blood pressure as a risk factor for developing cerebral edema, hemorrhage, and generally worse clinical outcomes after AIS [37].

In conclusions:

1. The vessel curvature and the thrombus structure significantly affect mechanical thrombectomy’s success, complexity, and duration during acute ischemic stroke.
2. With a smaller curvature of the ICA and its branches (larger ICA-M1 angle) and in the presence of “fresh” blood clots, the efficiency of operations increases, and the number of passages and the duration of mechanical thrombectomy decrease.
3. The MCA diameter in the M1 segment in the case of AIS is smaller than among the general population, which is probably related to vascular angiospasm.
4. The neurological status of patients at admission correlates with the functional outcome at the time of discharge, and glucose level, blood pressure, and blood coagulation parameters did not play a statistically significant role when comparing groups.

Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki, and approved by the Ethical Commission of MNE “First Territorial Medical Association of Lviv” (No.13 dated 08/09/2022).

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

References


