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•••••: Η μηχανική θρομβεκτομή (ΜΘ) είναι μια εγκεκριμένη θεραπεία σε ασθενείς με οξύ ισχαιμικό αγγειακό εγκεφαλικό επεισόδιο (ΙΑΕΕ) σε έδαφος οξείας απόφραξης μεγάλου ενδοκράνιου αγγείου (ΟΑ-ΜΕΑ). Η λειτουργική έκβαση των ασθενών που υποβάλλονται σε ΜΘ έχει βρεθεί να σχετίζεται με την επάρκεια του παράπλευρου αρτηριακού δικτύου κατά την οξεία φάση.

•• -€: Μελετήσαμε την επίδραση του παράπλευρου αρτηριακού δικτύου στη λειτουργική έκβαση ασθενών με ΟΑΜΕΑ που υποβλήθηκαν σε ΜΘ σε δύο τριτοταγή κέντρα αντιμετώπισης ΑΕΕ στην Ελλάδα.

•f••••: Μελετήθηκαν διαδοχικοί ασθενείς με ΟΑΜΕΑ που υποβλήθηκαν σε Μηχανική Θρομβεκτομή σε δυο ελληνικά κέντρα του αρχείου Safe Implementation of Thrombolysis in Stroke (SITS) κατά τη διάρκεια τριών ετών (Ιανουάριος 2015 - Δεκέμβριος 2017). Καταγράφηκε το παράπλευρο αρτηριακό δίκτυο (όπως αυτό απεικονίστηκε στην ψηφιακή αφαιρετική αγγειογραφία εγκεφάλου) με βάση την κλίμακα ASITN/SIR, τα δημογραφικά στοιχεία, η νευρολογική βαρύτητα εκδήλωσης του ΙΑΕΕ (με τη κλίμακα NIHSS ( καθώς και το επίπεδο λειτουργικής ανεξαρτησίας των ασθενών στους 3 μήνες μετά το ΑΕΕ (με την τροποποιημένη κλίμακα κατά Rankin).

•... , μ•...•: Ασθενείς με πτωχή παράπλευρο κυκλοφορία εμφάνισαν συχνότερα ταυτόχρονη απόφραξη της εξωκράνιας μοίρας της έσω καρωτίδας και της ομόπλευρης μέσης εγκεφαλικής (tandem occlusions) και είχαν βαρύτερη νευρολογική εικόνα κατά την είσοδο στο νοσοκομείο (20 έναντι 15 πόντων στην κλίμακα NIHSS,  $p = 0.038$ ). Το mRS score εξιτηρίου και στους 3 μήνες ήταν βαρύτερο ( $p < 0.05$ ) σε ασθενείς με πτωχή παράπλευρο κυκλοφορία. Οι ασθενείς αυτοί εμφάνισαν σημαντικά υψηλότερο ποσοστό θνητότητας (50% έναντι 10%,  $p = 0.015$ ) και σημαντικά μικρότερο ποσοστό λειτουργικής ανεξαρτησίας (70% έναντι 20%;  $p = 0.010$ ) στους 3 μήνες μετά το ΑΕΕ.

Συμπέρασμα: Η πτωχή παράπλευρη κυκλοφορία σε ασθενείς με ΟΑΜΕΑ που υποβάλλονται σε μηχανική θρομβεκτομή σχετίζεται με ΙΑΕΕ μεγαλύτερης βαρύτητας κατά την εισαγωγή στο νοσοκομείο και με μικρότερη πιθανότητα λειτουργικής ανεξαρτησίας στους 3 μήνες μετά το ΑΕΕ. Η θνησιμότητα των ασθενών με ΟΑΜΕΑ και ικανοποιητική παράπλευρη κυκλοφορία είναι μικρότερη στους 3 μήνες μετά το ΙΑΕΕ.

•† € ‡ ... •‡: Ισχαιμικό ΑΕΕ, μηχανική θρομβεκτομή, παράπλευρο δίκτυο

# BASELINE COLLATERAL CIRCULATION IS ASSOCIATED WITH EARLY OUTCOMES IN PATIENTS WITH LARGE-VESSEL OCCLUSION ACUTE ISCHEMIC STROKE TREATED WITH MECHANICAL THROMBECTOMY

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## Abstract

**Introduction:** Mechanical thrombectomy (MT) is an established treatment of acute ischemic stroke (AIS) due to large-vessel occlusion (LVO). Adequacy of brain collateral vessels has been shown to affect early outcomes of AIS patients treated with endovascular reperfusion therapies.

**Aim:** We sought to prospectively evaluate the impact of collaterals on the outcomes of AIS patients due to LVO treated MT in two tertiary stroke centers in Greece.

**Methods:** Consecutive LVO patients treated with MT in two SITS (Safe Implementation of Thrombolysis in Stroke) Registry centers in Greece were evaluated during a three-year period (January 2015-December 2017). Collateral status was assessed on digital subtraction angiography (DSA) using ASITN/SIR classification. Baseline characteristics, admission stroke severity (quantified by NIHSS-score) and three-month functional outcome (determined by modified Rankin Scale) were recorded.

**Results:** Patients with poor collaterals on DSA were more likely to harbor tandem (extracranial internal carotid artery & middle cerebral artery) occlusions and present with higher admission median NIHSS-scores (20 vs. 15 points;  $p = 0.038$ ). Patients with poor collaterals had higher ( $p < 0.05$ ) median mRS-scores at discharge and at three-months. The three-month mortality and functional independence rates were higher (50% vs. 10%;  $p = 0.015$ ) and lower (20% vs. 70%;  $p = 0.010$ ) respectively in LVO patients with poor collaterals.

**Conclusions:** Poor baseline collateral status is more common in LVO patients with tandem occlusions and is associated with higher baseline stroke severity and three-month mortality rates. Patients with good baseline collateral circulation are more likely to be functional independent at three-months following stroke onset.

**Key words:** Ischemic stroke, mechanical thrombectomy, collaterals

## Introduction

Stroke is a major cause of death and disability and ischemic stroke accounts for more of 80% of strokes [1]. Acute ischemic stroke (AIS) due to large-vessel occlusion (LVO) represents only a little more than one-third of AIS but is responsible for 62% of dependency and 96% of mortality after AIS [2]. Intravenous thrombolysis (IVT) and mechanical thrombectomy (MT) are the established treatments of LVO AIS and can be offered independently or combined together (bridging therapy) [3-7]. IVT has two major limitations compared to MT for LVO: shorter time window of opportunity and lower recanalization

rates [8]. In 15%-34% of achieved recanalizations, reocclusion and subsequent neurological deterioration may follow [9]. As a result, MT has emerged as the mainstay of treatment of LVO AIS either as rescue therapy after unsuccessful recanalization with IVT or as the only treating modality in IVT-ineligible AIS patients [10].

Neurons are extremely sensitive to hypoxemia with death occurring within minutes when totally deprived of oxygen [11]. Collateral circulation maintains cerebral blood flow and is the means to extend the window of opportunity for brain tissue salvage [12]. Collateral circulation bypasses the arterial occlusion via the circle

of Willis, the extracranial and intracranial arterial pial collaterals [13]. Adequacy of collaterals has been shown to improve recanalization and reperfusion rates, reduce infarct volumes and lead to better neurological outcomes following MT [14, 15]. Collateral status appears to be even more important than time for predicting outcome in LVO patients treated with MT during the first 6 hours of acute cerebral ischemia [16].

CT angiography (CTA) has been used to evaluate baseline collaterals in the acute phase of LVO [17]. However, DSA has many advantages over non-invasive modalities: accurate distinction between occlusion and subtotal occlusion, well standardized recanalization grading and detailed visualization of leptomeningeal collaterals [18]. The most widespread scale for measuring collaterals on DSA, the American Society of Interventional and Therapeutic Neuroradiology/Society of Interventional Radiology (ASITN/SIR) Collateral Flow Grading System (Table 1), uses a five-point grading system to score the extent of collaterals. Grade 0 or 1 collaterals signify marginal flow, grade 2 only partial filling and grades 3 and 4 imply complete filling of the occluded arterial territory at varying degree [19-20].

In view of the former considerations, we sought to prospectively evaluate the impact of collaterals on the outcomes of AIS patients due to LVO treated MT in two tertiary stroke centers in Greece.

## Methods

Consecutive LVO patients treated with MT in two SITS (Safe Implementation of Thrombolysis in Stroke) Registry centers in Greece were evaluated during a three-year period (January 2015-December 2017). The participating centers were Metropolitan Hospital in Piraeus and Attikon University Hospital in Athens, Greece.

Demographics and risk factors were prospectively recorded as previously described [21]. Stroke severity was assessed using measurements of NIHSS (National Institute of Health Stroke Scale) score at patient admission and discharge. ASITN score was evaluated by interventional neuroradiologist or radiologists that were involved in all endovascular procedures. Interventionalists were blinded to all assessments of stroke severity and functional outcome that were performed by certified vascular neurologists as previously described

[22]. Poor and good collateral status were defined by ASITN grades 0-2 and 3-4 respectively (Figure 1). Safety endpoints included the prevalence of peri-procedural complications, symptomatic intracranial hemorrhage (sICH) and mortality. sICH was defined using standard SITS registry definitions [23]. Reperfusion following MT was evaluated using Thrombolysis in Cerebral Infarction (TICI) grade [24]. Successful reperfusion was defined as TICI grades of IIb or III. Functional status at three months was evaluated using modified Rankin Scale (mRS) as previously described. More specifically, functional independence was defined as mRS-score of 0-2 at three months [25-26].

Continuous variables are presented as median with interquartile range, while categorical variables are presented as percentages. Statistical comparisons between the aforementioned groups were performed using the  $\chi^2$ -test and Mann-Whitney U-test, respectively, while the distribution of the mRS-scores at three months between the good and bad collaterals groups was compared with the Cochran-Mantel-Haenszel test. The differences in all clinical outcomes of interest between the two groups were tested under statistical significance hypotheses using an alpha value of 0.05. Statistical analyses were performed with the Stata Statistical Software Release 13 (College Station, TX, StataCorp LP).

## Results

### Baseline Clinical Characteristics

A total of 36 patients with AIS due to LVO (median age: 64 years, 39% women; median NIHSS score on admission: 17) were treated with MT during the study period. Baseline characteristics of patients are presented in Table 2. Patients with poor collaterals ( $n = 12$ ) were more likely to harbor tandem (extracranial internal carotid artery & middle cerebral artery) occlusions (33.3% vs. 4.2%;  $p=0.018$ ) and present with higher median admission NIHSS-scores (20 vs. 15 points;  $p = 0.038$ ). Posterior circulation LVO was found in 8% of both patient groups. Pretreatment with IVT was not significantly different in the two groups. Statin pretreatment tended to be more prevalent in patients with good baseline collateral circulation (16.7% vs. 8.3%) but this difference did not reach statistical significance ( $p = 0.495$ ).

**Table 1.** The American Society of Interventional and Therapeutic Neuroradiology/Society of Interventional Radiology (ASITN/SIR) Collateral Flow Grading System.

Collateral Grade	Definition
0	No collaterals
1	Slow peripheral collaterals with persistence of some of the defect
2	Rapid peripheral collaterals with persistence of some of the defect and to only a portion of the ischemic territory
3	Complete but slow blood flow by the late venous phase in the ischemic bed
4	Complete and rapid collateral flow to the entire ischemic territory by retrograde perfusion

**Table 2.** Baseline characteristics of large vessel occlusion patients with good and bad collaterals who were treated with Mechanical Thrombectomy

Variable	Good collaterals (n = 24)	Bad collaterals (n = 12)	p-value
Age (years)*	65 (53-76)	61 (55-72)	0.867
Men (%)	62.5%	58.3%	0.809
Hypertension (%)	58.3%	50.0%	0.635
Diabetes mellitus (%)	20.8%	0%	0.088
Atrial fibrillation (%)	33.3%	25.0%	0.609
Heart failure (%)	20.8%	25.5%	0.777
Coronary artery disease (%)	12.5%	16.7%	0.733
Dyslipidemia (%)	20.8%	33.3%	0.414
Smoking (%)	25.0%	25.0%	1.000
Anticoagulant treatment (%)	25.0%	41.7%	0.306
Antiplatelet treatment (%)	12.5%	25.0%	0.343
Statin (%)	16.7%	8.3%	0.495
Previous stroke/TIA (%)	12.5%	0%	0.201
Pre-morbid mRS>1 (%)	8.3%	8.3%	>0.999
NIHSS on admission*	15 (11-21)	20 (17-23)	0.038
SBP on admission (mmHg)*	137 (123-158)	140 (125-166)	0.662
DBP on admission (mmHg)*	80 (71-83)	77 (70-81)	0.556
Glucose on admission (mg/dl)*	110 (95-131)	116 (99-138)	0.491
ASPECTS score on CT*	9 (8-10)	8 (7-9)	0.206
Posterior circulation (%)	8.34%	8.34%	1.000
Tandem occlusion (%)	4.2%	33.3%	0.018
IVT treatment (%)	33.3%	50.0%	0.334
Onset-to-IVT time (min)*	136 (102-177)	140 (120-165)	0.746
Onset-to-MT time (min)*	259 (200-455)	240 (206-420)	0.754

SBP: systolic blood pressure

DBP: diastolic blood pressure

NIHSS: National Institutes of Health Stroke Scale

ASPECTS: Alberta Stroke Program Early CT Score

IVT: intravenous thrombolysis, MT: Mechanical thrombectomy

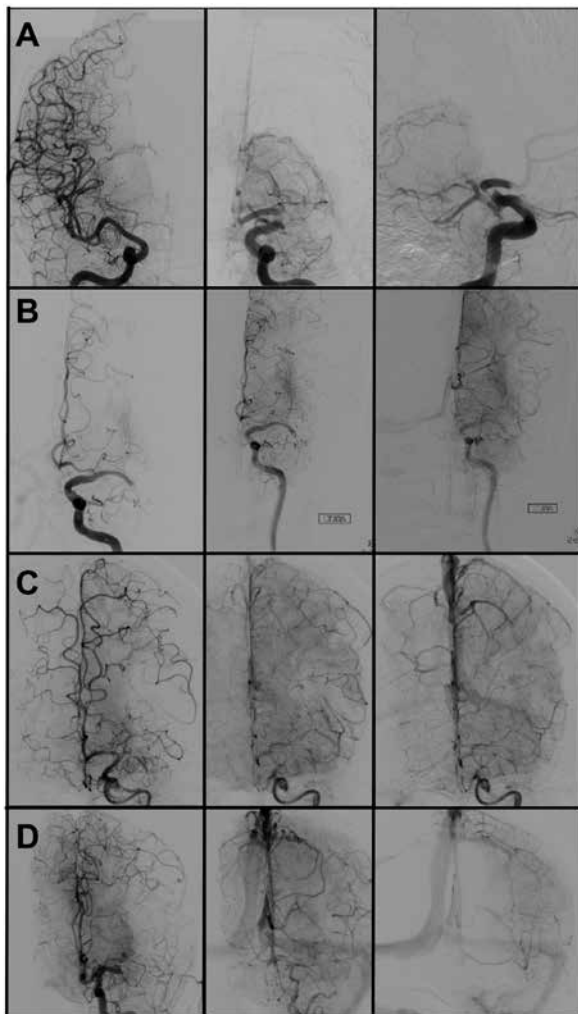
\*Continuous variables are presented with median values and inter-quartile range in brackets

**Efficacy and safety outcomes**

The efficacy and safety outcomes of our cohort are shown in Table 3. Rates of complete reperfusion were similar (79.2% vs. 83.3%,  $p = 0.766$ ). Time from stroke onset to MT initiation was similar between the two groups [76 (55-115) vs. 71 (40-90),  $p = 0.377$ ]. We documented only one SICH case in a patient with good collaterals (4.2% vs. 0%,  $p = 0.473$ ). NIHSS at discharge was higher in patients with bad collaterals [8 (2-13)

vs. 3 (2-6)], but this difference did not reach statistical significance ( $p = 0.208$ ). The functional outcome at discharge [5 (4-5) vs. 2 (1-3),  $p = 0.001$ ] and at 3 months [5 (3-6) vs. 2 (1-3),  $p = 0.016$ ; Figure 2] was worse in patients with poor collaterals, compared to patients with good collaterals. At 3 months, patients with poor collaterals had significantly higher mortality rates (50% vs. 10%,  $p = 0.015$ ) and were less likely to be functionally independent (20% vs. 70%,  $p = 0.010$ ).

**Figure 1.** Collateral grading in MCA occlusion. A. Grade 0 collaterals: No collaterals visible to the ischemic site. Absence of filling in the entire occluded territory (both ACA and left MCA), due to absence of A1 of the contralateral side. B. Grade 1 collaterals: Slow collateral filling to the periphery of the ischemic site, with persistence of some of the defect. C: Grade 2 collaterals: Rapid collateral filling to the periphery of the ischemic site, with persistence of some of the defect, and to only a portion of the ischemic territory. Filling of the MCA territory, through the ACA leptomeningeal anastomoses. D: Grade 4 collaterals, fill the entire MCA territory. There is complete and rapid collateral blood flow to the vascular bed in the entire ischemic territory by retrograde perfusion. MCA: Middle cerebral artery. ACA: Anterior cerebral artery.



### Discussion

Our study showed that poor baseline collateral status is more common in LVO patients with tandem occlusions and is associated with higher baseline stroke severity and three-month mortality rates. Patients with

good baseline collateral circulation are more likely to be functional independent at three-months following stroke onset.

The beneficial effect of good collaterals on outcome after endovascular treatment for LVO is well established. A meta-analysis of available studies before 2015 has shown that good pretreatment collateral status is associated with favorable functional outcome, lower rates of symptomatic intracranial hemorrhage and lower risk for mortality [27]. In the Interventional Management of Stroke (IMS) III trial, no benefit from treatment was found in the subgroup of patients with poor collaterals on baseline CTA [28]. Higher ASITN collateral grade on DSA in the same trial has also been shown to be a robust independent predictor of clinical outcome, associated with better recanalization, reperfusion and clinical outcomes [29]. In the Solitaire FR With the Intention for Thrombectomy (SWIFT) study higher ASITN collateral score was associated with greater likelihood of successful revascularization and with lower risk for hemorrhagic transformation, but also improved clinical outcomes [30]. In a subgroup analysis of the Multicenter Randomized Clinical Trial of Endovascular Treatment of Acute Ischemic Stroke in the Netherlands (MR CLEAN), MT failed to provide any significant benefit in patients with poor or absent collaterals on baseline CTA [31]. It is worth mentioning that in the aforementioned study mortality rates were (like in our series) around 50% for both the intervention and control group with grade 0 collaterals on baseline CTA, suggesting that in some patients with bad collaterals MT may lead to futile recanalization even in the first 6 hours after symptom onset.

Although the sample size in our cohort is very limited, our results are in line with previously published reports [27-31] and challenge current guidelines suggesting that collateral status should not be taken into account in clinical practice for AIS patients presenting up to 6 hours from symptom onset [32]. We consider that further research is required for the identification of those AIS patients that will not benefit from MT because of futile recanalization based on collateral circulation status but also to identify the AIS subgroup that will still derive benefit from MT in a delayed time window due to the adequacy of collateral circulation.

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Figure 2. Modified Rankin scale scores distribution at three months in patients treated with MT, stratified by collateral status [bad collaterals (upper bar) vs. good collaterals (lower bar) on Digital Substraction Angiography.

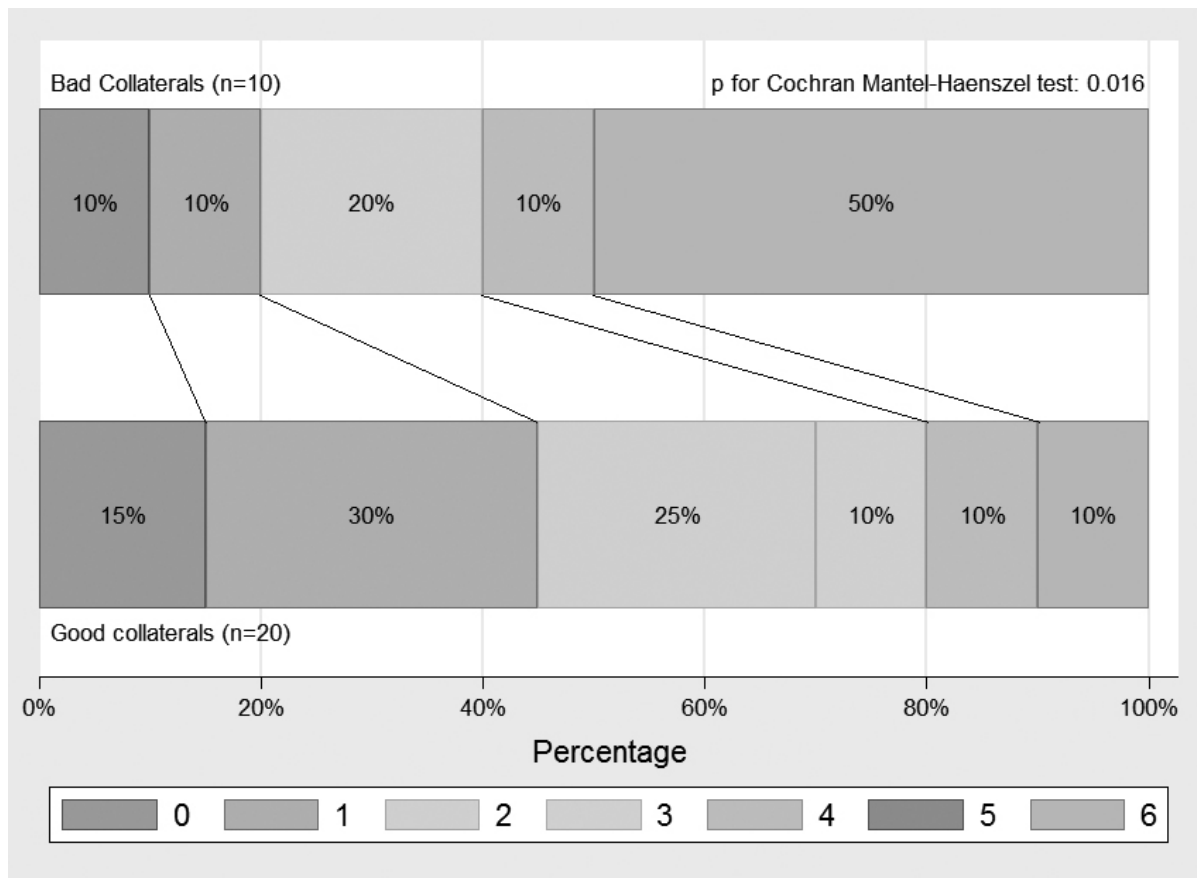


Table 3. Safety and efficacy outcomes of Mechanical Thrombectomy in large vessel occlusion patients with good and bad collaterals

Outcome	Good collaterals	Bad collaterals	p-value
Successful reperfusion (%)	79.2%	83.3%	0.766
Time from groin puncture to successful reperfusion (min)*	76 (55-115)	71 (40-90)	0.377
Symptomatic intracranial hemorrhage (%)	4.2%	0%	0.473
NIHSS at discharge*	3 (2-6)	8 (2-13)	0.208
Absolute NIHSS reduction at discharge (ΔNIHSS)*	8 (3-17)	9 (6-16)	0.798
Relative NIHSS reduction at discharge (%ΔNIHSS)*	77.3 (40.0-89.5)	55.4 (32.0-78.2)	0.421
mRS at discharge*	2 (1-3)	5 (4-5)	0.001***
mRS at 3 months*/**	2 (1-3)	5 (3-6)	0.016***
mRS 0-1 at 3 months (%)**	45.0%	20.0%	0.180
mRS 0-2 at 3 months (%)**	70.0%	20.0%	0.010
Mortality at 3 months (%)**	10.0%	50.0%	0.015

MT: Mechanical thrombectomy, NIHSS: National Institutes of Health Stroke Scale, mRS: modified Rankin Scale Score.

\* Continuous variables are presented with median values and inter-quartile range in brackets.

\*\* 6 patients were lost to follow-up.

\*\*\* Calculated using the Cochran Mantel-Haenszel test.

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