Predictive factors of poor functionnal outcome, mortality and hemorrhage after acute ischemic stroke treated by stent-retriever: the thrombus length is determinant.

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Authors: S. Soize, K. Kadziolka, L. Estrade, L. Pierot; Reims/FR
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Purpose

During the last decade, successive development and growing use of chemical and mechanical intra-arterial thrombolysis has revolutionized the treatment of acute ischemic stroke, which previously consisted mainly in intravenous thrombolysis [1]. Those techniques dramatically improved recanalization rate as well as clinical outcome [2,3]. Several mechanical retrievers allowed the recanalization of acutely occluded large intracranial arteries with acceptable levels of safety and efficacy, and with occasional failures. In 2008, a stent initially developed for the endovascular treatment of wide necked intracranial aneurysms was first used as a thrombectomy device [4]. It further demonstrated to be safe and efficacious for recanalization of intracranial vessels. This was the starting point for the development of a new generation of devices, now called "stent retrievers". This second generation of mechanical thrombectomy devices are now validated versus 1st generation devices (e.g. Merci device) and largely used for acute stroke treatment [5].

If the definitive place of mechanical thrombectomy would be determined only by large randomized trials [6], homogeneous monocentric series can already help to determine factors influencing the outcome in order to improve the selection of the patients and the procedure.

Some predictive factors related to neurological outcome or hemorrhage were identified for the patients treated with chemical or first generation of mechanical thrombectomy devices [7-9] but limited data is available regarding second generation devices [10].

The purpose of this study was to identify independent predictive factors of poor neurological outcome at 3 months, mortality at 3 months and intra-cranial hemorrhage at day1 in consecutive patients which underwent mechanical thrombectomy with a stent-retriever for an acute ischemic stroke. The identified predictors could be useful to improve the selection of patients' candidates for mechanical thrombectomy with these new devices.
Methods and Materials

Patient selection

We performed a retrospective analysis of medical history, clinical and imaging data to the onset of symptoms from the 3 months follow-up in consecutive patients with an acute ischemic stroke treated at our institution by mechanical thrombectomy with a stent-retriever from May 2010 to April 2012. The data was extracted from our prospectively maintained institutional stroke database.

Thrombectomy treatment

Patients treated by mechanical thrombectomy were either ineligible for intravenous tissue-type plasminogen activator (tPA) or did not presented clinical improvement (reduction of NIHSS 10 points or NIHSS # 8) from 30 to 1 hour after receiving IV tPA (0.9mg/kg) within 6 hours of stroke onset. Procedures were performed under conscious sedation (Midazolam) with the Solitaire FR device and intra-arterial tPA was allowed as an adjunct. Carotid angioplasty or stenting was allowed in cases of proximal stenosis or occlusion preventing the distal recanalization. Initial and final intra-cranial flow was graded on the Thrombolysis In Cerebral Infarction (TICI) scale (Fig. 1 on page 6) and revascularization was defined as TICI #2.

Imaging protocol

Imaging data was evaluated by an independent neuroradiologist blinded from clinical and angiographic data. All patients underwent an acute 3T MRI examination including DWI, FLAIR, T2*GRE sequences and an unenhanced intracranial MRAngiography, most of the time completed by an intracranial and cervical gadolinium-enhanced MRA. Extension of the ischemic lesion were evaluated on DWI using the Alberta Stroke Program Early CT Score (ASPECT) (Fig. 2 on page 6) and pc-ASPECT score (Fig. 3 on page 7) [11-12]. Leukoaraiosis assessment was done on transverse FLAIR MR Images using the visual rating scale proposed by Fazekas and Schmidt [13] and classified as absent or mild (Fazekas 0-1) versus moderate or severe (Fazekas 2-3). Measure of the thrombus was made on T2* GRE sequence for anterior circulation occlusions, using the "susceptibility sign" [14] (Fig. 4 on page 7) . When the thrombus was visible on 2 or 3 slices, superposition of the images using the Matlab software brought more reliability. For posterior circulation, the clot length was considered to be the zone with absence of contrast on coronal gadolinium-enhanced MRA images (Fig. 5 on page 7).
Data collection

**Collected demographic and clinical data**

- Medical history: age, gender, smoking, hypertension, diabetes mellitus, dyslipidemia, cardiovascular events, cancer.

- Clinical data:
  
  - admission: NIHSS, atrial fibrillation (electrocardiogram)
  - at 3 months: the modified Rankin Score (mRS) evaluated by an independent neurologist, subtype of stroke according to the TOAST classification [15]

Good neurological outcome was defined as mRS 0-2 whereas poor neurological outcome or death were mRS 3-6.

**Collected imaging data**

- acute MRI: Extension of the ischemic lesion evaluated on DWI using the ASPECT and pc-ASPECT score, the thrombus length, occlusion site, leukoaraiosis (Fazekas 2-3), images compatible with a former stroke.

- Endovascular procedure: Initial intra-cranial flow and recanalization status (TICI), number of device deployment, patient agitation (necessity to add Midazolam during the procedure), hemodynamic instability (systolic blood pressure # 180 mmHg and/or diastolic blood pressure # 110 mmHg) and intubation due to clinical worsening after the procedure.

- CT at 24 hours: new ASPECT score, Intra-Cranial Hemorrhage (ICH) defined as a parenchymal hematoma type 2 (PH-2) of the ECASS definition or a Subarachnoid Hemorrhage (SAH) [16] and symptomatic Intra-Cranial Hemorrhage (sICH) defined as any intra-cranial bleeding causing neurological deterioration (increase of #4 points of the NIHSS).

**Collected timing data**

- time from onset of symptoms to endovascular procedure (first angiographic run)

- duration of the endovascular procedure (from the first to the last angiographic run)

- time from symptoms onset to recanalization

Data analysis
Univariate (Student tests, Wilcoxon tests, Chi-square tests or Fisher’s exact tests) and multivariate (stepwise logistic regressions, with enter and removal limits set at 0.20 and factors significant at p=0.20 included) analysis were performed to determine factors associated with good functional outcome at 3 months, mortality at 3 months and haemorrhage at 1 day. A p value < 0.05 was considered significant.
Images for this section:

| Grade 0: | No Perfusion. No antegrade flow beyond the point of occlusion. |
| Grade 1: | Penetration With Minimal Perfusion. The contrast material passes beyond the area of obstruction but fails to opacify the entire cerebral bed distal to the obstruction for the duration of the angiographic run. |
| Grade 2: | Partial Perfusion. The contrast material passes beyond the obstruction and opacifies the arterial bed distal to the obstruction. However, the rate of entry of contrast into the vessel distal to the obstruction and/or its rate of clearance from the distal bed are perceptibly slower than its entry into and/or clearance from comparable areas not perfused by the previously occluded vessel, eg, the opposite cerebral artery or the arterial bed proximal to the obstruction. |
| Grade 2a: | Only partial filling (~2%) of the entire vascular territory is visualized. |
| Grade 2b: | Complete filling of all the expected vascular territory is visualized, but the filling is slower than normal. |
| Grade 3: | Complete Perfusion. Antegrade flow into the bed distal to the obstruction occurs as promptly as into the obstruction and clearance of contrast material from the involved bed is as rapid as from an uninvolved other bed of the same vessel or the opposite cerebral artery. |

Fig. 1: Thrombolysis In Cerebral Infarction (TICI) perfusion categories.


Fig. 2: Adaptation to DW images of the Alberta stroke program early CT score (ASPECTS), described by Pexman et al. (AJNR 2001.) It is a 10-point topographic scoring system for quantitative assessment of acute ischemic stroke of the MCA territory. The MCA territory is divided into 10 regions of interest. One point is subtracted from 10 for any ischemic change of each defined regions. C- Caudate, I- Insularribbon, IC- Internal Capsule, L- Lentiform nucleus, M1- Anterior MCA cortex, M2- MCA cortex lateral to the insular ribbon, M3- Posterior MCA cortex, M4, M5, M6 are the anterior, lateral and posterior MCA territories immediately superior to M1, M2 and M3, rostral to basalganglia.
**Fig. 3:** Adaptation to DW images of the posterior circulation Acute Stroke Prognosis Early CT Score (pc-ASPECTS). This is a 10-point grading system to quantify ischemic changes in the posterior circulation, described by Puetz et al. (Stroke 2008). The score works on the same principle as the ASPECT score. Points are allotted to midbrain, pons, bilateral thalami, posterior circulation territories and cerebellar hemispheres.

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**Fig. 4:** Axial (a) DW and (b) FLAIR MR images in a 57-years-old patient with ischemic infarct in the left deep Middle Cerebral Artery territory. Note the hyperintense vessels on FLAIR image corresponding to slow flow in the arterial collateral circulation. Axial (c) T2*-weighted GRE image with an hypointense thrombus enlarging the left M1 part of the MCA, with usual convex surfaces. Coronal MIP reconstructions of intra-cranial and cervical gadolinium-enhanced MRA (d) confirming the occlusion of the left M1 segment.

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Fig. 5: A 55-years-old woman presenting with dizziness and ataxia appeared 5 hours earlier. Axial DW MR Image (a) showing a right cerebellar and occipital ischemic infarct. Coronal MIP reconstruction of gadolinium-enhanced (b) intra-cranial MRA, with absence of the distal third of the basilar artery. Final angiogram (c) with recanalization of the basilar artery after two deployments of the device but the right posterior cerebral artery and superior cerebellar artery remained occluded. 24 hours follow-up CT scan (d) showing ischemic infarcts in the right cerebellar and occipital territories.

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Results

Patient characteristics

During the study period, 59 consecutive patients were treated. Forty-three patients (72.9%) received intravenous thrombolysis before the endovascular therapy.

![Table 1. Baseline characteristic of the 59 patients.](image)

**References:** S. Soize et al., Reims, FR
The thrombus length was measurable for 51 patients (86.4%). In 46 patients T2* GRE images were informative and for 5 patients with basilar artery occlusion the measure was made on gadolinium-enhanced CE-MRA. Thrombus size varied from 4 mm to 49 mm, with a mean of 17.2 ± 9.9 and median of 14 mm (9-23 mm). Fig. 6 on page 11

Analysis of factors predicting clinical outcome at 3 months

At 3 months, 34/59 patients (57.6%) had a good neurological outcome (mRS 0-2), 13 patients a moderate outcome (22%) and 12 patients were deceased (20.4%). On multivariate analysis, independent prognostic factors of poor neurological outcome (mRS 3-6) were a thrombus length > 14mm (p=0.02; OR 7.55; CI 95% 1.35-42.31) and endovascular procedure duration (p=0.01; OR 1.04; CI 95% 1.01-1.07). Fig. 7 on page 12

On the contrary, a higher baseline ASPECT score (p=0.04; OR 0.79 per point; CI 95% 0.63-0.99) and recanalization (p=0.02; OR 0.07; CI 95% 0.01-0.72) were independent predictors of good functional outcome. Fig. 8 on page 13 Fig. 9 on page 14

Analysis of factors predicting mortality at 3 months

After 3 months, 12 patients were deceased (20.4%); 5 of malignant cerebral oedema (8.6%) and 7 patients of hemorrhage (11.8%). On multivariate analysis, baseline ASPECT score (p<0.01; OR 1.53 per point; CI 95% 0.99-2.37) had a trend to influence mortality and ASPECT score at day 1 (p<0.01; OR 0.36 per point; CI 95% 0.17-0.76) independently predicted mortality at 3 months.

Analysis of factors predicting haemorrhage at 1 day

All patients underwent a follow-up CT scan at day 1 (or earlier if neurological status worsened). 5/59 patients presented a symptomatic haemorrhage (sICH) (8.5%) and ICH concerned 11/59 patients (18.6%): 9 were parenchymal hematoma type 2 and 2 were Subarachnoid Hemorrhage.

On multivariate analysis, baseline ASPECT score (p<0.01; OR 0.65 per point; CI 95% 0.54-0.78) independently predicted sICH at day 1. Independent factors associated with ICH at day 1 were atrial fibrillation on admission (p=0.01; OR 9.08; CI 95% 1.48-55.63) and hemodynamic instability during the procedure (p=0.04; OR 8.03; CI 95% 1.02-63.21).
Table 1. Baseline characteristic of the 59 patients.

<table>
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<td><strong>Demographics:</strong></td>
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<tr>
<td>Age (years) †</td>
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<td>Male sex</td>
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<td><strong>Medical history:</strong></td>
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<td>Atrial fibrillation</td>
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<tr>
<td>Hypertension</td>
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<td>Dyslipidemia</td>
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<td>Cardiovascular events</td>
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<td>Cancer</td>
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<td><strong>Clinical:</strong></td>
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<td>NIHSS †</td>
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<tr>
<td>Atrial fibrillation</td>
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<td>Intravenous thrombolysis</td>
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<td><strong>Imaging:</strong></td>
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<td>ASPECT on DWI †</td>
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<td>Moderate or severe leuкоaraiosis n/available</td>
<td>13/55 (22.0%)</td>
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<tr>
<td>Former stroke n/available</td>
<td>5/57 (8.5%)</td>
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<tr>
<td>Thrombus length (mm) †</td>
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<td>Basilar artery</td>
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<td><strong>Stroke mechanism:</strong></td>
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<td>Cardioembolic</td>
<td>28 (47.5%)</td>
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<tr>
<td>Large vessel atherosclerosis</td>
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<tr>
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<tr>
<td>Undetermined</td>
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</table>

*data are expressed as n (%) unless otherwise indicated; † data are expressed as mean ± standard deviation ‡ Thrombus length was available for 51/59 patients.

**Table 1**

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**Fig. 6:** Axial (a) DW MR image in a 38-years-old woman with left insular and putaminal ischemic infarct. Axial (b) T2*-weighted GRE image with an hypointense thrombus in the left M1 part of the MCA. Initial (c) and final (d) angiograms with complete recanalization (TICI3) after one deployment of the stent. The thrombus (e) was composed of a hard black central part and a red soft peripheral part.

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Fig. 7: Box and whisker plots showing thrombus length repartition in patients with a good (modified Rankin Score 0-2) and a poor (mRS 3-6) neurological outcome at 3 months. A thrombus > 14mm predicted poor neurological outcome in multivariate analysis (p=0.02; OR 7.55; CI 95% 1.35-42.31).

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Fig. 8: Correlation between Baseline ASPECT score and good neurological outcome. Baseline ASPECT score on DWI is an independent predictive factor of good neurological outcome at 3 months (p=0.04; OR 0.79 per point; CI 95% 0.63-0.99.)

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Fig. 9: Box and whisker plot showing thrombus length repartition in patients with successful and unsuccessful recanalization. Unsuccessfully recanalized patients had a longer thrombus (25.1 v 10.7 mm, p=0.01)

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Conclusion

Although thrombus length effect on recanalization with IV thrombolysis in MCA occlusions has been described [17], there was no significant effect on recanalization or good clinical outcome after thrombectomy with first generation of mechanical thrombectomy devices [18]. On the contrary, the results of this study show that a thrombus >14mm is a predictor of poor outcome after mechanical thrombectomy with a second generation device and does not seem to influence the risk of hemorrhage.

Patients which had unsuccessful attempts of recanalization had longer thrombus in this series. The stent used (Solitaire FR 4 x 20) has a total length of 31 mm and a retrieval zone of 20 mm (only 2/3 of the stent is deployed across the thrombus). The concomitant aspiration to reverse the flow in the intracranial vessel during the removing can enhance the efficacy of the thrombectomy. The limited retrieval zone could explain that the longest thrombi could not be removed. Nevertheless, the number of device deployment was not statistically different in case of poor outcome, maybe because of the number of patients included and possible interoperator variability in the procedure, that we did not evaluated.

The thrombus was often measurable (86.4%), especially on T2* GRE images (78%). Sometimes, the thrombus was not seen on T2* images probably due to its composition and rarely not measurable due to its location in a vertical artery (ICA, M2).

We also showed that some predictive factors identified after IV thrombolysis were also applicable to mechanical thrombectomy, such as pre-treatment DWI lesion volume influence on neurological outcome [9], probably underlining the pivotal role of arterial collateral support. This study showed that baseline ASPECT score predict neurological outcome at 3 months and symptomatic ICH at day 1.

In patients with acute ischemic stroke treated with a stent-retriever, a thrombus length >14mm is an independent predictive factor of poor neurological outcome at 3 months. Absolute baseline ASPECT score reflect early symptomatic hemorrhage risk and neurological outcome at 3 months. Further analyses are needed to determine the importance of the thrombus length in the selection of patient's candidates for mechanical thrombectomy in acute ischemic stroke.
References


Personal Information

Sébastien Soize MD, Service de radiologie, Centre Hospitalier Universitaire de Reims, Hopital Maison Blanche, Rue Cognac Jay, 51092 Reims Cedex, France; sebastien.soize@gmail.com

Krzitof Kadziolka MD, Service de radiologie, Centre Hospitalier Universitaire de Reims, Hopital Maison Blanche, Rue Cognac Jay, 51092 Reims Cedex, France

Laurent estrade MD, Service de radiologie, Centre Hospitalier Universitaire de Reims, Hopital Maison Blanche, Rue Cognac Jay, 51092 Reims Cedex, France

Laurent Pierot PhD, Service de radiologie, Centre Hospitalier Universitaire de Reims, Hopital Maison Blanche, Rue Cognac Jay, 51092 Reims Cedex, France. lpierot@gmail.com