

Length of Occlusion Predicts Recanalization and Outcome After Intravenous Thrombolysis in Middle Cerebral Artery Stroke

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Background and Purpose—The length of large vessel occlusion is considered a major factor for therapy in patients with ischemic stroke. We used 4D-CT angiography evaluation of middle cerebral artery occlusion in prediction of recanalization and favorable clinical outcome and after intravenous thrombolysis (IV-tPA).

Methods—In 80 patients treated with IV-tPA for acute complete middle cerebral artery/M1 occlusion determined using CT angiography and temporal maximum intensity projection, calculated from 4D-CT angiography, the length of middle cerebral artery proximal stump, occlusion in M1 or M1 and M2 segment were measured. Univariate and multivariate analyses were performed to define independent predictors of successful recanalization after 24 hours and favorable outcome after 3 months.

Results—The length of occlusion was measurable in all patients using temporal maximum intensity projection. Recanalization thrombolysis in myocardial infarction 2 to 3 was achieved in 37 individuals (46%). The extension to M2 segment as a category (odds ratio, 4.58; 95% confidence interval, 1.39–15.05; $P=0.012$) and the length of M1 segment occlusion (odds ratio, 0.82; 95% confidence interval, 0.73–0.92; $P=0.0007$) with an optimal cutoff value of 12 mm (sensitivity 0.67; specificity 0.71) were significant independent predictors of recanalization. Favorable outcome (modified Rankin scale 0–2) was achieved in 25 patients (31%), baseline National Institutes of Health Stroke Scale (odds ratio, 0.82; 95% confidence interval, 0.72–0.93; $P=0.003$) and the length of occlusion M1 in segment (odds ratio, 0.79; 95% confidence interval, 0.69–0.91; $P=0.0008$) with an optimal cutoff value of 11 mm (sensitivity 0.74; specificity 0.76) were significant independent predictors of favorable outcome.

Conclusions—The length of middle cerebral artery occlusion is an independent predictor of successful IV-tPA treatment. (*Stroke*. 2014;45:2010-2017.)

Key Words: computed tomography ■ middle cerebral artery ■ outcome ■ stroke ■ thrombolytic therapy

Natural history of acute stroke with middle cerebral artery (MCA) occlusion has a very poor prognosis and localization of occlusion is one of the most important factors.¹ Intravenous thrombolysis with application of recombinant tissue-type plasminogen activator (IV-tPA) is currently the only clinically proven method of acute ischemic stroke treatment²; however, its effect is limited in a significant percentage of patients with a large vessel occlusion (LVO). Recanalization of LVO after IV-tPA depends on several factors that have been identified such as location, extent, composition of occlusion, collateral status, and glycemia.^{3–8} Endovascular therapy (ET) is an alternative method, more effective in recanalization of occluded vessel, but the clinical superiority of IV-tPA has not yet been proved in large trials.^{9–11} In anterior circulation, recanalization rate and clinical

outcome after IV-tPA have been worst in patients with terminal intracranial artery occlusion and best in distal MCA occlusion.^{12–14} The impact of intravascular thrombus quantity has been evaluated using hyperattenuated arterial sign in noncontrast CT (NCCT) study¹⁵ and using CT angiography (CTA) with semi-quantitative scoring as Clot Burden Score.^{12,13}

With the advent of multidetector CT scanners allowing volumetric whole brain CT perfusion examinations, time-resolved 4-dimensional CTA (4D-CTA) of cerebral vasculature can be used for noninvasive cerebral hemodynamic assessment.^{16–18} The aim of this study was to identify predictors of IV-tPA successful recanalization and outcome in patients with MCA stem (M1) occlusion determined using 4D-CTA temporal maximum intensity projection (tMIP) datasets.

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Materials and Methods

Study Design

We performed a retrospective single-center study of a prospectively acquired data of consecutive patients with final diagnosis ischemic stroke treated with IV-tPA in the period January 2009 to December 2012. Clinical and imaging data, obtained as part of routine stroke care, were reviewed with the approval of The Institutional Review Board.

The standard imaging protocol in patients with suspected acute stroke consists of NCCT followed after exclusion of intracranial hemorrhage with volume perfusion CT examination (VPCT) and CTA of the neck and cerebral arteries for assessment of therapy. The inclusion criteria for our study was the isolated occlusion of the MCA in the M1 and M2 segments, IV-tPA therapy started up to 4.5 hours from symptoms onset, follow-up CTA examination during a time interval of 22 to 26 hours after the IV-tPA administration, and a complete 3-month clinical follow-up. Patients with incomplete M1 occlusion, isolated occlusion of the M2 segment, and occlusion involving internal carotid artery or insufficient technical quality of the VPCT and CTA examination were excluded.

Data on clinical history, demographics, laboratory results, risk factors, prestroke modified Rankin scale (mRS) score were obtained as a part of standard clinical workup by trained staff. The initial neurological deficit and its development 24 hours after IV-tPA administration were assessed using the National Institutes of Health Stroke Scale (NIHSS). Clinical outcome in the 3-month interval was assessed using mRS by a trained neurologist in outpatient clinic or by telephone contact with caregivers and dichotomized into favorable outcome (mRS 0–2) and poor clinical outcome (mRS 3–6). The pathogenesis of stroke was classified according Trial of Org 10172 (TOAST) criteria.

Imaging Protocol

CT examinations consisted of NCCT, VPCT, and CTA on admission and follow-up NCCT and CTA were performed on a dual-source computed tomograph (Somatom Definition, Siemens Healthcare, Erlangen, Germany). NCCT in the range of whole brain was performed in spiral mode with collimation 64×0.6 mm, rotation time 0.5 seconds, tube voltage 120 kV, and tube current 320 mAs. Series in orthogonal projections (6-mm section width) were performed for tissue evaluation. Thin series (1-mm section width) were performed for hyperdense MCA sign (HDMCAS) assessment. VPCT covering the whole brain (136 mm) was performed by using a spiral shuttle mode consisting of 25 repeated scans with a duration of 1.75 seconds (collimation 24×1.2 mm, rotation 0.33 seconds, 100 kV, 150 mAs). The acquisition was started together with the onset of intravenous application of 40 mL (350 mg/mL - Iomeron 350, Bracco, Italy) of iodine contrast agent at a flow-rate of 5 mL/s and a saline flush of 60 mL at the same rate (cubital vein or vein at the hand dorsum). Axial images with a 1.5-mm section width (increment 0.7 mm) were reconstructed (total 4800 images), processed in dedicated VPCT Neuro (Syngo, Siemens Healthcare, Erlangen, Germany) application, and tMIP series were created for further evaluation. The cranio-cervical CTA was performed (collimation 2×64×0.6 mm, 120 kV, 62 mAs, rotation 0.33 seconds, pitch factor 0.7) using 60 mL of iodine contrast agent (350 mg/mL - Iomeron 350, Bracco, Italy) at a flow-rate of 4 mL/s with a saline flush of 50 mL. The examination was started using bolus-tracking technique monitoring the density increase in the ascending aorta (threshold 100 Hounsfield Unit [HU]), the scanning direction being caudo-cranial. Series reconstructed at the section width 0.6 mm (increment 0.4 mm) was performed for further evaluation. The same parameters were used for follow-up examination after IV-tPA.

Image Analysis

Image analysis was performed at the Syngo Leonardo workstation (Siemens Healthcare, Erlangen, Germany). Two readers (radiologists with 8 and 5 years' experience in neuroimaging) blinded to clinical information assessed CT data set of all patients. To determine

intraobserver variability, all images were assessed twice in month interval and in randomized order. The presence of HDMCAS was defined by the following criteria^{19,20}: spontaneous visibility of the whole or part of horizontal segment of the MCA, density of the MCA higher than that of the surrounding brain, disappearance on bone windows, unilaterality, and absence of subarachnoid bleeding. The M2 dot sign was defined as hyperattenuation of an arterial structure in the Sylvian fissure relative to the contralateral side and was not considered sufficient for diagnosis of HDMCAS when present in isolation. CTA-based measurement of vessel attenuation in HU of occluded M1 and corresponding contralateral site was done by placing a small round region of interest throughout the artery, and the average of the 2 highest HU values was used for further analysis. Absolute HU of symptomatic site was also corrected for hematocrit using the HU ratio ($rHU = HU \text{ thrombus} / HU \text{ contralateral MCA}$).

VPCT data-sets were processed using a dynamic analysis package (VPCT Neuro, Syngo, Siemens Healthcare, Erlangen, Germany) with automatic motion correction and noise reduction technique. To assess initial extent of infarction, cerebral blood volume (CBV) maps were scored using the Alberta Stroke Program Early CT Scale (ASPECTS) score evaluated. Each ASPECTS region was visually evaluated for relatively low CBV compared with the mirror region in the contralateral hemisphere.^{21–23} To determine vascular occlusion, initially the differentiation between stenosis and complete occlusion was performed (tMIP and cine 4D-CTA).²⁴ Subsequently, the occlusion length measurement was performed in the standard viewing software (Syngo 3D, Siemens Healthcare, Erlangen, Germany) using the MIP reconstruction (2-mm section width). According to the thrombus orientation, 2 adapted oblique planes (2D measurement) were performed—in these planes, the occlusion length was measured manually between proximal and distal occlusion end using the freehand curve function with respect of anatomic course. The longer diameter of both planes that corresponded more to the anatomic course of the MCA was used in the statistical analysis. In case of continuous M1 and M2 segment occlusion with substantially different paths of both segments, the lengths were measured separately and were summed. The longest occlusion in the M2 segment was measured using the above-mentioned methods (Figure 1). Finally, the length of M1 proximal stump was measured.

We used 3 angiography parameters of quantitative values in our statistical analysis of recanalization and outcome prediction: (1) the whole length of occlusion including both occlusion in segment M1 and eventually M2, if involved (M1/M2), (2) the occlusion length only in the M1 segment (M1), and (3) the length of nonoccluded proximal part of M1 segment (M1 stump) for localization of clot origin in M1 segment. Moreover (4), we used qualitative parameters for differentiation of pure M1 segment occlusion (M1 only) and occlusion extended to M2 segment (M1+M2).

In addition thick sections tMIP were evaluated for the presence of collaterals in the MCA territory comparing with contralateral hemisphere on a 4-point scale: (0) absent (%), (1) >0 but <50%, (2) ≥50% but <100%, (3) normal (100%).^{13,18,25} For statistical analysis, the scale was divided into good (score 2–3) and poor collaterals (score 0–1).

Recanalization Assessment

In all the patients, the follow-up CTA examination was done in a time interval of 22 to 26 hours after the IV-tPA onset. The recanalization effect was evaluated using the thrombolysis in myocardial infarction criteria (Grade 0 – no recanalization of M1, Grade 1 – partial or complete filling of M1 with persistent occlusion a least 1 M2 branch, Grade 2 – partial or complete filling of M1 with complete filling of the distal M2 branches flow, Grade 3 – complete recanalization with filling of all distal branches, including M3 and M4) – grades 2 and 3 were considered to successful recanalization.^{26–28}

Statistical Analysis

Data are reported using standard descriptive statistics. Categorical variables were compared with χ^2 and Fisher exact tests and continuous variables with the Mann–Whitney *U* test. Logistic regression was

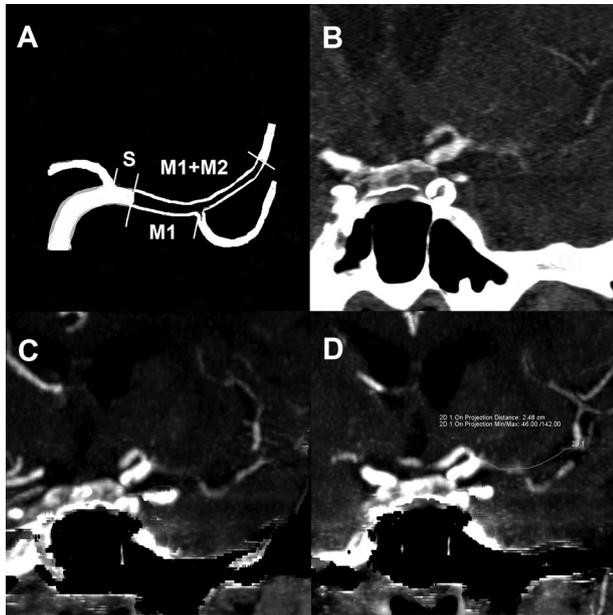


Figure 1. The diagram showing measured parameters: S indicates the length of proximal stump; M1, the occlusion length in M1 segment; M1+M2, the whole length of occlusion, the longest occlusion of M2 segment was measured (A). The comparison of conventional maximum intensity projection (MIP) of CT angiography (CTA) with poor filling of peripheral branches of middle cerebral artery behind M1 occlusion without identifiable distal end of occlusion (B) and temporal MIP (tMIP) reconstruction of 4-dimensional CTA data with 2D measurement, the longer distance was used in statistical analysis (C and D).

performed to determine the independent predictors of successful recanalization (thrombolysis in myocardial infarction 2–3), and favorable outcome (mRS 0–2). Variables of interest were age, sex, baseline clinical variables (NIHSS score on admission, atrial fibrillation, arterial hypertension, diabetes mellitus, hypercholesterolemia, previous antithrombotic and statin therapy, blood glucose and cholesterol), pathogenesis, onset-to-treatment time, the total length of M1/M2 occlusion, the length of occlusion in M1 segment, the extension of occlusion from M1 to M2 segment as a categorical variable, the length of M1 stump, presence of HDMCAS, absolute HU, rHU, collateral score, and CBV ASPECTS score. Successful recanalization (thrombolysis in myocardial infarction 2–3) was also included in outcome analysis. Each of these predictors was examined in univariate analysis. Forward stepwise logistic regression including all variables with $P < 0.2$ in univariate analysis was performed. The results are expressed as odds ratio (OR) with 95% confidence interval (CI). A probability value of < 0.05 was considered statistically significant. Receiver operating characteristic analysis and Matthews correlation coefficient was used to determine the optimal cut-off value of significant continuous variables. Inter-observer (HDMCAS, HU, collateral score, CBV ASPECTS, and CTA) and intraobserver (40 patients, 1 month later in random order, only tMIP) agreements were evaluated using intraclass correlation coefficients and κ statistics.

Results

Baseline Data

Among 411 patients treated with IV-tPA, we identified 142 patients with MCA impairment, 80 of whom with isolated M1-M2 occlusion were included in this study. The remainder were excluded because of significant impairment of ipsilateral common or internal carotid artery ($n=27$), incomplete M1 occlusion ($n=7$), occlusion originating beyond M1 ($n=25$),

and insufficient technical quality of CT data ($n=10$). The main baseline data are summarized in Tables 1 and 2. Mean age was 70.9 ± 12.8 (range, 34–96) years with 41% being male patients. Median baseline NIHSS score was 16 (range, 6–25) and onset to treatment time was 155 minutes (range, 90–275). The distal end of occlusion was not identifiable using CTA datasets in 32 patients (40%). The length of the complete MCA occlusion was measurable in all the patients using the tMIP datasets. In 57 (71%) patients, there was isolated M1 segment occlusion; in 23 patients (29%), there was extension to the M2 segment. The median length of MCA occlusion was 15.4 mm (range, 2.9–26.2), the median length of occlusion in M1 segment was 12.7 mm (range, 2.6–26.2), the median length of M1 stump was 7.8 mm (range, 0–23.0), and HDMCAS was present in 67 (84%) patients. There was no significant relation of HU values and rHU to stroke etiology ($P=0.886$ and $P=0.690$).

Recanalization

Successful recanalization after IV-tPA (thrombolysis in myocardial infarction 2 and 3) was achieved in 37 individuals (46%). Potential predictors of recanalization are summarized in Table 1. In the univariate analysis, baseline NIHSS score ($P=0.015$), the whole length of occlusion (M1/M2) ($P=0.009$), and the length of occlusion in M1 segment ($P=0.003$) were significant negative factors for successful recanalization. Neither presence of HDMCAS nor HU clot density did significantly affect recanalization. In multivariate logistic regression analysis, the length of M1 segment occlusion (OR, 0.82; 95% CI, 0.73–0.92; $P=0.0007$) and the extension to M2 segment as a category (OR, 4.58; 95% CI, 1.39–15.05; $P=0.012$) were significant independent predictors of recanalization with overall model fit $P=0.0004$. Other clinical and CT variables (vascular risk factors, pathogenesis, time to treatment, baseline NIHSS, the whole length of M1/M2 occlusion, the length of M1 stump, HDMCAS, HU, rHU, CVB ASPECTS score) were dropped from final model.

Based on the logistic regression analysis, we performed receiver operating characteristics curve analysis for determination of optimal cutoff value for the length of occlusion in M1 segment. The optimal value was found to be 12 mm, (Matthews correlation coefficient 0.373) with sensitivity 0.67 (95% CI, 0.518–0.833) and specificity 0.71 (95% CI, 0.551–0.844), and odds ratio 4.81 (95% CI, 1.86–12.40; $P=0.0012$) (Figure 2).

Outcome

Intracerebral hemorrhage developed after IV-tPA in 17 patients, and in 3 cases the hemorrhage was symptomatic. The outcome was assessed at a 3-month interval. Follow-up information was obtained in all patients. Favorable outcome (mRS 0–2) was achieved in 25 patients (31%; 6 patients with mRS 0, 10 patients with mRS 1, 9 patients with mRS 2, 8 patients with mRS 3, 10 patients with mRS 4, 22 patients with mRS 5), mortality during a 3-month follow-up was 19% (15 patients). In univariate analysis, lower baseline NIHSS ($P=0.0005$), successful recanalization ($P=0.0007$), and the length of both whole occlusion M1/M2 ($P=0.001$), the length in M1 segment ($P=0.0002$), and CBV ASPECTS score ($P=0.011$) were significant predictive factors for favorable outcome (Table 2).

Table 1. Baseline Characteristics of 80 Patients With Medial Cerebral Artery Occlusion Stroke in Context of Successful Recanalization

Characteristics	Patients With MCA Occlusion (n=80)	Patients With Recanalization TIMI 2–3 (n=37; 46%)	Patients With Recanalization TIMI 0–1 (n=43; 54%)	P Value
Age, y; median (range)	73 (23–91)	72 (41–96)	75 (23–91)	0.539
Female, n, %	47 (59)	14 (62)	23 (61)	0.566
Hypertension, n, %	65 (81)	30 (80)	35 (81)	0.971
Diabetes mellitus, n, %	26 (33)	14 (38)	12 (28)	0.346
Baseline glucose, median (range)	7.3 (4.8–27.5)	7.0 (4.8–14.8)	7.5 (5.1–27.5)	0.460
Atrial fibrillation, n, %	40 (50)	21 (57)	19 (44)	0.262
Statin therapy, n, %	13 (16)	8 (22)	5 (12)	0.233
Baseline cholesterol, median (range)	4.7 (2.4–6.8)	4.6 (2.4–6.5)	4.7 (2.4–6.8)	0.519
Antithrombotic therapy, n, %	25 (31)	12 (32)	12 (35)	0.832
Cardioembolic pathogenesis, n, %	46 (58)	22 (59)	24 (56)	0.742
Time-to-treatment, median (range)	155 (90–275)	165 (90–275)	160 (109–250)	0.858
Baseline NIHSS, median (range)	16 (6–25)	14 (6–22)	17 (6–25)	0.015*
Type of MCA occlusion				
M1 only, n, %	57 (71)	30 (81)	27 (62)	0.076*
M1+M2, n, %	23 (29)	7 (9)	16 (38)	
Length of MCA occlusion				
M1, median (range)	12.7 (2.9–26.2)	9.3 (2.9–20.5)	13.9 (5.3–26.2)	0.001*
M1/M2, median (range)	15.4 (2.9–44.5)	13.2 (2.9–27.2)	16.9 (6.3–44.5)	0.002*
Length of M1 stump, median (range)	7.8 (0–23.0)	7.1 (0–23.0)	8.0 (0–20.8)	0.317
HDMCAS, n, %	67 (84)	30 (82)	37 (86)	0.549
Absolute HU, median (range)	64 (48–76)	64 (48–72)	65 (49–76)	0.339
rHU, median (range)	1.26 (0.86–1.50)	1.25 (0.89–1.50)	1.26 (0.86–1.43)	0.822
tMIP collateral score, median (range)	2 (1–3)	2 (1–3)	3 (1–3)	0.360
CBV ASPECTS score, median (range)	8 (2–10)	8 (3–10)	7 (2–10)	0.561

ASPECTS indicates Alberta Stroke Program Early CT Scale; CBV, cerebral blood volume; HDMCAS, hyperdense MCA sign; HU, Hounsfield Unit; M1, occlusion length only in M1 segment; M1/M2, complete occlusion length (M1 or M1 and M2 segment); MCA, middle cerebral artery; NIHSS, National Institutes of Health Stroke Scale; and TIMI, thrombolysis in myocardial infarction.

*Variable included in multivariable model ($P < 0.2$).

In multivariate logistic regression analysis, baseline NIHSS (OR, 0.82; 95% CI, 0.72–0.93; $P = 0.003$) and the length of occlusion M1 in segment (OR, 0.79; 95% CI, 0.69–0.91; $P = 0.0008$) were significant independent predictors of favorable outcome with overall model fit $P < 0.0001$ (Table 3). Other clinical variables (vascular risk factors, pathogenesis, time to treatment, recanalization status after 24 hours, extension to M2 segment, the whole length of M1/M2 occlusion, the length of M1 stump, HDMCAS, HU, rHU, CVB ASPECTS score) were dropped from final model. The multivariate analysis was repeated with exclusion of recanalization and converged to the same final model.

As in case of recanalization analysis, receiver operating characteristic analysis was used for determination the optimal cut-off value for the M1 occlusion length in favorable outcome prediction. The optimal value was found to be 11 mm, (Matthews correlation coefficient 0.470) with sensitivity 0.74 (95% CI, 0.591–0.887) and specificity 0.76 (95% CI, 0.618–0.892), and odds ratio 8.74 (95% CI, 2.81–27.20; $P = 0.0002$) (Figure 3).

There was substantial interobserver agreements for HDMCAS ($\kappa = 0.71$) and good agreement for CVB ASPECTS

score ($\kappa = 0.86$), HU measurement (intraclass correlation coefficient=0.75), and occlusion length (intraclass correlation coefficient=0.93) and intraobserver agreement (intraclass correlation coefficient=0.97).

Discussion

In this study, the length of occlusion in M1 segment in patients with proximal MCA occlusion, measured by tMIP derived from CT perfusion data, was an independent predictor of IV-tPA recanalization after 24 hours and favorable outcome after 3 months. Patients with M1 and continuous M1/M2 segment occlusion were included in our study. Our results confirmed that M2 involvement despite its extent is a significant negative factor for IV-tPA recanalization, but a significant relation with clinical outcome was not proved. The main reason is probably the importance of occluded perforating arteries originating in M1 segment, but probably because of its extreme variability, we did not find any correlation with the length of proximal stump as a localizing parameter of M1 occlusion.²⁹

Our results support evidence that IV-tPA radiological and clinical effectiveness in MCA occlusion is limited and highly

Table 2. Baseline Characteristics of 80 Patients With Medial Cerebral Artery Occlusion Stroke in Context of Favorable Outcome

Characteristics	Patients With MCA Occlusion (n=80)	Patients With Favorable Outcome mRS (0–2) (n=25; 31%)	Patients With Poor Outcome mRS (3–6) (n=55; 69%)	P Value
Age, y; median (range)	73 (23–91)	69 (41–87)	76 (23–96)	0.062*
Female, n, %	47 (59)	14 (56)	33 (60)	0.736
Hypertension, n, %	65 (81)	20 (80)	45 (81)	0.847
Diabetes mellitus, n, %	26 (33)	7 (28)	19 (35)	0.563
Baseline glucose, median (range)	7.3 (4.8–27.5)	7.3 (5.3–13.2)	7.3 (4.8–27.5)	0.444
Atrial fibrillation, n, %	40 (50)	12 (48)	28 (51)	0.809
Statin therapy, n, %	13 (16)	3 (12)	10 (18)	0.233
Baseline cholesterol, median (range)	4.7 (2.4–6.8)	4.7 (2.4–6.5)	4.6 (3.1–6.8)	0.688
Antithrombotic therapy, n, %	25 (31)	7 (28)	18 (33)	0.673
Cardioembolic pathogenesis, n, %	46 (58)	14 (56)	32 (58)	0.855
Time-to-treatment, median (range)	155 (90–275)	150 (98–270)	160 (90–275)	0.834
Baseline NIHSS, median (range)	16 (6–25)	13 (6–21)	17 (6–25)	0.0005*
Type of MCA occlusion				
M1 only, n, %	57 (71)	20 (80)	37 (67)	0.248
M1+M2, n, %	23 (29)	5 (20)	18 (33)	
Length of MCA occlusion				
M1, median (range)	12.7 (2.9–26.2)	8.1 (3.0–18.8)	14.3 (2.9–26.2)	0.0002*
M1/M2, median (range)	15.4 (2.9–44.5)	9.2 (3.0–27.5)	16.5 (2.9–44.5)	0.001*
Length of M1 stump, median (range)	7.1 (0–23.0)	8.5 (0–20.8)	7.1 (0–23)	0.223
HDMCAS, n, %	67 (84)	18 (72)	49 (89)	0.063*
Absolute HU, median (range)	64 (48–76)	63 (48–72)	65 (49–76)	0.060*
rHU, median (range)	1.26 (0.86–1.50)	1.22 (0.89–1.40)	1.28 (0.86–1.50)	0.075*
Collateral score, median (range)	2 (1–3)	2 (1–3)	3 (1–3)	0.488
CBV ASPECTS score, median (range)	8 (2–10)	8 (3–10)	7 (2–9)	0.011*
Recanalization TIMI 2–3, n, %	37 (46)	19 (76)	18 (46)	0.0007*

ASPECTS indicates Alberta Stroke Program Early CT Scale; CBV, cerebral blood volume; HDMCAS, hyperdense MCA sign; HU, Hounsfield Unit; M1, occlusion length only in M1 segment; M1/M2, complete occlusion length (M1 or M1 and M2 segment); MCA, middle cerebral artery; mRS, modified Rankin scale; NIHSS, National Institutes of Health Stroke Scale; and TIMI, thrombolysis in myocardial infarction.

*Variable included in multivariable model ($P < 0.2$).

dependent on age, site of occlusion, amount and character of thromboembolic material, and collateral circulation with its reflection in initial neurological deficit.^{12–15,30} Similar predictive factors seem to affect results of ET.³¹ So there is a need for selection of reliable parameter which can be used in decision making in selection of more aggressive recanalization therapy.

In CTA the contrast level in an artery depends on scanning protocol and the circulation phase at the time of acquisition, and suboptimal timing of the data acquisition may lead to a significant bias of the examination result.³² 4D-CTA overcomes this problem because of its dynamic nature and selection of the optimal circulation phase with improvement in image quality especially in case of delayed filling of collateral circulation in LVO and ability of assess completeness of LVO.^{16–18} For this reason, we used 4D-CTA for precise evaluation of the presence, extent, and completeness of M1 occlusion.

Recent studies have been published that focused on the possibility of LVO extent determination using the special scoring system. The Clot Burden Score is 10-point scoring system to determine the occlusion extent, and a Clot Burden

Score of >6 (corresponding only proximal or distal half of M1 with only 1 M2 occlusion) predicted higher recanalization rate and good clinical outcome.^{12,13} However, the assessment was performed using the conventional CTA, a method that has limitations in detection of the distal end of the occlusion, according to our results. Until now, a single study focused on the determination of the absolute length of the LVO and possible prediction of recanalization success—the clot length >8 mm has nearly no potential for recanalization. The authors used the HDMCA sign in 2.5 mm NCCT slices to provide the assessment.¹⁵ This value does not correspond to our results; however, individual methods of the measurement and source datasets were different, and recanalization assessment after 20.7 ± 6.0 hours was done mainly using transcranial Doppler ultrasonography. We did not find such a clear cutoff value because recanalization appeared even in longer occlusions. ROC analysis for the occlusion length in M1 segment as a predictor of successful recanalization with almost linear shape means relatively low specificity and moderate sensitivity of resulting cutoff value.

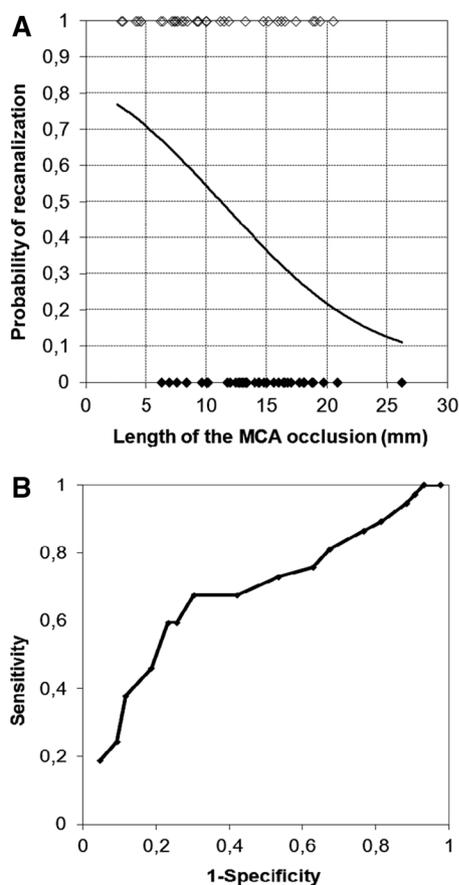


Figure 2. Logistic regression curve representing an estimate of successful recanalization probability by intravenous thrombolysis (IV-tPA), depending on the length of occlusion in M1 segment, odds ratio 0.87 (0.78–0.96) $P=0.0047$ (A). Receiver operating characteristic curve for the occlusion length in M1 segment as a predictor of successful recanalization by IV-tPA, the optimal value 12 mm, area under curve of 0.69, $P=0.0012$ (B). MCA indicates middle cerebral artery.

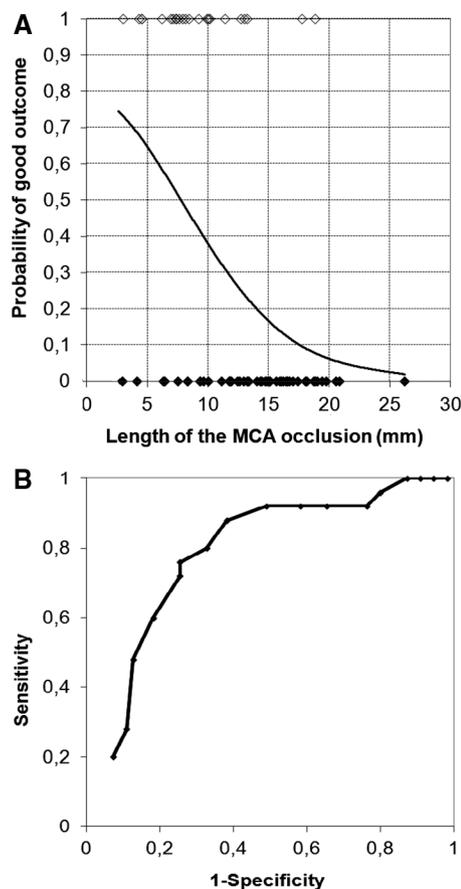


Figure 3. Logistic regression curve representing an estimate of a favorable functional outcome probability after intravenous thrombolysis (IV-tPA), treatment depending on the length of M1 occlusion, odds ratio 0.80 (0.71–0.90), $P=0.0004$ (A). Receiver operating characteristic curve for the occlusion length in M1 segment as a predictor of a favorable functional outcome after IV-tPA treatment, the optimal value 11 mm, area under curve 0.78, $P=0.0001$ (B). MCA indicates middle cerebral artery.

The main result of our study is identification of crucial impact of the length of M1 segment occlusion for prediction of IV-tPA clinical outcome. Other CT parameters were explored in recent studies. Clot composition assessed by HU density was a predictor of successful IV-tPA early recanalization and stroke subtype.³⁰ Because of later recanalization assessment,

we could not compare this findings. Our results correspond with other study, where neither HDMCAS nor clot HU values were useful for IV-tPA effect and pathogenesis prediction.¹⁹ Moreover, inconsistency in HU quantification methods and lower interobserver agreement limit these findings.

Table 3. Independent Predictors of Recanalization and Favorable Outcome

Independent Predictor	Odds Ratio (95% Confidence Interval)	PValue
Favorable outcome		
Baseline NIHSS	0.82 (0.72–0.93)	0.003
Length of M1 occlusion	0.79 (0.69–0.91)	0.0008
Overall model fit		<0.0001
Successful recanalization		
M1 occlusion only	4.58 (1.39–15.05)	0.012
Length of M1 occlusion	0.82 (0.73–0.92)	0.0007
Overall model fit		0.0001

NIHSS indicates National Institutes of Health Stroke Scale; and TIMI, thrombolysis in myocardial infarction.

There is lack of consensus in objective interpretation of CT perfusion parameters. We included the CBV ASPECTS score in our analysis as a predictor of baseline infarct extension, which proved to be a reliable parameter of outcome after IV-tPA and ET.^{21,22,33} Insufficient collateral circulation on CTA and 4D-CTA has been shown as a negative predictor in LVO stroke.^{13,18,25} We could not replicate this results because most of our patients have a good collateral status CBV ASPECTS score profile. One possible explanation is involvement of deep structures, which can be missed in collateral scoring and their clinical impact could be underestimated in the context of summary ASPECTS score.

Our study has some limitations that are necessary to mention. In a retrospective analysis of prospectively acquired data, there is a potential for bias in selection of subjects. The 24-hour interval from the IV-tPA onset for recanalization assessment, which we used, was considered to be suitable when other recanalization method was not available in our institution. The

main limitation of the occlusion length determination as an independent factor for IV-tPA recanalization is assessment of the effect after ≈ 24 hours and lack of information about early recanalization. Possibility of later reperfusion in patients with longer occlusion can cause bias in assessment of its effect on outcome. This hypothesis is supported by fact that recanalization status after 24 hours was dropped from final model. The limited number of subjects reduces statistical significance of multivariate analysis. The vessel analysis as gold standard could be questionable, but in our opinion, there is no method more suitable. The digital subtraction angiography is not indicated as the first vascular imaging modality. The comparison of both methods in patient indicated o ET may be limited by bridging IV-tPA therapy and time interval.

The importance of our study is based on detailed assessment of homogenous group of patients with MCA/M1 occlusion with relation to the effect of IV-tPA in the context of searching for a subgroup of patients, who would be optimal candidates for rapid triage for ET, because the position of this method has not been fully established.⁹ We identified single independent highly reproducible radiological predictor of IV-tPA clinical outcome. Comparison with results of ET in this subgroup of patients could help in better stratification of stroke patients in recanalization treatment planning.

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Disclosures

None.

References

- Hernández-Pérez M, Pérez de la Ossa N, Aleu A, Millán M, Gomis M, Dorado L, et al. Natural history of acute stroke due to occlusion of the middle cerebral artery and intracranial internal carotid artery [published online ahead of print November 19, 2013]. *J Neuroimaging*. doi: 10.1111/jon.12062. <http://onlinelibrary.wiley.com/doi/10.1111/jon.12062/full>. Accessed December 10, 2013.
- Wardlaw JM, Murray V, Berge E, del Zoppo G, Sandercock P, Lindley RL, et al. Recombinant tissue plasminogen activator for acute ischaemic stroke: an updated systematic review and meta-analysis. *Lancet*. 2012;379:2364–2372.
- Molina CA, Montaner J, Arenillas JF, Ribo M, Rubiera M, Alvarez-Sabín J. Differential pattern of tissue plasminogen activator-induced proximal middle cerebral artery recanalization among stroke subtypes. *Stroke*. 2004;35:486–490.
- Rubiera M, Ribo M, Delgado-Mederos R, Santamarina E, Delgado P, Montaner J, et al. Tandem internal carotid artery/middle cerebral artery occlusion: an independent predictor of poor outcome after systemic thrombolysis. *Stroke*. 2006;37:2301–2305.
- Tandberg Askevold E, Naess H, Thomassen L. Predictors for recanalization after intravenous thrombolysis in acute ischemic stroke. *J Stroke Cerebrovasc Dis*. 2007;16:21–24.
- Zangerle A, Kiechl S, Spiegel M, Furtner M, Knoflach M, Werner P, et al. Recanalization after thrombolysis in stroke patients: predictors and prognostic implications. *Neurology*. 2007;68:39–44.
- Ribo M, Molina C, Montaner J, Rubiera M, Delgado-Mederos R, Arenillas JF, et al. Acute hyperglycemia state is associated with lower tPA-induced recanalization rates in stroke patients. *Stroke*. 2005;36:1705–1709.
- Miteff F, Levi CR, Bateman GA, Spratt N, McElduff P, Parsons MW. The independent predictive utility of computed

- tomography angiographic collateral status in acute ischaemic stroke. *Brain*. 2009;132(pt 8):2231–2238.
- Broderick JP, Palesch YY, Demchuk AM, Yeatts SD, Khatri P, Hill MD, et al; Interventional Management of Stroke (IMS) III Investigators. Endovascular therapy after intravenous t-PA versus t-PA alone for stroke. *N Engl J Med*. 2013;368:893–903.
- Ciccione A, Valvassori L, Nichelatti M, Sgoifo A, Ponzio M, Sterzi R, et al; SYNTHESIS Expansion Investigators. Endovascular treatment for acute ischemic stroke. *N Engl J Med*. 2013;368:904–913.
- Kidwell CS, Jahan R, Gornbein J, Alger JR, Nenov V, Ajani Z, et al; MR RESCUE Investigators. A trial of imaging selection and endovascular treatment for ischemic stroke. *N Engl J Med*. 2013;368:914–923.
- Puetz V, Dzialowski I, Hill MD, Subramaniam S, Sylaja PN, Krol A, et al; Calgary CTA Study Group. Intracranial thrombus extent predicts clinical outcome, final infarct size and hemorrhagic transformation in ischemic stroke: the clot burden score. *Int J Stroke*. 2008;3:230–236.
- Tan IY, Demchuk AM, Hopyan J, Zhang L, Gladstone D, Wong K, et al. CT angiography clot burden score and collateral score: correlation with clinical and radiologic outcomes in acute middle cerebral artery infarct. *AJNR Am J Neuroradiol*. 2009;30:525–531.
- Mendonça N, Rodriguez-Luna D, Rubiera M, Boned-Riera S, Ribo M, Pagola J, et al. Predictors of tissue-type plasminogen activator nonresponders according to location of vessel occlusion. *Stroke*. 2012;43:417–421.
- Riedel CH, Zimmermann P, Jensen-Kondering U, Stinglele R, Deuschl G, Jansen O. The importance of size: successful recanalization by intravenous thrombolysis in acute anterior stroke depends on thrombus length. *Stroke*. 2011;42:1775–1777.
- Frölich AM, Psychogios MN, Klotz E, Schramm R, Knauth M, Schramm P. Angiographic reconstructions from whole-brain perfusion CT for the detection of large vessel occlusion in acute stroke. *Stroke*. 2012;43:97–102.
- Frölich AM, Schrader D, Klotz E, Schramm R, Wasser K, Knauth M, et al. 4D CT angiography more closely defines intracranial thrombus burden than single-phase CT angiography. *AJNR Am J Neuroradiol*. 2013;34:1908–1913.
- Smit EJ, Vonken EJ, van Seeters T, Dankbaar JW, van der Schaaf IC, Kappelle LJ, et al. Timing-invariant imaging of collateral vessels in acute ischemic stroke. *Stroke*. 2013;44:2194–2199.
- Topcuoglu MA, Arsava EM, Kursun O, Akpinar E, Erbil B. The utility of middle cerebral artery clot density and burden assessment by noncontrast computed tomography in acute ischemic stroke patients treated with thrombolysis. *J Stroke Cerebrovasc Dis*. 2014;23:e85–e91.
- Leys D, Pruvo JP, Godefroy O, Rondepierre P, Leclerc X. Prevalence and significance of hyperdense middle cerebral artery in acute stroke. *Stroke*. 1992;23:317–324.
- Psychogios MN, Schramm P, Frölich AM, Kallenberg K, Wasser K, Reinhardt L, et al. Alberta Stroke Program Early CT Scale evaluation of multimodal computed tomography in predicting clinical outcomes of stroke patients treated with aspiration thrombectomy. *Stroke*. 2013;44:2188–2193.
- Sillanpaa N, Saarinen JT, Rusanen H, Hakomaki J, Lahteela A, Numminen H, et al. CT perfusion ASPECTS in the evaluation of acute ischemic stroke: thrombolytic therapy perspective. *Cerebrovasc Dis Extra*. 2011;1:6–16.
- Sillanpaa N, Saarinen JT, Rusanen H, Hakomaki J, Lahteela A, Numminen H, et al. The clot burden score, the Boston Acute Stroke Imaging Scale, the cerebral blood volume ASPECTS, and two novel imaging parameters in the prediction of clinical outcome of ischemic stroke patients receiving intravenous thrombolytic therapy. *Neuroradiology*. 2012;54:663–672.
- Frölich AM, Psychogios MN, Klotz E, Schramm R, Knauth M, Schramm P. Antegrade flow across incomplete vessel occlusions can be distinguished from retrograde collateral flow using 4-dimensional computed tomographic angiography. *Stroke*. 2012;43:2974–2979.
- Calleja AI, Cortijo E, García-Bermejo P, Gómez RD, Pérez-Fernández S, Del Monte JM, et al. Collateral circulation on perfusion-computed tomography-source images predicts the response to stroke intravenous thrombolysis. *Eur J Neurol*. 2013;20:795–802.
- Zaidat OO, Lazzaro MA, Liebeskind DS, Janjua N, Wechsler L, Nogueira RG, et al. Revascularization grading in endovascular acute ischemic stroke therapy. *Neurology*. 2012;79(13 suppl 1):S110–S116.
- Arnold M, Nedeltchev K, Remonda L, Fischer U, Brekenfeld C, Keserue B, et al. Recanalisation of middle cerebral artery occlusion after intra-arterial thrombolysis: different recanalisation grading

- systems and clinical functional outcome. *J Neurol Neurosurg Psychiatry*. 2005;76:1373–1376.
28. Zaidat OO, Yoo AJ, Khatri P, Tomsick TA, von Kummer R, Saver JL, et al; Cerebral Angiographic Revascularization Grading (CARG) Collaborators; STIR Revascularization working group; STIR Thrombolysis in Cerebral Infarction (TICI) Task Force. Recommendations on angiographic revascularization grading standards for acute ischemic stroke: a consensus statement. *Stroke*. 2013;44:2650–2663.
 29. Marinkovic S, Gibo H, Milisavljevic M, Cetkovic M. Anatomic and clinical correlations of the lenticulostriate arteries. *Clin Anat*. 2001;14:190–195.
 30. Puig J, Pedraza S, Demchuk A, Daunis-I-Estadella J, Terres H, Blasco G, et al. Quantification of thrombus Hounsfield units on noncontrast CT predicts stroke subtype and early recanalization after intravenous recombinant tissue plasminogen activator. *AJNR Am J Neuroradiol*. 2012;33:90–96.
 31. Singer OC, Haring HP, Trenkler J, Nolte CH, Bohner G, Reich A, et al. Age dependency of successful recanalization in anterior circulation stroke: the ENDOSTROKE study. *Cerebrovasc Dis*. 2013;36:437–445.
 32. Pulli B, Schaefer PW, Hakimelahi R, Chaudhry ZA, Lev MH, Hirsch JA, et al. Acute ischemic stroke: infarct core estimation on CT angiography source images depends on CT angiography protocol. *Radiology*. 2012;262:593–604.
 33. Lin K, Rapalino O, Law M, Babb JS, Siller KA, Pramanik BK. Accuracy of the Alberta Stroke Program Early CT Score during the first 3 hours of middle cerebral artery stroke: comparison of noncontrast CT, CT angiography source images, and CT perfusion. *AJNR Am J Neuroradiol*. 2008;29:931–936.

Length of Occlusion Predicts Recanalization and Outcome After Intravenous Thrombolysis in Middle Cerebral Artery Stroke

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