Original Contribution

Clinical and Imaging Parameters Associated With Hyperacute Infarction Growth in Large Vessel Occlusion Stroke

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Background and Purpose—Large vessel occlusion stroke leads to highly variable hyperacute infarction growth. Our aim was to identify clinical and imaging parameters associated with hyperacute infarction growth in patients with an large vessel occlusion stroke of the anterior circulation.

Methods—Seven hundred twenty-two consecutive patients with acute stroke were prospectively included in our monocentric stroke registry between 2009 and 2017. We selected all patients with a large vessel occlusion stroke of the anterior circulation, documented times from symptom onset, and CT perfusion on admission for our analysis (N=178). Ischemic core volume was determined with CT perfusion using automated thresholds. Hyperacute infarction growth was defined as ischemic core volume divided by times from symptom onset, assuming linear progression during times from symptom onset to imaging on admission. For collateral assessment, the regional leptomeningeal collateral score (rLMC) was used. Clinical data included the National Institutes of Health Stroke Scale score on admission and cardiovascular risk factors. Regression analysis was performed to adjust for confounders.

Results—Median ischemic core volume was 34.4 mL, and median hyperacute infarction growth was 0.27 mL/min. In regression analysis including age, sex, National Institutes of Health Stroke Scale, clot burden score, diabetes mellitus, smoking, hypercholesteremia, hypertension, Alberta Stroke Program Early CT Score, and rLMC scores, only the rLMC score had a significant, independent association with hyperacute infarction growth (adjusted β=−0.35; P<0.001). Trichotomizing patients by rLMC scores yielded 65 patients with good (rLMC >15), 67 with intermediate (rLMC 11–15) and 46 with poor collaterals (rLMC <11) with an infarction growth of 0.17 mL/min, 0.26 mL/min, and 0.41 mL/min, respectively.

Conclusions—Hyperacute infarction growth strongly depends on collaterals. In primary stroke centers, hyperacute infarction growth may be extrapolated to estimate the stroke progression during transfer times to thrombectomy centers and to support decisions on which patients to transfer. **(*Stroke*. 2019;50:00-00. DOI: 10.1161/STROKEAHA.119.025809.)**

Key Words: collateral circulation ■ computed tomography angiography ■ infarction ■ stroke ■ thrombectomy

Stroke is the leading cause for severe disability, a major cause for cardiovascular death worldwide and one of the most time-critical emergencies in medicine.[1,2] Infarction growth is highly variable before hospital admission as demonstrated by the patients who were included in the DAWN (Clinical Mismatch in the Triage of Wake Up and Late Presenting Strokes Undergoing Neurointervention With Trevo) and DEFUSE 3 (Endovascular Therapy Following Imaging Evaluation for Ischemic Stroke 3) trials beyond 6 hours of symptom onset.[3,4]

As little is known about infarction growth dynamics in humans, our aim was to identify clinical and imaging parameters that affect the hyperacute infarction growth in patients with large vessel occlusion (LVO) stroke of the anterior circulation. Recently, it has been shown that the neuronal loss in patients with a vascular occlusion in the anterior circulation ranges from <35 000 to >27 million neurons per minute.[5] This circumstance is likely attributed to differences in the extent of arterial collaterals among patients with stroke. A highly developed leptomeningeal vascular network may be able to

Received April 2, 2019; final revision received June 22, 2019; accepted July 16, 2019.

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The online-only Data Supplement is available with this article at https://www.ahajournals.org/doi/suppl/10.1161/STROKEAHA.119.025809.

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decelerate infarct progression during the first hours of stroke. Yet, also clinical parameters such as the presence of stroke risk factors can lead to changes in the cerebral vasculature and may influence infarct lesion evolution.[6–15] In the era of extended time windows for endovascular thrombectomy (EVT) and intravenous thrombolysis for patients with salvageable brain tissue, infarction growth dynamics tremendously gain importance, and factors influencing individual stroke progression may guide clinical decision-making on further patient management (eg, treatment selection and decision, which patient to transfer for EVT).[3,4,16,17] Therefore, we used multivariable regression analyses in our study to test for independent associations of clinical and imaging parameters with the infarction growth rate.

Methods

The data that support the findings of this study are available from the corresponding author on reasonable request.

Study Design and Population

Our initial cohort consisted of 722 consecutive patients with stroke from our monocentric stroke registry, which was prospectively recruited from 2009 to 2017. Our retrospective study was approved by the Institutional Review Board, and the requirement for informed consent was waived. Subjects were included in our study if they:

1. Had an LVO stroke of the anterior circulation,
2. the time from symptom onset was documented, and
3. a multiparametric CT for suspected stroke, including CT perfusion (CTP) was performed on admission.

Patients with incomplete data sets were excluded from our analysis, leaving 178 patients for analysis. Figure 1 provides a flow chart of the patient selection. Forty-two patients (23.6%) received intravenous thrombolysis at a primary stroke center and were transferred to our comprehensive stroke center for EVT, but all of these patients had a persistent LVO on CT angiography on admission.

Image Acquisition and Analysis

A 2×192-slice CT-scanner was used for noncontrast CT, CT angiography (CTA) of cerebral vessels, and CTP on admission acquired in the same scanning session at our comprehensive stroke center (SOMATOM Force, Siemens Healthineers, Forchheim, Germany). For CTA, 35 mL of iodinated contrast agent was administered at a flow rate of 5 mL/s with a consecutive 40 mL saline flush at 5 mL/s. For CTP, an extended coverage of 22 cm in the z-axis with continuous sweeps every 1.5 seconds was applied.

Output maps of cerebral blood flow and cerebral blood volume (CBV) were created with a syngo.via commercial package (Siemens Healthineers, Germany) with additional threshold-based calculations of ischemic core volume (ICV) and ischemic penumbra volume. Briefly, cerebral blood flow and CBV are generated with a deconvolution algorithm after time and motion correction.[18,19] Applying a CBV threshold of <1.2 mL/100 mL yielded the ICV.

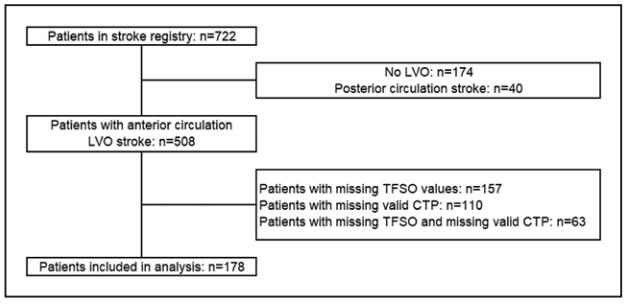

Figure 1. Patient selection flow chart. CTP indicates CT perfusion; LVO, large vessel occlusion; and TFSO, times from symptom onset.

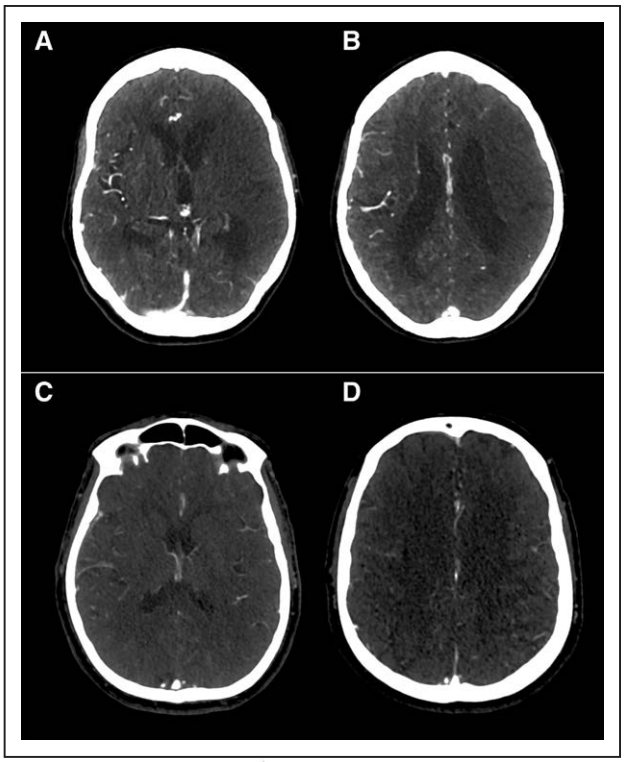

Figure 2. Patient examples with rLMC (regional Leptomeningeal Collaterals) scoring. **A** and **B**, Patient 1 with left-sided middle cerebral artery occlusion. **A**, Ganglionic level. **B**, Supraganglionic level. rLMC score is 9, hyperacute infarction growth is 0.64 mL/min. **C** and **D**, Patient 2 with left-sided middle cerebral artery occlusion. **C**, Ganglionic level. **D**, Supraganglionic level. rLMC score is 18, hyperacute infarction growth is 0.24 mL/min.

Images were read by 2 independent and experienced radiologists blinded to clinical and morphological outcomes. Noncontrast CT data sets were used to determine the Alberta Stroke Program Early CT Score.[20,21] CTA data were analyzed to identify the site of vessel occlusion, the occluded vessel or branch and to determine the clot burden score.[22,23] CTA was further used to assess the regional leptomeningeal collateral (rLMC) score according to Menon et al[24] by evaluating the collateral arteries in topographical regions in comparison with the contralateral side (0= no visible collaterals, 1= less collaterals, and 2= equal or more prominent collaterals than on contralateral side with double-weighted scores for vessels in the sylvian fissure) with an example shown in Figure 2. The rLMC score ranges from 0 to 20, with higher numbers indicating better collateral supply. The infarction growth rate in mL/min at the time of admission was calculated by the following formula,

$$infarction\ growth\ rate\left(\frac{mL}{min}\right)=\frac{ischemic\ core\ volume\left(mL\right)}{time\ from\ symptom\ onset\left(min\right)}$$

assuming linear infarct progression during the time from symptom onset to admission in the hyperacute phase. We provide penumbra volumes and (hypothetical) linear extrapolations for the time to infarct completion based on individual infarction growth dynamics in Figure I and Table I in the online-only Data Supplement. We also used a logarithmic model of infarction growth as experimental data support a logarithmic course of ischemic core development.[25,26] We provide the formula for the infarction growth per logarithmic time scale, the result of the multivariable regression analysis for the association of the rLMC with the infarction growth per natural logarithmic time scale in Table II in the online-only Data Supplement and the patient trichotomization according to rLMC scores with the corresponding

infarction growth per natural logarithmic time scale in Table III in the online-only Data Supplement. As the regression analysis yielded similar results for the independent association of the rLMC score with the infarction growth in our linear and logarithmic model during the hyperacute phase, we conclude that the linear function for the infarction growth in the hyperacute phase can be used as a straightforward approximation. This approach is in line with previous publications.[25,27,28] Follow-up infarction volumes are presented in Table IV in the online-only Data Supplement. Additionally, the association of the rLMC score with the relative ICV growth (relative volume=[core volume]) divided by total ischemic volume (core volume+penumbra volume) and relative volume growth=(relative volume divided by the time from symptom onset) is included in Table V in the online-only Data Supplement. We also performed calculations based on a 5-point filling score for collaterals.[29] The data are provided in Table VI in the online-only Data Supplement.

Clinical Data

The National Institutes of Health Stroke Scale on admission as well as cardiovascular risk factors (smoking, diabetes mellitus, hypercholesteremia, and arterial hypertension as documented in the patient's medical record) were included in our data analyses.

Statistical Analysis

All statistical analyses were performed using SPSS 25 for Windows (IBM Corp, Armonk, NY). All metric and ordinal variables are reported as median (interquartile range). For categorial variables, the numbers and the percentages are given. Analyses of predictive variables for infarction growth used a multivariable linear regression model including age, sex, diabetes mellitus, smoking, arterial hypertension, hypercholesterolemia, Alberta Stroke Program Early CT Score, clot burden score, rLMC score, and National Institutes of Health Stroke Scale on admission. To ensure that variables did not show collinearity, the variance inflation factor was found below the critical value of 2.[30] Figures were made with GraphPad Prism 5 (Graphpad Software, Inc, San Diego). Statistical significance was defined as P values lower than 0.05.

Results

Patient Characteristics

One hundred seventy-eight patients of our prospectively acquired stroke registry fulfilled the inclusion criteria and were selected for our analysis. The median age was 74 years (63–82), 46.6 % were male patients, the median National Institutes of Health Stroke Scale on admission was 13 (9–18). The patient characteristics are presented in Table 1. The median CBV deficit volume (ie, ICV) was 34.4 mL (17.2–58.1), and the median TFSO to the initial CT scan with CTP was 137 min (88–210).

Table 1. Patient Characteristics

	Overall (N=178)	
Patient data		
Age	74	(63–82)
Male, sex	92	(51.7%)
Time from symptom onset, min	137	(88–210)
NIHSS on admission	13	(9–18)
Treatment		
IV thrombolysis	141	(79.2%)
Endovascular therapy	126	(70.8%)
Imaging		
ASPECTS	8	(7–9)
Occluded vessels		
ICA	60	(33.7%)
Carotid T	38	(21.3%)
M1 segment of MCA	115	(64.6%)
M2 segment of MCA	25	(14.0%)
Clot burden score	6	(4–8)
rLMC score	14	(10–18)
Ischemic core volume, mL	34.4	(17.2–58.1)
Infarction growth rate, mL/min	0.27	(0.11–0.48)
Outcome parameters		
90d mRS available	105	(59.0%)
Favorable 90d mRS (0–2)	39	(37.1%)
90d mRS		
0	18	(17.1%)
1	10	(9.5%)
2	11	(10.5%)
3	9	(8.6%)
4	17	(15.6%)
5	5	(4.8%)
6	35	(33.3%)

Values presented are count (percentage) for categorical and median (interquartile range) for ordinal or continuous variables. ASPECTS, Alberta Stroke Program Early CT Score; ICA, internal carotid artery; IV, intravenous; MCA, middle cerebral artery; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; and rLMC score, regional Leptomeningeal Collateral score.

Infarction Growth Dynamics

Assuming linear progression of infarct growth during the hyperacute phase, we calculated a median infarction growth of 0.27 mL/min (0.11–0.48, N=178). A wide range of infarction growth rates is represented in our study sample. In linear regression analyses including age, sex, National Institutes of Health Stroke Scale, clot burden score, diabetes mellitus, smoking, hypercholesterolemia, arterial hypertension, Alberta Stroke Program Early CT Score, and rLMC scores, only the rLMC score showed a significant, independent association with hyperacute infarction growth (adjusted β=−0.35; P<0.001) as shown in Table 2.

Based on observations by Menon et al,[24] we trichotomized patients according to rLMC scores yielding 65 patients with good (rLMC >15; 36.5%), 67 with intermediate (rLMC, 11–15; 37.6%) and 46 with poor collaterals (rLMC <11; 25.8%). The prehospital infarction growth was 0.17 mL/min (0.08–0.32) in patients with good, 0.26 mL/min (0.11–0.44) in patients with intermediate, and 0.41 mL/min (0.25–0.65) in patients with poor collaterals according to the rLMC scores. Figure 3 shows corresponding box plots with the median infarction growth and the whisker boundaries showing the 10th and 90th percentiles for the different rLMC groups. A linear graphical illustration of our single-timepoint measurements for the infarction growth shows the unadjusted data of the ICV

Table 2. Predictors of Infarction Growth Rate

Independent Variables	Infarction Growth Rate		
	Unadjusted β	Adjusted β	*P* Value
Age	–0.004	–0.085	0.364
Male, sex	–0.203	–0.151	0.056
Diabetes mellitus	–0.212	–0.120	0.136
Smoking	–0.019	–0.013	0.874
Hypertension	0.226	0.153	0.092
Hypercholesterolemia	–0.063	–0.045	0.580
ASPECTS	0.059	0.178	0.059
Clot burden score	–0.028	–0.111	0.220
rLMC Score	–0.048	–0.354	<0.001*
NIHSS on admission	0.009	0.108	0.188

ASPECTS, Alberta Stroke Program Early CT Score; rLMC Score, regional Leptomeningeal Collaterals Score; and NIHSS, National Institutes of Health Stroke Scale.

*Statistically significant.

plotted against TFSO to the first CTP scan grouped by collateral grades (Figure 4).

Discussion

In our study, we found that hyperacute infarction growth is strongly associated with the leptomeningeal collateral (LMC) status. Our real-life data from a prospectively acquired stroke database show that an all-comer collective of 178 patients with an LVO stroke of the anterior circulation includes fast, intermediate, and slow stroke progressors. Our findings are in line with recent studies showing that the neuronal loss per minute in patients with an acute ischemic stroke is highly variable.[5] Several studies demonstrated that LMC have an influence on the final infarction volume and on neurological outcomes of patients with stroke.[23,24,29,31–36] CTA-derived collateral flow assessments with a scoring system for rLMC according to Menon et al[24] provide detailed

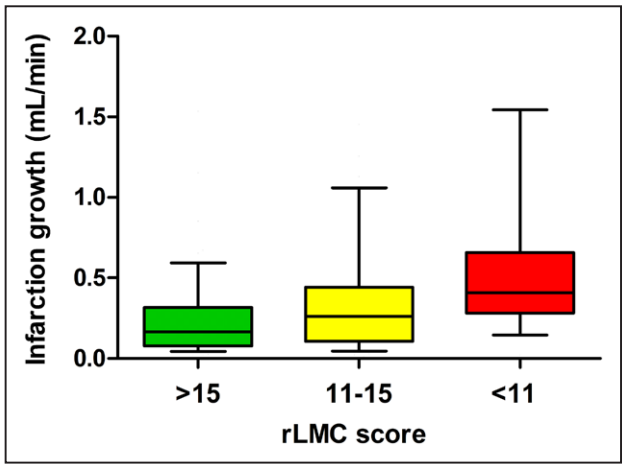

Figure 3. Box plots of infarction growth in patients trichotomized by rLMC (regional Leptomeningeal Collaterals) scores. Box plots showing the median infarction growth and the whisker boundaries showing the 10th and 90th percentiles for the different rLMC groups.

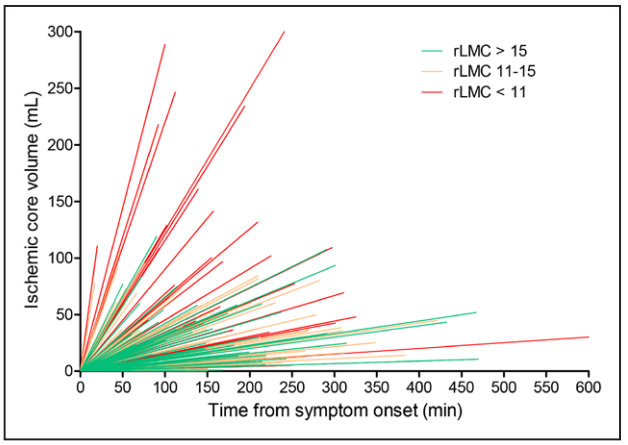

Figure 4. Hyperacute infarction growth in patients stratified by rLMC (regional Leptomeningeal Collaterals) scores. Unadjusted data of the ischemic core volume (ICV) and the times from symptom onset (TFSO) to the first CT perfusion (CTP) scan plotted by collateral grade for patients with low rLMC scores in red, patients with intermediate rLMC scores in yellow and patients with good rLMC scores in green. The figure shows that patients with poor collaterals (red) have a steeper slope of their infarction growth line, indicating a higher infarction growth rate compared with patients with better collateral networks (green and yellow).

information on the arterial collateral status of a patient. We found that the rLMC score is independently associated with the hyperacute infarction growth in patients having an LVO stroke of the anterior circulation in a linear as well as in a natural logarithmic model with similar results.

Recent studies have shown that the hypoperfusion intensity ratio as an automated assessment of collaterals on CTP or magnetic resonance imaging (MRI) is a strong predictor of the infarct progression in patients eligible for EVT.[37,38] It has also been shown that the ratio between cerebral blood flow and time to maximum enhancement >4s or >6s on MRI (within the area of brain tissue with a delay in contrast enhancement on perfusion-weighted imaging) predicts the quality of collaterals in patients with an acute ischemic stroke verified by angiographic assessments.[39,40] A recent study on 35 patients receiving a CTP at a primary stroke center with automated collateral assessment based on the hypoperfusion intensity ratio and undergoing a second CTP or MRI after transfer to a comprehensive stroke center showed a correlation of the collateral status with the infarct core development during transfer.[41]

In line with these results, we found that the hyperacute infarction growth per minute is highly variable and collateral flow assessment with the evaluation of the rLMC score on CTA data sets may be useful to estimate infarct progression in patients with stroke with LVO. By extrapolating the patient-individual infarct progression over her or his expected transfer time, an estimate of the salvaged brain tissue after EVT can be gained and may contribute to a more informed decision-making process. Futile attempts of revascularization with higher risks of consecutive bleeding may be avoided by careful selection of patients according to their collateral status. Furthermore, the collateral score might play a role as a surrogate parameter for the decision, which patients to revascularize after extended time windows if CTP is not available considering that patients with sufficient collateral networks have a slower infarction growth over time and a larger area of

salvageable brain tissue. However, this aspect remains to be elucidated in a separate late time window LVO stroke cohort.

The rLMC score is a very granular yet cumbersome scoring system for the evaluation of LMC. There are simpler scores, such as a 5-point scale for the evaluation of LMC by Maas et al,[29] which we used for additional analysis in the online-only Data Supplement. By applying this score, we did not observe an independent association with the infarction growth rate. This suggests a high individual variability of LMC, which is not represented in less granular scores.

The following limitations need to be considered for the interpretation of our study: First, ICV on admission was calculated with a syngo.via commercial package which uses an established algorithm based on CBV thresholds in CTP maps. It has to be acknowledged that the main software solution in recent trials was RAPID by the provider iSchemaView, which was not available for this study. Our results are, therefore, not directly translatable onto other image post-processing setups. As shown in a limited series of studies, there are small but significant differences in ICV calculations by different software packages, but linear correlations were observed.[18,19] According to a recent study comparing RAPID-derived ICV measures with Philips and Siemens post-processing, Siemens syngo.via outperformed Philips IntelliSpace.[42] Nevertheless, differences were observed with different software packages or different processing algorithms. Further, the determination of ICV with CTP on admission remains challenging and previous studies yielded heterogeneous results comparing CTP-derived ICV on admission with diffusion-weighted MRI.[43,44] Second, the LMC were evaluated visually by using the rLMC scoring technique. The assessment of this score thereby underlies interobserver variability. An automated assessment of LMC in CTA data sets may help to improve reliability. Third, the assumption of linear infarction growth is obviously limited in later stages of stroke development as ischemic volume is naturally limited by the brain volume at risk, which will eventually reach a plateau over time. We also used a natural logarithmic model for our calculations and found similar results for the independent association of the rLMC score with the infarction growth per natural logarithmic time scale as for our linear model. Thus, we conclude that the linear function for the infarction growth can be used as a straightforward approximation in the hyperacute phase in our setting. This is in line with previous publications.[25,27,28] Forth, 42 patients (23.6%) received intravenous thrombolysis at a primary stroke center before transfer to our comprehensive stroke center for EVT, yet all patients were included based on a persistent LVO on CTA on admission. In these cases, we assumed that infarction growth was similar to patients without thrombolytic treatment during transfer.

In conclusion, hyperacute infarction growth is highly associated with LMC status, and the rLMC score contains valuable information on stroke progression. Further studies should focus on the value of the collateral status for the estimation of individual infarction growth dynamics in the context of patient transfer between primary and comprehensive stroke centers.

Disclosures

None.

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