Thrombus Permeability in Admission Computed Tomographic Imaging Indicates Stroke Pathogenesis Based on Thrombus Histology

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Background and Purpose—Intracranial thrombi can be characterized according to their permeability as measured by contrast agent penetration. Thrombus composition and its associated pathogenesis are important factors affecting treatment and secondary prevention. We aimed to explore the histopathologic factors explaining the heterogeneity of thrombus permeability measures and evaluated potential correlations with stroke pathogenesis.

Methods—Thrombus densities were measured in thin-slice noncontrast computed tomography and automatically aligned computed tomographic angiography images of 133 patients with large-vessel occlusions of the middle cerebral artery. Change in thrombus attenuation (Δ_t) and corrected void fraction (ε; attenuation increase corrected for contralateral artery densities) were calculated. First, these thrombus perviousness measures were correlated with histological thrombus components (especially fractions of fibrin-platelet accumulation and red blood cells) and stroke pathogenesis (n=32). For validation, an association between perviousness and pathogenesis was assessed in a second, independent cohort (n=101).

Results—Thrombus perviousness estimates were correlated with both fibrin/platelets fractions (Δ_t: r=0.43, *P*=0.016/ε: r=0.45, *P*=0.01) and inversely with red blood cells counts (Δ_t: r=–0.46, *P*=0.01/ε: r=–0.49, *P*=0.006). In the first cohort, Δ_t was substantially higher in samples from patients with cardioembolic stroke pathogenesis as compared with noncardioembolic-derived thrombi (*P*=0.026). In the validation cohort, thrombus perviousness measures differed significantly between cardioembolic (Δ_t: median [interquartile range]=12.53 [8.70–17.90]; ε: median [interquartile range]=0.054 [0.036–0.082]) and noncardioembolic thrombi (Δ_t: median [interquartile range]=3.2 [2.17–6.44], *P*<0.001; ε: median [interquartile range]=0.020 [0.011–0.027], *P*<0.001) and were associated with pathogenesis (Δ_t: β=0.45, *P*=0.016/ε: β=83.6, *P*=0.013) in a binary logistic regression model.

Conclusions—Permeable thrombi showed a strong correlation with lower fractions of red blood cells counts and more fibrin/platelets conglomerations, concurrent with an association with cardioembolic origin. This novel information about thrombus perviousness may be valuable as a new and simple to acquire imaging marker for identifying stroke pathogenesis using early and readily available imaging. **(*Stroke*. 2018;49:2674-2682. DOI: 10.1161/STROKEAHA.118.021873.)**

Key Words: blood platelets ■ computed tomography angiography ■ erythrocytes ■ stroke ■ thrombectomy

The first clinical assessment of acute ischemic stroke requires urgent imaging that is primarily realized by computed tomography (CT) and computed tomographic angiography (CTA) because of their wide availability. In addition to the localization of vessel occlusion, the thrombus can be imaged directly. Characteristics, such as length, density, or perviousness of the thrombus, can be assessed, all of which have been associated with recanalization rates and functional outcome.[1–6]

The underlying factors accounting for the heterogeneity of thrombus appearances on CT imaging have not yet been clarified. However, a correlation of thrombus appearance with

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histological parameters is assumed. In particular, an association between the hyperdense middle cerebral artery sign and red blood cell (RBC) content of the thrombi has been observed.[7]

Endovascular mechanical thrombectomy, the current standard therapy for large-vessel occlusions of the anterior circulation,[8–12] allows for investigation of thrombus consistency and histology. An evaluation of the histological composition of ex vivo thrombi was previously conducted and defined the main histological thrombus components as fibrin/platelet (FP) conglomerations and RBC, supplemented by a small fraction of white blood cells (WBC).[7,13–17]

The correlation with underlying clot pathogenesis[13,18] and the effect of clot composition on mechanical recanalization procedures were examined.[19–21] An analysis of artificial clots showed a strong association of fibrin content and contrast agent uptake,[22] but the relationship of ex vivo thrombi to permeability measures in admission imaging is unclear.

Permeability is quantified by the level of contrast penetration, using derived metrics, such as change in thrombus attenuation and void fraction as thrombus perviousness measures, which have been associated with functional outcome and recanalization status.[1] The use of arterial-phase CTA appeared to be most suitable for the measurement of thrombus perviousness when compared with delayed phases.[23]

The assessment of perviousness measures is easy to implement during admission imaging of patients with stroke that consists of noncontrast CT (nCT) and CTA imaging and has the potential to give additional information about the occluding thrombus.

The present study aimed to further investigate the underlying factors of thrombus perviousness in admission CT imaging by investigating a possible correlation with histological composition. Based on the known correlation of histological composition with underlying clot pathogenesis,[13] an association of thrombus perviousness to pathogenesis was tested in a second, independent subcohort. Better characterization of thrombi might have a beneficial impact on the clinical management of patients with acute ischemic stroke and in decisions on secondary prevention.

Materials and Methods

The authors declare that all supporting data are available within the article and its online-only Data Supplement.

As a primary end point, a possible correlation between thrombus perviousness measures and percentages of the main histological thrombus component FP conglomerations, RBC, and WBC counts were examined in the first group, labeled histological cohort. Further assessment was done to see whether the association between histology and stroke pathogenesis, which is known from the whole in vivo thrombus cohort, could also be determined in the analyzed subgroup by showing a correlation between thrombus perviousness and stroke pathogenesis. For further validation purposes, the association of stroke pathogenesis with thrombus perviousness was tested in a second independent group of patients, labeled validation cohort.

This study was approved, and the need for patient consent was waived by our local ethics committee, in accordance with the ethical standards of the 1964 Declaration of Helsinki and its later amendments.

Patient Characteristics and Clot Collection

The histological cohort (n=32) was derived from a study sample of 145 patients with acute ischemic stroke, whose intracranial thrombi were collected between October 2010 and September 2012 during endovascular recanalization therapy, as previously described.[13] A subcohort was defined by applying prespecified inclusion criteria to obtain a homogenous collective of patients with stroke. Inclusion criteria were determined as follows: acute, singular, complete occlusion of the middle cerebral artery in the M1-segment or a proximal M2-segment with a large-vessel lumen; sufficient preinterventional imaging including nCT and immediately acquired arterial CTA with a thickness ≤3 mm, respectively; complete vessel occlusion without proof of residual blood flow, evaluated by a neuroradiologist with at least 2 years' experience (blinded).

The validation cohort (n=101) consisted of all patients with acute ischemic stroke who were treated in our department between January 2015 and December 2017 after applying the same inclusion criteria as described above.

Exact numbers and reasons for exclusion in both cohorts are summarized in the study flow chart presented in Figure 1. Basic demographic, clinical, and interventional data of patients were gathered. Stroke pathogeneses were determined according to the international TOAST (Trial of ORG 10172 in Acute Stroke Treatment) classification[24] on the basis of diagnostic and clinical information available for each patient, including CT and CTA imaging, magnetic resonance imaging, transcranial and extracranial duplex sonography, coagulation tests, long-term electrocardiography recording, and transthoracic or transesophageal echocardiography.[21]

Histological Analysis of Clots

Formalin-fixed and paraffin-embedded thrombi were sectioned in 2-μm-thick slides followed by hematoxylin-eosin staining and high-resolution scanning of the slides as previously described.[21] Based on color-guided segmentation, quantitative analysis of the main components (FP, RBC, and WBC as fractions in per cent) was done using custom-made quantification software (CAMPThrombus 1.0; not commercially available), which has been previously explained in more detail.[25] In the case of thrombus fragmentation, all fragments were included for histological analysis.

Thrombus Perviousness Assessment

Thrombus perviousness was assessed by contrast agent uptake in arterial CTA imaging, measured by the increase of Hounsfield units (HUs) between the nCT and CTA scans.[1,26] As a first step, the nCT scans were automatically aligned with the CTA scans, which were acquired one immediately after the other, using a rigid registration method.[27] The alignment was assessed by a neuroradiologist with at least 2 years' experience (blinded). The thrombus was manually segmented in the best fitting, axial slice on the overlaid CT images by a neuroradiologist with at least 2 years' experience, and blinded to all clinical data. Hereby, the stop of contrast agent in CTA and a possibly existing hyperdense vessel sign in nCT scan were used. In consideration of appositional thrombus growth, measuring points were placed 1.5 mm behind the occlusion site (Figure 2). Assessed volumes as well as HUs of aligned nCT and CTA images were extracted. As previously described,[1] the difference in mean HUs between nCT and CTA is defined as change in thrombus attenuation ($\Delta_t=\Delta$ within the thrombus). As a reference, the HUs in a corresponding position of the contralateral, not occluded, vessel were also measured, calculating the difference between nCT and CTA in the contralateral artery (Δ_c). According to Santos et al,[1] a thrombus void fraction (ε) was calculated as the ratio of change in thrombus attenuation in the thrombus and contralateral artery ($\varepsilon=\Delta_t/\Delta_c$). In the rare case of similar density values in nCT and CTA scans with slightly higher values in nCT scans (presumably caused by partial volume effect), this small difference was set to zero. To test for observer influence, a neuroradiologist with at least 3 years' experience, blinded to clinical data and the analysis performed, repeated the measurements for 10 randomly selected patients, followed by an analysis of the root mean square deviation of the HUs in nCT and CTA scans within the thrombus resulting only in a relative root mean square error of 1.05%.

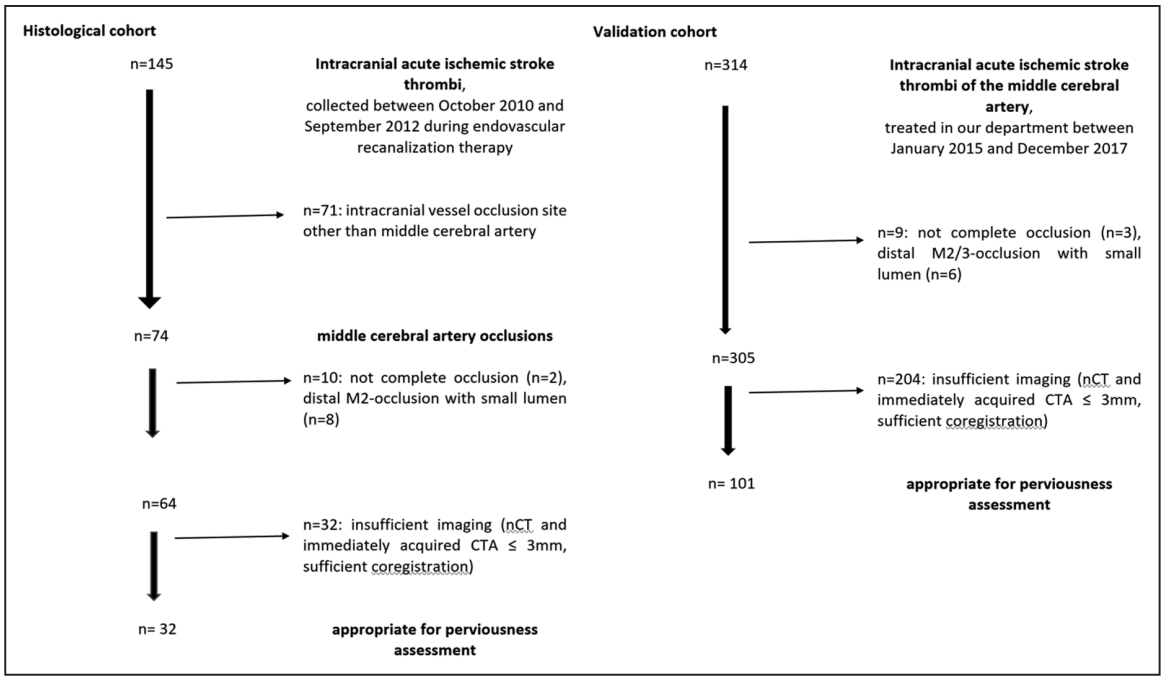

Figure 1. Study flow chart: exact numbers and reasons for exclusion in the histological and validation cohorts. CTA indicates computed tomographic angiography; and nCT, noncontrast computed tomography.

Statistical Analysis

Partial Spearman rank order correlations were performed between histological parameters and perviousness measures Δ_t and ε, controlling for the volume of thrombus assessment. Wilcoxon rank-sum tests were used for comparison of thrombus perviousness between etiological subgroups. Binary logistic regression was performed to test a possible prediction of stroke pathogenesis by thrombus perviousness, controlling for the volume of thrombus assessment and patient age. Receiver operating characteristic (ROC) analyses were implemented to identify a threshold beyond which perviousness measurements might show reasonable discriminatory power to indicate the cardioembolic origin of the thrombus. Pathogenesis was assessed by TOAST criteria, as mentioned above. Additional analyses were performed with dichotomized etiological groups, defined by noncardioembolic (TOAST 1+4) and mainly cardioembolic clots (TOAST 2+5), based on previous histological results.[13,18] To test for the reported dependency of density measurements on slice thickness,[28] Spearman rank order correlations were calculated between slice thickness and density measurements in the validation cohort. Hypothesis testing was run with exploratory, 2-sided 5% significance levels. All statistical analyses were performed using IBM SPSS Statistics (version 24, IBM Corp, Armonk, NY).

Results

Patient Characteristics

In total, 133 patients (32 in the histological cohort, 101 in the validation cohort) met the required inclusion criteria as indicated in Figure 2. Recanalization success, clinical outcome data, and assessed TOAST criteria are summarized in the Table.

Perviousness Shows Correlation With Histological Thrombus Composition

Median fractions of the quantified thrombus components were as follows: FP (median, 56%; interquartile range [IQR],

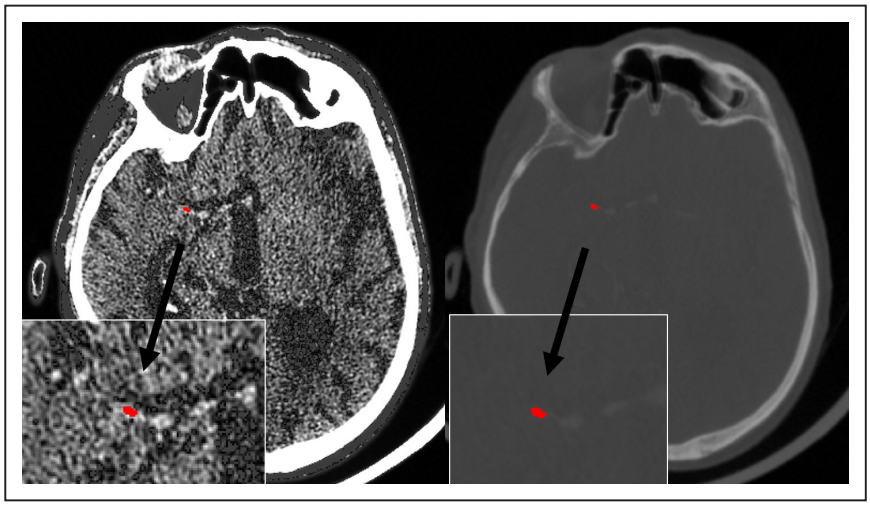

Figure 2. Example of measurements of thrombus density in automatically aligned noncontrast computed tomography (**left**, mean Hounsfield units [HU]=64.7) and computed tomographic angiography images (**right**, mean HU=92.0) of a patient with acute M1 vessel occlusion with known atrial fibrillation.

Table. Baseline Clinical Parameters, Recanalization Outcome, and Assessed TOAST Criteria for the Histological and Validation Cohort

Sample Characteristic	Histological Cohort (n=32)	Validation Cohort (n=101)
Age, y, median (IQR)	73 (65–81)	78 (71–86)
Sex, n (female/male)	18/14	49/52
TICI score post recanalization, n		
0	0	12
1	0	1
2a	3	5
2b	12	32
3	17	50
Additional intravenous thrombolysis, n (%)	20 (62.5%)	48 (47.5%)
NIHSS, median (IQR)		
Pre-treatment	15 (10–17)	14 (10–18)
Post-treatment	5 (0–8)	6 (1–12)
Difference pre-post-treatment	8.5 (3–12)	7 (2–11)
mRS score (90 d)		
0–2	9	23
>2	9	28
TOAST		
Arterioembolic (TOAST 1)	4	12
Cardioembolic (TOAST 2)	19	52
Other determined cause (TOAST 4)	1	1
Cryptogenic (TOAST 5)	8	36

IQR indicates interquartile range; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; TICI, Thrombolysis in Cerebral Infarction; and TOAST, Trial of ORG 10172 in Acute Stroke Treatment.

44%–69%), RBC (median, 39%; IQR, 27%–52%), and WBC (median, 5%; IQR, 4%–7 %). Perviousness measurements Δ_t (median, 9.6; IQR, 0.37–17.1) and ε (median, 0.042; IQR, 0.002–0.062) as well as volume of thrombus assessment (median, 6.92 mm^3; IQR, 4.93–10.01 mm^3) and volume of the measurements in the not-occluded contralateral vessel (median, 8.21 mm^3; IQR, 5.47–14.02 mm^3) were gathered. Quantified thrombus components correlated with perviousness measurements as evidenced by a significant positive correlation for FP (Δ_t: r=0.43, *P*=0.016/ε: r=0.45, *P*=0.01), a significant negative correlation for RBC (Δ_t: r=–0.46, *P*=0.01/ε: r=–0.49, *P*=0.006; Figure 3) and a positive correlation for WBC (Δ_t: r=0.34, *P*=0.06/ε: r=0.38, *P*=0.04; Figure 3).

Perviousness Shows Association With Stroke Pathogenesis in the Histological Cohort

Based on the known correlation between thrombus histology and stroke pathogenesis[13] with higher fractions of FP conglomerations in thrombi of cardioembolic origin, a corresponding association between histology and perviousness was expected. Despite the small sample size, we observed differences in perviousness measures between cardioembolic (Δ_t: mean, 11.90, median, 9.95, IQR, 0–19.16/ε: mean, 0.049, median, 0.050, IQR, 0–0.065) and noncardioembolic thrombi (Δ_t: mean, 2.45, median, 0, IQR, 0–6.14, *P*=0.088/ε: mean, 0.016, median, 0, IQR, 0–0.04, *P*=0.16). After dichotomizing TOAST 2 and 5 together, these mainly cardioembolic thrombi (Δ_t: mean, 12.51, median, 11.57, IQR, 2.94–17.51/ε: mean, 0.051, median, 0.050, IQR, 0.015–0.065) showed significant differences compared with the noncardioembolic thrombi (Δ_t: mean, 2.45, median, 0, IQR, 0–6.14, *P*=0.026/ε: mean, 0.016, median, 0, IQR, 0–0.04, *P*=0.087). The higher perviousness for (mainly) cardioembolic thrombi is in line with the presence of higher fractions of FP and lower fractions of RBC conglomerations in those thrombi.

The distributions of Δ_t and ε in the etiological groups are presented in Figure 4.

Perviousness Is Associated With Stroke Pathogenesis in a Large Independent Validation Analysis

The distribution of the perviousness measurements Δ_t and ε for the different etiological subgroups is shown in Figure 5. Thrombus perviousness measures of cardioembolic thrombi (Δ_t: median [IQR]=12.53 [8.70–17.90]; ε: median [IQR]=0.054 [0.036–0.082]) were significantly higher than those of noncardioembolic thrombi (TOAST 1+4) (Δ_t: median [IQR]=3.2 [2.17–6.44], *P*<0.001; ε: median [IQR]=0.020 [0.011–0.027], *P*<0.001) but showed no significant differences in comparison to cryptogenic thrombi (Δ_t: median [IQR]=11.6 [6.3–19.3], *P*=0.46; ε: median [IQR]=0.049 [0.029–0.088], *P*=0.51). After dichotomizing the etiological subgroups according to,[13] mainly cardioembolic thrombi (TOAST 2+5) showed higher perviousness measures (Δ_t: median [IQR]=12.37 [7.26–17.91]; ε: median [IQR]=0.052 [0.032–0.083]) compared with noncardioembolic thrombi (median [IQR]: see above, Δ_t/ε: *P*<0.001).

In a binary logistic regression model, dichotomized TOAST criteria (cardioembolic versus noncardioembolic, covariates: volume of thrombus and age of patients) were predicted by Δ_t (β=0.45, *P*=0.016). Similar results were also found for ε (β=83.6, *P*=0.013).

ROC analysis for perviousness measures Δt and ε indicated that these parameters are significant indicators of cardioembolic stroke pathogenesis (for Δt: area under the curve 0.92 [95% CI, 0.85–0.99], *P*<0.0001; for ε: area under the curve 0.86 [95% CI, 0.76–0.96], *P*<0.0001; Figure I in the online-only Data Supplement). According to the ROC analysis, a specificity of 100% to categorize a thrombus as cardioembolic would be reached for a cutoff value of >8.21 HU for Δt (specificity 100%, at a sensitivity of 79%) and a cutoff value of >5.6% for ε (specificity 100%, at a sensitivity of 46.2%). A higher sensitivity would be reached by defining a cutoff value of >4.8% for ε with a small loss of specificity (specificity 92.3%, at a sensitivity of 61.5%; Figure I in the online-only Data Supplement).

With an a priori probability (prevalence) of cardioembolic pathogenesis of 80%, classifying a thrombus with Δt >8.21 HU as cardioembolic corresponds to a positive predictive value of 100%. The detailed statistical values can be

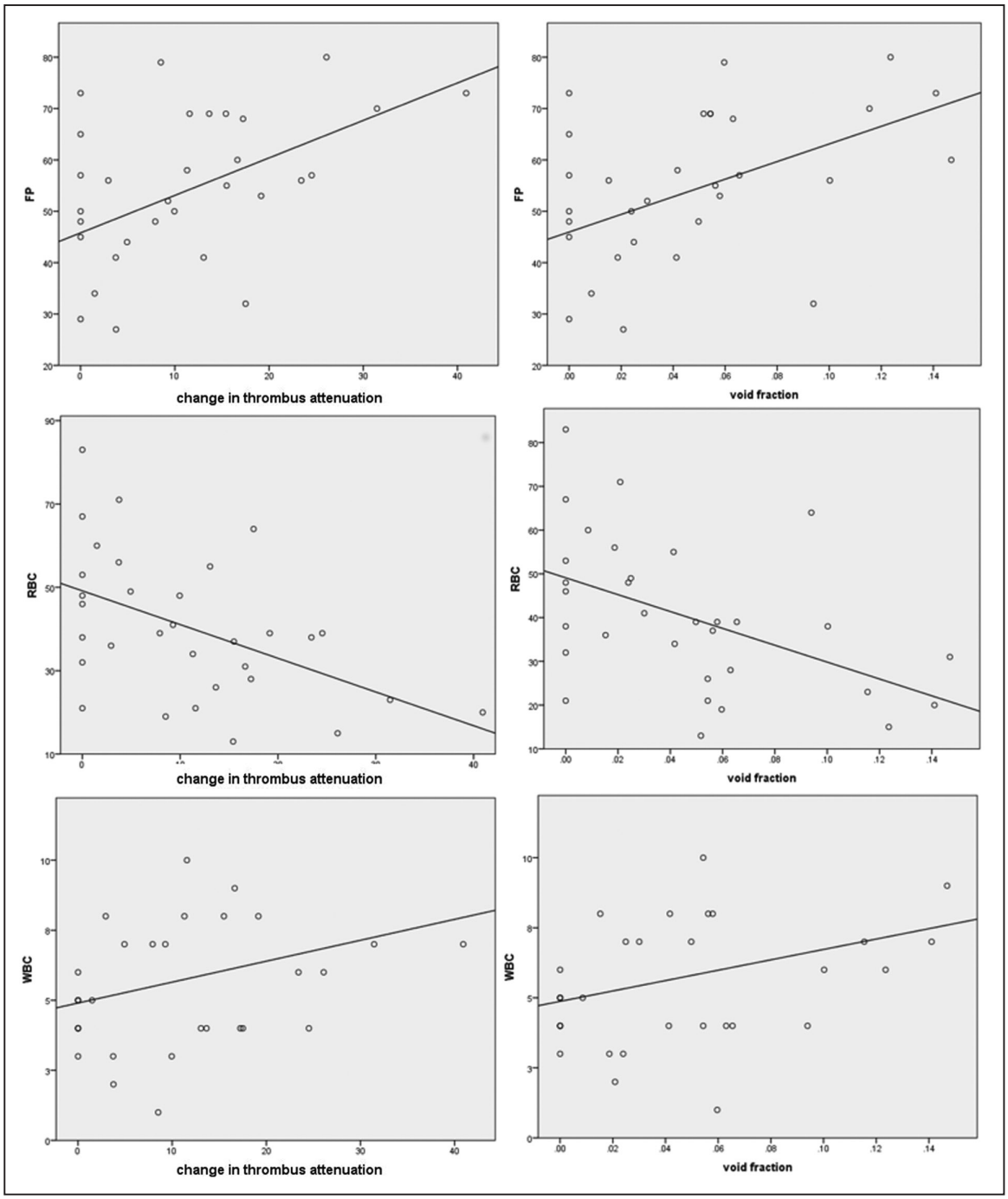

Figure 3. Correlation between change in thrombus attenuation (Δ_t; **left**) or void fraction (ε; **right**) and quantified thrombus components (fibrin/platelet [FP], red blood cell [RBC], and white blood cell [WBC] in %) in the histological cohort.

found in Table I of the online-only Data Supplement. The control analysis to address the impact of CT slice thickness on the analyses showed no significant correlation between measured densities and slice thickness (nCT: r=−0.14, *P*=0.15; CTA: r=−0.15, *P*=0.15) nor between perviousness measurements and slice thickness (Δ_t: r=0.06, *P*=0.55; ε: r=0.03, *P*=075).

Discussion

In the present study, permeable thrombi consisted of less RBC and increased FP conglomerations.

Because of known correlations between fibrin dominance and cardioembolic origin,[13,18] an association of thrombus perviousness with stroke pathogenesis was tested in one cohort, in which histological and imaging parameters were available for analysis. We found that more organized cardioembolic thrombi showed a higher perviousness. To validate the potential association of thrombus perviousness and cardioembolic pathogenesis, we confirmed our findings in a second, independent cohort with a larger sample size.

Because endovascular procedures as standard treatments for large intracranial vessel occlusions have a proven

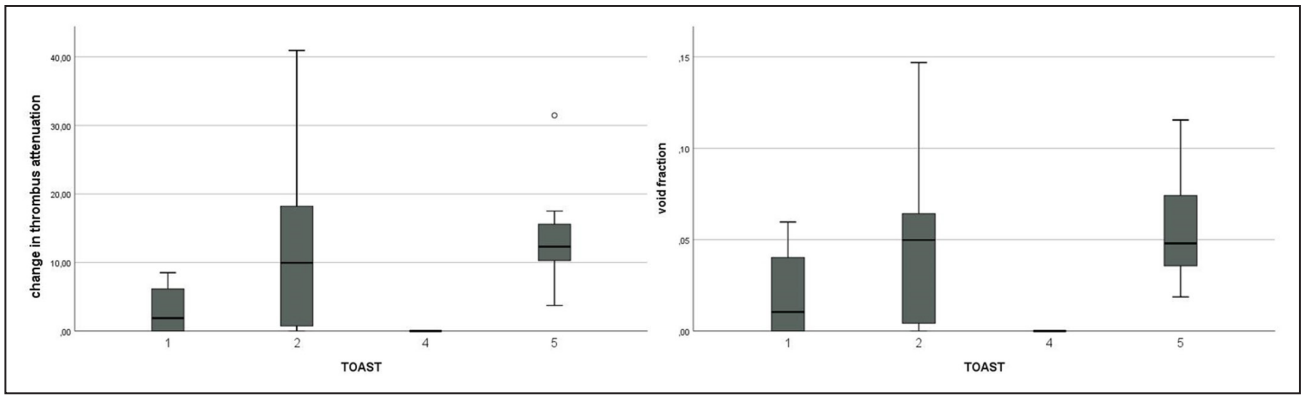

Figure 4. Boxplots of change in thrombus attenuation (Δ_t; **left**) and void fraction (ε; **right**) for the etiological groups (according to TOAST [Trial of ORG 10172 in Acute Stroke Treatment]: 1=arterioembolic, 2=cardioembolic, 4=other determined cause, 5=cryptogenic) in the histological cohort.

efficacy over best medical treatment alone,[8–12,29] questions arise on the optimal endovascular techniques, which may be guided by directly assessing thrombus characteristics. These characteristics can be assessed with admission imaging, which is still typically CT imaging because of its wide availability (eg, thrombus density measurements[4]). The assessment method for thrombus perviousness of quantifying the level of contrast penetration in CTA imaging is well established and has shown a strong impact on functional outcome and recanalization rate after endovascular treatment and pharmacological therapy.[1,30,31] However, the underlying characteristics that determine how the diversity of acute thrombi affects perviousness have not been analyzed. A previous analysis with artificial clots showed a strong association of fibrin content and contrast agent uptake.[22] To investigate such an association in patients with acute ischemic stroke, we selected a well-defined subgroup with only complete occlusions of the middle cerebral artery. This resulted in a homogenous cohort with direct contact from fresh flooding contrast agent in CTA preventing the problem of a stationary blood column, which can be observed in occlusions of the internal carotid artery, for example. An analysis in multiphase CTA imaging was previously performed to resolve the time issue but showed an optimal association between perviousness and functional outcome on arterial-phase CTA, rather than delayed phases, which we have not used in our cohort.[23]

Despite a certain statistical spread in our results, an association of thrombus perviousness with the main constituents FP and RBC was shown in the histological study cohort. The fibrin-rich thrombus, assumed to have a higher degree of organization,[13] seems to allow the contrast agent to penetrate the clot more easily, which fits with the results of previous studies on artificial thrombi.[22] Lower perviousness was shown for thrombi with higher fractions of RBC, assuming a tightly packed conglomerate with high concentrations of hemoglobin and accordingly high attenuation in nCT,[16] which would plausibly impede blood and contrast agent penetration.

A weak positive correlation was found between thrombus perviousness and WBC fraction. This result should be considered with caution because of the small WBC proportion of thrombus composition with fractions distinctly <10% and consequently higher susceptibility to errors in quantification.[13] Possibly, immunologic mechanisms occurring during an acute ischemic stroke[32,33] as well as the migration of leucocytes could lead to a modification of thrombus structure, affecting the degree of perviousness.

Based on previous histological analyses of retrieved thrombi,[13,18] an association between lower fractions of RBC counts and higher FP conglomerations with cardioembolic origin is known. In the present study, these fibrin-rich thrombi presented with higher perviousness. Consequently, a correlation between pathogenesis and thrombus perviousness was to be expected in this cohort. The current analysis consisted of a

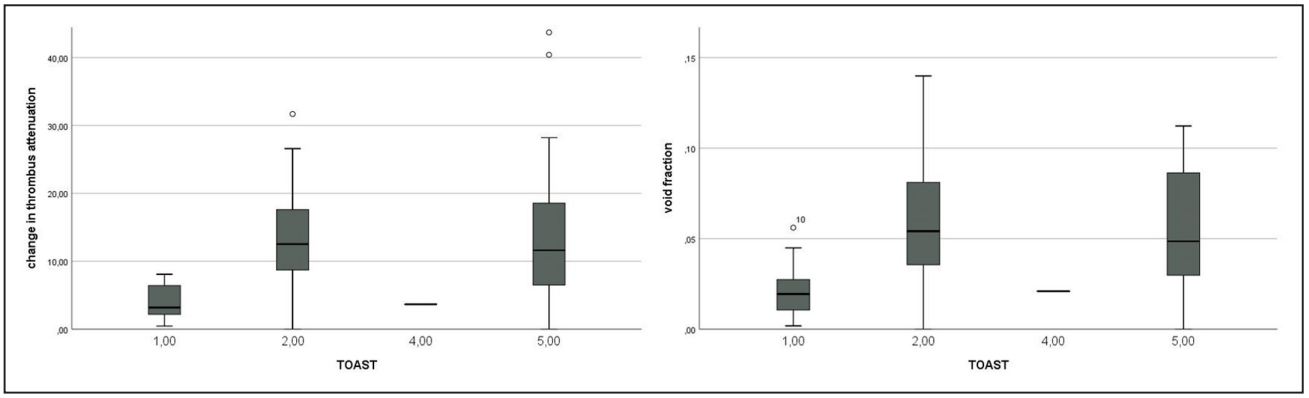

Figure 5. Boxplots of change in thrombus attenuation (Δ_t; **left**) and void fraction (ε; **right**) for the etiological groups (according to TOAST [Trial of ORG 10172 in Acute Stroke Treatment]: 1=arterioembolic, 2=cardioembolic, 4=other determined cause, 5=cryptogenic) in the validation cohort.

well-defined subcohort of the in vivo thrombi after applying inclusion criteria (Figure 1). Despite this deviation in sample composition, the expected correlation with higher perviousness for cardioembolic thrombi could be shown.

In a second step, the new findings of thrombus perviousness as a marker for thrombus composition and presumably thrombus pathogenesis were validated in a larger independent cohort by testing the association between perviousness and pathogenesis. A possible prediction of cardioembolic origin by perviousness was found. This fits the results of prior performed histological analysis showing an association of higher-organized, fibrin-rich, presumably cardioembolic thrombi with higher perviousness.

The ultimate goal of such an approach would be the possibility to make inferences on stroke pathogenesis using the assessment of thrombus perviousness in individual patients. The ROC analysis with a selected cutoff value of $\Delta t > 8.21$ HU resulted in a positive predictive value of 100%. The selected cutoff value obviously must be validated in independent patient cohorts, and superiority to the no information rate has to be shown in larger samples. However, in the future, this simple approach may serve as an additional tool in the diagnostic work up of patients with cryptogenic strokes also in individual patients.

In previous studies, similar characteristics were demonstrated for cardioembolic and cryptogenic strokes, assuming cardioembolic origins for the latter.[13,18] In the comparison of perviousness measurements, cardioembolic and cryptogenic thrombi also appeared to be similar with a minimal trend toward lower values within the cryptogenic group. This is reasonable when considering that thrombi of unknown cause would be preferential of cardioembolic origin, but indeed, include undetected causes of arterioembolic strokes or other noncardioembolic causes with lower values shown in the current analysis.

Different thrombus compositions have a strong impact on thrombus stability and mechanical recanalization procedure, as was shown in previous studies.[19–21] Preinterventional imaging characterization of these thrombi was previously done, indicating an association of the appearance of hyperdense middle cerebral artery signs in CT or blooming artifacts in magnetic resonance imaging with the RBC content of the thrombi.[7] In contrast to the previously mentioned histological studies,[13,18] which follow a more descriptive and by peri-interventional gained histology-driven approach, the actual study, while using histology, evaluates a further imaging marker to preinterventionally characterize the thrombi by perviousness, which could provide information about the underlying stroke mechanism. In the clinical setting, assessing thrombus characteristics in admission imaging could provide relevant information that might be helpful in intraoperative management on technical aspects of mechanical recanalization, for example, concerning the choice of aspiration versus stent retriever application[34] or the application of proximal flow-arrest to reduce the risk of thrombus fragmentation and distal embolization. The respective clot stability or rigidity may be associated with clot composition although conclusive and clear study results leading to distinct recommendations for adapting the interventional technique are lacking. Nevertheless, these associations may be further uncovered in future studies.

The above findings underscore the importance of characterizing underlying thrombus composition with a known association with pathogenesis. Here, we provide evidence that it is possible to determine stroke pathogenesis based on a novel CT/CTA imaging approach. Measuring thrombus perviousness with CT imaging is another biomarker and might be complementary to the time-consuming histological analysis of retrieved thrombi. However, future studies are necessary to derive clear therapeutic consequences in the preinterventional situation of acute ischemic stroke. Besides diagnostic and clinical information, such as duplex sonography, coagulation tests, long-term electrocardiography, and echocardiography, additional thrombus characteristics will be helpful to determine the underlying stroke pathogenesis, that could be relevant for therapeutic decisions on secondary stroke prevention.

The approach described herein should be easy to implement in clinical practice as the perviousness measurement can be easily performed. As previously discussed,[1] change in thrombus attenuation Δ_t only requires measurement in the thrombus itself, and it is quickly done and relatively robust against mistakes. In contrast, the calculation of void fraction ε, which represents the porosity of the thrombus, requires a more sophisticated performance, and it is not easily implementable in the clinical setting of acute ischemic stroke assessment. The current analysis of both Δ_t and ε showed comparable results assuming a sufficient prediction of perviousness by assessing change in thrombus attenuation only in the thrombus itself.

Limitations

Our comparisons were performed with acute middle cerebral artery occlusions to obtain a homogenous collective with similar circumstances in CT/CTA imaging and the subsequent recanalization, with an adverse effect on sample size and generalizability for other intracranial vessel occlusions.

By applying strict inclusion criteria, the study is not without the risk of selection bias. But we consider the risk of systematic bias to be low as the applied criteria were only anatomic and technical and should not have influenced perviousness itself. Meanwhile, using a homogenous collective by applying such inclusion criteria is mandatory to obtain reliable and replicable results.

In particular, the unequal distribution of stroke pathogeneses with more cardioembolic/cryptogenic causes than noncardioembolic ones makes further studies necessary to reinforce the new insights into thrombus composition and pathogenesis by assessing thrombus perviousness measures and to implement them in clinical processes. Regarding the histological cohort, discrimination between platelets and fibrin in the quantitative histological analysis was not possible owing to the use of hematoxylin and eosin staining. A correlation of these subcomponents with perviousness measurements should be assessed in future studies. In the histological cohort, a possible bias could occur as cases with TICI (Thrombolysis in Cerebral Infarction) grade 0, where no thrombus material could be gathered, are not represented. This bias is not present in the validation cohort.

Regarding the assessment of thrombus perviousness, a well-established method was applied with the aim of minimizing the influence of baseline thrombus density measures. However, in cases of minimal penetration of the contrast agent into the thrombus, this may have an influence on assessing high-density thrombi because the minimal increase may be masked by high baseline density. This possible effect was considered by using nonparametric statistical testing. Therefore, a relevant bias from this possible effect seems unlikely.

In a minority of cases, patients received imaging in external hospitals and the exact contrast bolus timing could not definitively be reconstructed, implying a possible selection bias. However, as we only included patients with the aforementioned minimum imaging quality requirements (especially concerning slice thickness for adequate thrombus segmentation), and bolus timing should not have a relevant impact on perviousness measurements,[23] we consider the possibility of a systematic bias arising owing to this limitation to be small.

Summary

Permeable thrombi consist of lower fractions of RBC and more FP conglomerations, in turn representing thrombi of cardioembolic origin. Our results suggest that the assessment of thrombus perviousness in early and readily available imaging could lead to a new imaging marker for identifying stroke mechanism and could help to identify potential underlying stroke pathogeneses. By implementing these measurements in clinical practice, this radiological assessment could aid in predicting cardioembolic origin with consequences for therapeutic decisions in the long term as well as for secondary stroke prevention.

Disclosures

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