Visualization of Clot Composition in Ischemic Stroke
Do We Get What We See?

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Sudden occlusion of a brain artery by a blood clot represents the pivotal event in ischemic stroke. Consequently, most of the therapeutic effort during the acute stage of cerebral ischemia aims at resolving the thrombus to restore blood flow. Because the clot is the primary target of thrombolytic therapy, the definition of clot characteristics that are associated with successful vessel recanalization could help to identify patients at risk and stratify treatment decisions. One promising approach is to visualize the thrombotic vessel by noninvasive imaging techniques. Indeed, early vessel signs indicative for occlusive clots have been described in ischemic stroke such as the hyperdense middle cerebral artery sign (HMCAS) on CT or blooming artifact (BA) on specific MRI sequences and their presence was shown to be associated with lower recanalization rates and worse outcomes.1,2 However, little is known about the histological basis, that is, clot composition, underlying the occurrence of these surrogate markers. The interesting question whether the molecular structure of a thrombus determines its visibility by neuroimaging means and even more important its susceptibility for clot breaking agents like recombinant tissue plasminogen activator has mainly been addressed in experimental studies.3-6 In animal models of embolic stroke and femoral artery thrombosis, white clots composed of platelets and fibrin displayed a relative resistance against thrombolysis, whereas erythrocyte-rich (red) clots showed higher response rates. Preliminary studies in human patients with stroke revealed similar results. Here, strokes caused by paradoxical embolism, which is considered to result from an erythrocyte-rich thrombus in the deep venous system, were found to be more sensitive to recombinant tissue plasminogen activator treatment compared with strokes of other etiologies,7 but detailed analyses are lacking due to limited clot accessibility. The increasing use of mechanical embolectomy devices now allows for retrieving fresh clots from patients with acute stroke and successive morphological characterization.8

The study by Liebeskind et al9 published in this issue of Stroke exactly followed this approach and correlated the presence of HMCAS and BA with clot morphology and clinical outcomes in 50 patients with acute ischemic stroke who had undergone endovascular thrombectomy. HMCAS on CT was present in 10 of 20 patients, and BA was detected in the MRI scans from 17 of 32 cases. Clot contents were extensively analyzed by histological means regarding the proportion of red blood cells, white blood cells, and fibrin. Both HMCAS and BA were significantly associated with the presence of red blood cell-dominant clots, whereas lack of HMCAS and BA was indicative for higher fibrin contents.

Which clinical implications might come along with this interesting observation? First, deduction of thrombus composition from radiological signs may help to identify patients who are likely to not respond to intravenous thrombolysis but rather need more aggressive treatment regimens such as intra-arterial thrombolysis or mechanical endovascular therapy. However, the presence of HMCAS and BA or thrombus histopathology were not predictive for stroke severity or functional outcome.9 This is in accordance with the broad efficacy of recombinant tissue plasminogen activator across all subtypes of ischemic stroke10 and to some extent dampens the practical significance of the results. Second, clot morphology may indicate the clot source. Red thrombi are predominantly formed by the activation of the plasmatic coagulation cascade in areas of reduced blood flow (stasis) present, for example, in the venous system or diseased heart (atrial fibrillation, heart failure), whereas white thrombi often originate from damaged endothelia (atherosclerotic vessels). Given that a considerable proportion of ischemic strokes remains “cryptogenic” despite an extensive diagnostic workup,10 including Holter electrocardiography and transesophageal echocardiography, imaging-based clot characterization could provide the rationale to further intensify the diagnostic effort or guide therapeutic decisions in terms of secondary stroke prevention (prescription of warfarin or platelet inhibitors, respectively). Unfortunately, the study by Liebeskind and colleagues9 also failed to demonstrate a clear relationship between thrombus composition and stroke etiology or mechanisms (eg, cardioembolism or atherosclerosis) thereby confirming previous reports.8 This may be owed to in situ clot aging, which is accompanied by structural reorganization, including attachment of erythrocytes and leukocytes, fibrin retraction, or calcification. These morphological alterations can finally mask the initial clot source.

A particular strength of the present investigation is the remarkable sample size and the thorough histopathologic characterization of the retrieved clots, which is exceptional so far. Although it is still premature to build diagnostic or
treatment decisions on clot imaging, more sophisticated approaches, including fibrin-specific MRI contrast agents or positron emission tomography-based as well as ultrasound-based technologies, may soon allow for a more accurate identification of thrombus composition.\textsuperscript{11,12} In this respect, the work by Liebeskind et al\textsuperscript{8} can be regarded as an important proof-of-principle study, which will hopefully stimulate larger multicenter trials in the future.

Disclosures
None.

References

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