Clots, Collaterals, and the Intracranial Arterial Tree
Bijoy K. Menon, MD, MSc; Mayank Goyal, MD

See related article, p 2061.

A cute ischemic stroke is a story of two parts; a thrombus blocks anterograde blood flow within the intracranial arterial tree while tiny vessels called collaterals sustain the brain until the thrombus is cleared. The location, size, and type of thrombus along with the degree and extent of collaterals likely determine the patient’s clinical symptoms, the likelihood of treatment success and the patient’s prognosis. A major focus of acute stroke research has been to image and measure various thrombus and collateral characteristics that help predict patient outcomes.

In vitro studies show that larger clots are less likely to lyse with thrombolytic agents, whereas clots with more surface area exposed to flowing blood are more likely to lyse early.1 This information can be used to create a theoretical framework for thrombus lysis within the intracranial arterial tree.2 Thrombi in proximal arteries such as the internal carotid or the M1 segment of the middle cerebral artery are likely to have greater volume than thrombi in smaller more distal arteries. Independent of thrombus volume, longer thrombi within the cylindrical framework of the intracranial arterial tree are likely to have less relative surface area (at the proximal and distal ends) exposed to blood flow. Poor collateral status is likely to result in less blood flow at the distal end of any thrombi within the arterial tree.3 Less number of arterial branches at the proximal and distal ends of thrombi are more likely to result in stasis of blood flow at the ends of thrombi.2 Thrombi that are structurally porous are likely to have more surface area exposed to blood flow. Thus, thrombus lysis within the intracranial tree will depend on the following characteristics:

1. Location
2. Length
3. Collateral status
4. Angioarchitecture of cerebral arterial tree
5. Thrombus porosity

Empirical evidence from studies in patients with acute ischemic stroke supporting this theoretical framework of thrombus lysis is accumulating.3–8 In their article, Santos et al8 showed that thrombus permeability as measured by comparing attenuation increase within the thrombus on computed tomographic angiography (CTA) when compared with attenuation of thrombus on the noncontrast CT is associated with increased likelihood of recanalization (measured at 24–48 hours) in patients administered with alteplase. Moreover, thrombus permeability is also associated with better clinical outcome in their study. Santos et al8 thus substantiate previous evidence about thrombus porosity identified using such imaging constructs like residual flow through thrombus on CT angiography and occult anterograde flow through thrombus on CT perfusion that are imaging markers of early thrombus lysis with alteplase.3 7 Other imaging constructs like thrombus location on CTA and Trans-cranial Doppler, thrombus length on noncontrast CT and CTA, clot burden score on CTA, forward flow through clot on dynamic CTA, collateral status on CTA and CT perfusion, Gradient Echo blooming on magnetic resonance imaging have all been shown to be markers of thrombus lysis with alteplase.3 4 Taken together, this growing body of literature is helping treating physicians who predict the likelihood of treatment success with alteplase in patients with acute ischemic stroke.

Although progress in understanding thrombus lysis within the intracranial tree in patients with acute ischemic stroke is gratifying, more needs to be achieved before this research can directly influence treatment decisions. Since time is of essence in determining stroke treatment outcome, studies testing the above imaging constructs need to use early recanalization as the primary outcome measure. Thrombi are also likely to differ in constitution across their entire length. We have previously demonstrated that a thrombus within the intracranial tree may have 2 components, that is, the original thrombus (either embolic or forming in situ because of adjacent arterial pathology, such as atherosclerotic plaque) and de novo thrombus formation around this original thrombus.2 This is in keeping with our personal experience where after successful endovascular thrombectomy the part of the thrombus that is captured on the stent retriever is significantly shorter than what was seen on the CT angiogram. If true, it is likely that these components may behave differently. Moreover, constitution of thrombi can evolve over time.2 Future studies need to account for this heterogeneity in thrombus constitution spatially and temporally when predicting recanalization with alteplase. Larger prospective studies collecting data on early recanalization with alteplase are needed because they can provide us with more precise estimates of early recanalization and consequently more reliable prediction models. Moreover, research needs to identify the value of each individual imaging construct vis a vis others and the rich interaction among them when building and validating...
these prediction models. Imaging modalities such as magnetic resonance imaging and transcranial Doppler, although less practical currently in the hyper-acute stroke workflow, may also help in this effort in the future.2,4

A theoretical framework of in vivo thrombus lysis within the intracranial arterial tree supported by empirical research is likely to help physicians make treatment decisions about the risks and benefits of thrombolysis. This evidence-supported framework also has the potential to inform future research on augmented thrombolysis technologies and better mechanical thrombectomy devices, thus improving clinical outcome in patients with acute ischemic stroke. This research by Santos et al8 is yet another important step toward this broad goal.

Disclosures
Dr Menon reports membership of the Steering and Executive Committee, ESCAPE trial (Endovascular Treatment for Small Core and Anterior Circulation Proximal Occlusion With Emphasis on Minimizing CT to Recanalization Times) that received support from Covidien Inc, Site Principal Investigator, SOCRATES trial (Acute Stroke or Transient Ischaemic Attack Treated With Aspirin or Ticagrelor and Patient Outcomes), sponsored by Astra Zeneca, honoraria from Penumbra Inc, a provisional patent 62/086077 for triaging systems in ischemic stroke, research funding from Canadian Institute of Health Research, Heart and Stroke Foundation of Canada, Alberta Innovates Health Solutions, Hotchkiss Brain Institute, and the Faculty of Medicine, University of Calgary. Dr Goyal reports partial support for ESCAPE trial provided to University of Calgary. He also helped in design and conduct of the SWIFT PRIME trial (Solitaire With the Intention for Thrombectomy as Primary Endovascular Treatment); Compensation: Significant (>$10k or 5%). In addition, Dr Goyal has received compensation for speaking engagements from Covidien Inc (significant) and Stryker Inc (modest). He also has a patent for Systems of stroke diagnosis licensed to GE Healthcare (compensation significant).

References

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