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Applications, and Future Directions**

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Radiology-Pathology Correlations of Intracranial Clots: Current Theories, Clinical Applications, and Future Directions

J.C. Benson, D.F. Kallmes, A.S. Larson, and W. Brinjikji



ABSTRACT

SUMMARY: In recent years, there has been substantial progression in the field of stroke clot/thrombus imaging. Thrombus imaging aims to deduce the histologic composition of the clot through evaluation of various imaging characteristics. If the histology of a thrombus can be reliably determined by noninvasive imaging methods, critical information may be extrapolated about its expected response to treatment and about the patient's clinical outcome. Crucially, as we move into an era of stroke therapy individualization, determination of the histologic composition of a clot may be able to guide precise and targeted therapeutic effort. Most radiologists, however, remain largely unfamiliar with the topic of clot imaging. This article will review the current literature regarding clot imaging, including its histologic backdrop, the correlation of images with cellular components and treatment responsiveness, and future expectations.

ABBREVIATIONS: MT = mechanical thrombectomy; HMCAS = hyperdense middle cerebral artery sign; NETs = neutrophil extracellular traps; RBC = red blood cell; SVS = susceptibility vessel sign; TAI = thrombus attenuation increase

The introduction of mechanical thrombectomy (MT) heralded the beginning of a new era in stroke research, in which retrieved clot tissue was available for histologic analysis. As it turned out, there was substantial heterogeneity in the histologic and physical characteristics of retrieved thrombi. This observation led to widespread exploration into the treatment implications, etiologic origins, and prognostic indicators of clot subtypes. It also accelerated the interest in the subfield of radiology-pathology correlation, in which attempts were made to use various imaging modalities to determine the histologic makeup of clots.

Two main methods have been used to characterize the histology of clot on imaging: the attenuation value of a clot on NCCT and its perviousness. MR imaging, too, has been used, but to a lesser degree. "Perviousness" refers to the degree with which blood—and, consequently, contrast—is able to flow into and through a clot. A highly pervious clot intuitively represents a porous structure that might confer increased responsiveness to thrombolysis and mechanical thrombectomy procedures. However, the still-emerging

field of clot perviousness imaging has been beset by inconclusive and, at times, contradictory data.

Nevertheless, the field of intracranial clot imaging holds promise for the future of individualization of stroke treatment. If the physical and histologic attributes of a clot can be inferred from its imaging characteristics, diagnostic imaging could allow early prognostication of various therapeutic efforts and could even be used to tailor specific pharmacologic and interventional therapies on the basis of clot subtypes. These substantial clinical implications have led to numerous scientific pursuits of perviousness imaging, particularly within the past few years. In this article, we will review the current literature on stroke clot imaging with a focus on both perviousness and radiology-pathology correlations.

Clot Histologic and Physical Characteristics

Clots are composed of 4 major components: red blood cells (RBCs), fibrin, platelets, and white blood cells. Substantial variability exists in the relative proportion of each component in various clots. The most commonly used terms to describe clot composition are RBC-rich/-poor, fibrin-rich/-poor, and platelet-rich/-poor (Fig 1). However, there is no standard definition for what makes a clot rich or poor in a given histologic component.

The histologic composition of a clot is used as a surrogate for its physical properties. RBC-rich thrombi are softer and more porous and have a lower static coefficient of friction; platelet-rich and fibrin-rich clots are harder and less porous and have a higher

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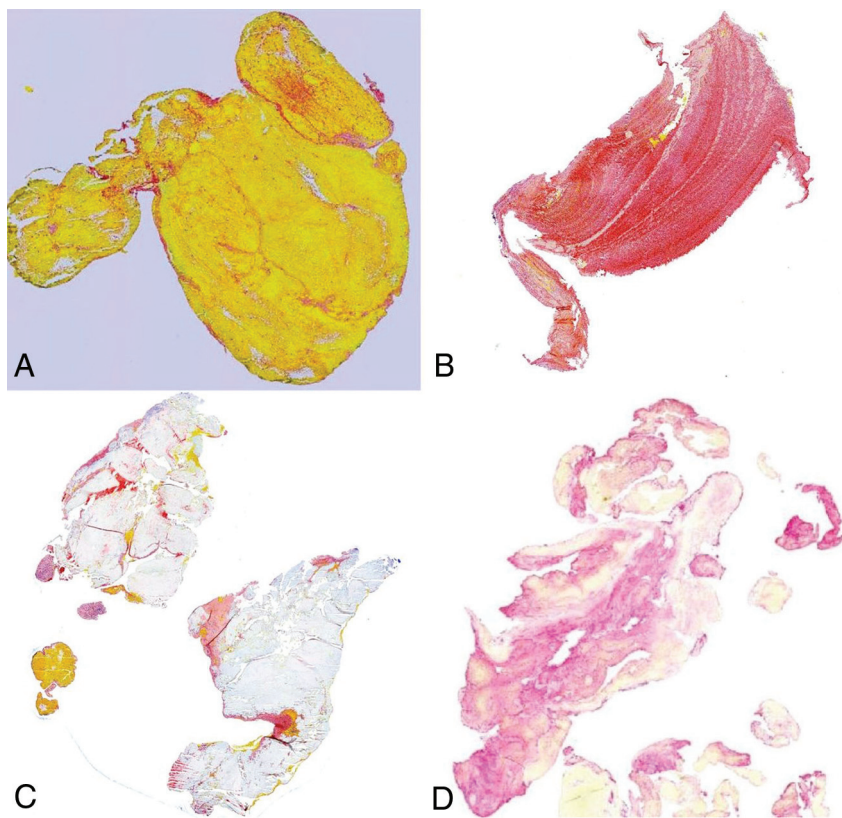


FIG 1. Histologic examples of various clot types. RBC-rich (A), fibrin-rich (B), platelet-rich (C) (all stained with Martius Scarlet Blue), and NET-rich (D) clots (immunohistochemistry using citrullinated H3 antibody) are shown, though standard definitions for these clot types have not yet been created.

static coefficient of friction.¹ However, there have not been extensive experiments into the histologic perviousness of clots.

Histologic differences among clots have direct clinical implications, particularly with regard to the ease, or difficulty, with which such clots are treated with MT or thrombolysis. RBC-rich clots are more responsive to tPA than fibrin-rich or platelet-rich clots.^{2,3} Fibrin-rich clots are also more difficult to remove during MT and require longer intervention times. Clots successfully retrieved with MT, meanwhile, exhibit higher RBC density.^{4,5}

Different pathomechanisms have been offered to explain these differences. For example, fibrin-rich clots are more likely to embolize during MT, suggesting the greater fragility of such clots.⁶ RBC-rich clots are less stiff, thus allowing better integration of stent devices into the thrombi during extraction.⁷ In addition, the greater friction exhibited by fibrin-rich clots may make them harder to remove during MT.^{1,8} However, frictional differences also make RBC clots more prone to intraprocedural migration.⁹

Perviousness Imaging

As stated above, perviousness is the extent to which blood flows through a clot. Because arterially timed contrast serves as a proxy for arterial flow, CTA represents the most conceptually straightforward technique with which to demonstrate the perviousness of a clot. The use of CTA for perviousness imaging is also an enticing

concept because it is nearly ubiquitous in stroke imaging. On CTA, perviousness is measured by comparing intracrotal radiodensity units before and after the administration of arterial phase IV contrast (so-called thrombus attenuation increase [TAI]). Therefore, highly pervious clots would display substantial differences in attenuation before and after contrast infusion; impervious clots, conversely, would change minimally.

TAI is typically measured by aligning thin-section NCCT images to CTA images. ROIs are then measured along the course of the thrombus on both image sets. Subtracting the mean NCCT ROI value from the CTA ROI value yields the TAI (Fig 2).¹⁰ The method with which the TAI is determined has varied among studies. Some authors have used coregistration of NCCT and CTA to ensure measurement of the entire clot. Others, however, have simply drawn ≥ 1 circular ROI within the clot segment, thereby resulting in a less precise measurement.¹⁰ Definitions of “perviousness” have also varied (Online Supplemental Data).

For both TAI and NCCT attenuation measurements, care must be taken when dealing with highly calcified thrombi because of both the substantial

impact of calcifications on attenuation values and the associated streak and partial volume artifacts. Thus, calcified thrombi are often excluded from analyses.¹¹

The use of multiphase CTA offers some potential advantages for clot perviousness imaging. Mostly, it solves the conundrum of suboptimal timing—that is, perviousness cannot be determined on CTA if the arterial phase contrast has not yet reached the thrombus in question. The additional acquisition of both venous- and delayed-phase images on multiphase CTA ensures the arrival of contrast to or through the thrombus during at least some time point. To date, however, evidence supporting the conceptual benefit of multiphase CTA in perviousness analysis remains sparse. Santos et al,¹² for example, found that venous and delayed-phase images had poorer associations with outcome than those obtained in the arterial phase. Chen et al¹³ used a more robust version of dynamic CTA, in which 26 phases were acquired as part of a CTP protocol. In doing so, the authors found that this method more successfully offset the contrast-timing issue: The maximum TAI was better associated with outcome than the standard arterial phase. Nevertheless, neither study assessed correlations between multiphase perviousness markers and the histologic composition of retrieved clots. Future studies will be needed to provide more direct evidence of the correlation between clot perviousness and findings on multiphase CTA and CTP.

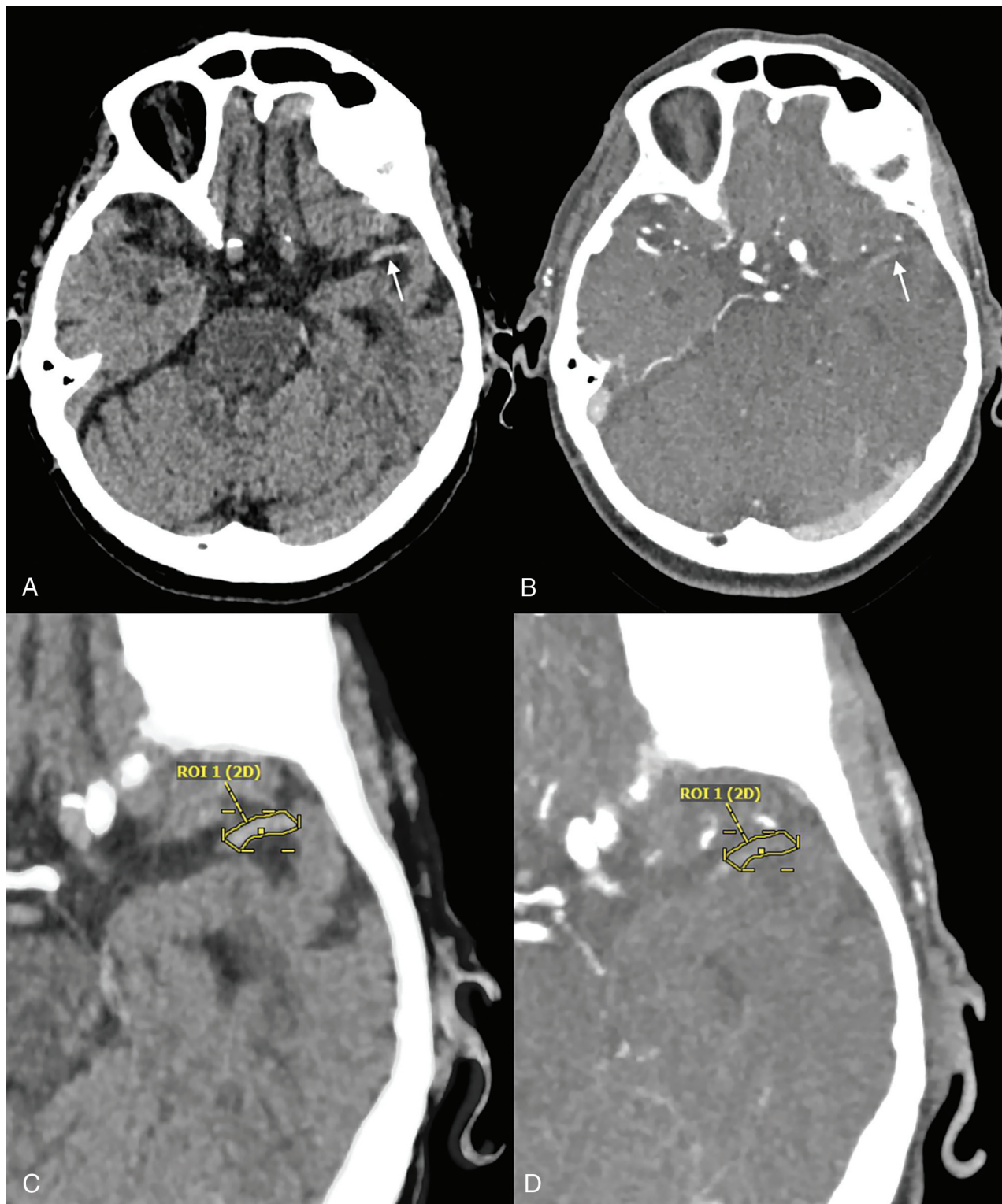


FIG 2. Measurement of clot perviousness on CT using TAI. NCCT (A) demonstrates a hyperdense vessel sign in the distal left M1 (arrow), with faint attenuation in this region also seen on CTA (arrow, B). Comparison of intracrotal attenuation between the NCCT (C) and CTA (D) yields a 23% increase in Hounsfield units following contrast administration.

Histologic Correlations

On NCCT, the most common methods of clot assessment are by absolute attenuation, relative attenuation, and the presence or absence of a hyperdense middle cerebral artery sign (HMCAS).

Absolute attenuation is determined by measuring an intracrotal ROI along the course of the thrombus.¹⁰ Relative attenuation is determined by comparing this calculation with similar measurements performed on the contralateral artery.¹¹ A relative measurement

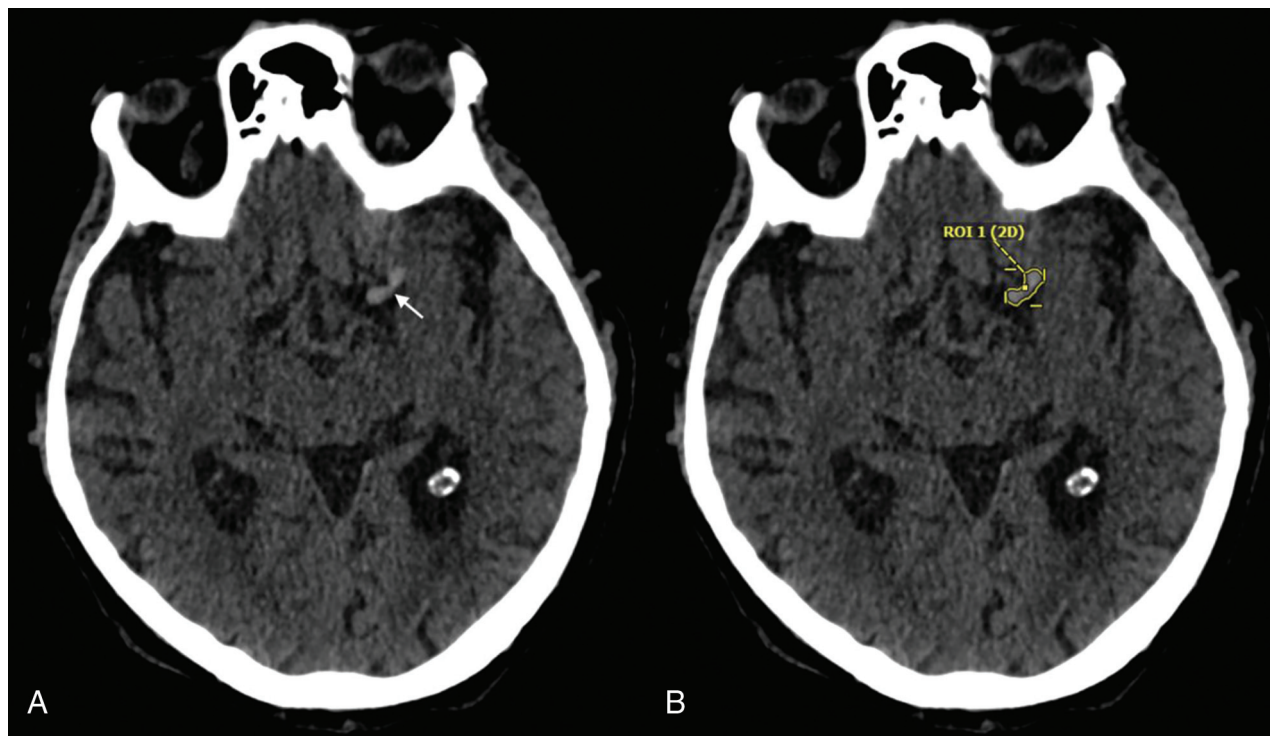


FIG 3. Intracranial clot evaluation on NCCT. Both the subjective presence of a hyperdense MCA sign (arrow in A) and objective measurement of intraclot attenuation (B) are predictive the histologic composition of a clot and responsiveness to treatment. Relative attenuation, in which the involved artery is compared with the contralateral side, may also be used (not shown).

may be useful because it corrects for underlying issues that might affect attenuation values, such as hematocrit or scanner differences (Fig 3).¹⁴ Generally, thin-section (≤ 2.5 mm) imaging is suggested for intraclot attenuation measurements.^{15,16} An HMCAS, conversely, is based on the subjective identification of an artery with pathologically hyperdense attenuation. MIP images are particularly useful to improve detection of HMCASs.¹⁷

Lower Hounsfield units are associated with fibrin- and/or platelet-rich clots, while higher Hounsfield units are associated with RBC-rich clots.^{2,6,7,18-20} The reported density of so-called RBC-rich clots has varied widely among reports, likely related to differences in CT scanning parameters and definitions of clot composition. Maekawa et al,²¹ for example, found the density of erythrocyte-rich clots to be 48.1 HU, compared with 32.1 HU in their fibrin-rich counterparts. Liebeskind et al,²² conversely, based their results on a subjective analysis of the presence or absence of an HMCAS, though they did report the mean density of clots having the HMCAS as 61 HU. Clot types were shown to be more accurately differentiated on dual-energy CT on an in vitro study, though this is yet to be validated with an in vivo cohort.²¹

On CTA, despite the theoretic ease with which the technique could be used to determine clot perviousness, conclusions from multiple prior attempts at histologic correlation have been frustratingly inconsistent. In the first major study to compare perviousness on CTA with histology, Berndt et al²³ found that pervious clots have greater fibrin/platelet conglomerations and less RBC fractions. Benson et al²⁴ subsequently found that pervious clots (defined as an increase in the intrathrombus Hounsfield unit of ≥ 10 on CTA compared with NCCT) were more likely to

be RBC-rich, while impervious clots were more likely to be fibrin- and white blood cell-rich. Most recently, Patel et al,⁵ using a cohort of 40 patients treated with MT, found that perviousness was associated with higher clot histologic percentages of both fibrin/platelet aggregates and was negatively correlated with the percentage of RBCs.

The reason for these contradictory results is befuddling. The superior therapeutic responses in both RBC-rich clots and pervious clots would seem to indicate that pervious clots would demonstrate erythrocyte-laden histology. However, there are several possible explanations for the observed differences. As Patel et al⁵ noted, inconsistencies in statistical methodology could have contributed to the variability in outcomes in these studies. The time between imaging and clot retrieval may also have played a role. Cines et al²⁵ found that clots undergo a natural contraction with time, and this type of histopathologic evolution could potentially have impacted the results. Next, there is some intrinsic bias in studies based solely on histologic analysis of successfully retrieved clots without any sort of postmortem analysis. Finally, the variability in results also raises the possibility that the observed differences were related to histologic markers that were not specifically assessed such as neutrophil extracellular traps (NETs) and the von Willebrand factor. Put more simply, is perviousness on imaging “seeing” markers of treatment response that we have not yet histologically determined?

On MR imaging, correlations between imaging findings and the histologic composition of clots remain relatively unknown. However, the so-called susceptibility vessel sign (SVS), a linear intravascular focus of hypointense signal on SWI, is highly

Summary of the most commonly used methods for determining clot histology and predicted treatment response on NCCT, CTA, and MR imaging^a

	Measurement Method	Histologic Correlation	Favorable Therapeutic Response
NCCT	HU	↑ HU = ↑ RBC, ↓ fibrin/platelets	↑ HU
CTA	TAI	Conflicting data	↑ TAI
MR imaging	SVS	SVS = ↑ RBC, ↓ fibrin/platelets	+ SVS

Note:—HU indicates Hounsfield unit.

^a Up and down arrows denote greater or lesser values (HU or TAI) and relative histologic composition. The plus sign denotes the presence of an imaging sign (ie, SVS).

specific for occlusive arterial thrombus.²⁶ Clots that demonstrate an SVS have been shown to be richer in RBC composition, thought to be related to the paramagnetic properties of deoxygenated hemoglobin.²⁷ Similar results have also been reported using gradient-echo sequences.^{22,28}

Treatment Response

Multiple studies have shown that treatment outcomes following IV thrombolysis are associated with thrombus density on NCCT. In general, the more dense (higher attenuating) the thrombus, the better the clot seems to respond to IV tPA.^{14,29} Puig et al,²⁹ for example, found that patients with lower relative intracort Hounsfield units had greater resistance to IV tPA. The authors found that a relative Hounsfield unit (the Hounsfield unit of MCA on the symptomatic side/Hounsfield unit of MCA on asymptomatic side) of <.382 predicted persistent occlusion after therapy, with a sensitivity and specificity of 100% and 87%, respectively. Similarly, Kim et al¹⁴ demonstrated superior recanalization rates of patients treated with tPA in whom the clot on NCCT demonstrated higher intrathrombus attenuation values.

Similarly, hyperdense clots on NCCT are generally associated with superior outcomes during MT.^{18,30,31} Froehler et al,³² for example, reported successful recanalization in 79% of hyperdense thrombi, but in only 36% of isodense thrombi. Moftakhar et al³³ found superior postintervention TICI grades in patients with higher thrombus density, regardless of intervention type (MT or IV or intra-arterial tPA). Likewise, on MR imaging, the presence of an SVS is predictive of higher rates of recanalization during MT and superior early clinical improvement, compatible with other results of RBC-rich clots.³⁴ Although some reports have presented data contradictory to the above findings, these represent a small minority of the current literature.³⁵

On CTA, multiple studies have demonstrated that perviousness, based on a greater TAI, predicts better recanalization in patients treated with tPA.^{10,36,37} Santos et al¹⁰ found that patients with pervious clots were more likely to have complete recanalization after tPA therapy compared with a conservatively treated cohort; there was no such significant effect of tPA treatment in patients with impervious thrombi. Mishra et al,³⁶ too, found that pervious clots were 5 times more likely to reperfuse than impervious thrombi. In theory, the superior responsiveness of pervious clots is related to the greater ability of tPA to travel through and thus act on a clot, similar to the blood in which it is administered. The tPA is, therefore, granted greater surface area on which to act; it is, thereby, hypothesized to act with greater efficiency in dissolving a clot.³⁸

Multiple studies have also explored the association between clot perviousness on imaging and the degree of success during attempts

at MT, which are also detailed in the Online Supplemental Data. Mokin et al,³⁰ for example, in examining the results from the Cardiovascular Outcomes for People Using Anticoagulation Strategies (COMPASS) trial, found that perviousness was associated with successful MT attempts. The authors reported that mean perviousness (as defined by the TAI) varied significantly between TICI subgroups: 32.6 for TICI 2c/3 and 17.7 for TICI 0-2a. Santos et al³⁹ reported data from a cohort of patients from the Multicenter Randomized Clinical Trial of Endovascular Treatment of Acute Ischemic Stroke in the Netherlands (MR CLEAN) trial. The authors found that pervious clots (defined as having a TAI of ≥10.9) were more likely to both recanalize and have a favorable outcome (mRS ≤2).

However, conflicting reports on this topic do exist. Borst et al,⁴⁰ for example, examined a number of thrombus characteristics on both NCCT and CTA: location (dichotomized as involving or not involving the ICA terminus), distance from ICA terminus to the thrombus, thrombus length and volume, density, and TAI. None of the studied clot characteristics on imaging were associated with treatment-effect modifications. Byun et al,⁴¹ similarly, found no correlation between perviousness on CTA and first-pass revascularization using stent retrievers.

Because recanalization is associated with better clinical outcomes in acute ischemic stroke, it seems implicit that pervious clots lead to more favorable outcomes. Indeed, an association between perviousness and outcome has been established.³⁹ In the study of Santos et al,¹⁰ for example, perviousness was independently associated with superior outcomes after adjusting for recanalization. The aforementioned study using dynamic CTA similarly found perviousness to predict favorable outcome on the basis of a 3-month mRS of ≤2.¹³ Multiple other studies have confirmed superior outcomes based on the 90-day mRS in patients with pervious thrombi (Table).^{15,42}

Radiomics

Radiomics, a subtype of machine learning, has recently been used to correlate clot appearance on imaging to histologic composition and clinical outcomes. Qiu et al,⁴³ for example, found that radiomic features derived from CTA and NCCT were more predictive of early recanalization following IV tPA than any single clot feature, including perviousness. Hofmeister et al⁴⁴ used radiomic features of clots on NCCT to predict both first-attempt recanalization and the overall number of passages needed to successfully recanalize a lumen. Most interesting, the radiomic features that correlated with recanalization included lower intrathrombus attenuation, in contradiction to the dogma that higher-density clots are more easily treated. The reason for the discrepancy between the study of Hofmeister et al⁴⁴ and numerous prior

studies is unknown, and reflects the need for additional investigation into this topic. An *in vitro* study using clot analogs by Velasco Gonzalez et al,⁴⁵ meanwhile, found that higher attenuation on NCCT was associated with greater composition of RBCs, while lower attenuation corresponded to greater composition of fibrin. Attempts to correlate MR imaging to clot composition with radiomics have remained sparse in comparison with CTA.⁴⁶

Other Imaging Biomarkers

Perviousness imaging and radiology-pathology correlations represent only small components of the massive field of clot imaging. Numerous other imaging biomarkers of intracranial clots exist, which hold substantial prognostic and therapeutic significance. Although this review is focused mainly on the subject of perviousness, some of these other imaging markers deserve mention, to grasp the scope of the ever-expanding field.

First, there is thrombus length, which can be measured on both CTA and NCCT.⁴⁷ On NCCT, the length of the thrombus is determined by the size of the increased intracot attenuation when an HMCAS is present. Thin-section images (≤ 2.5 mm) are required to adequately visualize clots in this manner.⁴⁸ On CTA, thrombus length is measured by the contrast gap, represented by an intra-arterial filling defect.⁴⁹ However, the distal end of the clot is essentially invisible unless pial collaterals permit opacification of the artery past the thrombus, thereby delineating the back end of the clot. Hence, CTA often leads to overestimation of thrombus length. Delayed-phase imaging, either as part of a multiphase CTA or contrast-enhanced CT, may help overcome this deficiency.⁵⁰ Shorter thrombi have more favorable metrics, including better functional outcome and reduced endovascular procedural times.¹⁵ Similar results have been reported using volumetric measurements of clots on 3D software: Smaller clots have significantly higher rates of recanalization.⁵¹

Then, there is thrombus location, which is often described on the basis of arterial segment involvement or by the “distance to thrombus” (the length between the ICA terminus and the proximal clot).⁴⁰ In general, patients with more proximal clots tend to fare worse, with poorer recanalization rates and outcomes.⁵² Bhatia et al,⁵³ for example, showed that thrombi in the distal ICA had a recanalization rate of 4.4%, while those in the M1 segment of the MCA had a recanalization rate of 32.3%. A meta-analysis by Seners et al⁵⁴ found that early recanalization was achieved in 52% of distal MCA clots, compared with 35% of clots in the proximal MCA and 13% of clots in the ICA. Such differences are at least, in part, related to the size of clots found in different locations: Larger-volume clots get lodged in the proximal arteries, while smaller clots are able to travel more distally.

The clot burden score is a semiquantitative method of measuring clot severity, which combines features of both size and location. The clot burden scoring system subtracts points on the basis of arterial segment involvement, with greater value placed on the supraclinoid ICA and MCA trunk; lower clot burden scores imply greater clot burden.⁵⁵ This feature can be assessed on both CTA or MR imaging (eg, using T2* sequences).⁵⁶ Not surprisingly, patients with increased clot burden scores (smaller clots) have better outcomes and higher rates of recanalization.^{57,58}

Future Directions

Where, then, do we currently stand in the field of clot perviousness imaging? Like the appearance of a clot on NCCT, the perviousness of a thrombus seems to predict its responsiveness to therapy. While the density of a clot on NCCT seems to also be associated with its histologic composition, a convincing correlation between perviousness and the histology of a clot remains elusive. Still, the better response of pervious clots to tPA does seem to indicate that pervious clots are more porous, allowing medications to better access and thereby act on the internal components of an occlusive thrombus. In short, what we are “seeing” with perviousness may be more related to intrinsic properties that determine therapeutic success—eg, porosity and composition that support MT—and less related to the major cellular makeup of clots.

In addition, there are complex histologic features of clots that could contribute to response or resistance to therapeutic efforts. Recently, clot components, such as NETs and von Willebrand factor, are increasingly thought to play a pivotal role in thrombus formation and stability. NETs, for example, are webs of DNA fibers that are typically used as a defensive mechanism against infectious organisms.⁵⁹ However, NETs have also been firmly implicated in the creation of thromboses: They influence the coagulation cascade, create a scaffold for RBCs, and promote platelet adhesion and aggregation.^{60,61} Not surprisingly, clots with greater composition of NETs exhibit greater resistance to endovascular therapy, with greater procedural times and number of device passes.⁶² Platelet-rich clots have higher levels of both von Willebrand factor and NETs, possibly explaining the resistance of such clots to thrombolytic effort.^{63,64}

Targeted therapies for these components are being developed. Recombinant a disintegrin and metalloprotease with thrombospondin type 1 repeats (ADAMTS13) cleaves von Willebrand factor and has been successfully used in mice to decrease infarct volume.⁶⁵ Deoxyribonuclease I has been shown to accelerate clot lysis by acting on intrathrombus NETs.⁶⁰ Eventually, novel therapeutic efforts such as these may be used as part of an increasingly complex arsenal of stroke treatment options.

More broadly, the goal of intracranial clot imaging is to individualize stroke therapy. As treatment options for stroke increase, effort will be needed to optimize recanalization on the basis of the specific imaging characteristics of intracranial thrombi. For example, if tPA were to be found to be associated with a virtually nil recanalization rate for impervious thrombi, one could use this finding as a reason to forgo fibrinolytic therapy and triage directly to endovascular therapy. Moving forward into this realm will require the rapid use of imaging features such as clot density, perviousness, and radiomics to predict the complex histologic composition of clots.

CONCLUSIONS

Today, the literature seems to support the growing consensus that perviousness is related to successful recanalization with IV tPA and MT. Effort to correlate perviousness with specific histologic compositions, meanwhile, has been relatively unrevealing. As we move into the future, it is likely that perviousness on CTA will be considered a first step in using imaging for clot characterization. Newer techniques, namely, machine learning, will likely

offer a substantial benefit for establishing etiologic mechanisms, offering prognostication on stroke outcome, and triaging patients with stroke on the basis of presumed responsiveness to various treatment strategies.

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