Topical Review

Computed Tomography Angiography in Hyperacute Ischemic Stroke
Prognostic Implications and Role in Decision-Making

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Computed tomography (CT) remains the initial imaging modality of choice in hyperacute stroke (HIS). CT scanners are more widely available than MRI scanners and are often located in emergency departments of district hospitals. Noncontrast CT (NCCT) excludes intracranial hemorrhage and tumor and detects early signs of infarction. Inclusion of arterial and parenchymal imaging with CT angiography (CTA) can rapidly provide useful information that may influence management and may indicate infarct size, location, and extent of vessel occlusion and collateral integrity, all of which can influence clinical outcome and recanalization in HIS. We will discuss the impact of these findings on prognosis and clinical decision-making, as well as practicalities of CTA in the HIS setting.

Site of Occlusion and Thrombus Load
CTA accurately localizes thrombus and quantifies clot burden. Both provide prognostic information in HIS and may guide management.

In the late 1990s, several relatively small trials demonstrated that CTA had excellent correlation with digital subtraction angiography (DSA), magnetic resonance angiography, and transcranial Doppler ultrasound. Using DSA as a reference standard, Lev et al. directly compared CTA and DSA findings in 224 vessel segments (divided into internal carotid artery [ICA], middle cerebral artery [M1 and M2-MCA], anterior cerebral artery [A1-ACA], posterior cerebral artery [P1 and P2-PCA], basilar artery [BA], and vertebral artery) in 44 patients with acute stroke. Sensitivity and specificity for the detection of large-vessel occlusion was 98.4% and 98.1%, respectively. More recently, Bash et al. assessed 672 vessel segments in 28 patients who underwent CTA and magnetic resonance angiography, using DSA as a reference standard. CTA had sensitivity and positive predictive value for occlusion of 100%, significantly better than magnetic resonance angiography (87% and 59%, respectively). When maximum intensity projection images have been compared with CTA source images (CTA-SI) for identification of occlusion, the latter seems slightly more sensitive. Dynamic angiographic information obtained during CT perfusion (CTP) imaging may help resolve this issue through demonstration of either anterograde flow or retrograde flow distal to the occlusive lesion. In addition, it is important to note that early arterial imaging can overestimate clot length; so appropriately timed CTA is necessary to allow retrograde flow to accurately delineate the distal thrombus extent (Figure 1).

Several studies have confirmed that occlusive thrombus in cervical or intracranial large vessels in HIS is a predictor of poor long-term functional outcome. These are summarized in Table 1. González et al. also analyzed 649 patients enrolled prospectively in the STOP Stroke trial and also demonstrated worse outcome with proximal thrombus (terminal ICA, M1 or M2-MCA, or BA). In addition, they found that combining the clinical (National Institutes of Health Stroke Scale) and CTA scores was more predictive of outcome than either parameter alone: 77.6% of patients with occlusion with significant neurological deficit (National Institutes of Health Stroke Scale >10) and CTA-proven proximal occlusion had poor outcomes versus 21.5% with National Institutes of Health Stroke Scale ≤10 or no proximal occlusion (P <0.0001), regardless of treatment. Furthermore, the STOP Stroke study also demonstrated that the presence of any large vessel occlusion on CTA was associated with a 4.5-fold increased odds of death. Good clinical outcome (modified Rankin Scale ≤2 at 6 months) was only obtained in 25% of patients with ICA or BA occlusions (BAO), 34% of M1, and 40% of M2 occlusions.

Thrombus extent on CTA may aid prognostication using scoring systems such as the semiquantitative Clot Burden Score (CBS), with a score of 10 indicating patency; a score of 0 indicates occlusion of all major intracranial anterior circulation arteries. Two points each are subtracted for absence of contrast opacification in the complete cross-section of any part of the proximal M1 segment, distal M1 segment, or supraclinoid ICA; and 1 point each for M2 branches, A1 segment, and infracerebral ICA. Partial filling defects suggesting stenosis or nonocclusive thrombus are rated as patent. It has been shown that patients with lower CBS (hence larger, more proximal thrombus) have significantly larger final infarcts, have worse collateral vessel status, and are significantly more likely to have parenchymal hematoma.

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Collateral Circulation

Collateral circulation is also an important consideration in HIS. In proximal artery occlusion, collateral vessels provide blood flow to preserve viable tissue and can potentially extend the time window for recanalization. The pial collateral circulation thus limits core infarct size by supporting penumbral tissue during acute ischemia. Multiple studies\(^2,4,7,8,26-32\) have evaluated collateral vessels using CTA and have demonstrated improved clinical outcomes in patients with superior collateral vessel filling (Table 2). The collateral circulation includes convexity leptomeningeal vessels and circle of Willis (anterior and posterior communicating arteries, presence and size).

CTA, however, only provides a snapshot in time, and if images are acquired too early, in the early arterial phase, then collateral status may be underestimated because slower-filling collaterals fail to opacify (Figure 2). Menon et al\(^11\) emphasize that visualization of the arterial phase, internal cerebral veins, and dural sinuses in the normal hemisphere are required to ensure adequate time for retrograde opacification of the leptomeningeal collateral–dependent slower-filling MCA branches distal to an M1 occlusion. Maximum intensity projection images improve interpretation over CTA-SI.\(^7\) It is possible that in the future, more dynamic information regarding collateral status is obtained via analysis of multiphase, or time-resolved CTA obtained from CTP data.\(^32\) An alternative, simple approach is to acquire a post-contrast head CT after initial CTA.\(^33\)

Collateral status has been shown to be inversely related to core infarct size on baseline NCCT\(^25,29-31\) and CTA-SI,\(^31\) baseline cerebral blood volume (CBV) maps,\(^10\) and diffusion-weighted imaging (DWI) lesion volume.\(^29\) Better collaterals demonstrated smaller pretreatment derangements of cerebral blood flow, mean transit time, and CBV.\(^15\) Good collateral status was significantly, but not invariably, associated with a larger baseline penumbra (as measured using a mean transit time/CBV mismatch) and also seems to maintain this penumbra by limiting infarct core expansion.\(^7,8\) Miteff et al\(^1\) found that median mismatch volume in the good collateral status group was higher compared with the reduced collaterals group (102 cm\(^3\) vs 73 cm\(^3\); $P=0.002$). It also has been demonstrated that final infarct volumes were smaller in patients with both persistent occlusion and recanalization, who exhibited a richer collateral network.\(^7\) Using dynamic angiographic information extracted from the CTP data, it has been shown that in the majority of patients, contrast visualized distal to a complete CTA occlusion is, in fact, because of retrograde flow.\(^8\)

The rate of clinical worsening was $\approx 4$ times greater in subjects with proximal MCA occlusion, but diminished collaterals.\(^27\) Patients with proximal occlusions, but normal or increased collateral flow, had similar outcomes after stroke compared with patients with no visible occlusions. Those with diminished flow experienced a significantly greater risk of in-hospital stroke progression, and patients with absent collaterals have a 10-fold increased risk of severe worsening or death.\(^27\)

Recently, Souza et al\(^29\) demonstrated that in patients with HIS secondary to terminal ICA or proximal MCA occlusions, the degree of collateral circulation on admission formation.\(^10,15\) Recanalization rates are also higher after IV recombinant tissue-like plasminogen activator (rtPA) in patients with smaller clot burden\(^15\) and conversely, lower in patients with larger thrombus burden. Patients with CTA CBS $\geq 6$ achieved higher recanalization rates (71%) with IV rtPA than those with CBS $\leq 6$ (44%; $P=0.04$).\(^15\) It has also been shown with NCCT that thrombus $>8$ mm fails to recanalize with IV rtPA.\(^22\)

Whether proximal occlusion on CTA becomes a routine indication for more effective means of recanalization using endovascular techniques remains to be seen. However, CTA is already being used for such decision-making in some centers: a recent historical cohort study of 290 patients with HIS found that a proximal arterial occlusion is independently predictive of the patient undergoing a neurointerventional procedure.\(^23\)

Also important, in patients who have clinically suspected stroke, brain infarction occurs in 74%, despite normal vessel status on CTA.\(^24\) It is therefore doubtful whether CTA can reliably exclude patients from IV thrombolysis. Absence of large-vessel occlusion on CTA or occult distal occlusion correlates with better outcome in those treated with IV rtPA,\(^23\) probably because small, distal thrombus load in small vessels is more likely to lyse with IV rtPa. Absence of large-vessel occlusion also correlates with a lower risk of hemorrhage.\(^13\)
CTA correlated with the admission DWI lesion volume. They identified a malignant CTA collateral profile that was highly specific for patients with large baseline infarcts at high risk for poor long-term outcome. Their CTA collateral score of 0 (absent collaterals in >50% of an M2 territory) had 95% specificity for an admission DWI lesion volume of 100 mL and a 90% rate of 3-month death or dependency.

**CT Angiographic Source Images**

**Anterior Circulation**

Analysis of the CTA-SI readily identifies areas of ischemic tissue more reliably than NCCT, and therefore is more accurate than NCCT in delineation of final infarct volume, and predicting outcome, despite treatment (Figure 3). Specifically, a CTA-SI Alberta Stroke Program Early CT Score (ASPECTS) >7 predicts a good clinical outcome. Extensive changes predispose to hemorrhagic transformation after recanalization.

Although hypoattenuation seen on NCCT is thought to reflect established cytotoxic edema, hypoattenuation seen on CTA-SI demonstrates regions of nonenhancement and is a form of perfusion imaging. CTA-SI span the entire brain, do not require postprocessing, and are available for interpretation immediately. This technique is widely available, affordable, and more straightforward to perform in critically ill patients than in MR imaging or formal CTP. For optimal interpretation, variable window width and center level settings may be used to optimize detection of ischemic lesions.

It is reported that those patients with an infarct volume of >70 mL (assessed using DWI) fail to achieve an independent outcome, despite endovascular recanalization and risk reperfusion hemorrhage. Furthermore, preliminary results from the Penumbra Stroke Treatment And Revascularization Therapy (START) trial suggests that higher pretreatment ASPECTS on CTA-SI is associated with better outcomes after endovascular therapy; ASPECTS >4 was the optimal threshold for identifying good outcomes (89% sensitivity, 38% specificity). Indeed, a swift but reliable, CT-based predictor of core infarct volume would be of great value in triaging patients for aggressive or conservative management. Whether CTA-SI represent core infarct is, however, a matter of debate, but it is likely that accuracy depends heavily on technique.

Timing of the CTA contrast injection relative to imaging is likely to be critical. If the CTA images are acquired too early, the ischemic penumbra may fail to enhance and therefore infarct core volume is overestimated (Figure 1).
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<td>Extent of collateralization and recanalization are independent predictors of final infarct volume in those treated with intra-arterial thrombolysis</td>
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(Continued)
Atrial fibrillation (implying reduced cardiac output) also predisposes to overestimation. Early CTA-SI evaluation, using older CT scanners, assumed that a steady state of arterial and tissue contrast was achieved during the scan acquisition, facilitated by lower contrast-injection rates, relatively long prep-delays, and longer scanning times. In keeping with this, CTA-SI approximated to CBV maps, and in 1 series, there was no evidence of reversibility in low density detected using CTA-SI. Furthermore, techniques that allow a steady state to be attained are used, CTA-SI volumes do not differ from and significantly correlate with initial DWI volumes. More recently, it has been suggested that with modern scanners, faster scan times and shorter time from injection to imaging in the early arterial phase, CTA-SI overestimate the core infarct (Figure 1), and some patients may therefore be inappropriately denied recanalization therapy. Sharma et al demonstrated that CTA-SI more closely approximated cerebral blood flow maps rather than CBV maps, using region of interest volume measurements. Others have demonstrated that CTA-SI overestimate final infarct size. When CTA-SI are acquired using a fast-acquisition protocol and compared with concurrent DWI, infarct core was overestimated in 30% of patients and tended to occur in patients with a poorer collateral vessel score. Furthermore, when CTA-SI acquired using older slower CTA protocols were compared with newer faster protocols using concurrent DWI as a reference standard, the latter significantly overestimated core infarct and did not correlate with DWI. It should therefore be emphasized that if CTA-SI are to be used for estimation of infarct core, then the images should be acquired on the venous side of the perfusion curve.
Cranial CT After CTA
An alternative approach to optimize parenchymal imaging and obtain an accurate estimation of core infarct is to perform a second cranial CT scan at a defined point after contrast injection for CTA. Pulli et al建议a delay of 40 seconds after contrast injection is optimal before further acquisition is obtained. However, Sharma has shown close approximation of CBV infarct volume with post contrast CT (CECT), obtained at 120 seconds following injection. Using an 80 second delay, Choi showed greater inverse correlation between pial collateral scores (assessed using DSA) and ASPECTS score using CECT rather than CTA-SI. On multivariate analysis, CECT was the only predictor of good clinical outcome. They propose that the delay between contrast injection and image acquisition allows enhancement of areas on CECT that result from pial collateral circulation. This technique also allows for a delayed phase CTA to be reconstructed from the source data for more accurate estimation of clot length and collateral status if an early arterial CTA was acquired initially.

Blood Volume Imaging
Whole brain perfused blood volume (PBV) imaging can be obtained via a short postprocessing step, using CTA-SI and NCCT data to gain an estimate of core infarct on a color-coded map (Figure 4). Wittkamp et al described an injection protocol with individualized delay for peak enhancement in the superior sagittal sinus using 80 mL of 370-mg iodine/mL concentrated contrast agent, at a flow rate of 4 mL/s, and 50 mL of saline flush. Timing peak enhancement within the superior sagittal sinus allows a steady state to be attained. They calculated whole brain PBV from the difference of NCCT data from the CTA-SI data. They noted a strong correlation between the PBV lesion volume and formal CTP CBV. Although whole brain PBV requires a second postprocessing stage, this is relatively quick and easy to perform with commercial software, and the sensitivity of PBV for cerebral ischemia is greater than that for CTA-SI. However, it has been suggested that PBV slightly overestimates core infarct and does not correlate completely with CTA-SI when using an ASPECTS score. It may be that viable tissue at the periphery of the core exhibits reduced blood volume but that this tissue does not go on to infarct. Nevertheless, this could potentially be a useful technique for core infarct estimation without the need for a second contrast injection or additional radiation and requires further investigation and validation.

Posterior Circulation
CTA-SI can also improve the conspicuity of hyperacute ischemic areas in the posterior circulation. Puett et al quantified early ischemic changes seen on CTA-SI to predict functional outcome in patients with BAO using the posterior circulation (pc)-ASPECTS score, which allocates the posterior circulation 10 points. One point each is subtracted for low density on CTA-SI in the left or right thalamus, cerebellum, or posterior cerebral artery territory, respectively, and 2 points each are subtracted for low density on CTA-SI in any part of the midbrain or pons. A pc-ASPECTS score of 10 indicates absence of visible posterior circulation ischemia; a score of 0 indicates low density in all pc-ASPECTS territories.

In their series, of 46 patients with BAO, 52% with a CTA-SI pc-ASPECTS score >8, but only 4% with a score <8, had favorable functional outcome (modified Rankin Scale score, 0–2). In contrast, patients with CTA-SI pc-ASPECTS score <8 were less likely to die. This difference was consistent in 21 patients with angiographic evidence of recanalization, and the authors concluded that the CTA-SI pc-ASPECTS score can identify patients who will have poor clinical outcome, despite recanalization. They suggest that pc-ASPECTS analysis of the CTA-SI in the posterior circulation reflects core infarct. In the second study, the same group showed that the extent of low density on the initial CTA-SI predicted the final infarct extent (based on the pc-ASPECTS score) in patients with BAO. This system was subsequently used to assess CTA of 158 patients from the Basilar Artery International Cooperation Study (BASICS) registry. This was a prospective, observational registry of consecutive patients with acute symptomatic BAO. They calculated unadjusted and adjusted risk ratios of pc-ASPECTS dichotomized at ≥8 versus <8. After adjustment...
for age, baseline National Institutes of Health Stroke Scale score, and thrombolysis, pc-ASPECTS ≥8 was not related to favorable outcome (modified Rankin Scale, 0–3), but it was related to reduced mortality and functional independence. In post hoc analysis, pc-ASPECTS dichotomized at ≥6 versus <6 predicted favorable outcome.

Combining Vascular and Parenchymal Information Obtained Using CTA
Combining information gleaned from vascular and parenchymal imaging may help to predict prognosis more accurately. This is emphasized in a study that incorporated thrombus score and CTA-SI low-density assessment into a single score in patients presenting within 3 hours of ictus and treated with IV or IV plus endovascular therapy. Only 1 of 24 patients (4%) with extensive low density on CTA-SI and extensive thrombus burden (assessed using ASPECTS and CBS score, respectively, combined score ≤10) were functionally independent. Mortality was 50%. In contrast, 57% of patients with less affected scores (combined score 11–20) were functionally independent, and mortality was 10% (9/90; P<0.001).

Parenchymal hematoma rates were 30% versus 8%, respectively, combined score ≤10) were functionally independent on initial imaging would be a good candidate for recanalization. Furthermore, collateral persistence or endurance may be erratic (dependent on as yet unknown factors), and collateral failure may ensue, which may result in infarct growth. Therefore, we advocate recanalization to ensure freezing the infarct core.

Conversely, if very poor collateral status is demonstrated or there is a wide region of hypointenntuation on CTA-SI representative of tissue likely to infarct, then conservative management may be more appropriate because recanalization is likely to be futile, and risk of symptomatic hemorrhage may be increased with treatment. Therefore, although questions remain as to whether CTA directly improves patient outcomes or not, there is a developing body of evidence that suggests that useful clinical information is provided by CTA that may prompt treatment and does impact directly on outcome, hence, the inclusion of CTA in ongoing clinical trials of endovascular therapy.

Interrelationship of CTA Markers
CTA-derived indicators, including status of collateral vessels and tissue ischemia (CTA-SI hypointenntuation), provide information at a single timepoint after ictus. However, these individual features are obtained using the same technique to acquire the same data that are postprocessed either through creation of maximum intensity projection images to assess collateral vessels or through rewindowing to assess tissue ischemia on source images. Therefore, whether the reader chooses to assess either 1 of these 2 features, it should be borne in mind that there is an inherent interrelationship and codependence. On comparing the prognostic information obtained from various aspects of CTA and NCCT information, it has been shown that CTA-SI did not have any additional information when NCCT and CTA collateral score were known. An explanation for this finding is that the hypointenntuation seen on CTA-SI that is not already seen on NCCT is tissue that is dependent on collateral flow.

CTA as a Decision-Making Tool
Information obtained from vascular and parenchymal imaging using CTA may indicate either favorable or unfavorable prognosis and may potentially impact on management. Aortic arch anatomy and proximal ICA stenoses can be assessed before neurointervention. A proximal intracranial occlusion with long thrombus may prompt triage directly to endovascular therapy or encourage a low threshold for endovascular therapy if intravenous thrombolysis does not result in an early clinical improvement. Additionally, a patient with small infarct core (high CTA-SI ASPECTS) and good collateral status on initial imaging would be a good candidate for recanalization. Good collateral status is associated with better clinical outcomes after treatment. However, others have found that CTA collaterals have a more important positive impact on the outcomes of patients who do not achieve recanalization.

We believe that although retrograde leptomeningeal collateral flow may temporarily maintain penumbra, these routes may fail to completely replace antegrade perfusion. Furthermore, collateral persistence or endurance may be erratic (dependent on as yet unknown factors), and collateral failure may ensue, which may result in infarct growth. Therefore, we advocate recanalization to ensure freezing the infarct core.

Potential Drawbacks of CTA: Treatment Delay and Safety Profile
Delay to Treatment
Outcomes for stroke treatment with intravenous tPA are associated with earlier delivery of the drug. Indeed, the American Heart Association/American Stroke Association has recommended that emergency treatment of stroke should not be delayed to obtain imaging studies, despite their clinical use. CTA does require insertion of an intravenous cannula, connection to a contrast pump, and acquisition of a second tomogram/localizer before image acquisition. However, image acquisition takes seconds with modern CT scanners, and delays can be minimized by prehospital alerts so that contrast pumps can be loaded before the arrival of the patient. Several studies have investigated whether use of CTA delays treatment times. Solatel et al demonstrated, in a retrospective cohort study, that the use of multimodal imaging, including NCCT, CTA, and CTP, in patients with HIS did not delay administration of IV rtPA beyond a goal of 60 minutes from patient arrival in the emergency department; and Bal et al compared door-to-needle times in 297 patients investigated using NCCT alone with 507 patients investigated with additional CTA: median door-to-needle times were 67 minutes and 62.5 minutes, respectively (P=0.519). There was no significant delay in thrombolysis for a CTA-based system of investigation.

Another approach is to use CTA after administration of IV rtPA when endovascular therapy is being considered as a salvage procedure. However, this may delay recanalization, and if there has been little response to IV rtPA, patients may be best served going directly to the interventional suite. In the authors’ experience, CTA is most useful at time of initial presentation and, with a coordinated response, does not delay administration of IV rtPA.
Contrast-Induced Nephropathy

Several studies have aimed to review the renal consequences of contrast administration for CTA in acute stroke. In 2 retrospective reviews of 175 patients and 224 patients, the incidence of contrast nephropathy was 2.9% and 3.0%, respectively. However, in a subsequent observational cohort study, contrast agents did not seem to cause rates of renal injury above those normally encountered in this population.

Radiation Dose

In a retrospective study of 95 patients undergoing NCCT and CTA, a mean effective dose of 2.7 mSv for NCCT and 5.4 mSv for CTA was recorded. In an anthropomorphic phantom study, effective doses ranged from 1.1 to 2.0 mSv for NCCT and from 0.3 to 4.1 mSv for CTA, demonstrating quite marked variability depending on technique. CTA dose may be reduced by the use of low tube voltages with a higher tube current.

Conclusion

It is evident that information gleaned from CTA images can be useful in prognosticating and decision-making in HIS. However, technique is key to obtain reliable clinical information, and attention should be paid to this in setting up local imaging strategies. Combining vascular and parenchymal imaging findings may aid in selecting patients for, or excluding patients from, more aggressive treatment options, with the aim of minimizing futile recanalization. Length of thrombus, site of occlusion, and size of core infarct may all be estimated using CTA, and these factors should be considered when triaging patients for intravenous or endovascular therapy. CT angiographic data are being included in endovascular stroke treatment trial design, and therefore, it will be interesting to see whether the findings of many of the published retrospective studies can be validated. What remains to be seen is whether patients presenting beyond the standard therapeutic time windows can be selected into recanalization therapy on the basis of imaging findings obtained using CTA. Specifically, a potential avenue for research is whether good collateral status could be used as an inclusive marker for late thrombectomy.

Disclosures

None.

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**Key Words:** CT angiography ■ CT angiographic source images ■ CTA ■ core infarct ■ endovascular therapy ■ perfused blood volume ■ stroke
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