Association Between CT Angiogram Collaterals and CT Perfusion in the Interventional Management of Stroke III Trial

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Background and Purpose—Collateral flow can determine ischemic core and tissue at risk. Using the Interventional Management of Stroke (IMS) III trial data, we explored the relationship between computed tomography angiogram (CTA) collateral status and CT perfusion (CTP) parameters.

Methods—Baseline CTA collaterals were trichotomized as good, intermediate, and poor, and CTP studies were analyzed to quantify ischemic core, tissue at risk, and mismatch ratios. Kruskal–Wallis and Spearman tests were used to measure the strength of association and correlation between CTA collaterals and CTP parameters.

Results—A total of 95 patients had diagnostic CTP studies in the IMS III trial. Of these, 53 patients had M1/M2 middle cerebral artery±intracranial internal carotid artery occlusion, where baseline CTA collateral grading was performed. CTA collaterals were associated with smaller CTP measured ischemic core volume (P=0.0078) and higher mismatch (P=0.0004). There was moderate negative correlation between collaterals and core (r_s=−0.45; 95% confidence interval, −0.64 to −0.20) and moderate positive correlation between collaterals and mismatch (r_s=0.53; 95% confidence interval, 0.29–0.71).

Conclusion—Better collaterals were associated with smaller ischemic core and higher mismatch in the IMS III trial. Collateral assessment and perfusion imaging identify the same biological construct about ischemic tissue sustenance. **(*Stroke*. 2016;47:535-538. DOI: 10.1161/STROKEAHA.115.011461.)**

Key Words: carotid artery, internal ■ collateral circulation ■ perfusion imaging ■ stroke ■ tomography, x-ray computed

Each of the recent positive endovascular trials in acute ischemic stroke used a slightly different imaging paradigm for patient selection with a common goal to identify patients with proximal vessel occlusion and a small ischemic core. A noncontrast head computed tomography (CT) ASPECTS (Alberta Stroke Program Early CT) score was used to evaluate the ischemic core; this was supplemented by CT angiogram (CTA) collateral assessment in Endovascular Treatment for Small Core and Anterior Circulation Proximal Occlusion with Emphasis on Minimizing CT to Recanalization Times (ESCAPE)[1] or CT perfusion (CTP) core measurement in Extending the Time for Thrombolysis in Emergency Neurological Deficits–Intra-Arterial (EXTEND IA)[2] and Solitaire With the Intention for Thrombectomy as Primary Endovascular Treatment (SWIFT PRIME) trials.[3] Collaterals can influence the rate of infarct growth, and perfusion may give indirect information about this downstream collateral sustenance of ischemic tissue, although the relationship between collaterals and perfusion is uncertain.

Our objective was to explore the relationship between CTA collaterals and perfusion parameters in a cohort of patients with baseline CTA and CTP in the Interventional Management of Stroke (IMS) III trial. We hypothesized that better collaterals are associated with smaller ischemic cores and larger mismatch, reflecting compensation from the collateral network preserving blood flow in the setting of acute ischemia.

Methods

Study Population

IMS III was a phase 3, randomized, open-label trial of endovascular treatment after intravenous tissue-type plasminogen activator versus

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intravenous tissue-type plasminogen activator alone.[4] Although not a prerequisite for inclusion, CTA and CTP were performed in a subset of enrolled subjects, depending on the enrolling center's standard of care imaging.

CTP Analysis

All CTPs were postprocessed using commercially available software (Olea Medical 2.3) using oscillatory index–regularized block circular, delay-insensitive algorithms. A semiautomated processing was used, where all steps, including motion correction, smoothing and evaluation of time density curves, arterial and venous input, were checked for errors. Tissue at risk of infarction was defined by T_{max} >6 s, and ischemic core was defined by a dual threshold (relative cerebral blood flow <30% to the mean of contralateral hemisphere and T_{max} >6 s).[5] Using these thresholds, automated volumes of tissue at risk, ischemic core, and mismatch ratios were generated.

CTA Collateral Grading

Collateral circulation in baseline CTA was measured only in patients with proximal vessel occlusion (middle cerebral artery M1/M2±intracranial internal carotid artery occlusion) because assessment of backfilling pial arteries in distal occlusions using single-phase CTA is technically difficult.[6] Because of significant topographical variability in CTA,[7] the collaterals were divided into 2 groups, namely anterior cerebral artery–middle cerebral artery and posterior cerebral artery–middle cerebral artery. The pial artery grading in each group used a 6-point scale (0=absent, 1=minimal, 2=significantly decreased prominence and extent with regions of no vessels, 3=moderately decreased prominence and extent, 4=mildly decreased prominence and extent, and 5=normal or increased prominence and extent) when compared with the opposite normal hemisphere.[6] Total CTA collateral score, calculated by summing the 2 regional scores, ranged from 0 to 10.

Statistical Analysis

Collateral status was trichotomized as good (8–10), intermediate (6–7), and poor (0–5).[6] Association of collateral status with CTP parameters was assessed using the Kruskal–Wallis test; if significant at α=0.05, pairwise tests were conducted to identify differences. Spearman correlation was used to measure strength of association between CTA collateral score (using total score of 0–10) and CTP parameters.

Results

Subject Characteristics

Of 656 subjects enrolled in IMS III, 104 patients had a CTP at baseline. Of these, 9 were excluded because of nondiagnostic CTP. Of the remaining 95 subjects, 85 (89.5%) had a concurrent baseline CTA, and 53 of 85 (62.4%) patients had M1/M2 middle cerebral artery±intracranial ICA occlusion where collateral status was measured (Table 1).

CTA Collaterals and CTP

Subjects with good CTA collaterals had smaller CTP measured ischemic cores and larger mismatch than subjects with poor collaterals. (Table 2; Figure) There was a moderate negative correlation between collaterals and core volume (r_s=–0.45; 95% confidence interval, –0.64 to –0.20) and moderate positive correlation between collaterals and mismatch (r_s=0.53; 95% confidence interval, 0.29–0.71). There was insufficient evidence to conclude an association and correlation between collaterals and tissue at risk (P=0.4484 and r_s=–0.14, 95% confidence interval, –0.40 to 0.12), respectively. Pairwise testing for ischemic core did not show a significant difference between good and intermediate (P=0.3950) or between intermediate and poor collateral grade (P=0.0728).

Discussion

We found that, among patients with M1/M2±internal carotid artery occlusions, better collaterals are associated with smaller ischemic cores and greater mismatch. The CTA collaterals correlated moderately well with CTP measured core with an inverse relation. The strength of our study is that we have demonstrated association between CTA collateral status and CTP parameters in a randomized trial setting.

It is well established that patients with better collaterals have smaller infarcts and better functional outcomes.[6,8,9] Using this premise, the recent ESCAPE trial used collateral assessment using multiphasic CTA for patient selection without additional CTP acquisition.[1] Although the EXTEND IA[2] and SWIFT PRIME[3] trials used CTP for patient selection utilizing automated software for CTP processing, it is important to note that there are numerous challenges for CTP imaging when performed outside of a well-controlled trial environment. These include variability in CTP acquisition and postprocessing methodology, as well as controversy, regarding readiness of CTP for prime time usage.[10]

Because of the positive endovascular trials, baseline CTA has become standard of care for acute stroke workup. Although, concurrent assessment of collateral status is relatively straightforward and can provide a good estimate of ischemic core, CTA collateral evaluation is a relatively new imaging tool with heterogeneity in CTA acquisition

Table 1. Subject Characteristics

Variables	Total, n=53
Age, y, median (minimum–maximum)	69 (33–83)
Men, n (%)	27 (50.9)
NIHSS, median (minimum–maximum)*	18 (7–40)
ASPECTS, n (%)	
0–5	16 (30.2)
6–10	37 (69.8)
Core volume, mL, median (minimum–maximum)	8.3 (0.0–81.6)
Hypoperfused volume, mL, median (minimum–maximum)	70.6 (2.1–383.4)
Mismatch ratio	4.9 (1.0–371.5)
Vessel occlusion, n (%)	
ICAT	13 (24.5)
M1	37 (69.8)
M2	3 (5.7)
Randomized to endovascular therapy, n (%)	35 (66.0)
CTA collateral status, n (%)	
Good (8–10)	21 (39.6)
Intermediate (6–7)	15 (28.3)
Poor (0–5)	17 (32.1)

ASPECTS indicates Alberta Stroke Program Early Computed Tomography score; CTA, computed tomography angiogram; ICAT, internal carotid artery terminus; and NIHSS, National Institutes of Health Stroke Scale.

*Subject missing (n=1).

Table 2. Associations Between CTA Collateral Grade and CT Perfusion Parameters

	CTA Collateral Status			
	Good (n=21)	Intermediate (n=15)	Poor (n=17)	*P* Value
Core volume (mL), median (minimum–maximum)	4.0 (0.0–19.0)	6.0 (0.0–41.7)	24.1 (0.0–81.6)	0.0078
Hypoperfused volumes (mL), median (minimum–maximum)	60.3 (2.1–197.5)	80.5 (8.4–248.7)	84.5 (7.2–383.4)	0.4484
Mismatch ratio, median (minimum–maximum)	12.4 (1.7–371.5)	8.0 (1.0–314.2)	2.8 (1.1–8.4)	0.0004

CTA indicates computed tomography angiogram.

and collateral grading. Our study suggests that collaterals and perfusion are measuring similar aspects of the ischemic pathophysiology. This finding is clinically relevant as CTA collateral assessment may be an alternative for CTP, potentially obviating the need for an additional CTP study.

Our study adds to the accumulating body of evidence related to association of collaterals and perfusion in acute ischemic stroke. A malignant CTA collateral profile, specific for large core volume on baseline magnetic resonance diffusion study correlated with poor outcomes.[11] Better collateral flow measured by magnetic resonance perfusion was associated with larger diffusion–perfusion mismatch and smaller baseline diffusion-weighted imaging lesion volume.[12] However, Bang et al[13] found no difference in the magnetic resonance mismatch depending on the angiographic collateral grade, but did show that patients with good collaterals had larger areas of milder perfusion delay than those with poor collaterals. Similarly, Marks et al[14] showed a relationship between angiographic collaterals and severity of magnetic resonance perfusion deficit but did not show an association between collaterals and DWI core and mismatch. A key explanation for the conflicting findings is the fact that angiographic collaterals were used in these studies, which may not necessarily quantify posterior cerebral artery middle cerebral artery collaterals.

Our study limitations include those inherent in a post hoc analysis along with a small sample size. Another important limitation is that the IMS III trial was a multi-institutional trial with significant heterogeneity in the CTP acquisition technique, although this resembles real-world circumstances. Although CTP techniques have evolved during and beyond the trial period (2006–2012), a large proportion of subjects (86%) had CTP brain coverage of <4 cm, and 95% subjects had <90-s duration of CTP acquisition. The CTA studies obtained were all single-phase acquisitions, which are dependent on bolus characteristics and can underestimate collateral status when compared with the newer multiphasic CTA techniques.

Conclusions

Better collaterals were associated with smaller ischemic core and higher mismatch in the IMS III trial. CTA collateral assessment and perfusion imaging identify the same biological construct about ischemic tissue sustenance.

Disclosures

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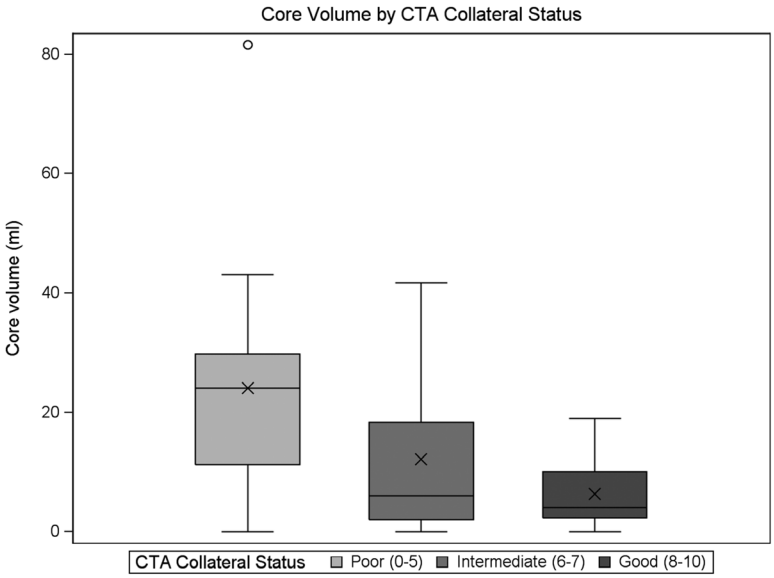

Figure. Boxplot of computed tomography angiogram (CTA) collateral status and CT perfusion ischemic core volume.

speaker's bureau for Covidien (Significant). Dr Hill has received research grant from Covidien AG (Medtronic) to the University of Calgary for partial funding of the Endovascular Treatment for Small Core and Anterior Circulation Proximal Occlusion with Emphasis on Minimizing CT to Recanalization Times (ESCAPE) trial (Significant) and has ownership interest in Calgary Scientific Inc, Imaging company (Significant). The other authors report no conflicts.

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