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ORIGINAL RESEARCH

Diagnostic Performance of Computed Tomography Angiography and Computed Tomography Perfusion Tissue Time-to-Maximum in Vasospasm Following Aneurysmal Subarachnoid Hemorrhage

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BACKGROUND: Vasospasm is a treatable cause of deterioration following aneurysmal subarachnoid hemorrhage. Cerebral computed tomography perfusion mean transit times have been proposed as a predictor of vasospasm but suffer from well-known technical limitations. We evaluated fully automated, thresholded time-to-maxima of the tissue residue function (T_{max}) for determination of vasospasm following aneurysmal subarachnoid hemorrhage.

METHODS AND RESULTS: Retrospective analysis of 540 arterial segments from 36 encounters in 31 consecutive patients with aneurysmal subarachnoid hemorrhage undergoing computed tomography angiography (CTA), computed tomography perfusion, and digital subtraction angiography (DSA) within 24 hours. T_{max} at 4, 6, 8, and 10 s was generated using RAPID (iSchemaView Inc., Menlo Park, CA). Dual-reader CTA and computed tomography perfusion interpretations were compared for patients with and without vasospasm on DSA (DSA+ and DSA–). Logistic regression models were developed using CTA and T_{max} as input predictors and DSA vasospasm as outcome in adjusted and unadjusted models. Imaging studies from all 31 subjects (mean age 47.3±11.1, 77% female, 65% with single aneurysm with mean size of 6.0±2.9 mm) were included. Vasospasm was identified in 42 segments on DSA and 59 segments on CTA, with significant associations across individual vessel segments (P<0.001). In adjusted analyses, DSA vasospasm was associated with CTA (odds ratio [OR], 2.43; 95% CI, 0.94–6.32; P=0.068) as well as territory-specific T_{max}>6 seconds delays (OR, 3.57; 95% CI, 1.36–9.35; P=0.009). Sensitivity/specificity for DSA vasospasm was 31%/91% for CTA, 26%/89% for T_{max}>6 seconds, and 12%/99% for CTA+T_{max}>6 seconds.

CONCLUSIONS: CTA and T_{max} offer high specificity for presence of vasospasm; their utility, even in combination, as screening tests is, however, limited by poor sensitivity.

Key Words: angiography ■ computed tomography angiography ■ digital subtraction ■ logistic models ■ retrospective studies ■ subarachnoid hemorrhage

Aneurysmal subarachnoid hemorrhage (aSAH) is a devastating subclass of hemorrhagic stroke, with an average case fatality rate of 51% and up to one third of survivors requiring long-term care.[1] Vasospasm is a major determinant of outcome in patients with aSAH and occurs in approximately 70% of patients, with typical onset between 4 and 15 days following aneurysm rupture.[2] Among patients with aSAH who develop vasospasm, up to 50% develop ischemic neurologic deficits, and one third progress to delayed cerebral infarction.[3] Several preventative therapies have been developed to reduce the risk of vasospasm-associated infarction.[4–7] Given the delay in onset of vasospasm and the availability of effective

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CLINICAL PERSPECTIVE

What Is New?

- Prior studies exploring the use of computed tomography perfusion in combination with computed tomography angiography for prediction of aneurysmal subarachnoid hemorrhage-related vasospasm have not investigated contemporary perfusion imaging paradigms, such as tissue time-to-maximum.

What Are the Clinical Implications?

- The use of computed tomography angiography or computed tomography perfusion tissue time-to-maximum as a screening examination for aneurysmal subarachnoid hemorrhage-related vasospasm, alone or in combination, may be poorly suited because of the low sensitivity and caution is recommended when applying these for clinical management.

Nonstandard Abbreviations and Acronyms

aSAH	aneurysmal subarachnoid hemorrhage
CTA	computed tomography angiography
CTP	computed tomography perfusion.

therapies, a narrow therapeutic window exists to assess for vasospasm and brain tissue at risk that may allow for prevention of vasospasm-induced infarction. The development of effective diagnostic and prognostic biomarkers to identify at-risk patients is therefore critical.

Cerebral computed tomography angiography (CTA) has been reported to be a reliable imaging modality for detecting and assessing the severity of vasospasm following aSAH.[8] However, the sensitivity and positive predictive value of CTA vary and have been reported to be as low as 57% and 43%, respectively.[9] Cerebral CT perfusion (CTP) has been proposed as a complementary test for the identification of hypoperfused and at-risk tissues in the setting of vasospasm; however, optimal perfusion profiles predicting vasospasm have yet to be established. Prior studies have suggested that qualitative CTP using capillary mean transit time (MTT) may be as accurate as reference-standard digital subtraction angiography (DSA) in predicting vasospasm in patients with SAH.[10] However, MTT may suffer in low signal-to-noise regions (as may occur in ischemic regions or more globally in those with elevated intracranial pressure), may be quantitatively affected by bolus truncation, or may be limited by poor lesion-to-background contrast precluding robust autosegmentation of at-risk volumes.[2,11,12] Furthermore, qualitative CTP evaluation using MTT may prove limited by interobserver variability, the subjectivity of visual assessment in gauging salvageable tissue and small infarcts, and the dependency upon expert evaluation, which may engender untoward delays in management of critically ill patients.[13,14]

Other CTP parameters extracted following dynamic bolus passage of iodinated contrast include cerebral blood volume and cerebral blood flow, which together with MTT are interrelated through the central volume theorem and Stewart Hamilton equation.[15] More recently, the time-to-maximum of a deconvolved tissue residue function (T_{max}) has been recognized as a superior predictor of hypoperfused and penumbral tissue volumes in the acute stroke setting.[12,16–20] In comparison to MTT, T_{max} may be less sensitive to patient motion and to underestimation related to data undersampling and is more uniform across gray and white matter.[12] However, the utility of T_{max} in the setting of vasospasm has not been explored.

The recent development of fully automated CTP postprocessing environments has addressed some of the shortcomings of visual qualitative assessment of perfusion deficits. Such fully user-independent platforms allow for fast, reproducible, and accurate voxel-level perfusion estimations mitigating subjectivity in perfusion analysis and outperforming qualitative and user-dependent interpretation.[13,21] In most currently available CTP postprocessing environments, thresholded T_{max} maps are automatically generated and prominently featured, in contrast to other metrics such as MTT.

The purpose of this study was to evaluate the screening utility of T_{max} in diagnosing vasospasm in patients with aSAH using estimations generated by fully automated processing software. We hypothesized that the addition of T_{max} would significantly improve predictive models of clinically important vasospasm identified on DSA in comparison to the use of CTA in isolation.

METHODS

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Study Design and Patient Population

Local institutional review board approval was obtained and the requirement for subject informed consent was waived. In this retrospective study, the institutional clinical data warehouse was queried for consecutive patients over a 5-year period who had (1) inpatient cerebrovascular CTA and CTP studies, including a baseline CTA performed at admission; (2) a DSA study

within 24 hours (before or after) of a contemporaneous CTA/CTP; and (3) a primary diagnosis of aSAH, defined as the presence of SAH on a noncontrast head CT or lumbar puncture, and with documentation of an intracranial aneurysm on subsequent DSA. Patients with evidence of acute thrombotic stroke on initial imaging or with nondiagnostic CTA, CTP, or DSA were excluded. In addition, patients who underwent either pharmacologic or mechanical interventions for their vasospasm at the time of a DSA preceding their CTA were excluded in order to eliminate the confounding effects of ongoing or waning treatment effects at the time of follow-up CTA. Relevant demographic and clinical data were recorded for all patients, which included patient age, sex, race, and comorbidities associated with aSAH, specifically, a history of hypertension, diabetes, smoking, and coronary artery disease.

All imaging studies were ordered at the discretion of the neurocritical care or neurosurgical physician to evaluate for vasospasm. Generally, CTA/CTP was ordered after the development of new clinical signs suggestive of vasospasm, including new focal neurologic deficits or increasing velocities on daily transcranial Doppler monitoring. At our institution, the finding of moderate-to-severe or severe vasospasm on CTA is considered clinically important and generally leads to DSA for confirmation and potential treatment.

Imaging Protocols and Post-Processing

Noncontrast head CT, CTA and CTP studies were acquired as per a standardized institutional protocol on a 40-mm, 64–detector row clinical system (LightSpeed VCT; GE Healthcare, Milwaukee, WI), as described previously.[13] Helical noncontrast head CT (120 kV; 100–350 auto-mA; CT dose index, ~43.15) was performed from the foramen magnum through the vertex at 5.0-mm section thickness. Two contiguous CTP slabs were obtained for 8-cm combined coverage of the supratentorial brain, obtained at 8 consecutive 5-mm sections per slab. Cine mode acquisition (80 kV; 100 mA; CT dose index, ~293.48), permitting high-temporal-resolution (1-second sampling interval) dynamic bolus passage imaging, was performed following the administration of 35-mL iodinated contrast (iopamidol, Isovue 370; Bracco, Princeton, NJ) power injected at 5 mL/s through an 18-gauge or larger antecubital intravenous peripheral line. Contrast administration was followed by a 25-mL saline flush at the same rate. Scan duration was 45 seconds for each slab. Following the dynamic scan, helical CTA (120 kV; 200–350 auto-mA; CT dose index, ~38.08) was performed from the carina to the vertex (section thickness/interval, 0.625/0.375 mm) after the intravenous administration of 70-mL iodinated contrast injected at 5 mL/s and followed by a 25-mL saline flush.

Primary Predictors and Outcomes

All CTA and DSA studies are reviewed by board-certified radiologists with subspecialty certification in neuroradiology. Vessel-by-vessel assessment for vasospasm on CTA was performed by comparing arterial calibers on the CTA of interest to that of the patient's index CTA obtained at initial presentation (before the typical onset of vasospasm following aSAH[2]) to mitigate confounding effects of anatomic hypoplasia or other variation. The CTA and DSA reports for all patients were retrospectively reviewed and were stratified according to reported vasospasm severity using the degree of vascular narrowing: minimal, mild, mild-to-moderate, moderate, moderate-to-severe, and severe. Per our institutional standard of practice, moderate-to-severe and severe vasospasm on CTA or DSA are deemed to be clinically important, and the study population was dichotomized into DSA+ and DSA– cohorts, as recently suggested by Darsaut et al.[22] Major intracranial artery segments were subdivided for assessment as follows: right and left supraclinoid internal carotid arteries, right and left M1 middle cerebral arteries, right and left distal middle cerebral arteries, right and left A1 anterior cerebral arteries, right and left distal anterior cerebral arteries, right and left vertebral arteries, and basilar artery, producing a total of 540 individual arterial segments and corresponding perfusion territories across the study population for analysis. Interrater agreement for determination of reference standard DSA vasospasm positivity was assessed with 2 blinded readers (a board-certified neuroradiologist with 24 years of experience and a vascular neurosurgeon with 4 years of experience) who independently scored the degree of vasospasm of 30 vessels on DSA. The interpretation of the DSA by the neuroradiologist was used in the logistic regression models. For statistical analysis, the CTA predictor was moderate-to-severe or severe vasospasm at the arterial segment level as per our institutional standard of practice.

All CTP studies were automatically exported to a dedicated network node running a fully user-and vendor-independent processing environment (RAPID) operating on standardized Digital Imaging and Communications in Medicine data and configured for entirely automated image preprocessing steps, thresholding, and segmentation.[13,14] Briefly, following preprocessing steps correcting rigid-body motion, arterial and venous input function selection is performed and deconvolved from the voxel time-attenuation course using a delay-insensitive algorithm for isolation of the tissue residue function. T_{max} is determined on a voxel-wise basis, with T_{max} maps incrementally thresholded between 4 and 10 seconds at 2-second intervals and overlaid upon source CTP data for analysis,[19] with results made available for review within approximately 2 minutes from the time of

data export. CTP quality was confirmed on each case by review of arterial input function and venous output function placement and quality, as well as by exclusion of any cases with metallic artifacts, such as from aneurysm repair or ventricular catheters, that may affect volumetric perfusion estimations. Each T_{max} value map was reviewed for involvement of the major intracranial vascular territories including right and left anterior cerebral arteries, right and left middle cerebral arteries, and right and left posterior cerebral artery. For statistical analysis, CTP predictor was T_{max} delay in the vascular territory corresponding to the T_{max} threshold evaluated.

Statistical Analysis

Cohen's kappa correlation was used to compare the interobserver agreement of the 2 independent DSA readers in diagnosing clinically important vasospasm, again defined as moderate-to-severe or severe vasospasm, versus no clinically important vasospasm. Kappa values of 0.00 to 0.20 were considered to indicate slight agreement, 0.21 to 0.40 fair agreement, 0.41 to 0.60 moderate agreement, 0.61 to 0.80 substantial agreement, and 0.81 to 1.00 almost perfect agreement.[23]

Patients were divided into 2 groups: DSA+ and DSA– for clinically important vasospasm. Fisher's exact test was used to compare categorical variables and 2-tailed *t* tests were used to evaluate the differences in mean time interval from DSA to CTA/CTP between the DSA+ and DSA– groups. To account for clustering, we used logistic regression with generalized estimating equation to determine the association between the predictors CTA vasospasm and T_{max} delay with the outcome DSA vasospasm. Prespecified variables were adjusted for in different models as follows: model 1 adjusting for age and sex, model 2 adjusting for age, sex, and covariates associated with vasospasm ($P<0.05$) on univariate analyses, model 3 including variables in model 2 as well as both predictors (CTA and CTP) in the same model, and model 4 including variables in model 3 as well as the modified Fisher score. Odds ratios were generated for each model. Analyses were performed using SPSS 25.0 (Chicago, IL) and $P<0.05$ was considered significant.

RESULTS

Aneurysm Characteristics and CTA/DSA Vasospasm

A total of 540 arterial segments from 36 studies obtained in 31 patients were included in the study. Five patients had 2 separate evaluations for vasospasm during a single admission that each included CTA, CTP, and DSA. No cases required exclusion for technical reasons or incomplete data. The majority of patients (65%) had a single intracranial aneurysm. Six patients (19%) had 2 aneurysms, 3 patients (10%) had 3 aneurysms, a single patient (3%) had 4 aneurysms, and a single patient (3%) had 5 aneurysms. The mean±SD aneurysm size was 6.0±2.9 mm and there was no significant difference in mean aneurysm size between DSA+ and DSA– groups. All aneurysms, with the exception of a single, spontaneously thrombosed aneurysm in 1 subject without vasospasm, had undergone aneurysm treatment at the time of the studies; however, no studies required exclusion on the basis of treatment-related artifacts. The majority of the patients (90%) had a modified Fisher scale grade of 4 on the initial noncontrast head CT at our institution; 3 patients (10%) had grade 3 and a single patient had grade 0. However, 17 of the patients (55%) had an external ventricular drain in place, all of whom had a grade 4 hemorrhage, limiting the reliability of the modified Fisher scale grade as intraventricular hemorrhage may have resulted from the drain placement. There was no significant difference in modified Fisher score between DSA+ and DSA– groups. Remaining demographic and clinical stroke risk factors are summarized in Table 1.

There was almost perfect agreement between the 2 independent readers with respect to vasospasm on DSA, with a kappa value of 0.84. Of the 36 included DSA studies, 29 (81%) demonstrated at least mild vasospasm of 1 or more vessels and 14 (39%) had at least 1 artery with moderate-to-severe or severe vasospasm, which was considered clinically important. Of the 14 DSA+ studies, 10 (71%) had more than 1 affected vessel. There was a total of 42 arteries with clinically important vasospasm on catheter angiography in the study population. The median time between the CTA/CTP and DSA was 10.8 hours (interquartile range 13.9 hours). There was no statistically significant difference ($P=0.589$) in the mean time interval from CTA/CTP to DSA between the DSA+ (9.9 hours) and DSA– (11.4 hours) groups and time was therefore not included among adjusted model variables. In 5 cases, the DSA preceded the CTA/CTP study. Four of these cases, including 1 for which the DSA was performed 18 m before the CTA/CTP, were in the DSA– group. Two of these patients were assessed as having vasospasm only on CTA whereas 1 of the 5 cases had clinically important vasospasm on both DSA and CTA. An example of concordant CTA and DSA vasospasm is shown in Figure.

Univariate Analyses

When comparing CTA to DSA for individual arterial segments, 31% of arteries in the DSA+ group had equivalent vasospasm estimations on the concurrent CTA, whereas only 9% of arteries in the DSA– group

Table 1. Subject Demographics, and Vessel-Level and Segmented Vascular Territory-Level Comparison Between Digital Subtraction Angiography, CTA, and CTP T_{max}

Variable*	Population	DSA– group	DSA+ group	*P* value
Number of patients	31	19	12	
Age	47.3±11.1	47.5±11.5	47.1±9.8	0.923
Sex (women)	23 (77%)	11 (58%)	12 (100%)	0.008
Race (White)	16 (52%)	10 (53%)	6 (50%)	0.890
Hypertension	20 (65%)	10 (53%)	10 (83%)	0.087
Diabetes	2 (6%)	1 (5%)	1 (8%)	0.745
Coronary heart disease	4 (13%)	4 (21%)	0 (0%)	0.094
Smoking	15 (48%)	7 (37%)	8 (67%)	0.113
Artery†	540	498	42	
Internal carotid artery	72	67	5	
Middle cerebral artery	144	130	14	
Anterior cerebral artery	144	123	21	
Vertebral artery	72	72	0	
Basilar artery	36	34	2	
Posterior cerebral artery	72	72	0	
CTA vasospasm‡	59	46 (9%)	13 (31%)	0.008
CTP delay§				
T_{max}>4 s	177	149 (30%)	28 (67%)	<0.001
T_{max}>6 s	64	53 (11%)	11 (26%)	0.021
T_{max}>8 s	42	35 (7%)	7 (17%)	0.058
T_{max}>10 s	26	20 (4%)	6 (14%)	0.057

CTA indicates computed tomography angiography; CTP, computed tomography perfusion; DSA, digital subtraction angiography; and T_{max}, tissue time-to-maximum.

*Age presented as mean±SD. All other variables presented as number (percentage).

†Values represent the number of arteries without or with DSA clinically important vasospasm.

‡Moderate-to-severe or severe vasospasm on CTA corresponding to same degree of vasospasm in the same artery on DSA.

§CTP delay in the arterial territory of vasospasm identified on DSA.

were reported to have clinically important vasospasm on CTA (*P*<0.001, Table 1). Furthermore, there were statistically significant associations between clinically important vasospasm on DSA and the presence of prolonged T_{max} >4, >6, >8, or >10 seconds in the territory supplied by the artery with vasospasm (Table 1).

Logistic Regression Models

As shown in Table 2, in unadjusted models there was increased odds of clinically important vasospasm on DSA on an arterial segment level when there was evidence of CTA vasospasm (odds ratio [OR], 4.41; 95% CI, 2.14–9.06; *P*<0.001), T_{max}>4 seconds delay in the territory supplied by that artery (OR, 4.69; 95% CI, 2.40–9.15; *P*<0.001), or T_{max}>6 seconds delay in the territory (OR, 2.98; 95% CI, 1.42–6.27; *P*=0.004). These associations persisted in full adjusted models (model 4, Table 2); CTA vasospasm (OR, 2.43; 95% CI, 0.95–6.27; *P*=0.065), T_{max}>4 seconds delay in the territory (OR, 9.11; 95% CI, 4.04–20.53; *P*<0.001), or T_{max}>6 seconds delay in the territory (OR, 4.05; 95% CI, 1.60–10.23; *P*=0.003).

Performance of Predictors (CTA Vasospasm, T_{max}>4 seconds Delay, and T_{max}>6 seconds Delay)

Sensitivity for these variables in isolation or in combination ranged from 12% to 69% and specificity from 63% to 99% (Table 3). The positive predictive value (PPV) of solely relying on CTA vasospasm, areas of T_{max}>4 seconds, or areas of T_{max}>6 seconds was poor (ranging from approximately 17%–22%); however, when CTA vasospasm was combined with areas of CTP T_{max}>4 seconds or T_{max}>6 seconds, the PPV increased to 50% and 46%, respectively (Table 3). The negative predictive value for all of the variables, either singly or in combination, was high (93%–96%, Table 3), potentially reflecting the generally low pretest probability in light of the comparatively poor sensitivity, and in contradistinction, the low PPV despite strong test specificity.

DISCUSSION

The goal of this study was to assess the screening utility of T_{max} in diagnosing clinically important vasospasm

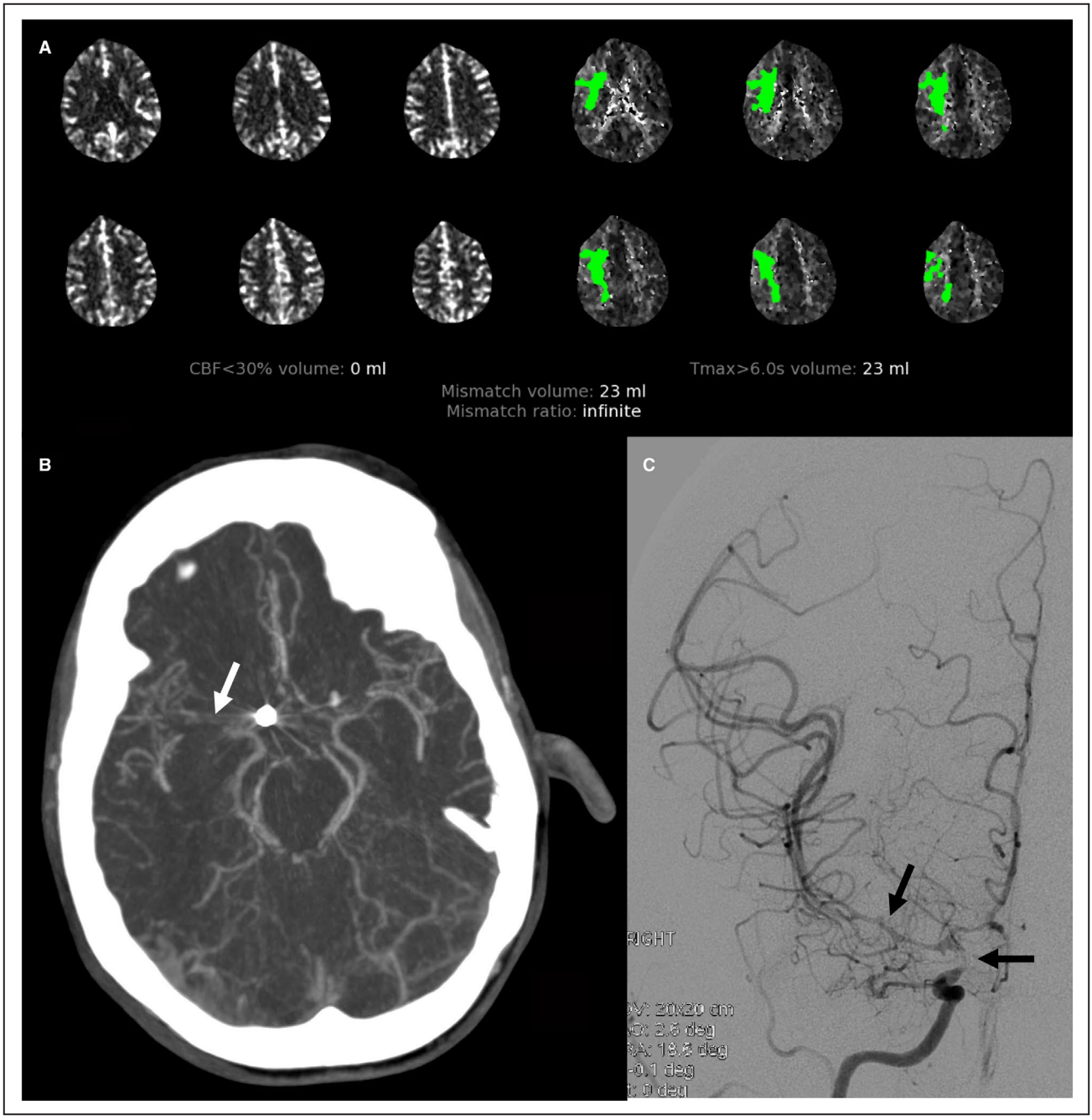

Figure 1. 40-year-old woman with coiled ruptured right internal carotid artery (ICA) aneurysm and concordant computed tomography perfusion (CTP), computed tomography angiography (CTA), and digital subtraction angiography (DSA) on posthemorrhage day #9.

Patient was symptomatic at the time of the studies. CTP processed with RAPID demonstrates region of prolonged tissue time-to-maximum (T_{max})>6 seconds within the right middle cerebral artery (MCA) territory (**A**). Severe vasospasm involving the right M1 MCA segment (white arrow) on simultaneously obtained CTA (**B**). Additional moderate-to-severe right supraclinoid ICA vasospasm seen on CTA not shown. Moderate-to-severe vasospasm of the right supraclinoid ICA and M1 MCA segment (black arrows) on DSA performed 5 hours after CTA (**C**). Aneurysm coil mass is visible both on CTA and DSA. CBF indicates cerebral blood flow.

on DSA. Although T_{max} has become recognized as the best predictor of hypoperfused and penumbral tissue volumes in the acute stroke setting,[12,16–18] its utility has not been evaluated to date in the assessment of aSAH vasospasm, despite its widespread use as a primary parametric output from most commercially available CTP processing software packages. Our findings demonstrate that although CTA vasospasm and CTP-derived T_{max} are relatively poor predictors of vasospasm on DSA when used in isolation, their performance may

Table 2. Logistic Regression Models and Odds Ratios of CTA and Thresholded T_{max} in Predicting Clinically Important Vasospasm on Digital Subtraction Angiography

Model	CTA vasospasm	T_{max}>4 seconds	T_{max}>6 seconds
Unadjusted	2.96 (1.32–6.63) *P*=0.008	5.86 (2.56–13.42) *P*<0.001	2.53 (1.15–5.55) *P*=0.021
Model 1	3.49 (1.48–8.21) *P*=0.004	8.73 (3.76–20.27) *P*<0.001	3.11 (1.28–7.53) *P*=0.012
Model 2	3.93 (1.34–9.43) *P*=0.002	9.05 (4.00–20.49) *P*<0.001	3.96 (1.57–9.96) *P*=0.003
Model 3	2.82 (1.11–7.19) *P*=0.030	7.92 (3.44–18.23) *P*<0.001	3.37 (1.30–8.71) *P*=0.012
Model 4	2.43 (0.94–6.32) *P*=0.068	9.00 (3.88–20.91) *P*<0.001	3.57 (1.36–9.35) *P*=0.009

Values represent odds ratio with 95% CIs and associated *P* values. Model 1 adjusted for age and sex; Model 2 adjusted for age, sex, hypertension, and smoking; Model 3 adjusted for age, sex, hypertension, and smoking and includes both variables (CTA vasospasm and CTP T_{max} delay); Model 4: adjusted for age, sex, hypertension, smoking, and modified Fisher score and includes both variables (CTA vasospasm and CTP T_{max} delay). CTA indicates computed tomography angiography; CTP, computed tomography perfusion; and T_{max}, tissue time-to-maximum.

be enhanced when used in combination, albeit with sensitivity likely still insufficient to serve as a meaningful screening test, even in combination.

We found a lower sensitivity CTA in isolation for diagnosing clinically important vasospasm on DSA than had previously been reported, although our observed specificity was similar.[8,9] However, the majority of prior studies compared the rates of vasospasm on CTA and DSA without comparing the severity, sometimes considering all vessels or groups of vessels together (eg, anterior circulation), or analyzed severity separately from arterial segment. Recently, Kim et al. reported sensitivity for CTA prediction of DSA vasospasm ranging from 44% to 100% depending upon the severity of vasospasm.[24] In the current study, we included both degree of severity and arterial segment in the sensitivity and specificity analysis, which may have contributed to the lower sensitivity rates, but which we felt produces more meaningful context for clinical practice in our experience.

The advantage of automated perfusion software as used here is the standardization of quantitative perfusion measurements, which eliminates user-dependent qualitative interpretation of CTP maps.[13,14] However, the use of these programs in settings other than acute ischemia has not been well studied, including for vasospasm prediction using more contemporary paradigms including automated T_{max} at penumbral delay thresholds. Despite the lack of supporting data, in our experience the use of these programs and T_{max} has proliferated to include clinical scenarios such as aSAH.

Prior studies have demonstrated good predictive value of qualitative CTP for DSA confirmed vasospasm, for example, demonstrating high correlation between qualitatively assessed MTT and DSA scores[10] as well as CTP- and DSA-derived cerebral circulation times (defined as difference in Time to Peak between an arterial territory region of interest and the superior sagittal sinus).[25] In a prior meta-analysis of CTP studies in patients with aSAH, cerebral blood flow and MTT were identified as having the highest diagnostic accuracy for vasospasm[9]; however, T_{max} was not included in this analysis. Unlike MTT, T_{max} maps are obtained following deconvolution of an automated or user-defined proximal arterial input function from the tissue time-attenuation course to isolate a hypothetical tissue impulse response,[19] providing an estimation of macrovascular delay while removing confounds related to the bolus injection or to more proximal (eg, extracranial) sources of delay. A prior study by Takahashi et al. demonstrated that whereas prolonged MTT in patients with aSAH was associated with changes in World Federation of Neurological Societies grade, there was no difference in average MTT between patients who developed delayed cerebral infarction (DCI) and those who did not[26]; thus we felt a contemporary

Table 3. CTA and Computed Tomography Perfusion T_{max} Sensitivity, Specificity, PPV, and NPV, for Clinically Important Vasospasm on Digital Subtraction Angiography

	Sensitivity	Specificity	PPV	NPV
CTA	0.31 (0.06–0.56)	0.91 (0.82–0.99)	0.22 (0.11–0.33)	0.94 (0.92–0.96)
T_{max}>4 s	0.67 (0.49–0.84)	0.70 (0.63–0.77)	0.16 (0.10–0.21)	0.96 (0.94–0.98)
T_{max}>6 s	0.26 (0.00–0.52)	0.89 (0.81–0.98)	0.17 (0.08–0.26)	0.93 (0.91–0.96)
CTA+T_{max}>4 s	0.29 (0.03–0.54)	0.98 (0.89–1.00)	0.50 (0.30–0.70)	0.94 (0.92–0.96)
CTA+T_{max}>6 s	0.12 (0.00–0.40)	0.99 (0.90–1.00)	0.45 (0.16–0.75)	0.93 (0.91–0.95)
CTA or T_{max}>4 s	0.69 (0.52–0.86)	0.63 (0.56–0.70)	0.14 (0.09–0.18)	0.96 (0.94–0.98)
CTA or T_{max}>6 s	0.45 (0.23–0.68)	0.81 (0.73–0.89)	0.17 (0.10–0.24)	0.95 (0.92–0.97)

Values with 95% CIs. CTA indicates computed tomography angiography; NPV, negative predictive value; PPV, positive predictive value; and T_{max}, tissue time-to-maximum.

investigation into the utility of T_{max} in this setting to be timely.

When considering all vascular territories in our population, the presence of prolonged T_{max} in any individual territory failed to yield group-level differences between patients with and those without clinically important vasospasm on DSA. As the imaging conditions for aSAH patients often differ from those in patients with acute ischemic stroke (including a greater likelihood for extensive blood products, increased intracranial pressure, and artifacts arising from extrinsic tubes and lines, aneurysm coil masses, stents, or clips, among other considerations) the likelihood for spurious T_{max} spikes may be greater, including in areas remote from vasospasm or even in nonanatomical distributions. This indeed may have been the case in our study and underscores the importance of cross-reference between structural imaging, raw perfusion time series, and perfusion maps at the time of interpretation to reconcile such confounds. Again, it merits discussion that the tracer kinetic principles optimized for predicting ischemia following large vessel occlusion acute ischemic stroke may differ in nontrivial ways from the hemodynamic conditions in vasospasm and warrants further study.

Notwithstanding, at the level of individual arterial segments, the OR for having clinically important vasospasm on DSA using prolonged T_{max} in the same vascular territory ranged from 2.53 to 9.05 depending upon model adjustments; importantly, however, the PPV of T_{max} in isolation remained poor, regardless of the threshold used, again reflecting the overall low pretest probability. We found similar findings for CTA vasospasm associated with DSA vasospasm in our study. As the arterial segment with vasospasm is not known a priori (ie, during the time of a screening CTA or CTP), caution is recommended when interpreting either of these studies in isolation in the prediction of DSA clinically important vasospasm.

Importantly, we found that regardless of which T_{max} threshold between 4 and 10 seconds was evaluated, despite high specificity, the use of T_{max} alone did not yield high PPV. This too may be owing to the skewed population characteristics resulting from the far greater number of arterial segments without clinically important vasospasm on DSA. In contrast to the weak PPV of either alone, the combination of CTA vasospasm and areas of T_{max}>4 seconds or T_{max}>6 seconds had a modest PPV of approximately 50% for DSA vasospasm, which is closer to several prior studies using MTT that reported PPV of 71% to 79%.[2,10,27] Conversely, the negative predictive value of CTA and T_{max} either in isolation or in combination was uniformly high despite the limited sensitivity. The composite results suggest that the likelihood of a patient without clinically important vasospasm being triaged to DSA is unlikely, particularly given the 99% specificity of a positive CTA with concordant T_{max}>6 seconds delay in the territory supplied by the vessel with vasospasm. In contradistinction, CTA and CTP with any T_{max} delay yielded low sensitivity despite uniformly high negative predictive value (>0.9), bringing performance of either study as a screening test into question.

Precisely what the likelihood of a combined, negative CTA and territorial T_{max} prolongation might be in a low-risk patient without neurologic deterioration remains to be determined. Further studies using risk models incorporating the use of pharmacologic treatment (vasopressors, calcium channel blockers), neurosonography, clinical neurologic/neurosurgical examination, endovascular treatment approaches (endovascular coiling with or without stent placement), and other emerging clinical and imaging biomarkers may provide benefit in understanding this patient population.

In conjunction with the current literature, our results pose an unanswered question: what type of test is optimal for patients with aSAH? Is sensitivity, specificity, PPV, or negative predictive value the most relevant metric of performance? The current automated CTP software programs were developed for use in acute ischemic stroke, with the prevailing tenet of not missing opportunities for beneficial intervention. Instrument calibration has therefore favored high overall volumetric accuracy after first minimizing any tendency for false positive classification.[28] This may be important for aSAH patients as well, although an important consideration must remain the capacity to perform screening DSA and, therefore, limiting the number of patients triaged to DSA to those most likely to benefit from intervention. As with all clinical tests, the results need to be interpreted in the clinical context and the potential change in management that may be instituted based on the outcome. A more sensitive test may be favored when contemplating initiation of medical therapy such as vasodilators before the onset of rapidly detrimental vasospastic ischemia, and in this scenario, T_{max}>4 seconds CTP thresholds in isolation may be viewed as most useful, with a sensitivity of 67%. However, even in this context, a number of patients with vasospasm will have falsely negative test results. In contrast, maximizing PPV may be more important if considering using catheter-based interventions. In this situation, the use of CTA in combination with T_{max} may be more appropriate.

The increasing availability of automated, user-independent CTP processing software has likely driven the anecdotal evidence of its use for the evaluation of suspected aSAH-related vasospasm. As most of these software packages were largely designed for the assessment of acute ischemic stroke, automated, thresholded T_{max} maps are generated and prominently featured. Notwithstanding, we would emphasize that

optimal thresholds may differ between vendors, even when ostensibly similar postprocessing steps are employed; the translatability of thresholds between vendor or research tools is therefore not necessarily to be taken for granted and performance at specific thresholds may vary considerably.[29,30]

Limitations

Several limitations merit discussion, including primarily those relating to the retrospective nature of our study, which may introduce biases unaddressed despite our attempt to produce a homogeneous and well-controlled cohort of aSAH together with adjustment for common confounders in this context. In particular, changes in patient status or treatments such as those directed at intracranial pressure or vasopressor management occurring between CTA and DSA may have affected our findings, or alternatively vasospasm diagnosed on CTA may have resolved without intervention before the subsequent DSA. However, both of the preceding are felt to be represent minor confounds given the relatively short median time between CTA and DSA in our population, in line with past studies also using 24 hours as a cutoff time between CTA and DSA studies for vasospasm.[8]

Another potential limitation of the study is the relatively short CTP scan duration of 45 seconds, which is shorter than that now widely recommended.[31,32] Because of the retrospective nature of our study, older acquisition paradigms preceding more contemporary recommendations were in use during the study period. However, all of the included CTP were screened before inclusion to ensure adequate return to baseline for venous time attenuation curves, and all scans were subjected to the in-line quality control tools in RAPID without error notification. Elevated intracranial pressure may potentially prolong delay-sensitive indices; however, this effect was also monitored to the extent possible through examination of the arterial and venous time attenuation curves as well as with RAPID in-line quality control tools to ensure that no cases with either severe bolus truncation or generalized underenhancement of the cerebral circulation were included.

Similar to other studies relying on vasospasm as an outcome, this study is also limited by the assumption that DSA vasospasm correlates with risk of DCI. We acknowledge that DCI/infarction are better predictors of clinical outcome; however, less than half of patients with cerebral vasospasm develop DCI, whereas a small subset of patients may develop DCI without ever having prior imaging-detected vasospasm.[33–35] Although management decisions based solely on vasospasm screening may lead to overtreatment and morbidity, untreated aSAH-induced vasospasm may result in disastrous, and preventable, neurologic deterioration. Although magnetic resonance imaging-detected infarction related to aSAH is a better predictor of clinical outcome than vasospasm alone, such patients are commonly too unstable to undergo magnetic resonance imaging, and consequently few patients in our initial cohort underwent follow-up magnetic resonance imaging for comparison. Furthermore, in our institution, patients with clinically important vasospasm detected on imaging undergo prompt therapy, decreasing the number of patients that ultimately develop DCI, compelling our use of DSA vasospasm as the primary outcome measure.

There is also a potential for verification bias related to using DSA as the gold standard for vasospasm. As DSA is an invasive test that requires trained operators, there may have been reluctance to order this test when CTA or CTP were reported as negative. This effect could lead to overestimation of sensitivity and underestimation of specificity.[36] This bias is inherent in retrospective studies of aSAH vasospasm using DSA and, therefore, a future prospective study is warranted.

The relatively small sample size of 31 patients should also be considered when interpreting our results, although our study population was larger than the sample size of the majority of prior studies (range 2–41 patients).[9,25,26] The study population is somewhat unique in that all patients had a CTA, CTP, and DSA within a 24-hour window. In addition, we evaluated our results both on a per-study and a per-vessel level, the latter of which increased the sample size to a more robust 540 segments. Finally, there is a possibility that clinically important vasospasm may have been present on the CTA/CTP study but resolved by the time the DSA was performed, or vice versa. This may be particularly true at our institution, where vasospasm is treated aggressively and frequently with intrathecal nicardipine that may be instituted before the DSA confirmation. This may have led to an underestimation of the predictive power of CTA and CTP, although, where present, its effect upon our primary observation that the combination of imaging outperforms either individual test would likely remain.

CONCLUSIONS

This is the first study to explore the utility of auto-thresholded and segmented T_{max} values to diagnose clinically important DSA vasospasm in patients with aSAH. Our results suggest that, depending upon the clinical scenario, a combination of CTA and CTP outperforms their use in isolation, with particular attention to concordance between CTA-detected vasospasm and prolonged T_{max} within that vascular territory. Thus, thresholded T_{max} maps generated by automated CTP software packages may be clinically useful but require

circumspection in the evaluation of aSAH-related vasospasm.

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Disclosures

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