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Assessment of a Bayesian Vitrea CT Perfusion Analysis to Predict Final Infarct and Penumbra Volumes in Patients with Acute Ischemic Stroke: A Comparison with RAPID

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ABSTRACT

BACKGROUND AND PURPOSE: Brain CTP is used to estimate infarct and penumbra volumes to determine endovascular treatment eligibility for patients with acute ischemic stroke. We aimed to assess the accuracy of a Bayesian CTP algorithm in determining penumbra and final infarct volumes.

MATERIALS AND METHODS: Data were retrospectively collected for 105 patients with acute ischemic stroke (55 patients with successful recanalization [TICI 2b/2c/3] and large-vessel occlusions and 50 patients without interventions). Final infarct volumes were calculated using DWI and FLAIR 24 hours following CTP imaging. RAPID and the Vitrea Bayesian CTP algorithm (with 3 different settings) predicted infarct and penumbra volumes for comparison with final infarct volumes to assess software performance. Vitrea settings used different combinations of perfusion maps (MTT, TTP, CBV, CBF, delay time) for infarct and penumbra quantification. Patients with and without interventions were included for assessment of predicted infarct and penumbra volumes, respectively.

RESULTS: RAPID and Vitrea default setting had the most accurate final infarct volume prediction in patients with interventions ([Spearman correlation coefficient, mean infarct difference] default versus FLAIR: [0.77, 4.1 mL], default versus DWI: [0.72, 4.7 mL], RAPID versus FLAIR: [0.75, 7.5 mL], RAPID versus DWI: [0.75, 6.9 mL]). Default Vitrea and RAPID were the most and least accurate in determining final infarct volume for patients without an intervention, respectively (default versus FLAIR: [0.76, −0.4 mL], default versus DWI: [0.71, −2.6 mL], RAPID versus FLAIR: [0.68, −49.3 mL], RAPID versus DWI: [0.65, −51.5 mL]).

CONCLUSIONS: Compared with RAPID, the Vitrea default setting was noninferior for patients with interventions and superior in penumbra estimation for patients without interventions as indicated by mean infarct differences and correlations with final infarct volumes.

ABBREVIATIONS: AIS = acute ischemic stroke; FIV = final infarct volume; MAE = mean absolute error; Tmax = time until the residue function reaches its peak

CTP is an imaging technique used to quantify infarct and penumbra tissue in patients with acute ischemic stroke (AIS) evaluated for endovascular thrombectomy.¹ CTP hemodynamic features include CBV, CBF, TTP, MTT, time until residue

function reaches its peak (Tmax), and delay time, which are compared between contralateral hemispheres to identify ischemic tissues.² Various perfusion thresholds can be used for each hemodynamic parameter to identify tissues as infarct and penumbra.³ Infarct is irreversibly damaged tissue that cannot recover in the event of reperfusion. Penumbra represents tissue deficient in blood flow but that can be salvaged through reperfusion.² As recommended by the American Heart Association, ischemic volume estimations should be used for selection of patients with AIS for mechanical thrombectomy when symptom onset is beyond 6 hours.⁴

Bayesian CTP software, based on a probabilistic approach, has been developed in Vitrea (Vital Images, Minnetonka, Minnesota) and Olea Sphere (Olea Medical, La Ciotat, France). This method relies on adjacent perfusion scan regions to calculate hemodynamic maps and implements postprocessing noise reduction.⁵ Quantitative analysis provided by Bayesian CTP maps allows

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infarct and penumbra volume estimations using all CTP parameters, including the normally excluded MTT temporal parameter.⁶ Investigation of thresholds using various parameters for the Bayesian algorithm has yet to be conducted. Investigations are necessary due to discrepancies in CTP thresholds across perfusion map calculation methods and vendors.⁷ In particular, Vitrea software allows 3 predefined threshold settings, each using distinct combinations of perfusion maps and contralateral hemisphere thresholds, for infarct and penumbra quantification as well as user-defined ROIs to outline ischemic regions.

In this study, we aimed to investigate the effects of 3 preset Bayesian CTP threshold settings for predicting final infarct volumes (FIVs) by comparing them with DWI and FLAIR in patients with AIS. Additionally, we compared performances of Vitrea and RAPID (iSchemaView, Menlo Park, California), a clinically studied CTP software, in quantifying infarct and penumbra volumes.^{8,9} The variability of user-defined ROIs was investigated for determining ischemic regions in the Vitrea software.

MATERIALS AND METHODS

Image and Data Collection

The University at Buffalo review board approval was obtained, and informed consent was waived for this Health Insurance Portability and Accountability Act retrospective study. Inclusion criteria were patients with AIS who underwent CTP evaluation on arrival at the stroke center and DWI and FLAIR 24 hours following CTP imaging. Before CTP imaging, patients underwent non-contrast CT to rule out hemorrhagic stroke, and scan results were considered for clinical decision-making. Between March and August 2019, one hundred five consecutive patients were split into intervention and nonintervention cohorts. Intervention cases ($n = 55$) were required to have an emergent large-vessel occlusion and to have undergone mechanical thrombectomy. Nonintervention cases ($n = 50$) were patients with large- and small-vessel occlusions who received neither thrombectomy nor tPA. Patients with and without interventions were included for evaluation of CTP infarct and penumbra volume predictions, respectively. For patients with interventions, TICI scores were measured by 2 independent operators not involved in data collection. All patients with interventions received successful reperfusion (TICI 2b/2c/3).

CTP data were obtained from two 2012 Aquilion ONE CT units (Canon Medical Systems, Otawara, Japan). CTP protocol involved acquisition of 19 scans, each with 320 images with 0.5-mm resolution. A total dose-length product of 13,739 mGy*cm and CT dose index volumes ranging from 15.3 to 44.4 mGy for each scan volume were used. Contrast was 50 mL of iohexol (Omnipaque 350; GE Healthcare, Piscataway, New Jersey) at a 5-mL/s injection rate. In the stroke work-up, reconstructed CTP volumes are provided within 5 minutes from the start of scanning.

DWI and FLAIR were performed using a Vantage Titan 1.5T MR imaging unit (Canon Medical Systems). DWI and FLAIR protocols involved TEs of 100 and 120 ms and TRs of 8,165 and 10,000 ms, respectively.

CTP Infarct Quantification

CBV, CBF, MTT, TTP, and delay time perfusion maps were calculated using the Vitrea 7.10 Bayesian algorithm. Stroke

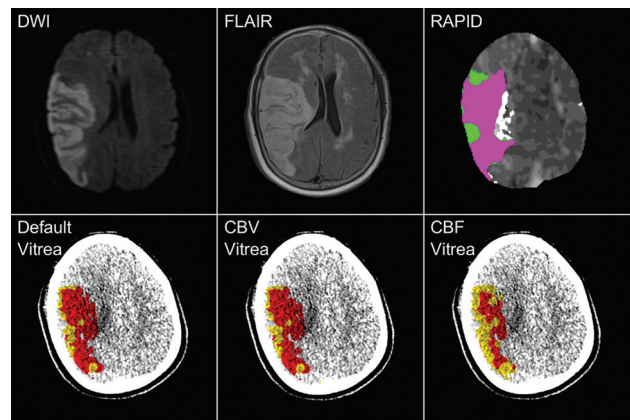


FIG 1. Ground truth infarct labels with the hyperintensified regions in the DWI and FLAIR identifying infarct. Default, CBV, and CBF Vitrea perfusion analysis demonstrates infarct as red and penumbra as yellow, while RAPID perfusion analysis represents infarct as pink and penumbra as green. For this nonintervention case, there is agreement between Vitrea and RAPID infarct volumes and their respective locations within the MR imaging scans. Final infarct volumes for each MR imaging method and CTP software (summation of infarct and penumbra due to it being a nonintervention case) are as follows: DWI = 135.0 mL, FLAIR = 167.6 mL, default Vitrea = 132.4 mL, CBV Vitrea = 141.2 mL, CBF Vitrea = 115.3 mL, RAPID = 176.0 mL.

regions were outlined throughout perfusion volumes. Three different combinations of perfusion map thresholds comparing contralateral hemispheres within Vitrea were used for infarct and penumbra quantification. Default Bayesian setting contralateral hemisphere thresholds were the following: A 38% reduction in CBV (with 5.3-second increase in TTP or 55% reduction in MTT) indicated infarct while a 5.3-second increase in TTP or 58% reduction in CBF or a 5.8-second increase in delay time (without CBV reduction) indicated penumbra. Reduction in MTT can occur within regions of deep infarction or when the CT scan starts too early, resulting in a truncated time-density curve.¹⁰ The CBV Bayesian setting, which use CBV to quantify infarct, thresholds were the following: A 38% reduction in CBV (with a 5.3-second increase in TTP or 55% reduction in MTT) indicated infarct; a 5.3-second increase in TTP or 76% reduction in CBF or 82% increase in MTT (without CBV reduction) indicated penumbra; and delay time was not used. The CBF Bayesian setting, which used CBF to determine infarct, thresholds were the following: A 72% reduction in CBF (with a 3.9-second increase in TTP) indicated infarct; a 3.9-second increase in TTP indicated penumbra; and MTT, CBV, and delay time were not used in volume quantifications. These 3 threshold combinations were predefined within Vitrea by the manufacturer, and contralateral hemisphere voxels exceeding these thresholds were classified as infarct or penumbra, accordingly. Infarct and penumbra volumes and penumbra-to-infarct ratios were recorded for automated- and user-segmented Vitrea analysis of stroke regions.

RAPID analysis was conducted offsite by sending CTP volumes from the CT scanner to iSchemaView and receiving predicted ischemic volumes through the PACS of the hospital. With RAPID, infarct is tissue with CBF <30% compared with the contralateral hemisphere and penumbra is volume of tissue with a Tmax of >6 seconds. Fig 1 compares all 3 Vitrea settings and

Table 1: Characteristics and outcomes of patients with ischemic stroke

Characteristic	All (n = 105)	Endovascular Intervention (n = 55)	Nonintervention (n = 50)
Male sex (%)	46.7% (49/105)	50.9% (28/55)	42.0% (21/50)
Age (mean) (yr)	67.1 ± 14.7	64.8 ± 16.3	69.6 ± 12.6
NIHSS score (median) (IQR)	11.0 (6.0–17.0)	12.0 (9.0–19.0)	6.5 (4.0–14.8)
Site of occlusion			
Middle cerebral artery	72.4% (76/105)	76.3% (42/55)	68.0% (34/50)
Posterior cerebral artery	12.4% (13/105)	7.3% (4/55)	18.0% (9/50)
Internal carotid artery	11.4% (12/105)	10.9% (6/55)	12.0% (6/50)
Basilar artery	3.8% (4/105)	5.5% (3/55)	2.0% (1/50)
Time from onset of stroke to perfusion imaging (median) (IQR) (min)	267.0 (116.0–710.0)	171.0 (91.0–364.0)	629.0 (147.5–976.8)
Time from onset of stroke to reperfusion (median) (IQR) (min)	–	243.0 (157.5–526.0)	–
Time from perfusion imaging to recanalization (median) (IQR) (min)	–	64.0 (52.0–104.0)	–
Default Vitrea infarct volume (median) (IQR) (mL)	6.7 (2.0–24.0)	4.7 (1.3–19.4)	6.8 (3.3–25.4)
CBV Vitrea infarct volume (median) (IQR) (mL)	6.5 (1.0–17.3)	4.0 (0.7–15.9)	8.5 (3.2–21.0)
CBF Vitrea infarct volume (median) (IQR) (mL)	2.5 (0.1–15.4)	0.3 (0.0–8.4)	6.6 (1.4–18.4)
RAPID infarct volume (median) (IQR) (mL)	6.0 (0.0–17.0)	0.0 (0.0–16.5)	28.0 (4.0–90.0)
Posttreatment reperfusion			
TICI 2b	–	38.2% (21/55)	–
TICI 2c	–	25.5% (14/55)	–
TICI 3	–	36.4% (20/55)	–
Final FLAIR MR imaging infarct volume (median) (IQR) (mL)	9.8 (3.2–25.1)	11.8 (4.4–32.4)	7.4 (2.7–18.4)
Final DWI MR imaging infarct volume (median) (IQR) (mL)	9.8 (2.3–25.7)	11.8 (3.2–36.0)	6.7 (2.0–17.7)

Note:—IQR indicates interquartile range; –, indicates data that was not obtained for the nonintervention patients and that cannot be quantified for all patients.

RAPID with DWI and FLAIR in predicting FIVs for the same patient without an intervention.

Final Infarct Volume

DWI and FLAIR were used as FIV ground truths because they are common standards for computing FIVs. DWI and FLAIR give accurate representations of infarct by locating regions of restricted diffusion and hyperintense lesions, respectively.^{11,12} Because DWI has shown lesion reversal in instances of rapid reperfusion, FLAIR MR imaging was the main infarct ground truth.¹³ Infarct volumes from DWI were quantified using 162% differences in intensities across hemispheres as demonstrated previously.¹⁴ FLAIR data were loaded into 3D Slicer software (<http://www.slicer.org>), and infarct was segmented and quantified using thresholding in which gray-scale pixel values of >80 indicate regions of infarct.¹⁵ For nonintervention cases, FIVs were compared against summations of infarct and penumbra because the entirety of penumbra should convert to infarct when no treatment occurs.¹⁶ Although vascular reperfusion may occur from embolus breakage leading to penumbra being salvaged.

Statistical Analysis

Frequency distributions for categorical data and summary statistics for continuous variables were tabulated for analyzed data. For intervention and nonintervention subgroups, differences

in infarct between predicted CTP and ground truth DWI and FLAIR volumes were determined. For patients without interventions, infarct was estimated as a summation of infarct and penumbra because all penumbra should convert to infarct. Mean absolute errors (MAEs) for each subgroup were calculated for all CTP threshold combinations. Shapiro-Wilk tests were conducted assessing the normality of infarct volume data. Regression analysis was performed to compare FIVs with predicted CTP volumes for intervention and nonintervention groups. Results were represented as scatterplots, and Spearman correlation coefficients were calculated. Software-processing times to predict ischemic volumes were determined. Vitrea and RAPID processing times were defined as the time from loading CTP volumes into Vitrea until the perfusion maps were generated and time from CTP scan completion until RAPID perfusion maps were uploaded to the PACS of the hospital, respectively. Interreader variability was assessed across 5 Vitrea users to determine the mean difference and MAE of segmented infarcts.

RESULTS

Patient Demographic Analysis

Predicted infarct volumes and patient characteristics are presented in Table 1. Tabulated data include separation into 55 intervention and 50 nonintervention cases. In Table 1, age is normally distributed, while all other continuous variables are

Table 2: Mean difference and MAE between final infarct using DWI and FLAIR and predicted infarct using CTP software

Parameter/Final Infarct Predictor	Perfusion Software	Endovascular Intervention	Nonintervention
Mean infarct difference (mL)	DWI	Default Vitrea	4.7
		CBV Vitrea	9.7
		CBF Vitrea	14.1
		RAPID	7.5
	FLAIR	Default Vitrea	4.1
		CBV Vitrea	9.1
		CBF Vitrea	13.5
		RAPID	6.9
Mean absolute error (mL)	DWI	Default Vitrea	13.0
		CBV Vitrea	13.6
		CBF Vitrea	20.5
		RAPID	14.5
	FLAIR	Default Vitrea	12.7
		CBV Vitrea	13.4
		CBF Vitrea	20.3
		RAPID	14.7
	Nonintervention	Default Vitrea	9.6
		CBV Vitrea	12.8
		CBF Vitrea	9.1
		RAPID	53.1

non-normally distributed on the basis of Shapiro-Wilks testing ($P < .05$). Normally and non-normally distributed data are represented as mean $\pm$ SD and median (interquartile range), respectively. Student t , Mann-Whitney-Wilcoxon, and χ^2 P values for normally distributed continuous, non-normally distributed continuous, and categorical data, respectively, are given in Table 1 to determine the statistical significance among the subcategories.

Software Analysis

Differences in the amount of predicted CTP and MR imaging FIVs using all software are shown in Table 2 with MAEs for intervention and nonintervention categories. Shapiro-Wilk testing indicated no statistical evidence ($P > .05$) suggesting that infarct difference values are non-normally distributed for all threshold settings. For patients with interventions, Student t analysis showed no statistical differences in MAEs in each tested software against FLAIR and DWI. For nonintervention cases, Student t analysis of MAEs showed statistically significant differences ($P < .05$) between RAPID and all Vitrea settings for FLAIR and DWI. Fig 2 shows that regression plots of the default Vitrea setting predicted infarct versus DWI and FLAIR FIV for intervention and nonintervention categories. The default setting frequently showed the lowest mean infarct difference, lowest MAE, and highest correlations with final infarct volumes. Regression plots for RAPID-predicted infarct-versus-MR imaging FIV measurements are shown in On-line Fig 1. Shapiro-Wilk testing indicated that infarct volume calculations were non-normally distributed, all with $P < .05$. Spearman correlations for each CTP setting against final DWI and FLAIR infarct measurements for patients with and without interventions are shown in Table 3. The On-line Table shows mean infarct differences and MAEs between automated Vitrea analysis for each setting and follow-up MR imaging. Mean penumbra-to-infarct ratios for patients with and without interventions using each CTP software are as follows: (intervention, nonintervention): default = (5.6, 1.4), CBV = (8.6, 2.3),

CBF = (17.4, 2.3), RAPID = (2.8, 9.2). Ninety-five percent CIs for processing times of Vitrea and RAPID software were 186.2 ± 5.3 seconds and 885.6 ± 66.1 seconds, respectively.

Interreader Variability Analysis

Interreader variability studies demonstrated a mean difference of 0.6 mL and an MAE of 3.1 mL in user-segmented regions of infarct in Vitrea software. No statistical significance was demonstrated among user-segmented infarct volumes ($P = .97$).

DISCUSSION

This study provided an analysis for the effects of perfusion-parameter and threshold selection on ischemic

tissue quantification in Bayesian CTP software. Comparisons with DWI, FLAIR, and RAPID were used to quantify these effects. Accurate quantification of penumbra is crucial because treatment decisions are based on the size of salvageable penumbra. Studies have shown that accurately quantifying infarct has directly indicated clinical outcome in patients with stroke.¹⁷ For instance, infarct overestimation can result in patients being excluded from reperfusion treatments, while infarct underestimation can increase the likelihood of poor clinical outcomes due to hemorrhage following revascularization procedures. Although optimal perfusion parameters for identifying infarct are patient-specific, infarct underestimation is preferred because it allows patients to reobtain lost neurologic function through enrollment in endovascular procedures.³

Differences in predicted volume and FIV along with MAEs for patients with interventions indicate the Vitrea default setting as optimal for Bayesian CTP software. Discrepancies in MR imaging and CTP infarct measurements may be due to the 24-hour delay between MR imaging and CTP imaging, allowing tissue to convert from penumbra to infarct at a rate of 10.1 mL/h in patients with hypoperfusion intensity ratios of >0.5 .¹⁸ The hypoperfusion intensity ratio represents the ratio of severely hypoperfused tissue to the volume of tissue with any hypoperfusion.¹⁹ Vitrea software was compared with RAPID and proved to be noninferior as seen by similar infarct differences and correlations with final infarct volumes.

For patients without interventions, default Bayesian was the most accurate for determining final infarct volumes. These patients did not receive mechanical thrombectomy or tPA because of minimal penumbra or contraindications to thrombolysis. Typically, endovascular interventions are not performed unless there is at least a 2:1 penumbra-to-infarct mismatch.²⁰ In this instance, tissue originally determined as penumbra on perfusion imaging would die and show up as infarct on follow-up MR imaging.²¹ Additionally, all penumbra converts to infarct in patients who delay initial perfusion imaging, indicated by the statistical

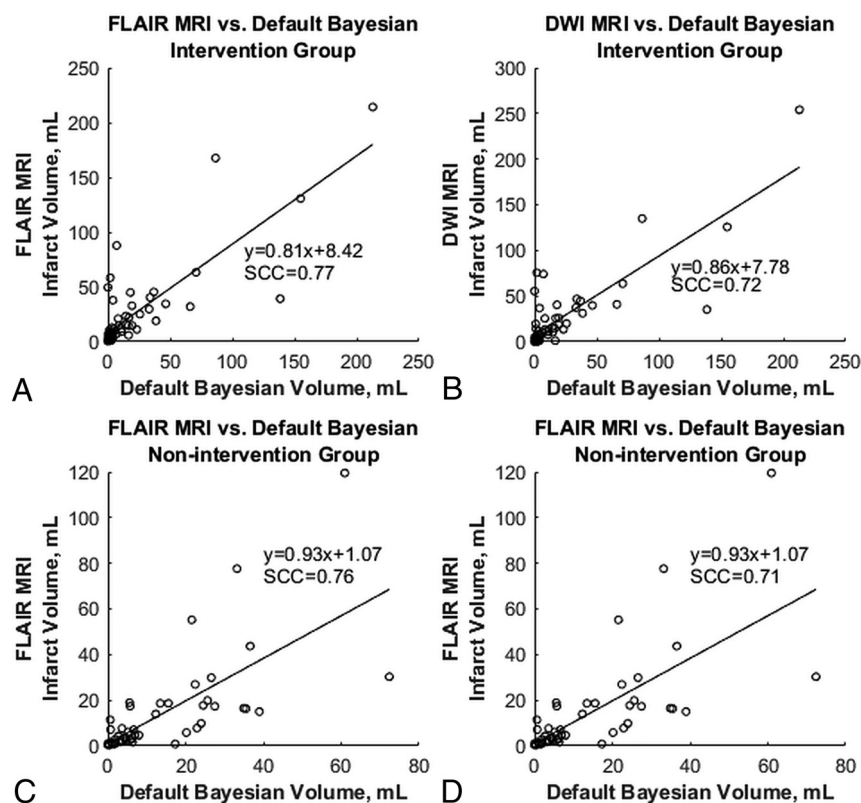


FIG 2. Correlation between final DWI and FLAIR infarct and predicted CTP infarct volumes for the default CTP software. A and B, Relationship between final (FLAIR and DWI) and predicted infarct volumes for intervention cases. C and D, The same relationship for nonintervention cases.

Table 3: Spearman correlation coefficients between predicted CTP infarct and final DWI and FLAIR infarct

Parameter/Final Infarct Predictor	Perfusion Software	Endovascular Intervention	Nonintervention
Spearman correlation coefficient DWI	Default Vitrea	0.72	0.71
	CBV Vitrea	0.71	0.58
	CBF Vitrea	0.53	0.67
	RAPID	0.75	0.65
FLAIR	Default Vitrea	0.77	0.76
	CBV Vitrea	0.72	0.64
	CBF Vitrea	0.53	0.69
	RAPID	0.75	0.68

significance between patients with and without interventions from the onset of stroke to perfusion imaging in Table 1. This significant difference could affect penumbra estimation results for patients without interventions. This possibility is due to most patients coming for perfusion imaging after all penumbra has turned to infarct, indicating that CTP software is only predicting infarct as opposed to an inclusion of infarct and penumbra in some cases. Patients without interventions, additionally, show lower median infarct volumes compared with patients with interventions due to inclusion of patients with small-vessel occlusion in the nonintervention category. NIHSS scores are statistically different between patients with and without interventions because the nonintervention group included patients with small-vessel occlusion, who have lower

NIHSS scores. Due to the default Vitrea algorithm indicating accurate infarct results before thrombectomy, it can be deduced that estimated infarct, not including penumbra, is accurate for nonintervention cases. This deduction, therefore, validates that penumbra estimations are accurate for patients without interventions because combined infarct and penumbra volumes agree with MR imaging infarct volumes.

Strong agreement of mean differences and correlations between RAPID- and Bayesian CTP-predicted infarct volumes with MR imaging FIVs for patients with interventions is significant due to ongoing discrepancies between CTP software in calculating infarct volume. A recent study showed that infarct predictions using IntelliSpace Portal (Philips Healthcare, Best, the Netherlands) and syngo.via (Siemens, Erlangen, Germany) CTP software did not correlate well with RAPID.²² This finding prevents a common standard from being established for when vascular interventions should be performed in patients with AIS.

For patients with interventions, significant differences are seen in summed infarct and penumbra estimations with FIVs due to the overestimation of penumbra by RAPID. These infarct differences are in the negative direction, indicating that predicted CTP-summed infarct and penumbra are larger than the FIV. Furthermore, the large penumbra-to-infarct ratio for patients without interventions using RAPID indicates that most estimated infarct and pe-

numbra summation is penumbra, showing that penumbra is causing the overestimation. This overestimation could be due to the use of Tmax to calculate penumbra in RAPID. The Tmax parameter is known to be sensitive to changes in the shape of the arterial input function, which is used to generate the Tmax parameter through deconvolution. Quantum noise can significantly alter the shape of the arterial input function, impacting the Tmax parameter and amount of quantified penumbra.²³ In a previous study using the Tmax parameter, lesion volumes differed by 13% depending on the amount of quantum noise present.²⁴

A potential reason that infarct volumes calculated using Bayesian CTP software indicated strong agreement with final DWI and FLAIR infarct volumes was the allowed user interaction

to segment regions affected by the occlusion. This segmentation allows exclusion of erroneous infarct volumes occurring around the skull due to improper software segmentation as seen in Online Fig 2. In Bayesian CTP software, it is evident which regions correspond to these erroneous volumes as demonstrated by inter-reader variability results indicating no statistical significance in infarct segmentation among 5 users.

Vitreia Bayesian CTP software has demonstrated great efficiency, with processing time being 12 minutes faster than with RAPID on average. Processing time included transfer time of RAPID perfusion maps to the PACS of the hospital. Because RAPID analysis was conducted offsite, transfer speeds may have hindered the rate that CTP data were analyzed.

Limitations of this study include no independent method to verify penumbra volumes. However, because mean penumbra-to-infarct ratios for each CTP software were above the Endovascular Therapy Following Imaging Evaluation for Ischemic Stroke 3 (DEFUSE 3) trial threshold of 1.5, some validity can be added to the penumbra estimations because each software is capable of determining patients' eligible for thrombectomy.⁹ Furthermore, this study is limited by the heterogeneous mixture of patients within the nonintervention group because it includes patients with large- and small-vessel occlusions, along with patients outside the tPA treatment window. Inclusion of patients with small-vessel occlusion can affect infarct estimation results because CTP does not pick up small infarcts well.

Additional limitations to this study are that it included only 10 patients with infarct measurements of >50 mL and did not evaluate spatial overlap of predicted and final infarct volumes. Furthermore, this study did not test all potential perfusion map thresholds. Possibly, an even more optimal grouping of infarct predictive perfusion thresholds exists. Use of DWI and FLAIR as FIVs is another limitation because each MR imaging method could present different ground truth infarct volumes, but FLAIR should be used as the main ground truth due to reversibility of lesions shown in DWI.¹³ The assumption that all penumbra turns to infarct in patients in this study is another limitation because it is possible that emboli could break apart, leading to reperfusion in patients without interventions. Last, this study did not include outside validation sets, yet it was conducted within a comprehensive stroke center that receives hundreds of cases of AIS per year.

CONCLUSIONS

The Vitrea default setting proved to be noninferior to RAPID as seen by similar calculated infarct differences and correlations with FIVs for patients with interventions. Additionally, the default Bayesian Vitrea setting appeared to estimate penumbra volumes more accurately than RAPID as indicated by lower infarct differences and higher correlations for the patients without interventions.

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