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Use of CTA Test Dose to Trigger a Low Cardiac Output Protocol Improves Acute Stroke CTP Data Analyzed with RAPID Software

J.B. Hartman, S. Moran, C. Zhu, J. Sharp, D.S. Hippe, D.A. Zamora, and M. Mossa-Basha



ABSTRACT

BACKGROUND AND PURPOSE: Contrast curve truncation in CTP protocols may introduce errors. We sought to identify risk factors and design a protocol to avoid truncation while limiting radiation.

MATERIALS AND METHODS: In an initial fixed-timing cohort, patients underwent a 65-second CTP with 2-second delay postcontrast injection. Multivariable analysis identified factors associated with truncation. A later case-specific cohort underwent either the original protocol or a low cardiac output protocol with a 7-second delay and 75-second scanning window, with selection determined by CTA test-dose enhancement upswing delay. Time-density curves were assessed for truncation and compared between the 2 groups, and the radiation dose was evaluated.

RESULTS: From September 2017 through May 2018, one hundred fifty-three patients underwent the standard fixed-timing protocol. Age (OR, 1.82/10-year increase; $P = .019$), reduced left ventricle ejection fraction (OR, 9.23; $P = .001$), and hypertension (OR, 0.32; $P = .06$) were independently associated with truncation in an exploratory multivariable model. From May 2018 through April 2019, one hundred fifty-seven patients underwent either the standard (72 patients) or low cardiac output protocol (85 patients). The fixed-timing cohort had 15 truncations (9.8%) versus 4 in the case-specific cohort (2.5%; $P = .009$). If the low cardiac output protocol were applied to those with $>10.6\%$ predicted risk of truncation based on age, left ventricle ejection fraction, and hypertension, the number of truncations would have decreased from 15 to 4 in the fixed-timing cohort.

CONCLUSIONS: Older age, left ventricle ejection fraction, and the absence of hypertension increase the risk of time-density curve truncation. However, a CTA test-dose-directed case-specific protocol can reduce truncation to ensure accurate data while mitigating radiation dose increases.

ABBREVIATIONS: AUC = area under the curve; DLP = dose-length product; LCO = low cardiac output; rLVEF = reduced left ventricular ejection fraction; TDC = time density curve

Stroke is a major source of morbidity and mortality, affecting $>600,000$ Americans per year.¹ CTP has become an integral part of the evaluation of acute ischemic stroke and often a decisive juncture in whether to pursue mechanical thrombectomy.^{2,3} The American Heart Association now recommends the use of CT or MR perfusion for patients with stroke 6–24 hours after symptom onset.⁴ Because it is faster and more readily available and accessible, CTP is more frequently used than MR perfusion.⁵

While the use of CTP is increasingly widespread, protocols are not standardized, with variable scan times.⁵ Quality control for CTP includes ensuring an adequate scanning duration—otherwise there is a risk of generating inaccurate data.^{5,6} Mistimed examinations, such as delayed arrival of the contrast bolus or early termination (truncation) (Fig 1), may prevent accurate CTP map generation (Fig 2).^{6–8} It has been suggested that patients with low cardiac output (LCO), cardiac arrhythmias, and flow-limiting atherosclerotic disease are particularly at risk for truncation and may benefit from increased scan times.⁵ However, CTP requires relatively high doses of radiation, which are directly proportional to the scan time.⁷ While this can be mitigated through the use of tools such as shuttle mode and CT scanners with higher detector-array numbers,⁹ using longer-than-necessary scan times on every patient would still needlessly increase the radiation dose. Prior studies have suggested that the solution to these competing concerns may be exploiting data from a patient's CTA test dose to guide case-specific CTP protocols.⁸

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We, therefore, sought to evaluate what factors lead to truncation of examinations and to design a case-specific CTP protocol in which the CTA test dose characteristics filter patients into either a standard-length examination or a longer LCO CTP examination, and to evaluate the ability of this protocol to avoid

truncation of time-density curves in patients with LCO, while keeping radiation doses as low as reasonably achievable.

MATERIALS AND METHODS

This retrospective study was approved by our institutional review board. Patients with concern for acute ischemic stroke who underwent CTP using RAPID postprocessing software (iSchemaView) between September 1, 2017, and April 14, 2019, were retrospectively reviewed. Inclusion criteria for the study were the following: 1) patients older than 18 years of age, 2) patients presenting for stroke work-up who underwent CTP, 3) CTP using either the standard or LCO protocol during the fixed-timing or case-specific time windows. Exclusion criteria were the following: 1) severely motion-degraded CTP acquisition (with curves no longer interpretable), failure of the arterial input function or venous output function selection, or otherwise indeterminate failure of perfusion map generation; 2) no echocardiogram performed to assess cardiac function (generally performed at our institution as part of standard stroke work-up); or 3) incomplete radiation-dose data.

Our CTP protocol was the result of a collaborative approach primarily between neuroradiologists and CT technologists, with additional valuable input from emergency radiologists and stroke neurologists. In the initial protocol, large-vessel occlusion was not a requirement for CTP; however, from December 5, 2017, onward patients underwent CTP only if large-vessel occlusion was first confirmed on CTA. Initially, our institution used a CTP protocol with a fixed 2-second delay after contrast injection and a 65-second imaging acquisition phase, which was used for all CTP scans. Additional parameters included the following: 180 mAs;

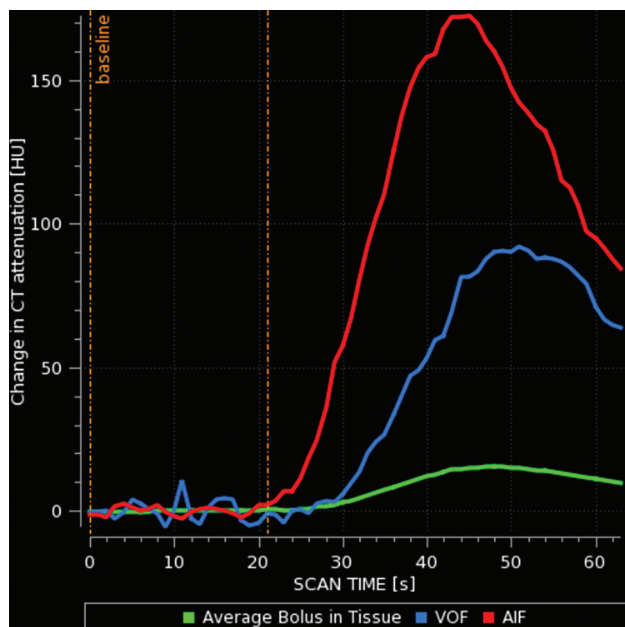


FIG 1. An example of early cutoff (truncation) of the arterial and venous time-density curves. VOF indicates venous output function; AIF, arterial input function.

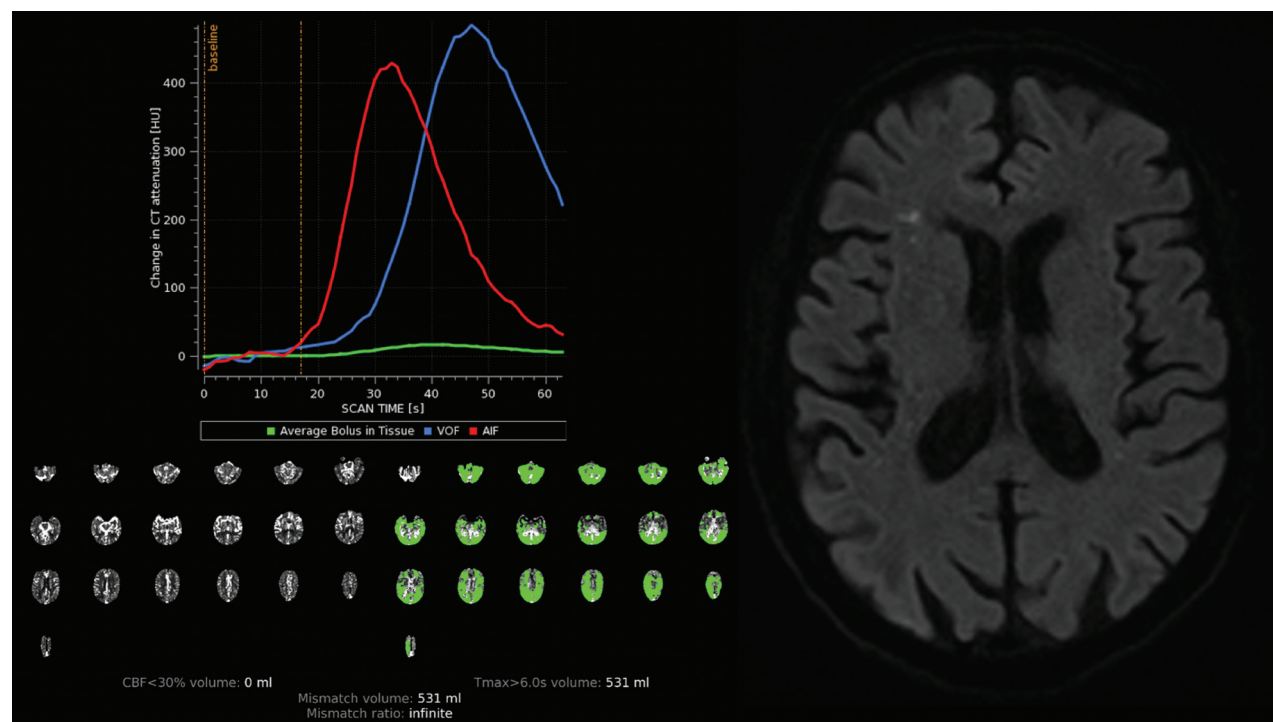


FIG 2. This case serves as an example of the potential pitfalls of truncation. A 78-year-old woman presented as a code stroke due to altered mental status. Contrast-enhancement curves demonstrate early termination of the venous output measurements. Perfusion maps erroneously suggest that nearly the entire brain is penumbra. Subsequent MR imaging demonstrated only a few scattered punctate infarcts.

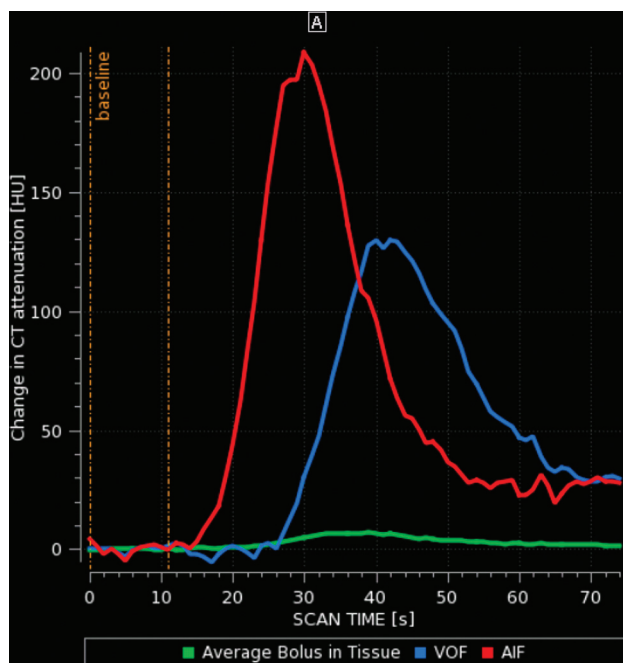


FIG 3. An example of the longer LCO protocol, triggered after the patient's time-to-enhancement upswing rise was >15 seconds. VOF indicates venous output function; AIF, arterial input function.

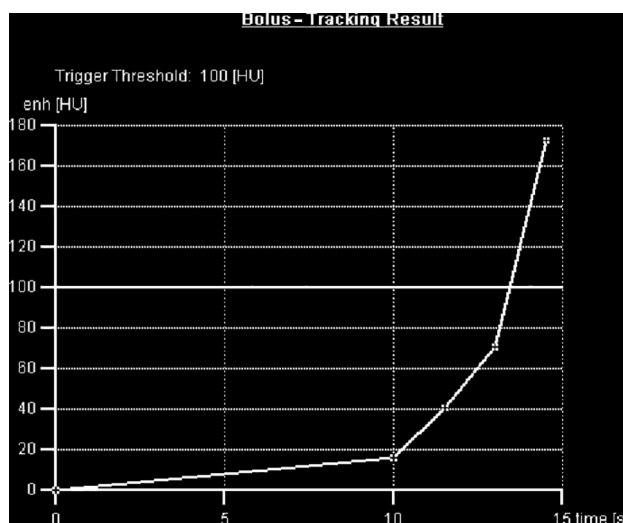


FIG 4. Example of the CTA test-dose curve; in this case the time-to-enhancement upswing rise was <15 seconds; therefore, the standard protocol was used. Enh indicates enhancement, measured in Hounsfield Units.

80 kV; section/acquisition, 5; 32×1.2 mm; 4D range, 175 mm; 1.75 seconds, scanned in a caudal-cranial direction; 36 scans total, with a rotation of 0.3 and cycle time of 1.75. We later introduced an additional LCO protocol, with an expanded scan delay of 7 seconds and a 75-second imaging-acquisition window (Fig 3). Selection of the standard or LCO protocol was determined by the patient's test-dose-enhancement rise characteristics on CTA before CTP (at our institution a CTA of the neck is always performed before CTP to evaluate large-vessel occlusion, a prerequisite for CTP). We used a bolus-tracking system in which a timer

starts at the initiation of contrast injection and measures the time until an ROI placed in the aortic arch registers 100 HU. For cases with a time-to-enhancement upswing rise of ≤ 15 seconds, the standard CTP protocol was selected, while >15 seconds triggered the LCO protocol (Fig 4). Patients were, therefore, separated into 2 cohorts: the earlier fixed-timing cohort (using only the standard protocol) and the later case-specific cohort, which used either the standard protocol or the longer LCO protocol.

Through chart review, data were collected on patient demographics, including the presence of atrial fibrillation, hypertension, hyperlipidemia, or diabetes mellitus and NIHSS scores. An ejection fraction of $<50\%$ on echocardiography was considered a reduced left ventricular ejection fraction (rLVEF). Radiation characteristics such as CT dose index and dose-length product (DLP) were also obtained as well as RAPID data including time-density curves (TDCs). RAPID output data were evaluated for technical adequacy while blinded to clinical data. If time-density curves maintained a negative slope at the end of the scanning window or did not reach the baseline, the study was considered truncated (Figs 1 and 2).

Statistical Analysis

The early fixed-length cohort underwent multivariable analysis to identify factors associated with truncation. The percentage of truncated CTP cases was compared between the fixed-timing and case-specific cohorts. We also examined how many patients with rLVEF in the case-specific cohort underwent the LCO protocol compared with patients without rLVEF. To evaluate differences in radiation dose, we compared actual DLP values of patients in the case-specific cohort (in which some were selected for the longer LCO protocol) against the theoretical DLP if all patients in the case-specific cohort had been scanned with the longer LCO protocol. To simulate scanning with the longer protocol (75 seconds), we assumed that the DLP was linearly associated with scan time because each CTP phase had identical radiation; therefore, the theoretical DLP was the following: (measured DLP using the short protocol / 65) \times 75. For the patients who underwent the longer LCO protocol, the actual DLP value was used. The factors (including age, rLVEF, atrial fibrillation, hypertension, hyperlipidemia, and diabetes mellitus) that were potentially associated with truncation were further investigated.

All analyses were performed using SPSS (Version 23.0; IBM) and R software (Version 4.0.3; <http://www.r-project.org/>). Continuous data were presented as mean (SD) or median (interquartile range). Categorical variables were recorded as frequency and percentages. Continuous variables between the 2 groups were compared via the independent-samples *t* test or Wilcoxon rank-sum test, and categorical variables were compared using the Fisher exact test. Univariable and multivariable binary logistic regression models were used to determine cardiovascular risk factors independently associated with truncation. An exploratory multivariable model was generated using forward selection based on minimizing the Akaike Information Criterion. The total number of factors included in the model was restricted to 3 to maintain at least 5 truncation events per variable.¹⁰ Receiver operating characteristic curve analysis was used to evaluate different thresholds of factors for predicting truncation. Optimal thresholds were selected by maximizing the Youden index (sensitivity +

specificity=1). The area under the curve (AUC) was also used to summarize how well each factor discriminated between patients who did or did not have truncation. Leave-one-out cross-validation was used to estimate the sensitivity, specificity, and AUC of the exploratory multivariable model. $P < .05$ was regarded as statistically significant, and all P values were 2-sided.

RESULTS

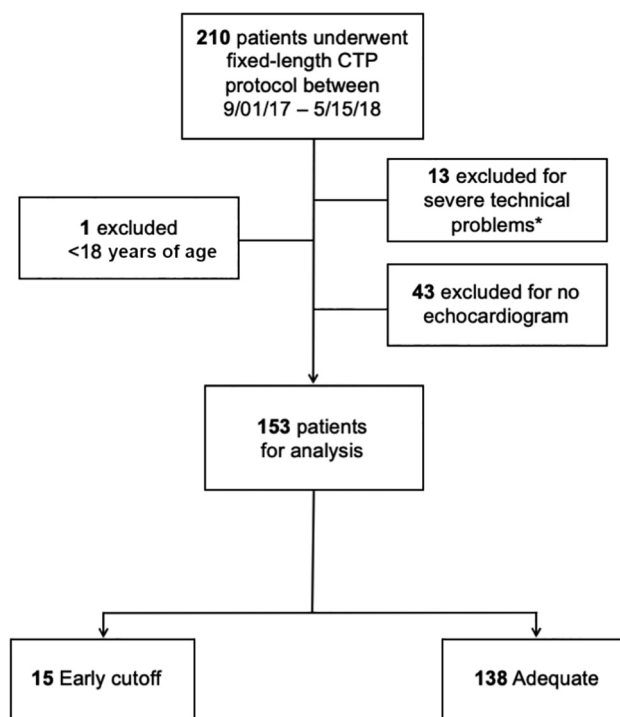
Between September 1, 2017, and May 15, 2018, two hundred ten patients underwent the standard protocol. After exclusions (Fig 5), including 13 examinations excluded for severe technical failure, a total of 153 patients were included in the fixed-timing cohort.

In evaluating these 153 patients, 15 examinations (9.8%) cut off early. The average age of patients with truncation was 72 years with an SD of 13 years versus 66 (SD, 15) years without truncation ($P = .09$) (Table 1). Seven of 24 (29%) patients with rLVEF had early

cutoff versus 8/129 (6%) of patients without rLVEF ($P = .002$). These 7 patients with early cutoff and rLVEF had an average cardiac output of 26%. The average ejection fraction of the 17 patients who did not experience early cutoff was 39%. Ten of 65 (15%) patients with atrial fibrillation had early cutoff versus 5/88 (6%) without atrial fibrillation ($P = .05$). In contrast, patients with hypertension were actually less likely to have early cutoff than patients without hypertension (7/103, 7%, versus 8/50, 16%; $P = .08$). After we applied forward selection, the resulting exploratory multivariable logistic regression model for early cutoff included age (OR, 1.82 per 10-year increase; $P = .019$), rLVEF (OR, 9.23; $P = .001$), and hypertension (OR, 0.32; $P = .06$) (Table 1). While atrial fibrillation had a slightly lower P value than the absence of hypertension, this situation was reversed in the course of constructing the model; therefore, atrial fibrillation was not included.

The performance of age (AUC = 0.63), rLVEF (AUC = 0.67), absence of hypertension (AUC = 0.61), and the other cardiovascular risk factors for predicting truncation are summarized in Table 2 and Fig 6. The exploratory multivariable model for truncation achieved a cross-validated AUC = 0.75. The Youden index selected a threshold of 10.6% for the predicted risk of truncation using the model (a function of age, rLVEF, and hypertension) that achieved a sensitivity and specificity of 73% (11/15) and 78% (108/138), respectively. There were 41/153 (27%) patients who had a predicted risk of truncation of $>10.6\%$, of which 11/41 experienced truncation. If the LCO protocol was used instead for the 41 patients who met this condition and it prevented the 11 associated truncations, the total number of truncations in the fixed-timing cohort would decrease from 15 to 4.

Between May 16, 2018, and April 14, 2019, one hundred eighty-seven CTP studies for acute stroke were performed; after exclusions (Fig 7), 157 patients were included in the case-specific cohort, and of these, 85 underwent the LCO protocol, while 72 underwent the standard protocol. Demographic data are presented in the Online Supplemental Data. The rate of rLVEF in the 2 cohorts (fixed-length cohort: 24/153, 16%, versus the case-specific cohort: 31/157, 19%; $P = .38$) was not significantly different. There was a significant difference between the 2 cohorts in the number of truncated time-density curves: In the fixed-timing cohort, 15/153 examinations (9.8%) had truncation, while in the case-specific cohort, 4/157 examinations (2.5%) had truncation ($P = .009$). Of the 4 patients in the case-specific cohort who still experienced truncation, the average age was 79 years (92, 89, 81, 55 years). Two of these patients had rLVEF (40% and 14%), and all 4 underwent the LCO protocol. The average ejection fraction of the 29 patients who did not experience truncation was 36%.



*Severe technical problems including failure to assign AIF, failure to generate images, severe motion, or exams otherwise uninterpretable.

FIG 5. Flow chart for the fixed-timing cohort. AIF indicates arterial input function.

Table 1: Comparison of patients with and without truncation in the fixed-timing cohort

Variable	Truncation		Univariable Models			Multivariable Model		
	Yes (n = 15)	No (n = 138)	OR ^a	95% CI	P Value	OR ^a	95% CI	P Value
Age (yr)	Mean, 72 (SD, 13)	Mean, 66 (SD, 15)	1.42	0.95–2.14	.09	1.82	1.10–3.01	.02
rLVEF	7 (47%)	17 (12%)	6.23	2.00–19.36	.002	9.23	2.53–33.69	.001
Atrial fibrillation	10 (67%)	55 (40%)	3.02	0.98–9.31	.05			
Hypertension	7 (47%)	96 (70%)	0.38	0.13–1.12	.08	0.32	0.10–1.05	.06
Diabetes mellitus	5 (33%)	45 (33%)	1.03	0.33–3.20	.95			
Hyperlipidemia	6 (40%)	65 (47%)	0.75	0.25–2.22	.60			

^a Odds ratio for age is presented per 10-year increase; the intercept term in the multivariable model was -6.33 on the log-odds scale.

Table 2: Performance of cardiovascular risk factors for predicting truncation

Variable	Sensitivity			Specificity			AUC	95% CI
	No.	%	95% CI	No.	%	95% CI		
Age ^a	10/15	67%	38%–88%	82/138	59%	51%–68%	0.63	0.47–0.78
rLVEF	7/15	47%	21%–73%	121/138	88%	81%–93%	0.67	0.54–0.81
Atrial fibrillation	10/15	67%	38%–88%	83/138	60%	51%–68%	0.63	0.50–0.76
Absence of hypertension	8/15	53%	27%–79%	96/138	70%	61%–77%	0.61	0.48–0.75
Diabetes mellitus	5/15	33%	12%–62%	93/138	67%	59%–75%	0.50	0.37–0.63
Absence of hyperlipidemia	9/15	60%	32%–84%	65/138	47%	39%–56%	0.54	0.40–0.67
Multivariable model (age, rLVEF, hypertension) ^b	11/15	73%	45%–92%	108/138	78%	70%–85%	0.75	0.60–0.90

^a Age was dichotomized at 68 years on the basis of the Youden index.

^b Multivariable model is shown; the predicted risk of truncation was dichotomized at 10.6% on the basis of the Youden index.

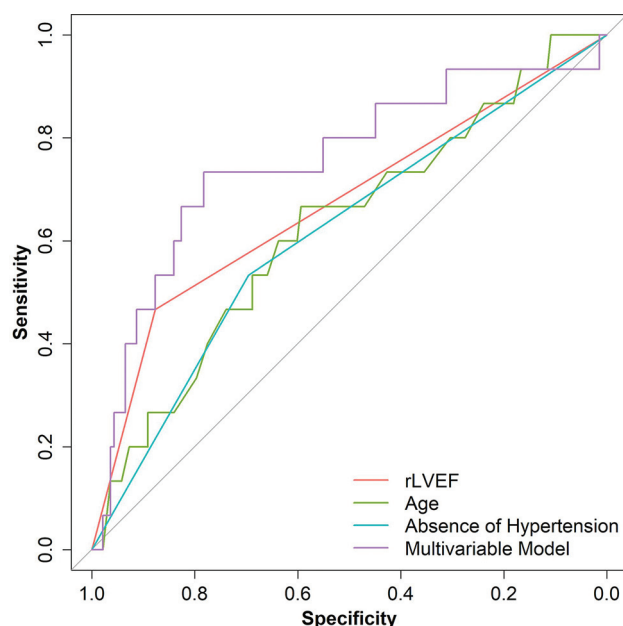
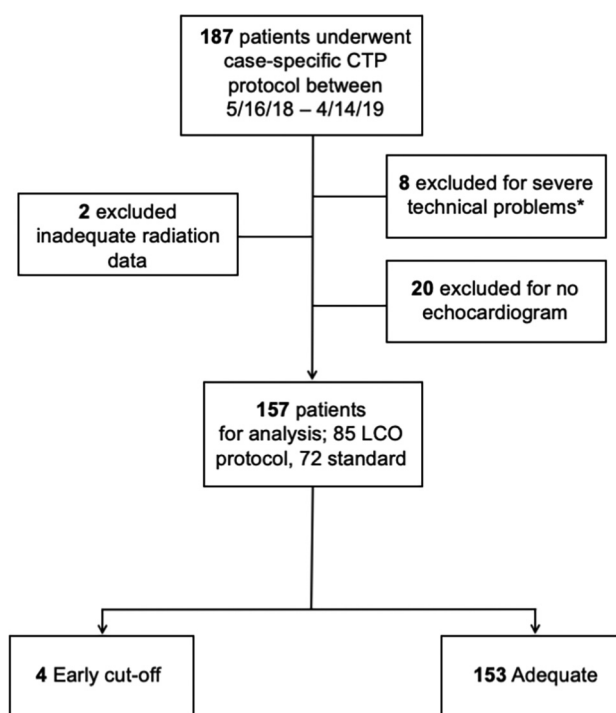


FIG 6. Receiver operating characteristic curves for the factors associated with truncation in the early fixed-timing cohort ($n=153$). The AUC value for age is 0.63, with optimized cutoff value of 69 (sensitivity of 67% and specificity of 59%). The AUC value for rLVEF is 0.67 (sensitivity of 47% and specificity of 88%). The AUC value for the absence of hypertension is 0.61 (sensitivity of 53% and specificity of 70%). When the 3 factors are combined, the AUC value increases to 0.75 (sensitivity of 73% and specificity of 78%). AIF indicates arterial input function.

In the fixed-timing cohort, 7/24 (29%) patients with rLVEF had early cutoff versus 2/31 (6.4%) in the case-specific cohort ($P=.03$). In the case-specific cohort of 157 patients, 26/31 (84%) patients with rLVEF underwent the LCO protocol versus 59/126 (47%) patients without a rLVEF ($P<.001$).

As for radiation dose, for the 85 patients in the case-specific cohort who underwent the LCO protocol, the average DLP was $4170 \text{ mGy} \times \text{cm}$ with an SD of $471 \text{ mGy} \times \text{cm}$, while the other 72 patients who underwent the standard protocol had an average DLP of $3737 \text{ mGy} \times \text{cm}$ with an SD of $699 \text{ mGy} \times \text{cm}$. Had all patients in the case-specific cohort undergone the longer LCO protocol, the simulated average DLP (measured DLP using the short protocol / 60×75 ; $n=157$) would be $4400 \text{ mGy} \times \text{cm}$ with an SD of $727 \text{ mGy} \times \text{cm}$ versus the measured average DLP ($n=157$) of $3971 \text{ mGy} \times \text{cm}$ with an SD of $623 \text{ mGy} \times \text{cm}$ ($P<.001$).



*Severe technical problems including failure to assign AIF, failure to generate images, severe motion, or exams otherwise uninterpretable.

FIG 7. Flow chart for the case-specific cohort. AIF indicates arterial input function.

DISCUSSION

As the use of CTP in the imaging evaluation of acute stroke grows more widespread with meaningful clinical implications, quality control is of vital importance. As prior authors have stated,^{5,6} a key component of quality control is ensuring adequate scan length, and prior reviews have directly communicated that truncation of CTP examinations is a technical pitfall.⁷ However, this must be balanced against our responsibility as radiologists to maintain radiation doses as low as reasonably achievable.

A 2016 study by Kasasbeh et al⁸ attempted to determine the ideal scan length of CTP studies and found dramatic changes in the volumes of tissue with time-to-maximum of >6 seconds (the estimated infarct penumbra) when scan times were inadequately short. On the basis of their study, the authors recommended a scan time of between 60 and 70 seconds, which others have also

advised.^{8,11} Kasasbeh et al also suggested that future studies might examine using CTA contrast-arrival data to create case-specific protocols. Prior studies have suggested that patients with LCO, cardiac arrhythmias, and flow-limiting atherosclerotic disease are particularly at risk for truncation and may benefit from increased scan times⁵

Our novel contribution is an investigation into why patients experience early cutoff, and the evaluation of a potential solution. We found that rLVEF, age, and the absence of hypertension were independently associated with early cutoff. rLVEF is likely associated with truncation due to the delayed arrival of contrast secondary to reduced cardiac output. Our finding that age is an independent risk factor is difficult to separate from the increased prevalence of heart failure in older populations and additionally may relate to senescent vascular changes such as tortuous vessels and/or carotid stenoses. Surprisingly, patients with hypertension were less likely to exhibit truncation, suggesting a protective effect secondary to altered physiology underlying hypertension or in response to it. Alternatively, the population presenting with concern for stroke with hypertension may differ from those without it.

Armed with this information, we evaluated a case-specific CTP protocol that used the assessment of CTA test-dose-enhancement peak times to select those patients who require an increased delay following contrast injection and increased scan time. We found that this approach significantly reduced the incidence of truncation and the associated risk of compromised CTP data and that this approach effectively targeted patients with rLVEF. Most importantly, the semiautomated nature of the protocol does not require the stroke team to collect any additional clinical information before imaging. This approach resulted in a significant reduction in the radiation dose compared with the alternative of using a longer scanning protocol in all patients, with those who do not require extended scanning, therefore, receiving as little radiation dose as possible. Because the approach to scan times has varied among institutions, this new approach could serve as a potential standardized model.

Our study is limited by the inclusion of patients from a single institution. Additionally, the exclusion of patients who did not undergo an echocardiogram may have introduced some selection bias; however, one of the 20 patients (5%) excluded from the second cohort had early cutoff versus 3 of 43 (7%) excluded from the first cohort, suggesting that this bias was minimal. We used only one of the several commercially available CTP-processing software programs, limiting the generalizability of the study to other software platforms. Future studies would ideally include multiple institutions and use a variety of postprocessing applications. There is also some limitation in comparing later data against earlier data because our technologists were initially less experienced with CTP in general, possibly resulting in more mistakes overall. However, we excluded studies with severe technical limitations not related to truncation, mostly from the earlier fixed-timing cohort, helping to mitigate this limitation.

Even in the case-specific cohort, 4 examinations still terminated early, despite the patients undergoing the LCO protocol, suggesting that these patients were appropriately targeted but

that there is further room for improvement in this protocol, such as extending the scan times to longer than 75 seconds. Our study is also limited by our approach to calculating the radiation dose because the DLP is a surrogate for dose; future studies would ideally use a phantom for dose calculations. From a technical standpoint, it is more accurate to design these protocols in terms of increasing the number of samples on the basis of the CTP sampling rate being used; however, we have presented our data as total scan time for simplicity and broader applicability.

CONCLUSIONS

Our study suggests that a rLVEF and increased age are risk factors for truncation of CTP data, while the presence of hypertension may decrease the risk, and it demonstrates that CTA test-dose dynamic enhancement characteristics can be used to facilitate a case-specific approach to CTP studies for stroke, in which those with delayed enhancement upswing are selected for a longer LCO CTP protocol, thus reducing the number of examinations with truncation, while keeping the radiation dose as low as reasonably achievable.

Disclosure forms provided by the authors are available with the full text and PDF of this article at www.ajnr.org.

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