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Delay-sensitive and delay-insensitive deconvolution perfusion-CT: similar ischemic core and penumbra volumes if appropriate threshold selected for each

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Abstract
Introduction Perfusion-CT (PCT) processing involves deconvolution, a mathematical operation that computes the perfusion parameters from the PCT time density curves and an arterial curve. Delay-sensitive deconvolution does not correct for arrival delay of contrast, whereas delay-insensitive deconvolution does. The goal of this study was to compare delay-sensitive and delay-insensitive deconvolution PCT in terms of delineation of the ischemic core and penumbra.
Methods We retrospectively identified 100 patients with acute ischemic stroke who underwent admission PCT and CT angiography (CTA), a follow-up vascular study to determine recanalization status, and a follow-up noncontrast head CT (NCT) or MRI to calculate final infarct volume. PCT datasets were processed twice, once using delay-sensitive deconvolution and once using delay-insensitive deconvolution. Regions of interest (ROIs) were drawn, and cerebral blood flow (CBF), cerebral blood volume (CBV), and mean transit time (MTT) in these ROIs were recorded and compared. Volume and geographic distribution of ischemic core and penumbra using both deconvolution methods were also recorded and compared.
Results MTT and CBF values are affected by the deconvolution method used ($p<0.05$), while CBV values remain unchanged. Optimal thresholds to delineate ischemic core and penumbra are different for delay-sensitive (145 % MTT, CBV 2 ml×100 g^{-1}×min^{-1}) and delay-insensitive deconvolution (135 % MTT, CBV 2 ml×100 g^{-1}×min^{-1} for delay-insensitive deconvolution). When applying these different thresholds, however, the predicted ischemic core ($p=0.366$) and penumbra ($p=0.405$) were similar with both methods.
Conclusion Both delay-sensitive and delay-insensitive deconvolution methods are appropriate for PCT processing in acute ischemic stroke patients. The predicted ischemic core and penumbra are similar with both methods when using different sets of thresholds, specific for each deconvolution method.

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Keywords Perfusion-CT · Deconvolution · Delay · Ischemic core · Ischemic penumbra

Abbreviations

PCT	Perfusion-CT
ASPECTS	Alberta stroke program early CT score
CBF	Cerebral blood flow
CBV	Cerebral blood volume
MTT	Mean transit time
ROI	Region of interest
NCT	Noncontrast head CT

Introduction

Perfusion-CT (PCT) is an imaging technique used to assess cerebral perfusion [1]. PCT applications encompass acute stroke [2], chronic cerebrovascular conditions [3], vasospasm [4], traumatic brain injury [5], etc. Several processing methods exist to extract meaningful information from the PCT raw data [6, 7]. The two main approaches include nondeconvolution models (or maximal slope models) or deconvolution models [8], the latter gaining more widespread acceptance recently [9]. The deconvolution operation is a complex mathematical operation that computes the perfusion parameters from the PCT time density curves and an arterial curve, in order to take into account the dispersion of the contrast bolus injected for the PCT study [10]. Deconvolution comes in several flavors [11–13], including delay-sensitive ones and delay-insensitive ones. Delay-sensitive deconvolution does not correct for the arrival delay of the contrast between the selected arterial input function and the examined parenchymal voxel, whereas delay-insensitive deconvolution does [6]. Recently, some have suggested that in the setting of acute ischemic stroke, delay-insensitive deconvolution may lead to more accurate delineation of the ischemic core and especially penumbra, while delay-sensitive deconvolution methods may overestimate the penumbra [14].

The goal of this study was to compare delay-sensitive and delay-insensitive deconvolution PCT in terms of delineation of the ischemic core and penumbra.

Material and methods

Study patients

The clinical and imaging data presented in this study belongs to a repository created from the data collected as part of the standard clinical stroke care at three participating institutions, including the University of Virginia Health System, Charlottesville, VA; the Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland; and the University of Pittsburgh Medical Center, Pittsburgh, PA. Collection and analysis of data for and from the repository were approved by the respective institutional review boards of the three contributing institutions.

We retrospectively identified all consecutive patients included in this repository who met the following inclusion criteria: (1) acute ischemic stroke without evidence of intracerebral hemorrhage; (2) performance of a stroke CT work-up upon admission including PCT and CT angiography (CTA); (3) performance of a follow-up vascular study to determine recanalization status; and (4) of a follow-up noncontrast head CT (NCT) or MRI, which was used to calculate the final infarct volume on the slices matching the baseline PCT slices.

The following demographic and clinical variables were recorded: age, gender, time from symptom onset to baseline imaging, and time from onset to follow-up imaging.

PCT image acquisition

PCT studies were obtained on 16- and 64-slice CT scanners. Each PCT study involved successive gantry rotations performed in cine mode during intravenous administration of one or two boluses of 40–50 ml of iodinated contrast material at an injection rate of 4–5 ml/s. Total PCT coverage ranged from 20 to 80 mm, with 5- or 10-mm slices. Acquisition parameters were 80 kVp and 100–200 mAs. Total PCT acquisition duration ranged from 50 to 70 s. Sampling rate ranged from 1 to 2 s (Table 1).

PCT image post-processing and interpretation

PCT data was analyzed using Philips Brain Perfusion software version 4.5.2 (Philips Medical Systems, Cleveland, OH,

Table 1 Perfusion-CT (PCT) protocols used in patients included in the current study

Scanner type	16 slice	16 slice	64 slice	64 slice
Slice thickness	10 mm	5 mm	5 mm	5 mm
Total PCT coverage (all boluses)	20 mm	40 mm	40 mm	80 mm
Acquisition parameters	80 kVp 200 mAs	80 kVp 100 mAs	80 kVp 100 mAs	80 kVp 100 mAs
Total PCT acquisition duration	50 s	50 s	70 s	70 s
Sampling rate	1 per second	1 per second	1 per 2 s	1–2 per second
Number of contrast boluses	1	2	1	2
Injection rate	4 cm^3/s	5 cm^3/s	5 cm^3/s	5 cm^3/s

USA), previously described [15]. This software is based on the central volume principle. Arterial input function and venous output selection is semi-automated and MTT maps are created using a closed-form deconvolution. Cerebral blood volume (CBV) values are calculated from the area under the time-density curves. Cerebral blood flow (CBF) is calculated as CBV divided by MTT. PCT was processed once using delay-sensitive deconvolution (singular value decomposition) and one using delay-insensitive deconvolution (block-circulant singular value decomposition).

Regions of interest (ROIs) were drawn manually to include the cerebral hemisphere, the basal ganglia, and the white matter in the frontal and parietal lobes. CBF, CBV, and mean transit time (MTT) values in these ROIs were recorded separately for the ischemic hemisphere and the contralateral hemisphere.

For delay-sensitive deconvolution, PCT ischemic core and penumbra were delineated using validated MTT and CBV thresholds (MTT >145 % of the contralateral side values and CBV <2.0 ml/100 g to define PCT ischemic core; MTT >145 % of the contralateral side values and CBV >2.0 ml/100 g to define PCT ischemic penumbra) [16]. For delay-insensitive deconvolution, various combinations of MTT and CBV thresholds were tested (Table 2). The volumes of PCT ischemic core and penumbra, automatically measured by the software, were recorded, both for the delay-sensitive and the delay-insensitive approaches.

Both for delay-sensitive and delay-insensitive deconvolution, and for each set of MTT and CBV thresholds, the anatomical distribution of the ischemic core and penumbra were recorded using a modified Alberta Stroke Program Early CT score (ASPECTS) approach [17]. Each of the 10 ASPECT regions, plus the superior and inferior anterior cerebral artery territories, plus the thalamus and the posterior cerebral artery territory, were recorded either as normal, ischemic core (>50 % occupied by ischemic core), or ischemic penumbra (>50 % occupied by ischemic penumbra). An ischemic core score ranging from 0 (no ischemic core) to 14 (ischemic core occupying the whole hemisphere), and an ischemic penumbra score also ranging from 0 to 14 (but the sum of the two scores not exceeding 14), were calculated both for delay-sensitive and delay-insensitive deconvolution, and for each set of MTT and CBV thresholds.

Statistical analysis

Descriptive statistics Continuous data (CBF, CBV, and MTT values in ROIs) were summarized by the mean±standard deviation. Frequency data (e.g., gender) were summarized by counts.

Analysis #1 The CBF, CBV, and MTT values measured in the ROIs using delay-sensitive and delay-corrected deconvolution were compared using Bland-Altman and linear regression analysis. Statistical significance was set at 0.05.

Analysis #2 The volumes of ischemic core and penumbra as calculated by delay-sensitive deconvolution were used as a reference standard. The volumes of ischemic core and penumbra calculated using delay-insensitive deconvolution and the different combinations of MTT and CBV thresholds were evaluated to determine the MTT/CBV combination for which the delay-insensitive core and penumbra volumes showed the strongest linear regression with the delay-sensitive core and penumbra volumes, used as reference standard.

Analysis #3 The modified ASPECT scores for ischemic core and penumbra obtained from delay-sensitive and delay-insensitive deconvolution were dichotomized and compared to each other using McNemar chi-square tests. Statistical significance was set at 0.05.

Analysis #4 Both for delay-sensitive and delay-insensitive deconvolution, the ischemic core volume was compared to the final infarct volume in the patients showing recanalization; and the ischemic core + penumbra volume was compared to the final infarct volume in the patients showing persistent arterial occlusion. Comparisons were performed using linear regression analysis.

Table 2 Online only. Various combinations of MTT and CBV thresholds were tested

		MTT				
CBV		>125 %	>135 %	>145 %	>155 %	>165 %
Ischemic penumbra	>1.8 ml/100 g	✓	✓	✓		
	>1.9 ml/100 g		✓	✓	✓	✓
	>2.0 ml/100 g		✓	✓	✓	✓
Ischemic core	<1.8 ml/100 g	✓	✓	✓		
	<1.9 ml/100 g		✓	✓	✓	✓
	<2.0 ml/100 g		✓	✓	✓	✓

Table 3 Mean±standard deviation of CBF and MTT values obtained with delay-sensitive and delay-insensitive deconvolution. 84/86/106

Variable	Location	Ischemic side		Nonischemic side	
		Delay-sensitive	Delay-insensitive	Delay-sensitive	Delay-insensitive
CBF (ml×100 g^{-1} min^{-1})	Whole hemisphere	22.26±10.98	31.94±23.28	44.33±22.64	68.00±57.24
	Basal ganglion	27.56±19.90	38.46±36.92	52.76±24.91	85.05±69.01
	White matter	10.43±8.05	15.38±27.16	18.58±9.67	25.39±23.70
MTT (second)	Whole hemisphere	10.47±4.31	9.03±3.27	5.85±1.84	4.75±4.74
	Basal ganglion	9.74±9.80	6.98±5.83	5.02±1.77	3.49±1.42
	White matter	16.10±10.17	11.89±8.73	7.79±5.73	6.17±3.16

Results

Patient characteristics

One hundred and six patients were retrospectively identified that matched our study inclusion criteria. Six patients were excluded because of significant motion artifact on the PCT series. One hundred patients remained that constituted our study population (56 males, 44 females, median age 65, range 18–91). Fifty-eight patients had ischemia on the right side and 42 patients had ischemia on the left. Seventy-one patients had middle cerebral artery strokes, 21 patients had anterior cerebral artery strokes, and 9 patients had posterior cerebral artery strokes. Twenty-seven patients received intravenous tPA, and 36 patients received endovascular revascularization therapy. Fifty-four patients showed recanalization, and 46 patients showed persistent arterial occlusion. Final infarct volume was measured at a median time of 26 days (interquartile range 7.3–70), and delineated on MRI in 66 patients and CT in 34 patients.

Comparison of delay-sensitive and delay-insensitive CBV, CBF, and MTT values

There was no difference in terms of CBV values between delay-sensitive and delay-insensitive deconvolution. This was expected as CBV is calculated as an indicator of partial volume averaging from the area of the time-density curves in each voxel of the image compared to a reference "venous" voxel [6]. CBV values are not influenced by the selection of the arterial input function and the type of deconvolution used.

For whole-hemisphere measurements, delay-sensitive MTT measurements were significantly greater than delay-insensitive MTT values ($p<0.05$), and delay-sensitive CBF values were significantly smaller than delay-insensitive CBF values ($p<0.05$) (Tables 3 and 4, Fig. 1). Similar observations were made in the basal ganglia and in the white matter. The higher the CBF or the MTT values, the greater the difference between delay-sensitive and delay-insensitive deconvolution. This explains why the difference was more marked in the nonischemic tissue for CBF (higher normal values) and in the ischemic tissue for MTT (higher ischemic values).

Comparison of delay-sensitive and delay-insensitive volumes of ischemic core and penumbra

Ischemic core and penumbra volumes calculated from delay-insensitive deconvolution using MTT 135 % and CBV 2 ml× 100 g^{-1} thresholds (ischemic core 33.51±30.56 ml, ischemic penumbra 58.90±35.49 ml, ischemic volume 92.43±

Table 4 Discrepancy (Δ = delay-insensitive − delay-sensitive) between delay-insensitive and delay-sensitive deconvolution for the whole hemisphere, basal ganglion, and the white matter measurements of CBF and MTT separately, for the ischemic side and nonischemic side

Variable	Location	Ischemic side				Nonischemic side			
		Mean	95 % CI	Slope	*p*	Mean	95 % CI	Slope	*p*
CBF	Whole hemisphere	8.9	6.2 to 11.5	0.65	<0.001	19.621	14.5 to 24.7	0.69	<0.001
	Basal ganglion	11.0	6.7 to 15.4	0.63	<0.001	27.845	21.1 to 34.6	0.74	<0.001
	White matter	3.5	0.9 to 6.2	1.57	0.009	5.536	3.2 to 7.8	0.81	<0.001
MTT	Whole hemisphere	−2.3	−3.1 to −1.5	−0.63	<0.001	−1.008	−1.9 to −0.1	−0.68	0.044
	Basal ganglion	−2.7	−4.3 to −1.1	−0.64	0.001	−1.498	−1.8 to −1.2	−0.58	<0.001
	White matter	1.9	−6.1 to −1.3	−0.86	0.003	−11.411	−2.6 to −0.6	−0.75	0.002

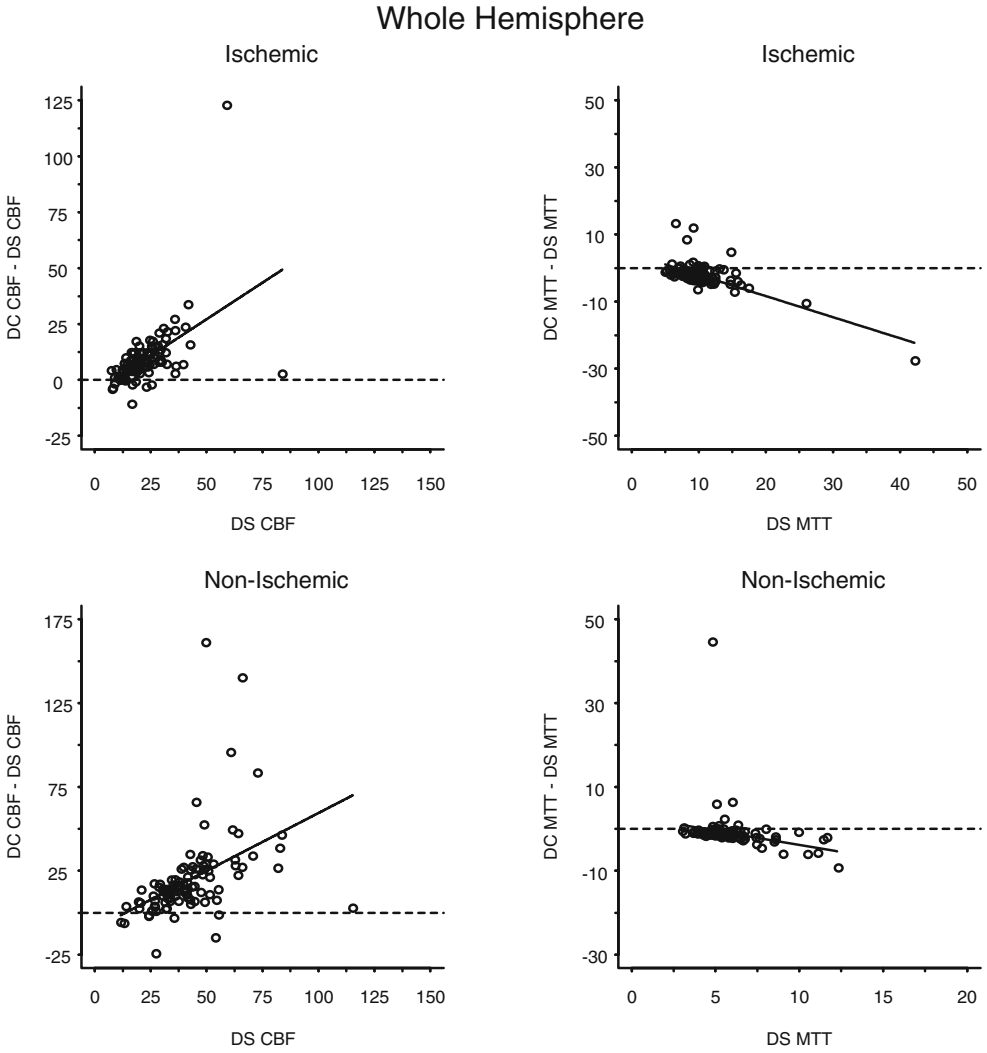

Fig. 1 Bland-Altman plots demonstrating the relationship between delay-sensitive CBF and Δ = delay-insensitive CBF − delay-sensitive CBF and between delay-sensitive MTT and Δ = delay-insensitive MTT − delay-sensitive MTT. *Dashed line* denotes 0 difference. *Solid line* denotes the regression line of best fit. Delay-sensitive MTT measurements were significantly greater than delay-insensitive MTT values ($p<0.05$), and delay-sensitive CBF values were significantly smaller than delay-insensitive CBF values ($p<0.05$)

Table 5 Discrepancy (Δ = delay-insensitive − delay-sensitive) between delay-insensitive and delay-sensitive deconvolution for the volumes of ischemic core, ischemic penumbra, and total ischemic volume. These volumes for delay-sensitive deconvolution were calculated using MTT threshold of 145 % of the contralateral side values to define PCT ischemic area, and CBV threshold of 2.0 ml/100 g to define PCT ischemic penumbra

Delay-insensitive MTT threshold (%)	Delay-insensitive CBV threshold (ml×100 g^{-1})	Ischemic core volume (ml)			Ischemic penumbra volume (ml)			Ischemic volume (ml)		
		Mean	95 % CI	*p*	Mean	95 % CI	*p*	Mean	95 % CI	*p*
135	2	−3.4	−7.3 to 0.6	0.091	6.1	1.2 to 11.1	0.15	2.7	−0.7 to 6.1	0.113
145	2	−6.6	−10.7 to −2.5	0.002	0.9	−3.8 to −5.7	0.690	−5.7	−9.4 to −2.0	0.003
155	2	−9.7	−14.0 to −5.2	<0.001	−4.1	−8.7 to 0.6	0.086	−13.5	−17.8 to −9.2	<0.001
165	2	−12.5	−17.1 to −7.8	<0.001	−7.9	−12.5 to −3.3	0.001	−20.3	−25.3 to −15.4	<0.001
135	1.9	−7.4	−11.3 to −3.4	<0.001	11.2	6.2 to 16.2	<0.001	3.8	0.5 to 7.2	0.026
145	1.9	−10.1	−14.3 to −5.9	<0.001	4.6	−0.1 to 9.3	0.051	−5.5	−9.1 to −1.9	0.003
155	1.9	−12.9	−17.3 to −8.4	<0.001	−0.6	−5.2 to 3.9	0.777	−13.5	−17.8 to −9.2	<0.001
165	1.9	−15.3	−19.9 to −10.5	<0.001	−4.9	−9.6 to −0.3	0.038	−20.2	−25.1 to −15.3	<0.001
125	1.8	−8.5	−12.5 to −4.5	<0.001	22.5	16.7 to 28.3	<0.001	14.0	9.9 to 18.1	<0.001
135	1.8	−11.3	−15.4 to −7.2	<0.001	14.4	9.3 to 19.6	<0.001	3.1	−0.6 to 6.8	0.104
145	1.8	−13.8	−18.1 to −9.5	<0.001	8.1	3.4 to 12.9	<0.001	−5.6	−9.2 to −2.0	0.003

51.98 ml) were not significantly different (p=0.091–0.150) from ischemic core and penumbras volume calculated from delay-sensitive deconvolution using MTT 145 % and CBV 2 ml×100 g^{-1} validated thresholds (ischemic core 36.93± 31.96 ml, ischemic penumbra 52.89±31.88 ml, ischemic volume 89.82±49.98 ml) (Table 5, Fig. 2).

Comparison of delay-sensitive and delay-insensitive modified aspect scores for ischemic core and penumbra

The modified ASPECT scores for the ischemic core obtained from delay-sensitive and delay-insensitive deconvolution (Table 6) showed a concordance of 89 % (95 % confidence

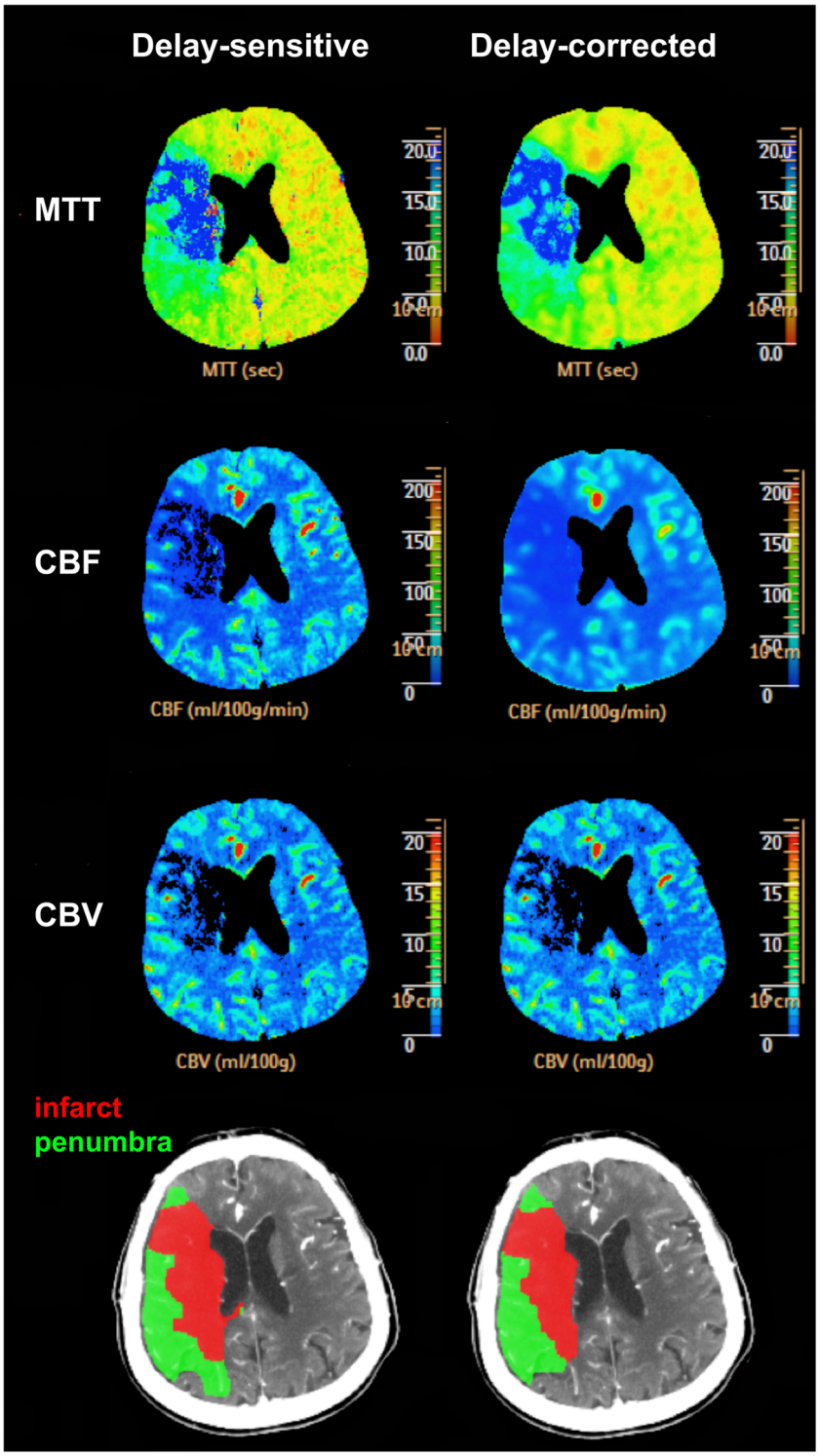

Fig. 2 Graphical illustration of the differences between delay-sensitive and delay-insensitive deconvolution. The same PCT data in the same patient with a right middle cerebral artery ischemic stroke was twice, using each of the two methods. CBV values do not differ between the two methods. MTT values are higher, and CBF values lower, with delay-sensitive deconvolution. However, with the appropriate, different thresholds (145 % MTT, CBV 2 ml× 100 g^{-1} min^{-1} for delay-sensitive deconvolution, and 135 % MTT, CBV 2 ml×100 g^{-1} min^{-1} for delay-insensitive deconvolution), the two methods yield very similar results in terms of prediction of the ischemic core (*red*) and penumbra (*green*) volumes

Table 6 ASPECT score concordance for the ischemic core between delay-sensitive and delay-insensitive deconvolution

Ischemic core		Delay-sensitive	
		0–7	8–14
Delay-insensitive	0–7	80	7
	8–14	4	9
Ischemic penumbra		Delay-sensitive	
		0–7	8–14
Delay-insensitive	0–7	76	8
	8–14	5	11

interval 81–94 %) and were not significantly different from each other (McNemar $p=0.366$).

The modified ASPECT scores for the ischemic penumbra obtained from delay-sensitive and delay-insensitive deconvolution (Table 6) showed a concordance of 87 % (95 % confidence interval 79–93 %) and were not significantly different from each other (McNemar $p=0.405$).

Assessment of tissue fate of delay-sensitive and delay-insensitive ischemic core and penumbra

In patients with persistent occlusion, the total ischemic areas (core + penumbra) defined on delay-sensitive and delay-insensitive deconvolution both correlated similarly with the final infarct volume on the slices matching the initial PCT (linear regression coefficients of 0.99 for delay-sensitive deconvolution and 1.09 for delay-insensitive deconvolution, correlation coefficients of 0.809 for delay-sensitive deconvolution and 0.794 for delay-insensitive deconvolution, Fig. 2).

In patients with recanalization, the ischemic core defined on delay-sensitive and delay-insensitive deconvolution both

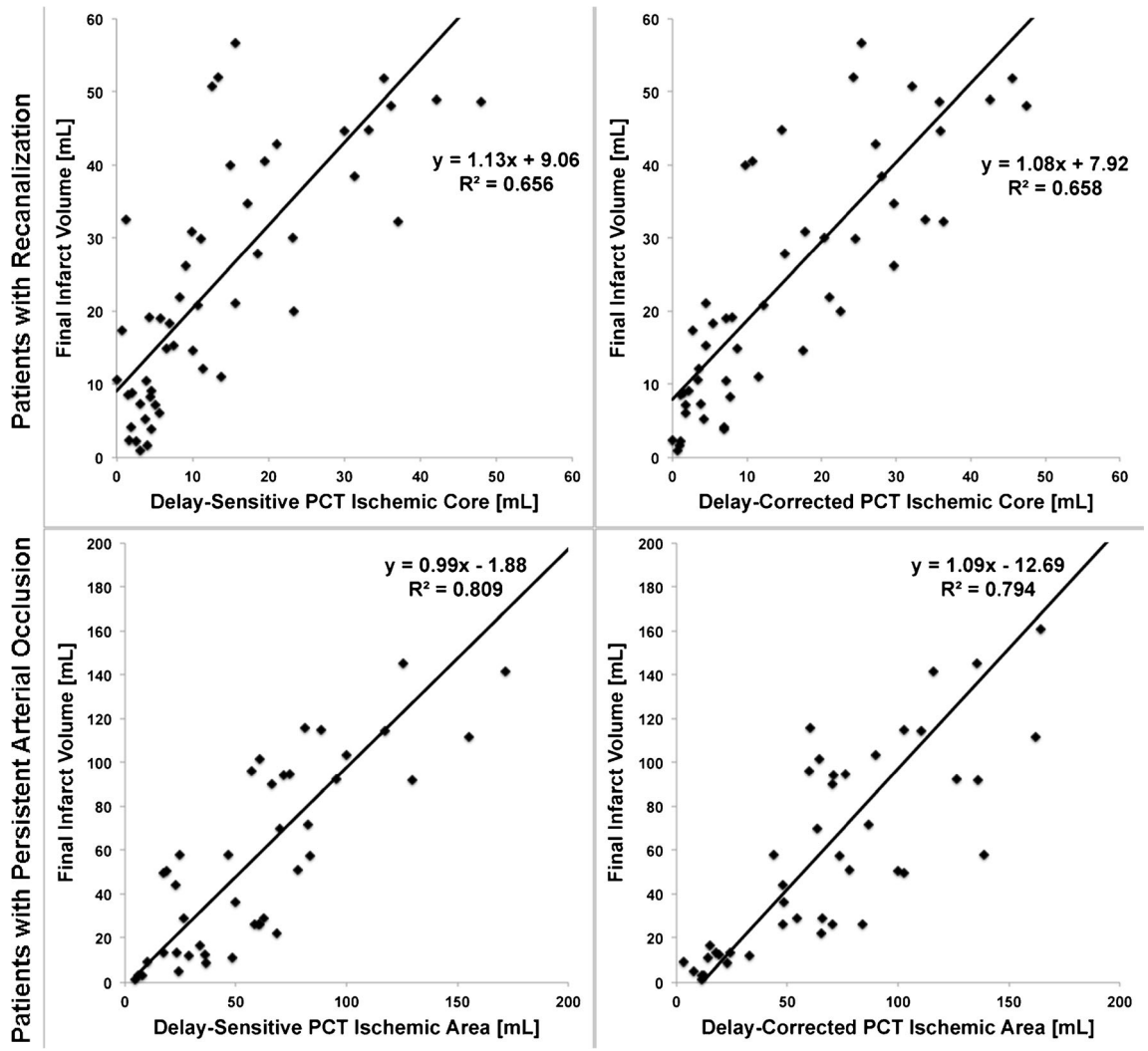

Fig. 3 Comparison of the final infarct volume with the delay-sensitive and delay-insensitive ischemic core (in patients with recanalization) and ischemic core + penumbra (in patients with persistent arterial occlusion)

correlated similarly with the final infarct volume on the slices matching the initial PCT (linear regression coefficients of 1.13 for delay-sensitive deconvolution and 1.08 for delay-insensitive deconvolution, correlation coefficients of 0.656 for delay-sensitive deconvolution and 0.658 for delay-insensitive deconvolution, Fig. 3). Of note, results were similar for 16- and 64-slice CT scanners.

Discussion

The goal of this article was to compare delay-sensitive and delay-insensitive deconvolution for PCT processing in patients with acute ischemic stroke. We found that CBV values were not affected by the type of deconvolution used for PCT processing. MTT values were higher, and CBF values lower, with delay-sensitive deconvolution compared to delay-insensitive deconvolution. However, when different, appropriate thresholds were applied to delay-sensitive (MTT 145 % and CBV 2 ml×100 g^{-1} min^{-1}) and to delay-insensitive (MTT 135 % and CBV 2 ml×100 g^{-1} min^{-1}) deconvolution, the resultant volumes of predicted ischemic core and penumbra were similar, as well as their anatomical distribution, and both showed similar association with final infarct volume when recanalization status was taken into account. Of note, in patients with recanalization, the final infarct tended to be underestimated by both delay-sensitive and delay-insensitive deconvolution PCT, likely because not all these patients underwent early recanalization, and the infarct grew between the time of the PCT and the time when recanalization occurred.

Our results are in agreement with previous studies. Prior MRI studies have shown that CBV values are not affected by the contrast arrival delay [11, 18]. On the other hand, CBF and MTT values are affected by the contrast arrival delay [14]. More specifically, the contrast arrival delay in the ischemic tissue typically introduces an underestimation in the calculated CBF values and an overestimation in the calculated MTT values [18, 11].

The optimal thresholds to delineate the ischemic core and penumbra are different for delay-sensitive and delay-insensitive deconvolution. However, when appropriate, yet different, thresholds are applied for delay-sensitive and delay-insensitive deconvolution, the resulting prediction of ischemic core and penumbra are comparable. The thresholds we used for delay-sensitive deconvolution and as reference standards in this study were previously validated in a large prospective study [3].

We acknowledge several limitations to our study. We use one PCT processing software provided by one CT manufacturer. The identified thresholds may not work for other software packages developed by other manufacturers, including those that use Tmax thresholds [19]. However, the general conclusions of the study regarding differences and similarities between delay-sensitive and delay-insensitive deconvolution are likely to hold. Similarly, the final infarct volume was determined with a wide range and using different techniques, but the general conclusions of the study should not be affected because each dataset served as its own control for the comparison analysis between the delay-sensitive and delay-insensitive deconvolution processing methods. Finally, our study sample included different imaging protocols. Because again, each dataset served as its own control for the comparison analysis between the delay-sensitive and delay-insensitive deconvolution processing methods, the different protocols do not affect the internal validity of our study. Rather, they increase its generalizability.

In conclusion, both delay-sensitive and delay-insensitive deconvolution methods are appropriate for PCT processing in acute ischemic stroke patients. Caution should be exercised when assessing MTT and CBV values as they are affected by the deconvolution method used. Similarly, optimal thresholds to delineate ischemic core and penumbra are different, but, when appropriate different thresholds are selected for delay-sensitive and delay-insensitive deconvolution, the predicted ischemic core and penumbra are similar with both methods. Thresholds need to be tailored to the specific software package in addition to the deconvolution method used.

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Ethical standards and patient consent We declare that all human and animal studies have been approved by the Institutional Review Board of the University of Virginia and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. We declare that all patients gave informed consent prior to inclusion in this study.

Conflict of interest We declare that we have no conflict of interest.

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