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Dynamic Perfusion CT: Optimizing the Temporal Resolution and Contrast Volume for Calculation of Perfusion CT Parameters in Stroke Patients

Max Wintermark, Wade S. Smith, Nerissa U. Ko, Marcel Quist, Pierre Schnyder, and William P. Dillon

BACKGROUND AND PURPOSE: Numerous parameters are involved in dynamic perfusion CT (PCT). We assessed the influence of the temporal sampling rate and the volume of contrast material.

METHODS: Sixty patients with ischemic hemispheric stroke lasting ≥ 12 hours underwent PCT. Groups of 15 patients each received 30, 40, 50, or 60 mL of contrast agent. Regional cerebral blood volume (rCBV), regional cerebral blood flow (rCBF), mean transit time (MTT), and time-to-peak (TTP) maps were calculated for temporal sampling intervals of 0.5, 1, 2, 3, 4, 5, and 6 seconds. Results were statistically compared. Signal-to-noise ratios (SNRs), duration of arterial entrance to venous exit, and radiation dose were also assessed.

RESULTS: Increasing temporal sampling intervals lead to significant overestimation of rCBV, rCBF, and TTP and significant underestimation of MTT compared with values for an interval of 1 second. Maximal allowable intervals to avoid these effects were 2, 3, 3, and 4 seconds for 30, 40, 50, and 60-mL boluses, respectively. Venous exit of contrast material occurred in 97.5% of patients after 36, 42, 42, and 48 seconds, respectively, for the four volumes. SNRs did not differ with volume. The effective radiation dose varied between 0.852 and 1.867 mSv, depending on the protocol. The cine mode with two 40-mL boluses and the toggling-table technique with one 60-mL bolus had the lowest doses.

CONCLUSION: Temporal sampling intervals greater than 1 second can be used without altering the quantitative accuracy of PCT. Increased sampling intervals reduce the radiation dose and may allow for increased spatial coverage.

The advent of multidetector-row CT (MDCT) has recently afforded a renewal of perfusion CT (PCT) techniques in the detection of stroke. Combined with CT angiography (CTA), PCT provides a comprehensive and accurate noninvasive survey of the site of arterial occlusion and its hemodynamic and patho-

physiologic repercussions in the brain parenchyma of patients with symptoms of acute stroke (1, 2).

PCT relies on the extraction of functional rather than morphologic information from the CT data. Two PCT techniques are currently in practice: whole-brain PCT and dynamic PCT. Whole-brain PCT provides information related to cerebral blood volume (CBV), and thus about the infarct core, but not about the ischemic penumbra, which is the target of acute stroke treatment (3–5). Dynamic PCT involves the dynamic acquisition of sequential CT sections in cine mode during the intravenous administration of iodinated contrast material. Dynamic PCT data analyzed according to the central volume principle has the major advantage of allowing the assessment of both cerebral blood flow (CBF) and CBV in a robust and reproducible quantitative way (6–9). Thus, the technique provides insight into cerebral vascular autoregulation and ischemic penumbra (10, 11). However, this technique is currently limited by the volume of contrast material

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and the radiation dose in the evaluation of selected portions of the brain, which are typically 40 mm thick.

The desire for increased spatial coverage and reduced radiation dose has resulted in various dynamic PCT protocols (10–13). However, the effect of the acquisition parameters on the accuracy of PCT results has not been systematically evaluated. The purpose of our study was to assess the impact of varying the temporal sampling rate and the volume of contrast material on the accuracy of calculated regional CBF (rCBF), regional CBV (rCBV), mean transit time (MTT), and time to peak (TTP).

Methods

Study Design

Under the auspices of our institutional review board, we reviewed imaging data from patient studies obtained as part of standard clinical care for stroke. In our institution, patients with suspected acute or subacute stroke undergo routine non-enhanced cerebral PCT at two cross-sectional positions, CTA of the cervical and intracranial vessels, and a contrast-enhanced cerebral CT. Informed consent was not required.

Between January and May 2003, 147 patients presented to the emergency room with strokelike symptoms and underwent our standard-of-care stroke CT protocol. Their data were included in this analysis if the patient presented to the emergency department with findings suggestive of hemispheric stroke of 12-hour duration or longer, if there was no evidence of intracerebral hemorrhage, and if a follow-up CT or MR image confirmed the final diagnosis of ischemic hemispheric stroke. Particular attention was devoted to the bolus volume used for the PCT examination. We identified 60 patients who fulfilled the inclusion criteria and whose PCT examinations varied only in the volume of contrast material. They included 33 men and 27 women aged 68 ± 12 years. The mean time of presentation was 18 ± 5 hours. The occluded arterial territory was the middle cerebral artery in 42, the anterior cerebral artery in 10, and the posterior cerebral artery in eight.

Imaging Protocol

Two successive PCT series were performed between the nonenhanced study and the CTA, separated by 5 minutes. PCT consisted of a 45-second series, with 45 gantry rotations performed in cine mode during the intravenous administration of iodinated contrast material. The temporal sampling rate was one rotation of the gantry per second on acquisition. Images were reconstructed at a temporal sampling rate of one image per second, resulting in a series of 45 images for each assessed section. Images were also reconstructed at a temporal sampling rate of two images per second, resulting in a series of 89 images for each assessed section location.

MDCT technology permitted the assessment of two adjacent, 10-mm-thick sections for each series. Two 10-mm-thick sections were preferred to four adjacent, 5-mm-thick sections per location to maximize the signal-to-noise ratio with the same acquisition parameters. The two sections of the first PCT series were at the level of the third ventricle and the basal ganglia; these were positioned above the orbits to protect the lenses. The second PCT series was selected at a level 3.5 cm rostral to the first section of the first series.

For each series of PCT, a bolus of iohexol (Omnipaque, 300 mg/mL of iodine; Amersham Health, Princeton, NJ) was administered into an antecubital vein by using a power injector at an injection rate of 4 mL/s. The acquisition parameters for both PCT studies included 80 kVp and 120 mAs. CT scanning was initiated 7 seconds after the injection. The time delay before

contrast material reached the brain parenchyma allowed the acquisition of baseline images without contrast enhancement.

In all patients, the PCT examinations varied only in the volume of contrast material used for the bolus. The patients were assigned to four groups of 15 each based on the volume of contrast material: group 1, 30 mL; group 2, 40 mL; group 3, 50 mL; and group 4, 60 mL.

Data Processing

PCT data were analyzed by using PCT prototype software (Philips Medical Systems, Best, the Netherlands). This software relies on the central volume principle, which is the most accurate method for low injection rates of iodinated contrast material (14). After correcting for motion and reducing noise with an anisotropic, edge-preserving spatial filter, the software applies least-mean-squares fitting to obtain mathematic descriptions of the time-attenuation curves. Then, it applies a closed-form (noniterative) deconvolution to calculate the MTT map (15–17). This operation requires a reference arterial input function, which the software selects in a region of interest (ROI) that the user draws around the anterior cerebral artery. The rCBV map is calculated from the area under the time-enhancement curves. It relies on a quantitative measurement of the partial volume averaging effect, taking into account the lack of partial-averaging effect at the center of the large superior sagittal venous sinus (18, 19). Finally, a simple equation combining rCBV and MTT values allows the calculation of rCBF, as follows: $rCBF = rCBV/MTT$ (15–17). The rCBF results afforded by the mathematic method of the software have been validated as being quantitatively accurate, as compared with comparison with stable xenon CT results (6). TTP maps were also measured.

For each group of patients, perfusion parameters were calculated by analyzing PCT data with seven temporal sampling intervals at 1 second (the criterion standard); at 0.5 second; and at 2, 3, 4, 5, and 6 seconds. From the 45 images acquired at one image per second, images were selected to calculate the parameter maps as follows: 1) For the sampling interval of 0.5 second, 89 PCT images were reconstructed. 2) For 2 seconds, one image was selected from every two in the raw PCT series of 45 images, resulting in a total of 23 images. 3) For 3 seconds, one image was selected from every three in the raw series, for a total of 15 images. 4) For 4 seconds, one image was selected from every four in the raw series, for a total of 12 images. 5) For 5 seconds, one image was selected from every five in the raw series, for a total of nine images. 6) For 6 seconds, one image was selected from every six in the raw series, for a total of eight images.

Data Analysis

The principal endpoint was the PCT result. Secondary endpoints included the signal-to-noise ratio, the duration of the PCT, and the radiation dose.

rCBV, MTT, rCBF and TTP maps were calculated for each data set. For each patient, similar ROIs of approximately 200 mm² were positioned on each of the seven temporal sampling interval datasets over the same anatomic features: 1) normal cortical gray matter (four ROIs for each section in each patient), 2) normal white matter (four ROIs for each section in each patient), 3) head of the caudate nucleus for each side (two ROIs in each patient), 4) lentiform nuclei for each side (two ROIs in each patient). An ROI was drawn to include the hypoattenuating ischemic area shown on the conventional non-enhanced CT scan in the volume of ischemic stroke. A large ROI was drawn to sample the asymptomatic hemisphere opposite that of the ischemic stroke.

For each patient, time-concentration curves were obtained from the raw data of 45 images acquired at an interval of 1 second in the ROI in the hypoattenuating ischemic area on the conventional nonenhanced cerebral CT scans, in the reference

TABLE 1: PCT rCBF values for the healthy hemisphere

Group	Sampling Interval						
	0.5 second	1 second*	2 seconds	3 seconds	4 seconds	5 seconds	6 seconds
1 (30 mL)							
Mean \pm SD	45.0 \pm 3.6	41.7 \pm 3.7	43.3 \pm 3.7	52.9 \pm 4.6	71.1 \pm 5.8	91.8 \pm 15.5	295.1 \pm 87.0
Range	-2.9% to +10.7%	NA	-4.9% to +8.4%	+2.6% to +28.3%	+47.0% to +139.4%	+84.2% to +170.1%	+379.7% to +748.2%
P value	.038	NA	.239	.001	<.001	<.001	<.001
2 (40 mL)							
Mean \pm SD	43.5 \pm 3.8	43.1 \pm 3.9	41.6 \pm 3.9	47.0 \pm 3.5	53.2 \pm 6.8	79.4 \pm 13.9	94.0 \pm 24.3
Range	-5.9% to +7.9%	NA	-7.6% to +6.1%	-2.8% to +9.6%	+24.2% to +60.4%	+59.8% to +113.0%	+107.3% to +277.5%
P value	.759	NA	.344	.052	<.001	<.001	<.001
3 (50 mL)							
Mean \pm SD	45.1 \pm 3.0	43.7 \pm 3.3	42.1 \pm 3.5	44.7 \pm 4.4	55.1 \pm 5.4	64.8 \pm 8.8	73.6 \pm 17.5
Range	-4.0% to +7.2%	NA	-6.9% to +6.3%	-5.4% to +8.2%	+12.3% to +49.1%	+44.9% to +81.5%	+79.4% to +108.1%
P value	.276	NA	.248	.494	.001	.001	.001
4 (60 mL)							
Mean \pm SD	45.7 \pm 3.8	44.2 \pm 3.7	41.6 \pm 3.6	42.5 \pm 3.8	47.6 \pm 4.6	54.6 \pm 6.4	60.4 \pm 9.3
Range	-4.8% to +7.4%	NA	-8.0% to +5.7%	-7.4% to +5.5%	-4.0% to +11.0%	+8.3% to +39.4%	+22.7% to +47.7%
P value	.306	NA	.112	.252	.012	.004	.001

Note.—No significant difference ($P = .886$, Kruskal-Wallis) was identified among the four groups for rCBF values obtained with an interval of 1 second. Range indicates the overestimation or underestimation compared with the reference. Values in boldface indicate the temporal sampling interval thresholds beyond which rCBF values were significantly overestimated.

* Reference for Wilcoxon (Mann-Whitney) tests performed in each group. NA indicates not applicable.

arterial pixel, and in the reference venous pixels. The time of entrance of the contrast material in the brain was designated as the moment when contrast enhancement in the arterial ROI was 10% above baseline precontrast values.

Venous and ischemic times of exit of the contrast material were designated when the attenuation value in the sagittal sinus ROI and ischemic ROI, respectively, decreased by one third of the total attenuation difference between baseline and peak values in the venous or infarction ROIs. This threshold was selected for accurate curve fitting of the raw data with the software.

After contrast enhancement, X-ray interaction with soft tissues at 80 kVp is related to the photoelectric effect due to the 33-keV k-edge of the iodine in the contrast material. Before contrast enhancement, X-ray interaction is mainly due to the Compton effect. Thus, the use of various bolus volumes may theoretically influence the relative enhancement with respect to background noise (20). To evaluate the effect of volume on the degree of enhancement and on background noise, we selected a baseline image and the peak image in the PCT series for the seven temporal sampling intervals for each patient. For each section, we determined the X-ray attenuation (mean and standard deviation [SD] in Hounsfield units) in an ROI that included the whole asymptomatic hemisphere opposite the ischemic stroke. For each temporal sampling intervals, an image-quality ratio was defined as follows: image-quality ratio = (peak mean/peak SD)/(baseline mean/baseline SD).

A high image-quality ratio indicated a greater increase in contrast enhancement compared with the noise increase after the administration of contrast material.

The evaluation of the radiation dose delivered by the different PCT protocols was calculated in conformity with the rules of the US Food and Drug Administration and the European Guidelines on Quality Criteria for Computed Tomography (21). The maximum absorbed dose to the brain was obtained by multiplying the total mAs locally delivered at the level of the perfusion images by the normalized and weighted CT dose index, which is 0.070 mGy/mAs at 80 kVp (22). To estimate the stochastic risks associated with the use of ionizing radiation, the effective radiation dose was calculated from the dose-length product of the acquisitions by using a conversion factor of 0.0030 mSv/(mGy \times cm).

Statistical Analysis

PCT results and other parameters were compared among the four patient groups and the seven temporal sampling intervals by using Kruskal-Wallis tests. When results were significant, each dataset was compared with the reference dataset (one image per second) by using Wilcoxon (Mann-Whitney) tests. The significance level was set at .01 to account for the multiple sampling (Bonferroni correction).

Results

PCT Results and Temporal Sampling Intervals

PCT rCBF values in the healthy hemisphere are reported in Table 1. rCBF values were significantly overestimated compared with reference values when temporal sampling interval was more than 2, 3, 3, and 4 seconds for the 30, 40, 50, and 60 mL bolus volumes, respectively. Similarly, PCT rCBF values in the ischemic area are reported in Table 2. The thresholds beyond which rCBF values were overestimated were 2, 3, 3, and 4 seconds for the 30, 40, 50, and 60 mL volumes, respectively.

The overestimation of rCBF values with sparsing sampling resulted from both the overestimation of rCBV and the underestimation of MTT. As demonstrated in Figure 1, areas under the curves were underestimated for higher temporal sampling intervals. This underestimation was more pronounced in the reference venous pixel (denominator) than in parenchymatous pixels (numerator), resulting in an overestimation of the rCBV values (Tables 3 and 4). On the other hand, increasing the temporal sampling interval beyond a threshold led to an underestimation of MTT values (Tables 5 and 6) and an overestimation of TTP values.

The absolute PCT results were similarly altered in the healthy hemisphere and in the ischemic area

TABLE 2: PCT rCBF values for the ischemic area

Group	Sampling Interval						
	0.5 second	1 second*	2 seconds	3 seconds	4 seconds	5 seconds	6 seconds
1 (30 mL)							
Mean ± SD	10.1 ± 4.7	11.7 ± 6.0	12.3 ± 6.1	24.4 ± 12.1	54.2 ± 27.4	102.2 ± 50.2	238.3 ± 188.0
Range	-9.2% to +17.3%	NA	-10.0% to +18.4%	+18.1% to +126.3%	+151.1% to +402.4%	+513.7% to +991.1%	+1183.9% to +2561.1%
P value	.450	NA	.803	.004	<.001	<.001	<.001
2 (40 mL)							
Mean ± SD	11.4 ± 5.1	12.9 ± 4.9	12.0 ± 5.1	13.8 ± 6.3	47.1 ± 23.3	85.9 ± 35.9	194.8 ± 137.9
Range	-10.0% to +16.2%	NA	-9.4% to +17.4%	-8.9% to +18.2%	+115.1% to +319.9%	+392.6% to +718.7%	+946.0% to +1945.8%
P value	.958	NA	.653	.683	<.001	<.001	<.001
3 (50 mL)							
Mean ± SD	9.8 ± 4.9	11.3 ± 4.5	9.6 ± 4.1	11.4 ± 5.3	25.6 ± 12.2	47.1 ± 20.7	60.3 ± 31.8
Range	-10.6% to +18.1%	NA	-10.0% to +18.8%	-9.5% to +19.8%	+55.8% to +171.1%	+251.6% to +439.4%	+380.4% to +795.1%
P value	.494	NA	.393	.939	.001	<.001	<.001
4 (60 mL)							
Mean ± SD	9.6 ± 4.4	9.7 ± 4.4	9.3 ± 4.0	9.2 ± 4.3	10.6 ± 5.7	23.4 ± 12.0	29.6 ± 19.0
Range	-9.7% to +19.8%	NA	-9.6% to +19.2%	-10.0% to +17.3%	-8.9% to +18.6%	+118.9% to +286.7%	+136.9% to +324.7%
P value	.970	NA	.777	.776	.216	.001	.001

Note.—No significant difference ($P = .166$, Kruskal-Wallis) was identified among the four groups for rCBF values obtained with an interval of 1 second. Range indicates the overestimation or underestimation compared with the reference. Values in boldface indicate the temporal sampling interval thresholds beyond which rCBF values were significantly overestimated.

* Reference for Wilcoxon (Mann-Whitney) tests performed in each group. NA indicates not applicable.

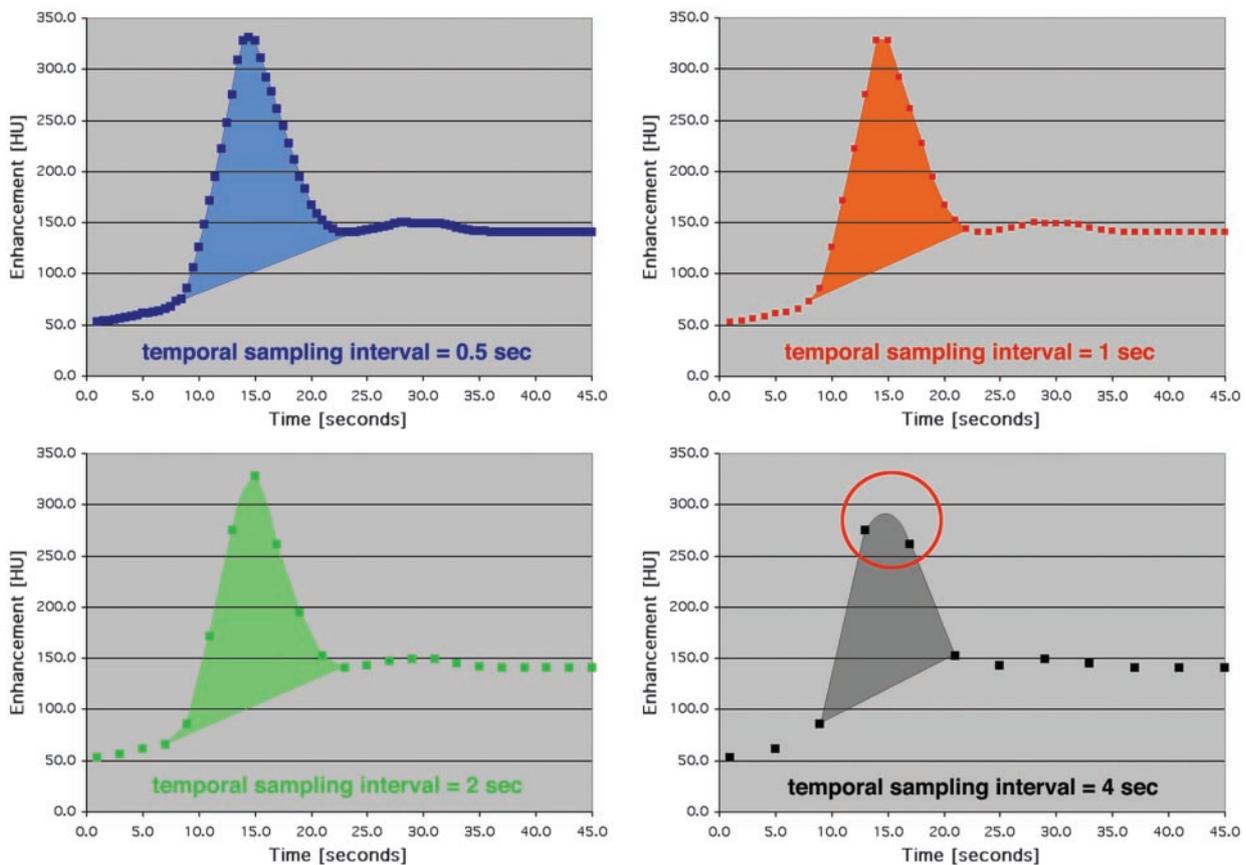


FIG 1. Time-enhancement curves for four temporal sampling intervals: 0.5 second, 1 second, 2 seconds, and 4 seconds. The area under the curve is approximately the same for the first three sampling intervals. For the interval of 4 seconds, however, the peak points of the curve are undersampled (circle), resulting in a reduction in the area under the curve. This would result in significant errors in the calculation of rCBV.

when temporal sampling intervals were increased; however, variances in the ischemic area were higher than those in the healthy hemisphere. The relative

values obtained by dividing PCT results in the ischemic area by those in the healthy hemisphere were also affected similarly, beyond thresholds re-

TABLE 3: PCT rCBV values for the healthy hemisphere

Group	Sampling Interval						
	0.5 second	1 second*	2 seconds	3 seconds	4 seconds	5 seconds	6 seconds
1 (30 mL)							
Mean \pm SD	3.0 \pm 0.4	2.8 \pm 0.5	2.9 \pm 0.4	3.0 \pm 0.5	3.9 \pm 0.7	4.8 \pm 1.3	14.9 \pm 4.8
Range	-6.5% to +8.0%	NA	-7.5% to +6.8%	-6.2% to +9.2%	+16.8% to +59.4%	+52.5% to +99.1%	+136.0% to +628.3%
P value	.213	NA	.700	.124	.004	.002	<.001
2 (40 mL)							
Mean \pm SD	3.1 \pm 0.5	3.0 \pm 0.4	2.8 \pm 0.4	3.2 \pm 0.5	3.2 \pm 0.6	4.3 \pm 0.7	4.9 \pm 1.2
Range	-5.8% to +7.1%	NA	-8.3% to +4.9%	-5.8% to +7.4%	-4.2% to +9.6%	+18.0% to +69.3%	+42.0% to +278.2%
P value	.225	NA	.595	.0196	.024	<.001	<.001
3 (50 mL)							
Mean \pm SD	3.2 \pm 0.4	3.1 \pm 0.5	2.9 \pm 0.4	3.0 \pm 0.3	3.3 \pm 0.5	3.9 \pm 0.6	4.1 \pm 0.8
Range	-7.2% to +6.2%	NA	-9.0% to +7.9%	-7.4% to +8.3%	-5.3% to +8.3%	+7.9% to +41.6%	+22.3% to +66.6%
P value	.708	NA	.243	.494	.139	.008	.007
4 (60 mL)							
Mean \pm SD	3.2 \pm 0.4	3.1 \pm 0.5	2.9 \pm 0.4	2.9 \pm 0.3	3.2 \pm 0.4	3.3 \pm 0.4	3.7 \pm 0.5
Range	-6.5% to +8.0%	NA	-8.3% to +10.2%	-8.1% to +9.0%	-5.8% to +7.6%	-4.8% to +9.6%	+8.5% to +32.6%
P value	.230	NA	.650	.420	.324	.038	.007

Note.—No significant difference ($P = .908$, Kruskal-Wallis) was identified among the four groups for rCBV values obtained with an interval of 1 second. Range indicates the overestimation or underestimation compared with the reference. Values in boldface indicate the temporal sampling interval thresholds beyond which rCBV values were significantly overestimated.

* Reference for Wilcoxon (Mann-Whitney) tests performed in each group. NA indicates not applicable.

TABLE 4: PCT rCBV values for the ischemic area

Group	Sampling Interval						
	0.5 second	1 second*	2 seconds	3 seconds	4 seconds	5 seconds	6 seconds
1 (30 mL)							
Mean \pm SD	1.0 \pm 0.4	1.2 \pm 0.5	1.1 \pm 0.5	2.2 \pm 0.4	3.7 \pm 0.6	5.4 \pm 1.5	12.1 \pm 4.8
Range	-14.4% to +8.6%	NA	-10.2% to +8.5%	+33.7% to +111.2%	+104.2% to +335.0%	+222.0% to +447.4%	+630.5% to +1275.2%
P value	.018	NA	.519	<.001	<.001	<.001	<.001
2 (40 mL)							
Mean \pm SD	1.1 \pm 0.3	1.2 \pm 0.4	1.1 \pm 0.4	1.2 \pm 0.4	3.2 \pm 0.5	5.1 \pm 0.9	10.9 \pm 2.8
Range	-13.0% to +13.7%	NA	-10.5% to +8.1%	-10.6% to +10.2%	+53.0% to +220.5%	+197.3% to +427.3%	+510.8% to +937.3%
P value	.156	NA	.076	.765	<.001	<.001	<.001
3 (50 mL)							
Mean \pm SD	0.9 \pm 0.5	1.1 \pm 0.3	1.0 \pm 0.3	1.1 \pm 0.6	2.3 \pm 0.3	3.4 \pm 0.5	4.3 \pm 0.9
Range	-12.4% to +10.6%	NA	-8.1% to +8.5%	-10.5% to +9.4%	+33.5% to +122.3%	+95.5% to +323.7%	+249.7% to +435.4%
P value	.021	NA	.033	.603	<.001	<.001	<.001
4 (60 mL)							
Mean \pm SD	1.0 \pm 0.4	1.0 \pm 0.5	0.9 \pm 0.6	0.9 \pm 0.4	1.1 \pm 0.3	2.0 \pm 0.3	2.4 \pm 0.4
Range	-11.3% to +10.4%	NA	-7.2% to +7.2%	-9.5% to +9.3%	-11.8% to +12.1%	+23.3% to +155.9%	+97.9% to +228.1%
P value	.614	NA	.164	.172	.014	<.001	<.001

Note.—No significant difference ($P = .556$, Kruskal-Wallis) was identified among the four groups for rCBV values obtained with an interval of 1 second. Range indicates the overestimation or underestimation compared with the reference. Values in boldface indicate the temporal sampling interval thresholds beyond which rCBV values were significantly overestimated.

* Reference for Wilcoxon (Mann-Whitney) tests performed in each group. NA indicates not applicable.

ported in Table 7. Figure 2 shows sample PCT datasets in one patient from the 40-mL group.

No statistically significant difference was identified among the four groups for rCBF, rCBV, MTT, and TTP at a temporal sampling interval of 1 second. (P values for the Kruskal-Wallis comparisons between groups at an interval of 1 second are reported in the Table notes.) P values for Kruskal-Wallis comparisons between sampling intervals in each patient group were all $< .01$, which allowed us to compare each dataset to the reference dataset (one image per second) using Wilcoxon (Mann-Whitney) tests. (P values of the tests are reported in the Tables.)

The final threshold for the global temporal sampling interval for each bolus volume was defined as the minimum threshold for any of the four parametric PCT results in any region of the brain. The global thresholds were 2 seconds for 30 mL, 3 seconds for 40 mL, 3 seconds for 50 mL, and 4 seconds for 60 mL.

Entrance and Exit of Contrast Material

Figure 3 shows the time to entrance of the contrast material into the arterial pixel and the time to exit in the venous and ischemic pixels. In all groups, the longer interval was that of the exit of the contrast

TABLE 5: PCT MTT values for the healthy hemisphere

Group	Sampling Interval						
	0.5 second	1 second*	2 seconds	3 seconds	4 seconds	5 seconds	6 seconds
1 (30 mL)							
Mean ± SD	4.0 ± 0.4	4.1 ± 0.5	4.0 ± 0.4	3.8 ± 0.5	3.3 ± 0.4	3.1 ± 0.4	3.0 ± 0.6
Range	-11.4% to +8.0%	NA	-10.0% to +9.8%	-11.1% to +4.1%	-6.2% to -33.6%	-3.1% to -40.3%	-27.0% to -53.5%
P value	.789	NA	.594	.016	.008	.006	.002
2 (40 mL)							
Mean ± SD	4.3 ± 0.5	4.2 ± 0.4	4.1 ± 0.4	4.0 ± 0.5	3.9 ± 0.5	3.4 ± 0.5	3.1 ± 0.6
Range	-6.7% to +10.1%	NA	-10.5% to +8.2%	-8.3% to +7.8%	-10.6% to +7.3%	-7.4% to -28.1%	-15.7% to -36.7%
P value	.202	NA	.889	.803	.169	.007	.002
3 (50 mL)							
Mean ± SD	4.2 ± 0.3	4.1 ± 0.5	4.1 ± 0.6	4.0 ± 0.4	3.9 ± 0.4	3.8 ± 0.5	3.4 ± 0.4
Range	-9.8% to +9.2%	NA	-9.5% to +8.6%	-9.9% to +7.0%	-10.6% to +2.8%	-11.1% to +7.0%	-9.9% to -28.3%
P value	0.783	NA	.485	.256	.043	.013	.009
4 (60 mL)							
Mean ± SD	4.1 ± 0.5	4.0 ± 0.5	4.2 ± 0.6	4.0 ± 0.5	4.0 ± 0.3	3.8 ± 0.4	3.7 ± 0.5
Range	-9.2% to +12.4%	NA	-8.3% to +10.1%	-10.5% to +9.1%	-10.7% to +9.5%	-10.6% to +8.6%	-10.5% to +8.5%
P value	.487	NA	.341	.873	.306	.129	.118

Note.—No significant difference ($P = .556$, Kruskal-Wallis) was identified among the four groups for MTT values obtained with an interval of 1 second. Range indicates the overestimation or underestimation compared with the reference. Values in boldface indicate the temporal sampling interval thresholds beyond which MTT values were significantly underestimated.

* Reference for Wilcoxon (Mann-Whitney) tests performed in each group. NA indicates not applicable.

TABLE 6: PCT MTT values for the ischemic area

Group	Sampling Interval						
	0.5 second	1 second*	2 seconds	3 seconds	4 seconds	5 seconds	6 seconds
1 (30 mL)							
Mean ± SD	5.8 ± 0.6	5.9 ± 0.7	5.6 ± 0.7	5.4 ± 0.6	4.1 ± 0.6	3.2 ± 0.6	3.1 ± 0.6
Range	-16.0% to +10.5%	NA	-17.6% to +7.8%	-13.3% to +16.3%	-13.6% to -44.3%	-32.1% to -67.5%	-42.4% to -75.2%
P value	.634	NA	.168	.099	.009	.002	.002
2 (40 mL)							
Mean ± SD	6.0 ± 0.7	5.8 ± 0.8	5.6 ± 0.7	5.4 ± 0.6	4.1 ± 0.5	3.5 ± 0.5	3.4 ± 0.5
Range	-9.2% to +18.1%	NA	-18.7% to +9.3%	-17.6% to +7.3%	-9.8% to -36.2%	-26.3% to -60.5%	-37.9% to -50.5%
P value	.205	NA	.623	.277	.004	.002	0.002
3 (50 mL)							
Mean ± SD	5.8 ± 0.6	5.9 ± 0.9	6.0 ± 0.6	5.7 ± 0.7	5.3 ± 0.7	4.3 ± 0.6	4.3 ± 0.6
Range	-17.1% to +16.5%	NA	-11.8% to +19.7%	-18.2% to +15.5%	-22.5% to +8.9%	-12.1% to -43.2%	-28.1% to -36.0%
P value	.611	NA	.652	.435	.057	.007	.006
4 (60 mL)							
Mean ± SD	6.1 ± 0.8	6.1 ± 0.8	5.9 ± 0.6	6.0 ± 0.7	5.6 ± 0.7	5.5 ± 0.6	4.8 ± 0.6
Range	-19.6% to +11.6%	NA	-19.5% to +12.3%	-18.4% to +12.4%	-17.7% to +9.5%	-16.1% to +10.35%	-13.0% to -33.1%
P value	.677	NA	.528	.649	.283	.017	.008

Note.—No significant difference ($P = .108$, Kruskal-Wallis) was identified among the four groups for MTT values obtained with an interval of 1 second. Range indicates the overestimation or underestimation compared with the reference. Values in boldface indicate the temporal sampling interval thresholds beyond which MTT values were significantly underestimated.

* Reference for Wilcoxon (Mann-Whitney) tests performed in each group. NA indicates not applicable.

material in the ischemic area. In two and three patients from the 50 and 60 mL groups, respectively, the definition of exit time could not be applied in either the venous or ischemic pixel. In these patients, the exit times were set at 45 seconds. No statistically significant difference ($P = .789$) was observed among the four groups with respect to the arterial entrance of contrast material. On the other hand, there was a nonsignificant trend for increasing exit times from the venous ($P = .516$) and ischemic ($P = .569$) pixels with increasing bolus volume.

A time interval equal to mean + 2 SDs would permit adequate imaging of the patients (and the

ischemic area, if any) in 97.5% of the cases. When we took optimal temporal sampling interval into account, optimal PCT scanning times were 36, 42, 42, and 48 seconds for the 30-, 40-, 50-, and 60-mL groups, respectively.

Image-Quality Ratio

We did not demonstrate a threshold for image-quality ratios below that which would have significantly altered PCT findings. The calculated ratios were 0.645 ± 0.193 in group 1 (30 mL), 0.712 ± 0.216 in group 2 (40 mL), 0.767 ± 0.240 in group 3 (50 mL),

TABLE 7: Thresholds beyond which PCT results were significantly different from reference results

Value and Region	Temporal Sampling Interval (seconds)			
	Group 1 (30 mL)	Group 2 (40 mL)	Group 3 (50 mL)	Group 4 (60 mL)
rCBF				
Healthy hemisphere	2	3	3	4
Cortical gray matter	3	3	4	5
White matter	2	3	3	4
Caudate nucleus	3	4	4	5
Lenticular nucleus	2	3	4	4
Ischemic area	2	3	3	4
Ischemic/healthy ratio	2	3	3	4
rCBV				
Healthy hemisphere	3	4	4	5
Cortical gray matter	3	4	5	6
White matter	2	3	3	4
Caudate nucleus	3	3	4	5
Lenticular nucleus	3	3	4	5
Ischemic area	2	3	3	4
Ischemic/healthy ratio	2	3	3	4
MTT				
Healthy hemisphere	3	4	5	6
Cortical gray matter	4	5	5	6
White matter	4	4	5	5
Caudate nucleus	3	4	5	6
Lenticular nucleus	3	4	4	6
Ischemic area	3	3	4	5
Ischemic/healthy ratio	3	3	4	4
TTP				
Healthy hemisphere	3	4	5	6
Cortical gray matter	4	5	6	6
White matter	3	4	5	6
Caudate nucleus	2	3	4	5
Lenticular nucleus	2	4	4	5
Ischemic area	2	3	4	5
Ischemic/healthy ratio	2	3	3	4
Global	2	3	3	4

Note.—Reference results were calculated from the raw acquisition PCT series (temporal sampling interval of 1 second). The final global threshold for each volume was defined as the minimum temporal sampling interval identified as accurate for any of the four parametric PCT results in any region.

and 0.850 ± 0.166 in group 4 (60 mL). There was a trend toward higher image-quality ratios with increasing volume of contrast material; however, this trend was not statistically significant ($P = .082$). Moreover, for each PCT result (rCBF, rCBV, MTT, and TTP) obtained with a temporal sampling interval of 1 second, no significant difference was identified in the four patient groups.

Radiation Dose (Table 8)

In the first group of patients (30 mL), the cerebral effective radiation dose would be 1.245 mSv for cerebral coverage of 4 cm and 1.867 mSv for spatial coverage of 6 cm, with an acquisition of 36 seconds at a temporal sampling interval of 2 seconds and with acquisition parameters of 80 kVp and 120 mAs. In the second (40-mL) and third (50-mL) groups, the effective dose would be 0.983 mSv for coverage of 4 cm,

with an acquisition of 43 seconds at an interval of 3 seconds (80 kVp and 120 mAs). In the fourth group (60 mL), the effective dose would be 0.852 mSv for coverage of 4 cm, with an acquisition of 48 seconds at an interval of 4 seconds (80 kVp and 120 mAs). As a reference, the dose for a standard cerebral CT examination is 2.5 mSv (21).

Discussion

The numerous parameters involved in the performance of PCT affect the accuracy of perfusion values, the radiation dose, and the spatial coverage. However, only a few of these parameters have been assessed thoroughly. For instance, the use of 80 kVp instead of 120 kVp has been demonstrated to increase contrast enhancement and reduce the patient's radiation dose (20). Other parameters are standard because they cannot be modified or because have been shown to be effective. A 300-mg/mL bolus of isosmolar iodinated contrast material is required, as this has been demonstrated to be safe in case of ischemic brain tissue (23). Similarly, the fastest possible injection rate should be used to deliver the bolus, to verify the assumptions of the central volume principle that underlies dynamic PCT data analysis (14). However, patients do not safely tolerate injection rates above 4 or 5 mL/s in the antecubital veins; therefore, this is the maximum rate typically used in PCT protocols.

In the present study, we evaluated the influence of temporal sampling rate and contrast-agent bolus on PCT results. All other acquisition parameters were equivalent among the different groups of patients. We found that the allowable temporal sampling interval is greater than 1 second. A temporal sampling interval of 0.5 second, which some authors advocate (12), does not result in more accurate calculation of PCT parameters.

The allowable temporal sampling interval depends on the volume of the bolus. For each of four volumes, we could define a threshold of temporal sampling below that in which absolute PCT results became inaccurate. Because of an underestimation of the areas under the time-concentration curves (predominantly in the reference venous pixel), rCBV values were overestimated. This, combined with MTT underestimation, led to an overestimation of rCBF values. MTT values do not simply depend on the difference in width between the arterial input and parenchymatous curves; they result from a more complex deconvolution operation. Sampling sparsing influences both the parenchymatous curves and the arterial input and thus has a complex influence on the deconvolution operation. The type of deconvolution, which varies for the commercially available deconvolution-based PCT software, is not likely to modify the influence of sparsing sampling on MTT results. These thresholds held true when the pathologic hemisphere is compared with the healthy contralateral hemisphere, as visually performed in clinical practice. Indeed, ratios obtained by dividing PCT results in the ischemic area by those in the healthy area were sig-

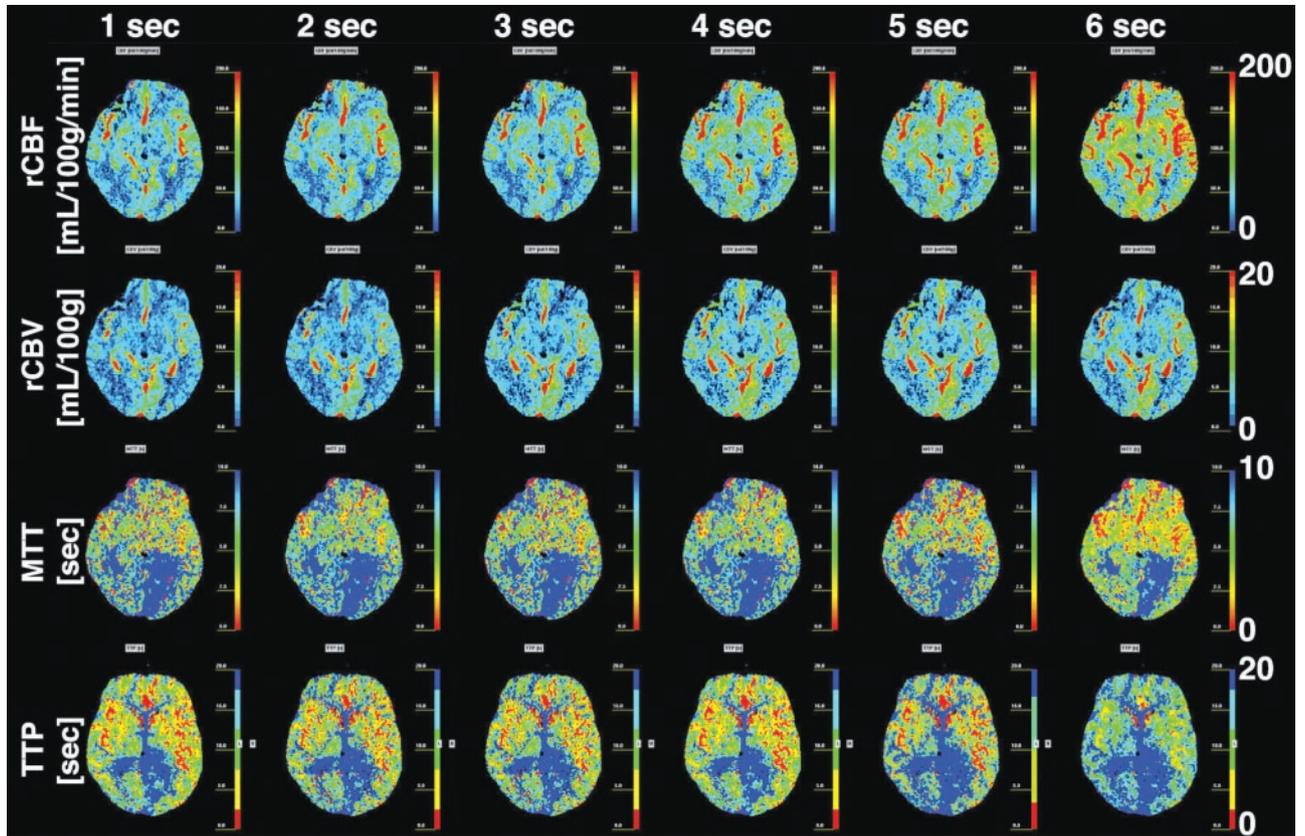


FIG 2. Sample PCT datasets in one patient from the 40-mL group. rCBF, rCBV, MTT, and TTP maps are displayed for six sampling intervals: 1, 2, 3, 4, 5, and 6 seconds. Sparsing sampling results in overestimation of rCBF, rCBV, and TTP values and in underestimation of MTT values.

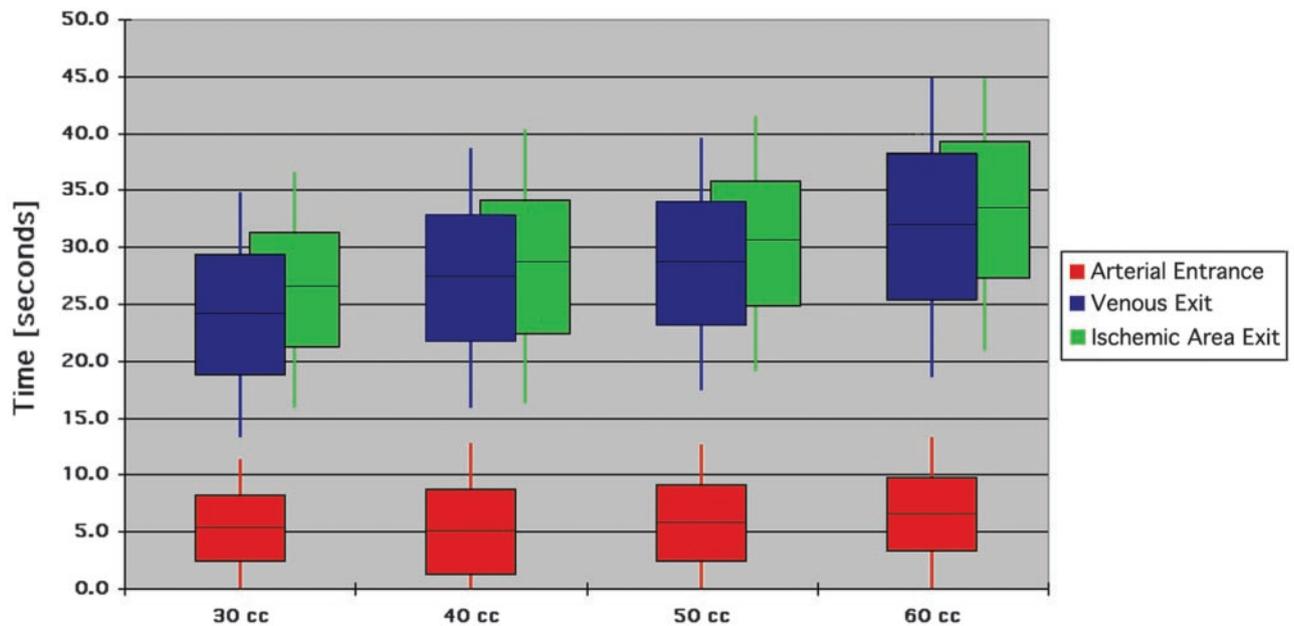


FIG 3. Time to entrance of the contrast material into the arterial pixel and time to exit of the contrast material in the venous and ischemic pixels, displayed for the four bolus volume groups. Boxes represent the mean \pm 1 SD, and vertical lines indicate the mean \pm 2 SDs. Time to arterial entrance does not vary with bolus volumes. However, time to exit does increase with increasing bolus volumes, resulting in longer acquisition times required for larger bolus volumes.

nificantly affected when we used sampling intervals greater than the thresholds established in our study.

The volume of contrast material did not affect

image quality or PCT results. Specifically, image-quality ratios were not significantly different among the four groups with various bolus volumes. Addition-

TABLE 8: Imaging protocols for acceptable PCT results

Bolus (mL)	No. of Boluses	Total (mL)	Scanning Duration (seconds)	Temporal Sampling Interval (seconds)	Images per Series (per section)	PCT Technique	MDCT			Dose-Coverage Ratio	Image-Quality Ratio	
							Spatial Coverage (cm)	kVp	mAs			
30	2	60	36	2	19	Cine	4	80	120	1.245	0.311	0.645
30	3	90	36	2	19	Cine	6	80	120	1.867	0.311	0.645
40	2	80	42	3	15	Cine	4	80	120	0.983	0.246	0.712
50	2	100	42	3	15	Cine	4	80	120	0.983	0.246	0.767
60	1	60	48	4	13	Toggling-table	4	80	120	0.852	0.213	0.850

Note.—Parameters in boldface indicate the recommended protocols with optimal dose-coverage ratios.

ally, no significant difference was identified in the PCT results of the four groups.

Whereas the arterial entrance of contrast material in the section depends mainly on the injection rate and the patients' cardiac output, the duration of contrast enhancement is influenced by the volume of the bolus. The absence of significant differences in the venous and ischemic exit times of contrast material among different volumes was due to the relatively high variances in the duration of contrast enhancement. This was related to the differing hemodynamic status of our patients and, in several cases, to issues involving the venous catheter (gauge too small, bent elbows, etc). However, for each bolus volume, it is possible to define an optimal scanning duration that is suitable for most patients.

Once the required temporal sampling interval, optimal scanning duration, and bolus volume are defined, it is possible to propose alternative PCT protocols, characterized by bolus volume, scanning mode, spatial coverage, and radiation dose. These alternative protocols are summarized in Table 8. One limiting factor for all protocols is the total volume of contrast material, which should be 150 mL or less to protect the patient's renal function. This dose has been proved safe in the emergency setting (24). Typically, CTA studies require approximately 50–70 mL, leaving 80–100 mL available for PCT studies. Thus, two or three boluses of 30 mL, two boluses of 40 or 50 mL, and one bolus of 60 mL are the possible injection volumes if PCT is to be performed at the same sitting as CTA. However, if CTA is unnecessary, additional boluses could be used to expand the coverage for PCT studies.

To increase coverage with PCT during a single bolus of contrast material, Roberts et al (13) developed a cine-mode technique, the toggling-table technique, in which the table is moved between two locations during the bolus. Because of restrictions in table movement, however, the minimal temporal sampling interval for current commercial CT scanners is 4–5 seconds. According to our calculations, this technique is limited to only a bolus of 60 mL. At temporal sampling interval superior to 4 seconds and at bolus volumes less than 60 mL, the current toggling-table technique results in significant differences in the calculation of CBV and CBF compared with our reference standard. This technique, however, is sensitive to large-vessel infarction and could conceivably be used

in situations in which the dose of contrast agent is an issue or in which spatial coverage is required, as long as the limitations are understood.

Selecting an optimal PCT protocol from among those summarized in Table 8 is a somewhat local issue and depends on the CT scanner available (eg, MDCT, number of detector-rows, pitch, volume of contrast material, requirement for CTA). The main decision requires a balance between spatial coverage and radiation dose. For instance, three boluses of 30 mL would afford coverage of 6 cm (assuming a detector width of 2 cm), but this would represent a radiation dose twice as high as that of the 40-, 50-, and 60-mL protocols. Therefore, we favor PCT protocols involving 40- or 60-mL bolus volumes (Table 8), which provide the optimal ratio of coverage to radiation dose. If possible, manufacturers should adapt the technical requirements of their CT scanners to permit use of the toggling-table technique at a sampling resolution of one image per 3 seconds. If implemented, this would allow the use of two or three 40-mL boluses for a total coverage of 80–120 mm. In this way, PCT assessment of the entire brain volume could be accurately performed.

Conclusions

A temporal sampling interval of greater than 1 second can be used for PCT without altering the quantitative accuracy of the results. Increasing the sampling interval reduces the radiation dose to the patient and may allow for increased spatial coverage in the near future. Optimization of PCT protocols may result in accurate estimation of perfusion values at acceptable radiation doses.

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