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AJNR Am J Neuroradiol 2006, 27 (1) 46-50

<http://www.ajnr.org/content/27/1/46>

This information is current as of April 19, 2024.

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Influence of Partial Volume on Venous Output and Arterial Input Function

BACKGROUND: CT perfusion (CTP) is an important diagnostic tool for the imaging of cerebral hemodynamics. To obtain quantitative values of cerebral blood volume (CBV), blood flow (CBF), and mean transit time (MTT), measurement of the arterial input function (AIF) is required. To correct for partial volume effects (PVEs), it is common to normalize the AIF with respect to the venous output function (VOF). This correction assumes that measurement of the VOF is unhampered by PVEs. The purpose of this study was to evaluate the effect of PVE on the measurement of the AIF and VOF and, consequently, on the absolute perfusion parameters.

METHODS: In 10 patients the mean area under the curve (AUC) of the AIF and VOF were quantified for 3-, 6-, and 12-mm-thick sections. Differences in the mean (1) AUC of the VOF, (2) AUC of the AIF, and (3) width of the AIF were compared for the 3 section thicknesses, and the influence on the absolute values of CBV, CBF, and MTT were studied.

RESULTS: With thinner sections, the AUC of the VOF and the AIF increased significantly and the width of the AIF decreased slightly. Differences in AUC between the 3 section thicknesses were larger for the AIF than for the VOF.

CONCLUSION: PVEs affect not only the AIF, but also the VOF. This results in an overestimation of CBV and CBF when a thicker section is used. To avoid PVE, VOF measurements should be performed at lower section thicknesses.

CT perfusion (CTP) is an important diagnostic tool for imaging of cerebral hemodynamics. It has a predictive value for stroke outcome^{1,2} and has successfully been applied to other brain pathologies. Examples are the detection and evaluation of the severity of vasospasm in patients with a subarachnoid hemorrhage³ and the evaluation of cerebrovascular reserve capacity in patients with stenotic occlusions of the internal carotid artery.⁴ CTP yields information at not only the cerebral perfusion level, but also the level of vasodilation (via the cerebral blood volume [CBV]), the perfusion pressure (related to the reciprocal of the mean transit time [MTT], the average time taken by the blood to cross the capillary network,⁵ and the efficiency of the blood supply (via the time to peak [TTP]). Like the identification of the penumbra in stroke patients² or identification of patients developing secondary ischemia after subarachnoid hemorrhages,³ for most applications of CTP it is essential to measure the perfusion quantitatively (ie, to report absolute values).

CTP is performed by monitoring the first passage of a bolus of contrast material through brain tissue. From these measurements relative estimates of the perfusion parameters can be obtained, but quantification requires the measurement of the arterial input function (AIF). In arteries such as the anterior cerebral artery (ACA) or median cerebral artery (MCA) the shape of the AIF can be measured accurately; however, because of partial volume effects (PVEs), the area under the curve (AUC) of the AIF (AUC_{AIF}) will be underestimated. To correct for these PVEs, the AUC_{AIF} is normalized with respect to the area under the venous output function (VOF) as measured in a large vein, such as the superior sagittal sinus (SSS).

This correction assumes that the measurement of the VOF is unhampered by PVEs, both in the in-plane and through-plane directions. In clinical practice, however, relatively thick sections are chosen to obtain a sufficient signal intensity-to-noise ratio (SNR) for the evaluation of the passage of the bolus through the tissue. The use of these thick sections might thus violate the assumption that PVEs do not affect the VOF, thereby causing systematic quantification errors in the perfusion parameters and reduced reproducibility. Such errors would affect all quantitative perfusion CT methods that scale the AIF by the AUC of the VOF. The purpose of this study was to evaluate the effect of the section thickness on the measurement of the AIF and VOF and, consequently, on the absolute perfusion parameters.

Theoretical Background

All methods quantifying cerebral perfusion from CT measure temporal changes in signal intensity during the first pass of a bolus of an iodinated contrast agent. Changes in signal intensity from the baseline signal intensity (that is, before the arrival of the contrast agent) are linearly related to the concentration of the contrast agent in that voxel. The CBV is then calculated as the ratio of the AUC of the first passage through the tissue to that of the AUC of the first passage through an artery^{6,7} with a correction factor, H , to account for the difference in the hematocrit in small versus large vessels:

$$1) \quad CBV = H \frac{AUC_{TISSUE}}{AUC_{AIF}}$$

Calculation of CBV, therefore, requires knowledge of contrast enhancement in an arterial pixel devoid of PVEs. When imaging at the level of the basal ganglia, however, no arterial pixel can be found that is unaffected by PVEs. A pixel in the center of one of the great sinuses (eg, the SSS) is therefore often preferred as reference because the AUC of the first passage of contrast agent through a vein is equal to the AUC of an artery

Received February 23, 2005; accepted after revision June 5.

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when the blood-brain barrier is intact. Effectively this means that the CBV is inversely related to the AUC of the VOF:

$$2) \quad CBV = H \text{AUC}_{\text{TISSUE}}/\text{AUC}_{\text{VOF}}.$$

The MTT is calculated by means of deconvolution analysis.^{6,7} Convolution describes the tissue contrast enhancement curve (C_{TISSUE}) at time t as a function of the arterial input curve (C_{ART}), the tissue residue function $R(t)$, and the cerebral blood flow (CBF; blood volume per unit time):

$$3) \quad C_{\text{TISSUE}}(t) = C_{\text{ART}}(t) \otimes R(t) \cdot \text{CBF}.$$

Conversely, knowledge of the tissue and arterial curve allows for the inverse operation, or deconvolution, which results in $R(t)$, the “residue function.” From the residue function, the MTT can be derived.⁸ In practice, the MTT can be thought of as the difference between the width of the tissue curve and the width of the AIF.

The calculation of the CBF is based on the central volume principle,⁹⁻¹¹ which states that the CBF is equal to the ratio of CBV and MTT:

$$4) \quad \text{CBF} = \text{CBV}/\text{MTT}.$$

Consequently, the CBF is inversely related to the AUC of the VOF and directly related to the widths of the AIF and the tissue curve.

From equations (2) and (4) it can be seen that an underestimation of the AUC of the VOF as caused by PVEs would translate to an overestimation of the CBV and thus also to an overestimation of the CBF. In this perspective, a section thickness that is thin enough to guarantee an accurate measurement of the AUF_{VOF} has to be chosen. A thinner section thickness, however, would decrease the SNR, thus degrading image quality and a compromise on the optimal section thickness has to be found. Theoretically, only negligible effects due to PVEs are expected on the width of the AIF.¹²

Materials and Methods

Experimental Design

To study whether PVEs of the VOF do occur for clinically used section thicknesses, the AUCs of the VOF were determined for 3 reconstructions of, respectively, 3-, 6-, and 12-mm-thick sections in 10 patients. For each patient, the AUCs were averaged over all sections with equal section thickness to obtain mean values. Differences in the mean AUC of the VOF for the 3-, 6-, and 12-mm-thick sections were tested by means of a paired t test (SPSS, version 11, SPSS, Inc., Chicago, Ill).¹³ The difference was considered statistically significant at $P < .05$. The AUC_{AIF} and the width of the AIF were also compared for the 3 section thicknesses.

In addition, the optimal VOF and AIF within the stack of sections were selected and the AUC and width of the resulting curves were compared for the 3-, 6-, and 12-mm-thick sections; as in clinical practice, the optimal VOF and AIF curves within the set of sections are used for the perfusion analysis. The best VOFs and AIFs were defined as the voxels with the largest AUC (AIF and VOF) and an early arrival time of the contrast agent (AIF). Differences were tested by means of paired t test statistics.

Mean values of CBV, CBF, and MTT of the 10 patients were calculated for 3-, 6-, and 12-mm section thickness in regions of interest in the peripheral anterior flow territory at the level of the basal gan-

glia, containing both white and gray matter. Perfusion values were averaged over all sections with equal section thickness to obtain mean values. Regions with perfusion abnormalities were excluded from the analysis.

Patients

The CTP scans of 10 consecutive patients who underwent CTP in a single institution during a 2-week period were used for this study. Indications for scanning were screening for new aneurysms or growth of known aneurysms in 4 patients, suspicion of sinus thrombosis or dissection in 2 patients (which was not present in both patients), subarachnoid hemorrhage in 3 patients, and intracerebral hematoma in one patient. In these patients CT angiography (CTA) was indicated. To perform CTA, a timing scan is needed to measure the required scan delay. For the purpose of this and other studies, this conventional timing scan was replaced by the CTP scan, which provides perfusion images in addition to the same timing information. The performance of CTP was approved by the ethics committees of the University Hospital. Informed consent was obtained from all patients.

CTP Acquisition, Reconstruction, and Measurements

The imaging studies were performed on a 16-section spiral CT scanner (Philips Mx8000 LDT).

CTP source data were derived from sequential scans covering a 2.4-cm-thick section selected 4 cm above the sella turcica and angulated parallel to the meato-orbital line to contain the upper parts of the lateral ventricles and the basal ganglia. Forty milliliters of non-ionic contrast agent (Iopromide, Ultravist, 300 mg iodine/mL; Schering, Berlin, Germany) was injected into the cubital vein (18-gauge needle) at a rate of 5 mL/s followed by a 40-mL saline flush at a rate of 5 mL/s by using a dual power injector (Stellant Dual CT injector; Medrad Europe, Beek, the Netherlands). The following parameters were used: 90 kVp, 150 mAs, 8×3 mm collimation, 512×512 matrix, 200 mm field of view, 1-second cycle time, UB filter, and standard resolution. To limit the analysis to the first passage of the contrast agent and thus eliminate recirculation effects, it is common to fit an analytical function through the concentration curves. In this study, a gamma variate function was used to fit the AIF and VOF.

Data were transferred to a Philips workstation for postprocessing. (We used Philips prototype software that was the predecessor of the extended Brilliance Workstation Perfusion software.) CTP scans were reconstructed at, respectively, 3-, 6-, and 12-mm-thick contiguous axial images, thus leading to, respectively, 8, 4, and 2 sections. Thereafter, a motion-correction algorithm was applied to correct for patient motion, and the results were visually inspected to exclude the possibility of severe residual motion artifacts.

The AIF and the VOF were obtained semiautomatically with the user selecting vascular structures of interest and the computer algorithm choosing the optimal AIF and VOF based on the AUC and the time of arrival (only for the AIF). In each patient, the VOF was selected from the same vein for the different section thicknesses. Because the inclusion of structures with high attenuation (eg, bone) would result in a baseline increase and thus an erroneously high AUC, the baseline attenuation as calculated as the mean attenuation value before contrast agent arrival was subtracted for each voxel from the passage curves when calculating the AUC. For all patients, the AUCs of the AIF and VOF and the width of the AIF were obtained for all sections of the 3-, 6-, and 12-mm series by drawing regions of interest in the ACA and one of the major sinuses (SSS, straight sinus, sigmoid sinus). The width of the AIF was defined as the full width at half

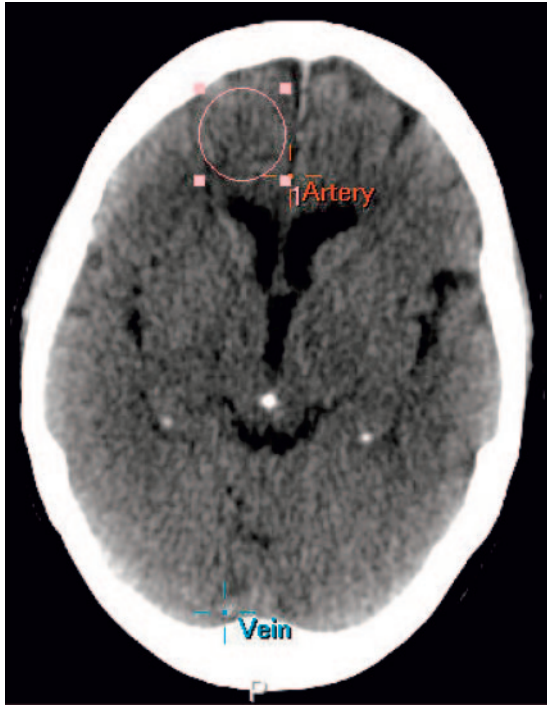


Fig 1. A circular region of interest with a standard size of 2.5 cm in diameter was drawn in the peripheral anterior flow territory at the level of the basal ganglia on a standard location containing both white and gray matter. The location of the measurement of the AIF (artery) and the VOF (vein) are also indicated.

maximum of the fitted gamma variate function. Finally, circular regions of interest with a standard size of 2.5 cm in diameter were drawn for each section, in the peripheral anterior flow territory at the level of the basal ganglia on a standard location for all patients and each section thickness (Fig 1), containing both white and gray matter. All regions of interest were placed manually by one experienced observer (I.v.d.S.). In all patients, the perfusion in this area was not affected by infarction or blood.

Results

The mean AUC of the VOF and AIF are shown in Fig 1 and Table 1, for 12-, 6-, and 3-mm section thicknesses. With a smaller section thickness, the AUC of the VOF and the AIF increased, and Fig 2 shows that for all patients a smaller section thickness resulted in an equal or larger AUC for both the AIF and VOF. This increase was statistically significant for the mean AUC of 6- versus 12-mm, 3- versus 12-mm and 3- versus 6-mm section thickness of both the VOF and AIF; however, the difference between 6 and 3 mm became borderline significant when the optimal VOF was compared (Table 1, right columns). Figure 3 shows the raw attenuation curves of the optimal VOF for 3-, 6-, and 12-mm section thickness. The differences in AUC between the 3 section thicknesses were larger for the AIF than for the VOF. With a smaller section thickness, the width of the AIF decreased slightly. This difference is statistically significant for the mean width of 3- versus 12-mm-thick sections. When the widths of the optimal AIF were compared, however, this difference was no longer significant.

Table 2 shows the mean values of perfusion parameters for different section thicknesses in the 10 patients. The mean CBV

and CBF decreased, and the mean MTT increased for smaller section thickness.

Discussion

CTP is considered a valuable method for the assessment of patients with acute stroke and has also been applied to other brain pathologies.^{11,12,14} For these clinical implications, quantitative perfusion parameters are essential. A requirement for the determination of quantitative values is that the AUC_{AIF} is unhampered by PVEs. Because this requirement is not met in most CTP experiments, the AIF is normalized with respect to the VOF, and it is assumed that the VOF is unhampered by PVEs. In a previous article on the influence of AIF and VOF properties on perfusion parameters, the determination of the AIF and VOF showed to be a source of variability in the estimation of perfusion values.¹⁵ We evaluated the influence of PVEs on the measurement of AIF and VOF and quantified the effect on absolute perfusion parameters. We observed that, for a section thickness of 6 mm or larger, PVEs affect not only the AIF, but also the VOF, leading to an overestimation of CBF and CBV.

To investigate the effect of section thickness on the AIF and VOF measurements and, consequently, on the quantitative perfusion parameters, the mean AUC of the AIF and VOF were determined for 3 reconstructions of, respectively, 3-, 6-, and 12-mm-thick sections in 10 patients. We observed in all subjects an increase in the AUC of both the AIF and VOF with decreasing section thickness. Selecting the optimal AUC_{VOF} and AUC_{AIF} , as occurs in clinical practice, yielded the same findings, except for the AUC_{VOF} of 3 versus 6 mm, which became borderline significant. Although more prominent for the AIF, these differences were also significant for the VOF. This implies that the selection of a great vein instead of an artery diminishes, but does not solve, the problem of PVEs. The perfusion slab is commonly positioned at the level of the basal ganglia. When the perfusion slab is angulated parallel to the meato-orbital line, the SSS passes diagonally through the slab in most patients.

This obviously introduces PVEs, with the extent being dependent on the individual size and anatomy of the SSS and degree of angulation of the slab; however, other factors could also explain the observed effects. When a multisection technique is used, the amount of attenuation can vary over the sections because of differences in beam hardening. This would result in an AUC of the VOF, which is consistently higher or lower for particular sections across the detector track. The influence of beam hardening is expected to be small, however, because the perfusion slab is only 2.4 cm thick and is not located near structures that are expected to cause the most severe beam hardening, such as the skull base or the protuberantia occipitalis. Another factor that could explain our findings is that the fit of the gamma variate function to the time-attenuation curve could behave differently for thinner sections because of the increased noise level in thin sections. Such differences would influence the shape and thus the AUC of the AIF and VOF. As can be seen in Fig 3, the SNR of the VOF at 3-mm-thick sections is high enough to guarantee a good fit. Therefore, it can be concluded that effects due to a low SNR in the fitting procedure are too small to explain the observed increase in the AUC of the VOF for thinner sections.

Table 1: Difference in AUC and width in 12-, 6-, and 3-mm-thick sections

	Difference (%)	P Value		Difference (%)	P Value
Mean AUC VOF			AUC of optimal VOF		
6 vs 12	+17	.017	6 vs 12	+17	.014
3 vs 12	+20	.004	3 vs 12	+20	.009
3 vs 6	+4	.006	3 vs 6	+3	.056
Mean AUC AIF			AUC of optimal AIF		
6 vs 12	+22	.000	6 vs 12	+25	.000
3 vs 12	+34	.000	3 vs 12	+39	.000
3 vs 6	+15	.004	3 vs 6	+19	.003
Mean width AIF			Width of optimal AIF		
6 vs 12	-7	.063	6 vs 12	-1	.88
3 vs 12	-8	.007	3 vs 12	-2	.42
3 vs 6	-2	.328	3 vs 6	-1	.44

Note:—AUC indicates area under the curve; VOF, venous output function; AIF, arterial input function.

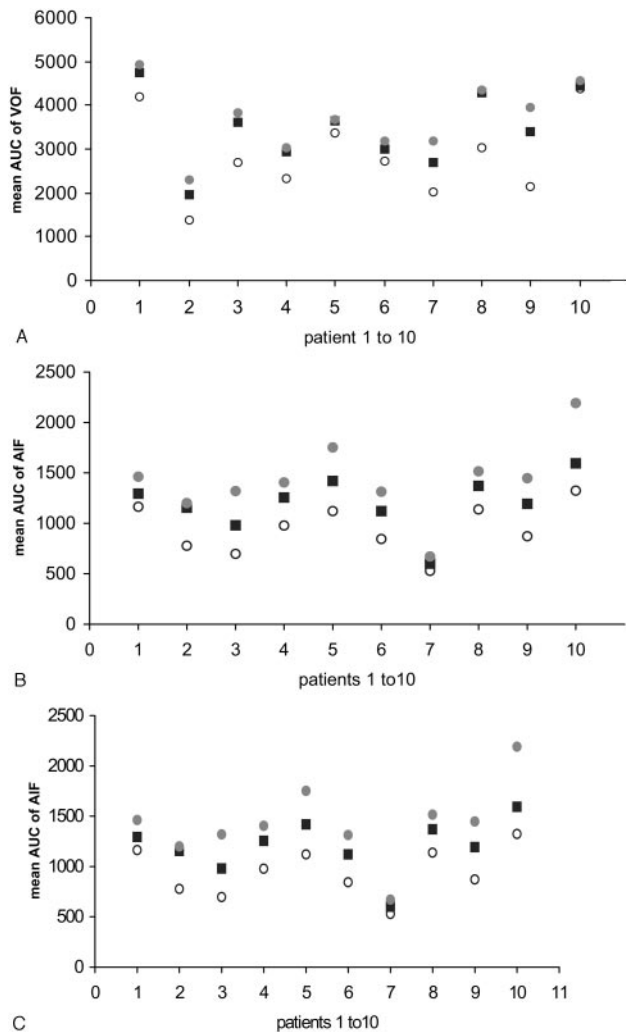


Fig 2. Mean AUC for the VOF (A), AIF (B) and mean widths of the AIF (C) for 12-mm (○), 6-mm (■), and 3-mm (●) section thickness in 10 patients. In all patients, a smaller section thickness results in an equal or larger AUC of the VOF (A) and AIF (B). The width of the AIF decreases slightly (C) with a smaller section thickness in most patients.

The section thickness had a slight effect on the width of the AIF, but selection of the optimal AIF, as occurs in clinical practice, resulted in insignificant differences in the width for the 3 section thicknesses. This means that the MTT is hardly influenced by the section thickness, because the MTT is di-

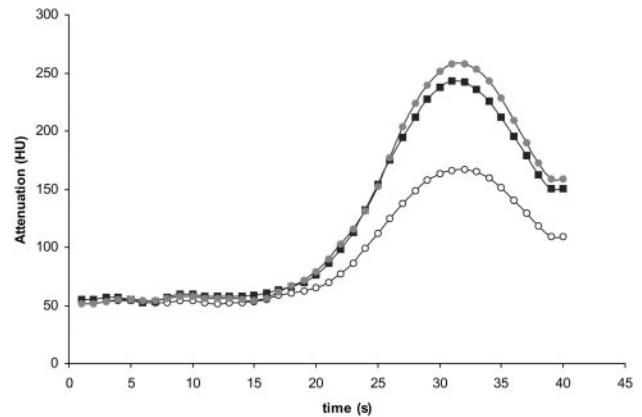


Fig 3. Raw attenuation curves of the optimal VOF for 12-mm (○), 6-mm (■), and 3-mm (●) section thickness (same patient as in Fig 1).

rectly related to the width of the AIF. In theory, a somewhat wider AIF could be explained by the incorporation of tissue in the arterial voxels because the wider tissue function combines with the AIF function; however, the gamma variate function fit, which restricts the AIF to the first pass of the bolus, would most likely eliminate these small effects. These results are in concordance with the findings of Kealey et al.¹⁵ In that article, PVEs, which were intentionally induced by a more peripheral placement of the region of interest, significantly increased CBF and CBV, whereas the MTT was not significantly changed compared with central placement of the region of interest.

Table 2: Values for CBV, MT, and CBF in 12-, 6-, and 3-mm-thick sections

Section Thickness (mm)	
CBV (mL/100 g)	
12	4.3 ± 1.53
6	3.7 ± 1.15
3	3.1 ± 0.99
CBF (mL/100 g/min)	
12	61.1 ± 15.7
6	48.6 ± 12.5
3	34.4 ± 8.07
MTT (s)	
12	4.2 ± 0.78
6	4.6 ± 0.79
3	5.1 ± 0.74

Note:—CBV indicates cerebral blood volume; CBF, cerebral blood flow; MTT, mean transit time. Values are means ± SD.

The CBV and CBF values we observed for a 3-mm section thickness are comparable with the literature. Regions of interest were placed in both gray and white matter, and the mean CBV value of 3.1 and CBF value of 34.4 are in line with a series of positron-emission tomography (PET) and single-photon emission tomography studies in which CBV values ranged between 4.6 and 2.0 for gray matter and 2.6 and 2.0 for white matter and CBF values ranged between 52.1 and 40.2 for gray matter and 20.3 and 26.0 for white matter.¹⁶⁻²⁰

It has been suggested that the substantial variability in perfusion values, related to manual region of interest placement and the definition of variables during postprocessing, could improve by use of a semiautomated system selecting the optimal time-attenuation curves.^{15,21} Despite use of a semiautomated system, as we did in this study, considerable variation in perfusion values was still observed. By using thinner sections for the VOF determination, this variability decreased, which shows that PVEs do contribute significantly to this variability.

Choosing the optimal section thickness in CTP is a trade-off between increasing PVEs with thicker sections and reducing SNR with thinner sections. The increase in noise affects both the VOF and the measurement of the bolus passage through the brain tissue; however, the effects of the increased noise on the VOF are small, as can be concluded from Fig 3. Therefore, the VOF measurements should be performed on thin sections of approximately 3 mm to minimize PVEs. When the same, small section thickness for the measurement of the bolus passage through the brain tissue is used, however, the SNR on tissue level will become too low to obtain high-quality CTP images. Therefore, the optimal approach is to obtain the AIF and VOF at a small section thickness and to perform subsequent analysis on thicker sections. Both reconstructions can be obtained from the same dataset. Because the SNR of the VOF at a small section thickness is high enough, such an approach does not need an increase in radiation dose. Eventually, the choice of the section thickness in CTP should be validated against a gold standard. This could be done by either correlating the VOF measurements to blood-sampling data or validating the entire CTP procedure against another brain perfusion imaging technique such as PET or stable xenon CT.²²

Conclusion

In conclusion, both AIF and VOF are affected by PVEs in sections of 6 mm or thicker, which results in an overestimation of the CBV and CBF. The MTT is hardly influenced by section thickness. We recommend performing VOF measurement on thin sections of approximately 3 mm and conducting subsequent analysis on thicker sections (for example, 10 mm).

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