AJNR

Reproducibility of Quantitative CT Brain Perfusion Measurements in Patients with Symptomatic Unilateral Carotid Artery Stenosis

A. Waaijer, I.C. van der Schaaf, B.K. Velthuis, M. Quist, M.J.P. van Osch, E.P.A. Vonken, M.S. van Leeuwen and M. Prokop

AJNR Am J Neuroradiol 2007, 28 (5) 927-932
http://www.ajnr.org/content/28/5/927

ORIGINAL RESEARCH

Reproducibility of Quantitative CT Brain Perfusion Measurements in Patients with Symptomatic Unilateral Carotid Artery Stenosis

A. Waaijer
I.C. van der Schaaf
B.K. Velthuis
M. Quist
M.J.P. van Osch
E.P.A. Vonken
M.S. van Leeuwen
M. Prokop

BACKGROUND AND PURPOSE: To establish intraobserver and interobserver variability for regional measurement of CT brain perfusion (CTP) and to determine whether reproducibility can be improved by calculating perfusion ratios.

MATERIALS AND METHODS: CTP images were acquired in 20 patients with unilateral symptomatic carotid artery stenosis (CAS). We manually drew regions of interest (ROIs) in the cortical flow territories of the anterior (ACA), middle (MCA), and posterior (PCA) cerebral arteries and the basal ganglia in each hemisphere; recorded cerebral blood volume (CBV), cerebral blood flow (CBF), and mean transit time (MTT); and calculated ratios of perfusion values between symptomatic and asymptomatic hemisphere. We assessed intraobserver and interobserver variability by performing a Bland-Altman analysis of the relative differences between 2 observations and calculated SDs of relative differences (SDD_{rel}) as a measure of reproducibility. We used an F test to assess significance of differences between SDD_{rel} of absolute CTP values and CTP ratios, and the Levine test to compare the 4 perfusion territories.

RESULTS: MTT was the most reproducible parameter ($SDD_{rel} \leq 10\%$). Intraobserver and interobserver variability were higher for absolute CTP values compared with CTP ratios for CBV (16%–17% versus 11%–16%) and CBF (18% versus 10%–13%) but not for MTT (5%–9%). Reproducibility was best in the MCA territory: SDD_{rel} was ≤11% for perfusion ratios of all 3 parameters.

CONCLUSION: MTT is the most reproducible CTP parameter in patients with unilateral symptomatic CAS. Measurement variability in CBV and CBF can be improved if CTP ratios instead of CTP values are used. The MCA territory shows the least measurement variability.

CT perfusion (CTP) is a widely available diagnostic tool that provides quick and minimally invasive assessment of brain perfusion.[1,2] Its main current use is to identify patients with acute stroke who may benefit from thrombolysis by discriminating penumbra (tissue with reduced perfusion but potentially salvageable) from irreversible ischemia. CTP has also been used for other kinds of cerebrovascular disease: to predict delayed ischemia in patients with subarachnoid hemorrhage,[3] to measure the reserve capacity in patients with carotid occlusive disease using acetazolamide,[4] and to evaluate the effect of endovascular treatment.[5]

Analysis of CTP can be based on visual interpretation of perfusion maps or on quantitative perfusion measurements. Visual interpretation relies on the analysis of color-coded perfusion maps, where regions with reduced perfusion can be detected by visual comparison with the surrounding tissue or the contralateral hemisphere.[6,7]

Quantitative analysis can be performed using a pixel-by-pixel analysis or by measuring average values in regions of interest (ROIs) in various anatomic perfusion territories of the brain. The pixel-based analysis is applied in acute stroke, where a threshold value has been suggested to distinguish between infarcted and potentially salvageable tissue.[8] Regional analysis using ROIs can rely on manual tracing of anatomic regions[9,10] or on placing circular ROIs.[11,12] ROIs can be mirrored to compare the affected to the nonaffected hemisphere.

Quantitative measurements are complicated by the large variability of absolute perfusion values found in normal subjects and clinical patients.[13] This variability makes the discrimination between normal and reduced perfusion difficult. Several authors have therefore suggested using relative perfusion data based on the ratio between measurements in the symptomatic and asymptomatic hemisphere.[14-16] This method takes advantage of the basic symmetry of the brain and may correct for interpatient variability of absolute perfusion values.

CTP is becoming a widely used tool for analyzing brain perfusion,[17,18] even though measurement variability (precision) is in the range of 15%–30% when ROI-based techniques are used.[12] This is due to observer-dependent postprocessing steps, which can strongly influence absolute perfusion values.[19-21] Several of these observer-dependent steps are likely to affect both hemispheres equally. The goal of our study was to examine whether variability of ROI-based measurements could be reduced when perfusion ratios between the symptomatic and asymptomatic hemispheres are used instead of absolute perfusion values. A secondary goal was to study whether the measurement variability differed between the various cerebral flow territories in patients with symptomatic unilateral carotid artery stenosis.

Received April 25, 2006; accepted after revision September 11.

From the Department of Radiology (A.W., I.C.v.d.S., B.K.V., M.J.P.v.O., E.P.A.V., M.S.v.L., M.P.), University Medical Center, Utrecht, The Netherlands; Philips Medical Systems (M.Q.), Best, The Netherlands; Department of Radiology (M.J.P.v.O.), Leiden University Medical Center, Utrecht, The Netherlands.

Address correspondence to Annet Waaijer, MD, Department of Radiology, University Medical Center Utrecht, Heidelberglaan 100, Utrecht NL-3508 GA, The Netherlands; e-mail: annetwaaijer@planet.nl/a.waaijer-2@azu.nl

Materials and Methods

Patient Group

Between September 2003 and May 2005, CTP imaging was performed in 27 patients with symptomatic carotid artery stenosis (CAS). Patients were known to have more than 50% CAS based on sonography

Table 1: Patient characteristics ($n = 20$)

Patient demographics	
Mean age ± SD	68 ± 11.1 years (range, 48–84 years)
Male:female	14:6
Presenting event	
Amaurosis fugax	2
Transient ischemic attack	9
Stroke	9
Carotid arteries	
Symptomatic side, left: right	10: 10
Mean stenosis ± SD, symptomatic side	88 ± 13 (range, 60% to 99%)
Mean stenosis ± SD, asymptomatic side	11 ± 17% (range, 0% to 50%)
Cerebral damage (noncontrast CT)	
No infarct	11
Small infarct (small branch area)*	5
Medium size infarct (major branch area)*	4

* Infarct size was classified according to Lodder et al.[36]

results and were referred to our department for endovascular treatment (carotid artery stent placement) or carotid endarterectomy (CEA) as part of the International Carotid Stent placement Study (ICSS) trial (http://www.cavatas.com). At our institution, CTP measurements were added to the ICSS protocol to study the effect of the intervention on brain perfusion. Our institutional review board approved the study, and all patients had signed informed consent.

Exclusion criteria were the presence of 1) >50% contralateral stenosis ($n = 2$), 2) motion artifacts ($n = 2$), or 3) manifest large territorial infarct ($n = 3$). Consequently, we could evaluate 20 scans from 20 patients. Patient characteristics are shown in Table 1.

CTP Scanning

The CTP scans were acquired on a 16-channel scanner (MX 8000 IDT or Brilliance-16; Philips Medical Systems, Cleveland, Ohio). The level of the scan was set at the basal ganglia, just above the level of the circle of Willis, with the scan angle parallel to the orbitomeatal line to prevent incorporation of the eye lenses. We used a collimation of 8 × 3 mm with a cycle time of 1 second and acquired 40 datasets during 40 seconds of scanning. For a compromise between patient dose and signal-to-noise ratio, a tube voltage of 90 kVp in combination with 150 mAs[22] was used. The CT dose index-volume for a single scan was 8.9 mGy, and the dose length product for the whole series of scans amounted to 854.4 mGy/cm. Using the dose calculator provided by IMPACT Website (http://www.impactscan.org), we estimated an effective dose of 1.8 mSv for the CTP examination. Reconstruction of 2 adjacent 12-mm slabs was performed by using a slightly smoothing head filter (UB) and a field of view of 160 mm. Thus, a total of 2 × 40 images were available from each examination and were processed to obtain perfusion maps of 2 adjacent slabs.

For all perfusion scans, we injected a bolus of 40 mL of contrast (Ultravist 300; Schering, Berlin, Germany) with 300 mg of iodine/mL at a flow rate of 5 mL/s followed by 40 mL of 0.9% saline using the same flow rate. Contrast material and saline chaser bolus were administered using a power injector with a dual head system (Stellant Dual CT injector; Medrad Europe BV, Beek, the Netherlands). To achieve nonenhanced baseline images, the scan was started 5 seconds after commencing the bolus injection in an antecubital vein.

Measurement of Absolute CTP Values and Relative CTP Ratios

CTP maps were calculated using CTP prototype software (Philips Medical Systems, Best, the Netherlands). The software first performs a motion correction and then uses an anisotropic, edge-preserving spatial filter to reduce image noise. The resulting spatially aligned and noise-reduced dataset is further processed to obtain CTP values for each voxel in the dataset.

CTP analysis is based on temporal changes in signal intensity during the first pass of a bolus of an iodinated contrast agent. Changes in CT numbers in a voxel over baseline (precontrast CT numbers) are linearly related to the concentration of the contrast agent in that voxel. Thus, a time concentration curve can be calculated for each voxel. The software used relies on the central volume principle to calculate perfusion values from the time concentration curve for each voxel.[23]

The first step in the evaluation process is the manual selection of the arterial input function (AIF) and venous output function (VOF). For that purpose, the user selects oval ROIs that incorporate the anterior cerebral artery (for AIF) and superior sagittal sinus (for VOF), after which the software then automatically identifies appropriate reference voxels for deriving AIF and VOF.

For each voxel, the cerebral blood volume (CBV) is calculated as the ratio of the area under the time-concentration curve (AUC) of this voxel to the AUC of the first passage through an artery. A correction factor, H, is applied to account for the difference in the hematocrit in small versus large vessels; $CBV = H \times AUC_{tissue}/AUC_{AIF}$. Therefore, an absolute measurement of the AIF is required; AIF should be measured in an arterial pixel devoid of partial volume effect. Because arterial pixels without partial volume effect are not available at this level, and because the AUC of the first passage of contrast agent through a vein is equal to the AUC of an artery when the blood-brain barrier is intact, usually the superior sagittal sinus is preferred as reference; $CBV = H \times AUC_{tissue}/AUC_{VOF}$. The mean transit time (MTT), the average time taken by the blood to cross the capillary network, is calculated by a deconvolution operation from the time concentration curve of a particular voxel and the AIF,[24] whereby the MTT is related to the difference between the width of the tissue curve and the width of the AIF. Cerebral blood flow (CBF) for each voxel is finally calculated according to the formula: CBF = CBV/MTT.[25] A threshold value of 85 HU was used for exclusion of vascular pixels.

Thereafter, free-form ROIs were drawn to outline various cerebral flow territories on each of the 2 slabs, separately for each hemisphere. The territories were selected according to the maps of Damasio,[26] assuring that the ROIs were securely within the margin of the territory that belonged to a certain artery and excluded possible watershed areas (Fig 1). We included the cortical flow territory of the anterior cerebral artery (ACA), middle cerebral artery (MCA), posterior cerebral artery (PCA), and the basal ganglia (BG), which contained both deep ACA and deep MCA territories. ROIs were chosen to include mainly gray matter and as little subcortical white matter as possible.

Given 4 territories per hemisphere and 2 slabs per patient, 16 ROIs per patient were available. The average values for CBV, CBF, and MTT within each ROI were recorded. We then calculated CTP ratios by dividing the CTP values in flow territories in the symptomatic hemisphere by the CTP values in the corresponding asymptomatic hemisphere.

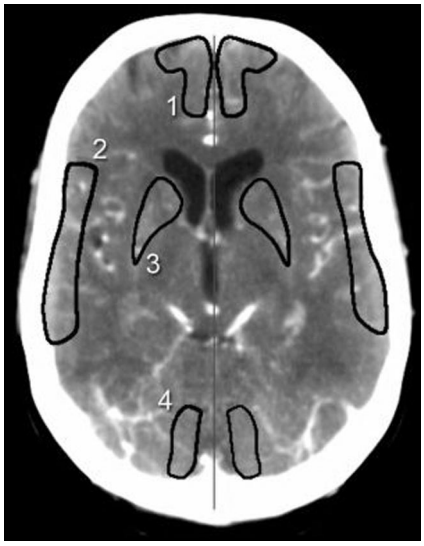

Fig 1. Analysis of manual outlined ROIs according to territorial division of Damasio.[26] *1,* ACA territory; *2,* MCA territory; *3,* basal ganglia; *4,* PCA territory.

Data Analysis

Measurements were acquired by 2 observers (A and B) and repeated after 1 week by observer A. For this purpose, all steps from loading of the 2 × 40 slabs to drawing and evaluating the ROIs in the various perfusion territories were repeated.

For assessment of intraobserver and interobserver variability, we determined the relative differences between 2 observations and calculated the mean relative differences (mean bias) and the SD of these differences (SDD_{rel}) according to the principle of Bland and Altman.[27] The relative difference indicates the difference for each pair of observations divided by the mean of the 2 observations (eg, [ΔCBV/mean CBV] × 100%) and allows for comparing absolute CTP values and CTP ratios. For determination of interobserver variability, the first of the 2 observations of observer A was used.

First, we pooled the perfusion data from all territories to calculate global numbers for intraobserver and interobserver variability. We performed an F test to compare the intraobserver and interobserver variability for absolute CTP values to that for CTP ratios. Second, we separately analyzed intraobserver and interobserver variability for each of the 4 flow territories and compared the variability for the various flow territories using the Levine test for homogeneity of variance. We also evaluated whether there was a difference in variability for absolute values between the symptomatic and asymptomatic hemispheres using a Student *t* test. A test result with a *P* value of less than .05 was considered statistically significant.

Results

Patient Characteristics

The mean and SD for the absolute CT perfusion values (CBF, CBV, and MTT) and relative CT perfusion ratios are shown in Table 2.

Intraobserver and Interobserver Variability

When evaluating the perfusion data from all territories together, analysis of intraobserver variability revealed a mean bias that varied between −1.1% and 2.2%. This range was slightly larger, between −4.4% and 2.7%, for interobserver variability. The relative SDs of the differences (SDD_{rel}) found for intraobserver and interobserver variability are given in Table 3.

Table 2: Perfusion characteristics

Territory	CBV (ml/100 g)	CBF (ml/100 g/min)	MTT (seconds)
CT perfusion values—symptomatic hemisphere			
ACA	4.1 ± 1.4	50.4 ± 18.8	5.0 ± 0.7
MCA	5.3 ± 1.4	56.1 ± 17.8	5.9 ± 1.3
Basal ganglia	4.3 ± 1.3	49.3 ± 17.6	5.5 ± 1.2
PCA	4.9 ± 1.4	50.9 ± 15.4	5.8 ± 0.7
CT perfusion values—asymptomatic hemisphere			
ACA	3.9 ± 1.3	50.9 ± 18.1	4.7 ± 0.7
MCA	5.3 ± 1.6	70.7 ± 22.3	4.5 ± 0.6
Basal ganglia	4.3 ± 1.3	57.2 ± 20.5	4.6 ± 0.9
PCA	5.0 ± 1.6	53.7 ± 16.9	5.6 ± 0.9
CT perfusion ratios (symptomatic/asymptomatic side)			
ACA	1.05 ± 0.14	1.01 ± 0.13	1.06 ± 0.10
MCA	1.01 ± 0.12	0.81 ± 0.14	1.28 ± 0.17
Basal ganglia	1.03 ± 0.09	0.88 ± 0.08	1.18 ± 0.12
PCA	1.05 ± 0.22	1.00 ± 0.17	1.06 ± 0.13

Note:—CBV indicates cerebral blood volume; CBF, cerebral blood flow; MTT, mean transit time; ACA, anterior cerebral artery; MCA, middle cerebral artery; PCA, posterior cerebral artery. Perfusion characteristics in our study group of 20 patients with symptomatic carotid artery stenosis. CT perfusion values and ratios (mean ± SD) are given for the various vascular flow territories. Note that numbers were calculated from mean values of 3 observations. For CT perfusion values, 80 data points (20 patients × 2 slabs × 2 hemispheres) were used for each territory. For CT perfusion ratios, 40 data points (20 patients × 2 slabs) were used for each territory.

Intraobserver and interobserver variability for absolute values separated for both hemispheres is shown in Table 4. Because no systematic difference was found, for further analysis, data from each hemisphere were pooled together. Intraobserver and interobserver variability was significantly lower for MTT than for CBV or CBF, independent of whether absolute CTP values or CTP ratios were considered. Intraobserver and interobserver variability for MTT values and MTT ratios were not substantially different. However, intraobserver variability for CBF and CBV ratios was significantly lower than for absolute CBF and CBV values. Interobserver variability for CBF ratios was also significantly lower than for absolute CBF values, but no significant improvement of interobserver variability could be shown if CBV ratios were used instead of absolute CBV values.

Bland-Altman plots that relate relative differences between observations to the various absolute perfusion parameters are given in Fig 2 (interobserver variability). The figures demonstrate that the relative differences were independent of the magnitude of the absolute perfusion values.

Dependence of Observer Variability on Flow Territories

Intraobserver and interobserver variability for absolute MTT values was less than 10% for all territories, and no significant differences between the different territories was seen (Table 5). Absolute perfusion values ranged from 11% to 18% for CBV and from 15% to 19% for CBF.

The introduction of ratios between CTP values in the symptomatic and asymptomatic hemisphere did not substantially change variability for MTT but mostly reduced variability for CBV and CBF. For intraobserver variability, the use of ratios improved reproducibility in all territories, but the difference between the 4 flow territories was significant for CBF only ($P < .05$). The variability was ≤8% for CBV, CBF, and MTT in the MCA and BG territory. For interobserver variabil-

Table 3: Comparison of intraobserver and interobserver variability for CT perfusion values and CT perfusion ratios

Variability	SDD_{rel} (Range of Relative Differences)		
	CBV	CBF	MTT
Intraobserver			
CT perfusion values	16% (−62%, 54%)	18% (−59%, 63%)	5% (−35%, 21%)
CT perfusion ratios	11% (−51%, 37%)	10% (−42%, 33%)	6% (−30%, 23%)
*P**	.000	.000	.048
Interobserver			
CT perfusion values	17% (−78%, 63%)	18% (−67%, 55%)	9% (−30%, 34%)
CT perfusion ratios	16% (−44%, 71%)	13% (−49%, 51%)	9% (−36%, 30%)
*P**	.135	.000	.295

Note:—SDD_{rel} indicates SDs of relative differences; CBV, cerebral blood volume; CBF, cerebral blood flow; MTT, mean transit time. Pooled data from all flow territories. Variability is expressed as the SD of the relative differences for each pair of observations (SDD_{rel}) and is thus expressed as a percentage. The range of relative differences is given in parentheses. Note that both intraobserver and interobserver variability are significantly lower for CBF ratios than for absolute CBF values, whereas for CBV, this effect was seen only in intraobserver variability. For MTT, the difference was small and significant for intraobserver variability only.
* F test.

Table 4: Comparison of intraobserver and interobserver variability for CT perfusion values separately for the symptomatic and asymptomatic hemisphere

Variability	SDD_{rel} (%)					
	Symptomatic Side			Asymptomatic Side		
	CBV	CBF	MTT	CBV	CBF	MTT
Intraobserver						
ACA	22	22	5	20	21	5
MCA	18	20	4	19	22	5
Basal ganglia	18	20	4	19	20	7*
PCA	20	22	8	20	20	4
Interobserver						
ACA	15	19	9	20*	22	8
MCA	12	17	6	14	19	8
Basal ganglia	15	15	8	21	18	9
PCA	22	16	11	14	13	6

Note:—SDD_{rel} indicates SDs of relative differences; CBV, cerebral blood volume; CBF, cerebral blood flow; MTT, mean transit time; ACA, anterior cerebral artery; MCA, middle cerebral artery; PCA, posterior cerebral artery.
* Difference between asymptomatic and symptomatic hemisphere significantly different ($P < .05$).

ity, improvement was seen in all territories except the PCA territory. The difference between the 4 territories was significant for all parameters and was best in the MCA territory ($\leq$11%).

Discussion

This study in patients with unilateral symptomatic carotid disease reveals 3 major findings: 1) the MTT is the most reproducible parameter for regional measurements of CTP, 2) the use of CBV and CBF ratios results in better reproducibility compared with absolute CBV and CBF values for this patient group, and 3) when separate flow territories are analyzed in such a patient group, the best reproducibility is observed in the MCA territory.

Our finding that MTT is the most reproducible parameter is in concordance with literature reports.[12] This may be explained by the fact that manual outlining of an ROI will inevitably introduce variability in the amount of included white matter. It is known that there is almost no difference in MTT between gray and white matter, whereas there are major differences in CBV and CBF between these 2 tissue types.[22,28,29] The fact that MTT showed less than 10% variability for both absolute and relative values indicates that absolute and relative values are robust measures for use in clinical practice. This is confirmed by a recent publication by Wintermark et al,[30] who showed that both relative and absolute MTT can be used as threshold for discrimination between final infarct size and penumbra.

Perfusion techniques such as positron-emission tomography and single-photon emission CT use CBF as the main perfusion parameter. MTT, which is defined as CBV/CBF, can be measured by using CT or MR imaging but has thus far been used as a nonspecific indicator of a perfusion disturbance. However, the inverse of this ratio (CBF/CBV) was shown to be strongly related to cerebral perfusion pressure (CPP) and has even been suggested as a surrogate for CPP, a parameter that thus far can only be measured invasively.[31] The CPP is responsible for maintenance of sufficient perfusion pressure in case of ischemia by means of the autoregulation mechanism. Although CBF is used mostly in clinical practice, the regional CBF is an insensitive indicator of the severity of occlusive cerebrovascular disease[32] because it does not change with small changes of CPP. In addition, clinical studies have shown that the ratio of CBF/CBV provides better information than either of these parameters alone.[32,33] MTT is easily obtained from CTP studies and has the lowest measurement variability. Given its close relation to CPP, it may become an important parameter for evaluating perfusion disturbances in clinical practice.

Our second result indicates that intraobserver and interobserver variability for absolute CTP values can be significantly improved when CTP ratios between measurements in the symptomatic and asymptomatic hemisphere are used in patients with unilateral stenoses. This can be explained by technical reasons. Calculation of ratios eliminates variations caused by the choice of the AIF and VOF. In addition, it may also reduce the variability in the proportion of gray and white matter that is included in the regional analysis; if the ROIs drawn in both hemispheres are symmetrically placed, the relative amounts of gray and white matter should be similar. Calculating ratios will therefore eliminate part of the resulting measurement variability.

The third result indicated least variability in the MCA territory. Placement and size of ROIs may be a factor that can help explain this finding. The ROIs in the MCA territory tended to be larger than the ROIs in the other territories. This makes it likely that there is a larger overlap between ROIs drawn at repeated measurements or by different observers, which should positively influence reproducibility. The ROIs in the ACA and PCA territories were smaller, and although the

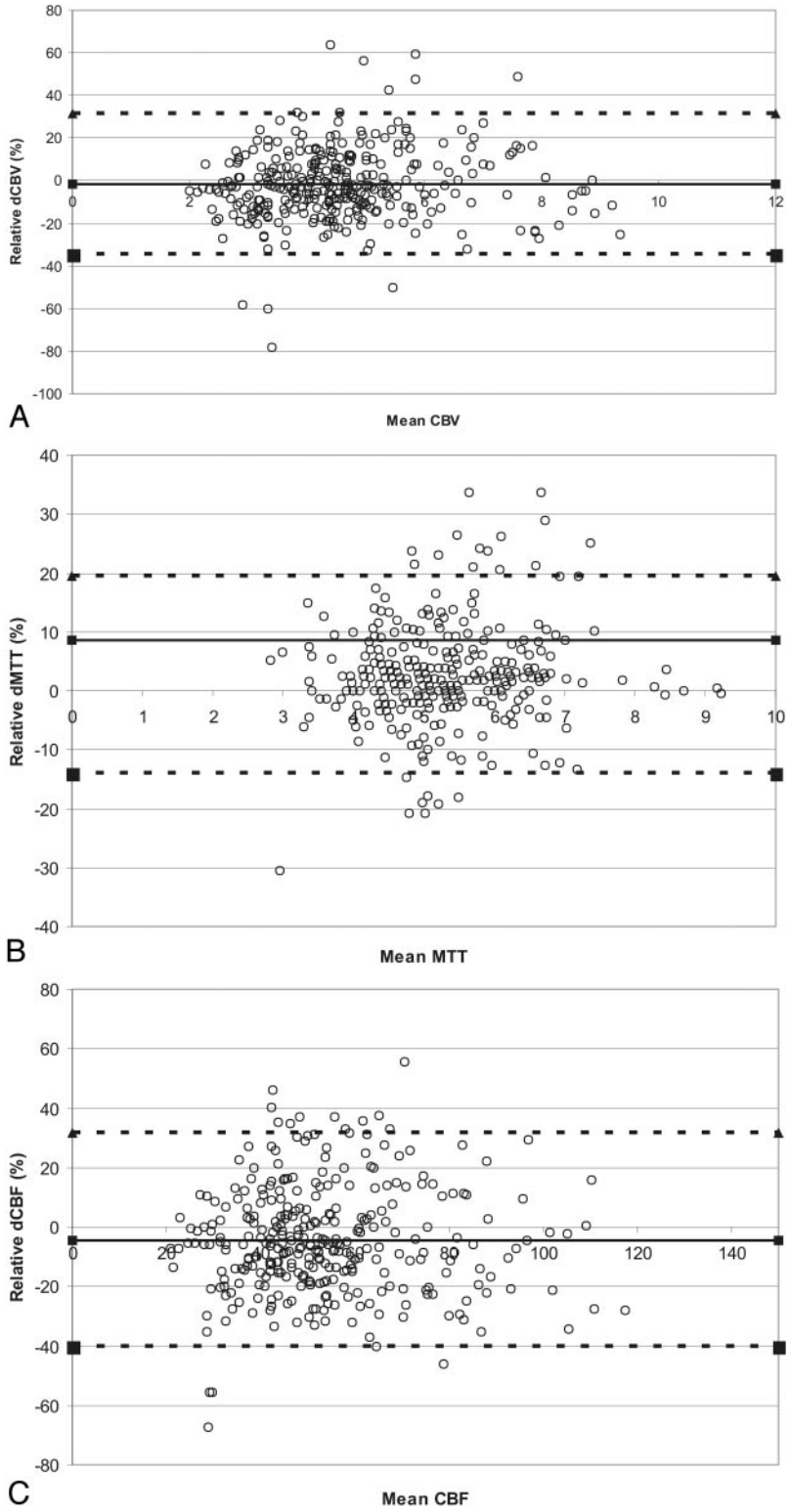

Fig 2. Bland-Altman plots of the relative differences (interobserver variability, pooled data) against the mean absolute value for CBF (milliliters per 100 g per minute) (*A*), CBV (milliliters per 100 g) (*B*), and MTT (seconds) (*C*). The relative ΔCBV, ΔCBF, and ΔMTT indicate the difference between 2 observations divided by the mean of those 2 observations, given as a percentage. The *thick line* represents the mean bias, and the *dotted lines* indicate the upper and lower limits of agreement. These upper and lower limits of agreement for the relative differences were 37% and −37% for CBV, 38% and −43% for CBF, and 21% and −16% for MTT, respectively.

medial extent of these territories is well defined by the interlobar fissure, the lateral extent is more difficult to define. This may result in variability in the amount of white matter that is included with resultant higher interobserver and intraobserver variability (Fig 1). Finally, intraparenchymal vessels such as distal ACA, MCA, and PCA branches or venous structures can lead to very high measured cerebral blood volumes when these are mistaken for parenchyma.[10] Although we set a threshold value for removing these structures, the absolute value of CBV and CBF is influenced by AIF and VOF selection, which can lead to observer dependency in the extent of the removal of vascular structures.

In summary, we found that in the most optimized situation a measurement variability of 5%–10% can be achieved. In this case, we used the relative perfusion values in the MCA territory. Normal left-right differences are known to vary ± 10%, whereas intrapatient differences for repeated measurements are in the range of 10%–20%.[13] Therefore, measurement variability between 2 observers should not be more than 10%. This implies that measurement of true perfusion abnormalities requires intrapatient comparison using relative values. In our hospital, no clinical decisions are yet based on quantitative perfusion data, but further research will have to reveal whether the use of CTP ratios could improve clinical care.

Our study has some limitations. First, the presence of a carotid artery stenosis influences the AIF and thereby the measured absolute MTT and CBF.[34] However, because we used relative differences for further analysis, the absolute height of perfusion values is no longer influencing the intraobserver and interobserver variability. A second difficulty in choice of AIF selection in the ACA is the assumption that this input function is equal over all brain voxels, which is probably not true in these patients. However, the search for a method to define the localized AIF is still problematic and is currently under study.[35] In addition, the determination of CBV carries uncertainty, because the VOF is also generalized for all voxels.[23] However, it is expected that the AUC of the VOF is unaffected by local pathology. In addition, these effects are expected to be equally distributed over voxels in both hemispheres and all territories; the use of relative data will largely eliminate these effects. Third, we have excluded patients with large territorial infarcts from further analysis. We have done so because perfusion measures are clinically more interesting for tissues with reduced perfusion and less so for manifest (chronic) infarcts. In the latter case, the abnormality is already immediately evident from noncontrast CT, and CTP has little added value.

Table 5. Comparison of intraobserver and interobserver variability (SDD_{rel}) in the four flow territories

	SDD_{rel} (%)					
Variability	CBV	CBF	MTT	CBV ratio	CBF ratio	MTT ratio
Intraobserver						
ACA	17	18	5	12	12	4
MCA	15	17	5	5	6	5
Basal ganglia	16	17	6	8	8	7
PCA	18	18	6	16	12	8
*P**	.730	.884	.210	.249	.029	.090
Interobserver						
ACA	16	19	8	15	16	8
MCA	11	15	6	11	9	6
Basal ganglia	17	15	8	13	8	8
PCA	18	15	9	23	17	10
*P**	.005	.005	.179	.000	.001	.001

Note:—SDD_{rel} indicates SDs of relative differences; CBV, cerebral blood volume; CBF, cerebral blood flow; MTT, mean transit time; ACA, anterior cerebral artery; MCA, middle cerebral artery; PCA, posterior cerebral artery. The test of Levine for homogeneity of variance was used to check whether variability differed between flow territories. The least variability was commonly seen for the MCA territory. For CTP ratios, the largest variability was usually found for the PCA territory.
* Test of Levine for homogeneity of variance

In conclusion, this study shows that when performing CTP studies, MTT is the most reproducible parameter independent of flow territory or the use of absolute values or perfusion ratios. Substantial intraobserver and interobserver variability ranging between 16% and 21% can be expected if regional measurements of absolute CBV and CBF values are performed. In clinical practice, such quantitative regional analysis of CBV and CBF values should therefore be interpreted with caution. Variability can be reduced by using the ratio between symptomatic and asymptomatic hemispheres. A variation on the order of ≤10% can be expected for CBV and CBF ratios in the MCA territory, which makes such ratios more suitable for clinical application. MTT measurements show a similar low variability, independent of flow territory or whether absolute or relative values are used.

References

1. Klotz E, Konig M. **Perfusion measurements of the brain: using dynamic CT for the quantitative assessment of cerebral ischemia in acute stroke.** *Eur J Radiol* 1999;30:170–84
2. Wintermark M, Reichhart M, Thiran JP, et al. **Prognostic accuracy of cerebral blood flow measurement by perfusion computed tomography, at the time of emergency room admission, in acute stroke patients.** *Ann Neurol* 2002;51:417–32
3. Nabavi DG, LeBlanc LM, Baxter B, et al. **Monitoring cerebral perfusion after subarachnoid hemorrhage using CT.** *Neuroradiol* 2001;43:7–16
4. Jain R, Hoeffner EG, Deveikis JP, et al. **Carotid perfusion CT with balloon occlusion and acetazolamide challenge test: feasibility.** *Radiology* 2004;231:906–13
5. Roberts HC, Dillon WP, Smith WS. **Dynamic CT perfusion to assess the effect of carotid revascularization in chronic cerebral ischemia.** *AJNR Am J Neuroradiol* 2000;21:421–25
6. Eastwood JD, Lev MH, Wintermark M, et al. **Correlation of early dynamic CT perfusion imaging with whole-brain MR diffusion and perfusion imaging in acute hemispheric stroke.** *AJNR Am J Neuroradiol* 2003;24:1869–75
7. Reichenbach JR, Rother J, Jonetz-Mentzel L, et al. **Acute stroke evaluated by time-to-peak mapping during initial and early follow-up perfusion CT studies.** *AJNR Am J Neuroradiol* 1999;20:1842–50
8. Wintermark M, Reichhart M, Cuisenaire O, et al. **Comparison of admission perfusion computed tomography and qualitative diffusion- and perfusion-weighted magnetic resonance imaging in acute stroke patients.** *Stroke* 2002;33:2025–31
9. Koenig M, Kraus M, Theek C, et al. **Quantitative assessment of the ischemic brain by means of perfusion-related parameters derived from perfusion CT.** *Stroke* 2001;32:431–37
10. Sase S, Honda M, Machida Ket al. **Comparison of cerebral blood flow between perfusion computed tomography and xenon-enhanced computed tomography for normal subjects: territorial analysis.** *J Comput Assist Tomogr* 2005;29:270–77
11. Hoeffner EG, Case I, Jain R, et al. **Cerebral perfusion CT: technique and clinical applications.** *Radiology* 2004;231:632–44
12. Fiorella D, Heiserman J, Prenger E, et al. **Assessment of the reproducibility of postprocessing dynamic CT perfusion data.** *AJNR Am J Neuroradiol* 2004;25:97–107
13. Parkes LM, Rashid W, Chard DT, et al. **Normal cerebral perfusion measurements using arterial spin labeling: reproducibility, stability, and age and gender effects.** *Magn Reson Med* 2004;51:736–43.
14. Powers WJ, Press GA, Grubb RL. Jr, et al. **The effect of hemodynamically significant carotid artery disease on the hemodynamic status of the cerebral circulation.** *Ann Intern Med* 1987;106:27–34
15. Soinne L, Helenius J, Tatlisumak T, et al. **Cerebral hemodynamics in asymptomatic and symptomatic patients with high-grade carotid stenosis undergoing carotid endarterectomy.** *Stroke* 2003;34:1655–61
16. Mayer TE, Hamann GF, Baranczyk J, et al. **Dynamic CT perfusion imaging of acute stroke.** *AJNR Am J Neuroradiol* 2000;21:1441–49
17. Furukawa M, Kashiwagi S, Matsunaga N, et al. **Evaluation of cerebral perfusion parameters measured by perfusion CT in chronic cerebral ischemia: comparison with xenon CT.** *J Comput Assist Tomogr* 2002;26:272–78
18. Wintermark M. **Simultaneous measurement of regional cerebral blood flow by perfusion CT and stable xenon CT: a validation study.** *AJNR Am J Neuroradiol* 2001;22:905–14
19. Kealey SM, Loving VA, Delong DM, et al. **User-defined vascular input function curves: influence on mean perfusion parameter values and signal-to-noise ratio.** *Radiology* 2004;231:587–93
20. Sanelli PC, Lev MH, Eastwood JD, et al. **The effect of varying user-selected input parameters on quantitative values in CT perfusion maps.** *Acad Radiol* 2004;11:1085–92
21. van der Schaaf I, Vonken EJ, Waaijer A, et al. **Influence of partial volume on venous output and arterial input function.** *AJNR Am J Neuroradiol* 2006;27:46–50
22. Wintermark M. **Using 80 kVp versus 120 kVp in perfusion CT measurement of regional cerebral blood flow.** *AJNR Am J Neuroradiol* 2000;21:1881–84
23. Wintermark M, Maeder P, Thiran J-P, et al. **Quantitative assessment of cerebral blood flows by perfusion CT studies at low injection rates.** *Eur Radiol* 2001;11:1220–30
24. Axel L. **Cerebral blood flow determination by rapid-sequence computed tomography: theoretical analysis.** *Radiology* 1980;137:679–86
25. Meier P. Zierler KL. **On the theory of the indicator-dilution method for measurement of cerebral blood flow and volume.** *J App Physiol* 1954;6:731–44
26. Damasio H. **A computed tomographic guide to the identification of cerebral vascular territories.** *Arch Neurol* 1983;40:138–42
27. Bland JM, Altman DG. **Statistical methods for assessing agreement between two methods of clinical measurement.** *Lancet* 1986;1:307–10
28. Nabavi DG, Cenic A, Dool J, et al. **Quantitative assessment of cerebral hemodynamics using CT: stability, accuracy, and precision studies in dogs.** *J Comput Assist Tomogr* 1999;23:506–15
29. Kluytmans M, van der Grond J, Viergever MA. **Gray matter and white matter perfusion imaging in patients with severe carotid artery lesions.** *Radiology* 1998;209:675–82
30. Wintermark M, Flanders AE, Velthuis B, et al. **Perfusion-CT assessment of infarct core and penumbra: receiver operating characteristic curve analysis in 130 patients suspected of acute hemispheric stroke.** *Stroke* 2006;37:979–85
31. Schumann P, Touzani O, Young AR, et al. **Evaluation of the ratio of cerebral blood flow to cerebral blood volume as an index of local cerebral perfusion pressure.** *Brain* 1998;121:1369–79
32. Powers WJ. **Cerebral hemodynamics in ischemic cerebrovascular disease.** *Ann Neurol* 1991;29:231–40
33. Gibbs JM, Wise RJ, Leenders KL, et al. **Evaluation of cerebral perfusion reserve in patients with carotid-artery occlusion.** *Lancet* 1984;1:310–14
34. Yamada K, Wu O, Gonzalez RG, et al. **Magnetic resonance perfusion-weighted imaging of acute cerebral infarction: effect of the calculation methods and underlying vasculopathy.** *Stroke* 2002;33:87–94
35. Calamante F, Morup M, Hansen LK. **Defining a local arterial input function for perfusion MRI using independent component analysis.** *Magn Reson Med* 2004;52:789–97
36. Lodder J, Hupperts R, Boreas A, et al. **The size of territorial brain infarction on CT relates to the degree of internal carotid artery obstruction.** *J Neurol* 1996; 243:345–49