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Background and Purpose—Different definitions have been proposed to define the ischemic penumbra from perfusion-CT (PCT) data, based on parameters and thresholds tested only in small pilot studies. The purpose of this study was to perform a systematic evaluation of all PCT parameters (cerebral blood flow, volume [CBV], mean transit time [MTT], time-to-peak) in a large series of acute stroke patients, to determine which (combination of) parameters most accurately predicts infarct and penumbra.

Methods—One hundred and thirty patients with symptoms suggesting hemispheric stroke ≤12 hours from onset were enrolled in a prospective multicenter trial. They all underwent admission PCT and follow-up diffusion-weighted imaging/fluid-attenuated inversion recovery (DWI/FLAIR); 25 patients also underwent admission DWI/FLAIR. PCT maps were assessed for absolute and relative reduced CBV, reduced cerebral blood flow, increased MTT, and increased time-to-peak. Receiver-operating characteristic curve analysis was performed to determine the most accurate PCT parameter, and the optimal threshold for each parameter, using DWI/FLAIR as the gold standard.

Results—The PCT parameter that most accurately describes the tissue at risk of infarction in case of persistent arterial occlusion is the relative MTT (area under the curve=0.962), with an optimal threshold of 145%. The PCT parameter that most accurately describes the infarct core on admission is the absolute CBV (area under the curve=0.927), with an optimal threshold at 2.0 ml×100 g^{-1}.

Conclusion—In a large series of 130 patients, the optimal approach to define the infarct and the penumbra is a combined approach using 2 PCT parameters: relative MTT and absolute CBV, with dedicated thresholds. (*Stroke.* 2006;37:979-985.)

Key Words: computed tomography ■ perfusion ■ ROC analysis ■ stroke

Rescuing the ischemic penumbra is the central premise of acute stroke thrombolysis.[1,2] Although the reanalysis of the National Institute of Neurological Disorders and Stroke (NINDS) trial data removed any suspicion regarding the effectiveness of recombinant tissue plasminogen activator within 3 hours,[3,4] data suggests that thrombolytic therapy can be safely administered beyond 3 hours.[5] Improved precision in identifying the ischemic penumbra is a mandatory requirement for extending the time window for thrombolysis and has become the holy grail of acute stroke imaging.

Recently, perfusion-CT (PCT) was reported to be one of the imaging techniques readily available in the emergency room to assess acute stroke patients for the presence and extent of an ischemic penumbra.[6] Assessment of both the penumbra and the infarct core is afforded by a slice-selective dynamic PCT technique that involves the acquisition of sequential CT data from a few locations during an intravenous bolus injection of iodinated contrast material.[7]

Different definitions have been proposed to define the ischemic penumbra from dynamic PCT data, based either on absolute cerebral blood flow (CBF) thresholds[8,9] or on the concept of cerebral vascular autoregulation with combined CBF and CBV thresholds.[10-16] These definitions were tested successfully in small pilot studies.[8-16] These studies, how-

ever, have 2 weaknesses: (1) they involved only a limited number of patients (12 to 22 patients),[8–16] and (2) they relied on parameters (CBF and CBV) and absolute or relative thresholds that were arbitrarily selected.[17]

In the present study, we performed a systematic evaluation of all the PCT parameters (CBF, CBV, mean transit time [MTT], time-to-peak [TTP]) derived from data acquired by dynamic PCT–technique evaluation in a large series of acute stroke patients. MRI was used as an end point for final stroke size. The ultimate goal was to determine what parameter or which combination of parameters would be the most accurate predictor of infarct and penumbra.

Materials and Methods

Design
A prospective international multicenter trial was designed to enroll 130 adult patients with suspected acute stroke. This study protocol was approved by the review boards among the different institutions involved in the trial, and institutional informed consent guidelines were observed.

Adult patients with no prior history of stroke were enrolled if they presented to the emergency room with symptoms suggesting hemispheric stroke, lasting 12 hours or less. Exclusion criteria included: (1) history of prior stroke, (2) intracranial hemorrhage on the admission noncontrast CT of the brain, (3) standard contraindications to iodinated contrast material, and (4) standard contraindications to MRI.

The imaging protocol of the study included a mandatory admission CT examination, an optional admission MRI examination, and a mandatory follow-up MRI examination. The admission CT examination included a noncontrast CT of the brain, followed by 4 level PCT, cervical and intracranial CT angiography (CTA), and finally by a postcontrast CT of the brain. The optional admission MRI examination included an axial fluid-attenuated inversion recovery (FLAIR) sequence, an axial diffusion-weighted imaging (DWI) sequence, and a time-of-flight MR angiogram (MRA). The mandatory follow-up MRI examination included an axial FLAIR sequence, an axial DWI sequence, and a time-of-flight MRA.

The time intervals from the symptom onset to the admission in the emergency room and to the imaging examinations were recorded.

Imaging Protocol
The PCT examination consisted of a 40 to 50-second series with 40 to 50 gantry rotations performed in cine mode during dynamic administration of intravenous iodinated contrast material. Images were acquired and reconstructed at a temporal sampling rate of 1 image per second, resulting in a series of 40 to 50 images for each assessed slice. Two successive PCT acquisitions were performed providing perfusion data for 2 separate axial locations with each acquisition, resulting in a total of 4 slice locations. The 2 PCT series were separated by a time interval of 4 to 5 minutes from each other. The 2 slices of the first PCT series were selected at the level of the third ventricle and the basal ganglia, and positioned above the orbits in order to protect the lenses. The second PCT series was selected at a level 3.5 cm rostral to the first slice of the first series. For each series, a 40-ml bolus of nonionic iodinated contrast material was administered into an antecubital vein using a power injector at an injection rate of 4 to 5 ml per second for all patients. The acquisition parameters were 80 to 90 kVp and 100 to 120 mAs. CT scanning was initiated 6 to 7 seconds after start of the injection of the contrast bolus.

PCT Raw Data Post-Processing
PCT data were analyzed using a research version of a PCT software developed by Philips Medical Systems. This software relies on the central volume principle, which is the most accurate for low injection rates of iodinated contrast material.[7] It applies a closed-form (non-iterative) deconvolution to calculate the MTT map.[18] The deconvolution operation requires a reference arterial input function, selected by the PCT software in a region of interest drawn by the user most often around the anterior cerebral artery. The CBV map is calculated from the area under the time-enhancement curves.[19] A simple equation combining CBV and MTT values allows the calculation of CBF ($CBF=CBV/MTT$).[18] Finally, the TTP maps were calculated, indicating the time interval until peak enhancement in each pixel.

Data Analysis: MRI Data
Based on the admission CTA and follow-up MRA findings, and on the optional admission MRI, patients were distributed into 4 groups. Group A included all patients whose admission CTA demonstrated a large artery occlusion, and follow-up MRA persistence of this large artery occlusion. Group B included all patients whose admission CTA demonstrated a large artery occlusion, and follow-up MRA a recanalization of this artery. Group C included all patients whose admission CTA did not demonstrate a large artery occlusion yet had symptoms of a stroke (the conditions diagnosed in Group C patients are described in the Results section). For Groups A, B and C, the reference MRI sequence was the FLAIR sequence from the follow-up MRI, reviewed in conjunction with DWI images also from the follow-up MRI.

In addition to being considered for comparison of their admission PCT with their follow-up MRI, patients from Groups A, B and C who underwent the optional admission MRI were also considered together in a Group D for comparison of their admission PCT with their admission MRI. For Group D, the reference MRI sequence was the DWI trace from the admission MRI.

The MR reference images underwent data interpolation in order to match the matrix size of PCT images. The MRI reference images were translated and rotated to obtain the same spatial position and axis orientation as the PCT maps (CBF, CBV, MTT, TTP). The PCT maps and MR images were coregistered using the centroidal principal axes method.[20] The incoherent MR images resulting from different slice thicknesses of PCT and MR images were replaced with MR slices reconstructed by averaging and interpolating MR slices so as to correspond to that of the thickness (10 mm) and location of the PCT slices.[21]

For Groups A, B and C, the reconstructed reference FLAIR images were reviewed in conjunction with DWI images by a neuroradiologist, who manually traced the final infarct volume corresponding to the acute event (the DWI images were used primarily to identify the acute events and exclude chronic ischemia). The pixels belonging to the final infarct volume were considered as "positive", and the remaining pixels of the brain parenchyma as "negative". Similarly, for Group D, the reconstructed reference DWI images were reviewed by the same neuroradiologist, who manually traced the volume of the acute DWI abnormality. The pixels belonging to the acute DWI abnormaility were considered as "positive", and the remaining pixels of the brain parenchyma as "negative".

Receiver Operating Characteristic Curve Analysis
For each patient, the MTT maps underwent a spatial filtering. Pixels with absolute MTT values which exceeded a threshold of 4 seconds ("selected pixels") were automatically segmented by a computer algorithm. Pixel-by-pixel comparison with the reference MR images (as described in the above paragraph for the different groups of patients) was used to determine whether the selected pixels (with an absolute MTT value >4 seconds) were "true positive" (TP) or "false-positive" (FP). The remaining pixels (with an absolute MTT value inferior to 4 seconds) were evaluated to be either "true negative" (TN) or "false-negative" (FN) by comparison with the reference images. Based on the number of TP, FP, TN and FN pixels among the total number of evaluated pixels, sensitivity (TP/TP+FN) and specificity (TN/TN+FP) to predict the volume delineated on the reference images were calculated for the absolute MTT threshold of 4 seconds.

Pixel-by-pixel comparison was repeated for absolute MTT thresholds increasing from 4 seconds to 14 seconds by increment of 1

TABLE 1.   Range and Increment Used to Calculate the ROC Curves of PCT Parameters Based on Pixel-by-Pixel Comparison With the References MRI Images

PCT Parameter	Range	Increment
MTT		
Absolute	4 to 14 s	1 s
Relative	100% to 250%*	15%*
TTP		
Absolute	2 to 12 s	1 s
Relative	100% to 350%*	25%*
CBF		
Absolute	5 to 49 ml$\times$100 g$^{-1}\times$min^{-1}	4 ml$\times$100 g$^{-1}\times$min^{-1}
Relative	40% to 90%*	5%*
CBV		
Absolute	0.5 to 3.5 ml$\times$100 g^{-1}	0.3 ml$\times$100 g^{-1}
Relative	40% to 90%*	5%*

These ranges were selected to encompass normal values, abnormal thresholds reported in the literature and abnormal values way beyond these thresholds.

*Percentage of the contralateral normal hemisphere.

second. Sensitivity and specificity were calculated for the different absolute MTT thresholds. The receiver operating characteristic (ROC) curve for absolute MTT, featuring 1-specificity on the X-axis and sensitivity on the Y-axis for the different thresholds, was calculated. The area under the ROC curve (AUC), and the first derivate of the ROC curve, corresponding to the best absolute MTT threshold, were determined.

According to a similar approach, ROC analysis was performed for relative MTT (values in the pathological hemisphere expressed as a percentage of the values measured in the contralateral normal hemisphere), absolute TTP, relative TTP, absolute CBF, relative CBF, absolute CBV, and relative CBV. The range and the increment used to evaluate each of these parameters were selected to encompass normal values, abnormal thresholds reported in the literature, and abnormal values way beyond these thresholds. They are summarized in Table 1.

ROC analysis was performed for each group (considering all pixels in all patients of the group) and separately for each patient (considering all pixels in each patient).

For Group B patients (showing recanalization), the optimal MTT thresholds calculated in each patient were plotted with respect to the final infarct volume as measured on the follow-up FLAIR images.

Results

Patients

One hundred and thirty patients suspected of acute hemispheric stroke were enrolled in the study (76 males and 54 females, median age: 63, age range: 24 to 85). The average National Institute of Health Stroke Scale (NIHSS) score on admission was 15.3 (range: 2 to 26).

All patients underwent an admission CT survey, including a noncontrast cerebral CT, 2 successive series of PCT, a cervical and head CTA, and a postcontrast CT of the brain. The admission CT survey was obtained between 15 minutes and 12 hours after symptom onset (median: 4 hours).

Twenty-five patients also received an optional MRI examination on admission, including FLAIR, DWI and MRA. The admission MRI examination was obtained between 30 minutes and 12 hours after symptom onset (median: 4.5 hours). The median time between the admission CT survey and the admission MRI examination was 25 minutes.

Forty-seven patients were treated for acute stroke (40 with recombinant tissue plasminogen activator and 7 with desmoteplase). Acute stroke treatment was performed between 20 minutes and 7 hours after symptom onset (median: 3.1 hours).

After a delay ranging from 2 to 7 days (median: 3.5 days), all patients underwent a follow-up MRI examination, including FLAIR, DWI and MRA.

The distribution of patients between Groups A, B, C and D is detailed in Table 2. Patients from Group D overlap with Groups A, B and C. The rationale for this overlap is that, in addition to being considered for comparison of their admission PCT with their follow-up MRI, patients from Groups A, B and C who underwent the optional admission MRI were also considered together in a Group D for comparison of their admission PCT with their admission MRI.

Group A: Patients With Persistent Large Arterial Occlusion on the Follow-Up MRA

Admission CTA in Group A patients demonstrated a large artery occlusion, and follow-up MRA persistence of this large artery occlusion. The results of the ROC analysis for all the pixels in all the patients of Group A, using the follow-up

TABLE 2.   Distribution of the Patients Enrolled in the Study in the 3 Study Groups

			Group D (Figure 2) 25 Patients With Admission DWI
130 patients enrolled in the study	Group A (Figure 1)	46 patients with persistent large artery occlusion on the follow-up MRA, for whom comparison of admission PCT with follow-up MRI as part of Group A analysis	Including 9 patients with admission DWI, for whom also comparison of admission PCT with admission DWI as part of Group D analysis
	Group B (Figure 3)	49 patients with recanalization of a large artery occlusion on the follow-up MRA, for whom comparison of admission PCT with follow-up MRI as part of Group B analysis	Including 10 patients with admission DWI, for whom also comparison of admission PCT with admission DWI as part of Group D analysis
	Group C	35 patients with no evidence of large artery occlusion on the admission CTA, from whom comparison of admission PCT with follow-up MRI as part of Group C analysis	Including 6 patients with admission DWI, for whom also comparison of admission PCT with admission DWI as part of Group D analysis

Group D overlap with Groups A, B and C. The rationale for this overlap is that, in addition to being considered for comparison of their admission PCT with their follow-up MRI, patients from Groups A, B and C who underwent the optional admission MRI were also considered together in a Group D for comparison of their admission PCT with their admission MRI.
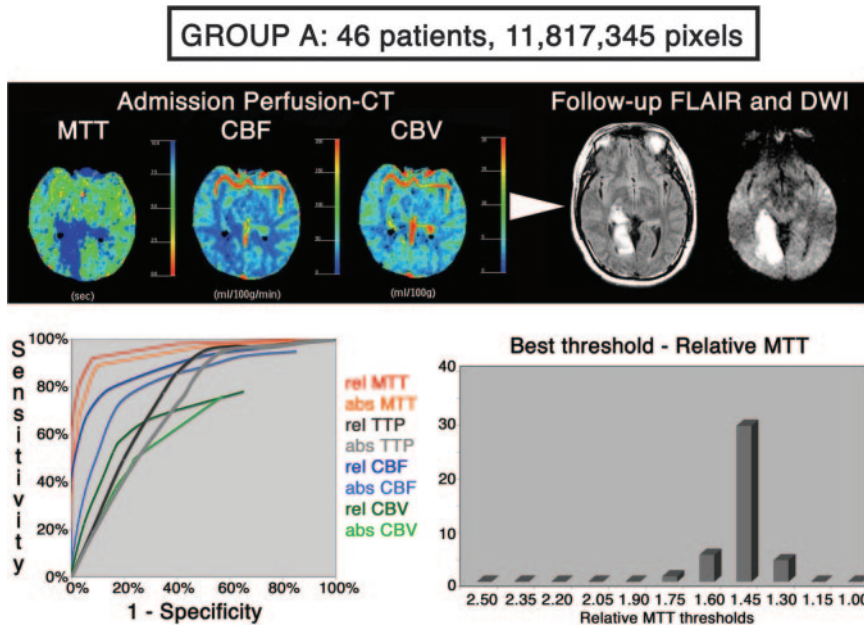
Figure 1. ROC curve analysis in the 46 patients of Group A, showing persistent arterial occlusion on the follow-up MRA (total of 11 817 345 pixels). The PCT parameter most accurately predicting the tissue at risk of infarction on the follow-up MRI study (FLAIR and DWI used as references) is the relative MTT (AUC=0.962). The optimal threshold for relative MTT is 145%. The histogram (inferior right) of the best thresholds obtained by the ROC analysis performed separately for each patient (considering all pixels in each patient) reveals a narrow distribution around the value of 145% obtained with the global analysis (inferior left).

FLAIR/DWI as a gold standard, are displayed in the left lower corner of Figure 1. The PCT parameter with the maximal AUC, representing the most accurate PCT parameter to predict the tissue at risk of infarction in case of persistent arterial occlusion, was the relative MTT (AUC=0.962). The optimal threshold for relative MTT was 145%. The second most accurate PCT parameter was the absolute MTT with a threshold at 7 seconds.

The histogram (right lower corner of Figure 1) of the best thresholds obtained by the ROC analysis performed separately for each patient revealed a narrow distribution around the value of 145% obtained from the global analysis.

Group D: Patients With Admission DWI

Admission DWI was obtained in Group D patients. The results of the ROC analysis for all the pixels in all the patients of Group D, using the admission DWI as a gold standard, are displayed in the left lower corner of Figure 2. The PCT parameter with the maximal AUC, representing the most accurate PCT parameter to predict the acute infarct core, was the absolute CBV (AUC=0.927). The optimal threshold for absolute CBV was 2.0 ml$\times$100 g^{-1}. The second most accurate PCT parameter was the relative CBV with a threshold at 60%.

The histogram (right lower corner of Figure 2) of the best thresholds obtained by the ROC analysis performed separately for each patient revealed a narrow distribution around the value of 2.0 ml$\times$100 g^{-1} obtained from the global analysis.

Group B: Patients With Recanalization of a Large Artery Occlusion on the Follow-Up MRA

Admission CTA in Group B patients demonstrated a large artery occlusion, and follow-up MRA recanalization of this
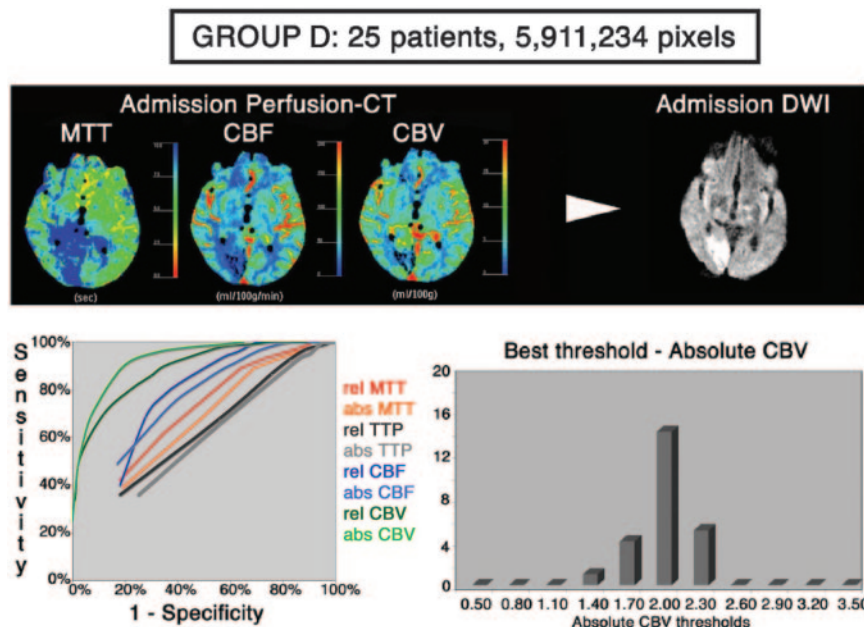

Figure 2. ROC analysis in the 25 patients of Group D, who underwent admission DWI (total of 5 911 234 pixels). The PCT parameter most accurately predicting the acute infarct volume on the admission DWI study is the absolute CBV (AUC=0.927). The optimal threshold for absolute CBV is 2.0 ml$\times$100 g^{-1}. The histogram (inferior right) of the best thresholds obtained by the ROC analysis performed separately for each patient (considering all pixels in each patient) reveals a narrow distribution around the value of 2.0 ml$\times$100 g^{-1} obtained with the global analysis (inferior left).
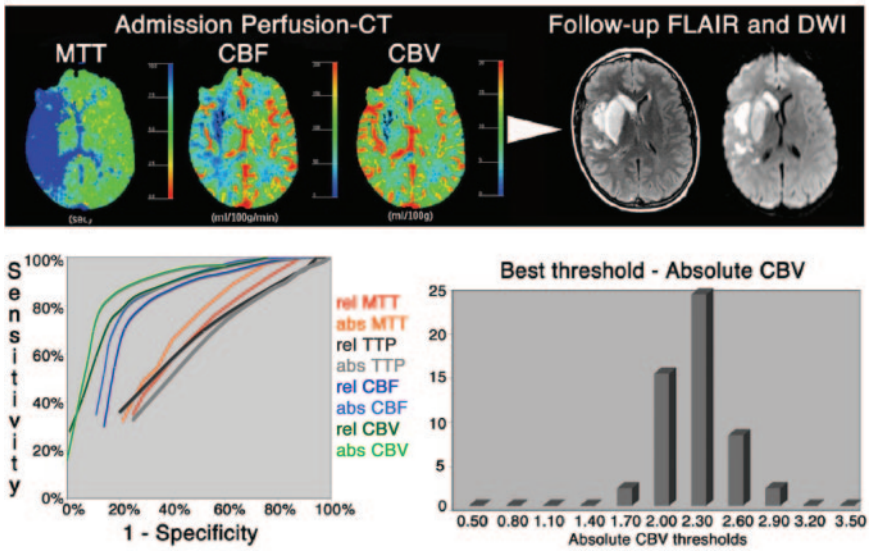
Figure 3. ROC analysis in the 49 patients of Group B, showing recanalization of a large artery occlusion on the follow-up MRA (total of 11 896 876 pixels). The PCT parameter most accurately predicting the infarct volume on the follow-up MRI study (FLAIR and DWI used as references) is the absolute CBV (AUC=0.893). The optimal threshold for absolute CBV is 2.3 ml×100 g^{-1}. The histogram (inferior right) of the best thresholds obtained by the ROC analysis performed separately for each patient (considering all pixels in each patient) reveals a relatively broad distribution around the value of 2.3 ml×100 g^{-1} obtained with the global analysis (inferior left).

large artery occlusion. The results of the ROC analysis for all the pixels in all the patients of Group B, using the follow-up FLAIR/DWI as a gold standard, are displayed in the left lower corner of Figure 3. The PCT parameter with the maximal AUC, representing the most accurate PCT parameter to predict the infarct core in case of arterial recanalization was the absolute CBV (AUC=0.893). The optimal threshold for absolute CBV was 2.3 ml×100 g^{-1}. The second most accurate PCT parameter was the relative CBV with a threshold at 65%.

The histogram (right lower corner of Figure 3) of the best thresholds obtained by the ROC analysis performed separately for each patient revealed a relatively broad distribution around the value of 2.3 ml×100 g^{-1} obtained from the global analysis.

Figure 4 displays the optimal thresholds obtained by ROC analysis performed separately for each patient of Group B, distributed with respect to the final infarct volume, as

measured on the follow-up MRI study. It appears from this figure that, in patients with a relatively small final infarct volume (20 ml), the optimal threshold for predicting the final infarct was an absolute CBV value of 2.0 ml×100 g^{-1}. For patients with an intermediate (50 ml) or relatively large final (80 ml) infarct volume, the optimal threshold for predicting the final infarct was an absolute CBV value of 2.3 ml×100 g^{-1}.

Group C: Patients With No Large Artery Occlusion on the Admission CTA

Group C included a variety of patients with different conditions. They shared the absence of evidence of large artery occlusion on the admission CTA. Among the 35 patients of group C, 8 patients received a final diagnosis of migraine, 6 patients with Todd paralysis, 2 patients with hypoglycemia, 7 patients with transient ischemic attacks (TIA; negative follow-up DWI and FLAIR), and 12 patients with acute ischemic stroke (positive follow-up DWI and FLAIR). In the
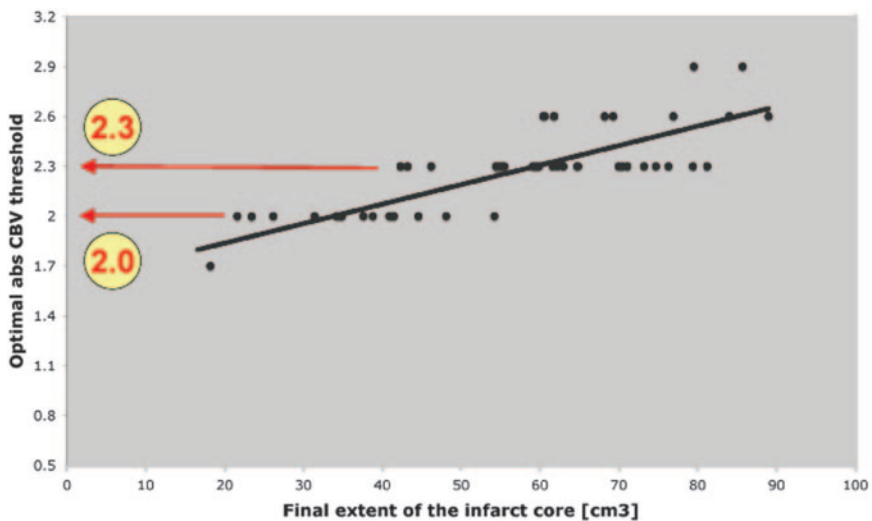

Figure 4. Distribution of the optimal thresholds obtained by ROC curve analysis performed separately for each patient of Group B with recanalization, distributed with respect to the final infarct volume, as measured on the follow-up MRI study (FLAIR and DWI used as references). In patients with a relatively small final infarct volume (20 ml), the optimal threshold for predicting the final infarct was an absolute CBV value of 2.0 ml×100 g^{-1}. On the contrary, in patients with an intermediate (50 ml) or relatively large (80 ml) final infarct volume, the optimal threshold for predicting the final infarct was an absolute CBV value of 2.3 ml×100 g^{-1}, or even higher.

12 patients with positive follow-up DWI and FLAIR, admission CTA and follow-up MRA were negative. Nine of the 12 patients had lacunes on the follow-up MRI, and the remaining 3 had a final infarct in a borderzone distribution.

In the 7 patients with TIA, an area characterized by increased MTT, increased CBV and preserved CBF were observed. The MTT increase was in all cases <145% compared with the contralateral normal side. In the 9 patients with lacunar infarctions, PCT examinations were negative. In 2 of the 3 patients with watershed infarcts, PCT examinations were negative, because the final infarcted regions were not incorporated in the limited coverage of the PCT. In 1 patient with a borderzone territory infarct the ischemic regions were more extensive, and prolonged MTT, decreased CBF, and preserved CBV were observed on PCT in the ischemic regions.

Discussion

The goal of this study was to perform a systematic review of all PCT parameters, considered both in an absolute and relative fashion, to identify the best predictors of infarct and penumbra in a large series of 130 patients suspected of acute stroke.

Our analysis shows that the optimal method to define both the infarct core and the penumbra is a combined approach using 2 distinct PCT parameters. According to our ROC analysis, this method is preferable to the use of successive absolute CBF values to define the penumbra and infarct core.[8,9] The combined approach using 2 distinct PCT parameters was suggested by prior pilot studies using a vascular-based definition of the penumbra, derived from the concept of cerebral vascular autoregulation. In the ischemic penumbra, brain perfusion is altered, but autoregulation is preserved; vasodilatation and recruitment of collaterals lead to increased CBV. Within the infarct core, autoregulation is lost, and CBV is decreased.[10–12] In these pilot studies, the tested combination of PCT parameters that had been arbitrarily selected was CBF and CBV, whereas our systematic ROC analysis in this study revealed that the optimal combination of PCT parameters is relative MTT and absolute CBV. MTT is a more reliable parameter than CBF because MTT values of normal gray and white matter are not significantly different ($\approx$5 to 6 seconds) as they are for CBF (average CBF value: 70 ml$\times$100 g$^{-1}\times$min^{-1} in gray matter, 20 ml$\times$100 g$^{-1}\times$min^{-1} in white matter). Differences in gray and white matter CBF values, and their respective ischemic thresholds (with ischemic gray matter CBF values being close from normal white matter CBF values), interfere with the use of CBF thresholds to define the penumbra. However, CBF is more specific than MTT for stroke[10] because MTT values can be prolonged in TIA as well as stroke. This explains why the MTT increase must be significant (>145%) in order to reliably identify the tissue at risk or penumbra in stroke patients.

In patients with persistent arterial occlusion (Group A), the tissue at risk on the admission PCT eventually evolves to infarction on the follow-up MRI study because of the absence of recanalization and insufficient collateral flow. Relative MTT, with an optimal threshold of 145%, provided the most accurate prediction of the final infarct size on the follow-up

MRI study and offered the most accurate delineation of the brain tissue at risk of dying in the absence of recanalization (ie, ischemic penumbra). In the circumstance where the contralateral (control) hemisphere has a pre-existing stroke (or another abnormality), an absolute MTT threshold of 7 seconds can be used to predict final infarct size.

Our ROC analysis shows that MTT is a more accurate parameter to identify the penumbra compared with TTP. The primary difference between MTT and TTP is that, as opposed to MTT, TTP values are calculated without this deconvolution operation that normalizes the parenchymal time-enhancement curves with respect to the arterial input curve. As a result, MTT is a tissue-specific parameter, whereas TTP values vary considerably depending on extracerebral factors, such as cardiac function, aortic and aortic arch branch vessel stenosis and occlusion, or even the quality of the injection of the intravenous contrast material. Consequently, post-processing algorithms affording only TTP measurements, such as those using the maximal slope model, are suboptimal,[13–16] and algorithms based on the central volume principle and using the mathematical operation called deconvolution to calculate tissue-specific MTT values[7] are to be preferred.

Assuming the generally accepted theory that the acute DWI abnormality is a reasonably accurate predictor of the acute infarct core,[22] the absolute CBV, with an optimal threshold at 2.0 ml$\times$100 g^{-1}, provides the most accurate prediction of the acute infarct on the acute DWI study (obtained in patients from Group D).

The interpretation of the data collected in patients showing recanalization of a large vessel occlusion (Group B) is more challenging because this group is more heterogenous, as illustrated by a relatively broad distribution of the best thresholds obtained by ROC analysis performed separately for each patient in this group. This may be related to the fact that the exact timing of the recanalization is unknown. Recanalization can theoretically occur immediately after the admission PCT; in this case, the whole penumbra demonstrated on the admission PCT has the potential to be salvaged, and the admission PCT infarct core should correspond to the final infarct on the follow-up MRI study. Alternatively, recanalization could occur several minutes or hours after the admission PCT. Delayed recanalization leads to a larger penumbra progressing to infarction and potentially sets the stage for a more extensive final infarct on the follow-up MRI study, despite some degree of late tissue salvage by the recanalization. A more extensive final infarct leads in turn to higher optimal CBV thresholds, verifying the observation on the distribution of the optimal thresholds obtained by ROC analysis performed separately for each patient of Group B (Figure 4). Delayed recanalization could explain why a higher CBV threshold (2.3 ml$\times$100 g^{-1}) was found in the patients showing recanalization of a large vessel occlusion (Group B) compared with patients from Group D with an acute DWI (2.0 ml$\times$100 g^{-1}). At the time of the admission, however, the optimal absolute CBV threshold to delineate the acute infarct core is 2.0 ml$\times$100 g^{-1}.

A general comparison of admission PCT and follow-up MRI studies on all patients was not performed because of the large variation in time interval between the 2 examinations (2

to 7 days apart). The patients also differed with respect to recanalization and type of infarction.

Our approach uses 1 single absolute CBV threshold to define the infarct core. It does not distinguish between gray and white matter. As explained in the Methods section, the algorithm used for the processing of PCT data in this study applies an anisotropic, edge-preserving spatial filtering to correct for the noise generated by the low acquisition parameters (80 to 90 kVp, 100 to 120 mAs) used to lower the patient's radiation dose. This spatial filtering results in an averaging of the PCT values measured in 1 pixel with the values measured in the neighboring pixels. As a consequence, the PCT values in the gray matter pixels are, at least partially, averaged with the PCT values in the white matter pixels, explaining our choice of one single CBV threshold to define the infarct core. The selected CBV threshold of 2.0 ml$\times$100 g^{-1} is lower than the CBV values for normal white matter ($\approx$3 ml$\times$100 g^{-1}). This constitutes a limitation of our model. The goal of this study was not to define a new complex model but to identify which one of the commonly used simple models (infarct and penumbra defined based on 1 or 2, absolute of relative PCT parameters) represents the optimal approach to interpret PCT studies.

In conclusion, our ROC analysis in a large series of 130 acute stroke patients shows that the optimal approach to define the infarct core and the penumbra is a combined approach using 2 distinct PCT parameters. The absolute CBV, with a threshold at 2.0 ml$\times$100 g^{-1}, is the parameter allowing the most accurate delineation of the acute infarct core. The mismatch between the absolute CBV, with a threshold at 2.0 ml$\times$100 g^{-1}, and the relative MTT, with a threshold at 145%, affords the most accurate delineation of the tissue at risk of infarction in the absence of recanalization.

Acknowledgments

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