Identification of Penumbra and Infarct in Acute Ischemic Stroke Using Computed Tomography Perfusion–Derived Blood Flow and Blood Volume Measurements

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Background and Purpose—We investigated whether computed tomography (CT) perfusion–derived cerebral blood flow (CBF) and cerebral blood volume (CBV) could be used to differentiate between penumbra and infarcted gray matter in a limited, exploratory sample of acute stroke patients.

Methods—Thirty patients underwent a noncontrast CT (NCCT), CT angiography (CTA), and CT perfusion (CTP) scan within 7 hours of stroke onset, NCCT and CTA at 24 hours, and NCCT at 5 to 7 days. Twenty-five patients met the criteria for inclusion and were subsequently divided into 2 groups: those with recanalization at 24 hours (n=16) and those without (n=9). Penumbra was operationally defined as tissue with an admission CBF <25 mL · 100 g^{-1} · min^{-1} that was not infarcted on the 5- to 7-day NCCT. Logistic regression was applied to differentiate between infarct and penumbra data points.

Results—For recanalized patients, CBF was significantly lower ($P<0.05$) for infarct (13.3 ± 3.75 mL · 100 g^{-1} · min^{-1}) than penumbra (25.0 ± 3.82 mL · 100 g^{-1} · min^{-1}). CBV in the penumbra (2.15 ± 0.43 mL · 100 g^{-1}) was significantly higher than contralateral (1.78 ± 0.30 mL · 100 g^{-1}) and infarcted tissue (1.12 ± 0.37 mL · 100 g^{-1}). Logistic regression using an interaction term (CBF×CBV) resulted in sensitivity, specificity, and accuracy of 97.0%, 97.2%, and 97.1%, respectively. The interaction term resulted in a significantly better ($P<0.05$) fit than CBF or CBV alone, suggesting that the CBV threshold for infarction varies with CBF. For patients without recanalization, CBF and CBV for infarcted regions were 15.1 ± 5.67 mL · 100 g^{-1} · min^{-1} and 1.17 ± 0.41 mL · 100 g^{-1}, respectively.

Conclusions—We have shown in a limited sample of patients that CBF and CBV obtained from CTP can be sensitive and specific for infarction and should be investigated further in a prospective trial to assess their utility for differentiating between infarct and penumbra. (***Stroke*****. 2006;37:1771-1777.)**

Key Words: blood volume ■ cerebral blood flow ■ cerebral infarction ■ computed tomography ■ penumbra

The concept of ischemic penumbra was introduced by Astrup et al as a region of hypoperfused, electrically silent and functionally impaired but viable tissue.[1] Since its introduction, penumbra has become the focus of intense imaging research to differentiate it from infarction. Accurate identification of this "tissue at risk" could be used to identify patients who would benefit most from treatment. Currently, tissue plasminogen activator (tPA) is the only approved drug for acute stroke patients in North America that showed significant benefit in clinical trials when administered intravenously <3 hours after stroke.[2,3] It has been suggested that thrombolysis may be beneficial up to 6 hours after stroke if given intra-arterially.[4] Because of the narrow time window and increased probability of hemorrhage, tPA is limited to ≈10% of stroke patients in most academic stroke centers and ≈2.4% of patients in the general population.[5] Imaging techniques may help select patients beyond the current 3-hour time window for intravenous thrombolysis because it has been shown in a meta-analysis that the odds of a favorable outcome with tPA does not decrease to 1.0 until ≈360 minutes after onset.[6]

Positron emission tomography (PET) is able to differentiate between normal, penumbral, and infarcted tissue in the acute stage of stroke.[7,8] However, because of logistic

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and practical limitations of PET, its clinical use in acute stroke is limited. MRI has also contributed significantly to stroke imaging. Although early studies suggested that various techniques such as perfusion- and diffusion-weighted imaging could differentiate between penumbra and infarct,[9] more recent studies have shown that this interpretation of diffusion-weighted imaging and perfusion-weighted imaging may be an oversimplification.[10,11] MRI sequences and analysis tools are constantly being developed and improved, and MRI will remain an important part of stroke imaging. These techniques are mainly limited by time in hyperacute stages when magnetic safety checklists and safety of monitoring equipment/personnel is a limiting factor.

Despite advances in various imaging modalities, computed tomography (CT) remains the most used imaging modality in acute stroke. CT scanners are readily accessed around the clock in urban and community hospitals, are relatively inexpensive compared with other imaging techniques, and studies can be performed rapidly. Recent studies have shown that contrast-enhanced CT can add to sensitivity, specificity, and accuracy of routinely performed noncontrast CT scan (NCCT)[12–14] for stroke diagnosis and may be able to delineate infarcted and penumbral tissue in acute stroke.[13,15,16]

In this study, we attempted to determine whether cerebral blood flow (CBF) and cerebral blood volume (CBV) maps obtained by dynamic contrast-enhanced CT (CT Perfusion 3; General Electric Healthcare) at admission could be used to accurately differentiate between penumbra and infarcted brain tissue. Patients were divided into 2 groups: those who experienced recanalization at 24 hours, and those without recanalization at 24 hours. In patients without recanalization, the CBF threshold for infarction was established to define tissue that would progress to infarction without reperfusion. Logistic regression was applied to data points from patients in the recanalized group to define the thresholds for separating infarcted from penumbra. Only patients with recanalization were used in the regression analysis to minimize the effects of tissue progression from penumbra to infarction.

Materials and Methods

Patients

Thirty patients who presented to the emergency department of 4 Canadian academic centers within 7 hours of acute stroke with signs and symptoms of middle cerebral artery occlusion were prospectively recruited. Exclusion criteria were: evidence of brain stem infarcts, intracranial hemorrhage, previous stroke with residual deficit, minor stroke symptoms with National Institutes of Health Stroke Scale score <4, clinically significant hypoglycemia, impaired renal function/known allergy to contrast media, pregnancy, and <18 years of age. Twenty-five patients contributed data to this study, and their information is summarized in the Table. Five patients were excluded after enrollment for the following reasons: 2 showed no ischemia on admission and no infarct on follow-up NCCT, and 1 experienced a large hemorrhage and edema causing damage secondary to ischemia; admission CT perfusion (CTP) scan was performed at the wrong levels in 1 patient; and 1 had excessive movement, and CTP maps could not be calculated. The 25 patients who contributed data were divided into 2 groups based on the 24-hour CT angiography (CTA) data: those who showed partial or complete recanalization within 24 hours (recanalized group: 16 patients, 6 no tPA, 2 intra-arterial tPA, 4 intravenous tPA, and 4 patients received combination intravenous and intra-arterial tPA), and those who remained occluded at 24 hours (occluded group: 9 patients, 5 no tPA; 3 intravenous tPA; and 1 patient received combination intravenous and intra-arterial tPA). Results from this study did not have any effect on treatment decision, and patients were enrolled regardless of whether they received thrombolytic therapy or not. Ethics approval was obtained from participating institutions, and informed consent was obtained from all patients or family members before enrollment in the study.

Imaging

All patients underwent NCCT, CTA, and CTP on admission, again ≈24 hours after admission, and follow-up NCCT at 5 to 7 days after stroke. NCCT helical scans were performed from the skull base to the vertex with the following imaging parameters: 120 kVp, 340 mA, 4×5-mm collimation, 1 second/rotation, and table speed of 15 mm/rotation. Each CTP consisted of injection of 0.5 mL/kg (maximum 50 mL) iodinated contrast agent (Iohexol; 300 mg/mL) at a rate of 2 to 4 mL/second followed by a 45-second cine scan at 80 kVp, 190 mA. Scanning was delayed by 3 to 5 seconds after the start of the injection. CTP studies covered a 20-mm slab of the brain from basal ganglia to lateral ventricles with either 4 5-mm or 2–10 mm sections. CTA was performed as follows: 0.7 mL/kg contrast (maximum 90 mL), 5- to 10-second delay, 120 kVp, 270 mA, 1 second/rotation, 1.25-mm thick slices, and table speed 3.75 mm/rotation. CTA covered from the carotid bifurcation through to vertex. Recanalization at 24 hours was classified as complete, partial, or absent by an experienced neuroradiologist (D.H.L.).

From each CTP, a time density curve (TDC), which displays the change in Hounsfield Units for a specified region over the duration of the scan, was obtained from a contralateral artery and from the superior sagittal or transverse sinus. CT Perfusion 3 software, an approved and commercially available product (General Electric HealthCare), was used to calculate quantitative parametric maps of CBF and CBV by deconvolution of tissue enhancement curves and arterial TDC in 2×2 pixel blocks. CBF and CBV derived from deconvolution-based CT imaging has been shown to be quantitative and accurate when compared with PET or Xenon CT imaging.[17,18] Partial volume averaging of the arterial input curve was corrected using the venous TDC.[19] In addition to CBF and CBV maps, CT Perfusion software was used to create a perfusion-weighted map by averaging cine images over the duration of the first contrast passage through the brain.

Image Analysis

All NCCT, CBF, CBV, and perfusion-weighted images were imported into custom software (IDL v5.6; RSI Inc.) for analysis. Delayed NCCT images were registered to baseline images to adjust for movement between scans. The perfusion-weighted map was used to segment gray and white matter based on thresholds of Hounsfield Units. The resulting gray matter mask was applied to the admission CBF and CBV maps to obtain average gray matter values for each of 3 tissue types: contralateral, penumbra, and infarct. CBF and CBV thresholds were applied to all tissue types to minimize the contribution of vascular pixels because it has been shown that CTP values correlate well with Xenon CT and PET when large vessels are excluded.[17,18] Pixels with CBF >100 $mL \cdot 100\ g^{-1} \cdot min^{-1}$ or CBV >8 $mL \cdot 100\ g^{-1}$ were excluded and not used in calculating average CBF and CBV values for regions of interest (ROIs).

For patients in the occluded group, ischemia was defined as CBF <25 $mL \cdot 100\ g^{-1} \cdot min^{-1}$, which is consistent with previously published thresholds for infarction in patients without recanalization.[20] The area of ischemic gray matter on admission CBF map and final infarct size on the corresponding 5- to 7-day NCCT images were calculated and compared to determine whether this CBF threshold was appropriate for defining tissue that would progress to infarction. Because of the loss of differentiation between gray and white matter in the final infarct, a

Summary of Patient Information

Patient	Age	Gender	Onset to Imaging (h:mm)	Admission NIHSS Score	tPA	Recanalization at 24 Hours
1	78	M	4:46	25	No	None
2	44	F	4:40	10	IA	Complete
3	77	F	2:43	6	IA	Complete
4	81	F	2:27	26	No	Complete
5	75	M	2:48	4	No	Complete
6	82	F	2:58	23	No	Partial
7	72	M	2:06	13	IV	None
8	89	F	2:13	18	No	Complete
9	64	M	2:55	19	IV	None
10	90	F	7:07	19	No	None
11	72	F	6:34	19	No	None
12	54	M	1:13	18	IV	Partial
13	67	M	2:49	12	IV	None
14	77	F	2:09	9	IV	Complete
15	53	M	6:40	22	No	None
16	77	F	1:22	10	IV	Complete
17	92	F	1:47	24	No	None
18	67	M	2:37	9	No	Complete
19	67	F	1:04	11	IV+IA	Complete
20	62	F	1:18	21	IV+IA	Partial
21	60	M	2:15	8	IV+IA	Partial
22	57	M	3:45	17	IV+IA	None
23	52	F	2:10	13	IV+IA	Complete
24	56	F	1:15	8	IV	Partial
25	86	F	2:17	14	No	Complete
Average±SD	70±13	10 M, 15 F	2:58±1:43	15.1±6.4	14/25 tPA	16/25

IA indicates intra-arterial; IV, intravenous; M, male; F, female.

"mirrored" template of the contralateral gray matter was applied to estimate the area of infarcted gray matter.

For patients in the recanalized group, analysis was performed in the following sequence by observers blinded to the clinical data of the patients: (1) outline infarct ROI on registered 5- to 7-day NCCT (performed by an experienced neuroradiologist; D.H.L.); (2) superimpose infarct ROI on admission CTP images; (3) outline ischemic tissue (<25 mL · 100 $g^{-1} \cdot min^{-1}$), if present, on admission CBF map; and (4) outline contralateral hemisphere. The gray matter mask obtained from the perfusion-weighted images was applied, and regions were labeled as infarct, ischemic, and contralateral. The penumbra region was operationally defined in this study as the difference between the infarct and ischemic regions. In this study, infarct regions were defined 5 to 7 days after stroke on an NCCT image, which could lead to an underestimation of the final infarct size because ischemic/penumbral tissue may still be evolving to infarction at this time point.

Statistical Analysis

Mean and SD of National Institutes of Health Stroke Scale score, onset to imaging time, and age were calculated for all patients and are given in the Table. For patients in the occluded group, a paired *t* test was performed to determine whether ischemic (CBF <25 mL · 100 $g^{-1} \cdot min^{-1}$) area on admission was significantly different from final infarct size for the corresponding 5- to 7-day NCCT. For patients in the recanalized group, 1-way ANOVA was performed with Tukey post hoc test for significant differences in CBF and CBV values between penumbra, infarct, and contralateral regions. Significant differences were defined as $P<0.05$ for all comparisons. Logistic regression analysis was performed using all data points obtained from the recanalized group. CBF, CBV, and an interaction term (including CBF and CBV) were included as potential predictors in the regression model. Sensitivity and specificity for infarction were calculated from the resulting regression model. All statistical analyses were performed using SPSS 13 for Windows (SPSS Inc).

Results

Occluded Group

For patients without recanalization (average onset to imaging time 256 minutes), total ischemic area on admission CBF map was not significantly different from final infarct area, suggesting that a CBF threshold of 25 mL · 100 $g^{-1} \cdot min^{-1}$ was appropriate for defining tissue that would progress to infarction if recanalization did not occur (penumbra). Average admission CBF and CBV values for regions that were infarcted on the 5- to 7-day NCCT were 15.1±5.67 mL · 100 $g^{-1} \cdot min$ and 1.17±0.41 mL · 100 g^{-1}, respectively.

Recanalized Group

Sixteen patients in the recanalized group (average onset to imaging time 133 minutes) contributed a total of 36 penumbra and 33 infarct regions (Figure 1). Penumbral tissue had a

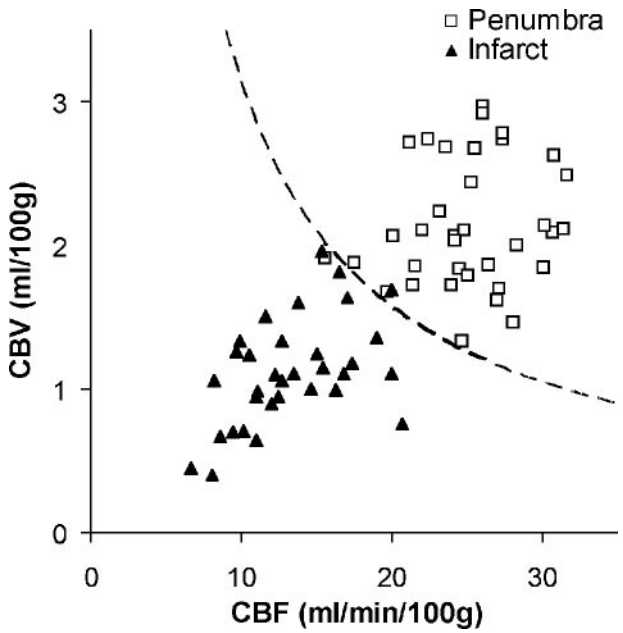

Figure 1. Scatter plot of CBV vs CBF including probability for infarction lines. Scatter plot of CBV vs CBF. Dashed line represents maximum separation between penumbra and infarct data points derived from logistic regression analysis. This line is defined by the equation CBF×CBV=31.3, where CBF is expressed in mL · 100 g^{-1} · min^{-1} and CBV in units of mL · 100 g^{-1}. With increasing distance above the line, the probability of the region being infarcted decreases; the further below the line, the higher the probability the region is infarcted. When the predicted group membership is compared with the true group membership (infarct or not on the 5- to 7-day NCCT), the calculated specificity for infarction of the model is 97.2%, and sensitivity is 97.0%.

significantly lower CBF (25.0±3.82 mL · 100 g^{-1} · min^{-1}) than contralateral brain tissue (37.3±5.01 mL · 100 g^{-1} · min^{-1}), and infarcted tissue had a significantly lower blood flow (13.3±3.75 mL · 100 g^{-1} · min^{-1}) than penumbral tissue (Figure 2A). CBV values in the penumbra (2.15±0.43 mL · 100 g^{-1}) were significantly higher than contralateral brain tissue (1.78±0.30 mL · 100 g^{-1}) and were significantly lower in the infarct (1.12±0.37 mL · 100 g^{-1}) compared with contralateral and penumbral tissue (Figure 2B).

Logistic regression analysis identified the interaction term between CBF and CBV as best predictor for differentiating between penumbra and infarct data points, significantly better than CBF or CBV thresholds alone ($P<0.05$). A nonlinear line (Figure 1) can be derived from the logistic regression model that provides the maximum separation between penumbra and infarct data points in the CBV versus CBF plot, defined by the equation CBF×CBV=31.3, where the units of CBF are mL · min^{-1} · (100 g)$^{-1}$ and that of CBV are mL · (100 g)$^{-1}$. The model classified any pair of CBV and CBF values above this line as penumbra and points below the line as infarct. Sensitivity for infarction (97.0%), specificity for infarction (97.2%), and overall accuracy (97.1%) are obtained by comparing the predicted group membership (from the regression model) to the actual group membership (defined on the 5- to 7-day NCCT).

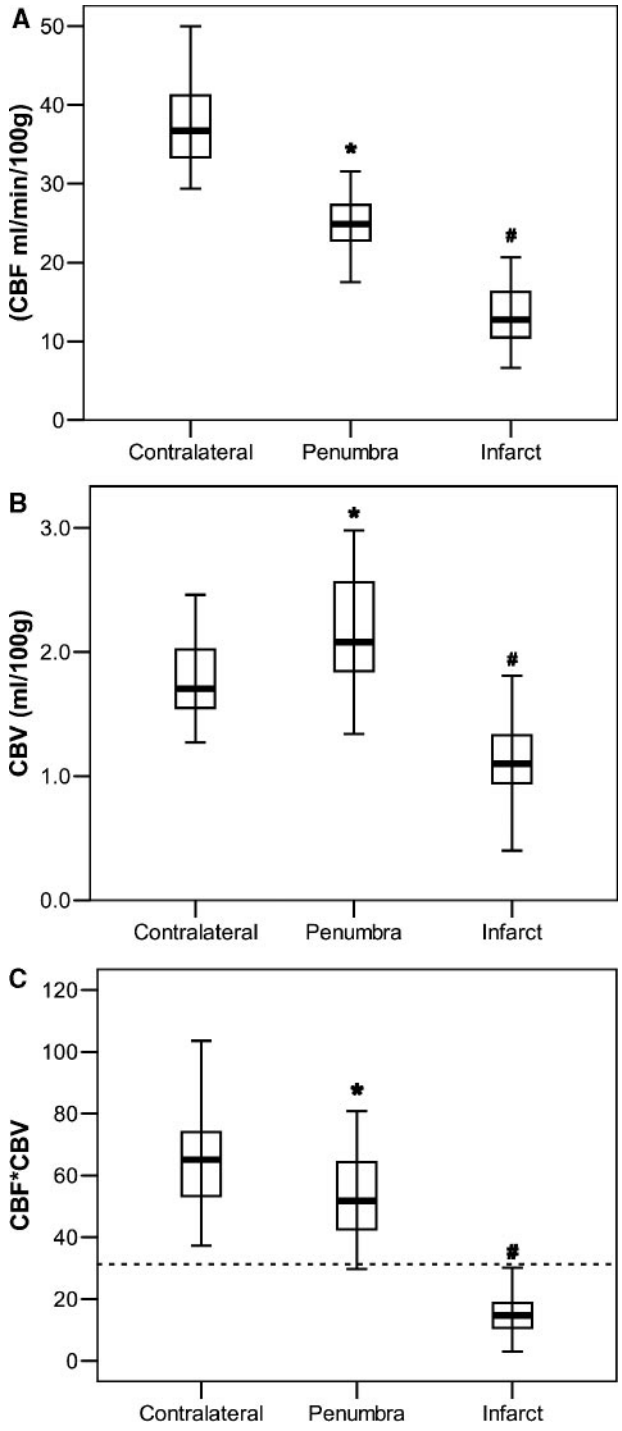

Figure 2. Box plots of CBF, CBV, and CBF×CBV in contralateral, penumbra, and infarct regions (A through C). Box and whisker plots showing median (bar), interquartile range (boxes), and data range (1.5× interquartile range whiskers) of CBF (A), CBV (B), and CBF×CBV (C; CBF in mL · 100 g^{-1} · min^{-1} and CBV in mL · 100 g^{-1}) for gray matter in the recanalized group. Dashed line in C represents CBF×CBV=31.3, which is the line derived from logistic regression that best separates penumbra from infarct regions. The product CBF×CBV results in a reduction in overlap between penumbra and infarct regions when compared with either CBF or CBV alone. *Significantly different ($P<0.05$) from infarct and contralateral values; #significantly different ($P<0.05$) from penumbra and contralateral values.

Discussion

In this study, penumbral regions were characterized by a mismatch between CBF and CBV, whereas infarcted areas showed a matched decrease in both parameters.[13,14] In the penumbra, CBF was reduced, and CBV was maintained or elevated above contralateral values. Infarcted tissue showed a matched decrease in both CBF and CBV, which was unique to infarcted regions (Figure 3). Some patients in the occluded group showed a matched decrease (low CBF, low CBV) in some portions of ischemic tissue and mismatch (low CBF, normal/elevated CBV) in other portions. Lack ofnormal/elevated CBV) in other portions. Lack of recanalization resulted in infarct of entire ischemic (CBF <25 mL $\cdot$ min^{-1} $\cdot$ 100 g^{-1}) area (Figure 3), suggesting that our CBF threshold for defining tissue that would progress to infarction was appropriate for this study. This model differs from previous work because it incorporates an interaction between blood flow and blood volume that resulted in a greater sensitivity and specificity for infarction than either CBF or CBV thresholds alone. The improved sensitivity and specificity of this model is a result of the matched decrease in CBF and CBV for infarcted tissue. Because infarct CBF is slightly lower and CBV much lower than penumbra tissue, the separation between the 2 groups of data points is maximized when the product of both values is used (Figure 2C). This method therefore minimizes the overlap between penumbra and infarct values when compared with using either a CBF or CBV threshold alone (Figure 2A and 2B). Although CBF$\times$CBV values improve differentiation between penumbra and infarct, the CBF and CBV independently provide important information regarding the status of the tissue, particularly compared with contralateral values. This is illustrated by the fact that the CBF map alone was used to define tissue at risk of infarction and comparison of CBF$\times$CBV shows considerable overlap between penumbra and contralateral values (Figure 2C).

Increased CBV in the penumbra is a result of direct autoregulatory responses by the brain to maintain CBF by dilating the precapillary vessels in response to decreased perfusion pressure.[21] Reduced CBV in infarcted tissue has been reported previously, but the mechanism for it is not completely understood.[13–15,22] One possible explanation for matched decrease in CBF and CBV is a result of failure of autoregulation in response to severe hypoperfusion.[21] Other theories that have been proposed for this matched decrease are metabolic mechanisms such as neuronal death, resulting in significantly elevated extracellular potassium concentrations causing vasoconstriction.[23] CBV thresholds for infarction identified in this study were lower than those defined by Wintermark et al[13] but could be a result of vascular pixel elimination or algorithm differences for calculation of CBV and CBF, possibly because of partial volume corrections. Additionally, the CBV threshold we identified varies with CBF and is not constant across various CBF values. Using logistic regression (Figure 1), sensitivity and specificity for infarction were 97.0% and 97.2%, respectively, comparable to, or higher than, previous studies using MRI or contrast-enhanced CT.[11,12,14] Therefore, this model could possibly be applied to ischemic regions in the acute stage of stroke to determine whether they are viable (penumbra) or infarcted.

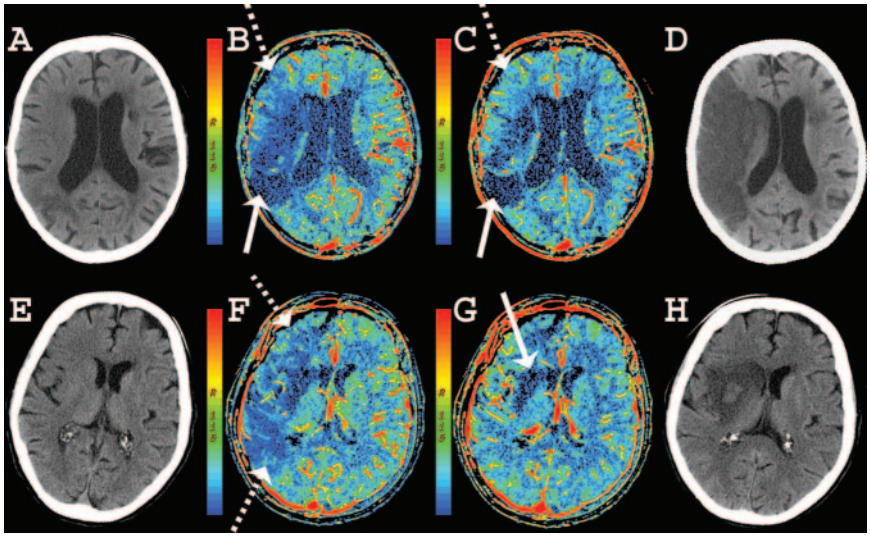

Figure 3. Patient 10 admission NCCT, CBF map, CBV map, and delayed NCCT (A through D) and patient 4 admission NCCT, CBF map, CBV map, and delayed NCCT (E through H). Patient 10, admission NCCT image (A), CBF map (B; scale 0 to 150 mL $\cdot$ 100 g^{-1} $\cdot$ min^{-1}), CBV map (C; scale 0 to 8 mL $\cdot$ 100 g^{-1}) obtained 7 hours after stroke onset. Initial CT hypodensity corresponds to area of reduced CBF and CBV (solid arrow), whereas the dashed area shows an area of decreased CBF with normal/elevated CBV. Without recanalization, entire ischemic area at admission (CBF=16.48; CBV=1.81) progressed to infarction on the 5-day NCCT (D). Subtle stripes of isodensity surrounded by the low density of infarction are typical for petechiae in cortex. Patient 4, Admission NCCT image (E), CBF map (F; scale 0 to 150 mL $\cdot$ 100 g^{-1} $\cdot$ min^{-1}), CBV map (G; scale 0 to 8 mL $\cdot$ 100 g^{-1}) obtained 157 minutes after stroke onset. Large ischemic area on the admission CBF (dashed arrows) with an area of severely reduced CBV in the deep gray matter (solid arrow). Spontaneous recanalization occurred before the 24-hour follow-up CTA. H, Five-day NCCT confirms infarct in the deep gray matter (matched decrease in CBF and CBV at admission) with progression of some surrounding tissue to infarction. A large portion of the mismatch area at admission (decreased CBF, normal/elevated CBV) recovered and did not show infarction on the 5-day NCCT. Isodense region central within the low-density infarction is typical for a hemorrhagic region.

This study is not without limitations. First, CBF and CBV thresholds were derived from an ROI analysis, and the exact time of recanalization could not be assessed within the first 24 hours, possibly allowing some conversion of penumbra to infarct between the admission CTP and recanalization. A second factor that may have caused an overestimation of the thresholds for infarction is the variability in onset to imaging time, as it is known that the CBF threshold for infarction increases with time.[20] Applying our thresholds would therefore result in an overestimation of infarct size for some patients, particularly those at earlier time points. In thrombolysis treatment of acute stroke, with the possibility of hemorrhagic complication, this overestimation would make our method more conservative than optimistic with respect to treatment decision. Additionally, defining infarcted tissue at 5 to 7 days after stroke on an NCCT image could result in errors because the tissue may still be evolving to complete infarction beyond the first week. Limitations of this CT imaging technique are limited anatomical coverage, use of iodinated contrast agent, and exposure to x-ray films. Advances in CT hardware and imaging techniques will lead to increased anatomical coverage or a reduction in radiation dose.[24,25] Studies have shown very good tolerance to iodinated contrast by patients,[26] and the x-ray dose from a CTP study is about double that of a whole-head NCCT (T.-Y.L., unpublished data, 2005).

Defining the penumbra and infarct using CBF and CBV values from CTP could help in selecting patients for thrombolytic therapy within and possibly outside the current 3- to 6-hour treatment window, where it has been shown that penumbra may persist for >12 hours.[27,28] CT imaging is available around the clock in most hospitals, is more rapidly accessible to stroke patients than MRI, and can be used to exclude intracranial hemorrhage, identify occlusion site, and possibly differentiate infarct from penumbra. Our study provides preliminary evidence that CBF and CBV derived from an admission CTP can identify infarct from penumbral tissue with sensitivity and specificity. This technique needs to be tested in a larger, randomized, prospective trial to examine its efficacy and whether it could be used to guide treatment decisions and possibly improve clinical outcome.

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Disclosures

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