

Quantitative Perihematomal Blood Flow in Spontaneous Intracerebral Hemorrhage Predicts In-Hospital Functional Outcome

Ashis H. Tayal, MD; Rishi Gupta, MD; Howard Yonas, MD; Tudor Jovin, MD; Ken Uchino, MD; Maxim Hammer, MD; Lawrence Wechsler, MD; James M. Gebel, MD

Background and Purpose—Few data on xenon computed tomography–based quantitative cerebral blood flow (CBF) in spontaneous intracerebral hemorrhage have been reported. We correlated perihematomal CBF in a retrospective series of 42 subacute spontaneous intracerebral hemorrhage patients undergoing xenon computed tomography with in-hospital discharge status and mortality.

Methods—We calculated 3 area-weighted mean CBF values: (1) within the computed tomography–visible rim of perihematomal edema, (2) within a 1-cm marginal radius around the hematoma, and (3) all cortical regions of interest immediately adjacent to the hematoma. Primary outcomes were in-hospital mortality and discharge status (ordinally as 0=home, 1=acute rehabilitation, 2=nursing home, 3=death). Discharge status was used as a surrogate for in-hospital functional outcome.

Results—Median hematoma volume was 14.4 cm³ (range, 2 to 70). Median perihematomal (low-attenuation rim) CBF was 21.9 cm³·100 g⁻¹·min⁻¹ (range, 6.1 to 81.1), and the median 1-cm marginal radius CBF was 26.8 cm³·100 g⁻¹·min⁻¹ (range, 10.8 to 72.8). The median regional cortical CBF was 26.7 cm³·100 g⁻¹·min⁻¹ (range, 6.9 to 72.6). Eight patients had 1-cm marginal radius or regional cortical CBF values <20 cm³·100 g⁻¹·min⁻¹. Hematoma volume (odds ratio [OR], 1.68 per 10-cm³ volume; *P*=0.036) and intraventricular hemorrhage (OR, 1.88 per grade of intraventricular hemorrhage; *P*=0.036) predicted mortality. Two CBF measures, hydrocephalus, and IVH predicted poor in-hospital functional outcome in bivariate analysis. Each CBF measure (OR, 0.34 to 0.43; *P*<0.001 to 0.003) and intraventricular hemorrhage (OR, 3.42; *P*<0.001) predicted in-hospital functional outcome in multivariable analyses.

Conclusions—Most spontaneous intracerebral hemorrhage patients lack perihematomal penumbra. Perihematomal CBF independently predicts in-hospital discharge status but not in-hospital mortality. Further studies are warranted to determine whether perihematomal CBF predicts long-term functional outcomes. (*Stroke*. 2007;38:319-324.)

Key Words: cerebral blood flow ■ intracerebral hemorrhage ■ outcomes

Intracerebral hemorrhage (ICH) accounts for 10% to 15% of all strokes and is associated with an overall 30-day mortality of 44% to 51%.¹⁻³ Reduced cerebral perfusion has been observed in reported series of patients with small to moderately sized hematomas (<60 cm³).⁴⁻⁷ Cerebral perfusion is variably reduced in local and remote areas around the hematoma, is related to hematoma size, and has not been associated with ischemia. Xenon-enhanced computed tomography (XeCT) cerebral blood flow (CBF) study is an emerging real-time, high-resolution technique for quantifying perihematomal, regional, and hemispheric CBF. We report our CBF measurement experience on 42 subacute spontaneous ICH (SICH) patients with small to moderately sized hematomas who underwent XeCT during a 3-year study period. We

also investigated the relation of CBF variables to in-hospital mortality and discharge status. In-hospital functional outcome was based on discharge status. We hypothesized that perihematomal CBF as assessed by XeCT CBF studies in SICH patients is not significantly reduced and not associated with a greater probability of poorer in-hospital functional outcome or mortality (null hypothesis).

Patients and Methods

Patients

This retrospective analysis was conducted with institutional review board approval. Forty-two subacute SICH patients who underwent an XeCT CBF study from 1997 to 1999 and who met the inclusion criteria for our study were identified by querying a prospectively

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From the Department of Neurology and University of Pittsburgh Medical Center Stroke Institute (A.H.T., R.G., T.J., K.U., M.H., L.W., J.M.G.); the Veterans Administration Pittsburgh Health Care System and University of Pittsburgh Medical Center Stroke Institute (T.J.), and the Department of Neurosurgery and University of Pittsburgh Medical Center Stroke Institute (H.Y.), University of Pittsburgh, Pittsburgh, Pa.

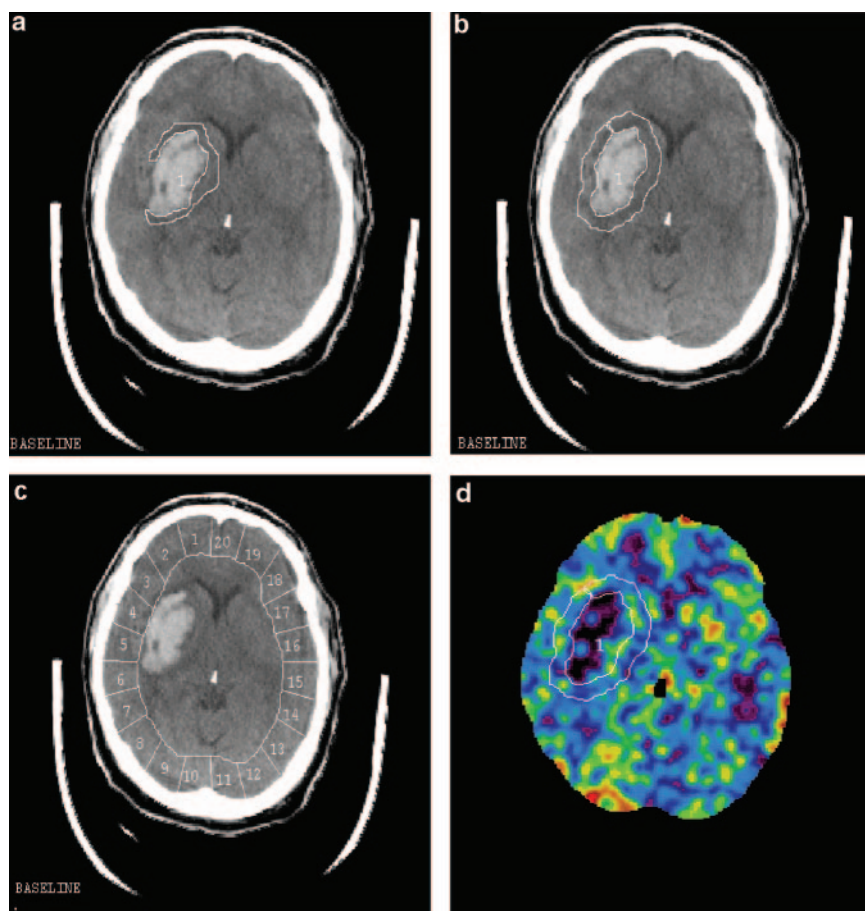
A.H.T. is currently at the Allegheny General Hospital Stroke Program, Pittsburgh, Pa. J.M.G. is currently at the Jewish Hospital Emergency Stroke Center, Louisville, Ky.

Correspondence to James M. Gebel Jr, MD, 6400 Dutchmans Ln, Suite 145, Louisville KY 40205. E-mail j.gebel@att.net

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a, CT image of head, with traced visible perihematomal edema. b, CT image of head, with traced 1-cm marginal radius around the hematoma. c, CT image of head, with superimposed regional cortical ROI. d, Corresponding XeCT CBF map, showing the traced 1-cm marginal radius around the hematoma.

collected XeCT imaging database. Clinical and radiographic data were retrospectively collected from medical records and film review. Inclusion criteria for this study were as follows: (1) age >17 years, (2) radiographic evidence of intraparenchymal hemorrhage, and (3) a good-technical-quality XeCT CBF study. Exclusion criteria included (1) head trauma, (2) radiographic evidence of subarachnoid hemorrhage, and (3) an underlying mass lesion or vascular malformation. Twelve subjects were excluded from this study because of poor-technical-quality XeCT studies related to motion artifact. Clinical data included demographic information, ICH onset time, admission blood pressure, time to XeCT CBF study, ICH risk factors, medical history, ICH onset symptoms, medications before admission, laboratory data, in-hospital treatment, and discharge status. Radiological data included hematoma volume, grade of hydrocephalus (0=none, 1=mild, 2=moderate, 3=severe), and grade of intraventricular hemorrhage (IVH) (0=none, 1=mild, 2=moderate, 3=severe). We have previously described the grading techniques for these 2 variables.⁸ Discharge status was recorded as home, acute rehabilitation, skilled nursing facility/subacute rehabilitation, and death.

XeCT CBF Study

The XeCT CBF technique has been previously published.^{9,10} Four contiguous CT-defined levels of 1-cm slice thickness were obtained along the orbitomeatal line. Voxels (1×1×10 mm) correspond to CBF in cubic centimeters per 100 g per minute and are color coded according to an ordinal scale of CBF values. A color-coded, quantitative CBF map is produced and displayed with individual CT images. XeCT computer software calculates the mean CBF within regions of interest (ROIs). Our analysis included hand-traced ROIs corresponding to the (1) hematoma; (2) perihematomal edema, defined as the visible rim of low attenuation immediately adjacent to the hematoma; and (3) a 1-cm radius around the hematoma. In

addition, we used a computer-generated template that is part of the XeCT computer software (Diversified Diagnostic Products Inc, Houston, Tex). The template divides the entire cerebral cortex into 20 ROIs (see the Figure). For each of 4 CT slices per study, we measured hematoma volume (in cm³), perihematomal edema volume (in cm³), CBF (in cm³·100 g⁻¹·min⁻¹), 1-cm radius CBF (in cm³·100 g⁻¹·min⁻¹; defined as the area-weighted CBF within brain tissue within a 1-cm radius of the hematoma edge), and regional cortical CBF (in cm³·100 g⁻¹·min⁻¹). We defined regional cortical CBF in our patients as the mean area-weighted CBF for all cortical ROIs occupied by any amount of hematoma.

Statistical Analysis

Data management and analysis were done with the use of the Intercooled Stata 7.0 (Stata Inc) statistical software package. Hematoma volumes and CBF values were summarized as medians and ranges. Correlations among CBF and other nonparametric variables were performed with the Spearman correlation coefficient (nonparametric) technique. Correlations were also calculated between CBF variables and (1) hematoma volume, (2) perihematomal edema volume, (3) time from ICH onset to XeCT, and (4) change in blood pressure from admission to XeCT.

All clinical and radiological variables were analyzed for bivariate associations with “good” versus “bad” outcomes and for their association with each of the 3 CBF measures. Proportions were compared with Pearson χ^2 . Normally distributed continuous variables were analyzed with an unpaired, 2-sided, Student *t* test, and nonnormally distributed continuous variables were analyzed with the Wilcoxon rank-sum test. Binary multiple logistic regression with good versus bad outcome as the outcome variables was used for multivariable analyses, with a maximum of 4 variables per model (including interaction terms). In-hospital mortality was analyzed separately as a second outcome variable. Finally, an ordinal logistic-

TABLE 1. Baseline Demographic and Clinical Risk Factor Variables for Primary Analysis of the Patient Population (N=42)

Variable	Percentage or Mean
Age, y	65.0 (15.1)
Diabetes	30%
Hypertension	63%
Tobacco use	23%
Anticoagulant use	4%
History of ICH	7%
Alcohol abuse	9%
Cocaine or amphetamine use	7%
Aspirin, ticlopidine, or clopidogrel use	7%
Admission SBP, mm Hg	186
Admission DBP, mm Hg	97
Admission MAP, mm Hg	127
XeCT SBP, mm Hg	151
XeCT DBP, mm Hg	77
XeCT MAP, mm Hg	100
Headache	35%
Loss of consciousness	35%

SBP and DBP indicate systolic and diastolic blood pressure, respectively. Other abbreviations are as defined in text. Categorical variables are reported as percent prevalence. Continuous variables are reported as mean.

regression model was created with use of the semiquantitative scale of discharge disposition, creating a third outcome variable. Outcome variables were defined before data collection and analysis. Only variables whose probability value was 0.20 or less on bivariate association or that were identified as changing the odds ratio (OR) for a CBF value associated with the respective primary outcome variable of interest by >15% were entered as candidate variables into each binary or ordinal multiple logistic-regression model with step-up and then step-down methodology. The final resultant parsimonious models for each outcome variable are presented.

Results

Selected baseline demographic, risk factor, and laboratory data for the primary study population are presented in Table 1. The median hematoma volume was 14.4 cm³, with a range of 2 to 70 cm³. The majority of hematoma volumes (75%) were <30 cm³, with 10% of hematomas volumes being >45 cm³. The CBF values in the 3 specified perihematomal ROIs are summarized in Table 2. The percentage of patients with a CBF between 8 and 20 cm³·100 g⁻¹·min⁻¹ (penumbra-range CBF) was also determined for each of the perihematomal ROIs. Forty-two percent of our patients had a penumbra-range CBF in the CT-visible perihematomal edema zone,

whereas 25% of patients had a penumbra-range CBF in the 1-cm radius around the hematoma, and 20% of patients had a penumbra-range CBF in the regional cortices immediately adjacent to the hematoma.

CBF in all 3 ROIs was highly correlated. Mean perihematomal edema CBF was strongly correlated with mean 1-cm radius CBF ($r=0.87$, $P<0.001$), mean regional cortical CBF ($r=0.68$, $P<0.001$), and even with mean global cortical CBF ($r=0.66$, $P<0.001$). There was a nonsignificant trend toward an inverse association between hematoma volume and each of the 3 CBF measures. A weak, negative correlation was observed between hematoma volume and perihematomal edema CBF ($r=-0.26$, $P=0.08$), 1-cm radius CBF ($r=-0.25$, $P=0.11$), and regional cortical CBF ($r=-0.26$, $P=0.09$).

Δ MAP was defined as the change in mean arterial pressure (MAP) from admission to XeCT acquisition. We found no significant association between Δ MAP and perihematomal blood flow and perihematomal edema CBF ($r=-0.06$, $P=0.72$), 1-cm radius CBF ($r=0.12$, $P=0.51$), regional cortical CBF ($r=0.14$, $P=0.40$), or hematoma volume ($r=0.13$, $P=0.41$). The time to XeCT acquisition in our study varied in the first 48 to 72 hours. Eighty-three percent of XeCT scans were performed within 48 hours of the ictus. Specifically, 10 XeCTs were obtained within 24 hours, 25 were obtained from 24 to 48 hours, 6 were obtained from 48 to 72 hours, and 1 was obtained at >72 hours. There was no correlation between time to XeCT and perihematomal edema CBF ($r=0.13$, $P=0.42$), 1-cm radius CBF ($r=0.04$, $P=0.79$), and regional cortical CBF ($r=0.06$, $P=0.72$).

Hematoma volume and IVH (OR, 1.88; 95% CI, 1.02 to 3.50 per grade of increasing IVH volume; $P=0.036$) significantly predicted in-hospital mortality (OR, 1.68; 95% CI, 1.04 to 2.73 per 10-cm³ increase in volume; $P=0.036$) based on bivariate analysis. These values were essentially unchanged after multivariable analysis (OR, 2.10; 95% CI, 1.01 to 4.36; $P=0.046$ for IVH; OR, 1.94; 95% CI, 1.11 to 3.41; $P=0.020$ for each 10-cm³ increase in hematoma volume). None of the 3 CBF measures predicted mortality.

Regarding in-hospital functional outcome, perihematomal CBF within the 1-cm marginal radius and regional cortical CBF were significant predictors of functional outcome in the bivariate analyses in the (2-variable) ordinal logistic-regression models (Table 2). Hydrocephalus ($\beta=0.710$; OR, 2.03; 95% CI, 1.15 to 3.56; $z=2.45$; $P=0.014$) and presence of IVH ($\beta=0.778$; OR, 2.17; 95% CI, 1.26 to 3.78; $z=2.76$; $P=0.006$) were also significantly associated with an increased likelihood of poor functional outcome at discharge by bivariate analysis. In the multivariable, ordinal logistic-

TABLE 2. Bivariate Association Between CBF Measures and Functional Outcome (Without Adjusting for Other Covariates)

ROI	Median CBF (N=42), cm ³ ·100 g ⁻¹ ·min ⁻¹	Range of CBF (N=42), cm ³ ·100 g ⁻¹ ·min ⁻¹	β Coefficient (SE)	z Value	P Value
Perihematomal edema	21.9	7.3–60.3	0.515 (0.274)	1.8	0.06
1-cm perihematomal radius	26.8	10.8–72.8	0.517 (0.247)	2.09	0.037
Regional cortex CBF	26.7	6.9–72.6	0.536 (0.023)	2.32	0.020

Abbreviations are as defined in text. Ordinal outcome variables were 0=death, 1=nursing home, 2=acute rehabilitation, 3=home. The model was an ordinal logistic regression.

TABLE 3. Respective Multivariable Ordinal Logistic-Regression Model Results for Functional Outcome Based on Discharge Disposition

Variable	β	OR	95% CI	z Value	P Value
IVH*	1.23	3.42	1.73–6.69	3.53	<0.001
Mean regional perihematomal CBF	-1.09	0.34	0.18–0.62	-3.49	<0.001
Mean 1-cm radius perihematomal CBF	-0.85	0.43	0.24–0.76	-2.92	0.003
Mean perihematomal rim CBF	-1.06	0.35	0.16–0.67	-3.03	0.002

Abbreviations are as defined in text. ORs for IVH are per increase in IVH grade (0=none, 1=mild, 2=moderate, 3=severe), and OR values for each CBF measure are per 10- $\text{cm}^3 \cdot 100 \text{ g}^{-1} \cdot \text{min}^{-1}$ increase in CBF. OR results represent the odds of achieving a 1-grade worsening in discharge status (0=home, 1=acute rehabilitation, 2=subacute rehabilitation/nursing home, 3=death).

*The median of the 3 β , OR, and z values for IVH is presented, specifically, the value obtained in the model with IVH and perihematomal edema.

regression models (models that adjusted for the effects of each of these and other clinical variables on outcome), each of the 3 CBF measures retained and actually increased its respective predictive association, both statistically and clinically (with point OR estimates ranging from 0.34 to 0.43 and *P* values ranging from <0.001 to 0.003; Table 3), whereas hydrocephalus became nonsignificant. In all such models, grade of IVH was the single strongest predictor of functional outcome, with ORs ranging from 2.93 to 4.01 (all *P* values <0.001; Table 3).

Discussion

This study represents the largest descriptive analysis of quantitative perihematomal CBF as assessed by XeCT CBF studies in subacute SICH patients. It is also the first study to describe a highly statistically and clinically significant, albeit crudely measured, association between perihematomal CBF and in-hospital functional outcome based on discharge status. This study does not prove any association between perihematomal CBF and long-term functional outcome, but it does provide significant, biologically plausible data to substantiate that this hypothesis is worth exploring.

Regarding the important issue of whether or not significant perihematomal ischemia exists in patients with subacute SICH, we observed that none of our 42 patients had infarction-level perihematomal CBF (<8 $\text{cm}^3 \cdot 100 \text{ g}^{-1} \cdot \text{min}^{-1}$). Furthermore, only 18% (8/43) of patients had penumbra-level perihematomal CBF (8 to 20 $\text{cm}^3 \cdot 100 \text{ g}^{-1} \cdot \text{min}^{-1}$), which extended beyond the immediately CT-visible perihematomal edema rim. These findings at first glance would seem to argue against the concept of a clinically significant perihematomal “penumbra” in most patients with SICH, as defined by the generally accepted CBF threshold. Our findings are consistent with other previously published studies of perihematomal blood flow in patients with small to moderately sized hematomas as assessed by magnetic resonance imaging, positron

emission tomography, and single-photon emission CT (SPECT).^{4,5,7,11–15}

However, despite the fact that our study also failed to identify a significant proportion of patients with spatially significant penumbral-range perihematomal CBF, our data also suggest that even a moderately reduced perihematomal CBF may be relevant to in-hospital functional outcome. We hypothesize that using the XeCT quantitative CBF measurement technique, which allows for greater precision in discriminating between perihematomal CBF values than semi-quantitative or relative CBF techniques, and our comparatively greater sample size versus other similar studies likely provided us with enough statistical power and CBF measurement precision to identify our reported associations between perihematomal CBF and in-hospital functional outcome.

Our CBF measurements failed to predict mortality. However, we believe that the widely promulgated concept that perihematomal CBF depression is too insignificant to be relevant to outcome, a contention that has been largely based on prior smaller studies and case series of SICH patients (which are likely to have been even more biased samples than ours), remains an inadequately tested hypothesis. Were perihematomal CBF ultimately to be shown to be causally associated with poorer long-term functional outcome in a future large, prospective study, this could have implications for acute blood pressure management or surgical/endoscopic intervention in SICH patients. Specifically, such CBF information (whether obtained by XeCT or another appropriate readily available technique) might define a role for stratifying individual patient treatment in this regard based on physiology, much in the same way that many institutions are using such information to tailor reperfusion therapy in acute ischemic stroke patients.

Diffusion-perfusion magnetic resonance imaging changes in the perihematomal region have been reported in 12 patients with acute SICH who were studied within 6 hours of onset and had a median hematoma volume of 13.3 mL.⁷ Perfusion maps did not show decreased perihematomal CBF, although most patients showed diffuse, ipsilateral mild hypoperfusion suggestive of diaschisis. A prospective trial has also been reported for stroke magnetic resonance imaging within 6 hours of onset in 32 SICH patients with small to moderately sized hematomas and found no significant mean transit time or apparent diffusion coefficient changes within a 1-cm radius of the clot.⁵ A positron emission tomography-based study of 19 patients with acute SICH at 5 to 22 hours from onset measured cerebral metabolic rate of oxygen, oxygen extraction fraction, and CBF within a 1-cm perihematomal radius.¹¹ The authors reported reduced CBF, cerebral metabolic rate of oxygen, and oxygen extraction fraction in the perihematomal ROI, suggestive of hypoperfusion but not ischemia. Perihematomal CBF has also been studied with technetium-99 hexamethylpropyleneamine oxime (HMPAO) SPECT. Eleven patients with acute SICH underwent 2 Tc-99 HMPAO SPECT scans within 2 days of the ictus and subsequently at 4 to 7 days. The authors found diminished perihematomal perfusion, which improved after surgical clot evacuation.⁶ Finally, a study cohort of 23 patients underwent

Tc-99 HMPAO SPECT during the acute and subacute (mean, 72 hours) period. The mean ICH volume was 18 mL, and the initially decreased perihematomal CBF normalized during the first 72 hours and corresponded to the development of perihematomal edema.¹²

We found that perihematomal edema CBF, 1-cm marginal radius CBF, and regional cortical CBF were highly correlated. Prior clinical studies of perihematomal CBF have measured CBF within the 1-cm radius around the hematoma and have not systematically investigated or reported correlations among multiple, potentially relevant perihematomal CBF measurements. We observed a weak, negative correlation between hematoma volume and perihematomal CBF. This finding is also consistent with prior published studies and suggests that the hematoma mass effect, at least in patients with small to moderate SICHs, does not significantly influence CBF beyond a small zone of immediately adjacent brain parenchyma. Thus, collateral blood supply, local cerebral autoregulation, systemic hypertension, and intravascular volume status are potential mechanisms that appear to effectively compensate for impaired perihematomal CBF in most patients with small to moderately sized hematomas. It should be reemphasized, however, that in a small but significant proportion of patients in our data set, perihematomal CBF was significantly depressed, and this subgroup might have been at increased risk for poor functional outcome. Perihematomal CBF improves during the subacute period, and such improvement has been reported in both human and animal studies.^{6,12,13} We observed no significant correlation between time from ICH onset to XeCT and CBF measures or outcome in our study, which was not a serial neuroimaging study. Previous studies based on Tc-99 HMPAO have reported improved perihematomal CBF in the first 5 to 7 days from the ictus.^{12,13}

Our Δ MAP was not correlated with perihematomal CBF. The MAP at admission was 127 mm Hg, and at the time of XeCT acquisition, it was 100 mm Hg for the study group. These findings suggest that brain compliance, local cerebral autoregulation, and collateral blood supply provide adequate compensatory perihematomal perfusion for most (but not all) patients. Specifically, our data suggest that a significant reduction of perihematomal CBF is unlikely to occur in small to moderately sized hematomas when the MAP is reduced to 100 mm Hg in the subacute time frame.

Common known independent predictors of functional outcome in acute SICH are hematoma volume, Glasgow Coma Scale score, age, mass effect, and the presence of hydrocephalus.^{15,16} We did not collect Glasgow Coma Scale data, and in our patient sample, age was not correlated with outcome; however, our findings regarding the remaining variables are consistent with other studies of ICH outcome. Gebel and colleagues¹⁷ have previously described relative perihematomal edema volume based on CT scan data as a measure that has been demonstrated to be a strong, independent predictor of 3-month functional outcome, but not mortality. Relative edema volume is associated with lesser odds of a poor 3-month functional outcome (modified Rankin Scale score >2), with an OR of 0.09 per 1.0-U (100%) increase (95% CI, 0.01 to 0.64; $P=0.016$).¹⁷

We now report perihematomal CBF as a second physiological measure potentially predictive of in-hospital functional outcome. Confirmatory future studies with prospectively and consistently collected 3-month or 6-month functional outcomes measured by accepted scales will be necessary to confirm the preliminary findings in this report and to firmly establish any valid association between perihematomal CBF and ultimate functional outcome.

Our study has the following limitations. Subjects in this retrospective cohort were included to select a study group with SICH and good-quality XeCT CBF studies performed within a time frame determined by the treating physicians during the course of ordinary care. Selection bias is thus probable, given the absence of a prospective protocol and systematic study of consecutive SICH patients. However, with the exception of age, our results for other common variables, which are well established as outcome predictors for SICH patients, were typical, which suggests that our study population was not grossly atypical. Standardized functional measures, including the modified Rankin Scale and the Glasgow Coma Scale scores, were unavailable and could diminish the predictive capacity of perihematomal CBF on in-hospital functional outcomes. Discharge status remains a crude marker of in-hospital functional outcome and is also based on multiple factors, including medical comorbidities, insurance status, and level of social support.

XeCT CBF data measurement within an individual voxel may be prone to error based on system noise and filtering.¹⁸ Up to 100 contiguous voxels are measured and averaged with an approximate error rate that is reduced to 10%.¹⁰ This voxel-based analysis is valid, based on the high degree of correlation among perihematomal edema CBF, 1-cm marginal radius CBF, and regional cortical CBF. Mean regional cortical CBF has been validated as a reliable method of CBF measurement.^{10,18}

Finally, flow thresholds chosen to define infarction-level CBF and penumbra-level CBF have not been validated as indicators of tissue viability by follow-up neuroimaging with CT or magnetic resonance imaging. Multiple animal and human studies with positron emission tomography and XeCT CBF have confirmed that perfusion thresholds correspond to cerebral ischemia.¹⁹ It is unlikely, however, that exact CBF thresholds consistently correspond to true penumbra or infarction in individual patients and that brain tissue viability also depends on other relevant factors such as time, temperature, glucose, and genetic factors. We established the CBF thresholds to define penumbra-range CBF on previously published reports by positron emission tomography.^{20,21} However, whether or not our selected CBF cutoff values for penumbra or infarction are correct or not does not invalidate or substantially diminish the observed statistical associations between CBF measures and the outcome measures reported herein.

Disclosures

None.

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