Association Between Perihematomal Cerebral Blood Volume and Intracerebral Hemorrhage Expansion: A Computed Tomography Perfusion Study

Andrea Morotti, MD,[1] Giorgio Busto, MD,[2] Andrea Bernardoni, MD,[3] Carmine Tamborino, MD,[4] and Enrico Fainardi, MD, PhD[5]

We investigated whether computed tomography (CT) perfusion can identify intracerebral hemorrhage patients at high risk of hematoma growth (HG). A total of 155 subjects underwent CT perfusion on admission. Variables associated with log-transformed absolute HG were explored with multivariable linear regression. Perihematomal cerebral blood volume (CBV) was inversely associated with HG (B = –0.20; $p < 0.001$), independently from blood pressure, hematoma volume, and other confounders. This association was not dose dependent, and only very low CBV (<1.4 ml/100 g) was significantly associated with HG (B = 0.25; $p < 0.001$). In conclusion, reduced perihematomal CBV is associated with HG, suggesting a potential role of the perihematomal region in the pathophysiology of hematoma enlargement.

ANN NEUROL 2019;85:943–947

Hematoma expansion is a common event in the natural history of acute intracerebral hemorrhage (ICH) and is independently associated with unfavorable prognosis.[1] The pathophysiology of ICH expansion is complex and controversial, and the role of the brain parenchyma surrounding the hemorrhage remains unclear.[2] One of the hypothesis to explain hematoma growth is that active bleeding continues until the counter pressure from the tissue around the hemorrhage balances the pressure coming from ruptured small vessels that started hemorrhage formation.[3] Following this model, reduced perfusion in the perihematomal region may promote hemorrhage enlargement.[4] In this computed tomography (CT) perfusion (CTP)-based study we aimed at investigating whether hypoperfusion in the perihematomal rim promotes ICH expansion.

Materials and Methods

All aspects of this study received approval from the Institutional Review Board of the Azienda Ospedaliera Universitaria, Arcispedale S. Anna (Ferrara, Italy). Informed consent was obtained from each patient or from close relatives before CTP acquisition. Consecutive patients admitted at a single academic hospital for spontaneous ICH from January 2010 to November 2015 were prospectively selected.[5,6] We included patients with age >18 years and diagnosis of supratentorial ICH within 24 hours of symptom onset or time last seen well. The main exclusion criteria were: (1) neoplastic or vascular intracranial lesion presumed to be the source of the hemorrhage; (2) surgical treatment before follow-up noncontrast CT (NCCT) scan; (3) unclear symptom onset; (4) pregnancy, and (5) contraindication to the administration of iodinated contrast material.

Clinical Variables

The following variables were collected: age, sex, history of hypertension, antiplatelet or anticoagulant treatment, admission systolic and diastolic blood pressure (SBP and DBP), national institute of health stroke scale (NIHSS), time from symptom onset to baseline NCCT, and modified Rankin Scale (mRS) at 3 months from the index event.

Image Acquisition and Analysis

All imaging was conducted on a 64-slice Lightspeed VCT scanner (GE Healthcare, Waukesha, WI). ICH diagnosis was based on baseline NCCT scan, obtained with axial technique with 5-mm slice thickness. NCCT images were reviewed for determination of ICH volume (ABC/2 method), ICH location (deep versus lobar), and presence of intraventricular bleeding. All patients underwent a follow-up NCCT scan at 24 ± 6 hours from baseline NCCT or earlier in case of neurological deterioration. ICH growth was analyzed as a continuous variable (absolute hemorrhage volume increase from baseline to follow-up NCCT) and as a dichotomous variable (hemorrhage volume increase >33% or >6 ml). CTP studies were performed with a dynamic first-pass bolus-tracking methodology, according to a

From the [1]Stroke Unit, IRCCS Mondino Foundation, Pavia, Italy; [2]Diagnostic Imaging Unit, Department of Experimental and Clinical Biomedical Sciences, University of Florence, Florence, Italy; [3]Neuroradiology Unit, Department of Radiology, Arcispedale S. Anna, Ferrara, Italy; [4]Neurology Unit, Ospedale dell'Angelo, Azienda Ulss 3 Serenissima, Mestre, Italy; and [5]Neuroradiology Unit, Department of Experimental and Clinical Biomedical Sciences, University of Florence, Florence, Italy

Address correspondence to Dr Andrea Morotti, Stroke Unit, IRCCS Mondino Foundation, Via Mondino 2, 27100, Pavia, Italy. E-mail: andrea.morotti85@gmail.com

Received Oct 26, 2018, and in revised form Mar 6, 2019. Accepted for publication Mar 6, 2019.

View this article online at wileyonlinelibrary.com. DOI: 10.1002/ana.25466.

one-phase imaging protocol, and cerebral blood flow (CBF), cerebral blood volume (CBV), and mean-transit-time (MTT) maps were generated using a commercially available delay-sensitive deconvolution software, as described elsewhere.[7] As previously reported,[6] CBF, CBV, and MTT maps were measured in four regions of interest drawn freehand on every section in which the hematoma was visible: (1) hemorrhagic core; (2) perihematomal rim; (3) 1-cm rim of normal-appearing brain tissue surrounding the perilesional area; and (4) a mirrored area, including the clot and the perihematomal region, located in the contralateral hemisphere.

Statistical Analysis

Categorical variables are expressed as count (percentage) and were compared with a χ^2 test. Continuous variables were summarized as median (interquartile range; IQR) or mean (standard deviation; SD) as appropriate based on their normal versus non-normal distribution evaluated with the Shapiro-Wilk test. Comparison between continuous variables was performed with the Mann–Whitney *U* test or *t* test, as appropriate. Log-transformed absolute hematoma growth was the main outcome of interest of the analysis. Univariable linear regression was used to explore unadjusted associations between covariates and hematoma growth. Variables associated with hematoma growth were assessed with multivariable linear regression using a step-wise model building method. The initial model included age, sex, covariates with $p < 0.10$ in univariable analysis, and predictors of hemorrhage growth identified from the literature such as time from onset to NCCT, ICH volume, and anticoagulation.[8] All these covariates were then backward eliminated to a significance level of 0.10. Collinear factors were also removed based on the variance inflation factor. In a secondary analysis, ICH expansion is expressed as growth >33% or >6 ml. Variables associated with ICH expansion were explored in a multivariable logistic regression model, adjusting for ICH volume, anticoagulant treatment, SBP and time from onset to NCCT.[2] All the analyses were performed with the statistical package, SPSS (version 21.0; www.spss.com), and *p* values <0.05 were considered statistically significant.

Results

A total of 155 subjects met the inclusion criteria of the study (median age, 68; 47.1% males; median ICH growth, 2 ml). CBV and CBF values in the hemorrhagic core and perihematomal rim were inversely associated with hemorrhage growth in univariable analysis, as summarized in Table 1. After adjustment for potential confounders, reduced perihematomal CBV was the only CTP variable independently associated with increased hemorrhage growth, as shown in Table 2. The analysis with perihematomal CBV stratified in quartiles showed that hemorrhage growth was significantly higher in Q1 as compared to all the other quartiles (Q1 versus Q2, B = 0.28, $p < 0.001$; Q1 versus Q3, B = 0.21, $p < 0.001$; Q1 versus Q4, B = 0.25, $p < 0.001$).

ICH volume, NIHSS and SBP were the other variables associated with ICH growth. Secondary analyses confirmed the inverse association between perihematomal CBV and risk of ICH expansion after adjustment for ICH volume, NCCT timing, anticoagulant treatment, and admission SBP (odds ratio, 0.70; 95% confidence interval, 0.50–0.97; $p = 0.033$). Figure 1 illustrates the predicted probability of ICH expansion stratified by perihematomal CBV quartiles.

Discussion

To our knowledge, this is the first study exploring the relationship between CTP values and ICH expansion. The inverse association between perihematomal CBV levels and hematoma growth is the main finding of our analysis. This association was not linear, and the odds of experiencing ICH expansion increased only with CBV below a critical threshold. In this setting, we found that perihematomal CBV with a cut-off point <1.4 ml/100 g was the best CTP parameter to identify patients with ICH expansion. The biological mechanisms explaining our findings remain unclear. Reduced CBV in the perihematomal region may reflect the mass effect from the hematoma, that is proportional to ICH volume.[9] Another possibility is that low CBV is a consequence of impaired cerebral perfusion pressure because of intensive SBP lowering. However, when included together in the same regression model, perihematomal CBV, ICH volume, and SBP were all associated with ICH growth, independently from each other. One possible explanation is that decreased CBV in the perihematomal area promotes ICH growth because of a low pressure counteracting the force of active bleeding from ruptured small vessels.[3] Another possibility may be that very low levels of CBV lead to ischemia of small vessels surrounding the hemorrhage, promoting further vessel rupture that contribute to hematoma enlargement.[3,10] In our study, hematoma expansion was associated with decreased perihematomal CBV rather than CBF or MTT levels. This is indirectly in line with previous reports demonstrating that only reduced CBV and not CBF or MTT values predicted hemorrhagic transformation in patients with acute ischemic stroke,[11,12] where it is widely accepted that CTP can differentiate irreversibly damaged tissue, the infarct core (characterized by low CBV and low CBF but high MTT) from tissue at risk of infarction, the ischemic penumbra (characterized by normal CBV and low CBF but high MTT).[13] This may suggest that reduced CBV reflects the severity of hypoperfusion promoting endothelial injury and blood–brain barrier impairment.[12]

Another interesting result was that CBV and SBP were both independently associated with hematoma growth. SBP reduction does not influence perihematoma perfusion,[14] and elevated SBP remains a plausible therapeutic target to limit ICH growth. More studies are needed to explore the complex and incompletely understood relationship between SBP and cerebral perfusion in acute ICH.

Our results should be interpreted as preliminary and hypothesis generating because of some important limitations.

TABLE 1. Cohort Characteristics and Univariable Linear Regression of Absolute Hematoma Growth

	All (n = 155)	B (SE)	*p*
Age, median (IQR), y	68 (61–74)	–0.02 (0.01)	0.815
Sex, male, n (%)	73 (47.1)	0.08 (0.07)	0.360
History of hypertension, n (%)	94 (60.6)	0.08 (0.10)	0.200
Antiplatelet treatment, n (%)	43 (27.7)	0.09 (0.06)	0.461
Anticoagulant treatment, n (%)	7 (4.5)	0.19 (0.15)	0.056
INR, median (IQR)	1.1 (1.0–1.2)	0.05 (0.16)	0.557
SBP, mean (SD), mm Hg	152 (28)	0.24 (0.002)	0.031
DBP, mean (SD), mm Hg	85 (14)	–0.16 (0.004)	0.145
NIHSS, median (IQR)	14 (10–19)	0.55 (0.006)	<0.001
Time from onset to NCCT, h	3.0 (2.2–3.5)	0.12 (0.04)	0.140
Baseline ICH volume, median (IQR) ml	12 (5–18)	0.51 (0.001)	<0.001
ICH location, deep, n (%)	96 (61.9)	–0.13 (0.09)	0.122
Presence of IVH, n (%)	37 (23.9)	0.30 (0.09)	<0.001
Perihematoma edema, median (IQR), ml	20.2 (10.5–32.0)	0.60 (0.07)	<0.001
Hematoma core			
CBF, ml/100 g/min, median (IQR)	9,1 (6.0–13.4)	–0.36 (0.14)	<0.001
CBV, ml/100 g, median (IQR)	0.8 (0.5–1.1)	–0.33 (0.18)	<0.001
MTT, sec, median (IQR)	5.5 (4.1–6.8)	0.12 (0.24)	0.205
Perihematoma region			
CBF, ml/100 g/min, median (IQR)	30.8 (21.1–47.2)	–0.29 (0.002)	<0.001
CBV, ml/100 g, median (IQR)	2.0 (1.4–3.0)	–0.30 (0.04)	<0.001
MTT, sec, median (IQR)	5.2 (4.5–6.6)	0.25 (0.03)	0.002
Normal appearing tissue			
CBF, ml/100 g/min, median (IQR)	57.7 (43.2–79.6)	–0.15 (0.18)	0.063
CBV, ml/100 g, median (IQR)	3.3 (2.5–4.1)	–0.12 (0.21)	0.138
MTT, sec, median (IQR)	4.4 (3.6–5.1)	0.22 (0.32)	0.005
Absolute ICH growth, ml, median (IQR)	2 (1–5)	n/a	n/a
ICH expansion, n (%)	54 (34.8)	n/a	n/a
mRS >2 at 90 days, n (%)	55 (35.5)	n/a	n/a

ICH = intracerebral hemorrhage; INR = international normalized ratio; IQR = interquartile range; CBV = cerebral blood volume; CBF = cerebral blood flow; MTT = mean transit time; IVH = intraventricular hemorrhage; mRS = modified Rankin Scale; NIHSS = National Institutes of Health Stroke Scale; SBP = systolic blood pressure; DBP = diastolic blood pressure; n/a = not applicable; SE = standard error.

First, our findings were obtained from a relatively small cohort collected at a single institution. The relatively small number of patients with ICH expansion and the use of a step-wise model building strategy raise the possibility of model overfit and highlight the need for prospective confirmation of our findings on a larger sample size. Second, many CTP acquisition parameters may influence image quality, and there is no consensus on the optimal CTP acquisition protocol, limiting the

TABLE 2. Multivariable Linear Regression of Absolute ICH Growth

	B (SE)	*p*
ICH volume	0.61 (0.06)	**<0.001**
Perihematoma CBV	–0.20 (0.12)	**<0.001**
NIHSS	0.19 (0.14)	**0.001**
SBP	0.11 (0.30)	**0.019**
	B (SE)	***p***
ICH volume	0.61 (0.06)	**<0.001**
Perihematoma CBV quartiles		
Q1 (<1.4 ml/100 g)	0.28 (0.15)	**<0.001**
Q2 (1.4–2.0 ml/100 g)	Reference	
Q3 (2.1–3.0 ml/100 g)	0.07 (0.15)	0.232
Q4 (>3.0 ml/100 g)	0.03 (0.15)	0.602
NIHSS	0.20 (0.14)	**<0.001**
SBP	0.11 (0.29)	**0.017**
	B (SE)	***p***
ICH volume	0.61 (0.06)	**<0.001**
Perihematoma CBV quartiles		
Q1 (<1.4 ml/100 g)	0.21 (0.15)	**<0.001**
Q2 (1.4–2.0 ml/100 g)	–0.07 (0.15)	0.232
Q3 (2.1–3.0 ml/100 g)	Reference	
Q4 (>3.0 ml/100 g)	–0.04 (015)	0.527
NIHSS	0.20 (0.14)	**<0.001**
SBP	0.11 (0.29)	**0.017**
	B (SE)	***p***
ICH volume	0.61 (0.06)	**<0.001**
Perihematoma CBV quartiles		
Q1 (<1.4 ml/100 g)	0.25 (0.16)	**<0.001**
Q2 (1.4–2.0 ml/100 g)	–0.03 (0.15)	0.602
Q3 (2.1–3.0 ml/100 g)	0.04 (0.15)	0.527
Q4 (>3.0 ml/100 g)	Reference	
NIHSS	0.20 (0.14)	**<0.001**
SBP	0.11 (0.29)	**0.017**

ICH = intracerebral hemorrhage; CBV = cerebral blood volume; NIHSS = National Institutes of Health Stroke Scale; SBP = systolic blood pressure; SE = standard error.

generalizability of our results.[15] Third, ICH volume measurement with the ABC/2 method may be inaccurate, especially compared to semiautomated analysis.[16] Fourth, only admission SBP values were analyzed, and therefore we were not able to further explore the interaction between perihematoma perfusion and blood pressure (BP) reduction. However, all patients received the same BP treatment, according to the American Heart Association/American Stroke Association guidelines.[17] Fifth, CTP may not be widely available, and it remains to be determined whether this technique can improve the stratification of ICH expansion risk compared with other imaging markers.[18] Sixth, the relationship between perihematomal perfusion and imaging signs of ICH expansion, such as the spot sign or NCCT markers, remain unclear. Future studies should investigate whether perihematomal CBV remains associated with ICH growth after adjustment for these markers and also test whether the integration of different CT modalities provides additional yield in the stratification of ICH expansion risk.[19] Finally, this is not a randomized study, and the influence of unmeasured confounding factors cannot be excluded. In conclusion, our results provide further insights into the pathophysiology of ICH expansion, raising the intriguing hypothesis that reduced CBV in the area surrounding the hemorrhage may promote ICH growth. Further studies appear warranted to characterize the biological mechanisms mediating this association.

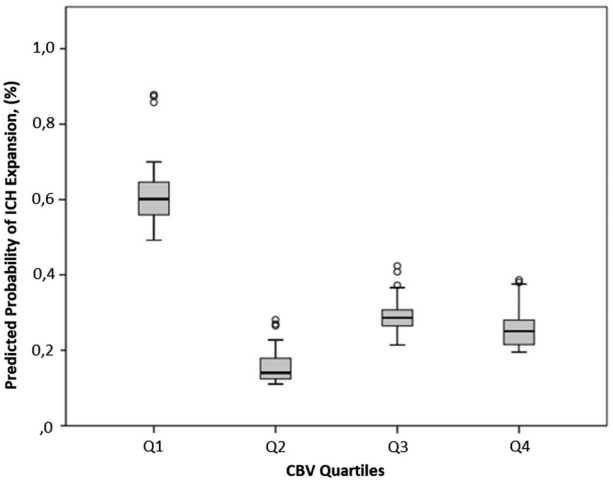

FIGURE 1: Predicted probability of ICH expansion stratified by perihematomal CBV quartiles. Q1, CBV <1.4 ml/100 g; Q2, CBV 1.4 to 2.0 ml/100 g; Q3, 2.1 to 3.0 ml/100 g; Q4, CBV (>3.0 ml/100 g). ICH expansion was defined as ICH growth >33% or >6 ml, and every patient's predicted probability of ICH expansion was calculated using individual data and logistic regression model estimates and is expressed as a continuous variable ranging from 0 to 1. CBV = cerebral blood volume; ICH = intracerebral hemorrhage.

Author Contributions

Conception and design of study: A.M., E.F. Acquisition and analysis of data: all authors.

Drafting manuscript and figures: all authors.

Potential Conflicts of Interest

Nothing to report.

References

1. Dowlatshahi D, Demchuk AM, Flaherty ML, et al. Defining hematoma expansion in intracerebral hemorrhage: relationship with patient outcomes. Neurology 2011;76:1238–1244.
2. Brouwers HB, Greenberg SM. Hematoma expansion following acute intracerebral hemorrhage. Cerebrovasc Dis 2013;35:195–201.
3. Schlunk F, Greenberg SM. The pathophysiology of intracerebral hemorrhage formation and expansion. Transl Stroke Res 2015;6:257–263.
4. Liebeskind DS. Imaging the future of stroke: II. Hemorrhage. Ann Neurol 2010;68:581–592.
5. Fainardi E, Borrelli M, Saletti A, et al. Temporal changes in perihematomal apparent diffusion coefficient values during the transition from acute to subacute phases in patients with spontaneous intracerebral hemorrhage. Neuroradiology 2013;55:145–156.
6. Fainardi E, Borrelli M, Saletti A, et al. CT perfusion mapping of hemodynamic disturbances associated to acute spontaneous intracerebral hemorrhage. Neuroradiology 2008;50:729–740.
7. Padroni M, Bernardoni A, Tamborino C, et al. Cerebral blood volume ASPECTS is the best predictor of clinical outcome in acute ischemic stroke: a retrospective, combined semi-quantitative and quantitative assessment. PLoS One 2016;11:e0147910.
8. Brouwers HB, Chang Y, Falcone GJ, et al. Predicting hematoma expansion after primary intracerebral hemorrhage. JAMA Neurol 2014;71:158–164.
9. Keep RF, Hua Y, Xi G. Intracerebral haemorrhage: mechanisms of injury and therapeutic targets. Lancet Neurol 2012;11:720–731.
10. Rosand J, Eskey C, Chang Y, et al. Dynamic single-section CT demonstrates reduced cerebral blood flow in acute intracerebral hemorrhage. Cerebrovasc Dis 2002;14:214–220.
11. Jain AR, Jain M, Kanthala AR, et al. Association of CT perfusion parameters with hemorrhagic transformation in acute ischemic stroke. Am J Neuroradiol 2013;34:1895–1900.
12. Batchelor C, Pordeli P, d'Esterre CD, et al. Use of noncontrast computed tomography and computed tomographic perfusion in predicting intracerebral hemorrhage after intravenous alteplase therapy. Stroke 2017;48:1548–1553.
13. Heit JJ, Wintermark M. Perfusion computed tomography for the evaluation of acute ischemic stroke: strengths and pitfalls. Stroke 2016;47:1153–1158.
14. Butcher KS, Jeerakathil T, Hill M, et al. The intracerebral hemorrhage acutely decreasing arterial pressure trial. Stroke 2013;44:620–626.
15. Kudo K, Sasaki M, Yamada K, et al. Differences in CT perfusion maps generated by different commercial software: quantitative analysis by using identical source data of acute stroke patients. Radiology 2010;254:200–209.
16. Huttner HB, Steiner T, Hartmann M, et al. Comparison of ABC/2 estimation technique to computer-assisted planimetric analysis in warfarin-related intracerebral parenchymal hemorrhage. Stroke 2006;37:404–408.
17. Hemphill JC III, Greenberg SM, Anderson CS, et al; American Heart Association Stroke Council; Council on Cardiovascular and Stroke Nursing; Council on Clinical Cardiology. Guidelines for the management of spontaneous intracerebral hemorrhage: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 2015;46:2032–2060.
18. Morotti A, Boulouis G, Romero JM, et al; ATACH-II and NETT investigators. Blood pressure reduction and noncontrast CT markers of intracerebral hemorrhage expansion. Neurology 2017;89:548–554.
19. Morotti A, Boulouis G, Charidimou A, et al. Integration of computed tomographic angiography spot sign and noncontrast computed tomographic hypodensities to predict hematoma expansion. Stroke 2018;49:2067–2073.