neurocritical care society Neurocrit Care (2008) 9:27–30
DOI 10.1007/s12028-007-9004-4

ORIGINAL PAPER

Reduced Ipsilateral Hemispheric Cerebral Blood Flow at Admission is Predictive of Vasospasm with Infarction after Aneurysmal Subarachnoid Hemorrhage

Rishi Gupta · Elizabeth A. Crago · Matthew Gallek · Michael Horowitz · Leslie Hoffman · Tudor Jovin · Howard Yonas

Published online: 30 October 2007

Abstract
Background and Purpose Cerebral vasospasm (CV) with infarction causes a significant degree of morbidity and mortality after aneurysmal subarachnoid hemorrhage (aSAH). We sought to determine if reduced cerebral blood flow (CBF) on Xenon CT within 48 h of the ictus was predictive of developing CV with infarction.
Methods This is a prospective study from 1999 to 2006 of 97 patients with aSAH who underwent Xenon CT within 48 h of their bleed. Demographic, clinical, radiographic, and angiographic parameters were investigated as potential risk factors for the development of CV with infarction. A binary logistic regression analysis was performed to determine the independent predictors of this endpoint.
Results A total of 97 patients with a mean age of 54 ± 12 years were studied. A total of 78 (80.4%) patients presented with a Fisher grade of 3 and 51 (52.6%) patients with a Hunt Hess score ≥3. CV with infarction was found in 33 (34%) patients. In univariate modeling, younger patients with a Fisher scale of 3 or a reduced ipsilateral mean hemispheric CBF had an association with developing CV with infarction. In binary logistic regression modeling, patients with lower initial hemispheric CBF's were at a significant risk of CV with infarction in the ipsilateral hemisphere.
Conclusions Lower initial CBF at presentation is a risk factor for developing CV with infarction. These findings may help in early prediction of this entity and may have therapeutic implications in the future.

Keywords Cerebral blood flow · Subarachnoid hemorrhage · Vasospasm · Xenon CT

R. Gupta
Department of Neurology, Division of Cerebrovascular Diseases, Michigan State University, East Lansing, MI, USA

R. Gupta · T. Jovin
Department of Neurology, Stroke Institute, University of Pittsburgh Medical Center, Pittsburgh, PA, USA

E. A. Crago · M. Gallek · L. Hoffman
School of Nursing, University of Pittsburgh Medical Center, Pittsburgh, PA, USA

M. Horowitz
Department of Neurosurgery, University of Pittsburgh Medical Center, Pittsburgh, PA, USA

H. Yonas (✉)
Department of Neurosurgery/MSC 10 5615, University of New Mexico, Albuquerque, NM 87131-0001, USA
e-mail: hyonas@salud.unm.edu

Aneurysmal subarachnoid hemorrhage (aSAH) occurs in 10 per 100,000 people in the United States [1, 2]. Despite advances in the treatment of the disease, cerebral vasospasm (CV) remains poorly understood and has been linked to higher rates of morbidity after aSAH [3]. The Fisher scale is commonly utilized as a predictor of patients at risk of developing CV [4]. Additional factors such as trends in transcranial doppler velocity and location of aneurysm in the anterior circulation have been linked to developing symptomatic CV [5]. The peak time of CV occurs between days 5 and 10 from the onset of hemorrhage [6], but it is unclear if physiologic parameters may be of value in predicting patients at risk.

Early prediction of patients at risk for CV can aid in understanding the physiologic and biochemical pathways involved. We hypothesized that patients at risk for CV with infarction likely have reduced hemispheric cerebral blood flow (CBF) within the first 48 h from the ictus of the

hemorrhage. This may point to CV being a continuous process that starts in small vessels not visualized on angiography, but represented by reduction of CBF.

Methods

Study Population and Design

This was a prospective study of a subset of patients recruited in an ongoing NIH funded clinical study (RO1NR004339). The study period was from 1999 to 2006 and included patients who were between the ages of 18 and 75 with a SAH secondary to a cerebral artery aneurysm and a Hunt and Hess grade of $\geq$2 and/or Fisher scale $\geq$1. Patients were included only if they underwent a Xenon CT within 48 h of symptom onset and after the aneurysm was secured either through coil embolization or microsurgical clipping in the operating room. Patients with a pre-existing neurological deficit, or a SAH resulting from trauma, arterio-venous malformation (AVM), or mycotic aneurysm were excluded. After screening criteria were completed, patients or their proxy were consented for study participation as approved by our hospital Institutional Review Board. A total of 97 patients met inclusion/exclusion criteria for this study. All patients were monitored from day 1 up to day 14-post-hemorrhage for purposes of data collection as part of the study.

Each patient underwent a CT head without contrast at the time of admission and a CT angiogram of the head and neck or a diagnostic cerebral angiogram to determine the location of the ruptured aneurysm. If any neurological deterioration was evident, a subsequent head CT was performed as part of standard of care to look for the cause of neurologic decline. If the head CT did not show evidence of rebleed or hydrocephalus and there was no evidence of metabolic or infectious etiology to explain the decline, a cerebral angiogram was performed to assess for CV. Prior to discharge, each patient underwent a follow up head CT between day 10 and 14. If an infarct was present on head CT in the same territory as CV defined as luminal narrowing of the ipsilateral cerebral vessel of >50% then the patient was classified as having CV with infarction. This group of patients were compared with the patients without evidence of CV or infarction to determine if a lower baseline cerebral blood flow (CBF) on Xenon CT was predictive of the development of CV with infarction.

As part of our protocol for managing patients with aneurysmal SAH, patients were maintained in a euvolemic state and the blood pressure parameters were liberalized after the aneurysm was secured. Triple H therapy was only instituted in patients who developed vasospasm. If the patient did not respond to triple H therapy they were brought to angiography for infusion of papaverine intra-arterially or nicardipine or balloon angioplasty if the vessel was amenable to this therapy.

Xenon Head CT

Xenon head CT's were completed on patients within 48 h of symptom onset using the protocol that has been previously published [7, 8]. The regions of interest (ROI) were also tabulated as previously published. The ROI's were averaged for each hemisphere and recorded. The mean hemispheric CBF was utilized in the analysis to determine if there were differences in patients who developed CV with infarction versus those who did not.

Data Collection

Clinical data was acquired by members of the research staff (MG and EC) using standardized data acquisition forms that were used to collect demographic information and prior medical historical information. Additionally, blood pressure values and carbon dioxide values at the time of XeCT were collected with standardized data sheets. CT studies were reviewed by two of the authors (MH and HY) to determine the initial Fisher grade and areas of hypodensity that were considered to be infarction on follow-up head CT scans. CT angiograms and diagnostic angiograms were reviewed by two authors (MH and HY) to review the location of the aneurysm, size of the aneurysm, and evidence of vasospasm defined as luminal narrowing >50%. XeCT images were reviewed by one of the authors (RG) who was blinded to the angiographic and CT angiographic images.

Statistics

A univariate analysis was performed using collected demographic, clinical, and radiographic parameters. Continuous variables were assessed using a student's *t*-test, while dichotomous variables were tested using a Fisher's exact test. The right and left hemisphere was analyzed separately. A binary logistic regression was performed of all univariate variables with a P-value < 0.10 using the enter method. Variables with a P-value < 0.05 were considered independent predictors of patients being at risk for the development of CV with infarction.

Results

A total of 97 patients were studied with a mean age of 54 $\pm$ 12 years. A total of 78 (80.4%) patients were noted

to have a Fisher grade of 3 and 51 (52.6%) patients presented with a poor clinical grade (Hunt Hess score ≥3). Table 1 summarizes the demographic information for our cohort. A total of 33 (34%) patients developed CV with infarction.

Table 2 summarizes the univariate analysis comparing patients who developed CV with infarction versus patients who did not. Patients who were younger, with a Fisher Grade of 3 or a reduced ipsilateral hemispheric CBF within 48 h from initial hemorrhage were more likely to develop CV with infarction.

In multivariate analysis, patient with a lower hemispheric CBF in the left MCA territory were at a significantly higher risk of developing CV with infarction in the left hemisphere [OR = 0.93, 95% CI (0.89–0.98), $P < 0.015$]. Similarly, patients with lower hemispheric CBF in the right MCA territory were at a significantly higher risk of developing CV with infarct in its territory [OR = 0.94, 95% CI (0.90–0.98), $P < 0.025$].

Discussion

This study shows that patients who present with lower baseline mean hemispheric CBF values are at a significantly higher risk of developing CV with infarction in the ipsilateral cerebral vessel. This finding may help better understand the pathophysiology of earlier prediction of patients at risk for CV with infarction. There are two plausible explanations for our findings in this study.

Table 1 Patient demographics

	All Patients
Age	54.1 (SD = 12.2)
Gender—Male	22 (22.7%)
Race—Black/Asian	9 (9.3%)
HH ≥ 3	51 (52.6%)
Fisher 3	78 (80.4%)
Aneurysm site	
ACA	39 (40.3%)
MCA	13 (13.4%)
ICA	12 (12.4%)
Vertebrobasilar	33 (34.0%)
Treatment	
Clip	64 (65.9%)
Coil	32 (32.9%)
Neither	1 (1.0%)
Cerebral vasospasm with infarct	
Right Hemisphere	20
Left Hemisphere	13

The first is that this may represent a state of dysautoregulation that we are detecting and thus patients who are not compensating adequately present with a lower CBF initially. Others have shown that in patients who present with impairment of autoregulation [9, 10] may be at risk of not being able to maintain perfusion the territories affected by CV. Brain tissue oxygenation measurements through Licox probes (Integra Neurosciences) placed in the brain parenchyma can offer continuous measurements and can be utilized to estimate CBF measurements in the brain [11]. Recently, it has been shown that patients with aSAH who develop a lower brain tissue oxygenation level between day 5 and 8 are at a higher risk for delayed cerebral infarction [12]. Interestingly, this study demonstrated that the brain tissue oxygen pressure reactivity was the most sensitive test in predicting patients at risk for ischemia as this measurement is a direct correlate to autoregulation of the brain [13]. The patients who developed ischemia presented with lower brain tissue oxygenation levels at day 1 and 2 but the levels reached a nadir between day 5 and 8 [12]. This finding is being corroborated by our current study that baseline CBF measurements may be detected on Xenon CT without placement of an invasive probe. We do not have measurements at day 5 on this cohort and further study into sequential imaging may detect further decreases in CBF which may help in defining thresholds that would be important for clinicians to utilize in predicting patients at risk for delayed ischemia due to vasospasm. Additionally, we do not have direct measurements of autoregulation in this cohort, which will be utilized in future study design to further understand the pathophysiology of early detection of patients at risk for this devastating condition.

The second explanation for our findings is that the low initial CBF represents a continuum of CV. It may be that the distal most branches that cannot be detected angiographically may undergo vasospasm early and this is not clinically detected until the medium sized vessels become involved. Angiographic studies looking at the cerebral circulation time to estimate vasospasm of the microcirculation have shown that regional CBF is lower in patients with prolonged cerebral circulation time despite mild angiographic vasospasm of a medium sized vessel [11]. It is not clear if there is progression of vasospasm from the microcirculation to more proximal vessels or if impairment of the microcirculation itself causes ischemia independently. In our cohort of patients with lower initial hemispheric CBF's were more likely to develop CV with infarct in the ipsilateral territory.

The limitations to this study include not having sequential Xenon CT imaging on our patients in the time period where CV most commonly peaks (days 5–10). A second limitation is that a large proportion of our patients in this study group presented with a Fisher Grade of 3.

Table 2 Univariate Analysis for predictors of cerebral vasospasm with infarction after aneurysmal subarachnoid hemorrhage

	No CV Left Hemisphere ($N = 84$), N (%)	CV with infarct Left Hemishpere ($N = 13$), N (%)	P-value	No CV Right Hemisphere ($N = 77$), N (%)	CV with infarct Right Hemisphere ($N = 20$), N (%)	P-value
Age, mean ± SD	56.2 ± 11.4	51.8 ± 10.9	0.034	55.5 ± 11.6	51.26 ± 11.3	0.042
Gender—Male	19 (23)	3 (24)	0.62	20 (26)	2 (10)	0.82
African American Race	5 (6)	3 (23)	0.11	6 (8)	2 (10)	0.34
HH $\geq$ 3	40 (48)	6 (46)	0.77	36 (48)	10 (50)	0.83
Fisher Grade 3	43 (51)	9 (69)	0.02	36 (48)	16 (80)	0.012
SBP, mean ± SD	132 ± 18	135 ± 19	0.87	132 ± 18	134 ± 18	0.91
pCO_2, mean ± SD	35.1 ± 3.6	34.9 ± 3.4	0.62	35.1 ± 3.5	34.8 ± 5.4	0.518
Ipsilateral Mean CBF	45.2 ± 13.9	35.7 ± 8.2	0.017	44.1 ± 12.1	38.1 ± 9.8	0.03
Clipping	54 (64)	10 (76)	0.53	51 (66)	13 (65)	0.53

There is thus some bias with severity of clinical presentation and amount of blood on the initial CT scan of the brain. Future investigations comparing early CBF with a later time point of CBF will help to dileneate thresholds for patients at risk for developing ischemia due to CV.

In conclusion, we have found that patients who present with a lower ipsilateral hemispheric CBF within 48 h from the ictus of the hemorrhage are at a significantly higher risk of developing CV with infarction.

Acknowledgements The authors would like to thank Yue Fang Chang for her assistance with data analysis and Holly Kromer for aiding in collection of the XeCT CBF data. We are also grateful to the nurses and staff in the Neurovascular ICU, Interventional Radiology and the CT department at the University of Pittsburgh Medical Center Presbyterian.

References

1. Wijdicks EF, Kallmes DF, Manno EM, Fulgham JR, Piepgras DG. Subarachnoid hemorrhage: neurointensive care and aneurysm repair. Mayo Clinic Proc 2005;80:550–9.
2. Schievink WI. Intracranial aneurysms. N Engl J Med 1997; 336:28–40.
3. Solenski NJ, Haley EC Jr, Kassell NF, Kongable G, Germanson T, Truskowski L, et al. Medical complications of aneurysmal subarachnoid hemorrhage: a report of the multicenter, cooperative aneurysm study. Crit Care Med 1995;23:1007–17.
4. Fisher CM, Kistler JP, Davis JM. Relation of cerebral vasospasm to subarachnoid hemorrhage visualized by computerized tomographic scanning. Neurosurgery 1980;6:1–9.
5. Qureshi AI, Sung GY, Razumovsky AY, Lane K, Straw RN, Ulatowski JA. Early identification of patients at risk for symptomatic vasospasm after aneurysmal subarachnoid hemorrhage. Crit Care Med 2000;28:984–90.
6. Weir B, Grace M, Hansen J, Rothberg C. Time course of vasospasm in man. J Neurosurg 1978;48:173–8.
7. Yonas H, Pindzola RP, Johnson DW. Xenon/computed tomography cerebral blood flow and its use in clinical management. Neurosurg Clin N Am 1996;7:605–16.
8. Gur D, Yonas H, Good WF. Local cerebral blood flow by xenon-enhanced CT: current status, potential improvements, and future directions. Cerebrovasc Brain Metab Rev 1989;1:68–86.
9. Yundt KD, Grubb RLJ, DIringer MN, Powers WJ. Autoregulatory vasodilatation of parenchymal vessels is impaired during cerebral vasospasm. J Cereb Blood Flow Metab 1998;18:419–24.
10. Lang EW, Diehl RR, Mehdorn HM. Cerebral autoregulation testing after aneurysmal subarachnoid hemorrhage: the phase relationship between arterial blood pressure and cerebral blood flow velocity. Crit Care Med 2001;29:158–63.
11. Ohkuma H, Manabe H, Tanaka M, Suzuki S. Impact of cerebral microcirculatory changes on cerebral blood flow during cerebral vasospasm after aneurysmal subarachnoid hemorrhage. Stroke 2000;31:1621–7.
12. Jaeger M, Schumann MU, Soehle M, Nagel C, Meixensberger J. Continuous monitoring of cerebrovascular autoregulation after subarachnoid hemorrhage by brain tissue oxygen pressure reactivity and its relation to delayed cerebral infarction. Stroke 2007;38:981–6.
13. Jaeger M, Schuhmann MU, Soehle M, Meixensberger J. Continuous assessment of cerebrovascular autoregulation after traumatic brain injury using brain tissue oxygen pressure reactivity. Crit Care Med 2006;34:1783–8.