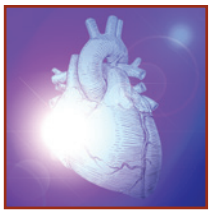

Cerebral Perfusion Pressure and Delayed Cerebral Ischemia After Aneurysmal Subarachnoid Hemorrhage

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Background Whether delayed cerebral ischemia (DCI) mediates the relationship between Hunt and Hess grade and outcomes after aneurysmal subarachnoid hemorrhage remains unknown.

Objectives To investigate the relationship between cerebral perfusion pressure, DCI, Hunt and Hess grade, and outcomes after aneurysmal subarachnoid hemorrhage.

Methods DCI was defined as neurological deterioration due to impaired cerebral blood flow. Relationships between minimum cerebral perfusion pressure and onset and occurrence of DCI were tested by using logistic regression and the accelerated failure time model. The mediation effect of DCI on relationships between Hunt and Hess grade and outcomes was tested by using the bootstrap confidence interval. Outcomes at 3 and 12 months included mortality and neuropsychological, functional, and physical outcomes.

Results DCI occurred in 211 patients (42%). About one-third of the patients had poor functional outcome at 3 (32%) and 12 (30%) months. Impaired neuropsychological outcome was observed in 33% of patients at 3 months and 17% at 12 months. For every increase of 10 mm Hg in cerebral perfusion pressure, odds for DCI increased by 2.78 (95% CI, 2.00-3.87). High perfusion pressure was associated with earlier onset of DCI ($P<.001$).

Conclusions DCI does not mediate the relationship of Hunt and Hess grade to functional outcome or death. The relationship between cerebral perfusion pressure and DCI was most likely due to induced hypertension and hypervolemia. Clinical guidelines may need to include limits for induced hypertension. (*American Journal of Critical Care.* 2015;24:e65-e71)

doi: http://dx.doi.org/10.4037/ajcc2015913

Mortality and severe morbidity after aneurysmal subarachnoid hemorrhage (aSAH) are often associated with delayed cerebral ischemia (DCI), a complication that occurs in 19% to 63% of patients with aSAH.[1-4] DCI typically occurs 3 to 15 days after the initial bleeding and peaks on day 7.[5] DCI is associated with poor outcomes and numerous complications, including myocardial infarction, arrhythmias, pulmonary edema, cerebral edema, inability to perform activities of daily living, cognitive impairment, and death.[2,6] Thus, prevention of DCI is key to improving outcomes after aSAH.

DCI occurs as a result of impairment in cerebral blood flow or hypoperfusion, which is not uncommon after aSAH.[2,7] Cerebral hypoperfusion can be local, due to focal vascular alterations such as vasospasm and microthrombi, or global, due to pressure or flow deficits such as inadequate cerebral perfusion pressure (CPP). Current interventions focus on treatment of focal vascular changes (eg, vasospasm), but these interventions have had limited success.[8] Attempts to prevent vasospasm and microthrombi by using endothelin antagonists and antiplatelet agents have not resulted in a marked reduction in DCI or an improvement in outcomes.[9,10] Most patients with moderate to severe angiographic evidence of vasospasm are asymptomatic,[11] suggesting that vasospasm and DCI are not strongly correlated and that treatment of focal perfusion deficits may be insufficient to prevent DCI.

Delayed cerebral ischemia occurs 3 to 15 days after the initial bleeding.

Exploring the relationship between DCI and CPP therefore appears warranted. For example, whether or not risk for infarction that leads to DCI varies with a change in CPP is not clear. Furthermore, severity of signs and symptoms at admission as indicated by the Hunt and Hess grade is associated with complications and poor outcomes.[12] However, the mechanistic link between Hunt and Hess grade and poor outcomes remains unclear. Whether or not DCI is an explanation, in part, of this relationship is unknown. The purposes of this study were to investigate the relationship between DCI and CPP and to determine if DCI mediates the relationship between Hunt and Hess grade and outcomes after aSAH.

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Methods

Sample and Setting

The sample population consisted of patients with aSAH admitted to a regional medical center between May 1999 and October 2011 and enrolled in an ongoing National Institutes of Health study (R01NR004339). SAH was diagnosed by using computed tomography (CT), and presence of an aneurysm was diagnosed by using digital subtraction angiography. Eligible patients were 21 to 75 years old and had spontaneous rupture of an aneurysm and an original Fisher grade of 2 or greater. In addition to the eligibility criteria of the parent study, the current study included patients who had external ventricular drains (EVDs) for measurement of intracranial pressure (ICP). Exclusion criteria included preexisting chronic neurological deficit or traumatic or mycotic aneurysm. Patients were recruited within the first 5 days after aSAH and followed up for 14 days after rupture of the aneurysm or until discharge.

Cerebral Perfusion Pressure

CPP was defined as the difference between mean arterial pressure (MAP) and ICP and was measured in millimeters of mercury. MAP was measured via an arterial catheter or a blood pressure cuff. ICP measurements were obtained by using the EVD. The transducer was leveled at the external acoustic meatus. MAP and ICP were measured every 2 hours or more frequently if a patient's neurological or systemic status was unstable. Data were available for 14 days unless patients were admitted more than 1 day after bleeding or discharged before 14 days.

Minimum CPP values were obtained within 12 hours before occurrence of DCI.

Delayed Cerebral Ischemia

DCI was defined as neurological deterioration not attributable to rebleeding, seizures, hydrocephalus, or cerebral edema and evidence of impaired cerebral blood flow.[3] DCI was diagnosed when a patient had neurological deterioration and 1 or more indications of impaired cerebral blood flow (Table 1). Indications of neurological deterioration included decrease in level of consciousness, new focal neurological deficit, deterioration in pupillary reaction, and worsening condition as indicated by the score on the National Institutes of Health Stroke Scale. Cerebral blood flow assessments within 12 hours of the observed neurological deterioration were evaluated.

Cerebral blood flow was assessed by using head CT and CT perfusion scans, cerebral angiography, and/or transcranial Doppler imaging for measurement of blood flow velocities. When patients had daily transcranial Doppler imaging, impaired cerebral blood flow was defined as a systolic velocity greater than 200 mL/s in the middle cerebral artery or a Lindegaard ratio greater than 3.0. Head CT and CT perfusion scans within the 12-hour temporal window of the neurological deterioration were reviewed for the presence of cerebral ischemia, infarction, and abnormal blood flow. Finally, cerebral angiographic findings obtained within the same temporal window were independently reviewed and evaluated for evidence of vascular narrowing, with narrowing greater than 25% indicative of clinically significant vasospasm.

Patients were excluded from analysis if their DCI status could not be determined (eg, they were comatose and sedated, and thus a decline in neurological status could not be evaluated). The variable time to DCI was defined as the number of hours from rupture of the aneurysm to the time of DCI diagnosis.

Severity of Signs and Symptoms

The Hunt and Hess grade was determined by using a 5-point scale to quantify the severity of nontraumatic SAH on the basis of signs and symptoms at the time of admission to the hospital.[13] For the analysis reported here, the grade was dichotomized into poor (grade 3-5) and good (grade 1-2).

Outcomes

A comprehensive set of measurements that included mortality and neuropsychological, functional, and physical outcomes were assessed as part of the ongoing parent study. Neuropsychological outcomes assessed at 3 and 12 months included 7 domains: attention, learning and memory, psychomotor speed, mental flexibility, executive function, visuospatial ability, and language (Table 2). Because of concerns about sample size in each domain, neuropsychological function was dichotomized as impaired and not impaired. All test scores in all domains were converted to *z* scores. A *z* score less than or equal to -1.5 in at least 2 tests or a *z* score less than or equal to -2.0 in at least 1 test indicated neuropsychological impairment.[14] Functional outcomes were assessed by using the Modified Rankin Scale (MRS): good, 0-2; poor, 3-6. The physical component score of the Medical Outcomes Study 36-Item Short-Form Health Survey II was used to assess physical function.[15] Validity and reliability of the preceding outcome measures have been well established in patients with neurological injury.[16]

Table 1
Diagnosis of delayed cerebral ischemia in 83 patients

Basis for diagnosis	No. of patients
Abnormal findings on angiography and deterioration in neurological status	7
Abnormal findings on transcranial Doppler and deterioration in neurological status	29
Abnormal findings on angiography and transcranial Doppler imaging and deterioration in neurological status	45
Abnormal findings on computed tomography or computed tomographic perfusion scan and deterioration in neurological status	2

Patients with preexisting chronic neurologic deficit or traumatic or mycotic aneurysm were excluded.

Confounding Variables

Because higher measures of depression and anxiety have been associated with poorer scores on neuropsychological tests,[17,18] controls for these variables were used in the analysis of neuropsychological outcomes. Depressive symptoms were assessed by using the Beck Depression Inventory II.[19] Anxiety was measured by using the State component of the State-Trait Anxiety Inventory.[20] Validity and reliability have been well established for both the Beck Depression Inventory II and the State-Trait Anxiety Inventory in patients with neurological injuries.[19,21] Age, years of education, Hunt and Hess grade, and aneurysm treatment method (surgical clipping or endovascular coiling) are often associated with DCI and outcomes after aSAH[22,23] and so were included as control variables.

Statistical Analysis

Data were analyzed by using IBM SPSS 19 (IBM SPSS), Mplus 6 (Muthén & Muthén), and SAS 9.2 (SAS Institute Inc) software. Descriptive statistics including means, standard deviations,

Table 2
Description of domains and tests of neuropsychological function after aneurysmal subarachnoid hemorrhage

Domain: Test	3 months			12 months		
	No. of patients	Mean (SD)	% Impaired per domain	No. of patients	Mean (SD)	% Impaired per domain
Attention: Trail Making Test A	77	49 (35)	0	63	47 (36)	0
Learning and Memory:			23			16
Digit Span Forward	75	6 (1)		63	7 (1)	
Digit Span Backward	75	4 (1)		62	5 (2)	
Logical Memory						
Story A immediate recall	77	11 (4)		62	11 (5)	
Story A delayed recall	76	7 (5)		62	9 (5)	
Story B immediate recall	77	10 (4)		62	9 (4)	
Story B second immediate recall	77	13 (5)		61	13 (5)	
Story B delayed recall	76	10 (6)		62	11 (5)	
Rey Complex Figure						
Immediate recall	76	13 (8)		—	—	
Delayed recall	75	13 (8)		—	—	
Psychomotor speed: Grooved Pegboard			0			0
Dominant hand	75	107 (50)		62	95 (41)	
Nondominant hand	72	114 (41)		62	101 (35)	
Mental Flexibility: Trail Making Test B	74	114 (63)	0	60	99 (55)	0
Executive Function: Stroop Color/Word Test	73	42 (11)	4	61	44 (12)	3
Visuospatial ability: Rey Complex Figure Test			7	—	—	—
Rey Figure copy score	77	29 (8)				
Language:			11			8
Controlled Word Association Test						
Number of F words	76	9 (4)		62	11 (5)	
Number of A words	76	7 (4)		62	8 (4)	
Number of S words	76	10 (4)		62	11 (4)	
Animal Naming Test						
Number of animals	75	15 (6)		62	16 (5)	

and percentages were used to describe the sample. Logistic regression was used to test the relationship between CPP and DCI. The accelerated failure time model was used to test whether CPP was associated with the onset of DCI. Finally, bias-corrected bootstrapping was used to determine if DCI mediates the relationship between Hunt and Hess grade and outcomes. All comparisons were performed a priori; thus no correction for α level was made.

Results

Sample Characteristics

The 211 patients in the study had a mean age of 53 (SD, 11) years and were predominantly female (66%) and white (88%). Mean years of education was 13 (SD, 2). Approximately 62% had aneurysm coiling, 67% had a poor Hunt and Hess grade (grade 3-5), 70% had EVDs, and 42% had DCI. DCI could not be determined for 13 patients (6%) because sedation or coma precluded assessment of deterioration in neurological status. The mean value for CPP was 53 (SD, 17) mm Hg. Mean scores on the Beck Depression Inventory II were 10 (SD, 8) at 3 months and 12 (SD, 10) at 12 months. Mean scores on the State component of the State-Trait Anxiety Inventory were 47 (SD, 6) at 3 months and 45 (SD, 6) at 12 months.

Association of High CPP Values With Increased Risk for DCI

Logistic regression was performed on DCI as a function of age, sex, Hunt and Hess grade, aneurysm treatment option, and CPP (Table 3). The overall model was significantly predictive of DCI: χ^2 ($df = 5$; $n = 196$) = 71.4; $P < .001$; Nagelkerke $R^2 = 0.41$. Analysis revealed a significant positive relationship between CPP and DCI; for every increase of 10 mm Hg in CPP, the odds for DCI increased by 2.78 (95% CI, 2.00-3.87). Furthermore, the mean value for CPP was significantly greater ($P < .001$) for patients with DCI (mean [SD], 64.6 [17] mm Hg) than for those without DCI (mean [SD], 46 [11] mm Hg).

Association of High CPP Values With Earlier Onset of DCI

The mean time for DCI diagnosis was 6 days (SD, 2.3 days) after bleeding. The analysis of the association between CPP and DCI was controlled for age, sex,

method of repair of the aneurysm, and Hunt and Hess grade. Table 4 shows that the estimate of CPP was negative (-0.283), indicating that high CPP values are associated with shorter time to DCI ($P<.001$).

DCI Did Not Mediate the Relationship Between Hunt and Hess Grade and Outcomes

Data on neuropsychological outcomes were available for 60 to 77 patients. Missing data were due to time of recruitment (neuropsychological assessments were not initiated until 2003), loss to follow-up, death, and refusal to participate in the study. Approximately one-third of the patients had a poor score on the MRS at 3 months (32%) and at 12 months (30%). Impaired neuropsychological function was observed in 33% of patients at 3 months and 17% at 12 months. Mean scores on the physical component score of the Medical Outcomes Study 36-Item Short-Form Health Survey were 0 (SD, 5) at 3 months and 22 (SD, 5) at 12 months. A total of 26% of patients were dead at 3 months and 29% at 12 months. The direct effects between Hunt and Hess grade and outcomes were assessed before the mediation effect was analyzed. The mediation effect was analyzed only when the direct effect was significant. Hunt and Hess grade was significantly related to mortality and functional outcomes at 3 and 12 months but not to physical or neuropsychological function (adjustments were made for age, method of repair of the aneurysm, education, and depression and anxiety). However, DCI did not significantly mediate the relationship between Hunt and Hess grade and functional outcome or death at either 3 months or 12 months (Table 5).

Discussion

The primary goal in this study was to determine whether a measure of global cerebral perfusion could explain, in part, the pathogenesis of DCI. Our findings indicate that CPP was positively associated with DCI and time to DCI. Further, the relationship between Hunt and Hess grade and outcomes was independent of DCI. To our knowledge, this study was the first to attempt to explain the relationship between Hunt and Hess grade and outcomes by using DCI as a mediating variable.

Relationship Between CPP and DCI

Our findings indicate that CPP was related to DCI, but the direction of the relationship was not

Table 3
Relationship between cerebral perfusion pressure and delayed cerebral ischemia: results of logistic regression

Predictor	Odds ratio	95% CI	*P*
Age	0.98	0.95-1.01	.20
Sex (female)	1.26	0.60-2.68	.54
Aneurysm treatment (coiling)	1.27	0.60-2.67	.53
Hunt and Hess grade (poor 3-5)	1.89	0.89-4.00	.10
Cerebral perfusion pressure[a]	2.78	2.00-3.87	<.001

[a] Odds ratio and 95%CI were calculated for every 10 mm Hg.

Table 4
Relationship between cerebral perfusion pressure and time to delayed cerebral ischemia: accelerated failure time model

Parameter	Estimate	SE	95% CI	χ^2	P
Age	0.002	0.006	-0.001 to 0.013	0.1	.76
Sex	-0.055	0.129	-0.308 to 0.198	0.2	.67
Aneurysm treatment	0.001	0.128	-0.250 to 0.252	0.0	.99
Hunt and Hess grade	-0.359	0.147	-0.647 to 0.071	6.0	.01
Cerebral perfusion pressure[a]	-0.283	0.035	-0.352 to 0.214	64.7	<.001

[a] Statistics calculated for every 10 mm Hg.

Table 5
Mediation effect of delayed cerebral ischemia on the relationship between Hunt and Hess grade and outcomes: bootstrap confidence interval

Variable	Coefficient	Structure coefficient with mediator	Indirect effect	
			Estimate	Bootstrap 95% CI
3-month mortality	0.48a	0.46b	0.02	-0.05 to 0.13
12-month mortality	0.54a	0.55a	0.01	-0.11 to 0.08
Score on Modified Rankin Scale				
3 months	0.63a	0.61a	0.02	-0.05 to 0.12
12 months	0.54a	0.53b	0.01	-0.07 to 0.11

[a] $P<.001$.
[b] $P<.01$.

as expected. High CPP values were associated with DCI. Most likely, high CPP values were, in part, the result of medical interventions (eg, drainage of cerebral spinal fluid and induced hypertension and hypervolemia) that most patients received prophylactically to prevent vasospasm. Because MAP and ICP (and thus CPP) are highly manipulated at the bedside, the CPP trends we observed were either a marker or a complication of treatment. Patients with higher bleeding grades (who have higher risk for complications such as vasospasm and DCI) most likely received more aggressive therapy. However, if the observed relationship between CPP and DCI were due to complications of treatment, this finding would raise several questions about induced hypertension as a prophylactic measure. Current guidelines recommend use of induced hypertension to treat or prevent DCI. However, no guidelines indicate when hypertension can be therapeutic or too aggressive or whether different treatment strategies should be used with normotensive patients compared with hypertensive patients. Future studies are needed to clarify these issues.

The relationship between aneurysm grade and outcomes was independent of delayed cerebral ischemia.

Bijlenga et al[24] reported that aSAH patients had higher CPP values during vasospasm than before vasospasm as a result of triple-H therapy (medically induced hypertension, hypervolemia, and hemodilution). Other investigators[25] found that CPP less than 70 mm Hg was associated with increased risk for brain tissue hypoxia and metabolic crisis. However, in those studies triple-H therapy was used to treat DCI, rather than as a prophylaxis, and thus did not affect CPP values before DCI. In our patients, induced hypertension and hypervolemia were used as prophylactic therapy to prevent vasospasm after the aneurysm was treated.

Outcomes and Severity of Signs and Symptoms

Our patients had impairment in 4 of the 7 neuropsychological domains (Table 2). The prevalence of impairment was highest in the learning and memory domain and lowest in the executive function domain. Other researchers[26] have reported a similar trend. Impairment (per domain) occurred in 3% to 23% of patients. A range of 14% to 61% for impairment was previously reported.[27,28] In our sample, the overall prevalence of neuropsychological impairment ranged from 33% at 3 months to 17% at 12 months. Haug et al[23] and Mayer et al[26] reported a prevalence of 27% to 46% at similar time points. Our patients' mean score on the Beck Depression Inventory II indicated normal variability at 3 months and mild mood disturbances at 12 months. However, the mean scores on the State component of the State-Trait Anxiety Inventory suggested clinically significant anxiety (score > 39 indicates significant anxiety).[29]

DCI did not mediate the relationship between Hunt and Hess grade and outcomes. This finding might be biased because of the missing data on neuropsychological function. However, the result suggests that the relationship between Hunt and Hess grade and poor outcomes is either direct or influenced by mediators other than DCI. Other potential mediators may include delayed neurological deficit, generalized cerebral edema, infarction, severity of initial bleeding, and early brain injury. These variables can have strong associations with poor outcomes after aSAH[28,30,31] and thus can be considered possible mediators. Unlike DCI, delayed neurological deficit incorporates many causes for neurological deterioration, such as hydrocephalus, fever, seizure, edema, and electrolyte abnormalities, with substantial influence on morbidity and mortality after aSAH.[32] Therefore, delayed neurological deficit might be an important mediator.

Our study had several limitations. All patients in the sample had EVDs, often used in patients with high-grade bleeding. Our results may therefore not be applicable to patients who do no have EVDs or who have low-grade bleeding. In addition, the incidence of DCI may have been overestimated in this sample of patients who required EVDs. We did not collect data on use of induced hypertension and hypervolemia or the intensity of these treatments. Such information might have provided further insight into our findings and might have helped us determine the effect of induced hypertension and hypervolemia on CPP. We did not use any formal assessment of cerebral blood flow, rather we used surrogates such as transcranial Doppler imaging. Last, patients' neuropsychological function was classified as impaired or not impaired because of concerns about the size of the sample in each domain. This classification may have resulted in loss of information. Future studies with more patients will be needed to address the effect of Hunt and Hess grade on specific domains or subdomains of neuropsychological function.

Conclusion

Patients with DCI had higher CPP values than did patients without DCI. For every increase of 10 mm Hg in CPP, the odds for DCI increased by 2.78. Future studies will need to determine whether this relationship is causal and whether increased CPP is bad or is simply a marker for interventions to treat or prevent DCI. High CPP was associated

with earlier onset of DCI. The relationship between Hunt and Hess grade and poor outcomes after aSAH was not mediated by DCI, suggesting that this relationship might be direct or due to other factors not identified in our study. Findings raise concerns about safety of induced hypertension and the need for studies that define limits for induced hypertension that are lacking in current guidelines.

ACKNOWLEDGMENTS

This research was done at the University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania.

FINANCIAL DISCLOSURES

Funding was provided by a grant (R01NR004339) from the National Institute of Nursing Research, the Nightingale Award of Pennsylvania, and the Neuroscience Nursing Foundation.

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