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Temporal Profiles of Cerebral Perfusion Pressure After Subarachnoid Hemorrhage

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Abstract

Introduction—Insufficient cerebral perfusion pressure (CPP) after aneurysmal subarachnoid hemorrhage (aSAH) can impair cerebral blood flow (CBF). We examined the temporal profiles of CPP change and tested whether these profiles were associated with delayed cerebral ischemia (DCI).

Method—CPP values were retrospectively reviewed for 238 subjects. Intracranial pressure and mean arterial pressure values were obtained every 2 hours for 14 days. Induced hypertension was utilized to prevent vasospasm. The linear and quadratic CPP change over time were tested using growth curve analysis. Multivariable logistic regression was utilized to examine the association between DCI and percentages of CPP values >110, >100, <70, and <60 mmHg. DCI was defined as neurological deterioration due to impaired CBF.

Results—Between-subjects differences accounted for 39% of variation in CPP values. There was a significant linear increase in CPP values over time ($\beta=0.06$, $SE=0.006$, $p<0.001$). The covariance ($\tau_{01} = -0.52$, $SE=0.09$, $p<0.001$) between initial CPP and linear parameter was negative, indicating subjects with high CPP on admission had a slower rate of increase whereas those with low CPP had a faster rate of increase. For every 10% increase in the proportion of CPP>100 mmHg or >110 mmHg, the odds of DCI increased by 1.21 and 1.43, respectively ($p<0.05$).

Conclusions—The longer the time patients spent with high CPP, the greater the odds for DCI. When used prophylactically, induced hypertension contributes to higher CPP values. Based on the

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CPP trends and correlations observed, induced hypertension may not confer expected benefits in patients with aSAH.

Keywords

Cerebral perfusion pressure; Mean arterial blood pressure; Subarachnoid hemorrhage; Delayed cerebral ischemia

Introduction

Impairment of cerebral blood flow is common in individuals who survive aneurysmal subarachnoid hemorrhage (aSAH). Causes include a sudden increase in intracranial pressure (ICP) that results from the initial bleeding and other secondary complications such as cerebrovascular infarction, and vasospasm.(Ansar & Edvinsson, 2008; Dankbaar et al., 2009; Gobiet, Grote, & Bock, 1975; Heinsoo et al., 1998; Nornes & Magnaes, 1972) Delayed cerebral ischemia (DCI) is often attributed to focal ischemia. When cerebral blood flow is impaired due to a focal perfusion deficit (e.g. infarction or vasospasm), collateral circulation may be recruited to keep tissue potentially recoverable (ischemic penumbra). In global ischemia (e.g. inadequate cerebral perfusion pressure), blood flow in the collateral circulation is also impaired which limits ability to preserve flow to brain tissue.(Roach, Bettermann, & Biller, 2010)

Focal perfusion deficits after aSAH, such as cerebral infarction and vasospasm, have been extensively studied as potential causes of impaired blood flow.(Carlson & Yonas, 2009; Etminan, Vergouwen, Ilodigwe, & Macdonald, 2011; Frontera et al., 2009; Juvela & Siironen, 2012; Macdonald, Pluta, & Zhang, 2007) Less attention has been given to global cerebral perfusion. Insufficient cerebral perfusion pressure (CPP) is associated with poor outcomes after aSAH.(Rasulo et al., 2012) This effect can be worse when cerebral autoregulation is impaired; a complication that is common after aSAH.(Carrera et al., 2010; Jaeger, Soehle, Schuhmann, & Meixensberger, 2012) When cerebral autoregulation is impaired, small changes in CPP might be poorly tolerated by the brain. To avoid further injury to the brain, it is important to characterize changes in CPP after aSAH and attempt to identify determinants of this change. The purpose of this study was to examine temporal profiles of CPP change after aSAH and test whether these profiles are associated with DCI.

Methods

Sample and Setting

This descriptive longitudinal study included 238 patients with aSAH recruited in an ongoing NIH-funded study (R01NR004339). Subjects were admitted to the neurovascular intensive care unit (NICU) at the University of Pittsburgh Medical Center (UPMC) between May 1999 and October 2011. Computed tomography (CT) was used to diagnose subarachnoid hemorrhage; cerebral angiography was used to diagnose the presence of an aneurysm. Inclusion criteria for the parent study were: 1) age of 21 to 75 years; 2) spontaneous aneurysm rupture, and 3) Fisher grade 2. In addition to these criteria, patients in the current study were required to have an external ventricular drain (EVD) for ICP measurement.

Patients with a preexisting chronic neurologic deficit or traumatic or mycotic aneurysm were excluded. Subjects were enrolled during the first five days after aSAH; data collection continued for 14 days after bleeding or until discharge.

Cerebral perfusion pressure (CPP)

CPP was defined as the pressure gradient between mean arterial pressure (MAP) and ICP. (Alvarez del Castillo, 2001) MAP and ICP values were retrospectively obtained from the medical record. Standards of care required MAP and ICP values be recorded every 2 hours, providing a minimum of 12 values each day, and more frequently if subjects exhibited neurologic or systemic instability. On the day of admission and discharge, fewer CPP measurements were available depending on time of admission or discharge. Data collection continued for 14 days after the bleeding onset. When a subject was admitted more than one day after bleeding or the subject was discharged before the 14-day period, CPP values were available for <14 days. MAP was measured either invasively using an arterial line or noninvasively using a blood pressure cuff. ICP was measured invasively by an EVD.

Delayed cerebral ischemia (DCI)

DCI was defined as neurological deterioration due to impaired cerebral blood flow not attributable to rebleeding, seizure, hydrocephalus, or cerebral edema. When both neurological deterioration and indications of impaired cerebral blood flow existed, a diagnosis of DCI was made. Neurological deterioration was defined as one of the following: a) deterioration in Glasgow coma scale score, b) new focal deficit, c) deterioration in pupillary reaction, or d) deterioration in the NIH Stroke Scale. Within 12 hours of the neurological deterioration (either before or after), assessment of cerebral blood flow was performed. Impairment in cerebral blood flow was indirectly assessed using the following surrogate measures: transcranial Doppler (TCD), CT and CT perfusion scans, or cerebral angiography. Daily TCD exams indicated impaired cerebral blood flow if systolic middle cerebral artery velocity was >200 ml/second or Lindegaard ratio >3.0. Head CT and CT perfusion scans were reviewed by a radiologist for the presence of cerebral ischemia and/or infarction. Cerebral angiography studies were reviewed for vascular narrowing, with narrowing > 25% indicating clinically significant vasospasm. When neurological deterioration could not be assessed due to coma or sedation and DCI status could not be determined subjects were excluded from the analysis.

Statistical analysis

Descriptive statistics using IBM SPSS 19 were used to characterize CPP changes. Admission (baseline) CPP values were defined as the first CPP value measured in the first 24 hours after bleeding was described. Admission CPP was divided into three categories using the cutoff values of <60 mmHg, 60-160 mmHg, and >160 mmHg. Next, line charts of CPP values versus time profiles over the whole observation period were created for 16 subjects randomly selected using IBM SPSS 19 “select random cases” function. This number of subjects (7%) was chosen in order to provide interpretable charts. Interpreting the charts to detect the trend of CPP change over time using all subjects would be difficult. Daily means and confidence intervals of CPP values were charted. In addition, daily means of CPP, MAP, and ICP were charted to determine whether ICP or MAP had a greater

influence on CPP. This analysis was followed up with quantitative assessment of this influence using Pearson correlation coefficients. Furthermore, the percentages of CPP values < 70 mmHg, and percentages of CPP values > 100 mmHg were obtained. Growth curve analysis was used to objectively examine the linear and quadratic rate of change of CPP over time. Three models were utilized. Model 1, an unconditional *mean* model was the baseline model that examined individual variations of CPP values with no regard to time. Because it had no time component, this model was used to assess the variation in CPP values due to between-subjects differences. Model 2, an unconditional *linear growth* model, examined individual variations/changes over time. This model was used to assess within-subject variations. Model 3, a *quadratic growth* curve model, was utilized because individual change trajectories of CPP were nonlinear; therefore using a higher order polynomial model was warranted. Lastly, the percentages of CPP values <70, <60, >100, and >110 mmHg were calculated and used as predictors of DCI. Because data were obtained intermittently and not continuously, these percentages were used as surrogate measures for the length of time subjects experienced low or high CPP. Each percentage was analyzed in a separate multivariable logistic regression model controlling for aneurysm treatment (endovascular coiling vs. surgical clipping), and Hunt and Hess grade (low grade: 1-2, high grade: 3-5).

Results

Subjects (n=238) were middle age adults (53 ± 11.4 years), predominantly female (69%) and Caucasian (88%). DCI data were available for 211 subjects, but deterioration in neurological exam could not be evaluated in 13 subjects. DCI was diagnosed in 41.9% of the remaining subjects (n=198). Other clinical characteristics are shown in table 1.

At baseline, the mean CPP was 70 ± 17.5 mmHg with a range of 30-129 mmHg. The minority (28%) had a CPP < 60 mmHg and the majority (72%) had CPP values that ranged from 60 to 160 mmHg. Patterns of change for the 16 subjects randomly selected (using IBM SPSS 19) from the sample are shown in Figures 1a-1c. After admission, CPP increased gradually from day 1 to day 5, and stabilized after day 5. The same trend was observed using the daily mean and 95% confidence interval of CPP values (Figure 2). The same figure also shows that the width of 95% confidence interval was narrow until day 10, indicating controlled MAP and ICP.

When daily means of CPP, MAP, and ICP were charted (Figure 3), we observed that the trend of CPP followed a similar trend of MAP, suggesting a greater influence of MAP on CPP compared to ICP. To objectively and quantitatively test this observation, we performed Pearson correlation to compare correlation coefficients between MAP and CPP vs. ICP and CPP (Table 2). We found that the correlation coefficients of MAP and CPP were higher than the coefficients of ICP and CPP over the observation period.

Figure 4 shows the daily percentages of CPP values < 70 mmHg and > 100 mmHg. Approximately, 65% of CPP values were < 70 mmHg immediately after admission; conversely, only 2% of CPP values were > 100 mmHg after admission. The percentage of CPP values < 70 mmHg began to decrease until day 5 and then stabilized around 20% after

day 5. Likewise, the percentage of CPP values > 100 mmHg began to increase until day 5 and then stabilized around 20% after day 5.

In addition, we objectively tested whether change rates were significant over time using growth curve analysis (Table 3). (Mirman, Dixon, & Magnuson, 2008) In *Model 1*, the interclass correlation coefficient was 0.39 [$133.73/(133.73 + 206.69)$], indicating that 39% of the total variation in CPP values was due to between subject differences. In *Model 2*, there was a significant linear increase in CPP values over time ($\beta = 0.06$, $SE = 0.006$, $p < 0.001$). The mean estimated initial CPP for the sample was 72.46 mmHg whereas the change rate was positive (0.06), indicating an increase of CPP values over time. Comparing variation in initial CPP values between model 1 and model 2, there was a significant decline in the residual variance of 38.29 (206.68 to 168.39). Thus, 18.5% ($38.29/206.68$) of the within subject variation in CPP values was associated with linear rate of change. The covariance ($\tau_{01} = -0.52$, $SE = 0.09$, $p < 0.001$) between the intercept and the linear change parameter was negative. This indicates that subjects with high CPP values had a slower rate of linear increase, while those with low CPP values had a faster rate of linear increase. In *Model 3*, all growth parameters were significant ($p < 0.001$). Between-subjects variations were significant in all (baseline, linear, quadratic) time trajectories. The grand mean of initial CPP was 64.11 ($\beta = 64.11$, $SE = 0.83$, $p < 0.001$). The significant linear effect for the CPP was positive ($\beta = 0.22$, $SE = 0.007$, $p < 0.001$), suggesting that the rate of linear change increased over time. The rate of quadratic change (-0.0006) was very small compared to the linear change trajectory (0.06). These findings support a pattern of change that varied after admission; CPP values increased after admission, but this trend slowed later in the hospital stay (approximately after day 5).

Lastly, we found that subjects who had greater percentages of CPP values > 100 mmHg and > 110 mmHg had greater odds for having DCI. For every 10% increase in the proportion of CPP values > 100 and > 110 mmHg the odds of DCI increased by 1.21 and 1.43, respectively (Table 4).

Discussion

Findings from this analysis can be summarized as follows: 1) CPP values were highly influenced by treatment, mainly induced hypertension, 2) MAP had more influence on CPP than ICP, and 3) the higher the proportion of CPP values > 100 mmHg and > 110 mmHg the greater the risk for DCI. Understanding temporal profiles of CPP after aSAH is important especially when cerebral autoregulation is impaired. When cerebral autoregulation is impaired, cerebrovascular resistance becomes relatively constant; an outcome that results in cerebral blood flow becoming highly dependent on CPP. In this situation, small changes in CPP can result in ischemic events. (Cipolla, 2009; Hossmann, 2006; Osol, Brekke, McElroy-Yaggy, & Gokina, 2002) To our knowledge this is the first report to extensively describe and objectively test temporal profiles of CPP over time in patients with aSAH.

Our observation that 28% of patients had baseline CPP values < 60 mmHg suggests that approximately one third of aSAH patients may have insufficient CPP on admission. For these patients, CPP values began to increase after admission, a change likely due to

treatment-induced hypertension to prevent vasospasm and drainage of CSF to control ICP. Standards of care in our subjects included a cap of 120 mmHg for systolic blood pressure before securing the aneurysm that was raised to 180 mmHg after securing the aneurysm. Also, the EVD was placed at 25 cm above the midbrain before securing the aneurysm and lowered to 10 cm after securing the aneurysm. Hence, once the aneurysm was secured more CSF was drained (lower ICP) and prophylactic hypertension was induced creating higher CPP.

In Figure (3) MAP showed a stepwise increment after admission, the same trend was noticed in CPP values (range of daily mean: 80.6 – 99.1 mmHg). However, ICP values were relatively constant throughout the observation period (range of the daily mean: 11.4-15.3 mmHg). These findings suggest that MAP had a greater influence on CPP than ICP, an observation that was corroborated by higher correlation coefficients for MAP and CPP compared to ICP and CPP (Table 2).

Changes in MAP can be explained, in part, by the catecholamine surge that is known to occur after aSAH and continue for up to 24 hours after bleeding.(Ogura et al., 2012) In addition, most subjects were managed using induced hypervolemia and vasopressors with the goal of inducing hypertension after aneurysm treatment and preventing vasospasm. We retrospectively and indirectly evaluated intravascular volume using central venous pressure (CVP) as a surrogate measure (Figure 5). The daily mean of CVP ranged from 9.05 to 11.42 mmHg indicating that subjects were hypervolemic (> 8 mmHg) during this time period. Hence, it is likely that the trend observed in CPP changes was strongly influenced by post-injury care and, particularly, induced hypertension and intravascular volume expansion. This speculation was corroborated by the observation that patients with high CPP had a slower change rate and those with low CPP a faster change rate. This suggests that treatment was likely more aggressive in patients with a low CPP on admission, either due to a high ICP or a low MAP, both of which are avoided after aSAH.

Our data show that patients who had a higher proportion of their CPP values > 100 and > 110 mmHg had greater odds of experiencing DCI. It remains unclear if this finding was a complication of therapy or a marker of treatment in sicker patients who required more aggressive treatment. If a complication of induced hypervolemia and hypertension, our findings suggest that aggressive therapeutic hypertension might not actually be therapeutic. The CVP values we observed also tend to confirm that subjects were hypervolemic during the observation period.

Previous reports have documented adverse effects of induced hypervolemia such as pulmonary edema and decrease cerebral oxygen delivery (in case of hemodilution).(Ekelund et al., 2002) Our findings suggest that induced hypertension is not without complication. Minimizing the time during which subjects are exposed to this treatment may be warranted to prevent DCI. Limiting the use induced hypertension and hypervolemia as treatment options to periods of vasospasm may reduce complications. Our findings also raise an important consideration regarding the safety of induced hypertension. Current standards of care do not identify safe limits for hypertension in aSAH patients or take into account the

baseline blood pressure when using hypertension as a treatment for vasospasm. Future studies are needed to better define optimal treatment targets.

This study has several limitations. CPP measurements were intermittent, rather than continuous. Continuous CPP and ICP monitoring would capture more values, but was not possible in our subjects as ICP was measured by an EVD, which needed to be clamped periodically to obtain valid ICP values. However, using this method, CPP values were obtained by the bedside nurse; therefore, they did not include artifacts often found in continuous monitoring. All subjects had EVDs, an intervention commonly used in high bleeding grades. Findings may therefore not be generalizable to patients with low bleeding grades or without EVDs. The EVD was open most of the time to allow for CSF drainage and ICP was measured only when the EVD was clamped. Therefore, the ICP measurement via the EVD might not represent the ICP value present the majority of time while the EVD was open. Lastly, data were collected over 12 years; therefore changes in standards of care may have confounded our findings.

Conclusions

In patients enrolled in this study, CPP increased significantly over time. This trend was most evident in the first 5 days after bleeding and likely influenced by treatment, particularly induced hypertension and hypervolemia. We observed that odds of DCI increased with higher proportions of CPP >100 and >110 mmHg. This suggests that the prophylactic use of induced hypertension and hypervolemia results in increased CPP values. Based on the trends and correlations of CPP found in this study, we conclude that induced hypertension and hypervolemia may not confer expected benefits in patients with aSAH. Therefore, the use of these treatment options may need to be limited to treat, rather than prevent, vasospasm in order to reduce complications. This study suggests the need to further investigate the safety of induced hypertension and examine limits for the length of exposure to this treatment.

Early detection of DCI is important for timely treatment to prevent further damage and to potentially recover the ischemic tissue. Therefore, nurses need to monitor signs of neurological deterioration when CPP values exceed 100 mmHg in patients with aSAH. This monitoring would be most critical in the first five days after admission.

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Figure 1.

- a. All CPP values for 16 subjects selected randomly (day 1-5)
- b. All CPP values for 16 subjects selected randomly (day 6-10)
- c. All CPP values for 16 subjects selected randomly (day 11-14)

Figure 2. Daily means and 95% confidence intervals for CPP

Figure 3. Daily means of ICP, MAP, and CPP

Figure 4. Daily percentages of CPP<70 and >100 mmHg

Figure 5. Daily CVP means showing hyervolemia (CVP>8 mmHg) during the observation period

Table 1
Clinical Characteristics (n=238)

Characteristics	Percent
Hunt and Hess grade	
Grade 1	6
Grade 2	28
Grade 3	40
Grade 4	20
Grade 5	6
Fisher Grade	
Grade 2	32
Grade 3	48
Grade 4	20
Aneurysm site	
Anterior circulation	82
Posterior circulation	18
Prophylactic Magnesium	78
Aneurysm repair	
Endovascular coiling	63
Surgical clipping	35

Table 2
Person correlation coefficients for the relationship between CPP, ICP, and MAP

Day From Injury	ICP	MAP
Day 1	-.331 *	.873 *
Day 2	-.508 *	.892 *
Day 3	-.410 *	.902 *
Day 4	-.340 *	.884 *
Day 5	-.192 *	.910 *
Day 6	-.279 *	.916 *
Day 7	-.284 *	.951 *
Day 8	-.303 *	.926 *
Day 9	-.368 *	.936 *
Day 10	-.370 *	.952 *
Day 11	-.382 *	.964 *
Day 12	-.458 *	.948 *
Day 13	-.341 *	.967 *
Day 14	-.408 *	.975 *

*
 $p < .001$

Table 3
Growth curve analysis of CPP linear and quadratic change

Parameters	Model 1	Model 2	Model 3
Fixed effect			
Intercept	79.64**	72.47**	64.11**
SE	.76	.82	.83
Linear time term	--	.06**	.22**
SE	--	.006	.007
Quadratic time term	--	--	-.0006**
SE	--	--	.00002
Random effect			
τ_{00}	133.73	148.04	142.91
τ_{11}	--	.007	.007
τ_{01}	--	-.52	-.52
σ^2	206.68	168.39	157.53
Overall Model test			
-2LL	193744.016	189534.872	188018.012
AIC	193750.016	189542.872	188026.012
BIC	193774.223	189575.147	188058.287

*
p<.01;

**
p<.001

Table 4
Multivariable logistic regression models for DCI as a function of percentage of CPP

Variables	Estimates	OR(95% CI)*	p value
Percentage of CPP value >100	.19	1.21(1.01-1.56)	.045
Percentage of CPP values >110	.36	1.43(1.01-2.05)	.044
Percentage of CPP values <70	-.06	.95(.83-1.07)	.392
Percentage of CPP values <60	-.05	.95(.78-1.15)	.610

Every variable was used in a separate multivariable model controlling for Hunt and Hess grade and aneurysm repair method.

* OR and 95% CI were calculated for every 10% increase in the percentage of CPP values.