Evaluating Indices of Delayed Cerebral Ischemia and Poor Outcomes after Subarachnoid Hemorrhage: *The Role of Cerebral Perfusion Pressure in Disease Pathogenesis*

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Evaluating Indices of Delayed Cerebral Ischemia and Poor Outcomes after Subarachnoid Hemorrhage: *The Role of Cerebral Perfusion Pressure in Disease Pathogenesis*

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Background and Purpose: Delayed cerebral ischemia (DCI) and Hunt and Hess (HH) grade are known risk factors for poor outcomes after aneurysmal subarachnoid hemorrhage (aSAH). DCI is often attributed to focal perfusion deficit (vasospasm/infarction). Global perfusion deficit (e.g. inadequate cerebral perfusion pressure (CPP)) can impair cerebral blood flow (CBF). The relationship between CPP and DCI remains unclear. Further, the exact mechanism of how HH grade relates to poor outcomes is uncertain. This study aimed to describe the temporal profiles of CPP change and to investigate the relationship between CPP, DCI, HH, and post-aSAH outcomes. ***Method***: DCI was defined as clinical deterioration due to impaired CBF. Growth curve analysis was used to examine temporal profiles of CPP change. Logistic regression was utilized to examine the association between DCI and percentages of CPP values >110, >100, <70, and <60 mmHg. The associations between minimum CPP (measured 12 hours prior to DCI), DCI, and DCI onset, were tested using logistic regression and accelerated failure time model. The mediation effect of DCI on the relationship between HH and outcomes was tested using bootstrap confidence interval. Outcomes were assessed at 3 and 12 months and included: mortality, neuropsychological, functional, and physical outcomes. ***Results***: There was a significant linear increase in CPP over time (β =0.06, SE=0.006, $p<0.001$). The covariance (-0.52) between the initial CPP and the linear change parameter was negative indicating that subjects with high CPP had a slower rate of increase and those with low CPP had a faster rate

(p<0.001). For every 10% increase in the proportion of CPP>100 or >110 mmHg, the odds of DCI increased by 1.21 and 1.43, respectively. For every 10 mmHg increase in CPP, the odds of DCI increased by 2.78 (95%CI 2.00-3.87). High CPP was associated with earlier onset of DCI (p<.001). DCI did not mediate the relationship between HH and outcomes. ***Conclusions:*** When used prophylactically, induced hypertension contributes to higher CPP values. Based on the CPP trends/correlations observed, induced hypertension may not confer expected benefits in patients with aSAH. Findings raise concerns about safety of induced hypertension and the need for determining limits for hypertension, which current guidelines lack.

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PREFACE

Indeed, leaving home and family five years ago was difficult. Different language, different culture, and different place… at the beginning, they were all challenges. Heba and I came to the United States 3 weeks after our wedding, and we had Yara and Maya later on…new family was just another challenge. These challenges have taught me how to be a dedicated student, a loving husband, and a caring father.

Without Allah's will and the infinite support I received from my mentors, my dream wouldn't come true. I thank every one of them; it's amazing how generously they provided me with their time and support without waiting for anything back. I have to admit that every one of my mentors has brought a unique experience and perspective in my scientific and personal life… the mentorship of each one of them was invaluable. I thank Dr. Paula Sherwood for her invaluable mentorship, for being my academic advisor, my mentor, and my dissertation chair, and for providing me with her experience in neurosurgical research and grant writing. Her support extends beyond the limits. Through her support and mentorship I was not only able to accomplish my dissertation but also to get 2 research grants and 2 travel grants, something that is not easy for international students. I thank Dr. Leslie Hoffman whose phenomenal support started from day one when she recruited me as a Graduate Student Researcher (GSR) in the Subarachnoid Hemorrhage Grant and lasts until this moment even after she retired. Her experience in research methodology and mentoring PhD students was crucial and important in

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I thank my Mom and my Dad for their prayers, I love you so much and can't wait to see you again. I thank my wife, Heba, and my girls, Yara and Maya, for giving me so much love and passion that were essential and fundamental for me to reach this point. This dissertation is not my achievement alone it is yours as well. Lastly, I want to thank the participants in this study and their families, our research team- past and present, and my fellow nurses in 4F and 5F neurovascular ICU at the University of Pittsburgh Medical Center.

Now when I think about going back home and leaving all these wonderful people I feel the same feeling that I had five years ago when I left Jordan. Indeed leaving the friends and the mentors will be difficult. I will be leaving in few months and I will miss you so much… I truly

believe that it is my destiny to leave that people I love, but I will keep dreaming of meeting you

again one day.

1.0   INTRODUCTION

1.1   INCIDENCE, PREVALENCE, AND FATALITY

Subarachnoid hemorrhage (SAH) is a sub-type of stroke defined by bleeding in the subarachnoid space where cerebrospinal fluid (CSF) circulates (Suarez, Tarr, & Selman, 2006). It represents 5% of all strokes and 25% of hemorrhagic strokes, affecting more than 30,000 North Americans each year with an annual cost to the United States of more than 1.7 billion dollars (Bederson et al., 2009; Graf & Nibbelink, 1974; Singer, Ogilvy, & Rordorf, 2011a; Wiebers, Torner, & Meissner, 1992). The most common cause for spontaneous SAH is aneurysm rupture (aSAH). The annual incidence of aSAH per 100,000 of population varies among different countries: 4.2 in South and Central America (lowest), 10 in North America, 12.4 in Sweden, 19.7 in Finland, and 21.9 in Japan (the highest). Overall, the annual worldwide incidence of aSAH is 9 per 100,000 of population (de Rooij, Linn, van der Plas, Algra, & Rinkel, 2007; King, 1997; Koffijberg et al., 2008). Ethnicity and gender have both been shown to be risk factors for aSAH. Previous studies report that the risk for aSAH in African Americans is 2.1 times the risk in Whites (Broderick, Brott, Tomsick, Huster, & Miller, 1992), and the risk for females is 1.6 times that of males (Lindsay, Teasdale, & Knill-Jones, 1983).

aSAH is often fatal and, for those who survive, is associated with severe morbidity and mortality which ranges between 32-67% (Hop, Rinkel, Algra, & van Gijn, 1997). The fatality

rate is particularly high for such a young patient population (mean age = 54 years) (Yousef, Crago, Kuo, Horowitz, & Hravnak, 2010). Those who survive the initial insult often suffer devastating inpatient and post-discharge complications. Common inpatient complications include increased intracranial pressure (ICP), cerebrovascular vasospasm, delayed cerebral ischemia (DCI), re-bleeding, hydrocephalus, seizure, electrolyte imbalance, and myocardial injury (Singer et al., 2011a). Complications continue after discharge and include moderate to severe physical disability, cognitive impairment, and even death (Frontera et al., 2009; Naidech et al., 2005). These complications can cause a significant impact on patients' ability to return to pre-stroke functioning and also increase costs for an already overburdened healthcare system. Thus, successful monitoring and interventions based on early detection and prevention of complications are vital to improving survivors' physical and neuropsychological function.

1.2 COMPLICATIONS POST SAH

Mortality and severe morbidity post aSAH are most commonly associated with DCI (Frontera et al., 2009). The Neurocritical Care Society's recent consensus definition characterizes DCI as "neurological deterioration represented by focal deficits (e.g., hemiparesis and/or aphasia) or global deficits (e.g., decrease in level of consciousness) related to cerebral ischemia that last for more than one hour and cannot be attributed to other radiographic, electrophysiologic or laboratory abnormalities" (Diringer et al., 2011; Vergouwen, Vermeulen, et al., 2010). DCI is associated with both systemic and neurological complications including septicemia, pneumonia, myocardial infarction and clinically significant arrhythmias, pulmonary edema, fever, and

cerebral edema (Frontera et al., 2009). Furthermore, DCI is associated with increased impairment in activities of daily living, cognitive impairment, poor quality of life, and severe disability and death (modified Rankin score 4-6) (Frontera et al., 2009; Springer et al., 2009). Thus, the prevention of DCI is key to improving outcomes after aSAH.

DCI occurs when impairment in cerebral blood flow (hypoperfusion) affects metabolism, which has been noted in patients with aSAH (Cahill, Calvert, & Zhang, 2006; Frontera et al., 2009; A. P. Huang et al., 2010). DCI-related cerebral hypoperfusion can occur locally (i.e., in only one part of the cerebral tissue) due to focal vascular alterations such as vasospasm and mircothrombi or globally due to pressure/flow deficits such as inadequate cerebral perfusion pressure (CPP). Current interventions focus on treatment of local vascular changes (cerebrovascular vasospasm and infarction), yet these interventions have had limited success (Rinkel & Klijn, 2009). Attempts to prevent cerebrovascular vasospasm and microthrombi using endothelin antagonists and antiplatelet administration did not result in a significant reduction in DCI or improvement in outcomes post aSAH (Dorhout Mees, van den Bergh, Algra, & Rinkel, 2007, 2008; A. Kramer & Fletcher, 2009; Macdonald et al., 2008; van den Bergh et al., 2006; van den Bergh, Kerr, Algra, Rinkel, & Molyneux, 2009). This lack of effectiveness may be due to the fact that one-half of all patients with vasospasm do not develop DCI (Dankbaar et al., 2009). In fact, studies have indicated that most patients with moderate to severe angiographic vasospasm are asymptomatic (i.e., do not develop neurological deterioration) (Vergouwen, Ilodigwe, & Macdonald, 2011), suggesting that vasospasm and DCI are not strongly associated and therefore treatment of focal perfusion deficits may be insufficient to prevent DCI.

Few studies have investigated the impact of ICP and mean arterial pressure (MAP) after aSAH, however, they did not include DCI per se as an end point and thus they are not sufficient

to well establish the impact of global hypoperfusion on DCI. Soehle et. al. suggested that ICP and MAP have a stronger influence on outcomes than vasospasm and that elevated MAP is significantly associated with poor outcomes after aSAH (Soehle, Chatfield, Czosnyka, & Kirkpatrick, 2007). Elevated ICP has also been found to be associated with cerebral ischemia, poor outcomes, high mortality, and clinical deterioration in other patient populations and lower cerebral perfusion pressure (CPP) has been associated with clinical deterioration after aSAH, yet studies to date have not investigated the pathogenesis through which cerebral perfusion affects outcomes (Cormio et al., 2001; Ryttlefors, Howells, Nilsson, Ronne-Engstrom, & Enblad, 2007). Collectively the data support the combination of ICP and MAP values captured by CPP as an important predictor of DCI and subsequent poor outcomes after aSAH. However, the association between changes in CPP and poor outcomes after aSAH has not been well established, nor has the role of DCI as a mediator between the two factors. For example, to date, no studies have been found that investigated the relationship between CPP and neuropsychological outcomes.

The novel evaluation of both global and regional causes of impaired cerebral blood flow will better elucidate the underlying pathogenesis of DCI and poor outcomes. This will potentially improve our ability to design monitoring and interventional approaches to early detect and prevent DCI and improve patient outcomes. This study will explore the relationships between minimum CPP values, DCI, and outcomes after aSAH. Evaluating this relationship is vital to inform current bedside treatment protocols through assessing whether CPP-directed monitoring and interventions would help to predict and prevent DCI and subsequent poor patient outcomes.

1.3   PURPOSE

The purpose of this study is to investigate the relationship between CPP, DCI and outcomes after aSAH.

1.4   SPECIFIC AIMS AND HYPOTHESES

1. **To describe and examine CPP changes during the 14 days after aSAH in regard to:**

    a. **baseline, absolute values, daily changes (range, mean, standard deviation), proportion of CPP values <70 mmHg, and proportion of CPP values >100 mmHg.**

    b. **trends of CPP values over time.**

       Hypothesis 1b: CPP values will change significantly over time.

2. **To examine the relationship between DCI and the lowest decrement in CPP during the 12 hours prior to DCI.**

    a. **To examine the association between DCI and the lowest decrement in CPP during the 12 hours prior to DCI controlling for Hunt and Hess grade and aneurysm repair method.**

       Hypothesis 2a: DCI will be associated with the minimum CPP measured 12 hours prior to onset of DCI.

    b. **To explore the threshold of CPP value associated with DCI**.

c. **To determine whether minimum CPP values are related to the onset of DCI controlling for Hunt and Hess grade and aneurysm repair method.**

Hypothesis 2c: Minimum CPP values will be associated with the onset of DCI.

3. **To determine whether DCI mediates the relationship between Hunt and Hess grade and neuropsychological outcomes, functional outcomes, physical outcomes, and death post aSAH controlling for age, aneurysm repair method, years of education, anxiety and depression.**

Hypothesis 3: DCI will partially mediate the relationship between Hunt and Hess grade and poor outcomes.

1.5   DEFINITION OF TERMS

1.5.1   Independent variables

1.5.1.1 Cerebral perfusion pressure (CPP)

CPP is the pressure gradient between mean arterial pressure (MAP) and ICP that allows blood to flow to the brain and is measured in mmHg (Alvarez del Castillo, 2001). The standards of care in the setting of this study include CPP measurement every two hours, thus a minimum of 12 values of CPP each day were available. However, subjects who exhibited neurologic or systemic instability had more nursing surveillance and thus more CPP values until stabilized. CPP values were included in the analysis as follows:

1. In specific aim #1a: absolute values, baseline, maximum, minimum, mean, standard deviation of CPP will be used in addition to the percentage of CPP values <70 mmHg, and the percentage of CPP values >100 mmHg.

2. In specific aim #1b: all CPP value measured during the 14 days post injury will be used

3. In specific aim #2 (a, b, and c): minimum CPP values measured during the 12 hours prior to the time of DCI diagnosis will be used.

1.5.1.2 Delayed cerebral ischemia (DCI)

DCI is defined as neurological deterioration represented either as focal neurologic deficit (i.e. hemiparesis, aphasia, apraxia) or global neurologic deficit (decrease in level of consciousness) that lasts for more than one hour and cannot be attributed to other radiographic, electrophysiologic or laboratory abnormalities (Diringer et al., 2011; Vergouwen, Vermeulen, et al., 2010). In this study, DCI was defined as neurologic deterioration accompanied by abnormal cerebral blood flow and cannot be explained by other abnormalities such as hydrocephalus, re-bleeding, seizure, and cerebral edema (Crago et al., 2011; Yousef et al., 2010).

1.5.1.3 Hunt and Hess (HH) grade

Hunt Higher bleeding severity grade measured by Hunt and Hess scale is associated with poor outcomes post aSAH (Kreiter et al., 2002; Otawara et al., 2009). It is unknown if the DCI mediates this relationship between Hunt and Hess grade and outcomes. Specific aim #3 tested whether the relationship between Hunt and Hess grade and post-aSAH outcomes is mediated by DCI.

1.5.2 Dependent variables

1.5.2.1 Subject Outcomes

Subject outcomes were measured in the areas of physical and neuropsychological health at 3 and 12 months post aSAH. Physical health includes subjective assessments of physical functioning, disability and objective measures of survival. The following are the domain examined in the parent study and included in the current study: attention, learning and memory, psychomotor speed, mental flexibility, executive function, visuospatial ability, and language. All test scores in all domains were standardized and converted to z scores. Patients with a z score of $\leq$ -1.5 in more than one test or patients with z score $\leq$ -2.0 in at least one test were considered to have impairment in neuropsychological funsction (Wefel et al., 2004). This comprehensive set of measurements potentially elicit the true status of aSAH patients after discharge.

1.5.3 Potential confounding variables

As potential confounders, the following variables were controlled for in this analysis:

I) Mood was assessed via depressive symptoms and anxiety. Patients with depression and anxiety have worse scores on neuropsychological tests suggesting an increased neuropsychological impairment in those patients compared to those without depression or anxiety (Basso et al., 2007; Castaneda, Tuulio-Henriksson, Marttunen, Suvisaari, & Lonnqvist, 2008). Thus, controlling for depression and anxiety was warranted when measuring neuropsychological outcomes (Specific Aim #3) in order to ensure that the relationship between

CPP, DCI, and poor neuropsychological function outcomes is not confounded by depressive symptoms/anxiety.

II) Age: older age has been associated with poor neuropsychological and functional outcomes in patients with aSAH (Haug et al., 2010; Kreiter et al., 2002; Ohwaki et al., 2006). Therefore, age was controlled for when testing neuropsychological and functional outcomes (Specific Aim #3) to ensure that the relationship between CPP, DCI, and outcomes is not confounded by age.

III) Years of education: having fewer years of education is associated with poor neuropsychological function in aSAH patients (Haug et al., 2010; Kreiter et al., 2002). Therefore controlling for number of years of education in Specific Aim #3 is important to make certain that these differences between subjects are due to neuropsychological impairment and not due to different levels of education.

IV) Hunt and Hess scale: higher bleeding severity grade measured by Hunt and Hess scale is associated with DCI (Frontera et al., 2009) and neuropsychological dysfunction (Kreiter et al., 2002; Otawara et al., 2009) and thus was controlled for to ensure that the relationship between CPP, DCI, and outcomes is not confounded by Hunt and Hess grade. Others have previously controlled for Hunt and Hess in similar analysis (Frontera et al., 2009). Hunt and Hess grade was controlled for in specific aims #2.

V) Aneurysm repair method: surgical clipping and endovascular coiling are the major methods for treatment intracranial aneurysms. Evidence suggests that the incidences of death, poor outcomes, and DCI are higher among those who have surgical clipping (Dorhout Mees, Kerr, Rinkel, Algra, & Molyneux, 2011; Scott et al., 2010). Therefore, aneurysm repair method was controlled for in specific aim #2 and #3.

2.0   BACKGROUND AND SIGNIFICANCE

Bleeding into the subarachnoid space is a medical emergency that can result from head trauma or spontaneous blood vessel rupture. There are several mechanisms that cause spontaneous SAH including: intracranial aneurysm, arteriovenous malformation (AVMs), dissection in the cerebral vasculature, vasculitides, amyloid angiopathy, or bleeding diatheses (Singer et al., 2011a). Often, SAH results when a cerebral aneurysm ruptures and bleeds into the subarachnoid space. Cerebral aneurysms are blood-filled pathological focal dilatations of the cerebral blood vessels (Krings et al., 2011). The risk factors, pathophysiology, and the complication for the rupture of cerebral aneurysms are discussed blow.

2.1   EPIDEMIOLOGY

In the United States, an individual experiences a stroke every 40 seconds and dies of a stroke every 4 minutes (Roger et al., 2011). Of these strokes, 20% are hemorrhagic (Singer et al., 2011a). While SAH represents 3-7% of all strokes, it accounts for approximately 25% of hemorrhagic strokes (de Rooij et al., 2007; Feigin, Lawes, Bennett, & Anderson, 2003; Lloyd-Jones et al., 2010; Roger et al., 2011). Although ischemic strokes are more common than

hemorrhagic strokes, individuals who experience SAH are twice as likely to die at 1-month post injury (32%) compared to those who experience an ischemic stroke (16%) (Feigin et al., 2003).

Aneurysm rupture is the most common cause for spontaneous SAH; accounting for 85% of all non-traumatic cases (Dupont, Wijdicks, Lanzino, & Rabinstein, 2010). Findings from prospective autopsy and angiographic studies indicate that 3.6%-6% of the population have a cerebral aneurysm (Wardlaw & White, 2000). Fortunately, most cerebral aneurysms do not rupture (Singer, Ogilvy, & Rordorf, 2011b; van Gijn, Kerr, & Rinkel, 2007). This is particularly true for aneurysms that measure <7mm.

Among aneurysm types, saccular aneurysms, also known as "berry" aneurysms because of their characteristic shape, are the most likely to rupture resulting in SAH (Krings et al., 2011; Singer et al., 2011b). The most common location for saccular aneurysms is the arterial junctions of the circle of Willis. Approximately, 80-85% of saccular aneurysms are formed in the anterior (carotid) circulation and 10% in the posterior circulation. Of anterior circulation aneurysms, 30-35% occur at the anterior communicating artery, 25-35% at the junctions of the internal carotid arteries with the posterior communicating arteries, and 20% at the bifurcation of the middle cerebral arteries (Bradač, 2011; Brisman, Soliman, Kader, & Perez, 2010; Schievink, 1997; Vega, Kwoon, & Lavine, 2002). Approximately, 10-40% of patients have more than one aneurysm and other estimates indicate as many as 75% have two aneurysms. Approximately, one-third of patients with multiple aneurysms have mirror aneurysms (bilateral aneurysm on the same arterial location); e.g. aneurysm on left and right posterior communicating artery (Bradač, 2011; Brisman et al., 2010; Brisman, Song, & Newell, 2006; Schievink, 1997).

2.2   RISK FACTORS

Many modifiable and non-modifiable risk factors for aneurysm formation are also risk factor for aneurysm rupture (Singer et al., 2011a). Modifiable risk factors include smoking, hypertension, alcohol consumption, and sympathomimetic drug use. Race, gender, and genetics are common examples of non-modifiable risk factors for aSAH.

2.2.1   Modifiable risk factors

Several case control studies report that smoking, hypertension, and alcohol consumption are strongly associated with aneurysm formation and rupture (Inagawa, 2010; Qureshi et al., 2001; Woo et al., 2009). Current and past smokers have 2-5 times and 1.5 times, respectively, the risk of nonsmokers for experiencing an aSAH. Fortunately, the risk decreases shortly after smoking cessation (Anderson et al., 2004; V. Feigin et al., 2005; V. L. Feigin et al., 2005). Hypertension is potentially the strongest modifiable risk factor for aneurysm formation (Inagawa, 2010). Individuals with hypertension have 2-2.5 times the risk of those who are normotensive for experiencing an aSAH (V. Feigin et al., 2005; V. L. Feigin et al., 2005). Excessive alcohol consumption increases the risk for SAH by 2-4 times compared to those who do not consume alcohol (V. L. Feigin et al., 2005; Sankai et al., 1999). The risk for aneurysm formation and rupture increases as the number of risk factors increases. For example, individuals who are both hypertensive and smoker have 6 times the risk of SAH compared to normotensive non-smokers. Further, men who are heavy drinkers and smokers have 6 times the risk of SAH compared to non-drinkers and non-smokers. Interestingly, men who have hypertension and are heavy drinkers

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have 13 times the risk of SAH compared to those who are non-heavy drinkers and normotensive or borderline hypertensive. The relative risk of heavy drinkers who are smokers and hypertensive is 17.5 (Sankai et al., 1999).

Sympathomimetic drugs such as cocaine and appetite suppressants are associated with aSAH. Notably, subjects with cocaine-associated aSAH are typically younger than the general population of aSAH (36 years vs. 52 years respectively). Cocaine use is not only a risk factor for aSAH but also an independent risk factor for vasospasm after aSAH (Conway & Tamargo, 2001). Other sympathomimetic substances used in appetite suppressants, namely phenylpropanolamine, have been also associated with increased risk for hemorrhagic stroke including intracerebral and subarachnoid hemorrhage (OR =15.9) (Kernan et al., 2000).

2.2.2 Non-modifiable risk factors

Racial and gender differences with regard to the incidence of aSAH have frequently been reported (Eden et al., 2008; Lindekleiv et al., 2011; Macpherson et al., 2011). For example, White Americans have a lower SAH risk and mortality rate compared to other races (Blacks, Hispanic, Asians, American Indians, Alaska Natives). Black men have the highest incidence and mortality (Bederson et al., 2009; Labovitz et al., 2006). These racial differences are similar to those seen in other types of stroke, including those caused by ischemia and intracerebral hemorrhage (Cruz-Flores et al., 2011). In addition, several studies have reported that the risk for aSAH in women is 1.24 -1.74 times that for men (de Rooij et al., 2007; Eden et al., 2008; Lindsay et al., 1983). Studies conducted in Scotland and Sweden have reported that the incidence of SAH per 100,000 is 13-14 for women compared to 8-10 in men (Koffijberg et al., 2008;

Macpherson et al., 2011). However, studies conducted in Finland reported the opposite with a higher incidence in men is compared to women (33 vs. 25 per 100,000 respectively) (Sarti et al., 1991). Thus, the notion that women have higher risk of SAH than men appears not to be true in all countries (Ingall, Asplund, Mahonen, & Bonita, 2000).

The role of genetics in the pathogenesis of intracranial aneurysms has been strongly supported by two observations; first, the familial occurrence of intracranial aneurysms and second, the association between heritable connective tissue disease and intracranial aneurysms. Polycystic kidney disease and Marfan's syndrome are two of the most important connective tissue diseases that have been associated with intracranial aneurysms (Schievink, 1997). Approximately, 5-40% of patients with polycystic kidney disease develop an intracranial aneurysm (Yanaka et al., 2004). In fact, autosomal dominant polycystic kidney disease is the most common genetic condition associated with intracranial aneurysm formation.

Several genes were identified as risk factors for intracranial aneurysms. Among those, ELN, COL1A2 alleles, eNOS gene T786C polymorphism, and IL-6 gene G572C polymorphism are the most promising candidates for this association. It is believed that several genes interact with environmental factors to formulate the inheritance pattern in intracranial aneurysms (McColgan, Thant, & Sharma, 2010; Ruigrok, Rinkel, & Wijmenga, 2005). Once these factors are identified in an individual screening is warranted. Screening is recommended for those who have ≥ 2 first degree family members with intracranial aneurysms or genetic conditions associated with aneurysm formation such as autosomal dominant polycystic kidney disease and Marfan's syndrome (Brisman et al., 2010).

2.3   PATHOPHYSIOLOGY AND HEMODYNAMIC CHANGES

The pathogenesis of aSAH involves two main processes; aneurysm formation and aneurysm rupture which results in bleeding into the subarachnoid space. The exact mechanism of intracranial aneurysm formation remains unclear. Prior to discussing the pathogenesis of aneurysm formation and rupture, it is essential to describe the vascular anatomy of intracranial arteries where aneurysms form. Figure (1) represents a cross sectional view of an intracranial artery. Intracranial arteries consist of 4 layers: the adventitia (outermost layer), the media (middle muscular layer), the intima (the innermost layer), and internal elastic lamina (separate intima from the media) (Bradač, 2011). Compared to extracranial arteries, intracranial arteries have thinner adventitia and no external elastic lamina (Stehbens, 1989). Potentially, this difference explains why aneurysm formation is more frequent in intracranial arteries compared to extracranial arteries (Schievink, 1997).
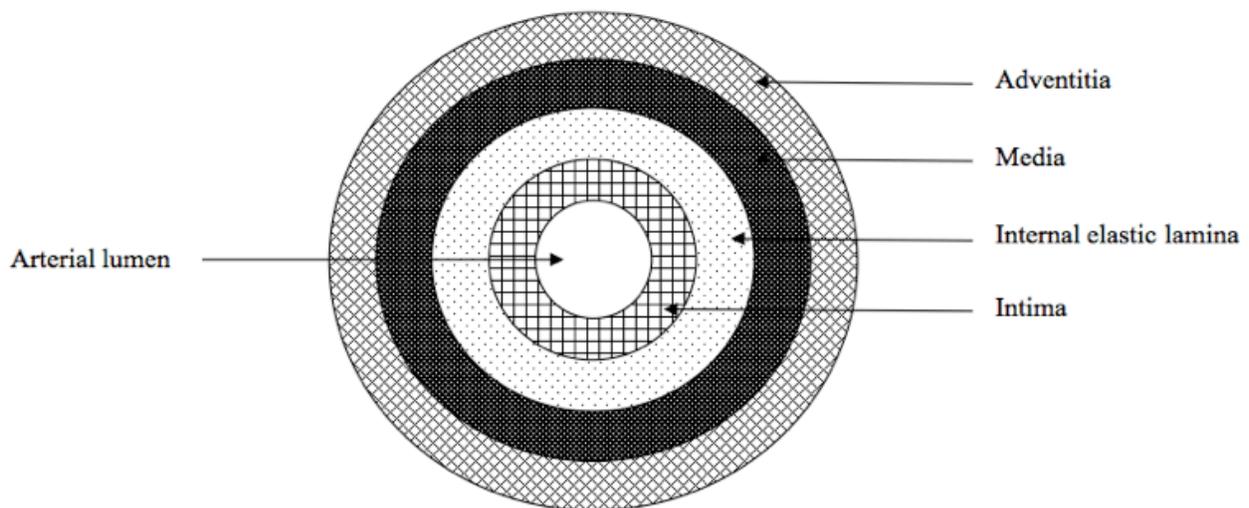
Figure 1. Cross sectional view of the intracranial arteries

For many years, it was believed that risk for aneurysm formation was solely congenital. Two major reasons were presented to support this belief: 1) macroscopic examination of the aneurysm wall suggested similar appearance as the parent vessel (Stehbens, 1989), and 2) histological studies conducted in the early 1930's found a congenital defect in the media of intracranial arteries. Thus, investigators concluded that this defect created a locus minoris resistentiae (Latin: an area of low resistance) where aneurysms occurred (Bradač, 2011). Later, these findings and interpretations were negated for three reasons. First, on microscopic examination the aneurysm wall was found different than the parent vessel (Stehbens, 1989), and an absence of the internal elastic lamina and tunica media from the aneurysm wall was observed (Bradač, 2011). These findings suggest that the aneurysm wall and the parent vessel wall were, in fact, not similar. Second, many normal individuals were found later to have the media defect without having an aneurysm (Bradač, 2011). Third, there was no experimental evidence that the media defect was a locus minoris resistentiae; that is the area with low resistance where the aneurysms form (Stehbens, 1989).

Series of preclinical experiments to model intracranial aneurysms in sheep, rabbits, rats, and monkeys were conducted by Hashimoto et al., in the late 1970's in Japan and by Stehbens et al., in the late 1980's in New Zealand. These experiments successfully produced aneurysms merely by hemodynamic stress even in the absence of connective tissue disease (Hashimoto, Handa, & Hazama, 1978, 1979a, 1979b; Hashimoto, Handa, Nagata, & Hazama, 1980; Hashimoto et al., 1987; Hassler, 1963; Kim, Kikuchi, Hashimoto, & Hazama, 1989; Stehbens, 1986, 1989). These experiments confirmed that aneurysms were acquired degenerative lesions and not congenital. Recent studies also corroborated the fact that aneurysm formation is an

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acquired disorder rather than congenital (Krings, Geibprasert, & terBrugge, 2010; Krings et al., 2011).

Despite the experimental evidence that aneurysms can be induced merely by hemodynamic stress, others did not find this explanation sufficient. Krings et al., argued that explaining aneurysm formation and rupture by hemodynamic stress alone was too narrow because it provided the same explanation for aneurysm formation regardless of the underlying pathology associated with different aneurysms. Further, this explanation did not consider other characteristics that distinguish aneurysms, e.g., different morphological and histopathological features. Thus, Krings and colleagues recommended that the pathogenesis of aneurysms should be explained by morphologic and histopathologic characteristics in addition to hemodynamic stress (Krings et al., 2011). According to Krings et al., aneurysms occur due to luminal forces (i.e. increased blood flow/pressure, hemodynamic stress) and abluminal factors (vessel wall pathology). Factors that increase the tension inside the blood vessels (luminal factors) and/or factors that change the vessels wall (abluminal factors) cause a disruption in the internal elastic lamina which leads to outpouching and the subsequent rupture in the intracranial blood vessels (Krings et al., 2011). Although the changes in blood pressure that result from hypertension are considered luminal forces, others believe that hypertension acts as an accelerator rather than being a cause for aneurysm formation (Stehbens, 1989). Yet, the explanation by Krings et. al. is notable for explaining causes of aneurysm rupture and formation and distinguishing or /classifying aneurysms that occur due to different disease processes (Krings et al., 2011). The classification they suggested for the aneurysms based on their cell wall pathology is presented in Table 1.

Table 1. Aneurysm types and pathogenesis

Aneurysm type	Pathology
Saccular (berry) aneurysm	Disruption of internal elastic lamina results from hemodynamic factors and/or inflammatory process and leads to focal dilation in the arterial wall.
Mycotic aneurysm	Disruption of internal elastic lamina results from bacterial invasion for the arterial cell wall.
Neoplastic aneurysm	Disruption of the arterial wall results from invasion of neoplastic cells.
Immunodeficiency related	Disruption on internal elastic lamina results from inflammatory process.
Segmental ectasia	Smooth muscle atrophy in addition to disruption and degeneration of the internal elastic lamina lead to circumferential dilatation of the arterial wall.
Dissecting aneurysm	Disruption of the internal elastic lamina is accompanied with blood accumulation through the intima.
Intramural aneurysm	Characterized by recurrent hemorrhage in the aneurysm wall in addition to inflammatory changes in the arterial wall.
Traumatic aneurysm	Pseudoaneurysm where no actual aneurysm wall is present but rather the clotted blood forms the wall of the aneurysm.

Immunohistochemical studies that compared the walls of ruptured and unruptured intracranial aneurysms support, in part, the hypothesis made by Krings et al. In these studies ruptured aneurysms showed significant endothelial damage, structural wall damage, and inflammatory cell invasion compared to unruptured aneurysms. The wall of ruptured aneurysms was found weak due to the loss of the smooth muscle cells and destruction of the matrix proteins caused by infiltration of macrophages into the vessel wall. These findings suggest that inflammation in the vessel wall, which precedes aneurysm rupture and can be considered as "*abluminal factors*", contributes to the aneurysm formation and rupture (Kataoka et al., 1999).

Once an aneurysm starts to grow, size becomes important indicator for rupture. Hemodynamic stress, blood flow turbulence, and pulsatile flow are the major factors contributing to increasing the size of the aneurysm (Wiebers et al., 2004). As the aneurysm grows in size, it may eventually rupture and cause aSAH. Aneurysms that rupture have twice the mean diameter (8.6 mm) of aneurysms that do not rupture (4.7 mm) (Chason & Hindman, 1958). This suggests that larger aneurysms are at a higher risk for rupture compared to smaller aneurysms. The increase in the size of an aneurysm can occur over various periods of time. It can take hours to years for the aneurysm to grow and eventually rupture. Fortunately, many aneurysms do not rupture and many resolve spontaneously (Wiebers et al., 2004).

2.3.1 Bleeding Into The Subarachnoid Space

For those aneurysms that rupture, blood moves into the subarachnoid space where cerebrospinal fluid (CSF) circulates. Thus, the bleeding often extends to the ventricles. The amount of blood in the subarachnoid space and the intraventricular extension are strong predictors of DCI post

aSAH (Claassen et al., 2001). The extent of the intracerebral bleeding is usually assessed on admission by computed tomography (CT) scan which is a very sensitive tools for identifying and localizing blood in the subarachnoid space (Boesiger & Shiber, 2005). Although CT scans are not very helpful in diagnosing presence of an aneurysm per se, the pattern of bleeding in can be suggestive of aneurysm rupture. A bleeding pattern which predominates in the prepontine cisterns with subarachnoid blood in the carotid cisterns, Sylvian fissures, and/or intrahemispheric fissure is suggestive of aneurysm rupture (Herrmann & Zabramski, 2007). Evidence suggests that the larger the amount of bleeding the higher the risk for complications. Therefore, it is important to quantify and assess the amount of bleeding on admission. There are several scales used for this purpose. The commonly used scales to assess the severity of the primary injury are: Hunt and Hess scale, Fisher grade, modified Fisher grade, Claassesn-Fisher scale, National Institute of Health stroke scale (NIHSS), and World Federation of Neurological Surgeons (WFNS) grading scale.

2.3.2 Summary and Critique of Evidence in the Pathophysiology of Aneurysms

These findings suggest the process of aneurysm formation and rupture is likely to be a complex process involving several factors. Although hemodynamic stress was proven in several experiments to cause intracranial aneurysms, these experiments do not explain why saccular aneurysms are more frequent on arterial bifurcations or why 80-85% of saccular aneurysms occur in the anterior circulation. If hemodynamic stress alone were responsible for aneurysm formation, the frequency of aneurysms should be similar in different locations of the cerebral circulation. These differences suggest that there are anatomical and/or hisological features that

make certain locations more susceptible for aneurysm formation or at least for hemodynamic changes. One could argue that hemodynamic stress is not the same in all sites of the circle of Willis. However, this also suggests that anatomical differences are involved in the pathogenesis of aneurysm formation and rupture. The major flaw in the current explanation for aneurysm formation and rupture, even that provided by Krings et. al., is that it does not clearly delineate factors that contribute solely to aneurysm formation or contribute solely to rupture.

Regardless the mechanism mechanistic process for aneurysms formation/rupture, securing the ruptured aneurysm is am emergency. These patients are typically admitted to the neuro-intensive care unit in order to be monitored for secondary injuries such as infarction, vasospasm and DCI. These secondary injuries can be more devastating than the primary injury (i.e., aneurysm rupture) and they are potentially preventable in many cases.

2.4   ASSESSING COMPLICATIONS

After securing the ruptured aneurysm for those who survive the primary insult, monitoring for secondary injuries is warranted to prevent further damage to the brain. Secondary injuries after aSAH are common and include: hyponatremia, rebleeding, seizure, hydrocephalus, cerebrovascular infarction, cerebrovascular vasospasm, impaired cerebral blood flow, and DCI. The complications that are related to the current study are discussed below.

2.4.1 Cerebral Infarction

After in-hospital admission, approximately 61% of aSAH survivors develop cerebral infarction. Of these infarctions, 40% occur in single cortical areas and 50% occur in multiple areas (Singer et al., 2011a). Cerebral infarction is a major predictor of post aSAH outcomes (Juvela & Siironen, 2012). It is believed that the relationship between cerebral infarction and functional outcomes is causal (Diringer et al., 2011; Vergouwen, Etminan, Ilodigwe, & Macdonald, 2011; Vergouwen, Ilodigwe, et al., 2011). Therefore, it was recommended that cerebral infarction should be used as an endpoint in aSAH research (Vergouwen, Etminan, et al., 2011). Potentially, the effect of infarction on post aSAH outcomes is mediated by DCI. Cerebral infarction has been attributed to vasospasm (Carlson & Yonas, 2009), and often used to define DCI (Claassen et al., 2001). The causal nature of the relationship between vasospasm and infarction has been debated (Vergouwen, Etminan, et al., 2011). In the CONSCIOUS-1 trial, successful prevention of vasospasm did not significantly reduce infarction rate (Macdonald et al., 2008). This suggests that vasospasm is not a sufficient explanation for infarction after aSAH. The mechanics of cerebral infarction remain unclear.

2.4.2 Cerebrovascular Vasospasm

Post-aSAH vasospasm was first described in 1951 (Ecker & Riemenschneider, 1951) as a narrowing in the diameter of cerebral arteries that can be detected by radiographic imaging or sonography (Vergouwen, Vermeulen, et al., 2010). If narrowing is significant, it can result in decreased blood flow to focal territories of the brain that may eventually result in cerebral

ischemia. When vasospasm induced-cerebral ischemia occurs, vasospasm is symptomatic; i.e. accompanied with neurologic deterioration such as aphasia, apraxia, and hemiparesis. Vasospasm can also be asymptomatic, i.e., not associated neurological deterioration (Frontera et al., 2009; Vergouwen, Vermeulen, et al., 2010).

Vasospasm has undergone intense exploration in patients post aSAH. However, studies have used different methods to measure vasospasm and therefore, different operational definitions were given. It is important to discuss these definitions for several reasons. First, different measurement methods result in different incidence rates. For example; Frontera et al., reported transcranial Doppler (TCD)-vasospasm in 45%, angiographic vasospasm in 31%, and symptomatic vasospasm in 16% of 580 subjects (Frontera et al., 2009). Second, it is believed that vasospasm contributes to DCI and cerebral infarction; major predictors of poor outcomes. Therefore, understanding different definitions of vasospasm is essential for accurate comparison of incidence rates and for understanding DCI; a major variable in the current study. These definitions include TCD vasospasm, angiographic vasospasm, and symptomatic vasospasm. Symptomatic vasospasm is defined as the development of a new focal neurologic deficit (such as hemiparesis, aphasia, and apraxia) or global neurologic deficit (deterioration in the level of consciousness) that is thought to be caused by arterial narrowing after excluding other causes of neurological deteriorations such as hydrocephalus, seizure, and infection (Frontera et al., 2009; Vergouwen, Vermeulen, et al., 2010). Angiographic vasospasm is defined as moderate or severe arterial narrowing after excluding other possible causes such as atherosclerosis and catheter induced vasospasm (Frontera et al., 2009). Cerebral angiography allows to quantify the degree of narrowing with >25% defining clinically significant vasospasm, 26-50% defining moderate

vasospasm, and >50% defining severe vasospasm (Dankbaar et al., 2009; Yousef et al., 2010). Angiographic vasospasm is a very objective measure but angiography is very invasive and cannot therefore be routinely used as a method for diagnosing vasospasm due to the risk associated with this procedure. TCD vasospasm is defined as: 1) mean arterial velocity >120 ml/s; 2) systolic arterial velocity >200 ml/s, or 3) Lindegaard ratio >3.0 (for middle cerebral artery) (Frontera et al., 2009; Yousef et al., 2010). TCD sensitivity is poor (Carrera, Schmidt, Oddo, Fernandez, et al., 2009) and thus may overestimate the incidence of vasospasm. Therefore, TCD-vasospasm is of concern when accompanied by evidence of clinical deterioration. When no clinical deterioration is present, TCD-vasospasm is usually followed by radiologic testing to confirm or rule out vasospasm.

Vasospasm was once thought to be a major cause for ischemia after aSAH, however, evidence shows that even though vasospasm results in a decrease in cerebral blood flow, approximately half of patients with severe vasospasm do not develop DCI (Dankbaar et al., 2009). This indicates that the impairment in cerebral perfusion that results from vasospasm may not be sufficient to result in cerebral ischemia in every instance. To test this hypothesis, a randomized double blind controlled trial (CONSCIOUS-1 trial) used an endothelin antagonist (Clazosentan) to prevent vasospasm. In the CONSCIOUS-1 trial, a significant reduction in angiographic vasospasm did not result in significant reduction of DCI or infarction or significant improvement in outcomes (Macdonald et al., 2008). A recent systematic review of randomized controlled trials similarly reported that effective reduction of vasospasm does not consistently result in improvement in outcome (Etminan, Vergouwen, Ilodigwe, & Macdonald, 2011). These

findings collectively suggest that role of vasospasm in the pathogenesis of DCI and poor outcomes after aSAH is not as strong as was once thought.

2.4.3   Delayed cerebral ischemia

The fact that the successful prevention of vasospasm did not improve post-aSAH outcomes increased the attention to explore DCI as a primary contributor for poor outcomes after aSAH. In their consensus paper, the Neurocritical Care Society defined DCI as a neurological deterioration that is thought to be due to ischemic deficit, lasts for > 1 hour, and cannot be attributed to other radiographic, electrophysiologic, or laboratory abnormalities (Diringer et al., 2011; Vergouwen, Vermeulen, et al., 2010). The term *delayed* suggests that DCI is not related to initial insults but rather to later pathological changes that develop; the secondary injury (Carlson & Yonas, 2009).

DCI typically occurs 3 -15 days after the initial aSAH, peaking on day 7 and is associated with poor outcomes in survivors (Claassen et al., 2001; van Gijn et al., 2007). DCI is common after aSAH occurring in 19-63% of patients (Carrera, Schmidt, Oddo, Fernandez, et al., 2009; Carrera, Schmidt, Oddo, Ostapkovich, et al., 2009; Claassen et al., 2001; Frontera et al., 2009; Hop, Rinkel, Algra, & van Gijn, 1999; Lanterna et al., 2010; Yousef et al., 2010). These incidence rates of DCI are underestimated because assessment of neurological deterioration requires that the patient be conscious and can undergo neurological examination. Therefore, in patients who are comatose or sedated, the presence of DCI cannot be determined (Vergouwen, Vermeulen, et al., 2010). Variations in DCI incidence is explained, in part, by the lack of a standardized definition used in different studies (van der Bilt et al., 2009). For instance, some authors have used vasospasm as one of the criteria to define DCI (Frontera et al., 2009), while

others have used infarction (Claassen et al., 2001). The most common definition for DCI used in studies published before the Neurocritical care consensus paper is: a clinical deterioration (new focal neurologic deficit or decrease in level of consciousness) not attributed to causes other than ischemia (rebleeding, seizure, hydrocephalus, hyponatremia, or cerebral edema) and/or cerebral infarction/vasospasm (Carrera, Schmidt, Oddo, Fernandez, et al., 2009; Carrera, Schmidt, Oddo, Ostapkovich, et al., 2009; Frontera et al., 2009; Vergouwen, van Geloven, et al., 2010; Vergouwen, Vermeulen, et al., 2010). The term DCI is often used interchangeably with symptomatic vasospasm and delayed ischemic neurologic deficit (DIND) (Al-Tamimi, Orsi, Quinn, Homer-Vanniasinkam, & Ross, 2010). However, the term delayed neurologic deficit (DND) refers to any neurologic deficit that occurs after initial bleeding, this includes deficits as a result of DCI, hydrocephalus, cerebral edema, seizure, electrolyte imbalance, and fever but excluding rebleeding (Diringer et al., 2011).

As mentioned previously, the definition of DCI has two components: impairment in cerebral blood flow and neurological deterioration. The decrease in cerebral blood flow leads to neuronal cell death and cerebral ischemia that are presented as symptomatic neurologic deficit. Cerebral ischemia-associated neuronal cell death can occur as a consequence of two mechanisms or processes; apoptosis or necrosis. Apoptosis; defined as programmed cellular death, is characterized by cellular shrinkage, chromatin aggregation, intact cellular membrane, and intact mitochondrial function (Thompson, 1995). Necrosis is not a regulated process. It results from severe cerebral ischemia and is distinguished by mitochondrial injury, cell swelling, lysis in the cellular membrane inflammation, and vascular damage. These two processes are not separate; rather they coexist on a continuum. The duration and intensity of the ischemic insult determine if

the cell is going through apoptosis or necrosis. Severe and longer ischemic insults are associated with cell necrosis. It is widely accepted that excitatory amino acids trigger an excitotoxic cascade which in turn leads to neuronal necrosis (Harukuni & Bhardwaj, 2006). On the other hand, apoptosis results from exposure of neurons with partially functional mitochondria to glutamate (Ankarcrona et al., 1995). An intrinsic pathway (mitochondria dependent pathway) and an extrinsic pathway (mitochondria independent pathway) are suggested to explain the pathway of apoptosis. In the intrinsic pathway, cerebral ischemia leads to disruption of the mitochondrial membrane caused by the release of proapoptotic factors. This eventually results in DNA fragmentation. In the extrinsic pathway, several death receptors induce and augment cellular apoptosis (Harukuni & Bhardwaj, 2006).

Prevention of neuronal death that results in DCI has been the focus of treatment for decades. Despite multiple treatment options, DCI, regardless of how defined, remains a primary cause of morbidity and poor outcomes after aSAH (Frontera et al., 2009; Laskowitz & Kolls, 2010; Rabinstein et al., 2005; Schutz et al., 1993; van Gijn et al., 2007). DCI is associated with severe disability, poorer performance of activities of daily living, increased cognitive impairment, reduced quality of life, and death (Frontera et al., 2009; Rabinstein et al., 2005; Schutz et al., 1993). On the other hand, there are several factors associated with DCI such as low cerebrovascular reactivity on day 4-7 and 8-10 after ictus (Carrera et al., 2010), loss of consciousness > 1 hour after the onset of aSAH (Hop et al., 1999), C-reactive protein, leukocyte and platelet count (Kasius, Frijns, Algra, & Rinkel, 2010), cisternal and intraventricular blood (Claassen et al., 2001; Ko et al., 2011), and thromboembolism (Stein, Levine, Nagpal, & LeRoux, 2006). Yet, treatment options that target these factors did not result in improvement in

post-aSAH outcomes. Vasospasm was thought to be strongly associated with DCI but recent evidence suggests that vasospasm does not always lead to DCI (Dankbaar et al., 2009). Thus the prevention of focal perfusion deficit is not a successful strategy to prevent DCI and improve outcomes post aSAH.

While the definition of DCI-related clinical deterioration includes evidence of focal and global (level of consciousness) neurologic deterioration, the cause for this deterioration is usually attributed to focal (regional) impairment in blood flow (i.e. cerebrovascular infarction and vasospasm) (Laskowitz & Kolls, 2010; Rabinstein et al., 2005; Stein, Browne, Chen, Smith, & Graham, 2006; Stein, Levine, et al., 2006). Treatment of focal (regional) cerebral hypoperfusion does not prevent DCI or significantly improve outcomes (Dorhout Mees et al., 2007, 2008; Macdonald et al., 2008; van den Bergh et al., 2006). Therefore, exploring global cerebral blood flow as a contributor to DCI and poor outcomes post aSAH is warranted.

2.4.4 Cerebral perfusion pressure, cerebral blood flow, and cerebral autoregulation

The brain is totally dependent on continuous and relatively constant blood flow; it consumes 15% of total cardiac output, 20% of total oxygen, and 25% of total glucose utilized by the whole body. Because neurons do not store glucose, the brain is not capable of tolerating the absence of blood flow for periods as short as 10 seconds. In such situations, neurons can become nonfunctional but remain alive for approximately 30 minutes. Conversely, when cerebral blood flow is impaired, neurons can remain alive for up to 6-8 hours (Roach, Bettermann, & Biller, 2010). Normal cerebral blood flow in an awaking adult is approximately 50ml/100g/min. The threshold for ischemia is 18ml/100g/min while the threshold for irreversible damage is

1ml/100g/min (Dagal & Lam, 2011). At the latter threshold, cells are permanently dead and brain damage is irreversible. When cerebral blood flow is impaired in certain territories (e.g. due to focal infarction or vasospasm), the collateral circulation is recruited to keep the tissue potentially recoverable (ischemic penumbra). In global ischemia (e.g. inadequate cerebral perfusion pressure), the blood flow in the collateral circulation is also impaired which limits the ability to recover brain tissue (Roach et al., 2010). Therefore, global cerebral perfusion deficit can be more devastating than focal perfusion deficit. A process called "cerebral autoregulation", which is often impaired in aSAH patients, normally regulates global cerebral perfusion.

Cerebral autoregulation refers to the ability of the brain to maintain a relatively constant blood flow in spite of changes in MAP and CPP (Paulson, Strandgaard, & Edvinsson, 1990). Typically, cerebral autoregulation functions within a MAP window of 60-150 mmHg or a CPP window of 50-100 mmHg (Paulson et al., 1990; Smith & Amin-Hanjani, 2011). This window is not fixed and depends on several factors such as carbon dioxide levels, sympathetic activity, and certain disease states. For example patients with chronic hypertension have higher thresholds compared to normotensive patients (Paulson et al., 1990; Strandgaard & Paulson, 1989). The cerebral vasculature reacts (dilate/constrict) according to changes in blood pressure to keep cerebral blood flow relatively constant. When CPP falls below the lower limit in intact autoregulation function, arteries and arterioles start to constrict to maintain the perfusion pressure (Gabrielli, Layon, & Yu, 2008). Impairment of cerebral autoregulation after aSAH has been noticed previously and can be predictive of poor outcomes (Hattingen et al., 2008; Lang, Diehl, & Mehdorn, 2001). Impaired autoregulatory function causes cerebral blood flow to be exclusively dependent on blood pressure thus small changes in blood pressure or cerebral

perfusion pressure can alter cerebral perfusion dramatically. Low CPP (<60 mmHg) can impair autoregulation, while increasing CPP in the absence of intact autoregulatory function (cerebral vessels are non-reactive) can lead to reperfusion hyperemia. Subsequently, this leads to increase in ICP, decrease in CPP, and finally reduced cerebral blood flow. This mechanism has been implicated in the pathogenesis of secondary brain injury (Czosnyka & Pickard, 2004; Dagal & Lam, 2011) and can be potentially employed in post-aSAH secondary insults such as DCI.

Normally, cerebral autoregulation maintains a relatively constant blood flow to the brain in spite of changes in CPP/MAP (Aaslid, Lindegaard, Sorteberg, & Nornes, 1989). Impairment of cerebral autoregulation after aSAH is associated with low CPP (Jaeger, Schuhmann, Soehle, Nagel, & Meixensberger, 2007; Lang et al., 2001). Elevated CPP values can also cause impairment in autoregulation (Czosnyka, Brady, Reinhard, Smielewski, & Steiner, 2009). When cerebral autoregulation is impaired, even small changes in CPP may not be tolerated by the brain; leading to cerebral hypoxia. In patients with head injury, CPP augmentation results in increased brain tissue oxygenation (Johnston et al., 2005). Increased cerebral tissue oxygenation improves outcomes after aSAH (Al-Rawi et al., 2010).

These findings suggest a role for CPP in the pathogenesis of cerebral ischemia and poor outcomes after aSAH. CPP is the pressure gradient between mean arterial pressure (MAP) and intracranial pressure (ICP) that allows blood to flow to the brain (Alvarez del Castillo, 2001). Changes in ICP, MAP, and CPP are common after aSAH. Approximately, ¾ of aSAH patients experience abnormal fluctuations in ICP, MAP, and CPP (Ryttlefors et al., 2007). These fluctuations result in decreases in cerebral blood flow; but it is unknown whether CPP changes are associated with DCI and poor outcomes post aSAH. Several studies have suggested that CPP

may serve as a clinically informative index of global cerebral perfusion deficit associated with DCI and poor outcomes (Cahill et al., 2006; A. P. Huang et al., 2010). Continuous cerebral blood flow monitoring at the bedside is not possible and patient transport to the radiology department for imaging can result in serious adverse events (Swanson et al., 2010), thus CPP may be a good indicator for continuous assessment of adequate cerebral blood flow. Schmidt and colleagues have recruited 30 subjects to study the relationship between CPP, brain tissue hypoxia, and metabolic crisis. They found that a CPP ≤ 70 mmHg was associated with metabolic crisis (OR 2.1) and brain tissue hypoxia (OR 2.0). In addition, brain tissue hypoxia and metabolic crisis were significantly associated with poor functional outcomes at 3 months following aSAH but not with mortality (Schmidt et al., 2011). However, this study did not investigate DCI per se and it was unclear if patients with brain tissue hypoxia were symptomatic. Further, this study did not examine that relationship between CPP and poor functional outcomes or poor neuropsychological outcomes, a frequently missed outcome measure.

2.5   OUTCOMES

During hospital stay post aSAH admission, patients are monitored for the complications discussed above in order to maintain stable hemodynamics as well as to prevent poor outcomes and death. After discharge, the physical and the cognitive functional levels are crucial for survivors. Up to 63% of aSAH survivors suffer long-term functional disabilities and up to 42% suffer cognitive disabilities (Mayer et al., 2002; van der Bilt et al., 2009). These disabilities include: inability to carry out activities of daily living, resume pre-injury activities and to return

to work (Al-Khindi, Macdonald, & Schweizer, 2010). DCI, cerebral infarction, and initial neurological status are the strongest predictors of poor outcomes after aSAH (Diringer et al., 2011; Frontera et al., 2009; Macdonald, Pluta, & Zhang, 2007; Springer et al., 2009; Vergouwen, Ilodigwe, et al., 2011). Despite that fact that these predictors are known, only nimodipine, a calcium channel blocker, has been proven in prospective randomized controlled trials to improve outcomes (Diringer et al., 2011). In spite of the different treatment options, outcomes after aSAH remain poor. This is becoming more prevalent as mortality decreases after aSAH; therefore more individuals are left with poor physical and neuropsychological functions.

Post aSAH outcomes are often measured through functional and neuropsychological assessments; however, functional assessments are more commonly measured (Diringer et al., 2011; Macdonald et al., 2007; Vergouwen, Ilodigwe, et al., 2011). The majority of studies that have investigated the effect of ICP, MAP and DCI on outcomes relied mainly on disability assessments (e.g., Glasgow outcome scale or modified Rankin scale) as primary endpoints (Beseoglu, Unfrau, Steiger, & Hanggi, 2010; Cormio et al., 2001; Jaeger et al., 2007; Kirkness, Burr, & Mitchell, 2009). While this approach evaluates the impact on functional outcomes, it does not evaluate neuropsychological impairment; an important source of disability and neurologic deficit in these patients (Saciri & Kos, 2002).

Functional outcomes are often classified as severe versus moderate disability or poor versus good. Assessment is usually made at 3, 6 and/or 12 months after bleeding. Severe disability occurs in 61% of patients at discharge and 21% at 3 months, while moderate disability occurs in 21% of patients at discharge, and 40% at 3 months (Beseoglu et al., 2010; Naidech et al., 2005). Poor functional outcomes occur in 20-40% of patients at 6 months, and in 34% after 1

year (Langham et al., 2009; Ohwaki et al., 2006; Soehle et al., 2007). Overall poor functional outcomes occur in 16%-63% of patients with aSAH (van der Bilt et al., 2009). Interestingly, variability in arterial blood pressure is related to 6 month functional outcomes (measured by GOS) with a greater and faster 5-second variability associated with better outcomes and greater 24-hour variability associated with worse functional outcomes (Kirkness et al., 2009). These findings suggest that factors that affect global cerebral perfusion are related to functional outcomes post aSAH. Predictors of poor functional outcomes include: DCI (Frontera et al., 2009), larger baseline intraventricular hemorrhage (A. H. Kramer et al., 2010), cardiac dysfunction (van der Bilt et al., 2009), cardiac arrhythmias (Frontera et al., 2008), age, hydrocephalus (Ohwaki et al., 2006), fever, anemia, hyperglycemia (Wartenberg et al., 2006), amount of initial bleeding, initial neurologic condition (Hijdra, van Gijn, Nagelkerke, Vermeulen, & van Crevel, 1988), elevated ICP (Karnchanapandh, 2008), and rebleeding (Hijdra, Braakman, van Gijn, Vermeulen, & van Crevel, 1987).

Poor neuropsychological outcomes are common post aSAH. Approximately, 21%-76% of patients have cognitive impairment post aSAH (Al-Khindi et al., 2010; Mayer et al., 2002; Springer et al., 2009). Mayer et al., recruited 113 patients with SAH to evaluate the impact of cognitive impairment on functional outcomes and quality of life after SAH. Three-month neuropsychological assessment was performed in 7 domains: verbal memory, visual memory, motor functioning, reaction time, executive function, visuospatial functioning, and language functioning. The highest proportion of impairment was found in the verbal memory domain (42%) and the lowest percentage of impairment was found in the executive function domain (18%). After the adjustment for age, race, and education, none of the seven domains were

associated with global handicap measure (assessed by modified Rankin scale) (Mayer et al., 2002). Findings from a recent systematic review to determine the impact of aSAH on neuropsychological function and functional outcomes indicate that the most common areas of cognitive impairment in aSAH patients are: memory, executive function, and language. Others report that cognitive impairment negatively impacts the activity of daily living, ability to return to work, and quality of life (Al-Khindi et al., 2010). Variables that are associated with neuropsychological impairment include: DCI, symptomatic vasospasm (Frontera et al., 2009; Springer et al., 2009), global cerebral edema, left sided infarction (Kreiter et al., 2002), fever, anemia with blood transfusion, and cerebrospinal fluid 20-HETE (Crago et al., 2011).

In summary, development of DCI has been associated with poor functional and neuropsychological outcomes after aSAH (Al-Tamimi et al., 2010; Frontera et al., 2009; Schutz et al., 1993; Springer et al., 2009) but no monitoring approach has been shown to be effective in guiding medical management to prevent these sequelae. Continuous monitoring of cerebral blood flow and the bedside is critical but not possible. CPP can be used as an indicator of cerebral blood flow.

2.6   SIGNIFICANCE AND INNOVATION

Diagnosis of DCI is often late and occurs after the patient develops symptoms. Moreover, medical centers do not often perform serial radiographic testing to assess cerebral blood flow (Frontera et al., 2009), thus finding indicators for cerebral blood flow can be used as a screen-in tools to determine patients who need further investigation. These tools can potentially maximize

the use of hospital resources, reduce cost, and enable early detection of complications. Monitoring cerebral blood flow continuously at the bedside is not possible. However, CPP can be indicative of cerebral blood flow and thus used as a tool for determining patients who may need further investigation. Therefore, findings from the current study are expected to improve methods for monitoring complications and poor outcomes after aSAH. The outcome measurement in the current study is unique in using multidimensional longitudinal assessment including functional and neuropsychological evaluation at 3 and 12 months post aSAH. Our hypothesis is novel in proposing global cerebral perfusion deficit (i.e. low CPP) as a risk factor for DCI post aSAH as well as proposing DCI as a mediator for poor outcomes in patients with aSAH.

It is important to emphasize that the question in this study is not whether low CPP results in cerebral ischemia (this is already known). Rather, this study addresses the question of whether DCI that is thought to happen due to local vascular alteration (vasospasm/infarction) is related to global cerebral perfusion deficit (i.e. CPP). Understanding this question is important to utilize the findings optimally and to assess the innovation of this study. There are several other unique aspects in this study:

1. The literature supports a relationship between MAP, ICP, DCI, and poor functional outcomes (Frontera et al., 2009; Kirkness et al., 2009; Soehle et al., 2007). Despite these known relationships, the relationship between CPP and DCI has not been evaluated in prior studies. The current study evaluated the relationship between CPP, DCI, and post aSAH outcomes.

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2. CPP is a relatively simple and low-cost monitoring tool. It is a single parameter that can be used as a surrogate measure of cerebral blood flow. This is particularly important because continuous bedside assessment of cerebral blood flow is not possible. Patients must be transported to the radiology department to obtain this assessment, which has known risks in unstable patients.

3. Changes in CPP impact global cerebral perfusion (overall cerebral blood flow). Blood flow in collateral circulation is also impaired in global cerebral hypoperfusion. Therefore, the ability of collateral cerebral blood flow to compensate is limited compared to the case focal perfusion deficit (insufficient blood flow in certain cerebral territories). Improving focal cerebral blood flow does not significantly improve outcomes or prevent DCI. Our hypothesis represents an innovative approach to explaining the pathogenesis of DCI and poor outcomes.

4. The majority of studies that have investigated the effect of ICP, MAP and DCI on outcomes have used gross functional outcome measures (Glasgow outcome scale, modified Rankin scale) as indicators of function (Beseoglu et al., 2010; Cormio et al., 2001; Jaeger et al., 2007; Kirkness et al., 2009). Such measures are inadequate to identify specific areas to target for interventions to compensate for neuropsychological dysfunction. The current study has used more comprehensive measures of both functional and neuropsychological outcomes to provide data to guide future interventions.

5. This is the first study to investigate the relationships between Hunt and Hess grade, CPP, DCI, and neuropsychological outcomes after aSAH and to test whether DCI mediates the relationship between Hunt and Hess grade and poor outcomes. Understanding these

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relationships will potentially aid clinicians and administrators to develop clinical guidelines to minimize complications.

2.7 IMPLICATIONS TO PRACTICE

Monitoring is an essential task for nurses in intensive care settings. Monitoring cerebral blood flow is a key task for preventing such complications after aSAH. Nursing is being tasked with frequent monitoring but limited in scope. Therefore, it only alerts the nurses to a symptom, not the underlying cause. Monitoring of CPP as a marker DCI is beyond monitoring symptoms; it involves monitoring risk factors and thus opens new areas for nursing research and interventions for controlling CPP that will potentially prevent DCI and improve patients' lives.

3.0   METHODS

3.1   DESIGN

This is a descriptive longitudinal study that investigated the relationship between CPP, DCI, severity of bleeding and poor outcomes post aSAH. *Data sources* included medical records and charts from a parent study. The parent study is an ongoing NIH funded study (R01 NR004339-10, Dr. Samuel Poloyac and Dr. Paula Sherwood, Co- PIs), which recruits patients with aSAH to examine the physiologic predictors of complications and outcomes post aSAH. The study is conducted at the University of Pittsburgh - School of Nursing, School Pharmaceutical Sciences, and University of Pittsburgh Medical Center (UPMC).

3.2   SETTING

The data collection site for the parent study is a 20-bed neurovascular intensive care unit (NICU) at the UPMC-Presbyterian Hospital. Fourteen percent of admissions to the NICU are patients with aSAH. UPMC-Presbyterian, an adult medical-surgical referral hospital and site of ongoing research located in southwest Pennsylvania, is a Level I Regional Resource Trauma Center with well-established neurology and neurosurgery departments. The Department of Neurological

Surgery is nationally and internationally recognized for innovative research and high-quality training programs. UPMC has a state of the art Comprehensive Cerebrovascular Neurosurgery Center that includes the Center for Endovascular Therapy that provides care for patients with intracranial aneurysms. The Cerebrovascular Neurosurgery Center collaborates with the UPMC Stroke Institute and has a specialized multidisciplinary team that is available 24 hours a day, 7 days a week and includes neurologists, neurosurgeons, radiologists, neurointensivists, physiotherapists, speech therapists, social workers, and nurses.

3.3   SAMPLE

The sample included monitored patients 21-75 years of age with aSAH admitted to UPMC Presbyterian NICU between May 1999 and October 2011, and enrolled in the parent study. On average, the research team recruits 40-50 subjects each year, approximately 75-85% of whom have an external ventricular drain (EVD) placed for ICP monitoring and cerebrospinal fluid drainage. Those subjects either have an arterial line for continuous blood pressure monitoring or a blood pressure cuff for noninvasive intermittent blood pressure monitoring every two hours. The sample was inclusive of the general population; there was no restrictions based on gender, race, or socioeconomic status.

3.3.1 Inclusion and exclusion criteria

Inclusion criteria for this analysis were: 1) new diagnosis (within 5 days) of spontaneous SAH due to aneurysm rupture (verified via computed tomography [CT] scan and cerebral angiography), 2) Hunt and Hess grade of ≥ 3 and/or Fisher grade ≥ 2, 3) admitted to the NICU, 4) blood pressure and intracranial pressure measurements available, 5) 21-75 years of age, and 6) able to read/speak English. *Exclusion criteria were:* 1) preexisting chronic neurologic disease, 2) traumatic SAH, or 3) traumatic aneurysm rupture or mycotic aneurysm.

3.3.2 Sample size estimates for the current study

Using PASS 11, Optimal Design software, and sample size tables; the results of power analyses to calculate sample size for the current study were as follow:

- Specific Aim #1a: This aim is exploratory descriptive in nature and does not require sample size calculation.

- Specific Aim #1b: Growth curve power analysis revealed that 205 subjects are needed to achieve 80% power at a level of significance of 0.05 to detect effect size as small as 0.4.

- Specific Aim #2a: Logistic regression power analysis for DCI as a function of CPP revealed that 210 subjects are needed to achieve 80% power to detect odds ratio as small as 1.47 at a level of significance of 0.05.

- Specific Aim #2b: ROC curve power analysis revealed that a sample of 68 from the DCI(-) group and 91 from the DCI(+) group will achieve 80% power to detect a difference of 0.1 between the area under the ROC curve (AUC) under the null

hypothesis of 0.80 and an AUC under the alternative hypothesis of 0.90 using a two-sided z-test at a significance level of 0.05. Total number of subject need is 159.

- Specific aim #2c: power analysis revealed that 202 subjects are needed to achieve 80% power at a 0.05 significance level to detect regression coefficient equal to 0.3.

- Specific aim #3: utilizing sample size estimate table for mediation analysis proposed by Fritz and MacKinnon (2007), we found that analyzing this aim using biased corrected bootstrapping requires 148 subjects to achieve 80% power and detect an effect size as small as 0.26 at a level of significance of 0.05 (Preacher & Hayes, 2004).

By comparing all sample size estimations, the largest sample size needed is 210. In the parent study, we have data available for an estimated sample size of 211 subjects. Thus, all 211 subjects were included in this analysis.

3.4   RECRUITMENT

Subjects are recruited within 5 days of the onset of the hemorrhage and data are collected from the time of consent through 14 days after aSAH or until discharge. Approximately 85% of eligible subjects are enrolled in the parent study. After screening patients newly admitted to the NICU and determining their eligibility status, a comprehensive explanation for the study including the purpose, risks, benefits, and data collection procedures was provided. All patients who agreed to enroll and be part of the study, were asked to sign the consent. Subjects were also informed that the participation is completely voluntary and their decision to enroll in the study

will not affect their standards of care. Further, subjects were informed that they can withdraw from the study at any time.

3.5   DATA COLLECTION

To extract medical record data, the PI (KY) has collaborated with the Center for Assistance in Research using eRecords (CARe) at the University of Pittsburgh to obtain study variables. The parent study does not collect CPP values prospectively, thus CARe programmers has retrieved the requested data. The data collection procedure in the parent study that is related to this analysis included: 1) Screen all subjects admitted to the NICUs, 2) Determine eligibility, 3) Consent eligible subjects, 4) Collect baseline data, 5) TCD to assess cerebral blood flow velocities, 6) Review angiography and CT scan reports that are ordered by the medical team, 7) Follow up for in-hospital clinical deterioration, and 8) Disability and neuropsychological assessment at 3 and 12 months (post bleeding), through phone calls and home visits.

3.6   TIMETABLE FOR THE STUDY

Table 2. Timetable of the study

Study activities	Year 1				Year 2		
	Q1	Q2	Q3	Q4	Q1	Q2	Q3
Meet with the Co-Is	X	X	X	X	X	X	X
Data collection		X	X				
Data entry and merging relevant datasets		X	X				
Data cleaning and analysis			X	X			
First Manuscript preparation				X	X		
Second Manuscript preparation					X	X	
Dissertation manuscript preparation						X	X
Dissertation defense							X
Sending manuscripts to relevant journals						X	X

3.7   STUDY VARIABLES

3.7.1   Delayed cerebral ischemia (DCI)

DCI was defined as the presence of clinical deterioration, not attributable to rebleeding, seizures, hydrocephalus, and cerebral edema, accompanied by evidence of abnormal cerebral blood flow (Yousef et al., 2010). Subjects were classified as DCI-present if they had both clinical deterioration and one or more indicators of abnormal cerebral blood flow, and DCI-absent if they had no evidence of clinical deterioration or no evidence of abnormal cerebral blood flow on any of the below diagnostic modalities. Subjects with a DCI status that could not be determined according to the above definition were excluded from this analysis (e.g., subjects who are comatose or sedated and thus their neurologic decline cannot be evaluated). The variable "Time to DCI" was defined as the number of hours from aneurysm rupture to the time of DCI diagnosis and was analyzed as ratio dependent variable

Indications of clinical deterioration included: a) decrease in level of consciousness measured by Glasgow coma scale, b) presence of a new focal neurologic deficit, c) deterioration in pupillary reaction, or d) worsening score on the National Institute of Health Stroke Scale (NIHSS). Cerebral blood flow assessments within 12 hours (before, after, or both) of the observed neurologic deterioration were evaluated. Cerebral blood flow was assessed by any of the following methods:

1) Transcranial Doppler (TCD) assessments performed daily, indications of abnormal blood flow included a) mean middle cerebral artery velocity >120 ml/second; b) systolic middle cerebral artery velocity >200 ml/second or c) Lindegaard ratio >3.0.

2) Head CT and CT perfusion scans, which provide accurate and reliable measurement of cerebral blood flow (Wintermark, Thiran, Maeder, Schnyder, & Meuli, 2001), within the 12-hour temporal window of the clinical deterioration, were reviewed for the presence of cerebral ischemia, infarction or abnormal blood flow.

3) Cerebral angiography studies within the same temporal window were independently reviewed and evaluated by a neurosurgeon for vascular narrowing, with narrowing > 25% considered as indication for cerebral vasospasm.

3.7.2 Cerebral perfusion pressure (CPP)

CPP was defined as the difference between mean MAP and ICP and measured in mmHg. In the parent study, MAP was measured either invasively using an arterial line or noninvasively using a blood pressure cuff. ICP was measured invasively by an external ventricular drain (EVD). CPP was measured at least every two hours. However, subjects who exhibited neurologic or systemic instability had more nursing surveillance and thus more CPP values. Typically, data collection lasted for 14 days after the bleeding onset unless a subject was admitted more than one day after bleeding onset or subject was discharged before the 14-day period. In either case, CPP values were available for <14 days. Due to the nature of ICP and CPP measurement in these subjects, CPP values were intermittent rather than continuous. While continuous CPP and ICP monitoring is more likely to capture all abnormal values, it was not possible in our subjects as ICP was measured by EVD, which needed to be clamped intermittently to obtain valid ICP. Further, the EVD in these subjects was open most of their time for CSF drainage, while the ICP was

measured only when the EVD was clamped. Therefore, the ICP measurement via the EVD might not represent the precise ICP values that the subject had most of the day while the EVD was open. In Specific Aim #1, CPP values were used as follows:

- Absolute CPP values (CPP_{all}): all CPP values measured for patients overtime.

- Baseline CPP (CPP_{base}): the first CPP value obtained in the first 24 hours after admission.

- Maximum CPP (CPP_{max}): the daily highest value of the measured CPP.

- Minimum CPP (CPP_{min}): the daily lowest value of the measured CPP.

- Mean of CPP (CPP_{mean}): the daily average of CPP values.

- Standard deviation of CPP (CPP_{SD}): daily standard deviation of CPP values.

- Percentage of CPP values less than or equal 70 ($\%CPP_{<70}$).

- Percentage of CPP values more than or equal 100 ($\%CPP_{>100}$).

The above CPP measurements were used only in Aim 1a to describe CPP changes over time after aSAH. In Aim 1b, all CPP values measured during the 14 days post bleeding were used to test the significance of CPP changes overtime. In Specific Aims 2, the minimum CPP values measured 12 hours prior to time of DCI diagnosis were used.

3.7.3   Patient outcomes

Post-discharge outcome interviews that include functional and neuropsychological assessment for the parent study were conducted in the neurosurgery clinic or in the subject's home by personnel trained in conducting outcome evaluation. These interviews were conducted without distractions or interruptions.

I) Neuropsychological outcomes were determined using a comprehensive battery of neurocognitive tests at 3 and 12 months following aSAH. Seven cognitive domains were assessed: attention, learning and memory, psychomotor speed, mental flexibility, executive function, visuo-spatial ability, and language. The selected tests have detailed scoring methods, excellent psychometric properties (Franzen, 1989; Mitrushina, Boone, & D'Elia, 1999) and have been demonstrated to be sensitive to changes in cognitive function or to cognitive impairment in large clinical trials studying the effects of neurological conditions on long-term neuropsychological outcomes (Butters et al., 1990; Hachinski et al., 2006). To minimize practice effects, alternate versions of tests were used at follow up testing when possible.

- *Attention:* was assessed by the Trail Making Test (Part A) which required the subject to draw a line connecting circled numbers in numerical sequence as quickly and accurately as possible. The test is highly sensitive to neurological impairment and has been used to detect cognitive impairment in multiple populations (Moertel, Reitemeier, Bolton, & Shorter, 1964; R. Reitan, 1958; Wieneke & Dienst, 1995). The test was scored by the number of seconds needed to complete the task; higher numbers indicated poor function.

- *Learning and Memory:* Three tests were administered within this domain.
  - Digit Span Forward and Backward measured immediate verbal memory and required the subject to listen to series of digits and orally repeat them in the order given (forward) and in reverse order (backward). The test was scored by the total number of digit sequences subjects were able to correctly recall as well as the longest number of digits in each sequence they were able to recall. Lower scores

indicated poor function. Validity has been established in studies of subjects with aSAH (Ogden, Mee, & Henning, 1993).

o Logical Memory, a well-known subtest from the Wechsler Memory Scale, assessed short and long term verbal memory and required the subject to recall a meaningful story (Morris, Kunka, & Rossini, 1997). Two meaningful stories (A and B) were read to the patients. Story A was told once to the subject who was asked to immediately recall the story to the examiner (short term recall) and then recall it again 30 minutes later (delayed recall). Story B was told twice to the subject who was asked to recall the story after each telling (short term recall) and after a 30-minute delay (delayed recall). The score was the total number of items that the subject was able to recall from each of the stories immediately after they were read as well as when they were recalled 30 minutes later. Lower scores indicated poor function. This test has been effective in differentiating between demented and non-demented individuals (Johnson, Storandt, & Balota, 2003).

o The Rey Complex Figure Test is a nonverbal memory task that requires subjects to copy a complex geometric design, and then draw it from memory both immediately and 30 minutes later (Meyers & Meyers, 1995). This test was scored by the number of elements in the figure the subject was able to correctly recall as well as how accurately they were placed while drawing it from memory. The score ranges between zero and 36; lower scores indicate poor function. Validity has been established in subjects with brain injury (Hinchliffe, Murdoch, & Chenery, 1998).

- *Psychomotor Speed*: The Grooved Pegboard was used as a measure of finger dexterity, eye-hand coordination (i.e., psychomotor integration), and motor speed (Rourke, Yanni, MacDonald, & Young, 1973). The subjects were asked to put notched pegs into a board that has 25, irregularly positioned holes as fast as possible. The test was performed using both the dominant and non-dominant hand. The subjects were instructed to put the pegs in order; left to right for the right hand and right to left for the left hand. This test was scored by the number of seconds needed to complete the task. Higher scores indicate poor function. The test is sensitive to hemispheric disability (Matthews, Cleeland, & Hopper, 1970).

- *Mental Flexibility:* The Trail Making Test B is a well-known test of mental flexibility and visuomotor tracking (R. M. Reitan & Wolfson, 2004). In this test, the subjects were asked to connect circles that have letters (A-L) and numbers (1-13) in an ascending order alternating between numbers and letter (e.g. 1-A-2-B-3-C…). This test was scored by the number of seconds needed to complete the task and higher numbers indicate poor function. Validity information is described above with the Trail Making Test A.

- *Executive Function*: The Stroop Color Word Test measures how accurately and quickly a person can shift perceptual set and choose an unusual response in place of a habitual response. This test required the subject to firstly read the name of color typed in black ink as quickly as possible. Secondly, x's were printed out in red, green and blue and the subjects were required to name the ink color. Thirdly, the subject was required to name, as quickly and accurately as possible, the ink color that was incompatibly typed with a different color name (e.g., BLUE, GREEN, RED). The test was scored by the number of

items completed in 45 seconds. Lower scores indicate poor function. The Golden version was used in the parent study (Golden, 1978).

- *Visuospatial Ability:* Visuospatial ability was assessed with the 'copy' component of the Rey Complex Figure Test described above.

- *Language*:

    o The Controlled Word Association test assesses the ability of subjects to spontaneously generate a list of words beginning with designated letters (F, A, S) of the alphabet in one minute (Lezak, 1995). Subjects were given 60 seconds for each letter.

    o The Animal Naming test requires subjects to say as many animal names as possible within one minute.

    The total number of words correctly generated in 60 seconds scored these tests. Validity for both tests has been well established in subjects with a variety of neurologic insults (Binetti et al., 1995; Shoqeirat, Mayes, MacDonald, Meudell, & Pickering, 1990).

Patients were classified as either having a neuropsychological impairment or not having a neuropsychological impairment. This classification may have resulted in loss of information as a consequence of summarizing the individual tests into one variable. To compensate for this loss of information, descriptive statistics (means and standard deviations) for each test in each domain are provided in the results section of this analysis. There are several approaches for classifying cognitive function (Shilling, Jenkins, & Trapala, 2006). One approach/method used by Wefel and colleagues (2004) was adopted in this study. In this method all test scores in all domains were standardized and converted to z scores. Patients with a z score of $\leq$ -1.5 in more

than one test or patients with z score $\leq$ -2.0 in at least one test were considered to have neuropsychological impairment (Wefel et al., 2004). One advantage of this method is that it uses all tests scores rather than using domain scores or factor analysis to determine neuropsychological impairment, both of which minimize the number of tests utilized in the analysis. Using all test scores minimizes information loss that results from the classification of the neuropsychological function as impaired vs. not impaired. This method was also compared with other methods for classifying cognitive function by Shilling and colleagues (Shilling et al., 2006). In this report, the authors compared 7 different methods for classifying neuropsychological function by performing the classification using each method on 92 breast cancer patients and 42 healthy controls. This report has shown that the method used by Wefel and colleagues (2004), when compared to other methods, neither overestimates nor underestimates the proportion of patients with cognitive impairment.

II) Functional outcome was assessed using:

- Modified Rankin scale (MRS) which incorporates mental and physical adaptations to the deficits resulting from neurologic injury using a scale from 0 (no symptoms at all) to 6 (death). Reliability and validity of the scale have been established in subjects suffering strokes (Sturm et al., 2002; Sulter, Steen, & De Keyser, 1999; van Swieten, Koudstaal, Visser, Schouten, & van Gijn, 1988). MRS was assessed on 3 and 12 months after the onset of aneurysm rupture.

- The Medical Outcomes Study 36-item Short-Form Health Survey version 2 (SF-36) physical component summary measures (Ware, Kosinski, & Dewey, 2000), ask subjects to indicate limitations to overall physical health using Likert-type scales. The score for the physical functioning component was generated by summing individual

items within that component was used in the analysis (question #3). Higher scores

indicate more limitations in physical function. Validity for the SF-36 as a measure of

overall physical health has been demonstrated in numerous patient populations

(Failde & Ramos, 2000; Hollingworth et al., 2002; Riley et al., 2003).

III) Mortality was tracked in the parent study through the subject's clinic chart and, when

necessary, by following up through the Social Security Death Index (SSDI) [Social security

administration]. Due to the integrated inpatient and outpatient electronic record system at

UPMC, information on the majority of deaths were available through medical records.

3.7.4   Hunt and Hess (HH) grade

Hunt and Hess grade is a 5-point scale that quantifies the severity of bleeding based on the

presenting signs and symptoms; where grade I represents the least severe symptoms and V

represent the most severe symptoms. We believe that patients with higher bleeding grades have

higher risk for poor outcomes and thus Hunt and Hess grade was used as an independent variable

in the analysis of specific aim #3.

3.7.5   Confounding variables

The following potential confounding variables were controlled for in this analysis.

I) Mood was assessed in the parent study via depressive symptoms and anxiety. Patients with

depression and anxiety have worse scores on neuropsychological tests suggesting an increased

neuropsychological impairment in those patients compared to those without depression or

anxiety (Basso et al., 2007; Castaneda et al., 2008). Thus, controlling for depression and anxiety was warranted when measuring neuropsychological outcomes (Specific Aim #3) in order to ensure that the relationship between Hunt and Hess grade, DCI, and neuropsychological function outcomes was not confounded by depressive symptoms/anxiety.

- Depressive symptoms were assessed using the Beck Depression Inventory II, a 21 item self-report measure on which subjects rate depressive symptoms and attitudes on a 5-point Likert scale. The total score was used in the analysis. Validity has been established with the Structured Clinical Interview for DSM-IV Axis I Disorders (Arnarson, Olason, Smari, & Sigurethsson, 2008).

- Anxiety was measured using The State-Trait Anxiety Inventory (STAI). The STAI is a 40-item scale that comprises a trait anxiety scale and a state anxiety scale. The trait scale measures longstanding personality trait anxiety whereas the state scale measure temporary anxiety that is specific to certain situations. The state anxiety scale, which was used in this study, ranges between 20 and 80 with higher scores indicting greater levels of anxiety (Spielberger, Gorsuch, & Lushene, 1983). STAI has been used previously with aSAH patients as well as other patient populations (Al-Khindi et al., 2010; Karlsgodt, Lukas, & Elman, 2003; Passier et al., 2010). Validity and reliability for the STAI are well established in various patient populations (Rule & Traver, 1983; Smeets, Merckelbach, & Griez, 1996). The total score of the state scale was used in this study.

II) Age: older age has been associated with poor neuropsychological and poor functional outcomes in patients with aSAH (Haug et al., 2010; Kreiter et al., 2002; Ohwaki et al., 2006). Therefore, age was controlled for when testing neuropsychological and functional outcomes

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(Specific Aim #3) to ensure that the relationship between Hunt and Hess grade, DCI, and post-aSAH outcomes was not confounded by age.

III) Years of education: having fewer years of education is associated with poor neuropsychological function in aSAH patients (Haug et al., 2010; Kreiter et al., 2002). Therefore controlling for number of years of education in Specific Aim #3 was important to make certain that these differences between subjects were due to neuropsychological impairment and not due to different levels of education.

IV) Hunt and Hess grade: is a 5-point scale that quantifies the severity of bleeding based on the presenting signs and symptoms; where grade I represent the least severe symptoms and V represent the most severe symptoms. Higher bleeding severity grade measured by Hunt and Hess scale is associated with DCI (Frontera et al., 2009) and neuropsychological dysfunction (Kreiter et al., 2002; Otawara et al., 2009) and thus was controlled for to ensure that the relationship between CPP and DCI was not confounded by Hunt and Hess grade. Others have previously controlled for Hunt and Hess in similar analysis (Frontera et al., 2009). Hunt and Hess grade was controlled for in specific aims #2. However, it was used as an independent variable in specific aim #3.

V) Aneurysm repair method: Functional and neuropsychological outcomes are affected by the method of aneurysm repair (i.e. endovascular coiling vs. surgical clipping) (Al-Khindi et al., 2010). Evidence from the International Subarachnoid Aneurysm Trial (ISAT), a multicenter randomized controlled trial that compared the impact coiling and clipping on patient after aSAH, suggests that endovascular coiling is associated with lower mortality and better outcomes at 1 year post aSAH (Scott et al., 2010). Further, Recent evidence suggests that surgical clipping is associated with higher risk for DCI compared to coiling (Dorhout

Mees et al., 2011). Therefore, aneurysm repair method was controlled for in specific aim #2 and #3. This will eliminate the confounding effect of the aneurysm repair method.

3.8   DATA ANALYSIS

IBM SPSS 19 and Mplus 6 were used to perform the analyses. Data distributions were checked for normality, outliers, and linearity. Normality and outliers were examined subjectively through histograms, boxplots, normality probability plots, and objectively by the Shapiro-Wilk's test. Multivariate outliers will be screened objectively by Mahalanobis distance and subjectively by bivariate plots. When outliers were found, verifications were made to ensure that these outliers were part of the sample and were not due to entry error. Linearity was examined subjectively by scatter plots and objectively by Box Cox transformation.

3.8.1   Specific Aim #1

To describe and examine CPP changes during the 14 days after aSAH in regard to:

   a. **baseline, absolute values, daily changes (range, mean, standard deviation), proportion of CPP values <70 mmHg, and proportion of CPP values >100 mmHg.**

   Descriptive statistics and chart builder were used to graph all CPP values over time as well as daily ranges, means, and standard deviations.

   b. **trends of CPP values over time.**

Growth curve analysis was used to test whether repeated measured CPP trajectories over time are significant. This analysis was performed using IBM SPSS 19 using a 0.05 level of significance.

3.8.2 Specific Aim #2

To examine the relationship between DCI and the lowest decrement in CPP during the 12 hours prior to DCI

a. **To examine the association between DCI and the lowest decrement in CPP during the 12 hours prior to DCI controlling for Hunt and Hess grade and aneurysm repair method.**

Binary Logistic regression was conducted with DCI as a dichotomous dependent variable and CPP as a ratio predictor variable to determine if CPP predicts DCI. This analysis was performed using IBM SPSS 19 and a 0.05 level of significance controlling for Hunt and Hess grade and aneurysm repair method.

b. **To explore the threshold of CPP value associated with DCI**.

Receiver operating characteristic (ROC) curve was conducted to estimate the area under the curve and find the cutoff value for CPP that is associated with DCI. The cut-off CPP value was determined by the value that has the highest level of sensitivity and specificity for DCI.

c. **To determine whether minimum CPP values are related to the onset of DCI controlling for Hunt and Hess grade and aneurysm repair method.**

Accelerated failure time model using SAS 9.2 was used to determine the relationship between CPP and onset of DCI.

3.8.3 Specific Aim #3

To determine whether DCI mediates the relationship between Hunt and Hess grade and neuropsychological outcomes, functional outcomes, physical outcomes, and death post aSAH controlling for age, aneurysm repair method, years of education, anxiety and depression.

In order to determine whether DCI mediates the relationship between Hunt and Hess grade and outcomes, Mplus 6 was used to conduct bias corrected bootstrapping test. Bootstrapping test is a nonparametric procedure and, unlike Sobel test, it does not assume normality of sampling distribution of the indirect effects in the mediation model. Also it is not based on large sample theory and typically requires less sample size than Sobel test does. Thus, it can be conducted more confidently with small sample size. Moreover, bootstrapping, unlike Baron and Kenny approach, it does not require zero measurement error (Preacher & Hayes, 2004). We expected measurement error in Hunt and Hess grade and DCI assessment as well as non-normal distribution of the indirect effects in the mediation model. Therefore, bootstrapping was the best approach for analyzing data in this specific aim. The level of significance was the standard 0.05. The comparisons in the study aim were made a priori and thus no correction for the inflation in type I error was made.

3.9   STUDY LIMITATIONS

The current study has several limitations. *First*, there might be discrepancy between the MAP measured invasively using arterial lines and those measured noninvasively using blood pressure cuff. It was not be possible to limit subjects to those with an arterial line because it would significantly decrease available subjects. UPMC clinicians tend to use noninvasive monitoring once the patient stabilized to lower the risk of complications. *Second*, due to the variability in days of follow up and variability of subjects' conditions, there may be different numbers of CPP values for different subjects. However, the statistical analyses in this study do not require the same number of observations for every subject; thus, it is unlikely to change our results. *Third*, it is likely that more subjects with a higher aSAH grade had an external ventricular drain which could limit the generalizability to high grade aSAH, however, the current analysis controlled for the severity of aSAH in all multivariate analyses. *Fourth*, CPP values were recorded intermittently. Continuous CPP monitoring is more likely to capture all abnormal values; however, this was not be feasible in our subjects due to the nature of ICP measurement at the bedside. The EVDs used to measure ICP needed to be clamped intermittently to obtain valid ICP measurements. Further, the EVD in these subjects was open most of their time for CSF drainage, while the ICP was measured only when the EVD was clamped. Therefore, the ICP measurement via the EVD might not represent the precise ICP values that the subject had most of the day while the EVD was open. Finally, the above mentioned method for analyzing CPP does not distinguish between patients who had few episodes but long duration of low CPP and those who had more frequent and shorter episodes of low CPP. However, since our analysis has used the lowest CPP value measured 12 hours prior to DCI, the number of CPP measurements will

typically be 6 values for those 12 hours. Therefore, it is likely that the chance of encountering the situations of few episodes but long duration of low CPP versus more frequent and shorter episodes of low CPP was minimal and did not affect our findings.

3.10   HUMAN SUBJECTS/ETHICAL CONSIDERATIONS

This secondary analysis that has utilized data collected for the parent study R01 (NR004339-10) and approved by the Institutional Review Board (IRB) at the University of Pittsburgh (REN11040212 / IRB021039). The risk in the current study was minimal and was restricted to potential loss of confidentiality. All subjects have study identification numbers and data for the current study was analyzed after it was de-identified. Data was kept protected in a secure password protected computer in locked office. During the consent procedure for the parent study, subjects were informed that their participations are completely voluntary and the decision whether to enroll in the study will not affect their standards of care. There was no exclusion based on gender, ethnicity or race.

4.0 RESULTS

The purpose of this study was to examine the relationship between CPP, DCI, and onset of DCI and to test whether DCI mediates the relationship between HH grade and poor outcomes after aSAH. Two articles describing the results of this study have been prepared for submission to Neurocritical Care (Aim 1) and Stroke (Aim 2 and 3) are appended to this chapter.

4.1 FINDINGS RELATED TO AIM 1

Aim 1: To examine the temporal profiles of CPP changes after SAH.

Subjects (n=238) were relatively young (53 ± 11.4 years), predominantly female (69%) and Caucasian (88%). Other clinical characteristics are shown on table 3. 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 from the sample are shown in Figures 2a-2c. 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 3).

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 4), we observed that the trend of CPP and followed a similar trend of MAP, suggesting a greater influence of MAP on CPP compared to ICP. To objectively and quantitatively test that observation, we performed Pearson correlation to compare correlation coefficients between MAP and CPP vs. ICP and CPP (Table 4). We found that the correlation coefficients of MAP and CPP were higher than the coefficients of ICP and CPP over the observation period.

Figure 5 shows the percentage 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 5) (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

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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 (β = 64.11, *SE* = 0.83, *p* <0.001). The significant linear effect for the CPP was positive (β = 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 6).

4.2   FINDINGS RELATED TO AIM 2

This analysis included 211 subjects, who were relatively young (53±11 years), predominantly female (66%) and white (88%). Mean education was 13 years at 3 (SD=2) and 12 (SD=2.5) months. Approximately, 62% underwent aneurysm coiling, 67% had a poor HH grade (3-5), and

42% experienced DCI. DCI could not be determined for 13 patients (6%) due to inability to assess neurological decline due to sedation or coma. The mean value for CPP was 53±17 mmHg. The mean BDI score was 10±8 at 3 months and 12±10 at 12 months. The mean State Anxiety score was 47±6 at 3 months and 45±6 at 12 months.

Logistic regression was performed on DCI as a function of age, gender, HH grade [good (1-2) or poor (3-5)], aneurysm treatment option (clipping vs. coiling), and CPP (Table 8). The overall model significantly predicted DCI; χ^2(5, N=196) = 71.43, $p < 0.001$, Nagelkerke R^2 = .41. There was a significant positive relationship between CPP and DCI. For every 10 mmHg increase in CPP, the odds of DCI increased by 2.78 (95%CI 2.00-3.87). Furthermore, the mean value for CPP was significantly greater for subjects with DCI (64.6±17), compared to those without DCI (46±11), p<.001.

The mean time for DCI diagnosis was 6±2.3 days after bleeding. This analysis controlled for age, gender, aneurysm repair method, and Hunt and Hess grade. Table 9 shows that the estimate of CPP was negative (-0.283) indicting that high CPP values are associated with shorter time to DCI (p<0.0001).

4.3   FINDINGS RELATED TO AIM 3

Data on neuropsychological outcomes were available for 61-77 subjects. Missing data resulted from time of recruitment (neuropsychological assessments were not initiated until 2003), loss to follow up, death, and refusal. Approximately one third had a poor MRS at 3 (32%) and 12 (30%) months and impaired neuropsychological function at 3 (33%) and 12 (17%) months. Mean SF36

score was 20±5 and 22±5 at 3 and 12 months, respectively. Approximately, one-fourth of subjects were dead at 3 (26%) and 12 (29%) months. The direct effects between HH grade and outcomes were tested before testing the mediation effect. Mediation was tested only when the direct effect was significant. HH grade was significantly related to mortality and functional outcomes at 3 and 12 months, but not physical or neuropsychological function (controlling for age, aneurysm repair method, education, depression and anxiety). However, DCI did not significantly mediate the relationship between HH grade and functional outcome or death at both 3 and 12 months (Table 10).

5.0   RESULTS MANUSCRIPT #1

Temporal Profiles of Cerebral Perfusion Pressure After Subarachnoid Hemorrhage

5.1   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 (β =0.06, SE=0.006, $p<0.001$). The covariance (τ_{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.

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

5.2 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 bleeding and other secondary complications, 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 et al., 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 et al., 2011; Frontera et al., 2009; Juvela & Siironen, 2012; Macdonald et al., 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

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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.

5.3   METHODS

5.3.1   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.

5.3.2 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.

5.3.3 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.

5.3.4   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 >60 mmHg. Next, all CPP values for 16 randomly selected subjects were used to create line charts of CPP values versus time profiles over the observation period and 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 Spearman 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 (Table 5). 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).

5.4   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 3.

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 from the sample are shown in Figures 2a-2c. 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 3). 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 4), we observed that the trend of CPP and followed a similar trend of MAP, suggesting a greater influence of MAP on CPP compared to ICP. To objectively and quantitatively test that observation, we performed Pearson correlation to compare correlation coefficients between MAP and CPP vs. ICP and CPP (Table 4). We found that the correlation coefficients of MAP and CPP were higher than the coefficients of ICP and CPP over the observation period.

Figure 5 shows the percentage 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 5) (Mirman et al., 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 (τ_{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 (β = 64.11, *SE* = 0.83, *p* <0.001). The significant linear effect for the CPP was positive (β = 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 6).

5.5   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. 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 (4) 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 4).

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 6). 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 a high CPP had a slower change rate and those with a 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.

5.6   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.

Table 3. Subjects' 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
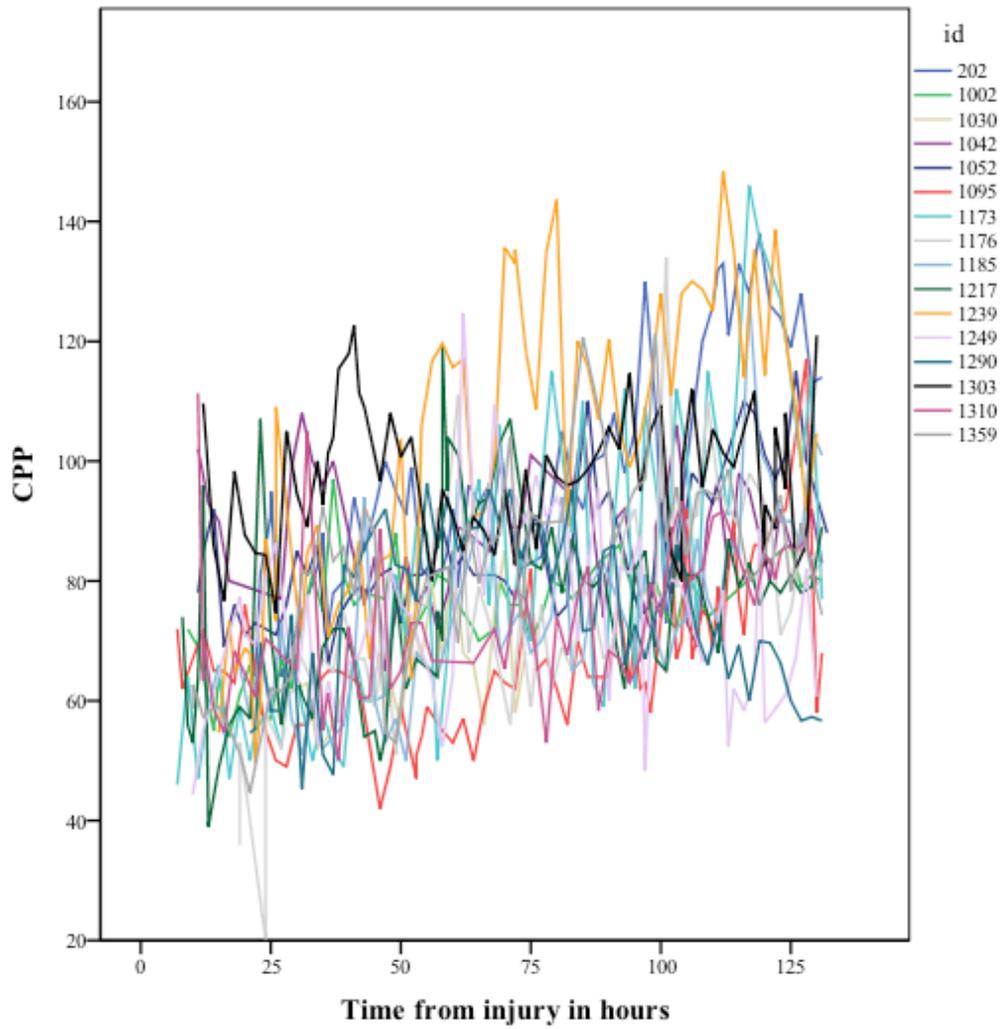
Figure 2a. All CPP values for 16 randomly selected subjects (days 1-5)
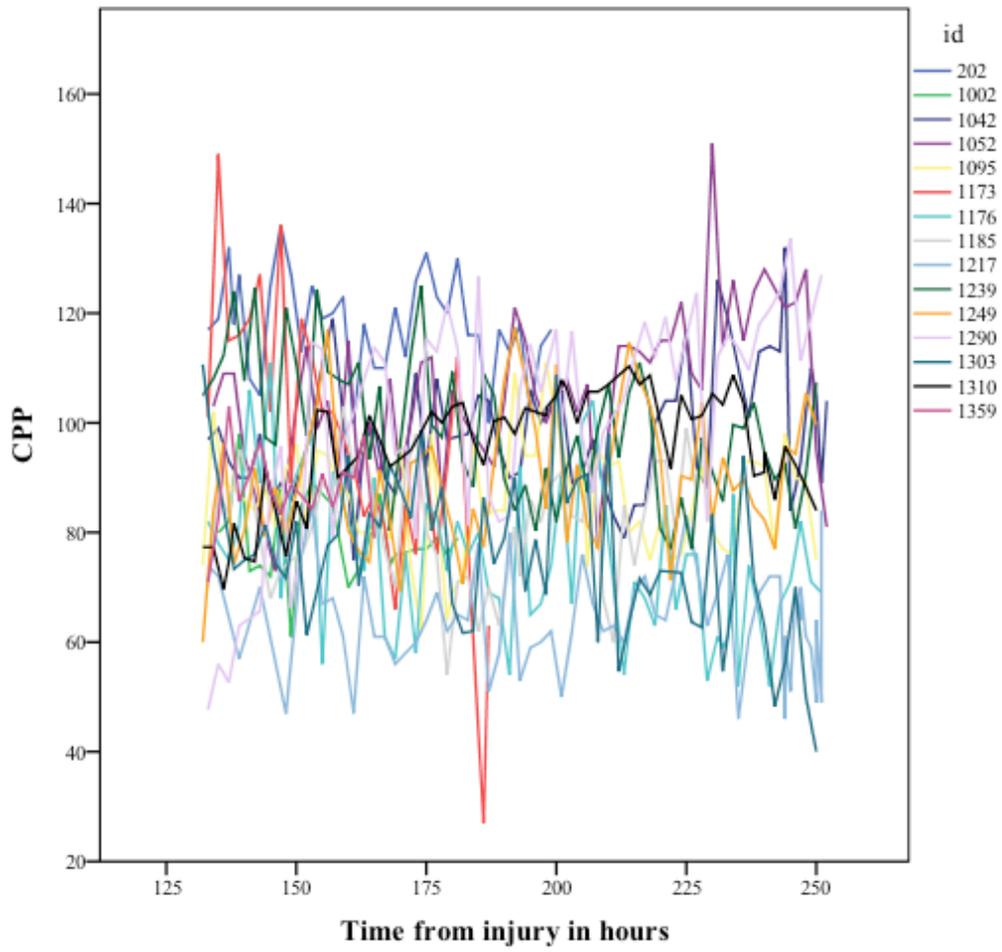
Figure 2b. All CPP values for 16 randomly selected subjects (days 6-10)
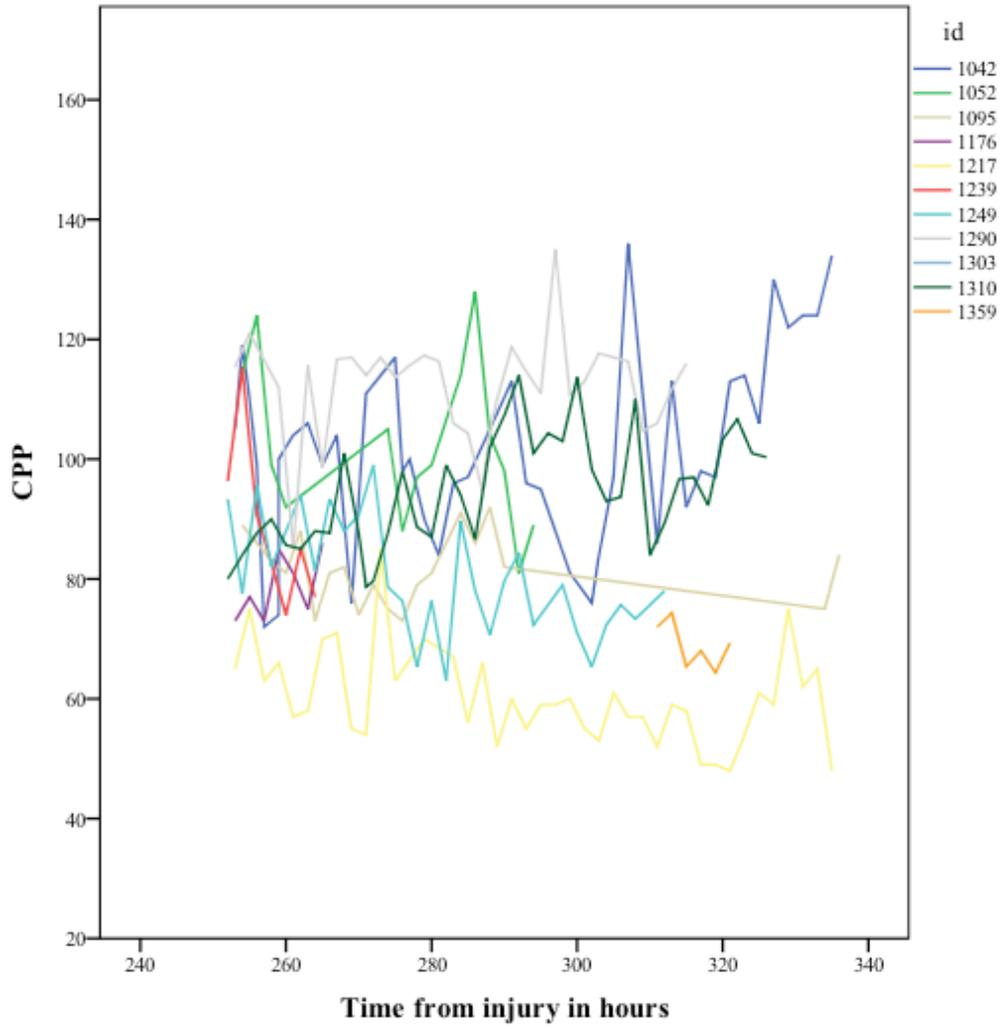
Figure 2c. All CPP values for 16 randomly selected subjects (days 11-14)
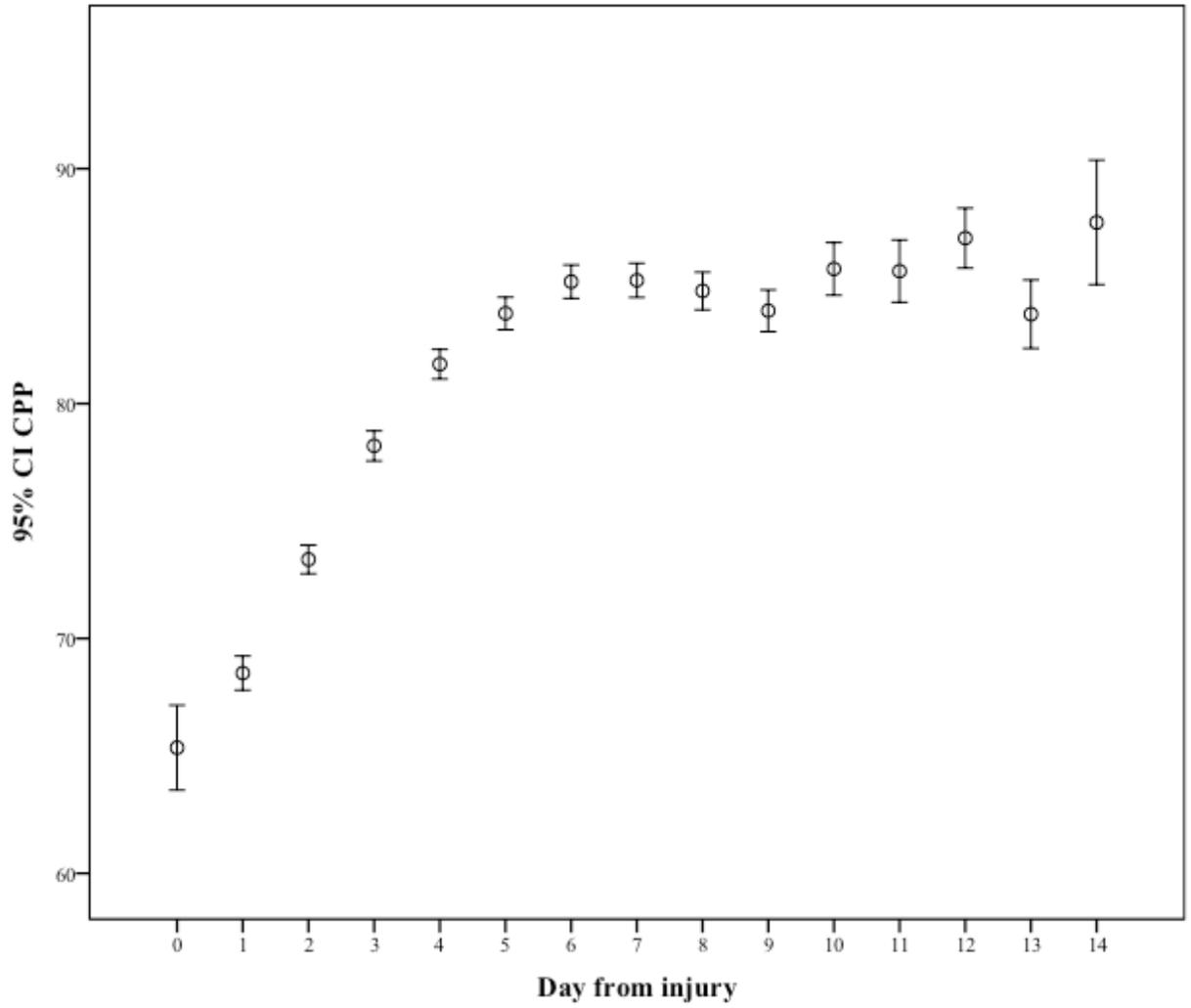
Figure 3. Daily means and 95% confidence intervals for CPP

Table 4. Pearson correlation coeffecients 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[*]

$* p < .001$
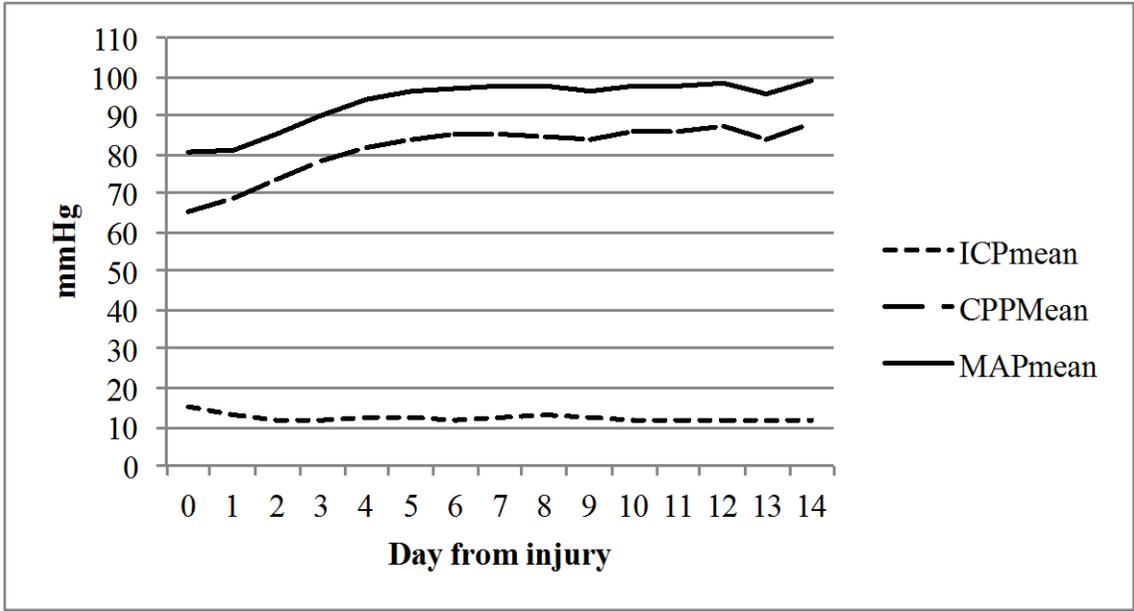
Figure 4. Daily means of ICP, CPP, and MAP
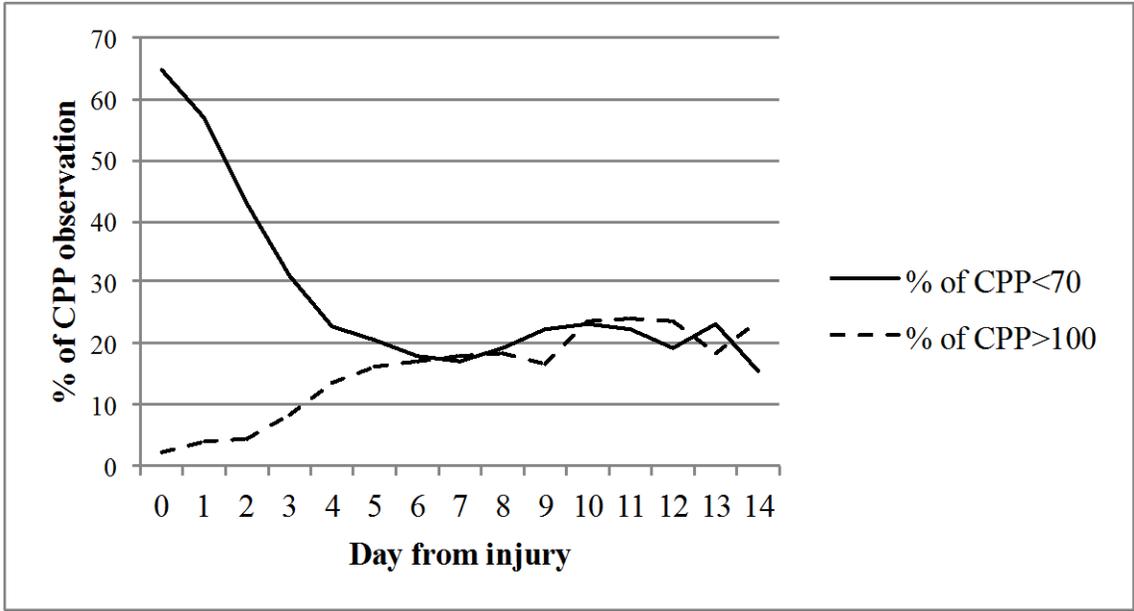
Figure 5. Percentages of CPP<70 mmHg and >100 mmHg

Table 5. Growth curve analysis of CPP changes over time

Parameters	Model 1	Model 2	Model 3
Fixed effect			
Intercept	79.64	72.47	64.11
SE	(.76)	.82	.83
p-value	<.0001	<.0001	<.0001
Linear time term	--	.06	.22
SE	--	.006	.007
p-value	--	<.0001	<.0001
Quadratic time term	--	--	-.0006
SE	--	--	.00002
p-value	--	--	<.0001
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

Table 6. Multivariable logistic regression 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.
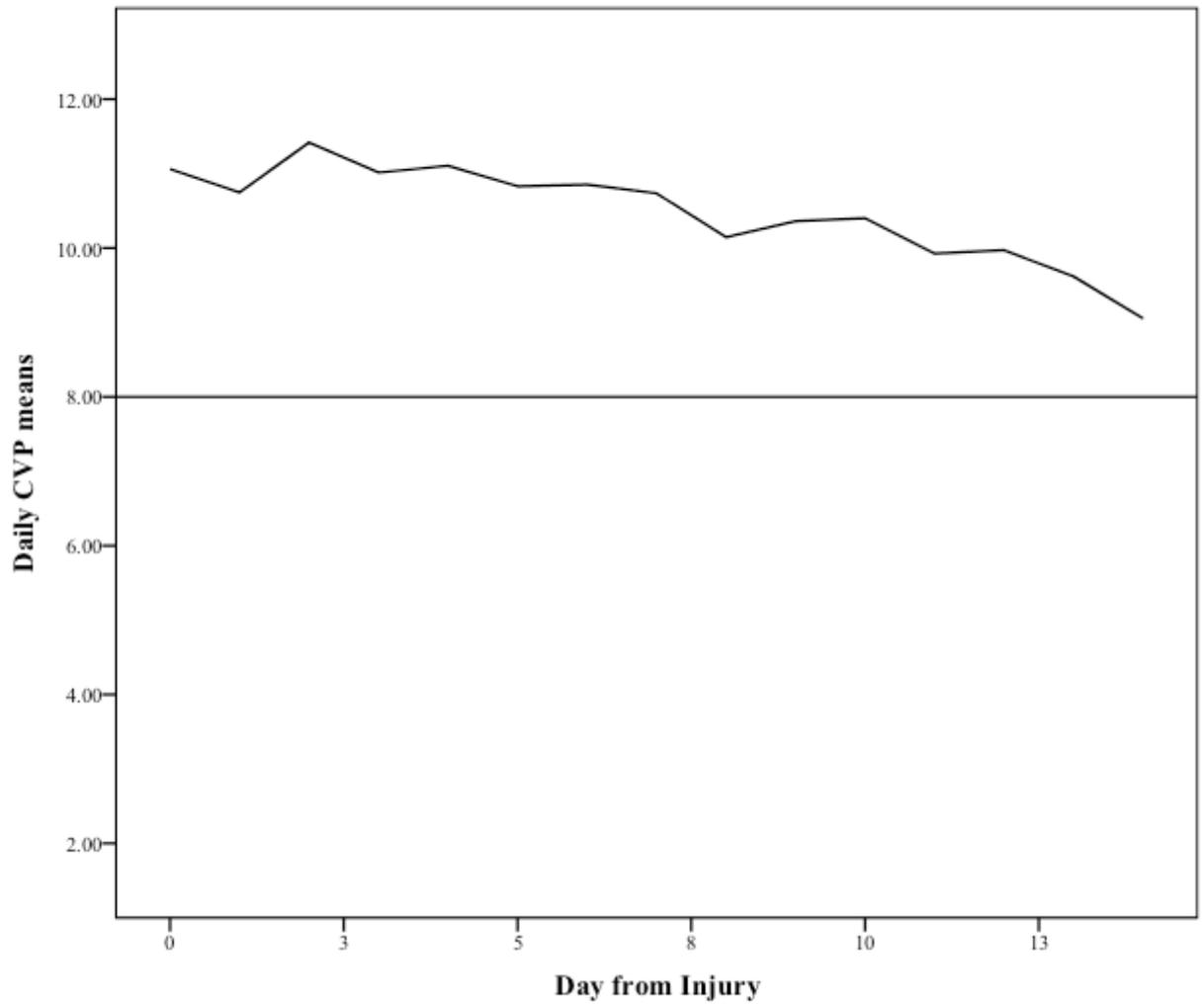
Figure 6. Daily CVP means showing hypervolemia (CVP>8) during the observation period

6.0   RESULTS MANUSCRIPT #2

Association of Cerebral Perfusion Pressure With Delayed Cerebral Ischemia After Aneurysmal Subarachnoid Hemorrhage

6.1   ABSTRACT

Background and Purpose: Delayed cerebral ischemia (DCI) and Hunt and Hess (HH) grade are known risk factors for poor outcomes after aneurysmal subarachnoid hemorrhage (aSAH). The relationship between DCI and global cerebral perfusion is unclear. Whether DCI mediates the relationship between HH grade and outcomes remains unknown. This study aimed to investigate the relationship between cerebral perfusion pressure (CPP), DCI, HH grade, and outcomes following aSAH.

  Methods: DCI was defined as clinical deterioration due to impaired cerebral blood flow. The relationship between minimum CPP (within12 hours prior to DCI), DCI onset, and DCI were tested using logistic regression and the accelerated failure time model. The mediation effect of DCI on relationships between HH grade and outcomes was tested using the bootstrap confidence interval. Three and 12-month outcomes included mortality, neuropsychological, functional (modified Rankin scale [MRS]) and physical (SF36) outcomes.

Results: DCI occurred in 42% of subjects (n=211). One-third of subjects had a poor MRS at 3 (32%) and 12 (30%) months and impaired neuropsychological function at 3 (33%) and 12 (17%) months. For every 10 mmHg increase in CPP, the odds of DCI increased by 2.78 (95% CI 2.00-3.87). High CPP was associated with earlier onset of DCI ($p < 0.0001$). DCI did not mediate the relationship between HH grade and functional outcome or death.

Conclusions: The positive relationship between CPP and DCI was likely due to induced hypertension and hypervolemia. Findings raise concerns about safety of induced hypertension and the need for determining limits for hypertension, which current guidelines lack.

6.2   INTRODUCTION

Mortality and severe morbidity after aneurysmal subarachnoid hemorrhage (aSAH) are often associated with delayed cerebral ischemia (DCI), a complication that occurs in 19-63% of patients with aSAH (Carrera, Schmidt, Oddo, Fernandez, et al., 2009; Carrera, Schmidt, Oddo, Ostapkovich, et al., 2009; Claassen et al., 2001; Frontera et al., 2009; Hop et al., 1999; Lanterna et al., 2010; Yousef et al., 2010). DCI typically occurs 3-15 days after the initial bleeding and peaks on day 7 (Claassen et al., 2001; van Gijn et al., 2007). DCI is associated with poor outcomes and numerous complications, including myocardial infarction, arrhythmias, pulmonary edema, fever, cerebral edema, inability to perform activities of daily living, cognitive impairment, and death (Frontera et al., 2009; Springer et al., 2009). Thus, prevention of DCI is key to improving outcomes after aSAH.

DCI occurs as a result of impairment in cerebral blood flow or hypoperfusion; a complication that has been reported previously after aSAH (Cahill et al., 2006; Frontera et al., 2009). Cerebral hypoperfusion can occur locally due to focal vascular alterations, such as vasospasm and mircothrombi, or globally due to pressure/flow deficits, such as inadequate cerebral perfusion pressure (CPP). Current interventions focus on treatment of focal vascular changes (e.g. vasospasm), yet these interventions have had limited success (Rinkel & Klijn, 2009). Attempts to prevent vasospasm and microthrombi using endothelin antagonists and antiplatelet administration have not resulted in a significant reduction in DCI or improvement in outcomes (Dorhout Mees et al., 2007, 2008; A. Kramer & Fletcher, 2009; Macdonald et al.,

2008; van den Bergh et al., 2006; van den Bergh et al., 2009). Most patients with moderate to severe angiographic vasospasm are asymptomatic (Vergouwen, Ilodigwe, et al., 2011), suggesting that vasospasm and DCI are not strongly correlated and therefore treatment of focal perfusion deficits may be insufficient to prevent DCI.

Exploring the relationship between DCI and CPP therefore appears warranted. It is unclear, for example, if risk for infarction that leads to DCI varies with a change in CPP. Furthermore, severity of symptoms at admission measured by Hunt and Hess (HH) grade is known to be associated with complications and poor outcomes (Frangiskakis et al., 2009; Mustonen et al., 2008). However, the mechanistic link between HH grade and poor outcomes remains unclear. It is unknown whether DCI can explain, in part, this relationship. The purpose of this study was to investigate the relationship between DCI and CPP and determine if DCI mediates the relationship between HH grade and outcomes after aSAH.

6.3   METHODS

6.3.1   Sample and setting

Subjects were patients with aSAH admitted to a regional medical center between May 1999 and October 2011 and enrolled in an ongoing NIH study (R01NR004339). Subarachnoid hemorrhage was diagnosed using computed tomography (CT) and presence of an aneurysm was diagnosed using digital subtraction angiography. Eligible subjects were 21-75 years of age with a

spontaneous aneurysm rupture and Fisher grade ≥2. In addition to the eligibility criteria of the parent study, the current study included patients with external ventricular drain (EVD) for intracranial pressure (ICP) measurement. Exclusion criteria included preexisting chronic neurologic deficit or traumatic or mycotic aneurysm. Subjects were recruited within the first 5 days after aSAH and followed for 14 days after aneurysm rupture or until discharge.

6.3.2 Cerebral perfusion pressure

CPP was defined as the difference between mean arterial pressure (MAP) and ICP and measured in mmHg. MAP was measured by an arterial line or a blood pressure cuff. ICP measurements were obtained using the EVD. MAP and ICP were measured every two hours or more frequently if subjects exhibited neurologic or systemic instability. Data were available for 14 days unless subjects were admitted more than one day after bleeding or discharged before 14-days. Minimum CPP values were obtained within 12 hours prior to the time of DCI.

6.3.3 Delayed cerebral ischemia

DCI was defined as clinical deterioration, not attributable to rebleeding, seizures, hydrocephalus, or cerebral edema, accompanied by evidence of impaired cerebral blood flow (Yousef et al., 2010). DCI was diagnosed when clinical deterioration and one or more indicator of impaired cerebral blood flow existed. Indications of clinical deterioration included: a) decrease in level of consciousness, b) new focal neurologic deficit, c) deterioration in pupillary reaction, or d)

worsening the NIH Stroke Scale. Cerebral blood flow assessments within 12 hours of the observed neurologic deterioration were evaluated (before or after).

Cerebral blood flow was indirectly assessed using transcranial Doppler (TCD), head CT and CT perfusion scans, and/or cerebral angiography. Using daily TCD, impaired cerebral blood flow was defined as a systolic middle cerebral artery velocity >200 ml/second or Lindegaard ratio >3.0. Head CT and CT perfusion scans within the 12-hour temporal window of the clinical deterioration were reviewed for the presence of cerebral ischemia, infarction or abnormal blood flow. Finally, cerebral angiography studies within the same temporal window were independently reviewed and evaluated for vascular narrowing, with narrowing > 25% considered as clinically significant vasospasm.

Subjects whose DCI status could not be determined were excluded from analysis, e.g., comatose and sedated and thus unable to evaluate neurologic decline. The variable "Time to DCI" was defined as the number of hours from aneurysm rupture to the time of DCI diagnosis.

6.3.4   Severity of Symptoms

HH grade uses a 5-point scale to quantify the severity of non-traumatic SAH based on symptoms on admission (Hunt, Meagher, & Hess, 1966). In this analysis, HH grade was dichotomized into poor (grade 3-5) or good (grade 1-2).

6.3.5 Outcomes

A comprehensive set of measurements that included mortality, neuropsychological, functional, and physical outcomes were assessed as part of the ongoing NIH study. Neuropsychological outcomes were assessed at 3 and 12 months for seven domains: attention, learning and memory, psychomotor speed, mental flexibility, executive function, visuo-spatial ability, and language (Table 7). Because of concerns about sample size in each domain, neuropsychological function was dichotomized as "impaired" vs. "not impaired". All test scores in all domains were converted to z-scores. A z-score of $\leq$ -1.5 in at least two tests or a z-score of $\leq$ -2.0 in at least one test indicated neuropsychological impairment (Wefel et al., 2004). Functional outcomes were assessed using the modified Rankin scale (MRS) [good (0-2), poor (3-6)]. The Medical Outcomes Study 36-item Short-Form Health Survey version 2 (SF-36) physical component score was used to assess physical function (Ware et al., 2000). Validity and reliability of these outcome measures have been well established in patients with neurological injury (Hinchliffe et al., 1998; Ogden et al., 1993).

6.3.6 Confounding variables

Because higher measures of depression and anxiety have been associated with poorer scores on neuropsychological tests (Basso et al., 2007; Castaneda et al., 2008), we controlled for these variables when analyzing neuropsychological outcomes. Depressive symptoms were assessed using the Beck Depression Inventory II (BDI) (Arnarson et al., 2008). Anxiety was measured using the "State" component of the State-Trait Anxiety Inventory (STAI) (Spielberger, Gorsuch,

& R.E, 1970). Validity and reliability have been well established in patients with neurologic insults (Arnarson et al., 2008; Smeets et al., 1996). Age, years of education, HH grade, and aneurysm treatment method (surgical clipping vs. endovascular coiling) are often associated with DCI and post-aSAH outcomes (Haug et al., 2010; A. J. Molyneux et al., 2005; Yousef et al., 2010), therefore were also included as control variables.

6.3.7 Statistical analysis

IBM SPSS19, Mplus6, and SAS9.2 were used to perform the analyses. Descriptive statistics including means, standard deviations, and percentages were used to describe the sample. Logistic regression was used to test the relationship between CPP and DCI. Accelerated failure time model was used to test whether CPP was associated with the onset of DCI. Finally, bias corrected bootstrapping was used to test if DCI mediates the relationship between HH grade and outcomes. An alpha level of 0.05 was used to indicate significance. All comparisons were performed *a-priori*, thus no correction for alpha level was made.

6.4   RESULTS

6.4.1   Sample characteristics

Subjects (n=211) were relatively young (53±11 years), predominantly female (66%) and white (88%). The mean for the years of education was 13±2 years. Approximately, 62% underwent aneurysm coiling, 67% had a poor HH grade (3-5), and 42% had DCI. DCI could not be

determined for 13 (6%) patients due to inability to assess neurological decline due to sedation or coma. The mean value for CPP was 53±17 mmHg. The mean BDI score was 10±8 at 3 months and 12±10 at 12 months. The mean State Anxiety score was 47±6 at 3 months and 45±6 at 12 months.

6.4.2 High CPP values are associated with increased risk for DCI

Logistic regression was performed on DCI as a function of age, gender, HH grade [good (1-2) or poor (3-5)], aneurysm treatment option (clipping vs. coiling), and CPP (Table 8). The overall model significantly predicted DCI; χ^2(5, N=196) = 71.43, $p < 0.001$, Nagelkerke R^2 = .41. There was a significant positive relationship between CPP and DCI. For every 10 mmHg increase in CPP, the odds of DCI increased by 2.78 (95%CI 2.00-3.87). Furthermore, the mean value for CPP was significantly greater for subjects with DCI (64.6±17), compared to those without DCI (46±11), p<.001.

6.4.3 High CPP values are associated with earlier onset of DCI

The mean time for DCI diagnosis was 6±2.3 days after bleeding. This analysis controlled for age, gender, aneurysm repair method, and Hunt and Hess grade. Table 9 shows that the estimate of CPP was negative (-0.283) indicting that high CPP values are associated with shorter time to DCI (p<0.0001).

6.4.4   DCI does not mediate the relationship between HH grade and outcomes

Data on neuropsychological outcomes were available for 61-77 subjects. Missing data resulted from time of recruitment (neuropsychological assessments were not initiated until 2003), loss to follow up, death, and refusal. Approximately one third had a poor MRS at 3 (32%) and 12 (30%) months and impaired neuropsychological function at 3 (33%) and 12 (17%) months. Mean SF36 score was 20±5 and 22±5 at 3 and 12 months, respectively. Approximately, one-fourth of subjects were dead at 3 (26%) and 12 (29%) months. The direct effects between HH grade and outcomes were tested before testing the mediation effect. Mediation was tested only when the direct effect was significant. HH grade was significantly related to mortality and functional outcomes at 3 and 12 months, but not physical or neuropsychological function (controlling for age, aneurysm repair method, education, depression and anxiety). However, DCI did not significantly mediate the relationship between HH grade and functional outcome or death at both 3 and 12 months (Table 10).

6.5   DISCUSSION

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

6.5.1 The relationship between CPP and DCI

Factors that lead to cerebral ischemia involve disruption of one or more of four mechanisms: pressure, chemical, metabolic, and neurogenic regulation (Pires, Dams Ramos, Matin, & Dorrance, 2013; Ter Laan, van Dijk, Elting, Staal, & Absalom, 2013). We targeted pressure regulation mechanism to investigate whether DCI is related to a perfusion pressure deficit. Utilizing Ohm' and Poiseuille laws, we can infer that cerebral blood flow (CBF) is inversely related to cerebrovascular resistance (CVR) and positively related to CPP: CBF=CPP/CVR. When cerebral autoregulation is disrupted, which is common after aSAH, cerebral vessels dilate and CVR becomes very low. Cerebral blood flow is consequently highly dependent on CPP.

Our findings indicated that CPP was related to DCI, but the direction of the relationship was not as expected. High CPP values were associated with DCI. Likely, high CPP values were, in part, the result of medical interventions, e.g., CSF drainage and induced hypertension and hypervolemia, which most subjects received prophylactically to prevent vasospasm. Because MAP and ICP (thus CPP) are highly manipulated at the bedside, the observed CPP trends were likely either a marker or complication of treatment. Potentially, patients with higher bleeding grades (who have higher risk for complications such as vasospasm and DCI) likely received more aggressive therapy. However, if this observed relationship between CPP and DCI was due to complications of treatment, this would raise several questions about induced hypertension. Current guidelines recommend use of induced hypertension to treat/prevent DCI. However, there are no guidelines that identify when hypertension can be therapeutic or too aggressive, or

whether different treatment strategies should be used with normotensive versus hypertensive patients. Future studies are needed to clarify these issues.

Bijlenga and colleagues reported that aSAH patients had higher CPP values during vasospasm than before vasospasm as a result of Triple-H therapy (Bijlenga et al., 2010). Others have found that CPP <70 mmHg were associated with increased risk for brain tissue hypoxia and metabolic crisis (Schmidt et al., 2011). However, in these studies Triple-H therapy was used to treat DCI, rather than as a prophylaxis, and thus did not affect CPP values prior to DCI. In our subjects, induced hypertension and hypervolemia were used as prophylactic therapy after securing the aneurysm to prevent vasospasm.

6.5.2   Outcomes and Severity of symptoms

Four of the seven neuropsychological domains showed impairment (Table 7). The learning and memory domain had the highest prevalence of impairment, whereas executive function had the lowest prevalence. Others have reported a similar trend (Mayer et al., 2002). Impairment (per domain) ranged from 3%-23% of subjects. Others have reported a range of 14%-61% for impairment (Al-Khindi et al., 2010; Kreiter et al., 2002). The overall prevalence of neuropsychological impairment ranged from 33% to 17% at 3 and 12 months, respectively. Others have reported a prevalence of 27%-46% at similar time points (Haug et al., 2010; Mayer et al., 2002; Scott et al., 2010). Subjects' mean BDI score indicated normal variability at 3 months and mild mood disturbances at 12 months. However, the State Scale score of our subjects suggested clinically significant anxiety (score > 39 indicates significant anxiety) (Knight, Waal-Manning, & Spears, 1983).

We attempted to explain the relationship between the severity of symptoms and poor outcomes through DCI. However, DCI did not mediate the relationship between HH grade and outcomes. This finding might be biased due to the missing neuropsychological function data. However, it suggests the relationship between HH grade and poor outcomes is either direct or influenced by mediators other than DCI. Other potential mediators may include delayed neurologic deficit, generalized cerebral edema, infarction, severity of initial bleeding, and early brain injury. These variables have shown strong associations with poor outcomes after aSAH (Cahill, Zhang, Cahill, & Zhang, 2009; Hutter et al., 1999; Kreiter et al., 2002), and thus can be considered as candidate mediators. Unlike DCI, delayed neurologic deficit incorporates many causes for clinical deterioration, such as hydrocephalus, fever, seizure, edema, and electrolytes abnormalities, with substantial influence on morbidity and mortality after aSAH (Diringer et al., 2011). Therefore, delayed neurologic deficit might be an important candidate mediator. It remains crucial to determine mediators for poor outcomes as their identification will likely assist in designing interventions to improve outcomes after aSAH.

This study had several limitations. CPP measurements were not continuous. Although continuous CPP measurement is more desirable, it was not feasible because ICP was measured by EVD. All subjects had EVDs, often used in high bleeding grades. Our results may therefore not apply to those without EVDs and/or low bleeding grades. We did not collect data concerning use of induced hypertension and hypervolemia or their intensity. Such information may have provided further insight into our findings. Data were collected 12 years and therefore changes in care may have confounded the results. We did not use any formal assessment of cerebral blood flow, but used surrogates such as TCD. Lastly, subjects' neuropsychological function was

classified as "impaired" or "not impaired" because of concerns about sample size in each domain. This classification may have resulted in loss of information. Future studies with larger sample size will be needed to address the effect of HH on specific domain or subdomains of neuropsychological function.

6.6   CONCLUSION

Patients with DCI had higher CPP values, compared to those without DCI. For every 10 mmHg increase in CPP, the odds of DCI increased by 2.78. High CPP was associated with earlier onset of DCI. The relationship between HH 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 this study. Findings raise concerns about safety of induced hypertension and the need for studies that define limits for hypertension which are lacking in current guidelines.

Table 7. Description of domains and tests of neuropsychological function after aSAH

Domain: Test	3-month			12-month		
	N	M±SD	Impaired	N	M±SD	Impaired
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						
o Story A immediate recall	77	11±4		62	11±5	
o Story A delayed recall	76	7±5		62	9±5	
o Story B immediate recall	77	10±4		62	9±4	
o Story B second immediate recall	77	13±5		61	13±5	
o Story B delayed recall	76	10±6		62	11±5	
• Rey Complex Figure						
o Immediate recall	76	13±8		--	--	
o Delayed recall	75	13±8		--	--	
Psychomotor speed: Grooved Pegboard			0%			0%
• Dominant hand	75	107±50		62	95±41	
• Non-dominant 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						
o Number of F words	76	9±4		62	11±5	
o Number of A words	76	7±4		62	8±4	
o Number of S words	76	10±4		62	11±4	
• Animal Naming Test						
o Number of Animals	75	15±6		62	16±5	

Table 8. Relationship between CPP and DCI, *logistic regression*

Predictor	OR	95%CI	P value
Age	0.98	0.95-1.01	0.203
Gender (female)	1.26	0.60-2.68	0.544
Aneurysm treatment (coiling)	1.27	0.60-2.67	0.529
Hunt and Hess (poor 3-5)	1.89	0.89-4.00	0.097
CPP*	2.78	2.00-3.87	<0.001

*Odds ratio (OR) and 95%CI were calculated for every 10 mmHg

Table 9. Relationship between CPP and time to DCI, *accelerated failure model*

Parameter	Estimate	E	95%CI	Chi square	P value
Age	0.002	0.006	-0.001-0.013	0.09	0.76
Gender	-0.055	0.129	-0.308-0.198	0.18	0.67
Aneurysm treatment	0.001	0.128	-0.250-0.252	0.00	0.99
HH grade	-0.359	0.147	-0.647-0.071	5.97	0.01
CPP*	-0.283	0.035	-0.352-0.214	64.72	<0.0001

*Statistics calculated for every 10 mmHg

Table 10. DCI mediation effect on the relationship between HH grade and outcomes; *bootstrap confidence interval*

Variable	Coefficient	Structure coefficient with mediator	Indirect effect Estimate	Indirect effect Bootstrap 95% CI
3-month mortality	0.48*	0.46†	0.02	(-0.05, 0.13)
12-month mortality	0.54*	0.55*	0.01	(-0.11, 0.08)
3-month MRS	0.63*	0.61*	0.02	(-0.05, 0.12)
12-month MRS	0.54*	0.53†	0.01	(-0.07, 0.11)

*<0.001, † <0.01

APPENDIX A

PARENT STUDY IRB APPROVAL

University of Pittsburgh
Institutional Review Board

Memorandum

To: Paula Sherwood RN, PhD

From: Aviva Katz MD, Vice Chair

Date: 3/25/2013

IRB#:   REN13020176 / IRB021039

Subject: Detection of Physiologic Predictors of Complications and Outcomes Following SAH

At its full board meeting on 3/12/2013, the University of Pittsburgh Institutional Review Board, Committee B, reviewed the Renewal for the above referenced research study and approved it pending minor modifications. Your responses to these comments have been reviewed and the research submission, in its currently modified form, adequately addresses the concerns of the IRB and is therefore approved.

The risk level designation is Greater Than Minimal Risk.

Please note the following information:

Approval Date: 3/22/2013
Expiration Date: 3/11/2014

The following documents were approved by the IRB:
consent form

Please note that it is the investigator's responsibility to report to the IRB any unanticipated problems involving risks to subjects or others [see 45 CFR 46.103(b)(5) and 21 CFR 56.108(b)]. Refer to the IRB Policy and Procedure Manual regarding the reporting requirements for unanticipated problems which include, but are not limited to, adverse events. If you have any questions about this process, please contact the Adverse Events Coordinator at 412-383-1480.

The protocol and consent forms, along with a brief progress report must be resubmitted at least one month prior to the renewal date noted above as required by FWA00006790 (University of Pittsburgh), FWA00006735 (University of Pittsburgh Medical Center), FWA00000600 (Children's Hospital of Pittsburgh), FWA00003567 (Magee-Womens Health Corporation), FWA00003338 (University of Pittsburgh Medical Center Cancer

Institute).

Please be advised that your research study may be audited periodically by the University of Pittsburgh Research Conduct and Compliance Office.

APPENDIX B

SUBARACHNOID HEMORRHAGE: SCALES, CLINICAL PRESENTATION, DIAGNOSIS, AND TREATMENT

B.1   SCALES FOR ASSESSING THE SEVERITY OF BLEEDING AFTER ASAH

Claassen-Fisher grading scale has been introduced in 2001 as a modification for the Fisher grading scale which does not account for intraventricular (IVH) extension of the SAH. Unlike the original Fisher grade which predicts vasospasm, the Claassen-Fisher grading scale was introduced to predict delayed cerebral ischemia after SAH (Claassen et al., 2001).

Table 11. Claassen-Fisher grading scale

Grade	Criteria
0	No SAH or IVH
1	Minimal/thin SAH but no IVH in lateral ventricles
2	Minimal/thin SAH with IVH in both lateral ventricles
3	Thick SAH (completely filling $\geq$ cistern or fissure) without IVH in lateral ventricles
4	Thick SAH (completely filling $\geq$ cistern or fissure) with IVH in both lateral ventricles

World Federation of Neurological Surgeons (WFNS) uses Glasgow coma score and the presence/absence of motor deficit to grade the severity of subarachnoid bleed ("Report of World Federation of Neurological Surgeons Committee on a Universal Subarachnoid Hemorrhage Grading Scale," 1988).

Table 12. WFNS grading scale

Grade	Glasgow Coma Score	Presence of motor deficit
1	15	No motor deficit
2	13-14	No motor deficit
3	13-14	Motor deficit is present
4	7-12	Motor deficit is present of absent
5	3-6	Motor deficit is present of absent

B.2   **APPENDIX SUBSECTION**

B.2.1   Clinical manifestations and diagnostic studies

The most common manifestation for aSAH is severe headache, present in two-thirds of patients and is often described as "the worst headache in life". Headache may or may not be accompanied with nausea and vomiting. Other typical manifestations include decrease level of consciousness,

focal neurologic deficit (i.e. hemiparesis, dysphasia, visual field impairment and abnormal pupillary reaction), and meningismus (neck stiffness, photophobia, and headache without actual inflammation or infection of the meninges). Atypical signs include seizure, thunderclap headache, confusion, trauma that result from the loss of consciousness after aneurysm rupture, ataxia, nystagmus, third nerve palsy, sixth nerve palsy, retinal hemorrhage, and papilledema (Edlow & Caplan, 2000; Suarez et al., 2006; Togha, Sahraian, Khorram, & Khashayar, 2009; Vindlacheruvu & Mendelow, 2002). For patients who present with these signs and symptoms, non-contrast computerized tomography (CT) scan - the gold standard for diagnosing SAH- is indicated to rule out/confirm bleeding. If bleeding is found, then CT angiography or cerebral angiography is indicated to rule out/confirm cerebral aneurysm. If no aneurysms found, CT angiography or cerebral angiography must be repeated in 1-3 weeks followed by proper imaging for the brain, brain stem, and spinal cord. If the initial CT scan was negative for bleeding, a lumber puncture is required to test for blood in the cerebrospinal fluid (CSF). Elevated red blood cells or xanthochromia (yellowish appearance of the CSF) indicate bleeding in the subarachnoid space and thus CT/cerebral angiography will be needed to identify the source of bleeding (Suarez et al., 2006).

B.2.2 Treatment

Once the diagnosis of aSAH is confirmed, securing the aneurysm/s would be the next critical step. There are two major options for treating ruptured aneurysms: endovascular coiling and surgical clipping. In endovascular coiling a detachable platinum coil is inserted in the aneurysm through a wire that goes through the femoral artery (Suarez et al., 2006). A stent may be placed

horizontally to the blood vessel (vertical to the aneurysm) to keep the coil inside the aneurysm and prevent it from projecting to the circulation (Q. H. Huang et al., 2011; Hwang et al., 2011; Suarez et al., 2006). Aneurysm clipping involves surgical craniotomy and placing a clip on the neck of the aneurysm which would close the aneurysm and prevent further bleeding. The choice whether to use endovascular coiling or surgical clipping depends on several factors such as: medical condition, age, location of the aneurysm, the width of the aneurysm neck, and whether the aneurysm causes a mass effect on the brain tissue. Usually, younger patient, patients with lower Hunt and Hess grade (Klompenhouwer et al., 2011), and patients with aneurysm deep in the skull (basilar and vertebral aneurysm) that are hard to reach surgically are treated with endovascular coiling. Aneurysms with wide neck are treated with clipping because it would be difficult to keep the coil in place (Suarez et al., 2006). The International Subarachnoid Aneurysm Trial (ISAT) is a multicenter randomized controlled trial that recruited aSAH patients suitable for both coiling and clipping. The ISAT compared the two treatment options and found that the number of independent survivors was significantly higher among patients who underwent endovascular coiling compared to those who underwent surgical clipping. However, rebleeding was more frequent in patients with endovascular coiling compared to surgical clipping (A. Molyneux et al., 2002; A. J. Molyneux et al., 2005). Findings from the ISAT study have changed the practice; these changes resulted in lower mortality rate but higher cost of treatment (Qureshi et al., 2011). Evidence from the same trial also suggests that coiling is associated with better neuropsychological functions at 1 year after bleeding (Scott et al., 2010). Therefore, endovascular coiling is preferred over other treatment options (Lopes, Mangubat, Keigher, & Cogan, 2011).

After securing the aneurysm with either endovascular coiling of clipping the patient need to be in a neuro-intensive care unit to be monitored and managed for neurologic and systemic complications. Neurologic complications include: rebleeding from secured aneurysm, cerebral vasospasm, delayed cerebral ischemia, hydrocephalus, and seizure. Systemic complications include: myocardial injury and arrhythmias, pulmonary edema, and deep venous thrombosis (Diringer et al., 2011; Rose, 2011; Suarez et al., 2006).

The Neurocritical Care Society has published a consensus guidelines for managing patients with aSAH, below are the most important recommendations:

- Patients with aSAH should be treated in large volume centers.

- Oral nimodopine (60mg every 6 hours for 21 days after the ictus): the only treatment option was proven in randomized clinical trials to improve outcomes.

- Stop using triple H therapy (hypertensive hypervolemic hemodilution) due to lack of supporting evidence and complications such as lowering cerebral tissue oxygen delivery.

- Early aneurysm repair is crucial to prevent rebleeding.

- Baseline cardiac function evaluation; including cardiac enzymes, ECG, and echocardiography.

- Maintain euvolemia and avoid hypovolemia due to increased risk of DCI.

- Avoid hypoglycemia and keep blood sugar below 200mg/dl.

- Treat infection and fever.

- Incorporate measures to prevent deep venous thrombosis in the standard care of all aSAH patients.

- Continue statin therapy for aSAH patients who had it prior to the ictus.

- Monitor patients for vasospasm and DCI.

- Use inotrpic agents to augment blood pressure in patients with DCI who do not show improvement.

- Use intraarterial vasodilators and angioplasty for DCI due to vasospasm.

- Manage anemia, avoid blood loss from blood drawing, and consider elevating hemoglobin for DCI patients.

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