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The Importance of Early Brain Injury after Subarachnoid Hemorrhage

Fatima A. Sehba, **Jack Hou**, **Ryszard M. Pluta**, and **John H. Zhang**
Departments of Neurosurgery and Neuroscience, Mount Sinai School of Medicine, New York (FAS); the Surgical Neurology Branch, National Institutes of Neurological Disorders and Stroke, National Institutes of Health, Bethesda, MD (RMP) and the Department of Neurosurgery, Loma Linda University Medical Center, Loma Linda, CA (JH and JHZ)

Abstract

Aneurysmal subarachnoid hemorrhage (aSAH) is a medical emergency that accounts for 5% of all stroke cases. Individuals affected are typically in the prime of their lives (mean age 50 years). Approximately 12% of patients die before receiving medical attention, 33% within 48 hours and 50% within 30 days of aSAH. Of the survivors 50% suffer from permanent disability with an estimated lifetime cost more than double that of an ischemic stroke. Traditionally, spasm that develops in large cerebral arteries 3-7 days after aneurysm rupture is considered the most important determinant of brain injury and outcome after aSAH. However, recent studies show that prevention of delayed vasospasm does not improve outcome in aSAH patients. This finding has finally brought in focus the influence of early brain injury on outcome of aSAH. A substantial amount of evidence indicates that brain injury begins at the aneurysm rupture, evolves with time and plays an important role in patients' outcome. In this manuscript we review early brain injury after aSAH. Due to the early nature, most of the information on this injury comes from animals and few only from autopsy of patients who died within days after aSAH. Consequently, we began with a review of animal models of early brain injury, next we review the mechanisms of brain injury according to the sequence of their temporal appearance and finally we discuss the failure of clinical translation of therapies successful in animal models of aSAH.

1. Introduction

"When persons in good health are suddenly seized with pains in the head, and straightway are laid down speechless, and breathe with stertor, they die in seven days." Hippocrates 460-37-BC, *Aphorisms on Apoplexy* (Clarke, 1963).

Hippocrates recognized the presentation of spontaneous subarachnoid hemorrhage followed by subsequent delayed neurological deterioration more than 2400 years ago. It was named for the rupturing of an intracranial aneurysm leading to arterial blood filling up the subarachnoid space. Today, despite the time lapse, diagnosis of aneurysmal subarachnoid hemorrhage (aSAH) continues to present daunting challenges for patients and their physicians. Becker's study estimated that in the North America approximately 30,000

Corresponding author: Fatima A. Sehba, PhD, Departments of Neurosurgery and of Neuroscience, Mount Sinai School of Medicine, New York, NY 10029, USA. Fax: 212 241 0697, Phone: 212 241 6504, fatima.sehba@mssm.edu.

people suffer from non-traumatic, spontaneous SAH due to a ruptured aneurysm each year (Becker, 1998). This accounts for 5% of all stroke cases (Le Roux and Winn, 1998). The early mortality rate after aSAH remains high at 40%, 10-20% of whom never reach medical attention or die during transportation (Huang and van Gelder, 2002). Moreover, most victims of aSAH are in the prime of their lives; mean age 50 years (Nieuwkamp *et al.*, 2005). The proportion of years of potential life lost due to aSAH (approximately 25%) is comparable with ischemic stroke and intracranial hemorrhage (Hop *et al.*, 1997; Huang *et al.*, 1990; Johnston *et al.*, 1998; Sudlow and Warlow, 1997).

Approximately 85% of aSAH episodes are caused by rupturing of an intracranial aneurysm (Wirth, 1986), 10% fit into the pattern of the so-called perimesencephalic hemorrhage of unknown etiology, and the remaining 5% into various rare entities of congenital and acquired lesions of cerebral arteries and systemic disorders such as sickle cell disease, coagulopathies, tumors, and cocaine abuse (van Gijn *et al.*, 2007).

Even though the clinical syndrome of aSAH varies in severity, few physicians will fail to recognize the classic and dramatic presentation of a 50-year-old female who collapses at home with sudden onset of the “worst headache of my life”, subsequently vomits, briefly loses consciousness, and is noted to have subhyaloid ocular hemorrhages (Terson syndrome) and a rigid neck. These are the symptoms of a ruptured cerebral aneurysm that violently ejects blood into the subarachnoid basal cisterns; a rigid non-expandable space restricted by the bony skull, causing severe elevation of intracranial pressure, which may exceed the blood pressure, diminish cerebral blood flow and lead to transient global arrest of intracranial circulation. Although reduced blood flow promotes hemostasis, if continued can lead to loss of consciousness and death.

The first choice diagnostic modality for patients suspected of aSAH is computed tomography without contrast enhancement, which, when patient is evaluated within the first few days after aSAH, detects blood in the subarachnoid space in over 95% of cases (Adams *et al.*, 1985; Kassell and Torner, 1984). However, as aging blood become isodense with brain tissue, computed tomography fails to diagnose SAH in patients whose first evaluation occurs several days after a suggestive headache. Lumbar puncture with evidence of red blood cells or xanthochromia works best for diagnosing a days-old SAH (Frontera *et al.*, 2009).

Two major complications significantly worsen the prognosis of aSAH; aneurismal rebleeding and delayed cerebral vasospasm with or without delayed ischemic neurological deficits (DINDs). Rebleeding is an early complication and occurs within the first 72-hours whereas DIND is a delayed secondary brain injury which manifests between day 3 to 12 post aSAH (Frontera *et al.*, 2009). Other medical complications that negatively affect overall morbidity and mortality include cardiac arrhythmias and neurogenic pulmonary edema (for review, see (Bruder and Rabinstein, 2011).

Approximately 8% to 23% of ruptured aneurysms rebleed (Ando *et al.*, 1989; Fujii *et al.*, 1996; Gruber *et al.*, 1997; Hillman *et al.*, 1988; Inagawa *et al.*, 1987; Kitsuta *et al.*, 2006; Naidech *et al.*, 2005; Ohkuma *et al.*, 2001). Rebleeding occurs early and contributes to early mortality (first 72 hours, 40% to 80%) (Fujii *et al.*, 1996). DIND remains the leading cause of delayed mortality and morbidity (Dorsch, 2002); it kills 7% patients, causes severe morbidity in another 7% (Kassell *et al.*, 1985) and poor outcome in one third of all SAH patients (Haley *et al.*, 1992; Tettenborn and Dycka, 1990).

DIND is a clinical diagnosis that was proposed by Vergouwen and colleagues in the consensus report in 2010 and was later refined by Wong et al. in the IMASH trial (Vergouwen *et al.*, 2010; Wong *et al.*, 2010b). DIND is defined as a “acute or sub-acute new

focal neurological deficit (motor or speech deficit) that had developed after aSAH or a decrease on Glasgow coma score of ≥2 points lasting >6 hours that is not related to treatment (coiling or clipping) complications, re-bleed, progressive hydrocephalus, electrolyte or metabolic disturbance, or infection" (Vergouwen *et al.*, 2010; Wong *et al.*, 2010b). This is a subjective exclusion diagnosis that implies worsening prognosis of unknown etiology despite favorable or good initial presentation. DIND can be difficult to assess in poor-grade, comatose patients, where variations in examination may be subtle or imperceptible.

The pathogenesis of DINDs is poorly understood and to date no single mechanism by itself or in combination with others is identified as its source. Delayed vasospasm is present in some but not all SAH patients with DIND. The spasm of large cerebral arteries of the circle of Willis was first noted in 1951 by Ecker and Riemenschneider who, while reviewing the angiograms of aSAH patients, observed that "spasm was maximal at the lesion but extended several cm along adjacent arteries in lesser degree" (Ecker and Riemenschneider, 1951). Although Ecker and Riemenschneider did not correlate arterial spasm with clinical deterioration they noted that spasm disappeared after a few weeks in patients who survived and suggested that it may play a considerable role in the production of intra-aneurismal thrombosis and may produce unfavorable effects by impairing the blood flow to the area of brain supplied by the affected artery (Ecker and Riemenschneider, 1951). Since then the advanced radiological technology, a digital subtraction cerebral angiography, has confirmed that delayed vasospasm appears in approximately 70% of aSAH survivors 3 to 12 days after the initial hemorrhagic event (Alaraj *et al.*, 2009; Eddleman *et al.*, 2009). As the time of vasospasm development coincides with the period of DINDs, DINDs have traditionally been considered the direct result of delayed vasospasm. Consequently, majority of basic and clinical research has been directed towards finding strategies against delayed vasospasm with hope to prevent DINDs and to improve outcome. However, a limited and often controversial positive effect of such therapies in preventing DINDs proves that this approach does not provide expected results (explained below and for review see (Sehba *et al.*, 2011)).

A search of aSAH literature (animal and clinical) provides a large body of evidence that suggests that presence of delayed vasospasm is not a prerequisite for DINDs and poor outcome. Early research in this area was pioneered mostly by Weir and colleagues and was carried out on two non-human primate models of aSAH. The first model mimicked SAH by injecting autologous blood into the cisterna magna and the second by placing blood clot around major arteries of circle of Wills (Weir *et al.*, 1970). The blood injection produced early hemodynamic changes associated with aSAH (explained below) including severe elevation in intracranial pressure, immediate reduction in cerebral blood flow, and cerebral perfusion pressure (Rothberg *et al.*, 1980), as well as a moderate vasospasm with high mortality and severe neurological deficits (Boisvert *et al.*, 1978; Echlin, 1971; Rothberg *et al.*, 1980; Weir *et al.*, 1970). Furthermore, Weir and colleagues found that none of the early hemodynamic changes occurred upon clot placement and whereas majority of animals developed severe vasospasm, only few 6.7 to 33% of the animals developed mild neurological deficits and mortality remained low; below 14% (Espinosa *et al.*, 1984; Handa *et al.*, 1987; Nosko *et al.*, 1987; Stoodley *et al.*, 2000). Others report similar results (Zhang *et al.*, 2001). n their own words "the degree of vasospasm in the animals which were dead the following day and the animals which were sitting up and eating normally was identical in the post-SAH angiograms" (Weir *et al.*, 1970). Similar observations are made in other species using other aSAH models. Landau et al. in a rabbit puncture model observed that some animals developed severe spasm yet did not display any obvious neurological deficits whereas others that developed neurological deficit were without vasospasm (Landau and Ransohoff, 1968). Weir et al., further showed that removal of blood clot could prevent and reverse delayed vasospasm (Handa *et al.*, 1987; Nosko *et al.*, 1987; Stoodley *et al.*, 2000;

Zhang *et al.*, 2001). These findings are in congruence with clinical studies where the occurrence of angiographic vasospasm correlates with the amount of blood present in the basal cisterns (Dupont *et al.*, 2009; Fisher *et al.*, 1980).

Clinical studies also support dissociation between DIND and vasospasm. Wilkins et al. reported no difference in responsiveness and hospital mortality in aSAH patients with and without vasospasm (Wilkins *et al.*, 1968). In fact, they noted that in many cases vasospasm was present in the presence of clinical improvement (Wilkins *et al.*, 1968). Other investigators have also found that delayed vasospasm does not necessarily lead to cerebral infarction after SAH (Rabinstein *et al.*, 2004), as cerebral infarcts occur even in the absence of vasospasm (Carlson and Yonas, 2009; Dankbaar *et al.*, 2009; Frontera *et al.*, 2009; Parsons *et al.*, 2007; Stein *et al.*, 2006b). Over all, vasospasm literature indicates that of the 70% of aSAH survivors that develop delayed vasospasm, only 20-30% actually suffer from DINDs (Alaraj *et al.*, 2009; Eddleman *et al.*, 2009). This dissociation between the presence of vasospasm and development of a delayed ischemic injury is also found in clinical trials. Agents such as Nimodipine (a calcium channel blocker) which reduce the incidence and severity of delayed ischemic injury and improve neurological outcome in aSAH patients do not relief angiographic vasospasm (Biondi *et al.*, 2004; Deshaies *et al.*, 2009; Petruk *et al.*, 1988; Philippon *et al.*, 1986; Pickard *et al.*, 1989). In contrast, agents such as Clazosentan, an ET-1A antagonist, which reduce the incidence of vasospasm do not improve neurological outcomes (Kramer and Fletcher, 2009; Macdonald *et al.*, 2011; Macdonald *et al.*, 2008; Nogueira *et al.*, 2007; Shaw *et al.*, 2000; Vajkoczy *et al.*, 2005; Vergouwen, 2009). This failure in part may involve deleterious side effects associated with most drugs (pulmonary complications for Clazosentan) that counterbalance their therapeutic benefits (Macdonald *et al.*, 2011) or aggressive use of rescue therapy that may dilute the overall results (Macdonald *et al.*, 2011). Rescue therapies (intravenous vasopressor with or without fluid therapy, or intra-arterial vasodilator or balloon angioplasty) are associated with significant morbidity and can have a considerable effect on the large-vessel component of angiographic vasospasm. Consequently, a drug that minimizes the need and amount of rescue therapy is desirable.

All of the above findings indicate that pathophysiology of DINDs is more complicated than previously assumed. Furthermore, recent studies suggest that genetic variations may predispose some patients to development of vasospasm and DIND while protect others from it. For example; aSAH patients with polymorphisms in apolipoprotein E (APOE; neurotrophic and neuroprotective) and endothelial nitric oxide synthase (eNOS; synthesis nitric oxide; a potent vasodilator) are at greater risk of vasospasm and worse functional outcome (Alexander *et al.*, 2009; Ko *et al.*, 2008; Kokubo *et al.*, 2000; Lanterna *et al.*, 2005; Leung *et al.*, 2002; Starke *et al.*, 2008). Whereas a gain-of-function; reduced risk of DIND, is observed in aSAH patients with polymorphisms of the cystathionine β-synthase (metabolizes homocysteine to hydrogen sulfide; a vasodilator, regulator of neuronal ion channels and intracellular signaling pathways) (Grobelny *et al.*, 2011). Another factor that is gaining recognition in pathogenesis of DIND is brain injury that occurs during the early phase of SAH. Increasing number of studies indicate that mechanisms deleterious to brain activate at aneurysm rupture, evolve with time and contribute to overall outcome of aSAH (Inagawa, 1997; Nau *et al.*, 2002; Stein *et al.*, 2006a; Stoltenberg-Didinger and Schwartz, 1987).

2. Animal Models of Acute (Early) aSAH

Controllable and reproducible animal models that simulate human condition closely are essential for studying the pathophysiology and developing a treatment for any disease. Unfortunately, the nature of the aSAH (aneurysm rupture) is a sudden, unpredictable

phenomenon and consequently most information on events that occur at clinical aSAH comes from observations made during rebleeds in patients. A number of investigators have used this information to develop and characterize animal models of aSAH (Barry *et al.*, 1979; Bederson *et al.*, 1995; Delgado-Zygmunt *et al.*, 1992; Honma *et al.*, 1989; Kader *et al.*, 1990; Khajavi *et al.*, 1997; Ram *et al.*, 1991; Solomon *et al.*, 1985; Veelken *et al.*, 1995; Wanebo *et al.*, 1998). These animal models are accepted as mimics of clinical aSAH and are widely used to study early and delayed brain injury after aSAH (Lee *et al.*, 2009b; Megyesi *et al.*, 1997; Prunell *et al.*, 2003). Broadly these models can be divided into two categories: an injection model and a vascular perforation model. Below we discuss them individually.

2.1. The Injection Model

Blood released upon aneurysm rupture at SAH fills subarachnoid cisterns enveloping and compressing major conductive arteries (Figure-1A and B). Based on this fact, an injection model mimics aSAH by introducing autologous fresh blood under adequate pressure into the subarachnoid space. Since its introduction, an injection model has been adapted and modified in number of ways to ensure that injury induced is reproducible, is of desired intensity, and is similar to human aSAH. The modifications of injection model have used fresh blood, blood products, and blood clots for injection (Echlin, 1971; Peterson *et al.*, 1990b). The most common site for blood injection is the cisterna magna (Ram *et al.*, 1991; Solomon *et al.*, 1985). Other sites include prechiasmatic cistern (Hansen-Schwartz *et al.*, 2003), vicinity of an intracranial (Tsuji *et al.*, 1996) or extracranial artery (Megyesi *et al.*, 1997; Pickard *et al.*, 1984). The volume of blood and infusion pressure is preselected and kept constant to ensure reproducibility of hemorrhage intensity (Hansen-Schwartz *et al.*, 2003; Matz *et al.*, 2000). To examine consequences of acute SAH, a single injection is sufficient. In contrast, to study delayed vasospasm double injection is necessary, in which the same volume of blood is injected twice through the same injection site 24 or 48 hours apart (Gules *et al.*, 2002; Meguro *et al.*, 2001b). The injection model has been modified by many investigators. One modification presented previously in cats by Trojanowski and colleagues and more recently in rabbit by Marbacher and colleagues creates aSAH by extracranial-intracranial shunting of blood from the subclavian artery into the cistern magna. Bleeding is stop by closing the three way stopcock when the intracranial pressure stabilizes (Marbacher *et al.*, 2010; Trojanowski, 1982a). This modified model is considered more appropriate for studying a delayed and not acute SAH.

Advantages of the injection model are an easy control of hemorrhage intensity and the use of saline injection for the control group. Disadvantage is a lack of arterial stress that a rupture of aneurysm creates in human aSAH. There is also a possibility that blood injected would not remain in the subarachnoid space and get dispersed in the intracranial space and in the spinal canal diluting blood and diminishing deleterious effects of the clot presence in the subarachnoid cisterns. However, this can be addressed by tilting the head of the animal during and after blood injection to ensure that blood pools in the subarachnoid space. The angle and the time of head tilt vary among species.

Hemodynamic changes upon blood injection include increase in ICP and fall in CBF (see Figure-1C and below). The intensity of SAH in this model however, is of lesser degree compared with endovascular model (Gules *et al.*, 2002; Prunell *et al.*, 2003). Nevertheless, the ability to have a proper saline-injected control and investigator control of hemorrhage intensity has made this model quite popular and extensively used.

2.2. The Arterial Puncture Model

The rupture of an intracranial aneurysm is a key event of aSAH. The arterial puncture model mimics this initial event. SAH is created by puncturing an intracranial artery. The arteries

commonly ruptured to create aSAH include the basilar artery (Barry *et al.*, 1979; Kader *et al.*, 1990) and the bifurcation of internal carotid artery (Bederson *et al.*, 1995; Veelken *et al.*, 1995). A puncture model has been used to study both acute and delayed effects of SAH. Although frequently used, a puncture model suffers from the major drawback of poor control of hemorrhage intensity leading to wide variation of data making interpretation of results challenging and requiring significant number of animals to assure statistical power for a study.

The size of filament and force used to rupture an artery play important role in SAH intensity (Schwartz *et al.*, 2000a). Studies show that SAH intensity is proportionate to filament size; the smaller the diameter of filament (such as 3′O) the smaller the intensity. A complication that can associate with the puncture model is a superimposed regional ischemia. This problem usually arises when the filament is left in the artery for some time obstructing the normal arterial perfusion. Control group in this model consists of sham-operated animals, which undergo the same surgery as SAH animals including insertion of a filament into the intracranial artery with the exception of perforation. However, a lack of saline injection that helps isolating the effects of blood from those from ICP elevation has led to questioning the adequacy of this control (Schwartz *et al.*, 2000a)

A number of investigators have compared SAH models to find the one that best mimics the human aSAH (Lee *et al.*, 2009b; Prunell *et al.*, 2003). There is an overall agreement that whereas injection model is easy to perform, allows better control of SAH intensity and has low mortality rate, perforation model fits the human condition the best and is better suited for research investigating early injury (Lee *et al.*, 2009b).

3. Early Brain Injury after aSAH (first 72 hours)

A large body of animal and significantly smaller human autopsy data establishes that brain injury initiates within minutes after the initial bleed (Bederson *et al.*, 1998; Friedrich *et al.*, 2010a; Inagawa, 1997; Nau *et al.*, 2002; Stein *et al.*, 2006a; Stoltenberg-Didinger and Schwartz, 1987). Since in typical clinical scenarios there is a delay in patients reaching medical attention after aSAH, most of the information about the first hours comes from animal studies.

The nature of early brain injury after aSAH appears to be ischemic (Cahill *et al.*, 2006b; Sehba and Bederson, 2006b; Trojanowski, 1982b). Microdialysis studies indicate that cerebral ischemia starts early after aSAH and is associated with decreased survival. In both blood injection and vessel perforation rat models, an increase in cerebral lactate/pyruvate ratio and glutamate concentration occurs within 15 minutes after aSAH (Gewirtz *et al.*, 1999; Schubert *et al.*, 2008a). In patients, similar findings were reported 24-48 hours after aSAH (Enblad *et al.*, 1996; Samuelsson *et al.*, 2009a; Schulz *et al.*, 2000) and often preceded delayed vasospasm and neurologic deterioration (Sarrafzadeh *et al.*, 2002). Interestingly, patients who remain asymptomatic after aSAH do not develop significant increase in cerebral ischemia-related metabolites (Sarrafzadeh *et al.*, 2002). Hence, early detection of cerebral ischemia may prognosticate the course of aSAH and help individualize therapeutic strategy to prevent early mortality and development of delayed ischemic injury.

Below we review events that occur within the first 72 hours after SAH (Figure-2).

4. Early Events after aSAH

4.1. Physiological Changes

Rapid changes in intracranial pressure (ICP), cerebral perfusion pressure (CPP), and cerebral blood flow (CBF) occur after aSAH and are closely followed by impairment of CBF

autoregulation (see Figure-1C) (Bederson *et al.*, 1995; Bederson *et al.*, 1998; Kamiya *et al.*, 1983; Rasmussen *et al.*, 1992; Travis and Hall, 1987; Trojanowski, 1982b).

4.1.1. Intracranial Pressure (ICP)—ICP rises as blood is released upon aneurysmal rupture and results in what most patients describe as the "the worst headache of my life" (Nornes and Magnaes, 1972). Experimental studies show that ICP peaks to a value near diastolic blood pressure and then falls and settles to a value that is near but above the baseline (Bederson *et al.*, 1995; Trojanowski, 1982b; Voldby, 1988). In some cases, ICP remains elevated, possibly due to mass effect from enlarging hematoma or the development of acute hydrocephalus (Asano and Sano, 1977; Kamiya *et al.*, 1983; Kuyama *et al.*, 1984; Voldby, 1988). Animal and clinical studies link ICP increase to the hemorrhage volume, obstruction of CSF outflow, partial and/or diffuse vasoparalysis, and distal cerebral arteriolar vasodilation (Brinker *et al.*, 1990; Grote and Hassler, 1988; Kosteljanetz, 1984; Le Roux *et al.*, 1996; Nornes, 1973). In most cases the severity of increase in ICP can be correlated with the outcome (Heuer *et al.*, 2004; Nagel *et al.*, 2009a; Pereira *et al.*, 2007; Westermaier *et al.*, 2009). Severe ICP increase is also associated with changes in cerebral metabolism (Samuelsson *et al.*, 2009b; Sarrafzadeh *et al.*, 2005), inflammation (Graetz *et al.*, 2010; Sehba *et al.*, 2008), a fall in cerebral blood flow (Fukuhara *et al.*, 1998; Hayashi *et al.*, 2000; Losiniecki and Zuccarello, 2008), and development of early and delayed cerebral ischemia (Gambardella *et al.*, 1998; Miranda *et al.*, 2006; Soehle *et al.*, 2007). CSF drainage with the goal of controlling the increased ICP is used to manage high-grade aSAH patients. More recently, decompressive craniectomy has been advocated to control the increased ICP in aSAH patients; however, its benefit remains to be determined (Burger *et al.*, 2008; Jaeger *et al.*, 2003; Nagel *et al.*, 2009b).

4.1.2. Cerebral Perfusion Pressure (CPP)—CPP falls profoundly during, and immediately after aSAH (Fisher, 1975; Nornes, 1973, 1978). Decreased CPP contributes to early ischemic brain injury but is not solely responsible for it (Bederson *et al.*, 1995). Experimental studies indicate that decrease in CPP at the onset of aSAH is not sufficient to cause perfusion arrest (Dorsch *et al.*, 1989; Kuyama *et al.*, 1984; Steiner *et al.*, 1975). In addition, CPP reductions in animals and in humans are not always associated with poor neurological outcome after aSAH (Heuer *et al.*, 2004; Jakubowski *et al.*, 1982).

4.1.3. Cerebral Blood Flow (CBF)—Animal studies demonstrate that CBF falls after aSAH and may or may not recover depending upon the severity of the bleed (Bederson *et al.*, 1995). Aneurismal SAH patients who are conscious at admission display a slight reduction in CBF while patients who are unconscious exhibit severe global hypoperfusion (Jakobsen, 1992). In the rat arterial puncture model, CBF reduction is accompanied by constriction of large cerebral blood vessels that normally are 1500 to 500mm in diameter (Bederson *et al.*, 1998; Sehba *et al.*, 1999). In humans, cerebral arteriography shows little evidence of acute arterial spasm (Grosset *et al.*, 1993; Weir *et al.*, 1978). Hence, in humans, initial fall in CBF is attributed to a period of "no-reflow", due to elevation of ICP (Brinker *et al.*, 1992; Grote and Hassler, 1988). The term "no-reflow" was coined by Ames in 1968 to describe a period of lack of blood filling the vessels directly after ischemia (Ames *et al.*, 1968) and was first used by Asano and Sano in 1977, to describe early perfusion deficits due to increased ICP in SAH animals (Asano and Sano, 1977). Other factors that contribute to the initial CBF fall in humans include presence of subarachnoid blood (Clower *et al.*, 1994; Ebel *et al.*, 1996; Solomon *et al.*, 1985; Umansky *et al.*, 1983), hypovolemia caused by cerebral salt wasting and excessive urinary output (Solomon *et al.*, 1988), and disturbed autoregulation (Ebel *et al.*, 1996; Jakubowski *et al.*, 1982; Kamiya *et al.*, 1983; Rasmussen *et al.*, 1992). The early CBF reduction after aSAH is accompanied by reduced cerebral metabolic rate of oxygen (Frykholm *et al.*, 2004; Hayashi *et al.*, 2008; Hayashi *et al.*, 2000;

Jakobsen *et al.*, 1990; Kawamura *et al.*, 2000) and signs of clinical deterioration (Kobayashi *et al.*, 1979; Miranda *et al.*, 2006).

4.1.4. CBF Autoregulation—CBF autoregulatory mechanisms are frequently impaired after aSAH (Ebel *et al.*, 1996; Jakubowski *et al.*, 1982; Kamiya *et al.*, 1983; Rasmussen *et al.*, 1992). In patients, this impairment is most pronounced during the first 72 hours after aSAH, correlates well with the severity of aSAH and affects both aspects of CBF autoregulation; the pressure autoregulation (response to change in systemic blood pressure) and chemoregulation (response to change in partial pressure of carbon dioxide) (Schmieder *et al.*, 2006). There is some evidence that indicates that impairment of CBF autoregulation post aSAH may have dissociative characteristics; i.e. chemoregulation remains impaired even when pressure autoregulation has recovered (Schatlo *et al.*, 2008). It is interesting to note that patients with initially preserved autoregulation are at less risk of developing DINDs compared with patients with an initially disturbed autoregulation (Lam *et al.*, 2000; Ratsep and Asser, 2001). In many cases autoregulation impairment precedes vasospasm (Lang *et al.*, 2001) and worsens in the presence of vasospasm (Lam *et al.*, 2000; Lang *et al.*, 2001). Disturbance in autoregulation after aSAH may result from acidic cerebral environment (Voldby *et al.*, 1985), hydrocephalus (Heilbrun *et al.*, 1972; Kamiya *et al.*, 1983), and impaired endothelium-dependent control of vessel diameter, all of which are present during the early phase of aSAH (Gewirtz *et al.*, 1999; Kamiya *et al.*, 1983; Park *et al.*, 2001; Sehba *et al.*, 1999; Sugi *et al.*, 1975).

4.2. Ionic Changes

Ionic distribution within and across brain cell is rapidly impaired after aSAH and promotes disturbance in brain electrical activity.

4.2.1. Cortical Spreading Depolarization (CSD)—Cortical spreading depolarization (CSD) is a wave of mass neuronal depolarization in the cortex associated with the progressive breakdown of ion homeostasis; massive neuronal of sodium and calcium influx. The increasing body of evidence from experimental and human aSAH studies indicate that changes in ionic contents of neurons leading to CSDs occur early and late after aSAH, and contribute to acute pathophysiology and the later occurring DINDs (Dreier *et al.*, 2000; Dreier *et al.*, 1998; Dreier *et al.*, 2006; van den Bergh *et al.*, 2002).

Depression of cortical activity upon placement of blood or blood products in the subarachnoid space of cats was reported by Levitt et al. in 1971 (Levitt *et al.*, 1971). However, occurrence of CSDs after SAH was first described by Hubschmann and colleagues who identified self-propagating waves of cellular depolarization over cerebral cortex upon placement of blood or blood products in the subarachnoid space of cats (Hubschmann and Kornhauser, 1980, 1982). The same group later reported that cortical depolarization is accompanied by a profound decrease in extracellular calcium, accumulation of extracellular potassium and a transient depression of spontaneous electro-cortical activity and speculated that it may play an important role in the development of vascular spasm (Hubschmann, 1987). More recently, Dreier et al. used artificial CSF that mimicked the composition of SAH-CSF to generate CSDs in rats and noted that the hemodynamic response to CSD was changed in presence of subarachnoid erythrocyte products. CSD caused spreading ischemia (inverse hemodynamic response) in presence of SAH-CSF instead of spreading hyperemia (normal hemodynamic response) under physiological conditions (Dreier *et al.*, 1998). Such spreading ischemias led to cortical infarction in contrast to normal CSDs that associate with spreading hyperemia (Dreier *et al.*, 2000). In human SAH, CSDs can occur as clusters or as isolated events (Dreier *et al.*, 2009). The Cooperative Study on Brain Injury Depolarization (COSBID) group in their initial

studies on aSAH patients performed after craniotomy noted that clustered CSDs occurred at the start of neurological deterioration (Dreier *et al.*, 2006). More recently this group examined cortical electrical activity, regional blood flow, and measured tissue oxygenation in 13 aSAH patients for two weeks after surgery and found that CSD clusters are located in close proximity to the injured brain area and are associated with prolong hypoperfusion and ischemia (Dreier *et al.*, 2009). Electro-cortical and regional cerebral blood flow recordings provided evidence of three different neurovascular responses to CSD in SAH patients similar to the findings in animals: (1) the normal response, (2) the inverse response and (3) neurovascular uncoupling (Dreier *et al.*, 2009). Some of mechanisms implicated in a development of CSDs after aSAH include subarachnoid presence of oxyhemoglobin (Petzold *et al.*, 2003) and hemolyzed blood products, elevated extracellular potassium (Dreier *et al.*, 2002; Hubschmann and Kornhauser, 1980, 1982; Levitt *et al.*, 1971; Petzold *et al.*, 2008), reduced cerebral NO (Petzold *et al.*, 2008; Windmuller *et al.*, 2005), increased glutamate receptor activity (Petzold *et al.*, 2005b), and increased endothelin-1 concentration (Petzold *et al.*, 2003). The exact contribution of these mechanisms in development of CDS remains to be determined.

4.2.2. Impaired Calcium Homeostasis in Cerebral Vessels—Cellular calcium homeostasis is impaired in brain parenchyma and in cerebral endothelial and smooth muscle cells early after aSAH (Hubschmann, 1987; Hubschmann and Kornhauser, 1982; Kohno *et al.*, 1991; Sakaki *et al.*, 1989). Calcium homeostasis is essential for physiological cell function and depends on adequate supply of adenosine triphosphate (ATP) for maintaining ionic gradients across the cell membrane. Experimental studies suggest that a pathological rise in intracellular calcium concentration in both endothelial and smooth muscle cells of cerebral vessels occur early after aSAH (Ishiguro *et al.*, 2008; Kohno *et al.*, 1991; Meguro *et al.*, 2000; Minato *et al.*, 1996; Wang *et al.*, 1994). For example Kohno et al. using a blood injection canine model found that intracellular calcium concentration in the smooth muscle cell of basilar artery increase 15 minutes after aSAH (Kohno *et al.*, 1991). The mechanisms involved in early calcium rise are studied and include: a marked influx of calcium via voltage sensitive calcium channels opened during membrane depolarization (Ishiguro *et al.*, 2008), activation of NMDA receptor by glutamate released during ischemia leading to excessive release of calcium ions from endoplasmic reticulum and from mitochondria, increased calcium influx through agonist dependent calcium channels, rapid depletion of ATP stores during global ischemia (Enblad *et al.*, 1996; Gewirtz *et al.*, 1999; Schubert *et al.*, 2008a; Schulz *et al.*, 2000) leading to a depletion of energy for ATPase-dependent sodium and calcium efflux and potassium influx (Hubschmann and Kornhauser, 1980, 1982; Kohno *et al.*, 1991; Wang *et al.*, 1994). Clinical and experimental studies show that early ionic disturbances can last for days after aSAH (von Holst and Mathiesen, 1990; Wang *et al.*, 1994). Moreover, experimental studies suggest that the pathological rise in intracellular calcium can promote persistent contraction of cerebral arteries, release of neurotransmitters including glutamate, activation of various enzymes including those that are detrimental to cell such as iNOS and enzymes mediating cell death (Debdi *et al.*, 1993; Hubschmann, 1987; Meguro *et al.*, 2000; Minato *et al.*, 1996; Sakaki *et al.*, 1989). Hence, calcium channel blockers (such as Nimodipine) are frequently used after surgical management of ruptured aneurysm to prevent severity of ischemic deficits in aSAH patients (Tomassoni *et al.*, 2008).

4.2.3 Decreased Serum Magnesium—In 1982 Altura and Altura suggested that a magnesium loss may occur and contribute to traumatic and non traumatic brain injury (Altura and Altura, 1982). Since then the same group and others have found that serum and CSF magnesium level decreases after experimental and clinical aSAH (Altura *et al.*, 1995; Altura *et al.*, 1997; Miura, 1988; van den Bergh *et al.*, 2003). It is found that the total serum magnesium level remains unchanged and the biologically active free ionized form of

magnesium falls upon brain injury (Memon *et al.*, 1995). Decrease in free magnesium occurs within 30 minutes after subarachnoid bleeding in animals (Altura *et al.*, 1995) and 1-8 hours after hemorrhagic strokes in humans (Altura *et al.*, 1997). Approximately 38% of patients admitted within 48 hours after aSAH exhibit abnormally low serum magnesium (van den Bergh *et al.*, 2003). Magnesium is a physiological antagonist of calcium and plays an important role in maintaining intracellular calcium concentration. In addition, it maintains intracellular calcium level by keeping a block on NMDA receptor activation. The pharmacological actions of magnesium involve vasodilation, inhibition of platelet aggregation, inhibition of excitatory amino-acids release and inhibition of ET-1 synthesis (Berthon *et al.*, 2003; McLean, 1994; van den Bergh *et al.*, 2004). Magnesium mediated vasodilation involves the release of endothelial NO (Yang *et al.*, 2000), increase in synthesis and release of prostacyclin (Nadler *et al.*, 1987), and reduction in calcium influx and competition for calcium binding sites at calmodulin, rendering calmodulin unable to stimulate myosin light chain kinase to promote contraction (McLean, 1994). Consequently, decrease in magnesium after aSAH can lead to unchecked increase in intracellular calcium, increase in neurotransmitters release, activation of calcium dependent enzymes, vasoconstriction and neuronal damage (Miura, 1988; van den Bergh *et al.*, 2004).

The effect of increasing serum magnesium levels against early brain injury after aSAH has been examined (Altura *et al.*, 1995; Miura, 1988; Pyne *et al.*, 2001; van den Bergh *et al.*, 2002). Whereas pilot studies showed that increasing magnesium in serum and CSF of aSAH patients is safe and well tolerated, clinical trial failed to demonstrate any clinical benefits of this treatment (Wong *et al.*, 2010a). A low CSF penetration of peripherally infused magnesium or earlier administration may be required to obtain benefits of magnesium therapy post aSAH.

4.2.4. Hyponatremia—Hyponatremia is a biochemical change that either present in aSAH patients at admission or develops in 1-2 days from ictus (Berendes *et al.*, 1997). Approximately 10% to 30% of aSAH patients suffer from hyponatremia (Naval *et al.*, 2006; Wartenberg *et al.*, 2006). Hyponatremia in aSAH patients is difficult to treat and is associated with the risk of developing cerebral ischemia and infarctions (Hasan *et al.*, 1990; Wijdicks *et al.*, 1985). The exact mechanism underlying aSAH-related hyponatremia is not fully understood, however, a role of cerebral salt-wasting syndrome (CSWS) and inappropriate secretion of anti-diuretic hormone (SIADH) is suggested (Bruder *et al.*, 2009; Doczi *et al.*, 1981).

CSWS causes fluid depletion and compensatory hypersecretion of ADH. Many studies report an early increase in humoral (such as brain natriuretic peptide and atrial natriuretic peptide) factor-induced natriuresis in patients after aSAH (Audibert *et al.*, 2009; Berendes *et al.*, 1997; Espiner *et al.*, 2002; Isotani *et al.*, 1994; Nakamura *et al.*, 2009; Tomida *et al.*, 1998). In SIADH, on the other hand, water retention results in hypertonic urine, hypo-osmolar serum, and apparent euvolemia without renal, adrenal, or thyroid diseases (Kao *et al.*, 2009). In a study consisting of 179 aSAH patients, Sherlock et al. found that in 62% of aSAH patients, hyponatremia was related to SIADH, and in 6.5% to CSWS. They concluded that SIADH is the most common cause of hyponatremia (Sherlock *et al.*, 2006).

Distinguishing CSWS from SIADH as the source of hyponatremia can be difficult since they share many biochemical parameters, including elevated serum ADH (Kao *et al.*, 2009). However, this distinction is crucial for formulating a rational treatment strategy, which goes in two opposite directions: fluid and sodium restrictions for CSWS, large sodium intake for SIADH. The volume of blood may help distinguish between these two situations; hypovolemia for CSWS and normal or increased volemia for SIADH (Audibert *et al.*, 2009; Ellison and Berl, 2007).

4.3. Mechanical and Biochemical Changes

Mechanical stress and biochemical changes occur at aSAH and influence the outcome. These changes are as follows:

4.3.1. Mechanical Stress—Mechanical stress is probably the first stress exert on brain upon the aneurysm rupture. Animal studies indicate that stress constricts the artery as its wall is ruptured and stretches the subarachnoid space due to pooling of blood (Arutiunov *et al.*, 1970; Kapp *et al.*, 1968; Simeone *et al.*, 1968). The stretching of the subarachnoid space is mechanically transferred to the nearby vessels and promotes constriction of the arteries with normal walls (Arutiunov *et al.*, 1974). Over the course of its presence subarachnoid blood clot associates with the early brain injury in animals (Schwartz *et al.*, 2000a) and with the severity of the delayed spasm in aSAH patients (Fisher *et al.*, 1980). Hence, immediate events involved by aSAH-induced mechanical trauma have early and delayed consequences.

4.3.2. Hydrocephalus—Hydrocephalus is one of the most common mechanical complications after aSAH (Diringer, 2009). In animals, signs of hydrocephalus are reported as early as 60 minutes after aSAH and are associated with the intensity of CBF reduction and ischemia (Kamiya *et al.*, 1983; Kuyama *et al.*, 1984; Milhorat, 1987). Patients with aSAH who develop hydrocephalus are at greater risk of neurologic impairment and mortality than patients without hydrocephalus (Suarez-Rivera, 1998).

In humans, three phases of aSAH-related hydrocephalus are recognized. These phases are separated by time of presentation from ictus; acute (≤3 days), subacute (4–13 days), and chronic (≥14 days) (Demirgil *et al.*, 2003; Vale *et al.*, 1997). Approximately 20% to 30% aSAH patients suffer from acute phase hydrocephalus (Diringer, 2009; Milhorat, 1987). Most cases of aSAH complicated by acute hydrocephalus have large bleeds, poor cerebral perfusion, reduced CBF (van Asch *et al.*, 2010) and present with poor clinical grade and higher Fisher Scale scores on admission (Brisman and Berenstein, 2004; Dorai *et al.*, 2003). Milhorat studied division of clinical status in aSAH patients with acute hydrocephalus and found Grade I in 3%; Grade II in 5%; “Good” Grade III in 21%, “Bad” Grade III in 40%, Grade IV in 42%, and Grade V in 26% (Milhorat, 1987). Risk factors of acute hydrocephalus post aSAH are studied and include presence of blood in intraventricular space (Dorai *et al.*, 2003; Suarez-Rivera, 1998), hemorrhage from posterior circulation aneurysms, diffuse spread of subarachnoid blood (Graff-Radford *et al.*, 1989), rebleeding, hypertension (Mehta *et al.*, 1996) and increased sympathetic activity (Jadhav *et al.*, 2008; Lambert *et al.*, 2002).

The exact mechanism underlying the development of acute hydrocephalus after aSAH is not established, however, sudden obstruction of cerebrospinal fluid circulation is considered an important contributor (Graff-Radford *et al.*, 1989; Milhorat, 1987). Majority of patients with acute hydrocephalus exhibit clinical improvement after ventricular drainage (Bederson *et al.*, 2009).

4.3.3. Increase in Extracellular Glutamate—In the arterial puncture rat model, cerebral glutamate level increases within minutes after aSAH and reaches a stable peek in approximately 40 minutes (Bederson *et al.*, 1998; Sehba *et al.*, 1999). This biochemical change found in both clinical and experimental studies is associated with the intensity of initial insult (Bederson *et al.*, 1998; Enblad *et al.*, 1996; Samuelsson *et al.*, 2007; Sarrafzadeh *et al.*, 2002; Schubert *et al.*, 2008a; Schulz *et al.*, 2000) and correlates well with clinical status and outcome of aSAH patients (Hutchinson *et al.*, 2002; Nilsson *et al.*, 1996; Sarrafzadeh *et al.*, 2002; Sarrafzadeh *et al.*, 1998; Saveland *et al.*, 1996; Schulz *et al.*, 2000; Skjoth-Rasmussen *et al.*, 2004; Staub *et al.*, 2000). Elevated interstitial glutamate

concentration is considered one of the markers of excitotoxicity (Hillered *et al.*, 2005) and is linked to cellular leakage, altered synaptic transmission, blood–brain barrier disruption, and inhibited glutamate uptake (Hillered *et al.*, 2005). Mechanisms of glutamate mediated toxicity include excessive activation of N-methyl-D-aspartate (NMDA) receptor causing massive calcium influx and subsequent necrosis and apoptotic cell death (McCulloch, 1992; Owens *et al.*, 1997). Experimental studies indicate that the early inhibition of glutamate receptors prevents aSAH associated blood-brain barrier leakage (Palmer *et al.*, 1995) and development of delayed vasospasm (Zuccarello *et al.*, 1994). A number of investigators have used magnesium to block NMDA receptor activity in attempt to prevent the development of delayed vasospasm and DINDs in aSAH patients (Dorhout Mees *et al.*, 2010; Wong *et al.*, 2006). These studies have met little success (Dorhout Mees *et al.*, 2010; Wong *et al.*, 2006).

4.4. Magnetic Resonance Imaging (MRI) Changes

Experimental studies indicate that early cerebral changes after aSAH can be detected by MRI (Busch *et al.*, 1998; Jadhav *et al.*, 2008; Piepgras *et al.*, 2001; Schubert *et al.*, 2008a; van den Bergh *et al.*, 2002). Busch et al. used MRI with diffusion weight imaging (DWI) in a rat aSAH model and found decrease in apparent diffusion coefficient (ADC) interpreted as acute cytotoxic edema within 2 min after aSAH (Busch *et al.*, 1998). In addition, they noted DWI changes representing spreading depression after a delay of 1–3 min (Busch *et al.*, 1998). On whole, experimental studies suggest that decrease in ADC 3 hours after aSAH is accompanied by ischemia (indicated by changes in cerebral energy metabolites) and can be reversed by hypothermia (Piepgras *et al.*, 2001; Schubert *et al.*, 2008b). Ischemic ADC changes are known to precede persistent neuronal death (Rojas *et al.*, 2006). Indeed, using a canine aSAH model, Zhang et al. found delayed (7 days) neuronal injury in animals that had displayed ADC changes 48 hours after aSAH (Jadhav *et al.*, 2008). They concluded that MRI is useful for a non-invasive study of early cerebral injury after aSAH (Jadhav *et al.*, 2008).

In aSAH patients' the often lack of availability of MRI and risks involved in scanning unstable patients have limited the use of early MRI (Bederson *et al.*, 2009; Fiebach *et al.*, 2004; van Gijn and Rinkel, 2001) and as the results early MRI data in aSAH patients in scarce. One early clinical MRI study in patients who were diagnosed by computed tomography within 6 hours of aSAH showed no perfusion deficits (Fiebach *et al.*, 2004). However, as patients enrolled in this study were of low-grade aSAH (low Hunt and Hess grades 1 or 2) and had good recovery, this study may have limited value. At least three investigators have reported the early MRI detecting cerebral infarct after SAH (Hadeishi *et al.*, 2002; Shimoda *et al.*, 2001; Weidauer *et al.*, 2008). Weidauer et al. reported that MRI detected cortical infarcts in grade 3 aSAH patients with mild angiographic vasospasm within 72 hours from the ictus (Weidauer *et al.*, 2008). Shimoda et al. and Hadeishi et al. report similar findings (Hadeishi *et al.*, 2002; Shimoda *et al.*, 2001). Hence, it appears that MRI when used early after aSAH can provide information about presence of cerebral injury. However, the benefits of using MRI early in the course of disease remain to be examined.

4.5. Pathological Changes

Vascular and non-vascular cerebral structures endure pathological changes early after aSAH (Figures 3 and 4).

4.5.1. Cerebral Vessels—Experimental studies have shed light on the early response of large and small parenchymal vessels to aSAH. The effect of aSAH on parenchymal vessels appears to be comparatively greater than on large cerebral vessels (Bederson *et al.*, 1998; Debdi *et al.*, 1992, 1993; Sehba *et al.*, 2010; Sehba *et al.*, 2007b). Most of data on early

vascular changes come from animal models; however, some human studies report similar findings (Bevan *et al.*, 1998; Hatake *et al.*, 1992; Hoelper *et al.*, 2003; Pennings *et al.*, 2004; Uhl *et al.*, 2003).

Animal studies demonstrate that large and small cerebral vessels constrict within minutes after aSAH (Bederson *et al.*, 1998; Sehba *et al.*, 1999; Sehba *et al.*, 2007b). Two phases of constriction are recognized in large vessels and in most cases accompany CBF reduction and perfusion deficits. The first phase is present as early as 10 minutes after aSAH and persists for at least 6 hours (Alkan *et al.*, 2001; Bederson *et al.*, 1998; Clower *et al.*, 1994; Ono *et al.*, 1997; Ono *et al.*, 2003; Sehba *et al.*, 2007b) and the second phase appears 48-72 hours later (Ohkuma *et al.*, 1997; Ono *et al.*, 2003; Yoshimoto *et al.*, 1993; Zubkov *et al.*, 2000; Zubkov *et al.*, 2002b). Constriction of parenchymal vessels is also noted in patients during surgery for aneurysm repair within first 72 hours after aSAH (Pennings *et al.*, 2004; Uhl *et al.*, 2003).

Endothelial dysfunction is considered one of the key factors in early vasoconstriction and in delayed vasospasm after aSAH (Iuliano *et al.*, 2004; Jung *et al.*, 2004; Kassell *et al.*, 1985; Miller *et al.*, 2010; Park *et al.*, 2001; Sobey and Faraci, 1998). In normal physiology, endothelium controls vascular tone and blood flow by releasing various contractile (such as Endothelin-1) and relaxant agents (such as nitric oxide, prostaglandin-I(2) and others) (Andresen *et al.*, 2006). Animal studies show that morphological and functional changes occur in vascular endothelium post aSAH. Morphological changes include corrugation of endothelium membrane, appearance of endothelial cytoplasmic flaps or microvilli that extend to the vessel lumen and are characteristic of cerebral ischemia and local endothelial denudation (Clower *et al.*, 1994; Friedrich *et al.*, 2010a; Ono *et al.*, 1997; Sehba and Friedrich, submitted). Functional changes include decrease in response of vasodilators that require a functional endothelium for eliciting their effect; such as acetylcholine thrombin, and bradykinin (Hongo *et al.*, 1988; Nakagomi *et al.*, 1987) or due to inhibition of endothelium-based vasodilation (ADMA) (Iuliano *et al.*, 2004; Jung *et al.*, 2004). Consequently, cerebral arteries become hypersensitive to contractile agents (such as serotonin, norepinephrine and others) after aSAH (Debdi *et al.*, 1992). Decreased dilation by agents requiring functional endothelium and hypersensitivity to contractile agents is also found in arterial specimens acquired from patients who died within the first 72 hours post aSAH (Bevan *et al.*, 1998; Hatake *et al.*, 1992). Apoptotic death of endothelial cells of large cerebral arteries is observed 3 days after aSAH (Zubkov *et al.*, 2002b). Parenchymal vessels display earlier and more severe morphological changes compared with large vessels. The endothelium lining of the parenchymal vessels is disrupted and detached from the basal lamina layer within 10 minutes (Friedrich *et al.*, 2010a) and apoptotic enzymes are activated in endothelial nuclei within 3 hours after aSAH (Friedrich *et al.*, in press). Hence, it is not surprising that endothelium of small parenchymal vessels becomes dysfunctional much earlier, within 20 minutes after aSAH (Park *et al.*, 2001). Another morphological change that to date is found limited to parenchymal vessels only (at least in the initial hours after aSAH) is the destruction of basal lamina. This phenomenon is a frequent finding in animal studies but is yet to be established in clinical aSAH. Animal studies demonstrate that degradation of major proteins of basal lamina starts within minutes after aSAH and persists for at least 24 hours (Guo *et al.*, 2010; Scholler *et al.*, 2007; Sehba *et al.*, 2004b; Yatsushige *et al.*, 2007). It has been suggested that this degradation may represent the initiation of compensatory, yet clinically inefficient angiogenesis in response to hypoxia (Josko *et al.*, 2001). Regardless of the cause, pathological consequence of basal lamina degradation on parenchymal vasculature is destabilization of microcirculation, increase of vascular permeability and edema (Hamann *et al.*, 1995). Indeed, a marked increase in permeability of cerebral microvessels is documented both in animal and human studies (Doczi *et al.*, 1986a; Doczi *et al.*, 1986b; Friedrich *et al.*, 2010b; Germano *et al.*, 2000). Moreover, this increase

correlates with the development of DINDs (Doczi, 1985; Doczi *et al.*, 1986a; Germano *et al.*, 1992; Germano *et al.*, 2000; Imperatore *et al.*, 2000; Symon, 1978) and poor clinical outcome in aSAH patients (Doczi *et al.*, 1986a; Scholler *et al.*, 2007; Smith *et al.*, 1997; Yatsushige *et al.*, 2006).

4.5.2. Cell Death (necrosis, apoptosis and autophagy)—Except for few early autopsy cases almost all first hand information on the early cell death after aSAH comes from animal studies. These studies demonstrate that cell death starts within 24 hours after aSAH. Serum levels of neuron specific enolase, a marker of neuronal injury, is elevated in patients and associated with the amount of subarachnoid blood and poor neurological status on admission, as well as it correlates with the development of delayed ischemic neuronal damage (Cunningham *et al.*, 1994; Kuroiwa *et al.*, 1994; Mabe *et al.*, 1991). In addition, serum concentration of S100-B, a marker of glial injury, is increased in patients within 3 days after aSAH (Oertel *et al.*, 2006). Consequently, it appears that although neurons are experiencing deleterious effects of aSAH very early, they are not the only target of cell death pathways. Indeed, Prunal et al. using animal aSAH models have found that in addition to neurons, astrocytes, and oligodendrocytes also undergo apoptosis 24 hr after aSAH (Prunell *et al.*, 2005). Other investigators report apoptosis of smooth muscle and endothelial cells 24 - 72 hours after aSAH (Cahill *et al.*, 2006a; Friedrich *et al.*, in press; Park *et al.*, 2004; Yatsushige *et al.*, 2007).

Most animal studies find necrosis and apoptosis to be the modes of cell death post aSAH (Akpinar *et al.*, 2005; Cahill *et al.*, 2006a; Dreier *et al.*, 2000; Matz *et al.*, 2001; Prunell *et al.*, 2005; Zubkov *et al.*, 2002b). More recently, Lee et al. have found autophagic death of neurons 24 hours after aSAH (Lee *et al.*, 2009a). It appears that more than one mode of cell death is active at any given time after aSAH (Dreier *et al.*, 2000; Friedrich *et al.*, in press; Lee *et al.*, 2009a; Matz *et al.*, 2001). Dreier et al. reported necrotic and apoptotic cell death and cerebral infarction in animals 24 hours after aSAH (Dreier *et al.*, 2000). Similarly, Matz et al. found necrosis and apoptosis at 24 hours in mice after heme injection (Matz *et al.*, 2001). More recently, Lee et al. reported neuronal death via apoptosis in the superficial layers of the fronto-basal cortex, and via autophagy in deep cortical structures in animals 24 hours after aSAH (Lee *et al.*, 2009a). Human autopsy studies involving patients who died 24 hours to 10 days after aSAH have found neuronal apoptosis in dentate gyrus (Nau *et al.*, 2002).

Animal studies indicate that apoptotic cell death after aSAH is evoked via extrinsic and intrinsic mechanisms (Cheng *et al.*, 2009; Meguro *et al.*, 2001a; Park *et al.*, 2004). Intrinsic mechanisms appear to be mainly caspase dependent (Cheng *et al.*, 2009; Meguro *et al.*, 2001a); however, some evidence of caspase independent intrinsic mechanisms involving free radicals mediated apoptosis exists (Endo *et al.*, 2007; Satoh *et al.*, 2001).

Caspase dependent intrinsic pathway activates upon pathological rise in intracellular calcium concentration (Broughton *et al.*, 2009). Its main events include activation of calcium-activated proteases (calpains), cleavage of Bcl-2 interacting domain (BID) to the truncated active form (tBID), and activation of proapoptotic proteins including Bak, Bax, Bad, and Bcl-XS and release of pro-apoptotic proteins by tBID to activate caspase dependent apoptosis (Broughton *et al.*, 2009). A number of studies suggest that caspase dependent intrinsic pathway is activated early after aSAH (Gules *et al.*, 2003; Yamaura *et al.*, 1993; Zhou *et al.*, 2004; Zubkov *et al.*, 2002a). For example, Yamaura et al. demonstrated that calpain (proteolytic enzyme that hydrolysis its substrate resulting in apoptosis) activates within 40 minutes in canine basilar artery and contributes to vasoconstriction that can be inhibited by calphostin, an intrinsic inhibitor of calpain (Yamaura *et al.*, 1993). Other studies demonstrate that calpain inhibitors used early after

aSAH prevent the BBB opening and neurological deficits (Germano *et al.*, 2002), and attenuate cerebral vasospasm (Cappelletto *et al.*, 1997; Fujikawa *et al.*, 1999). Similar benefits are reported upon inhibition of caspase activity after aSAH (Gules *et al.*, 2003; Zhou *et al.*, 2004; Zubkov *et al.*, 2002a). Caspases involved in apoptosis after aSAH are caspase-3, 8 and 9 (Park *et al.*, 2004; Prunell *et al.*, 2005; Zhou *et al.*, 2004).

Extrinsic mechanisms of apoptosis commonly called “death receptor pathway” involve the death receptors located on the cell surface (Broughton *et al.*, 2009). These receptors belong to the tumor necrosis factor receptor (TNFR) superfamily, and include TNFR-1, Fas, and p75NTR (Loh *et al.*, 2006) and mediate apoptosis via caspase-3 activation (Sugawara *et al.*, 2004). Fas-associated death domain protein (FADD) is a component of the death-inducing signaling complex and is recruited to the signaling complex in response to death receptor-mediated signaling. Jayaraman et al. found that FADD is up-regulated in the wall of human ruptured and unruptured aneurysms indicating that this pathway contributes to aneurysm formation and growth (Jayaraman *et al.*, 2005). In animals, the only report of apoptosis occurring via extrinsic mechanism after aSAH comes from Zhou and colleagues who show co-localization of TUNEL immunostaining with caspase-3 and TNFR1 in endothelial cells of canine basilar arteries 7 days after aSAH (Zhou *et al.*, 2004). Hence, extrinsic mechanisms of apoptosis appear to contribute to aneurysm formation and in late phase cell death after aSAH and their importance in the early phase cell death after aSAH remains to be elucidated.

4.6. Molecular Changes

4.6.1. Nitric oxide/Nitric Oxide Synthase Pathway—Pathological alteration in nitric oxide (NO)/nitric oxide synthase (NOS) pathway occurs early after aSAH and contributes to early ischemic brain injury (Schwartz *et al.*, 2000b; Sehba *et al.*, 1999; Sehba *et al.*, 2000) and to the pathogeneses of delayed vasospasm and DINDs (Afshar *et al.*, 1995; Durmaz *et al.*, 2008; Edwards *et al.*, 1992; Khaldi *et al.*, 2001; Ng *et al.*, 2001; Pluta *et al.*, 1997b; Suzuki *et al.*, 1994; Woszczyk *et al.*, 2003). Animal studies demonstrate that cerebral NO level decreases within 10 minutes (Sehba *et al.*, 2000) and increases above basal level at 24 hours after SAH (Yatsushige *et al.*, 2006). In humans, increased cerebral NO level is found 24 hours after aSAH and is associated with poor outcome (Durmaz *et al.*, 2008; Khaldi *et al.*, 2001; Ng *et al.*, 2001). Mechanisms underlying alteration in cerebral NO level are investigated and it is suggested that initial decrease in cerebral NO involves scavenging by hemoglobin, (Afshar *et al.*, 1995; Kajita *et al.*, 1994; Watkins, 1995), free radicals (Sobey and Faraci, 1998), and vascular neutrophils (Friedrich *et al.*, 2011; Provencio and Vora, 2005) or nitrite reduction” (Pluta *et al.*, 2005) rather than impairment of NO synthesis because the overall NOS activity remains unchanged during the first 90 minutes after aSAH (Sehba *et al.*, 2004a). The temporary recovery and increase NO above the basal level appears to involve saturation of scavenging mechanisms and/or an increase in NOS expression and activity (Sehba and Bederson, 2006b; Sehba *et al.*, 2004a).

An active NO/NOS pathway is crucial in the regulation of cerebral blood flow and blood pressure (Sobey and Faraci, 1998). In addition, NO plays an important role in smooth muscle cell proliferation, inhibition of platelet aggregation, and adherence of leukocytes to the endothelium in responses to vessel injury (Cooke and Dzau, 1997). Hence, it is not surprising that constriction of large and small cerebral vessels and luminal aggregation of platelets occurs within minutes after aSAH (Bederson *et al.*, 1998; Sehba *et al.*, 2005); the time when cerebral NO is reduced (Sehba *et al.*, 2000). Since the capacity of arteries to synthesize cGMP (involved in NO mediated vasodilatation) and dilate in response to an NO donor remains unchanged during this early period, many investigators have used NO donors

to dilate arteries and recover CBF and prevent early ischemic injury after experimental SAH (Park *et al.*, 2001; Sehba *et al.*, 1999; Sehba *et al.*, 2007b; Sobey and Faraci, 1998).

Large increase in cerebral NO at the time when its vascular response is no longer needed can also be devastating to brain (Iadecola, 1997); i.e. a pathological rise in cerebral NO level beyond baseline 24 hour after aSAH has been proved detrimental (Ayer and Zhang, 2008; Petzold *et al.*, 2005a; Sehba and Bederson, 2006b). In this setting, NO acts as a free radical itself and in the form of peroxynitrite (a powerful oxidant) attacks cell membrane causing pathological changes in the endothelium and smooth muscle cell structures (Beckman *et al.*, 1990). Putative mechanisms of NO-mediated cell injury involve activation of poly(ADP-ribose) synthase and subsequent depletion of cellular β-nicotinamide adenine dinucleotide and ATP (cellular energy depletion) leading to cell death (Carson *et al.*, 1986; Szabo and Dawson, 1998), mitochondria damage (Higuchi *et al.*, 1996; Iadecola, 1997; Leist and Nicotera, 1998), and changes in ion flux of sodium, potassium, and calcium channels leading to axonal degeneration (Petzold *et al.*, 2005a). Most of these mechanisms are found active in animals and in humans early after aSAH (Ayer and Zhang, 2008; Petzold *et al.*, 2005a; Petzold *et al.*, 2008) and are associated with early brain injury, pathogenesis of DINDs, and poor clinical outcome (Durmaz *et al.*, 2008; Jung *et al.*, 2007; Khaldi *et al.*, 2001; Medele *et al.*, 1996; Ng *et al.*, 2001; Sayama *et al.*, 1999; Woszczyk *et al.*, 2003; Yamamoto *et al.*, 1997).

Over all it appears that whereas increasing cerebral NO level few hours after aSAH preserves brain functions, beyond this time, vigilant monitoring of cerebral NO level is warranted to not exceed past physiological level.

4.6.2. Endothelin-1 (ET-1)—Animal studies show that CSF level of ET-1 increases within minutes after aSAH (Josko *et al.*, 1998; Wang *et al.*, 1995). In aSAH patients, increase in CSF and plasma ET-1 is observed 24 hours from ictus (Kobayashi *et al.*, 1995), and is associated with the occurrence of delayed vasospasm (Gruber *et al.*, 2000a). Animal studies indicate that the increase in cerebral ET-1 after aSAH results from excessive release by astrocytes during the period of initial ischemia (Pluta *et al.*, 1997a). It is suggested that the early increase in ET-1 level along with decease in cerebral NO (above) after aSAH disturbs the delicate balance between vasoconstrictive and vasodilatory forces necessary to maintain physiological vessel tone and flow and leads to unopposed constriction via activation of ET-1 receptors (Afshar *et al.*, 1995). Consequently, it is possible to inhibit vascular constriction post aSAH by increasing cerebral NO; such as by an NO donor, and/or by inhibiting ET-1 activity such as by ET-1 antagonism (Agrawal *et al.*, 2009; Clozel and Watanabe, 1993; Macdonald *et al.*, 2008; Pluta *et al.*, 2005; Sehba *et al.*, 1999).

ET-1 is a peptide secreted in the brain by vascular endothelium, neurons, astrocytes and macrophages (Levin, 1995). It acts through three receptors: ET-A, ET-B1 and ET-B2 receptors (Rothoerl and Ringel, 2007). ET-A receptor is expressed in vascular smooth muscle cells and mediates vasoconstriction; ET-B1 receptor is expressed in vascular endothelial cells and mediates endothelium-dependent vasodilation and ET-B2 receptor is expressed in smooth muscle cells and mediates vasoconstriction (Levin, 1995). Studies show that expression of ET-1 receptors increases 24 to 48 hours after aSAH (Hansen-Schwartz *et al.*, 2003; Vikman *et al.*, 2006). In normotensive animals, intracisternal administration of ET-1 causes widespread long lasting vasoconstriction and profound cerebral ischemia (Asano *et al.*, 1989; Macrae *et al.*, 1991).

One key finding made in animals and in humans that points at ET-1 as the dominant culprit in the pathogenesis of delayed vasospasm after aSAH is that it produces long-lasting constriction (Kobayashi *et al.*, 1991; Papadopoulos *et al.*, 1990). Additional factors

establishing importance of ET-1 in delayed vasospasm include: (1) ET-1 is increased early in CSF and plasma after aSAH (Josko *et al.*, 1998; Kobayashi *et al.*, 1995; Wang *et al.*, 1995), (2) agents that promote ET-1 release in CSF and plasma (thrombin and oxyhemoglobin) increase early after aSAH, and (3) ET-1 produces degenerative morphological changes in the vascular wall that are similar to those observed after aSAH (Asano *et al.*, 1990; Kasuya *et al.*, 1993; Kobayashi *et al.*, 1991; Peltonen *et al.*, 1997).

Connecting delayed vasospasm to DINDs a number of investigators have attempted to use ET-1 receptor antagonists to prevent delayed vasospasm and cortical infarctions after aSAH. These agents successfully reduced the incidence and intensity of vasospasm but had little effect on DINDs and on the long-term outcome (Kramer and Fletcher, 2009; Macdonald *et al.*, 2011; Macdonald *et al.*, 2008; Nogueira *et al.*, 2007; Shaw *et al.*, 2000; Vajkoczy *et al.*, 2005; Vergouwen, 2009).

4.6.3 Oxidative and Nitrosative Stress—Substantial amount of data supports early generation of oxygen free radicals (ROS) and oxidative stress after aSAH (Gaetani *et al.*, 1990b; Gaetani *et al.*, 1994; Marzatico *et al.*, 1993; Marzatico *et al.*, 1998; Sano, 1994; Schulz *et al.*, 2000) and their association with early brain injury and pathogenesis of delayed vasospasm and/or DINDs (Asaeda *et al.*, 2005; Gaetani *et al.*, 1997; Imperatore *et al.*, 2000; Kamezaki *et al.*, 2002; Liu *et al.*, 2007; Marzatico *et al.*, 1998; Pyne-Geithman *et al.*, 2009; Sano, 1994; Shin *et al.*, 2003). Animal studies show that activities of enzymatic and non-enzymatic antioxidant systems decrease within 60 minutes (Marzatico *et al.*, 1993), and the products of lipid peroxidation increase 1-6 hours after aSAH (Gaetani *et al.*, 1990b). In humans, decrease in antioxidant systems (Gaetani *et al.*, 1997; Gaetani *et al.*, 1998; Lin *et al.*, 2006; Marzatico *et al.*, 1998), and increase in lipid peroxidation products is found within 72 hours from ictus and correlates well with poor clinical status and outcome (Asaeda *et al.*, 2005; Gaetani *et al.*, 1997; Hsieh *et al.*, 2009; Kamezaki *et al.*, 2002; Polidori *et al.*, 1997).

ROS generated after aSAH include superoxide anion (O_2*) (Marzatico *et al.*, 1993), hydroxyl radical (OH*), hydrogen peroxide (H_2O_2) (Gaetani *et al.*, 1994), nitric oxide (NO*), and peroxynitrate (ONOO-) (Asano and Matsui, 1999; Ayer and Zhang, 2008; Lin *et al.*, 2006; Petzold *et al.*, 2005a). Animal studies indicate that majority of these ROS are generated during auto-oxidation of hemoglobin upon erythrocytes lysis in the subarachnoid space (Asano, 1999; Asano and Matsui, 1999; Misra and Fridovich, 1972; Sercombe *et al.*, 2002). Other sources of post aSAH ROS include increased NOS activity (Ayer and Zhang, 2008; Petzold *et al.*, 2005a; Sehba *et al.*, 2004a), disrupted mitochondrial respiration (Piantadosi and Zhang, 1996), hypoxic conversion of endothelial xanthine dehydrogenase to xanthine oxidase (Kim *et al.*, 1987; Lindsay *et al.*, 1991; Sermet *et al.*, 2000; von Holst and Sollevi, 1985), lipid peroxidation (Sano, 1994; Schulz *et al.*, 2000), and up-regulation of NADPH oxidase (Liu *et al.*, 2007). For review see Ayer and Zhang (Ayer and Zhang, 2008).

Consequences of oxidative stress after aSAH may include injury to smooth muscle and endothelium of vascular wall, disruption of the blood brain barrier, production of strong spasmogens such as leukotriene C_4 and prostaglandin D_2 from the lipoxygenase and cyclo-oxygenase pathways of arachidonic acid metabolism (Gaetani *et al.*, 1990b). In addition, oxidative stress induces enzymes of apoptotic pathway including p53, caspase-3 and 9 to promote apoptotic cell death (Ayer and Zhang, 2008). Consequently, overexpression of CuZn superoxide dismutase (SOD; a potent endogenous antioxidant) in transgenic mice prevents apoptotic cell death (Matz *et al.*, 2000), and reduces mortality (Endo *et al.*, 2007) after aSAH. Antioxidants have successfully have been used to prevent oxidative stress and decrease early brain injury in animals (Gaetani *et al.*, 1990a; Hall and Travis, 1988) but have met little success in improving outcome in clinical trials (Gomis *et al.*, 2010; Zhang *et al.*, 2010).

4.6.4. Inflammation—Numerous different inflammatory pathways are activated early after aSAH (Handa *et al.*, 1995; Kaynar *et al.*, 2004; Mack *et al.*, 2002; Mocco *et al.*, 2002; Tanriverdi *et al.*, 2005). An early inflammation in aSAH patients is linked to poor neurological grade on admission, fever, malaise, leukocytosis, increased BBB permeability, brain edema, small vessel thrombosis, pathogenesis of vasospasm and DINDs (Barone and Feuerstein, 1999; Chaichana *et al.*, 2010; Frijns and Kappelle, 2002; Kaynar *et al.*, 2004; Kubo *et al.*, 2008; Mack *et al.*, 2002; Neil-Dwyer and Cruickshank, 1974).

Neutrophils, the cells of innate immune response, accumulate in cerebral vessels within 10 minutes after aSAH in animals and persist for at least 24 hrs (Friedrich *et al.*, 2011). Similarly, soluble and tissue markers of inflammation increase within 24 hrs after aSAH in animals (Bavbek *et al.*, 1998; Handa *et al.*, 1995; Lin *et al.*, 2005), and within the first 3 days from ictus in patients (Dumont *et al.*, 2003; Fassbender *et al.*, 2001; Fountas *et al.*, 2009; Gruber *et al.*, 2000b; Kacira *et al.*, 2007; Mack *et al.*, 2002; Peterson *et al.*, 1990a; Rothoerl *et al.*, 2006; Takizawa *et al.*, 2001). Parenchymal migration of leukocytes, a major step in inflammation begins early after aSAH and contributes to poor outcome (Bavbek *et al.*, 1998; Friedrich *et al.*, 2011; Handa *et al.*, 1995; Kaynar *et al.*, 2004; Lin *et al.*, 2005; Mack *et al.*, 2002; Mocco *et al.*, 2002; Tanriverdi *et al.*, 2005). Leukocyte migration requires endothelial expression of adhesion molecules (vascular cell adhesion molecule-1 (VCAM-1), intercellular adhesion molecule-1 (ICAM-1), and E-selectin to aide in their endothelial adherence and subsequent transit into the brain parenchyma (Rothlein, 1997; Springer, 1994). Hence, in animals, leukocyte migration and its contribution to brain injury is established as increased endothelial expression of adhesion molecules within 24 hours after aSAH and their selective inhibition leads to improved outcome (Bavbek *et al.*, 1998; Handa *et al.*, 1995; Lin *et al.*, 2005). In aSAH patients, an increase in soluble forms of adhesion molecules is found within the first 3 days and is associated with poor outcome (Kaynar *et al.*, 2004; Mack *et al.*, 2002; Mocco *et al.*, 2002; Tanriverdi *et al.*, 2005).

C-reactive protein (CRP) is another early sensitive marker of systemic inflammation (Pepys and Hirschfield, 2003). Studies find that CRP level increases in serum and CSF within 2-3 days after aSAH (Fountas *et al.*, 2009; Kacira *et al.*, 2007; Rothoerl *et al.*, 2006; Takizawa *et al.*, 2001). Moreover, in aSAH patients the elevated CRP level on admission correlates well with low GCS scores, high Hunt and Hess and Fisher grades, and the occurrence of delayed vasospasm (Fountas *et al.*, 2009).

Pro-inflammatory cytokines (interleukin-1β (IL-1β) and interleukin-6 (IL-6), interleukin-1 receptor (IL-1Ra) and tumor necrosis factor (TNF-α)) orchestrate inflammatory cascade in response to any injury. Cytokines modulate vessel tone by inducing synthesis of vasoconstrictors such as endothelin-1 (Marsden and Brenner, 1992), by expression of adhesion molecule responsible for focal leukocyte recruitment (Handa *et al.*, 1995), and by impairing vascular permeability (McKeating and Andrews, 1998) and the blood-brain barrier function (Holmin *et al.*, 1998; Sozen *et al.*, 2009). Furthermore, IL-6 contributes to intracranial hypertension (Argaw *et al.*, 2006; Paul *et al.*, 2003), and TNF-α in hemolysis-induced vasoconstriction (Vecchione *et al.*, 2009). In aSAH patients, serum and CSF level of cytokines increases within 1-3 days from ictus (Dumont *et al.*, 2003; Fassbender *et al.*, 2001; Graetz *et al.*, 2010; Gruber *et al.*, 2000b; Hendryk *et al.*, 2004; Peterson *et al.*, 1990a) and is associated with hyperthermia, vascular spasm, and unfavorable outcome (Dumont *et al.*, 2003; Jedrzejowska-Szypulka *et al.*, 2009; Mathiesen *et al.*, 1997). Although the exact source of cytokine release after aSAH is not known, endothelial cells, neutrophils, macrophages, astrocyte, microglia, and neurons are implicated (Dumont *et al.*, 2003; Takizawa *et al.*, 2001; Vecchione *et al.*, 2009). Inflammasome are yet another source of pro-inflammatory cytokines (de Rivero Vaccari *et al.*, 2009), their importance in inflammation after SAH remains to be elucidated.

4.6.5. Platelets—Experimental and clinical studies indicate that platelets activate early after aSAH (Clower *et al.*, 1988; Denton *et al.*, 1971; Haining *et al.*, 1988; Hirashima *et al.*, 2005; Ishikawa *et al.*, 2009; Sehba *et al.*, 2005; Stein *et al.*, 2006a). Reduction in venous jugular platelet counts and shape change indicating sequestration and activation is observed 5 minutes after experimental (Denton *et al.*, 1971), and 48 hours after clinical aSAH (Hirashima *et al.*, 2005). Moreover, platelet aggregates are found lodged in major cerebral arteries at 2 hours (Clower *et al.*, 1988; Haining *et al.*, 1988), and in the parenchymal vessels 10 minutes after experimental aSAH (Ishikawa *et al.*, 2009; Sehba *et al.*, 2005). Autopsy specimen of humans died within 2 days after aSAH demonstrate micro-emboli in small arteries (Stein *et al.*, 2006a). The aggregates lodged in parenchymal vessels may have originally formed at the site of the aneurysm rupture in a large cerebral vessel at aSAH and traveled downstream to parenchymal vessels. Alternatively, they may have formed in the vessels due to activation of endothelium and the reduction in blood flow after aSAH.

The presence of platelet aggregates in parenchymal vessels may promote the “no-reflow” phenomenon (Abumiya *et al.*, 2000), the absence of vascular filling after a period of global cerebral ischemia (Ames *et al.*, 1968). In addition, parenchymal platelets aggregates can stimulate or initiate events that can devastate an injured brain. Most of these events are found active within minutes after experimental aSAH and include: (1) the mechanical obstruction of vessel lumen (Friedrich *et al.*, 2010b); (2) vasoconstriction via release of serotonin, ADP and PDGF (del Zoppo, 1997; Fukami *et al.*, 2001; Okada *et al.*, 1994; Reed, 2002; Sehba *et al.*, 2007b); (3) denudation of endothelium thereby promoting further platelet aggregation (Friedrich *et al.*, 2010a; Rosenblum, 1997; Said *et al.*, 1993) and finally, (4) destruction of major proteins of the vessel wall by releasing collagenases such as matrix metalloproteinases-2 and 9 (MMP-2 and 9) (Fernandez-Patron *et al.*, 1999; Friedrich *et al.*, 2010a; Rosenberg *et al.*, 1998; Rosenberg *et al.*, 1992; Sehba *et al.*, 2007a; Sehba *et al.*, 2007b; Sehba *et al.*, 2004b). Moreover, the recent study demonstrates that luminal platelet aggregates escape into the brain parenchyma within 10 minutes after aSAH and that this process is still active at 24 hours (Friedrich *et al.*, 2010a). The presence of platelets in the brain parenchyma may activate additional inflammatory mechanisms and further aggravate brain injury.

4.7. Neurological, Cognitive and Functional Deficits

Majority of aSAH patients at admission present disturbed consciousness and change in cognition, together with perceptual (such as illusions and hallucinations), and emotional disturbances (such as agitation and anger) (Reijneveld *et al.*, 2000). The Hunt and Hess, the Glasgow comma scale (GCS), and the World Federation of Neurological Surgeons (WFNS) Grading scales are routinely used to assess patient status during early phase of aSAH and to make treatment decisions (Starke *et al.*, 2009). Studies show that the patients’ status on admission correlates well with the outcome,, i.e., patients in low grades on admission usually have poor outcome (Hutter *et al.*, 2001). Similarly, the presence of acute focal neurological deficits on admission is also associated with non-favorable outcome (Sarrafzadeh *et al.*, 2003). Cerebral microdialysis in aSAH patients with acute focal neurological deficits reveals low glucose, high glutamate and glycerol levels confirming the presence of ischemia, excitoxicity, and lipid peroxidation, (Kerner *et al.*, 2007; Sarrafzadeh *et al.*, 2003).

Animal studies present a more complete picture of behavioral changes and deficits occurring during the early phase after aSAH. These studies show decrease in appetite (Guo *et al.*, 2010), weight (Germano *et al.*, 2007; Germano *et al.*, 2002), but little or no change in motor functions except some possible losses of coordination skills (Germano *et al.*, 1994; Silasi and Colbourne, 2009; Thal *et al.*, 2008). Germano and colleagues studied animals for

coordination skills from ictus to 5 days after aSAH and found transient reduction in beam balance at 24 hours and persistent reduction in traverse beam walking ability for 4 days (Germano *et al.*, 2002). Thal et al., however, found no significant change in animals coordination skills during the first 48 hours after aSAH using beam balance or rotarod tests (Thal *et al.*, 2008). In contrast to coordination, the overall neurological status of animals is significantly impaired 72 hours after aSAH (Ostrowski *et al.*, 2005; Park *et al.*, 2004; Thal *et al.*, 2009). Thal et al. used a 100 point neuro-score to examine general behavioral deficit, cranial nerve reflexes, motor deficit, sensory deficit, coordination and found a significant reduction in overall score of animals 24-48 hours after aSAH (Thal *et al.*, 2009). Silasi et al. used a battery of tests to check motor and cognitive skills in animals 3-7 days after aSAH and found minor non-significant changes (Silasi and Colbourne, 2009). Taken together animal studies indicate significant neurological and behavioral impairment and some coordination impairment during the early phase of aSAH.

5. Failure to Translate Successful Animal Therapies to Clinical Settings

Although animal research has undeniably advanced our understanding of injury after aSAH, it has failed to provide a therapy (see Table 1). This research helped in elimination of compounds that are not found effective or were too toxic for clinical evaluation; nevertheless many compounds that were found promising in animals failed in clinical trials. This failure questions the value of animal research in development of an effective therapy against aSAH and its complications. A number of factors have been recognized making translation of animal research results into clinics difficult.

5.1. Animal Species

Quite a few species have been used to study early and delayed injury after aSAH. This list includes non-human primates, pigs, goats, dogs, cats, and rodents (rat and mice, for review see (Sehba and Bederson, 2006a)). In recent years, rodents have become increasingly popular to study aSAH as they are relatively inexpensive, amenable to genetic alteration, and easy to manipulate in a laboratory setting. However, it is clear that though mammals, rodents are physiologically, neuroanatomically and metabolically different from humans; they lack gall bladder, process fat and cholesterol in different ways, and require greater mg/kg drug doses to produce a response similar to larger animals (Bergen and Mersmann, 2005; Mordenti and Chappell, 1989). In addition, rodent cerebral vasculature is anatomically different than humans. For instance, it lacks interadventitial space in arterial walls and has abundant collaterals (Frederickson and Low, 1969; Kader *et al.*, 1990). Moreover, studies of focal ischemia demonstrate that a similar occlusion of middle cerebral artery causes larger infarction and more extensive cell death in rodents as compared with humans (Carmichael, 2005).

Non-human primates are closer to human in physiologically, neuroanatomy, and metabolism and more likely to produce data that could be readily translated to human condition. However, cost and ethical issues of primate research has made their wider use by most laboratories difficult, if not impossible. Despite, the recognition of role of primate research for translational medicine (Cook and Tymianski, 2011) without better funding, institutional change in animal facilities, and costs its use will remain limited and rodent models will continue to provide the predominant basic science research into the mechanisms of brain injury and its treatment. Perhaps confirmation in primate of a treatment found effective in rodents or other species may reduce the number of failures in clinical trial. However, this cannot be guaranteed either, a fact observed as the recent failure of clinical trial of stroke that was based on the robust evidence of effectiveness in a non-human primate model of stroke (Diener *et al.*, 2008; Lees *et al.*, 2006; Shuaib *et al.*, 2007). A better collaboration between laboratories and a better funding mechanism may solve some of the problems. This

will allow for compounds found effective in rodent models in small laboratories to be examined in primates in other research centers; large laboratories of pharmacological companies, or government supported facilities before their clinical evaluation. These solutions may result in fewer clinical disappointments.

5.2. Methodological Flaws in Animal Studies

5.2.1. Age, Health, and Gender Issues—Methodological flaws in animal experimentation can contribute to inability of clinical translation of their results. Methodological flaws can come in different forms. Critical disease specific disparities between the animal models and the clinical trials testing the treatment strategy are major flaws. Most often experiments are carried out in young, non-diseased animals and do not simulate the age or condition of patients at risk of aSAH (45-55 year old, majority hypertensive). Similarly, most experiments are performed on male animals to avoid the variability caused by female hormone cycling, whereas in reality not only more females then males suffer from aSAH but some agents (such as Tirilazad mesylate) have a gender specific activity and their effectiveness differs between sexes (Kassell *et al.*, 1996; Kongable *et al.*, 1996; Lanzino and Kassell, 1999).

5.2.2. Animal Allocation, Control Group, Blinded Assessment, and Statistical Power—Another methodological flaw is the lack of random allocation of animals. Not many studies indicate if animals used for particular experiment were randomized. Furthermore, quite often the experimental study does not have control group or the control group is inadequately established. Blind assessment is essential for a non-biased meaningful study. Unfortunately, not many experimental studies indicate whether assessments were performed in a blind manner. Similarly, season and time of the day is known to influence the outcome of aSAH (Gallerani *et al.*, 1996; Hughes *et al.*, 2010 ; Muroi *et al.*, 2004). To our best knowledge, these elements are seldom, if ever, addressed in research models. If investigator is not blinded to the identity of the drug that an animal receives then there is possibility that its effect on the animal is overrepresented. Sample size that is sufficiently powered to allow statistical analysis provides inadequate data that is more observational and can lead to incorrect conclusions about efficacy. The bottom line is that we need more stringent requirements for reporting animal data (Hackam, 2007).

All of the above factors make it essential that systematic reviews and meta-analyses of outcomes of animal studies using the agent(s) of interest are performed before a clinical trial. Such a close analysis of all available experimental data may facilitate detection of toxicity and efficacy, and aid in the selection of the most promising compounds for clinical trials.

5.2.3. Focus of Therapy; Study Endpoints—Failure of animal studies to translate in human may also results from the difference in the end points considered important for a drug or treatment. Since delayed vasospasm has been considered the most important determinant of outcome after aSAH, most animal studies have focused on prevention and treatment of vasospasm to improve aSAH outcome. However, the results of a recent clinical trial indicate that this approach may not be proper (see table 1) and that it is time to revise treatment strategy. As discussed above, brain injury after aSAH begins at the initial bleed and plays an important role in the outcome. Although research on early brain injury after aSAH is still in its infancy and most data describing it comes from laboratory, massive brain injury observed during autopsy of patients that died early after aSAH confirms its importance in the outcome (Nau *et al.*, 2002; Stoltenberg-Didinger and Schwartz, 1987). It is suggested that many of the early mechanisms evolve with time and contribute to the outcome of aSAH (Sehba *et al.*,

2011). Consequently, these mechanisms and their timely addressing need to be considered while designing a therapeutic strategy against aSAH.

It is also important to define outcome measure of a drug efficacy. For many patients and their families, the quality of life is as important as prolongation of life. Consequently, maintenance and recovery of damaged neuronal circuits important for everyday life activities such as cognitive and motor functions, speech and memory could be a better measure of a drug efficacy (Chahal *et al.*, 2011; Hutter *et al.*, 1995; Vieira *et al.*, 2011). Thus, for experimental compounds to become a successful therapy in humans, a therapy that goes beyond prevention of cell death and addresses the acute and delayed deficits that affect quality of life of aSAH victims is required. Perhaps neurobehavioral status is a better assessment of patient outcome and should be the focus of therapy. This requires identification of the neurobehavioral function (such as memory, life style, etc) affected by aSAH and preparation of an assessment method that would allow their proper scaling and grading. This could only be achieved by a long-term evaluation of aSAH patients, perhaps in form of a multicenter project. Better animal models that exhibit neurobiological deficits similar to those in humans post SAH are also needed, so that therapeutic strategies that ameliorate them could be identified.

6. Conclusion

Despite extensive research the patient outcome post aSAH remains poor. Findings that prevention of delayed vasospasm does not improve outcome indicate that its importance in patient outcome has been misinterpreted. More recently, early brain injury has emerged as a new frontier and requires a better understanding and consideration in devising therapeutic strategy for improving aSAH outcome. In addition, better end points such as measurements of neurobehavioral deficits endured by aSAH patients are essential and their translation to the animal models is critical in identifying a potential therapy. Relevant animal models and timely treatment focused on prevention of early brain injury may establish a therapy, which if found beneficial for animals could be successfully translated in human aSAH trials.

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List of nonstandard abbreviations

aSAH	aneurysmal subarachnoid hemorrhage
DIND	delayed ischemic neurological deficits
ICP	intracranial pressure
CPP	cerebral perfusion pressure
CBF	cerebral blood flow
CSD	cortical spreading depolarization
NMDA	N-methyl-D-aspartate
CSWS	cerebral salt-wasting syndrome
SIADH	secretion of anti-diuretic hormone
MRI	magnetic resonance imaging

DWI	diffusion weight imaging
ADC	apparent diffusion coefficient
BID	Bcl-2 interacting domain
tBID	truncated Bcl-2 interacting domain
TNFR	tumor necrosis factor receptor
FADD	Fas-associated death domain protein
NO	nitric oxide
NOS	nitric oxide synthase
eNOS	endothelial nitric oxide synthase
CSF	cerebral spinal fluid
ET-1	endothelin-1
ROS	oxygen free radicals
BBB	blood brain barrier
CRP	C-reactive protein
TNF-α	tumor necrosis factor
MMP-2 and 9	matrix metalloproteinases-2 and 9
GCS	Glasgow comma scale
WFNS	World Federation of Neurological Surgeons
cGMP	cyclic guanosine 3′,5′-monophosphate

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Highlights

1. Despite extensive research patient outcome post aSAH remains poor.
2. Delayed vasospasm is not the sole determinant of poor outcome in aSAH patients.
3. Brain injury begins at aneurysm rupture and contributes to overall outcome.
4. Understanding mechanisms of early brain injury is essential for its prevention.
5. Clinically relevant animal models will help us achieve this objective.

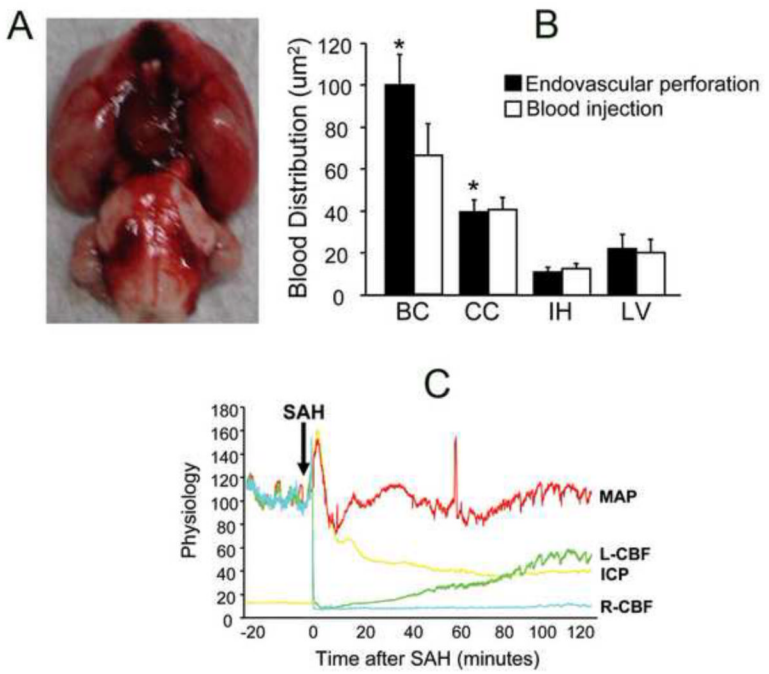

Figure 1. Experimental SAH

A shows an image of rat brain post SAH. Note thick blood clot around circle of Willis. B shows quantitative analysis of blood distribution across brain after SAH. Note most blood accumulates around base of the cortex (BC). CC: convexity cortex, IH: interhemispheric space (adapted from (Schwartz *et al.*, 2000a), LV: lateral ventricle. C represents a typical physiological recording of SAH. Note intracranial pressure (ICP) increases and cerebral blood flow (CBF) fall at SAH. Mean arterial blood pressure (MAP) fluctuates at SAH but returns to basal values soon after. L-CBF: left CBF, R-CBF: right CBF.

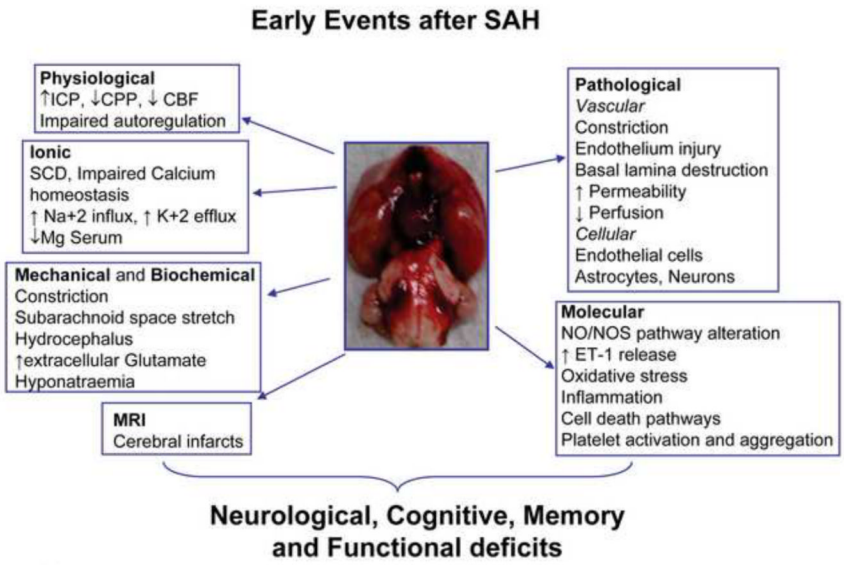

Figure 2. Early alterations after SAH

Events that occurs after SAH contribute to over all outcomes are listed.

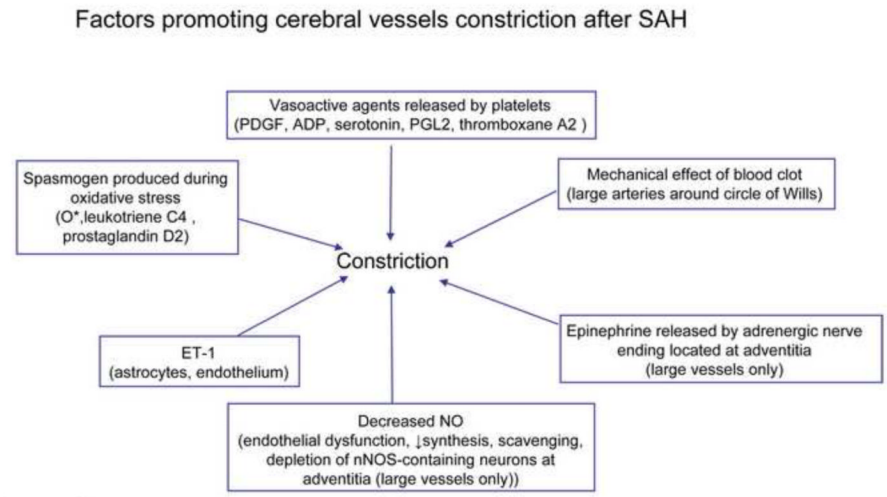

Figure 3. Factors promoting cerebral vessels constriction after SAH

Large and small cerebral vessels constrict after SAH. Major contributors of this constriction are listed.

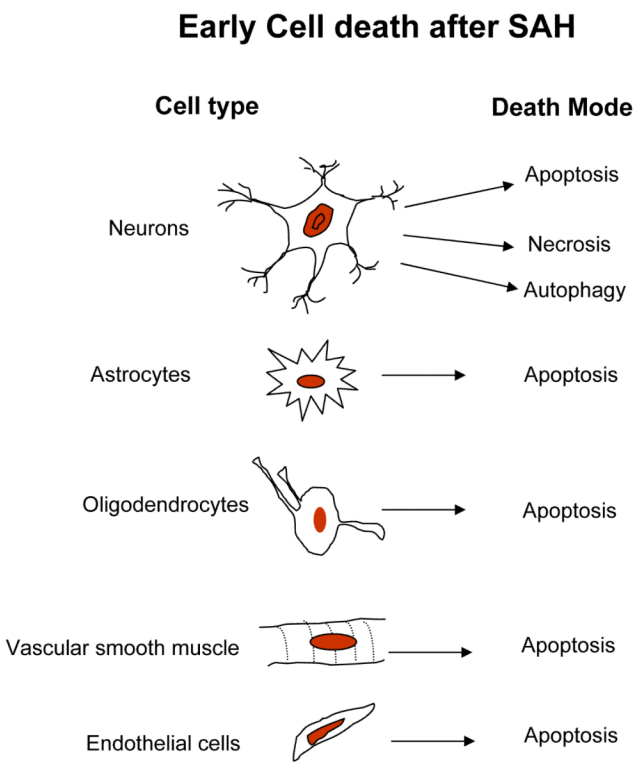

Figure 4. Early cell death after SAH

Lists the identity and the mode of death cells early after SAH.

Table 1

Failure of Clinical trials against SAH

We list some of the most significant clinical trail failures to date. Agents listed were beneficial against animal SAH were not found successful against human SAH.

A) Agents Studied Against Vasospasm			
***i.* Vasospasm Prevention**			
Agent	**Mechanism of action**	**Preclinical Success**	**Clinical success**
Clazosentan	ET-1 receptor antagonist	Prevents constriction and hypoperfusion (Schubert *et al.*, 2008; Vatter *et al.*, 2007; Vatter *et al.*, 2005)	Reduces the incidence vasospasm without improvement in overall outcome (Kramer and Fletcher, 2009; Macdonald *et al.*, 2011; Vergouwen, 2009)
Magnesium therapy	Recovers Serum Magnesium	Reverses constriction, reduces duration of ischemic depolarization and ischemic brain lesions (van den Bergh *et al.*, 2002)	Reduces the incidence of vasospasm, some improvement in overall outcome (Westermaier *et al.*, 2010; Wong *et al.*, 2010)
Tirilazda mesylate	Antioxidant	Protects vascular endothelium and blood- brain barrier (Hall and Travis, 1988; Smith *et al.*, 1997; Smith *et al.*, 1996)	Some gender specific (male) benefits (Haley *et al.*, 1995; Jang *et al.*, 2009; Kassell *et al.*, 1996; Lanzino and Kassell, 1999)
Statins	Inhibit HMG CoA reductase, Increase eNO synthesis	Reduces vasospasm and improves neurological functions in severe SAH (McGirt *et al.*, 2006; Sugawara *et al.*, 2008)	May reduce the incidence of vasospasm, some improvement in overall outcome (Kern *et al.*, 2009; Kramer *et al.*, 2008; McGirt *et al.*, 2009; Tseng *et al.*, 2007)
Erythropoietin	Erythropoietin receptor agonist	Reduces edema, inflammation, microcirculatory impairment and neuronal death (Grasso, 2001; Murphy *et al.*, 2008)	May reduce the incidence of vasospasm without improvement in overall outcome (Springborg *et al.*, 2007; Tseng *et al.*, 2010)
Fasudil hydrochloride	Rho-kinase inhibitor	Reduces endothelial injury, arterial constriction and neuronal damage, improves cognitive deficits (Huang *et al.*, 2008; Satoh *et al.*, 1999; Takanashi *et al.*, 2001)	Reduces the incidence vasospasm, some improvement in overall outcome (Suzuki *et al.*, 2008; Zhao *et al.*, 2006)
ii. **Vasospasm Reversal**			
Papaverine	Vasodilator	Dilates blood vessels depending upon on treatment time and vasospasm severity (Macdonald *et al.*, 1995)	Transient reduction in vasospasm, has serious side effects and little clinical benefits (Polin *et al.*, 1998; Vajkoczy *et al.*, 2001)
Fasudil hydrochloride	Rho-kinase inhibitor	Reduces endothelial injury, arterial constriction and neuronal damage, improves cognitive deficits (Huang *et al.*, 2008; Satoh *et al.*, 1999; Takanashi *et al.*, 2001)	Reduces the intensity of vasospasm, some improvement in overall outcome (Shibuya *et al.*, 1992; Tachibana *et al.*, 1999; Tanaka *et al.*, 2005).
Nimodipine	Calcium channel inhibitor	Improves blood supply and attenuates constriction (Bilginer *et al.*, 2009; Sun *et al.*, 2003)	May reduce the intensity of vasospasm, some improvement in overall outcome, is *only FDA approved drug for post SAH use* (Allen *et al.*, 1983; Bederson *et al.*, 2009)
Nicardipine	Calcium channel inhibitor	Reduces constriction (Debdi *et al.*, 1992)	Reduces the intensity of vasospasm without improvement in overall outcome (Haley *et al.*, 1993; Rinkel *et al.*, 2005)
B) Agents Studied Against Delayed Ischemic Neurological deficits (DINDs)			
3H-therapy* (hypervolemia, hypertension, hemodilution)	Improve CBF and brain tissue oxygenation	Little or no improvement in CBF and brain tissue oxygenation (Dueck *et al.*, 2001; Muench *et al.*, 2007)	Somewhat effective in reducing DINDs but has significant serious side effects, *is commonly used against DINDs and vasospasm* (Awad *et al.*, 1987; Lee *et al.*, 2006; Meyer *et al.*, 2011)

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***i.* Vasospasm Prevention**			
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Nimodipine	Calcium channel inhibitor	Improves blood supply and attenuates constriction (Bilginer *et al.*, 2009; Sun *et al.*, 2003)	Somewhat reduction in DINDs with little improvement in vasospasm , is *only FDA approved drug for post SAH use* (Allen *et al.*, 1983; Bederson *et al.*, 2009; Rinkel *et al.*, 2005)
Statins	HMG CoA reductase inhibitors, increase eNO synthesis	Reduces vasospasm and improves neurological functions in severe SAH (McGirt *et al.*, 2006; Sugawara *et al.*, 2008).	Some reduction in DINDs and in vasospasm (Sillberg *et al.*, 2008; Tseng *et al.*, 2005; Vergouwen *et al.*, 2010)

* triple H therapy is often limited to increase of blood pressure (1H) and sometimes modulation (2H) (Chittiboina *et al.*, 2011; Treggiari, 2011).