Endovascular Surgery of Cerebral Aneurysms

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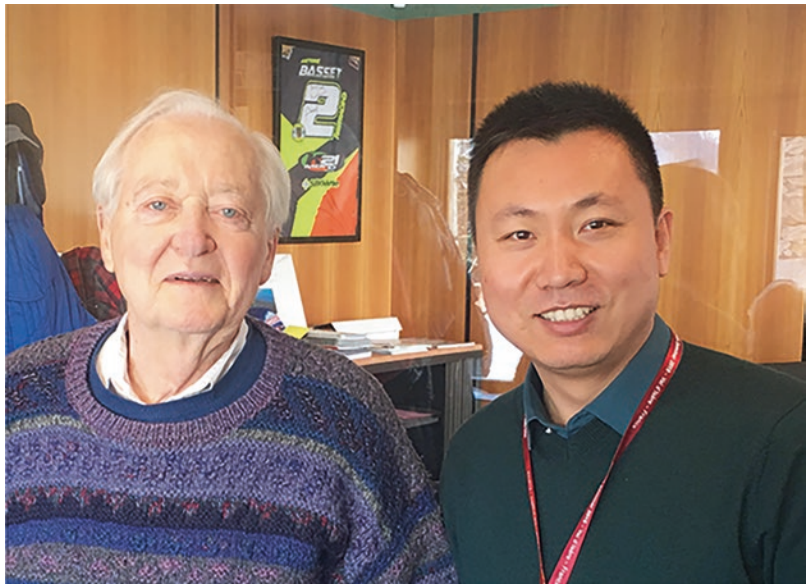
In memory of Academician Zhongcheng Wang.

Prof. Zhongcheng Wang (December 20, 1925, to September 30, 2012), Academician of Chinese Academy of Engineering

In memory of Prof. Luc Picard

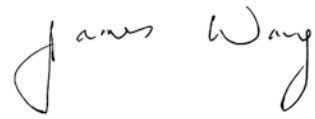


Professor Luc Picard (1937–2021), a pioneer of Interventional Neuroradiology, Professor of Neuroradiology of the Faculty of Medicine in Nancy, France

Foreword

Neurosurgeons have a long history of treating cerebral aneurysms. Understanding the vascular anatomy and physiology of the nervous system and management of patients with abnormalities of these vascular structures are vitally important aspects of neurosurgery resident training. Over the past few decades, the treatment of cerebral aneurysms has been evolving toward endovascular strategies for many patients. Interventional neuroradiologists play an important role in developing this area of therapy, but the number of neurosurgical trainees in neuroendovascular treatment is increasing. Other specialties, including neurology and vascular surgery, are now entering the field of neuroendovascular treatment, the neurosurgeons are better trained and provide safe treatment options. We have compiled and edited this book to report current neuroendovascular techniques and their impact on the treatment of cerebral aneurysms. Readers will benefit from the perspicacity among some of our most experienced practitioners on the treatment strategies for cerebral aneurysms. Even today, the number of neurosurgeons who had formal training in both endovascular and surgical treatment of cerebrospinal vascular diseases remains limited; the complexity of these difficult problems clearly calls for more neurosurgeons who can be efficient and knowledgeable

in both treatment modalities. This book will be very helpful for both practitioners and trainees alike pursuing the practice of excellence in neurovascular surgery.



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Preface

Endovascular neurosurgery provides effective and minimally invasive treatment of a broad spectrum of diseases. This area of expertise has continued to gain both wider application and greater depth as new and better techniques are developed and as landmark clinical studies are performed to guide their use. The treatment of cerebral aneurysms has evolved substantially, increasing the number of aneurysms that can be treated successfully with minimally invasive therapy. The book aims to report current neuroendovascular techniques and the efficacy and safety of procedures used for cerebral aneurysms and to summarize key aspects of best practice. Attendees, fellows, residents, medical students, or anyone interested in sharpening their diagnostic and therapeutic skill set will benefit from reading this text. Finally, I must thank all the authors who have contributed so much of their time, wisdom, and experience in creating the final product you hold in your hands. On behalf of everyone associated with this work, I sincerely hope you enjoy learning and implementing your new skills as much as I have enjoyed organizing the material.

Beijing, China
March 6, 2020

Xianli Lv

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Acknowledgment

Thanks Prof. Zhongxue Wu(left), my great teacher, who is a human being of immense qualities, a man of incredible energy, and an extraordinary individual whom we will always love and admire.

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About the Editor

Xianli Lv, M.D., is an associate professor of Endovascular Neurosurgery, Neurosurgery Department, at Beijing Tsinghua Changgung Hospital, School of Clinical Medicine, Tsinghua University, in Beijing (China). His research focuses on endovascular neurosurgery of intracranial aneurysm, cerebral AVM, intracranial dural arteriovenous fistula, spinal AVM, and pediatric cerebrospinal AVMs. He has authored 195 peer-reviewed scientific articles indexed in international databases. He is an editorial member of the journals: *Interventional Neuroradiology*, *Stroke and Vascular Neurology*, *Journal of Neuroradiology*, and *the Neuroradiology Journal*. He is also a deputy editor of *Neuroscience Informatics*. Dr. Lv is a member of the World Federation of Interventional Therapeutic Neuroradiology (WFITN).

Pathophysiology of Cerebral Aneurysms

1

Zaid Aljuboori, Samer S. Hoz, Zahraa Al-Sharshahi, and Mohammed A. Alrawi

Abstract

Understanding the pathophysiology of the formation and growth of cerebral aneurysms is crucial for early detection, risk assessment, and therapeutic monitoring of intracranial aneurysms. A multifactorial model can be applied to study the formation and growth of cerebral aneurysms. This model is mainly based on patient and aneurysm-specific characteristics. Potential patient-specific factors include smoking status, hypertension, inflammatory disease, bone mineral loss, and sex hormone exposure. Aneurysm-specific factors include aneurysm size, bifurcation site, multiplicity, presence of a daughter sac, higher dome-to-neck ratio, multi-lobularity, and adjacent arterial geometry. Other factors that can affect the development and growth of aneurysms include female sex, short stature, bone fragility, malnutrition, and the existence of genetic disorders, and a range of aortic pathologies, including bicuspid aortic valve, dilated aortic root, aortic aneurysm, and arterial dissection. The goal of this chapter is to summarize the existing evidence and potential prospects for cerebral aneurysm pathophysiological studies.

Keywords

Intracranial aneurysms · Pathophysiology
Formation · Growth · Risk factors

Abbreviations

ADPKD	Autosomal dominant polycystic kidney disease
CA	Cerebral aneurysms
IL-1β	Interleukin 1B
MMPs	Matrix metalloproteinases
SAH	Subarachnoid hemorrhage
SNPs	Single nucleotide polymorphisms
TNF	Tumor necrosis factor
UIA	Unruptured intracranial aneurysm

1.1 Introduction

Cerebral aneurysms (CAs) represent areas of focal dilatations of the vascular lumen caused by weakness of the vessel wall, most commonly located around the bifurcation sites of the circle of Willis. It is estimated that 5% of the population have cerebral aneurysms, with 20–30% of this cohort harboring multiple aneurysms [1].

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Furthermore, 20% of patients with unruptured CAs have a positive family history for a CA. Aneurysmal subarachnoid hemorrhage (SAH) accounts for approximately only 5% of all strokes, and the consequences are devastating due to high mortality and morbidity rates [2].

Unruptured cerebral aneurysms are primarily asymptomatic and are most commonly detected incidentally or by screening those at high risk. Cerebral aneurysms are mostly acquired lesions resulting from a defective vascular wall response to local hemodynamic stress forces. The structural deterioration of the arterial wall involves inflammation and tissue degeneration with degradation of the extracellular matrix and smooth muscle cell apoptosis [3]. Three-fourth of all cerebral aneurysms occur at one of three locations—the middle cerebral artery, the posterior and the anterior communicating arteries, at the bifurcation, the internal carotid artery junction and the anterior cerebral artery junction, respectively. Less than 5% of patients with unruptured intracranial aneurysms (UIAs) are children. There are substantial differences in the risk factors and mechanisms of UIAs formation between children and adults. In children, 50–70% of UIAs cases are due to infection, trauma, or dissections, only 20–30% have a cystic shape, and the majority have clinical symptoms [4].

CAs can be divided into "True" and "False" aneurysms. True aneurysms are abnormal focal dilatations of the vascular lumen due to areas of vessel wall weakness, while false or pseudoaneurysms represent sites of contained perivascular hematoma that do not possess the same histological layers of the parent vessel. False aneurysms are primarily caused by penetrating trauma but may also result from periadventitial infections, or rarely, an infiltrating malignancy.

Morphologically, CAs can be saccular or fusiform. Saccular ("berry") aneurysms are rounded outpouchings from the vessel wall, characterized by the presence of a neck and dome. Saccular aneurysms can be subdivided into seven categories based on their etiology: Developmental aneurysms develop secondary to congenital weakness in the arterial wall. Hemodynamically induced aneurysms are the result of high shear forces at the bifurcation sites, mostly presenting at the apex of the bifurcation where these forces are most pronounced. High-flow aneurysms develop in the vicinity of arteriovenous malformations, especially where its feeder vessels are located. Other subtypes include traumatic and oncotic aneurysms as well as those related to vasculitis, connective tissue disease, and medication side effects.

Fusiform (dolichoectatic) aneurysms have no identifiable neck and include atherosclerotic, mycotic (infectious), and dissecting aneurysms. Atherosclerotic aneurysms form when an unusual form of atherosclerosis damages the media leading to arterial stretching and elongation that could extend over a considerable length, leading to a serpentine, giant, and bizarre aneurysm shape. Such aneurysms tend to predominate in the older age group, affect proximal arteries (the vertebrobasilar system is commonly affected), have perforating branches over the entirety of its length, harbor intraluminal clots leading to ischemic symptoms, and present with mass effect (bleeding is rare). Mycotic (infectious) aneurysm is the term used when an infectious process destroys the vessel wall. Examples of such infection sources include septic emboli secondary to intravenous drug use of infective endocarditis, and meningitis. Dissecting aneurysms result when an intramural hematoma extends into the subadventitial plane and are most commonly located at the extracranial segments of the internal carotid and the vertebral arteries.

1.2 Structure of the Cerebral Arteries

The cerebral arteries are similar to other systemic arteries in that their wall is composed of the tunica intima, tunica media, and the adventitia. The internal elastic lamina partitions the tunica intima and tunica media. The internal elastic lamina partitions the tunica intima and tunica media, while the external elastic lamina marks out the adventitia from the tunica media.

Cerebral arteries can be further classified as "muscular" or "elastic" with respect to the com-

position of their tunica media. For example, the common carotid artery is an elastic artery, while the internal carotid and intracranial arteries are muscular. The intra- and extradural segments of the intracranial arteries vary in their histopathology; the adventitia is thinner in the intradural portion than in the extradural portion, and the collagen part of adventitia plays an important role in decreasing the risk of rupture in the event of a sudden blood pressure change [5]. The intradural segments also lack the external elastic lamina, which could explain the higher propensity of these vessels to develop aneurysms with higher risk of rupture.

Location is an important risk factor for aneurysm formation. For example, vasculature remodeling capability is higher in the posterior as opposed to the anterior circulation. Also, arterial bifurcation sites are preferred locations for aneurysm formation, given the higher level of hemodynamic stress created by the blood flow-associated deflection and oscillation forces. Aneurysmal changes usually involve multiple vessels with a shared embryonic origin, a phenomenon attributed to neural crest malposition and/or malfunction. Epidemiological observations revealed that patients with thoracic aortic aneurysms have a ninefold increased risk of cerebral aneurysms, as compared to the general population [6].

Recently, it has been found that ascending aortic aneurysms occur more frequently in association with anterior and middle cerebral artery aneurysms, while abdominal aortic aneurysms tend to co-occur with internal carotid artery aneurysms. Anecdotal studies have shown that cerebral aneurysms can be considered as a typical pathological phenomenon of neurocristopathy, such as congenital heart disease, bicuspid aortic valve, type 1 neurofibromatosis, and fibromuscular dysplasia. In line with this concept, patients with multiple, larger, and ruptured aneurysms tend to have a dilated aortic root. Clinically, multiple defects of the extracellular matrix have been detected in patients with connective tissue diseases linked to aneurysms, including osteogenesis imperfecta, vascular Ehlers-Danlos syndrome, and Marfan's syndrome [7–9].

Clinically, several abnormalities of the extracellular matrix have been detected in patients with connective tissue disorders such as osteogenesis imperfecta, vascular Ehlers-Danlos syndrome, and Marfan syndrome, which are generally associated with cerebral aneurysms [7–9].

1.3 Formation of Intracranial Aneurysms

Aneurysm formation is a gradual process that entails the combination of hemodynamic, vascular genetic, molecular, and hormonal variables [10].

1.3.1 Hemodynamic Factors and Associated Structural Changes

The walls of cerebral arteries have a sparse tunica adventitia and a lower proportion of elastic fibers. Moreover, cerebral arteries are immersed in the cerebrospinal fluid of the subarachnoid space rather than in connective tissue. These structural factors are thought to make cerebral arteries susceptible to aneurysm formation [10].

In the wall of a healthy cerebral artery, the internal lamina maintains the elasticity and structural integrity of the vessel wall at the bifurcation sites. Degeneration or disruption of the internal elastic lamina at a bifurcation is a key event in the formation of an intracranial aneurysm. The definite cause of the degeneration and why it only occurs in certain individuals, however, remains unclear. Anatomical variations such as bifurcations comprising hypoplastic branching arteries or bifurcations with particularly sharp angles are considered to be a crucial factor in intracranial aneurysm formation [11].

Common sites for aneurysm formation include the anterior and posterior communicating arteries, middle cerebral artery, and basilar artery bifurcation sites, where local shear stress forces on the vessel wall are most pronounced. Blood flow at the arterial junctions, bifurcation sites with wide

angles, or locations with abrupt changes in vascular angulation create an environment of turbulent blood flow with higher levels of shear stress. This wall induces a cascade of changes, including endothelial cell damage, smooth muscle degeneration, and media layer thinning. Smoking, on the other hand, is linked with both higher prevalence of cerebral aneurysms and higher risk of rupture. The mechanisms by which smoking can cause cerebral aneurysm formation and rupture are suggested to be elevated wall shear stress due to increased blood volume and viscosity and nicotine-induced vasoconstriction [12].

1.3.2 Genetic Factors

Although evidence suggests that individuals with a family history of intracranial aneurysms or SAH are at increased risk of an intracranial aneurysm formation, no specific genes have yet been identified. One meta-analysis which included (32,887) sporadic aneurysms and (83,683) controls has identified three single nucleotide polymorphisms (SNPs) that were associated with the presence of sporadic intracranial aneurysms. The SNPs were located on chromosome 9 within the CDKN2B-AS1 gene, on chromosome 8 near the SOX17 transcription regulator gene, and on chromosome 4 near the endothelin receptor gene [13].

The strongest confirmation for the linkage was with a locus on 7q11 near the gene that encodes elastin, which is a protein that is involved in the preservation of integrity of the vessel wall [4]. Some heritable connective tissue diseases are also associated with an increased risk of cerebral aneurysms and SAH. Autosomal dominant polycystic kidney disease (ADPKD) is the most common genetic disorders associated with SAH. Ehlers-Danlos type IV (caused by mutation of collagen type III), fibromuscular dysplasia, and possibly Marfan syndrome (mutation of fibrillin-1 gene) are other inherited disorders associated with the CAs and SAH [14].

1.3.3 Molecular Changes

In addition to the disruption of the internal elastic lamina and the resulting mechanical overload and tensile force shift, the vascular smooth muscle cells, and fibroblasts synthesize type I and V collagens, which are the main molecular constituents of intracranial aneurysms. As the molecular mechanisms fail to compensate for the mechanical overload of the vessel wall and the myointimal injury, the cellular and humoral inflammatory responses serve as the key drivers of aneurysm development. These responses, which are mediated by inflammatory cytokines such as tumor necrosis factor (TNF), IL-1β and matrix metalloproteinases (MMPs), facilitate the flow of macrophages and continuous degradation of collagen and elastin fibers [15].

1.3.4 Hormonal Changes Related to Aneurysm Formation and Rupture

There is evidence to support the difference in incidence and rate of cerebral aneurysm formation and rupture between men and women, and between pre- and postmenopausal women, indicating that aneurysm formation may be affected by hormonal changes. Estrogen and its interactions with estrogen receptors have been shown to be associated with regulation of arterial cell wall matrix, mediation of inflammation, and regulation of proteolytic and apoptotic pathways. Estrogen's effect on the regulation of the cerebrovascular system and its association with various vascular diseases, including stroke, trauma, and dementia, has been demonstrated and thought to be related to the reduction of inflammation and preservation of vessel wall integrity. Early menopause is associated with the development of cerebral aneurysms, whereas the use of hormone replacement therapy is protective against the formation of aneurysms [16].

1.4 Risk Factors Associated with Formation and Rupture of Cerebral Aneurysms

1.4.1 Conventional Risk Factors

Many risk factors have been linked to the formation of aneurysms, including cigarette smoking, heavy alcohol consumption, cocaine usage, familial history, ethnicity, gender, age, and most importantly, hypertension. From the above risk factors, some are thought to cause aneurysm formation via mechanisms that increase blood pressure and hemodynamic stresses. For example, heavy alcohol consumption has been shown to be an independent risk factor for spontaneous aneurysmal SAH, potentially through its effects on blood pressure and hemodynamic factors. Cocaine and its metabolites increase the risk and severity of aneurysms and SAH through its vasoconstrictor properties, which act via nervous stimulation of the vascular smooth muscle, causing profound hypertension.

As far as race is concerned, the risk of aneurysm tends to be comparable in whites, blacks, and Hispanics. It is well known that women are at higher risk of aneurysm formation, but the female preponderance is apparent only in the perimenopausal and postmenopausal periods. Finally, regular physical exercise may decrease the risk of aneurysm formation [14, 17].

Currently, screening for cerebral aneurysms is recommended for patients with a positive family history. Experts suggest screening of all individuals with two affected first-degree relatives due to the high incidence of CAs in this population. It may also be advisable to screen patients who have one affected first-degree relative if they have other risk factors for developing CAs such as female sex, older age, heavy smoking, hypertension, having an affected sibling, or having an affected relative with multiple aneurysms manifesting at an early age [14, 18].

1.4.2 Innate Risk Factors

Genetic disorders with a number of phenotypes have been identified with cerebral aneurysms. ADPKD is associated with defects in one of two genes; PKD1 and PKD2. Approximately, 20–40% of ADPKD cases have cerebral aneurysms, and 10–30% have multiple aneurysms. The prevalence of cerebral aneurysms in fibromuscular dysplasia is estimated to be 13 percent, which is around six times higher than that of the general population.

Cerebral aneurysms are also common in patients with aortic coarctation and bicuspid aortic valve. Cardiac outflow tracts and cerebral arteries share the origin of neural crest cells and pathological changes. Hence, the combination of these congenital heart diseases and the development of cerebral aneurysms are called neurocristopathic phenotypes. It has also been found that dilated aortic roots with no apparent heart disease are associated with nonconventional aneurysm features, such as multiple lesions, larger sizes, or early rupture [19].

1.4.3 Acquired Risk Factors

Acquired inflammatory conditions such as trauma, atherosclerosis, and infection can damage the arterial wall, leading to the formation of CAs. The development of CAs at relatively older ages is connected to age-related risk factors as well as the accumulation of atherosclerosis during the aging process.

There are other acquired risk factors to be recognized as aneurysm-inducing factors. Smoking induces the inflammatory response in the cerebral vessel and weakens the wall. Sex hormones may contribute to the acquired arterial wall weakness. Women are more susceptible to having a CA and occurrences of multiple aneurysms, as they experience a variety of reproductive and hormonal phases in menarche, menopause, oophorectomy, and hormone replacement ther-

apy over their life. As a consequence, a shift in the degree of exposure to estrogen can cause women to have different vulnerabilities to cerebral aneurysms. Gender-related differences may also support the link between sex hormones and extracellular matrix degeneration. Osteoporosis shows a female predominance, and bone mineral density reflects a cumulative estrogen exposure. Recent studies have shown that reduced bone mineral density is associated with cerebral aneurysms, large aneurysms, and multiple aneurysms [20, 21].

1.5 Common Risk Factors for Cerebral Aneurysm Rupture

Risk factors for CA rupture include both aneurysmal and patient factors. Aneurysmal factors include size, location (specifically in the posterior circulation and aneurysms arising from the posterior and anterior communicating arteries), and morphology (aneurysms with a daughter sac have higher rates of rupture). Patient factors include aging, female gender, current smoking, alcohol consumption, hypertension, history of SAH, and positive family history. Aneurysms larger than 10 mm have a 1% risk of rupture per year. Aneurysms of the anterior communicating artery rupture more easily in smaller sizes than those in other locations. Although larger aneurysms usually have a higher risk of rupture, ruptured aneurysms are generally small. If the size surges or morphological changes take place within a brief time period, the probability of rupture increases.

Multiple aneurysms are predominately found in the pediatric age group and younger adults and they pose a higher risk of recurrence. Morphological changes suggestive of an increased risk of rupture include the presence of a daughter sac, a high dome-to-neck ratio, and multilobular appearance. Recently, the PHASES study found that geographical location, e.g., Finnish or Japanese origin, was also a strong risk factor for aneurysmal rupture, possibly supporting a genetic influence on rupture risk [22, 23].

Cigarette smoking has been reliably documented as an important risk factor for SAH. Even those undergoing embolization, cigarette smoking is a risk factor for aneurysm recurrence, and patients should also be advised to quit smoking [24].

High blood pressure has been shown to predispose to SAH in prospective cohort studies. Blood pressure management is therefore yet another simple intervention to minimize the risk of aneurysm rupture [25].

While heavy alcohol consumption has been shown to increase the risk of SAH, it does not predispose to aneurysm development. The increased risk of SAH with alcohol use is possibly due to a fleeting rise in blood pressure [14]. Some factors have been identified as immediate triggers for aneurysm rupture, including coffee and Cola consumption, anger, startling, straining for defecation, sexual intercourse, nose blowing, and vigorous physical exercise [26].

Generally, aneurysms ≥7 mm in diameter should be treated as a result of their tendency to rupture, except in older patients and those with severe medical comorbidities and short life expectancy. Factors that permit strong consideration for treatment regardless of the aneurysm's size include young age, change in the size or configuration of the aneurysm, and the presence of many, daughter sac, or symptomatic aneurysms. Factors that can give priority to intervention over observation are active smoking, hypertension, posterior circulation aneurysm, anterior/posterior-anterior communicating artery aneurysms, previous SAH, history of familial SAH, and high aspect ratio [27].

A multitude of CA geometric indices have been studied as potential determinants of the probability of rupture. The aspect ratio is identified as cerebral aneurysm height divided by the diameter of the neck, it is the most studied and perhaps the most useful shape parameter. Studies have shown that 80% of ruptured aneurysms have an aspect ratio of >1.6, while 90% of unruptured aneurysms have an aspect ratio of <1.6. Another simple and useful geometric index, particularly suitable for small aneurysms, is the aneurysm-to-vessel size ratio, more commonly referred to as

the size ratio. In clinical practice, this means that a 3-mm aneurysm arising from the anterior communication artery has a higher risk of rupture than a 3-mm aneurysm of the paraclinoid internal carotid artery [27]. The growth of a CA is a strong risk factor for future rupture. As such, several experts recommend treating any aneurysm that has increased in size during the follow-up period. The annual risk of rupture was found to be 2.4% in aneurysms with growth compared with just 0.2% in those without growth (i.e., 12-fold increase in risk of rupture) [28].

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2 Aneurysmal SAH Induced Vasospasm: Pathogenesis and Management

Ashis Pathak

Abstract

Introduction: Vasospasm remains a major cause of poor outcome after subarachnoid hemorrhage (SAH) following rupture of intracranial aneurysms. The pathogenesis still remains misty due to its complexity even though a lot of progress has been made in understanding various causative mechanisms through intense clinical and experimental research.

Method: Study carried out by a review of English literature on topics related to pathogenesis and management of post SAH induced vasospasm.

Result: Evidence-based information available points toward multifactorial biochemical phenomena instigated by Ferrous Hemoglobin which revolve around:

(a) Concept of early brain injury and evidence of cortical spreading depression
(b) Effect of ischemia in pre-vasospasm period and blood–brain barrier disruption.
(c) Role of Nitric oxide (NO), Endothelin-1 levels, and oxidative stress on smooth muscle cells.
(d) Changes induced by free radical production, lipid peroxidation, and alteration of ionic channels.
(e) Differential upregulation of genes.

Conclusion: To date the understanding of pathophysiology of delayed vasospasm has made significant stride for which the role of research using animal models cannot be overemphasized. The treatment of this complex condition still remains vague.

Keywords

Delayed vasospasm · SAH · Aneurysm
Cerebral ischemia

2.1 Introduction

Vasospasm remains a major cause of poor outcome after subarachnoid hemorrhage (SAH) following rupture of intracranial aneurysms. The pathogenesis still remains misty due to its complexity even though a lot of progress has been made in understanding various underlying mechanisms through intense clinical and experimental research. Though statistically 3.4% of population harbor incidental aneurysm [1] yet, depending on the risk factors, their rate of rupture varies from 0% to 100% with an annual rupture rate of 0–6.5% [2]. The risk factors vary from size of aneurysm, age of patient, history of smoking, and

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hypertension to pathophysiology of aneurysm formation. In familial aneurysms, however, the risk of rupture is threefolds the normal [3]. Despite lot of progress in understanding of the molecular changes culminating into delayed vasospasm, the exact interplay of various pathophysiological substrates remains an enigma. Interestingly, aneurysmal SAH was recognized since the time of Hippocrates and the outcome remains quite grim even to date [4].

2.2 Delayed Cerebral Vasospasm

Though management of aneurysmal SAH remains a major neurocritical care issue delayed cerebral vasospasm, which occurs usually between 3 and 14 days of SAH, remains the most elusive challenge [5]. Based on the belief that vasospasm is the main culprit for deterioration in SAH patients several trials antagonizing the suspected precursors of vasospasm were conducted, however, they failed to achieve a good functional outcome [6, 7]. Hence the role of vasospasm as the sole prognostic factor in clinical outcome after SAH remains questionable. On the contrary, it now seems evident that the pathological events starting at the very onset of SAH, which culminates into various biochemical changes, need to be understood better. Vasospasm and DCI may be the extreme manifestation of the same pathophysiological process rather than isolated phenomena. This has led to the concept of "Early Brain Injury."

Most of the management regimes for treatment of vasospasm has been directed toward the end result of pathophysiological phenomenon rather than treating the causative mechanism. Based on it, till now, the main treatment modalities include partial Triple H therapy (Hypervolemia, Hemodilution, and Hypertension), calcium channel antagonists, chemical or mechanical vasodilation. As a result, it still remains to be proven whether any of these treatment modalities have an evidence-based prognostic benefit in a patient with refractory vasospasm [8]. The diversity of opinion is reflected on the deliberations in 15 international conferences dedicated to vasospasm and SAH till the year 2019.

The process of vasospasm is far from the mere feature of spasm of blood vessels [9] and its ischemic consequences [10]. Clinical observation and experimental evidence point to the evolution of vasospasm as a complex multifactorial phenomenon that may remain subclinical or may progress to clinically manifested vasospasm with its devastating consequences [11–15]. There are various other pathophysiological mechanisms implicated in the clinical manifestations after SAH apart from vasospasm namely microcirculatory dysfunction, ionic disbalance, cortical spreading depolarization, micro-thrombosis, and inflammation at neuronal cell level [16].

2.3 The Pathophysiological Changes After SAH

2.3.1 Understanding Early Brain Injury

The event of SAH initiates a process of transient global ischemia which has a consequential bearing on the further pathophysiological events that follow. These may be in the form of brief microcirculatory arrest, blood–brain barrier disruption, microvascular constriction, brain edema [17]. The impact of these phenomena weighs heavily on the further events which progress in complex chain manifesting in the form of cerebral inflammation, dysregulation of blood flow, cortical spreading depolarization, microthrombi formation, and apoptosis [18]. These changes may be self-limiting with minimal or no clinical consequence or may progress into severe form leading to clinical deterioration with poor prognosis or fatal outcome.

2.4 What Leads to Vaso Constriction?

To date, a wide-ranging biochemical and molecular mechanisms have been implicated in vasospasm. These processes include mopping up of

nitric oxide (NO), high levels of endothelin 1 (ET-1) activity [19], alteration of ionic channels [20], lipid peroxidation, and free radical production [21]. These contribute to smooth muscle changes through oxidative stress [15] and apoptosis of endothelial cells [22]. There is now clear identification of upregulation of genes, which can point to individual susceptibility [23, 24]. Needless to say, the root cause of all these phenomena is triggered off by the release of ferrous components from the disintegrated hemoglobin released by the ruptured aneurysm in the subarachnoid space.

The role of oxidative stress [25]seems to have taken a center stage through its mechanism of direct activation of calcium channels and also through production of vasoactive molecules. The action of reactive oxygen species leads to vasoconstriction by its action on arachidonic acid which in turn leads to release of vasoactive lipids. Though the role of bilirubin oxidative products, formed as a result of hemoglobin break down, has been also considered but its role is not convincing [26] (Fig. 2.1).

2.4.1 Endothelin 1 (The Physiological Vasoconstrictor)

There are several substrates that contribute to the progression of vasospasm. ET-1 is a potent vasoconstrictor released in vascular wall whose levels are detected to be high in CSF following SAH. The exact levels, which can induce vasoconstriction, are still not determined because experimental studies need much higher levels than what is normally witnessed clinically after SAH. This raises the question of whether ET-1 needs potentiation by other factors [27, 28]. There is also evidence of enhanced ET-1 receptor expression and function in experimental animals suggesting its activation after SAH [29]. The role of Ca^{+} in the smooth muscle contraction is evident in acute phase of SAH as influx of Ca^{+} in the cells leads to phosphorylation of myosin light chain by stimulation of myosin light chain kinase [30]. The sustained contraction of the smooth muscles is regulated by the postulated mechanism of RhoA kinase activity which is stimulated by ET-1. Rho kinase is formed by ET-1 activation of Rho A. This initiates a cascade of chemical changes whereby Rho kinase inhibits myosin phosphatase subunit (MYPT1) of myosin light chain phosphatase (MLCP) augmenting phosphorylation of myosin light chain (MLC) [31]. Thus, once triggered the prolonged contraction of vascular smooth muscle is sustained by the enhanced phosphorylated MLC independent of intracellular Ca^{+} levels [32]. Further studies endorsed these postulates whereby the expression of Rho-associated protein kinase (ROCK), MYPT1 subunits, Protein kinase C (PKC), and upregulation of ET-1 receptor are demonstrated after SAH [33].

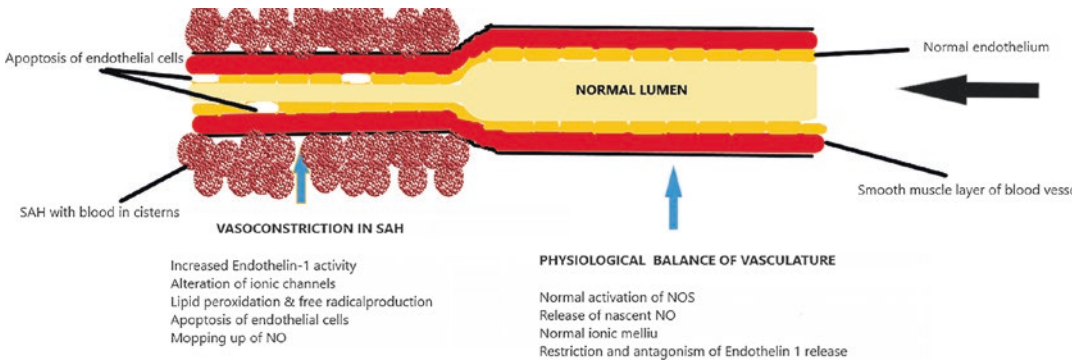

Fig. 2.1 Factors contributing to vasospasm

2.4.2 Nitric Oxide (The Physiological Vasodilator)

Endothelial nitric oxide is a potent physiological vasodilator that maintains a balancing act with ET-1 to maintain a steady patency of vessel lumen. It is produced by activation of endothelial nitric oxide synthase (eNOS). It produces cyclical guanine monophosphate (cGMP) through its stimulation effect of guanyl cyclase. The end result, which is vascular smooth muscle relaxation, is achieved by dephosphorylation of MLC through activation of cGMP-dependent protein kinases [34]. Following SAH the nascent NO liberated by the endothelium is mopped by hemoglobin to which it has a very strong affinity leading to reduction of local NO concentration tilting the balance for other substrates to induce vasospasm in an unchallenged situation. Furthermore, various molecular cascades of events lead to endothelial cell apoptosis reducing the NO secreting cell population [35]. There is also activation of protein kinase C after SAH which has an inhibitory regulation on NOS resulting in lower levels of NO [36]. Hence, it is derived that in normal situation a steady balance between NO and Endothelin-1 plays a vital role in maintaining the lumen of cerebral blood vessels.

2.4.3 Inflammatory Changes Leading to Apoptosis

Investigations of cerebral arteries of patients who died after SAH and vasospasm revealed apoptotic changes of vascular endothelial cells [36]. The endothelial loss further reduces NO production exposing the bare vascular smooth muscles to spasmogenic substances like ET-1 to act directly. This apoptotic change is in response to a molecular cascade of events which is demonstrated in experimental studies and takes place through inflammatory mediators, e.g., tumor necrosis factor alfa and interleukin-1beta [37] and activated caspase-3 [35, 38].

In addition, release of inflammatory substances as a reaction to blood in the subarachnoid space potentiates spasmogenic effect and brain ischemia. Potent among them are thromboxane A2, serotonin released from platelets [39, 40], and ET-1 released from leucocytes [41]. Elevated ICAM-1 (intracellular adhesion molecule 1), TNF alfa, CD18 suggests interplay of various inflammatory mediators in response to SAH [42–44]. Studies suggest that there is c-Jun N-terminal kinase (JNK) pathway activation after SAH which is one of the signalling cassettes of mitogen-activated protein kinase (MAPK) pathways [45]. JNK is known to play an important role in cytokine production, inflammatory changes, and also apoptosis.

2.4.4 The Ischemic Insult

The very critical event after SAH is a sudden rise in the ICP which is dependent on the amount and duration of blood released in the subarachnoid space. Decreased perfusion of the brain contributes to global ischemia which has a serious consequence if it does not reverse early. An immediate impact on the cerebral blood flow is reflected in reduction of brain parenchymal oxygen pressure [46]. Though many patients may not survive the immediate impact of raised ICP, severe ischemic secondary insult in the surviving patients leads to blood–brain barrier (BBB) disruption [47] contributing to further brain damage, progressive cerebral edema [48] and delayed apoptosis of cerebral and vascular cells [22]. Any ischemia in the brain lasting for more than a few minutes will trigger a cascading chain reaction at the molecular level due to release of various biochemical substrates, which propagates BBB disruption. One of the inducible factors is HIF-1 which, when excessively activated, overexpresses its target gene VEGF (vascular endothelial growth factor) which increases BBB permeability. It also overexpresses BNIP3 and Nip3-like proteins, which are known mediators of apoptosis [49, 50]. Experimental studies using HIF-alpha inhibitors show attenuated expression of HIF-alpha with a reduction in vasospasm [51]. In addition to apoptosis triggered by activated HIF-1alpha and BNIP3 [50], elevated levels of pro-apoptotic p53

proteins in vasospastic cerebral arteries seem to play a role in the phenomenon of induction of vasospasm [52–54].

2.4.5 Free Oxygen Radicals

Autoxidation of hemoglobin leads to liberation of reactive oxygen species (ROS), which play a role in arterial narrowing. The use of antioxidants demonstrated reversal of its effect on experimental vasospasm [55, 56]. The effect of ROX on bilirubin leads to oxidation products of bilirubin which has an inhibiting effect on endothelial nitric oxide synthase (NOS) leading to dampening of physiological vasodilation because of reduced production of NO [57]. The role of ROS in vasoconstriction is also postulated because of its stimulation effect on production of vasoconstrictor metabolites of arachidonic acid which have shown to decrease cerebral blood flow by blocking calcium-activated potassium channels in experimental animals [58]. The superoxide radicals (SOR) produced after SAH from NADPH oxidase have an indirect vasoconstrictive effect as these SOR combine with NO to produce peroxynitrite which in turn inhibits eNOS [59]. This mechanism is corroborated by reversal of vasospasm using NADPH inhibitors experimentally [60].

2.4.6 Is Vasospasm All About Cerebral Vasculature?

Until recent past, cerebral vasospasm was related to constriction changes in cerebral vasculature as a result of reactive changes secondary to effect of blood and its products released in the subarachnoid space after SAH. However, the mechanism seems to be related to the phenomenon of spreading depression set off by glial cell dysfunction (Cortical Spreading Depolarization) which is heavily dependent upon the changes secondary to pathophysiology of SAH [61–64]. Following the event of SAH there is a marked change in the milieu of ions in the neuroglial cells resulting in a significant increase of extracellular potassium with simultaneous decrease of extracellular sodium, chloride, and calcium ions due to their influx in the cell along with water. This results in a state of EEG silence [65–67].

Normally increase in functional activity of brain is directly proportional to increase blood flow and oxygen uptake, which enhances metabolism and glucose uptake [68, 69]. This coupling of flow and metabolism is regulated by interaction between astrocytes, neurons, and endothelial cells, which is mediated by electrical and chemical changes in milieu contributed by agents like nitric oxide (NO), carbon dioxide, endothelin 1, alteration of ionic channels**,** adenosine**,** lipid peroxidation, and free radical production. The role of astrocytes in maintaining the local extracellular potassium concentration is important as they are described as perfect potassium electrodes [70], acting as a spatial buffer in local change of potassium [71].

Extracellular acidosis and hypercapnia have a linear correlation with cerebral vasodilation with maximum dilation achievable up to pH 7. This acidosis-induced dilation due to high extraluminal H^+ concentration is mediated through activated K_{ATP} & $K_{Ca'}$. Even though there is contribution of NO in moderate increase in extraluminal proton concentration however its role becomes ineffective at a lower pH of 7 [72–75]. The aggravation of cerebral ischemia is augmented by periodic waves of Cortical Spreading Depolarization (CSD), which develop as a complex biochemical change secondary to oxyhemoglobin, ET-1, and K^+ ions [76]. The major trigger for CSD is changed in ionic milieu which happens due to inactivation of Na^+/K^+-ATPase activity at synaptic membrane level after SAH [77]. CSD thus contributes to spasm in distal small vessels and cellular necrosis (Fig. 2.2).

2.5 Diagnosis of Vasospasm

The diagnosis of vasospasm is best performed with a modality that can demonstrate the cerebral blood vessels and their caliber. Hence, CT angiogram (CTA), MR angiogram (MRA), or Digital Subtraction Angiography (DSA) are the options

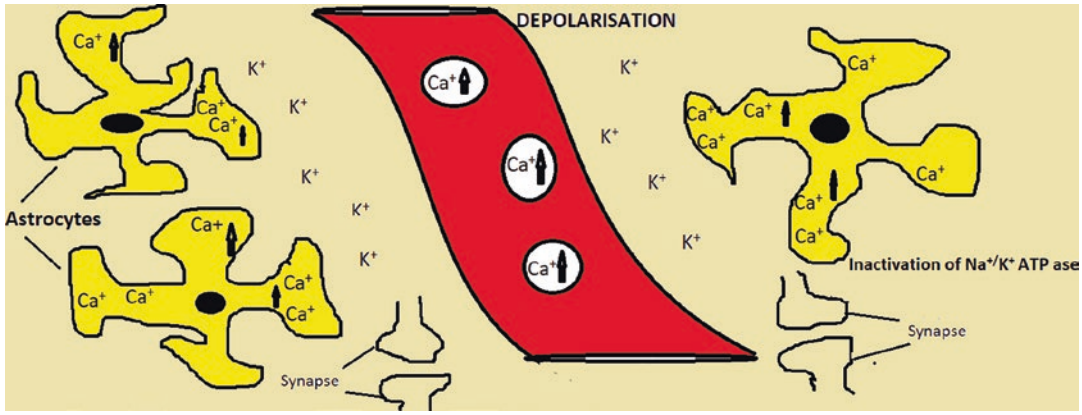

Fig. 2.2 Cortical Spreading depolarization

to study the vascular territory involved in vasospasm. However, all these modalities are appropriate to diagnose spasm in large and medium-size intracranial vessels but their utility in diagnosis of small vessels vasospasm is very limited. Though the diagnostic ability of these modalities is good for moderate-to-severe vasospasm but the logistic feasibility of repeating these studies precludes them for use in daily monitoring of status of vasospasm. DSA provides a more detailed picture of the status of vessels and the cross circulation but the intraluminal maneuvering of catheters and use of contrast medium can aggravate vasospasm in a spastic vessel [78]. CT perfusion studies are a useful substitute and can be helpful in diagnosing the imminent ischemia as well as the status of perfusion but the exact degree and distribution of spasm in the vasculature would not be apparent through this investigation.

Transcranial Doppler Ultrasound (TCD) is now being extensively used as a handy modality to assess the degree and extent of vasospasm. It has the logistic advantage of being noninvasive, easy to repeat, available at the bedside, and user friendly. The assessment through TCD is not only operator dependent but it has bearing on the anatomy of cerebral vasculature, exact site of vasospasm, the thickness of temporal bony window, viscosity of blood, ICP status, fluctuation of CO_2, and systemic blood pressure levels. Though it does not fulfil all the needed criteria for a detailed diagnosis, it gives a fair reading of velocity of blood flow in all the major vessels, thus alerts the observer on the magnitude of impending or existing vasospasm. TCD diagnosis of vasospasm in the MCA has a sensitivity of 39–94% and specificity of 85–100% [79]. There are different windows of access to mainly three intracranial vessels namely, the most commonly used middle cerebral artery (MCA) and anterior cerebral artery (ACA) both through the thin temporal squama, the basilar artery (BI) through the foramen magnum, and the transorbital window for the anterior cerebral vessels. TCD monitoring should ideally be done on a daily basis and the mean velocity of MCA would normally be between 80 and 100 cm/s. The respective values for mild, moderate, and severe vasospasm of MCA are 100–120, 120–200, and >200 cm/s, respectively [80].

The Lindegaard ratio of flow velocity between MCA and extracranial Internal Carotid Artery (ICA), which has got an almost 90% accuracy of detecting angiographic vasospasm, is a useful method for diagnosis of vasospasm whereby vasospasm is established if the ratio of MCA/ICA is more than 3 and a value of 6 or more indicates very severe vasospasm [81, 82]. A similar ratio of flow between BA and extracranial vertebral artery (EVA) has been advocated to establish vasospasm of BA [83].

2.6 Management Options for Vasospasm

2.6.1 Trials on Targeted Substrates

2.6.1.1 Lipid Peroxidation Inhibitors

Since lipid peroxidation induced by free radicals has a potent role in inducing vasospasm hence its inhibition by a nonglucocorticoid 21-aminosteroid (Tirilazad mesylate) was tried by virtue of its radical scavenging action and membrane stabilizing properties. Tirilazad mesylate underwent a global multi-centric randomized, double-blind trial with an aim to look for improvement in vasospasm and outcome at 3 months follow up. Though there was a significant reduction of vasospasm using 6 mg/kg/day, the benefits failed to reach a statistical significance even though it showed better efficacy in males in contrast to female patients [84].

2.6.2 Role of Endothelin-1 Antagonist

Endothelin-1 an endogenous potent vasoconstrictor which maintains a balancing act with nascent NO, is a potent vasodilator, released by the endothelium of cerebral arteries. CSF studies after SAH demonstrate an increase in ET-1 levels. There are two types of Endothelin-1 receptors, Endothelin A (ETA) receptor and Endothelin B (ETB) receptor [85]. ETA is directly responsible for smooth muscle contraction and hence a random placebo-controlled trial (CONSCIOUS 1) with Endothelin 1A antagonist (Clazosentan) was carried out to look for relief from ischemia and infarction of the brain [6]. Though the trial demonstrated significant benefit in terms of angiographic vasospasm, it did not show any impact on DCI [7]. Subsequently, CONSCIOUS-2 and CONSCIOUS-3, Phase III trials were conducted, respectively, for clipped and coiled patients with no significant advantage on either mortality, morbidity, or long-term functional outcome [86].

2.6.3 Is There Any Role of Statins?

Due to the unique combination of anti-inflammatory properties, dampening effect on reactive oxygen production, upregulating effect on NO synthase, and reduction of excitotoxicity the statins were also tried to look for amelioration of vasospasm and DCI. Limited studies endorse some beneficial effects of statins but there was asymptomatic alteration in liver function noted as a side effect [87]. However, the STASH trial (Simvastatin in Aneurysmal Subarachnoid Hemorrhage Trial) could not establish the use of statins in acute phase of treatment of SAH [88].

2.6.4 Augmenting NO Activity

2.6.5 Sildenafil Citrate

Sildenafil citrate is a phosphodiesterase inhibitor which along with NO is known to relax the smooth muscles by preventing hydrolysis of cyclic guanosine monophosphate (cGMP) and inducing smooth muscle relaxation. Its role is already established in vertebrobasilar insufficiency, angina, and erectile dysfunction. Experimental studies suggested a beneficial effect of intrathecal sildenafil apart from its smooth muscle relaxation to produce changes in cognitive function [89]. To avoid the logistic implication of intrathecal sildenafil therapy, treatment through enteral route was tried on a series of patients in a pilot study which claims to show benefit in limited number of patients with refractory vasospasm. However, there were considerable side effects of the drug and no controlled study has been undertaken to prove its efficacy [90].

2.6.5.1 Nascent NO Donors

The mopping up of nascent NO released from the vascular endothelium by oxyhemoglobin is an important biochemical phenomenon that has a major implication in the pathophysiology of

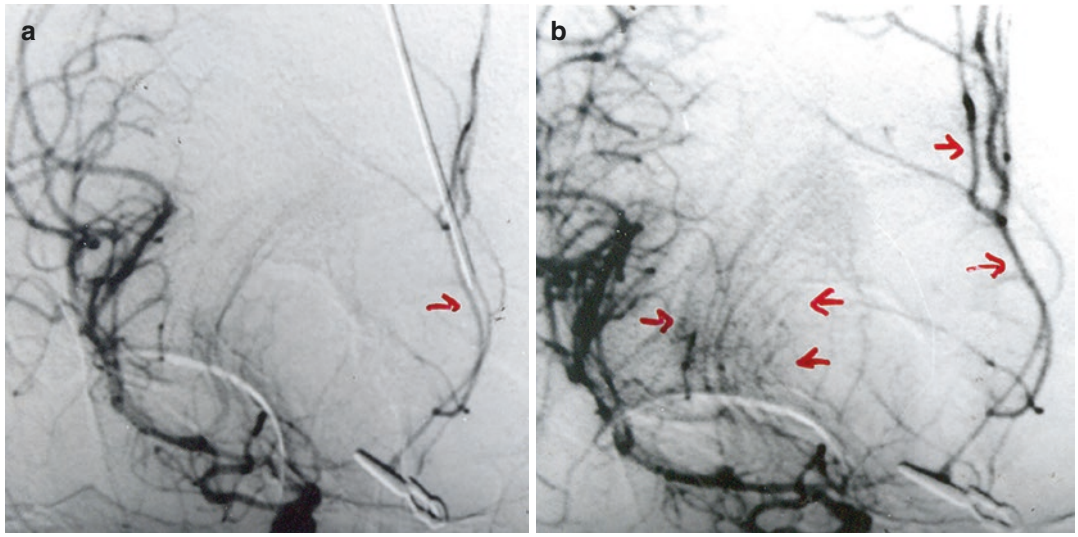

Fig. 2.3 (**a**, **b**) Treatment of vasospasm using NO donor. (**a**) Pre-treatment and (**b**) Post-treatment. Reversal of vasospasm in a clipped patient with TCD value of 300 cm/s using intrathecal NO donor (sodium Nitroprusside) instillation. Note may be made on the effect of therapy on perforators

vasospasm. Hence, any therapy to augment the availability of NO would be a logical and efficacious way to prevent or reverse vasospasm [91]. The main hurdle is the ultra-short life of NO which remains active for a very brief period. Accordingly, intrathecal instillation of sodium nitroprusside as a potent NO donor was carried out in a study with very good angiographic evidence of reversal of vasospasm (Fig. 2.3). Though the study showed reversal of early vasospasm with its prevention in imminent cases, however, its role in refractory vasospasm was not established [92]. Other nitric oxide donors like $NaNO_2$ were reported to be useful in animal models [93], but its efficacy in humans is yet to be established.

2.6.5.2 Magnesium Sulfate

Magnesium is long known to be an important cation, which has a role in various metabolic processes. Its role resembling a physiological calcium antagonist [94] was intensely studied with considerable improvement in DCI and vasospasm in animal studies [95, 96]. Magnesium Sulfate ($MgSO_4$) was therefore put through Phase I and Phase II trials with potentially encouraging results. A subsequent Phase II trial IMASH (Intravenous Magnesium Sulfate for Aneurysmal Subarachnoid Hemorrhage) was undertaken which, however, failed to show any significant good outcome at 6 months [97]. A further MASH-II (Magnesium in Aneurysmal Subarachnoid Hemorrhage II Study) using Mg therapy for 20 days after SAH failed to demonstrate any beneficial effect [98]. The lower CSF penetration and the side effects of Mg therapy were considered as important reasons for the suboptimal response.

2.7 Treatment Regime for SAH/Vasospasm

2.7.1 Optimizing Physiological Disruption

2.7.1.1 Catecholamine Surge and Increased Sympathetic Activity

SAH is associated with increased catecholamine surge, which has a bearing on the prognosis [99, 100]. This in turn enhances sympathetic activity manifested in the form of cardiovascular changes recorded in ECG and also neurogenic pulmonary

edema in severe cases [101]. Hence, close monitoring of cardiac and pulmonary function is of utmost importance specifically in patients manifesting with extracranial sympathetic manifestations and appropriate remedial measures are to be instituted, e.g., positive pressure ventilation for neurogenic pulmonary edema.

2.7.1.2 Controlling Body Temperature

Fever is a recognized entity in SAH which is common in patients with poor grade SAH or intraventricular hematomas [102]. For every degree Celsius change in body temperature, the glucose utilization demand in different areas of brain increases by 5 to 10%. Poor outcome has been documented with patients of SAH associated with fever [103]. Contrarily hypothermia has a protective effect on brain by reducing the rate of metabolism and free radical production, maintaining integrity of blood–brain barrier and aerobic metabolism and also lowering excitatory neurotransmitters release [104, 105]. The role of targeted temperature control therapy, therefore, is claimed in several studies to have a significantly beneficial role in restoring the alteration in brain metabolism secondary to SAH [106–108].

2.7.1.3 Electrolyte Management

Fluctuation in serum sodium levels is well known in SAH with observation of initial rise followed by significant fall in the second week [109]. The reason for hyponatremia is related to various factors which include cerebral salt wasting syndrome, SIADH, glucocorticoid deficiency. Despite hyponatremia being a known cause of reduced cerebral function and infarction of the brain, its contribution to poor outcomes is not clear [110].

Hypernatremia is commonly a manifestation of hypothalamic insult and may be associated with diabetes insipidus. It has been shown to have a poor outcome as per studies available [111, 112]. Based on the above observations serum sodium level within the normal physiological range is ideal even though the exact relationship of sodium imbalance with outcome is not fully established.

2.7.1.4 Maintaining Cerebral Perfusion

To counter the effects of decreased perfusion and poor blood flow secondary to vasospasm and DCI the triple H therapy (Hypervolemia, Hypertension, and Hemodilution) was in vogue with the aim to improve circulatory blood volume, cerebral perfusion pressure, and reduce the viscosity of blood. Low molecular weight dextran, mannitol, and albumin were used for volume expansion as a routine measure in the past. However, there was mounting evidence that hypervolemia and hemodilution were not be of much benefit [113, 114] with convincing evidence to suggest harmful effects of hemodilution [115, 116]. Hence induced hypertension, to maintain a high mean arterial pressure (MAP), remains one of the efficacious components of the regime, which is followed routinely in most of the centers [115]. Maintaining a high level of hemoglobin has also been seen to have contributed to better outcomes [116]. Since cerebral perfusion is guided by a balance between the intracranial pressure and the MAP there remains a role of anti-edema measures through pharmacological means as well as ventilation. Mannitol, which is a commonly used drug to reduce ICP, was also popular because of its volume expansion effect. However, there remains a concern in long-term use of mannitol due to its effect on blood rheology through serum osmolality changes, electrolyte imbalance, and rebound rise in ICP after its withdrawal. ICP reduction, in order to improve cerebral perfusion, is therefore better managed through controlled ventilation.

2.7.1.5 Calcium Channel Antagonists

Calcium channel blockers are known to act on the “slow calcium” channels and hence have a relaxing effect on vascular smooth muscles and cardiac muscles without any effect on skeletal muscle. Apart from their action on smooth muscle vasculature they are known to play a significant role in blood rheology, calcium entry in ischemic cells, dilation of collateral leptomeningeal vessels, and platelet aggregation [117–119].