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Neurovascular Events After Subarachnoid Hemorrhage

Towards Experimental and Clinical Standardisation

Vasospasm2013

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Neurovascular Events after Subarachnoid Hemorrhage
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Preface

Forty-two years after the first International Conference on Cerebral Vasospasm (ICCV) was held in Jackson, Mississippi, USA, a new horizon of translational research and interdisciplinary interests motivated our community to change the name of this traditional meeting. It was in fact during the last ICCV in Cincinnati, OH, USA, in 2011, that a new name arose to embrace all disciplines and events related to subarachnoid hemorrhage. After celebrating venues on all five continents, we had the privilege to hold the newly baptized *12th Conference on Neurovascular Events After Subarachnoid Hemorrhage* (former ICCV) in Lucerne, Switzerland. During a magical week, from July 10 to 12, 2013, surrounded by the beautiful Lake of Lucerne and the Swiss Alps, more than 300 participants had the opportunity to meet and exchange experiences and visions, which will led us *Toward Experimental and Clinical Standardization* in this field. This book contains the proceedings of the Conference. We were motivated by the superb quality of 102 submitted abstracts, most of them included in this book. The collection of papers were divided into topical chapters: Aneurysm Formation, Early Brain Injury and Neuroprotection, Macro- and Microcirculatory Disturbances, Pathophysiology of DIND, Imaging and Endovascular Management, Techniques and Surgical Innovations, Neurocritical Care, and Clinical Trials. For the first time the Conference included a session on Animals Models which allowed the participants to have an overview of all experimental techniques routinely used worldwide. This summary will contribute to the standardization of laboratory techniques and will enable the application of data into clinical trials in a more reliable fashion. We want to acknowledge the authors of the chapters of this book and would like to express our deepest gratitude to all of those who made the meeting in Lucerne possible, especially Mrs. Anna Scrowther and Mrs. Antonella Ricci. Finally, we are indebted to our institution, the Kantonsspital Aarau, and its CEO, Mr. Hans Leuenberger, for the support and encouragement throughout the organization of the conference. This book will contribute to a better understanding of cerebrovascular events related to subarachnoid hemorrhage.

Aarau, Switzerland — Javier Fandino

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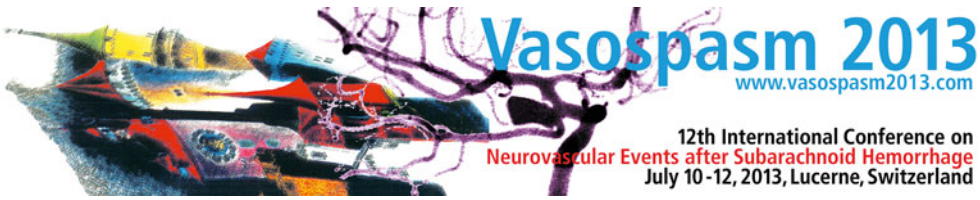

Contents

Vasospasm: My First 25 Years—What Worked? What Didn't? What Next?

R. Loch Macdonald

Abstract Angiographic vasospasm as a complication of aneurysmal and other types of subarachnoid hemorrhage (SAH) was identified about 62 years ago. It is now hypothesized that angiographic vasospasm contributes to delayed cerebral ischemia (DCI) by multiple pathways, including reduced blood flow from angiographic vasospasm as well as microcirculatory constriction, microthrombosis, cortical spreading ischemia, and delayed effects of early brain injury. It is likely that other factors, such as systemic complications, effects of the subarachnoid blood, brain collateral and anastomotic blood flow, and the genetic and epigenetic makeup of the patient, contribute to the individual's response to SAH. Treatment of aneurysmal SAH and DCI includes neurocritical care management, early aneurysm repair, prophylactic administration of nimodipine, and rescue therapies (induced hypertension and balloon or pharmacologic angioplasty) if the patient develops DCI. Well-designed clinical trials of tirilazad, clasozentan, antiplatelet drugs, and magnesium have been conducted using more than a 1,000 patients each. Some of these drugs have almost purely vascular effects; other drugs are theoretically neuroprotective as well, but they share in common the ability to reduce angiographic vasospasm and, in many cases, DCI, but have no effect on clinical outcome. Experimental research in SAH continues to identify new targets for therapy. Challenges for the future will be to identify the most promising drugs to advance from preclinical studies and to understand why clinical trials have so frequently failed to show drug benefit on clinical outcome. Similar issues with treatment of ischemic stroke are being addressed by suggestions for improving the quality of experimental studies, collaborative preclinical trials, and multinational, multicenter clinical studies that can rapidly include many patients and be large enough to account for numerous factors that conspire to disrupt clinical trials.

Keywords Subarachnoid hemorrhage • Vasospasm • Brain injury

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History

There have been at least 12 meetings focused on angiographic vasospasm and now on additional causes of neurological injury after subarachnoid hemorrhage (SAH) (Table 1). The first meeting was arranged by Robert R. Smith and James T. Robertson in Jackson, MS, in 1972. Echlin [18] wrote there was an earlier meeting in Bari, Italy, in 1970, chaired by Umberto Izzo, medical director of the Ospedali di Acquaviva, and Vincente Lombardi, also from the Ospedali di Acquaviva. The focus of these meetings has expanded as knowledge about the pathophysiology of brain injury after SAH has been gained. The honored guests and many participants at these meetings were or are leaders who have generated the knowledge that has led to improvement in outcomes of patients with SAH. I thank the organizing committee for recognizing me as an honored guest. I do not feel that I necessarily deserve it yet; I believe this honor would fit someone who made a definitive advance in terms of pharmacologic or other treatment for SAH, but few have met this high bar.

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Table 1 Meetings on angiographic vasospasm, delayed cerebral ischemia, and early brain injury

Meeting title	Location, organizer(s)	Honored guest(s)	Topics	Resulting book
Subarachnoid Hemorrhage and Cerebrovascular Spasm. The First International Workshop	Jackson, Mississippi, USA, 1972, Robert R. Smith, 18 attendees	Dedicated to Francis A. Echlin	Mainly focused on acute effects of blood, prostaglandins on large cerebral arteries	Smith, R.R., Robertson, J.T., eds. Subarachnoid Hemorrhage and Cerebrovascular Spasm. The First 'International' Workshop. Springfield: Charles C. Thomas Publisher, 1975.
2nd International Workshop on Cerebral Arterial Spasm	Amsterdam, The Netherlands, 1979, A.J.M. van der Werf, 200 participants	C. Miller Fisher	More understanding of vascular contraction, animal models focused on in vitro and large animal in vivo, time course of angiographic vasospasm and effect on cerebral blood flow recognized, dependence on subarachnoid clot and its removal suggested; treatments suggested were antiplatelet agents, nitroprusside, hydrocortisone, induced hypertension	Wilkins, R.H., ed. Cerebral Arterial Spasm. Proceedings of the Second International Workshop. Amsterdam, Netherlands, Baltimore: Williams & Wilkins, 1980.
3rd International Symposium on Cerebral Vasospasm	Charlottesville, Virginia, USA, 1987, Neal Kassell, 197 contributors	Keiji Sano (Honored guest), Charles G. Drake, (Honorary president)	Transcranial Doppler, role of the endothelium, brain microvessels examined, free radicals, prostaglandins, platelets; treatments included clot removal (fibrinolysis), intracisternal irrigation, papaverine and nimodipine, as well as systemic nimodipine, nicardipine, balloon angioplasty	Wilkins, R.H., ed. Cerebral Vasospasm. Proceedings of the III International Symposium in Charlottesville. New York, Raven Press, 1988.
4th International Conference on Cerebral Vasospasm	Tokyo, Japan, 1990, Keiji Sano, K. Takakura, Tomio Sasaki	Bryce K.A. Weir	Transcranial Doppler, smooth muscle contraction and biology, hemoglobin, perivascular nerves, inflammation, endothelium and endothelin; treatments included cisternal irrigation and fibrinolysis, hemodynamic therapy, steroids, immunosuppression, balloon angioplasty, nimodipine, nicardipine, fasudil	Sano, K., Takakura, K., Kassell, N.F., Sasaki, T., eds. Cerebral Vasospasm. Proceedings of the International Conference on Cerebral Vasospasm, Tokyo, 1990: University of Tokyo Press.
5th International Conference on Cerebral Vasospasm	Edmonton and Jasper, Alberta, Canada, 1993, Bryce Weir	Neal Kassell	Cerebral hemodynamics, other causes of delayed ischemia, smooth muscle contraction and biology, hemoglobin, free radicals, nitric oxide, endothelins, structural changes; treatments similar to last meeting, but in addition tirilazad, FUT-175	Findlay, J.M., ed. Cerebral Vasospasm. Proceedings of the V International Conference on Cerebral Vasospasm, Edmonton, Amsterdam: Elsevier Publishing Company, 1993
6th International Conference on Cerebral Vasospasm	Sydney, Australia, 1997, Nicholas Dorsch	Robert R. Smith	Experimental pathophysiology and treatments, mostly the same targets as above, in addition iron chelators, biomarker studies; new treatments included ebselen and flunarazine	Dorsch NWC (ed): Cerebral Vasospasm VI. Proceedings of the VIth International Conference on Cerebral Vasospasm. Oslington, Leichhardt, Australia, 1999
7th International Conference on Cerebral Vasospasm	Interlaken, Switzerland, 2000, Rolf Seiler, 75 participants	Helge Nornes	Vascular biology, nitric oxide, endothelins, gene therapy, magnetic resonance imaging, microdialysis; treatments included cisternal drugs, intraarterial pharmacologic or balloon angioplasty, nicardipine pellets	R.W. Seiler, H.-J. Steiger (eds): Cerebral vasospasm. Acta Neurochirurgica, Supplement 77, Springer, Wien New York, 2001

8th International Conference on Cerebral Vasospasm	Chicago, Illinois, USA, 2003, R. Loch Macdonald, 90 participants	Shigeharu Suzuki, Tomio Ohta	Vascular biology, inflammation, computed tomographic perfusion, biomarkers; treatments included magnesium, phosphodiesterase inhibitors, lumbar drainage, cisternal drugs	Macdonald RL (ed): Cerebral Vasospasm. Advances in Research and Treatment. New York, Thieme Medical Publishers, 2005
9th International Conference on Cerebral Vasospasm	Istanbul, Turkey, 2006, Talat Kiris, 75–100 participants	None	Much discussion of vascular biology, electrophysiology, noninvasive monitoring; treatments included clazosentan, magnesium, fasudil, statins, cilostazol	Kiris T, Zhang JH (eds): Cerebral Vasospasm. New Strategies in Research and Treatment. Springer-Verlag, Wien, Acta Neurochir Suppl, 2008
10th International Conference on Cerebral Vasospasm	Chongqing, China, 2009, Hua Feng, 90 participants	Nicholas Dorsch (Honored guest), Ryszard Pluta (distinguished keynote speaker)	Early brain injury, apoptosis, microvascular changes, cortical spreading depolarization, systemic effects of subarachnoid hemorrhage; treatments included statins, phosphodiesterase inhibitors, osteopontin, minocycline, many others discussed above	Feng H, Mao Y, Zhang JH (eds): Early Brain Injury or Cerebral Vasospasm. Volume 1: Pathophysiology. Acta Neurochir Suppl 110/1, Springer, New York, 2011 Feng H, Mao Y, Zhang JH (eds): Early Brain Injury or Cerebral Vasospasm. Volume 2: Clinical Management. Acta Neurochir Suppl 110/2, Springer, New York, 2011
11th International Conference on Neurovascular Events after Subarachnoid Hemorrhage	Cincinatti, Ohio, USA, 2011, Mario Zuccarello, Joseph F. Clark	Frank H. Mayfield	Clinical trials discussed (clazosentan, nicardipine pellets, magnesium, sodium nitrite), neuromonitoring, neurocritical care, spreading depolarizations, early brain injury, microcirculation	Zuccarello M, Clark JF, Pyne-Geithman G, Andaluz N, Hartings JA, Adeoye OM (eds): Cerebral Vasospasm: Neurovascular Events After Subarachnoid Hemorrhage. Acta Neurochir Suppl 115, Springer, New York, 2013
12th International Conference on Neurovascular Events after Subarachnoid Hemorrhage	Lucerne, Switzerland, 2013, Javier Fandino, 300 participants	R. Loch Macdonald	Early brain injury, neuroprotection, macrocirculation and microcirculation, inflammation, spreading depolarization, animal models, nitric oxide, neurocritical care; new treatments (nimodipine microparticles, albumin)	Fandino J, Marbacher S, Fathi AR, Muroi C, Keller E (eds): Neurovascular Events After Subarachnoid Hemorrhage - Towards Experimental and Clinical Standardisation. Acta Neurochir Suppl. Springer, Wien, 2014

What Worked: Etiology and Pathogenesis

The response to SAH includes an acute increase in intracranial pressure to varying degrees, as well as deposition of blood into the subarachnoid space or other brain compartments [38] (Fig. 1). Figure 1 summarizes some of the current pathways and processes leading to poor outcomes after SAH; these are discussed below and were demonstrated statistically in one study [57]. There can be transient global (and possibly focal) cerebral ischemia, and the pathogenesis of early brain injury probably includes some combination of effects of ischemia and the subarachnoid blood [46]. Animal models demonstrate that the etiology of angiographic vasospasm is a subarachnoid blood clot, and that removal of the clot, even in humans, lessens angiographic vasospasm [33]. The effect of clot removal on early brain injury has not been studied; the relative contributions of ischemia and subarachnoid blood to early brain injury are unknown.

Angiographic vasospasm correlates strongly with delayed cerebral infarction, although the correlation is imperfect, and it is theorized that multiple other processes contribute to whether a patient develops delayed cerebral ischemia (DCI) after SAH [6, 7]. Cortical spreading ischemia is one such process and has been documented in animal models and humans with SAH [16]. Associative evidence that it contributes to DCI is that nimodipine, an effective treatment to improve outcome after SAH, reduced cortical spreading ischemia in animals [17]. Microthrombi also have been demonstrated in the brain after experimental and clinical SAH [48]. It is a reasonable hypothesis that they contribute to brain injury, and nimodipine also could abrogate this process through its fibrinolytic activity [59]. On the other hand, clinical trials of antiplatelet drugs, which should reduce microthrombosis, have not documented marked improvements in outcome [15].

The relationship between microthrombi and microcirculatory constriction after SAH is not fully worked out yet.

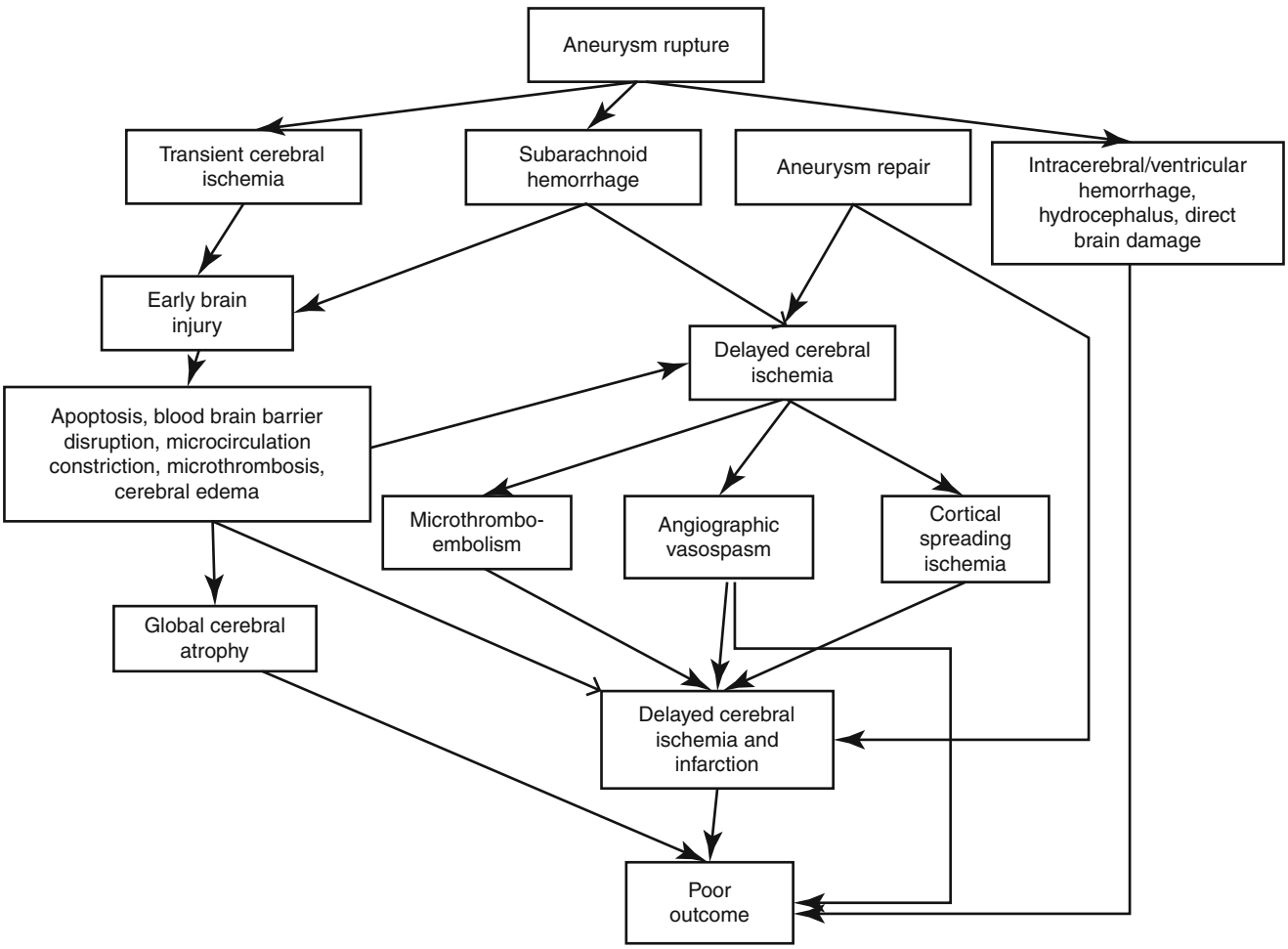

Fig. 1 Some aspects of the pathophysiology of SAH

Studies in animals show that subarachnoid blood alone causes pial arteriolar constriction, thrombosis, and blood brain barrier disruption [12]. These effects occur acutely, but also have been documented days after experimental SAH as well as acutely in penetrating blood vessels [22]. The extent to which these events occur in humans is not well studied [54].

Some evidence links early brain injury with DCI. Worse admission neurological grade, which means worse early brain injury, increases the risk of DCI [40]. Loss of consciousness at the time of SAH, which also should reflect an acute brain injury, also may increase the risk of DCI [9].

The pathogenesis of early brain injury after experimental SAH includes neuronal and endothelial cell apoptosis [23]. Humans dying 0–33 days after SAH exhibited neuronal apoptosis in the dentate gyrus [43]. About half of patients with SAH and no focal cerebral lesions were found to have cerebral atrophy on computed tomography (CT) scans weeks after SAH [50]. It is of note that many of these patients had good clinical grades and did not develop DCI, leading to the hypothesis that early brain injury diffusely injures the brain. To the extent that initial clinical grade reflects early brain injury, population-based studies suggest that the initial effect of the SAH contributes significantly to poor outcome [3].

The impact of the aneurysm repair procedure on clinical outcome has been investigated decades ago, although a lot has changed since then, prompting renewed interest [21, 53]. In one randomized clinical trial, 43 % of patients undergoing neurosurgical clipping of ruptured aneurysms experienced neurological deterioration immediately after surgery [41]. Deterioration was associated with poor outcome. The contribution of DCI to poor outcome is underestimated if only mortality is considered, because most patients can be saved with aggressive interventions including decompressive craniectomy. This comes with a high cost, both financial and in terms of morbidity. Rescue therapy costs approximately US $40,000 and DCI at least doubles the risk of poor outcome [4, 13].

What Worked: Diagnosis

Understanding the time course of angiographic vasospasm and DCI was fundamentally important [62]. It led to the differentiation of DCI from perioperative complications, and to the concept, which is now widely applied, that the aneurysm could be repaired early after rupture without more risk than if performed days later. I described previously the history of the discovery of the other fundamental finding that subarachnoid clot on CT scan is the best predictor of angiographic vasospasm and DCI [37]. Studies showing no relationship fail to account for clot clearance over time, lack of correlation between transcranial Doppler ultrasound and angiographic vasospasm, and numerous other factors.

Consensus has been obtained on definitions for angiographic vasospasm, DCI, and delayed cerebral infarction (Table 2) [60]. The authors wrote that angiographic vasospasm might be an appropriate surrogate outcome measure for proof-of-principle studies. Phase 2 and 3 clinical trials were recommended to use delayed cerebral infarction and a clinical outcome measure. There are limitations to this approach, however (vide infra). The definition and diagnosis of DCI was believed to be subjective and to probably have high interobserver variability.

A group of specialists who manage patients with SAH was convened in 2010 [10]. The GRADE system was used to assess evidence for different diagnostic tools for DCI [26]. While catheter angiography remains the gold standard for diagnosis of angiographic vasospasm, its limitations are that it does not assess brain perfusion or metabolism very well or at all, and it is invasive and complicated and time consuming to obtain. The current trend is to use CT angiography and perfusion to diagnose angiographic vasospasm and DCI [61]. Complications from contrast administration are uncommon but reported. Risk of developing cancer from radiation also has to be considered. Smith-Bindman and colleagues estimated that for every 8,100 CT scans in women of median age 40 years, one radiation-induced cancer would develop [47].

Table 2 Results of an international consensus on definitions of angiographic vasospasm and DCI [60]

Term	Definition	Comments
Angiographic vasospasm	Describes a radiologic test showing artery narrowing	This is the recommended term for artery narrowing on computed tomographic, magnetic resonance, or catheter angiography
Delayed cerebral ischemia	Focal neurologic deficit or decrease of at least 2 points in Glasgow coma scale, lasting longer than 1 h, with no identifiable cause, such as the aneurysm repair procedure, rebleeding, infections, seizures, hyponatremia, or hydrocephalus	The threshold for diagnosis and the duration of deficit are empirically derived and not based on scientific evidence. Detection in comatose or sedated patients can be difficult
Delayed cerebral infarction	Cerebral infarction on computed tomography scan, magnetic resonance imaging, or autopsy, present after the time of DCI within 6 weeks of SAH and not 24–48 h after aneurysm repair procedure	Does not include encephalomalacia from intracerebral hemorrhage or ventricular drains. Presumably includes only lesions consistent with arterial territories

For men, the corresponding number was 11,080 CT scans. Transcranial Doppler ultrasound is still used, although its limitations are recognized.

What Worked: Treatment

Guidelines for management of SAH from the American Heart Association list nimodipine (class 1, level of evidence A), maintenance of euvolemia (class 1, level of evidence B), endovascular coiling (class 1, level of evidence B), and, if the patient develops DCI, then induction of hypertension (class 1, level of evidence B) as recommended at the highest class of evidence [5]. Nimodipine and endovascular aneurysm repair appear to have contributed to improved outcome after SAH; indeed, mortality has declined 0.9 % per year from about 50 to 35 % over the past two decades [36]. But, have other changes in management contributed? The American Heart Association Guidelines also recommend not using prophylactic hemodynamic manipulations; administering fludrocortisone acetate and hypertonic saline to treat hyponatremia; controlling the blood pressure before aneurysm repair; neurologic, transcranial Doppler, and hemodynamic monitoring; treatment of hydrocephalus; prophylactic anticonvulsants; rescue therapy with balloon or pharmacologic angioplasty; and avoidance of hypoglycemia, fever, hypovolemia and hypervolemia at class 2–3, level of evidence B [5]. European guidelines are similar but they do not address all of the same factors [49]. The main difference in the European guidelines is induced hypertension for treatment of DCI was considered to have no evidence for its use [49]. A potentially important factor that is not mentioned in the American Heart Association guidelines is timing of ruptured aneurysm repair, perhaps because it is considered standard of care to repair the aneurysm immediately [5]. European guidelines suggest repair as soon as possible, independent of grading [49]. The evidence is not based on large randomized trials. Despite this, early aneurysm repair has been associated with reduction in mortality caused by rebleeding, resulting in other factors, such as the effects of the SAH and medical complications, contributing increasingly to mortality [32]. Combining the better medical management of patients with SAH and procedures that can reduce mortality, such as decompressive craniectomy, led to a shift to a greater portion of mortality being caused by the SAH itself and by medical complications. As noted above, however, morbidity from DCI remains high.

Of the treatments for SAH that have been subjected to metaanalysis, two, fasudil and intrathecal fibrinolysis, are not widely used despite evidence to suggest they improve outcome [33, 35].

Some Noteable Failures

Treatments for DCI that have undergone metaanalysis include corticosteroids, antiplatelet drugs, calcium channel antagonists, hemodynamic therapy, statins, tirilazad, intrathecal fibrinolytics, fasudil, endothelin receptor antagonists, and magnesium [8, 14, 15, 20, 24, 25, 28, 33, 35, 56]. Antiplatelet drugs, tirilazad, endothelin receptor antagonists, and magnesium have been studied in randomized trials totaling at least 1,385; 3,821; 2,024; and 2,401 patients, respectively [38]. There are limitations to the metaanalyses including the quality of the data in some studies and combining different drugs and doses together. It is notable, however, that tirilazad, endothelin receptor antagonists (principally clazosentan), and magnesium reduced DCI, but had no effect on clinical outcome. Why the drugs did not improve outcome has been discussed (Table 3) [38]. Statins and corticosteroids have probably not been adequately studied, but sample sizes seem adequate for tirilazad, clazosentan, and magnesium. The modified Rankin scale may or may not be very sensitive, but it did detect a difference in outcome between clipping and coiling in the International Subarachnoid Aneurysm Trial [42]. The issue of rescue therapy warrants discussion.

Table 3 Some possible reasons for failure of drugs to improve outcome in clinical trials of SAH

1. The drug is truly ineffective
2. The dose, timing, and duration of administration, route of administration, etc. were wrong
3. The sample size was too small
4. The outcome measure was insensitive or did not detect a clinically meaningful improvement in outcome
5. The drug benefit was offset by drug adverse effects
6. Rescue therapy was as effective in the placebo group as the drug was in the treatment group, leading to no overall difference in outcome
7. Practice misalignment led to application of the drug to patients who could not benefit from the drug or who were at increased risk of adverse effects
8. The wrong patient subgroup was studied
9. The drug was not manufactured properly, randomization codes were wrong, etc.

If rescue therapy is effective, then unless the drug treatment being tested is very effective, increased use of rescue therapy in the placebo groups will reduce the difference in clinical outcome between the groups. On one hand, it seems impossible to withhold rescue therapy but, on the other hand, European guidelines do not strongly support use of induced hypertension, and there is even an ongoing randomized trial comparing induced hypertension to no induced hypertension (NCT01613235, www.clinicaltrials.gov).

What Next?

There are many examples of great successes in treatment of diseases such as acquired immunodeficiency syndrome and breast cancer. Another example of success is cystic fibrosis, from which median survival has increased from 6 months in 1959 to 27 years in 2007 [2]. This is an orphan disease, as is SAH. It has the advantage for study of having a known molecular target. In addition and in common with some other successfully treated conditions, there is a very well-organized and -funded patient advocacy group that generates $10 million a year in the United States for research. The Cystic Fibrosis Foundation provides many research tools and candidate preclinical drugs to researchers for free. Can those of us studying SAH learn something from them?

When examining causes for the unsuccessful clinical trials, the question arises regarding which of the numerous preclinical treatments to advance into clinical trials. At this meeting alone, papers and posters describe 19 experimental treatments for SAH that have not been studied or have had only limited study in humans (inhaled nitric oxide, minocycline, pitavastatin, melatonin, deferoxamine, valproic acid, intrathecal magnesium, cilostazol, eicosapentanoic acid, ADAMTS13, rhinacanthin, curcumin, ecdysterone, baivalein, molsidomine, exercise, cystatin C, imatinib, and Ro 25-6981). Guidelines have been proposed for the conduct of experimental studies and there is evidence that studies that do not follow these guidelines overestimate the benefit of the treatment [31, 34]. I support adherence to the guidelines. They reflect good scientific design; however, bear in mind that the studies of nimodipine, which is the only US Food and Drug Administration-approved treatment for SAH, would probably not qualify for study in humans and the animal studies often showed it did not affect its suspected mechanism of action, angiographic vasospasm [19]. There is also the implication that animal models exist or can be created that are externally valid or, in other words, that efficacy in the animal model would translate to humans if the guidelines were followed [55]. Whether this is true in SAH remains to be seen. Adhering to at least some of the guideline recommendations is going to be necessary because granting agencies are requiring this to some extent. The recommendations for multiple studies in multiple laboratories will require increased cooperation between investigators and centers. Dirnagl et al. noted that this already occurs in some fields such as physics (and astronomy), where some obvious barriers such as authorship, student independence, intellectual property, collaboration of funding bodies between countries, communications, governance, and monitoring have been overcome [11].

Moving to clinical trials, there is the question of the outcome measure (Table 3). The modified Rankin scale has been used in a SAH clinical trial with a positive result, but whether adding cognitive assessments would disclose differences in outcome in the group of patients classified as good outcome patients, generally modified Rankin score 0–2 in other SAH studies, is an open question [45]. There is little agreement about what cognitive tests to use to assess outcome after SAH, and the number of studies is almost the same as the number of tests used [1]. National and international cooperation might be recommended here. Another reason for this is the observation that, among models of prognostic factors for outcome after SAH, one study of 3,567 patients found that a detailed logistic regression explained only 36 % of the variance in outcome [44]. What is the cause of the rest of the variation? Why do some patients with angiographic vasospasm not develop DCI? Why does one grade 4 patient recover and the other die? In addition to the probable multifactorial pathogenesis, there are physiologic differences in anatomy and blood flow and genetic and epigenetic variations that affect individual responses to SAH, but this personalized approach to medicine is only beginning to be studied in SAH [30, 58]. Ultimately, treatments might need to be adjusted depending on the genetic makeup of the patient, as in other diseases where personalized medicine has already been applied. Some of these discoveries required large, multinational collaborative efforts [29, 63]. Practice misalignment also may result from differing patient responses [52]. Some clinical trials in SAH focus on the treatment, with varying degrees of patient subgroup selection, taking a pragmatic approach [51]. Another option is to focus on very specific hypotheses and more on the individual characteristics of the patient and pathology, which is the explanatory trial (Fig. 2). There is no correct answer, although success was seen in a narrowly focused neuroprotection trial in humans [27]. Finally, it is of note that 34 years ago, clinical use of steroids was described at the second vasospasm meeting. Their use is still being investigated in SAH in small, single-center studies. Why don't we know the answer to whether they are efficacious in SAH or not, three decades later? Would it be beneficial to cooperate nationally and internationally to pool clinical, genetic, radiologic, and such data, develop common definitions and data elements, both retrospectively and then on a prospective basis? The SAH international trialists repository seeks to do this [39].

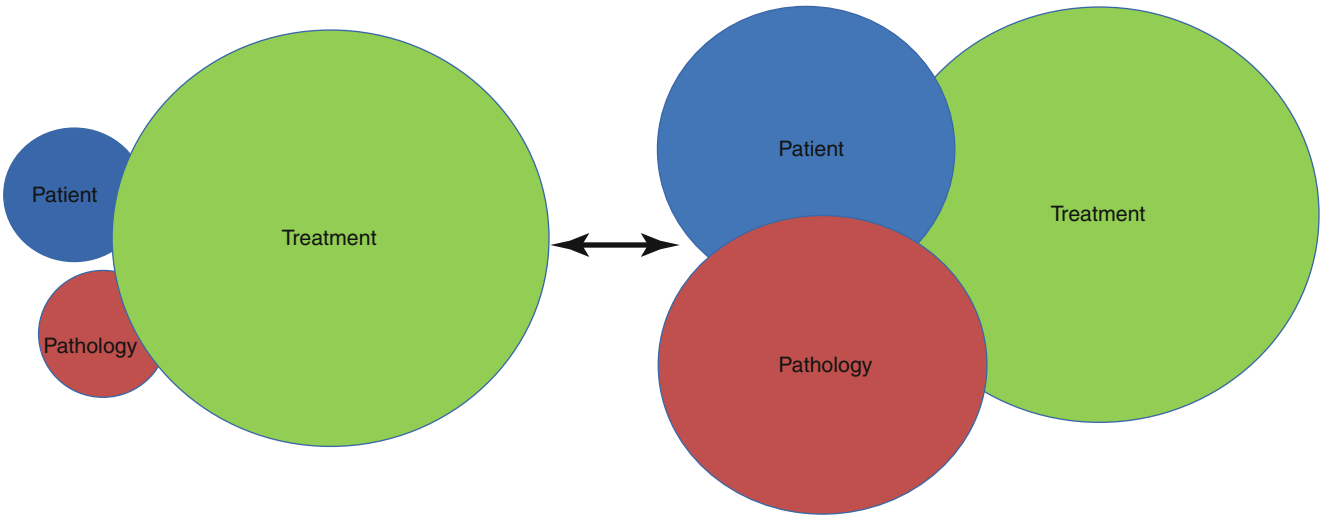

Fig. 2 Simplistic view of pragmatic versus explanatory clinical trials, presented in detail by Thorpe et al. [51]. Clinical trials may be pragmatic and focus on administering a single treatment to unselected patients with little attention to patient- or pathology-related factors or they may be explanatory and test a very specific hypothesis in a well-defined patient subgroup

Summary

The pathophysiology of DCI is probably complex and multifactorial. Progress has been made in improving outcome but there is still no cure for DCI. Many promising preclinical treatments were described at this meeting and others are in early stage clinical trials. To reduce the chances of failure of translation, it has been recommended that the quality of preclinical studies be improved, and that treatments be studied in collaboration between multiple laboratories. Similarly, on the clinical side, many centers already work together, but it may be beneficial for investigators to work cooperatively to develop common definitions and outcome measures, and to redefine these as new data become available. Funding agencies are increasingly interested in this approach and it may be beneficial from the position of a relatively uncommon disease such as SAH for garnering philanthropic and other sources of support.

Conclusion

Outcome from aneurysmal SAH has improved in the past decades, in association with introduction of nimodipine pharmacologic prophylaxis, early aneurysm repair and endovascular coiling. Advances in treatment of angiographic vasospasm and DCI also have likely contributed, but they are less well based on randomized clinical trials. Further reductions in morbidity and mortality will require cooperative efforts of centers around the world to bring new therapies identified in preclinical studies into the clinic.

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Conflict of Interest Statement RLM is Chief Scientific Officer of Edge Therapeutics.

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Aneurysm Formation

Molecular Basis for Intracranial Aneurysm Formation

Miyuki Fukuda and Tomohiro Aoki

Abstract Intracranial aneurysm (IA) is a socially important disease both because it has a high prevalence and because of the severity of resultant subarachnoid hemorrhages after IA rupture. The major concern of current IA treatment is the lack medical therapies that are less invasive than surgical procedures for many patients. The current situation is mostly caused by a lack of knowledge regarding the regulating mechanisms of IA formation. Hemodynamic stress, especially high wall shear stress, loaded on arterial bifurcation sites is recognized as a trigger of IA formation from studies performed in the field of fluid dynamics. On the other hand, many studies using human specimens have also revealed the presence of active inflammatory responses, such as the infiltration of macrophages, in the pathogenesis of IA. Because of these findings, recent experimental studies, mainly using animal models of IA, have revealed some of the molecular mechanisms linking hemodynamic stress and long-lasting inflammation in IA walls. Currently, we propose that IA is a chronic inflammatory disease regulated by a positive feedback loop consisting of the cyclooxygenase (COX)-2 – prostaglandin (PG) E_2 – prostaglandin E receptor 2 (EP2) – nuclear factor (NF)-κB signaling pathway triggered under hemodynamic stress and macrophage infiltration via NF-κB-mediated monocyte chemoattractant protein (MCP)-1 induction. These findings indicate future directions for the development of therapeutic drugs for IAs.

Keywords Intracranial aneurysm • Subarachnoid hemorrhage • Inflammation • Nuclear factor (NF)-κB • Macrophage • Prostaglandin • Cyclooxygenase-2 (COX-2) • EP2 • Monocyte chemoattractant protein-1 (MCP-1) • Statin

Findings from Studies Performed with Human Intracranial Aneurysms

Recent studies in the field of fluid dynamics demonstrated the close interactions of hemodynamics with intracranial aneurysm (IAs) [10]. For example, among various parameters of hemodynamics, high wall shear stress loaded on the arterial bifurcation sites, where IAs are formed, is associated with IA formation and growth [10]. High wall shear stress can, therefore, be recognized as a trigger of IA formation.

On the other hand, in the field of histopathological analyses, gene linkage analyses and comprehensive gene expression analyses have revealed that active inflammatory responses, such as macrophage infiltration and the expression of various cytokines, are present in human IAs [8]. For example, Shi et al. [11] analyzed gene expression profiles in human IA lesions using a microarray technique and revealed that inflammation-related biological pathways, inflammatory response and apoptosis, were associated with IA development. Consistent with this, they also confirmed the upregulation of proinflammatory genes in human IA walls, including interleukin (IL)-1β, tumor necrosis factor (TNF)-α, vascular cell adhesion molecule (VCAM)-1, C-X-C chemokine receptor type 4 (CXCR4), and chemokine ligand (CCL) 5 [11].

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However, studies using human IA specimens have considerable limitations, such as the heterogeneity of individual genetic backgrounds and the difficulty of pathological analyses at each period of IA formation from the same patient, in elucidating the mechanisms underlying IA formation and development. We, therefore, have developed experimental models of IA to overcome this situation.

Molecular Mechanisms Regulating IA Formation Through Linking Hemodynamic Stress and Long-Lasting Inflammation

We established experimental models of IAs by increasing the hemodynamics at the bifurcation sites of cerebral arteries through the ligation of the carotid artery and salt overloading [5]. Because experimental IA and human IA share histological similarities characterized by the degeneration of the arterial wall, the disruption of internal elastic lamina, and the infiltration of inflammatory cells, these animal models are suitable for analyses of the pathogenesis of IAs. Indeed, results from recent experimental studies using these models remarkably accelerated our understanding of the mechanisms regulating IA formation and development.

Through the studies using animal models, we identified nuclear factor (NF)-κB as a critical transcription factor for IA formation [1, 8]. NF-κB leads the induction of various proinflammatory genes, such as monocyte chemoattractant protein (MCP)-1, a factor that recruits macrophages in IA walls [7, 8]. Macrophages recruited in cerebral arterial walls by NF-κB-mediated MCP-1 induction produce a large amount of cytokines and proteinases and exacerbate the inflammation associated with IA formation and growth [7, 8]. However, how high wall shear stress induces NF-κB-mediated inflammation and how the inflammation becomes chronic remain to be elucidated.

We recently demonstrated that the positive feedback loop consisting of the cyclooxygenase (COX)-2 – prostaglandin (PG) E_2 – prostaglandin E receptor 2 (EP2) – NF-κB signaling pathway is formed under high wall shear stress and induces a long-lasting (chronic) inflammation in IA walls [6, 7]. As previously discussed, at the sites of IA formation, which are mostly at arterial bifurcations, high wall shear stress is loaded and recognized as a trigger of IA formation [7]. An in vitro study, using a primary culture of endothelial cells from human carotid arteries, demonstrated the induction of COX-2, a prostaglandin-producing enzyme, and its receptor, EP2, under high wall shear stress. Both COX-2 and EP2 expression were also consistently upregulated in experimentally induced IAs during IA formation and their expression was well colocalized in endothelial cells where wall shear stress was loaded. Here, because either the administration of Celecoxib (a selective COX-2 inhibitor) or EP2 deficiency significantly suppressed both IA formation and inflammatory responses in IA walls, such as NF-κB activation and macrophage infiltration, the shear stress-activated prostaglandin pathway was identified as a mediator of NF-κB-induced inflammation during IA formation. Indeed, in endothelial cells, treatment with PGE_2 or a selective EP2 agonist activated NF-κB and its target, MCP-1. Importantly, COX-2 inhibition suppressed EP2 expression, and vice versa. Thus, once hemodynamic stress induces COX-2 expression in endothelial cells at the bifurcation sites of cerebral arteries, the positive feedback loop consisting of COX-2 – PGE_2 – EP2 – NF-κB was formed, resulting in the amplification and the chronicity of inflammation (Fig. 1).

Future Prospects for the Development of Therapeutic Drugs for IA

The recent experimental results indicate that NF-κB is a potential therapeutic target for IA treatment [4]. The significant suppression of IA formation and growth in animals with NF-κB deficiency or treated with a NF-κB inhibitor, decoy oligonucleotides, further supports this notion [1].

Statins (3-hydroxy-3 methylglutaryl coenzyme A reductase inhibitors) were originally developed as therapeutic drugs for lipid metabolic abnormality. In addition, statins are well recognized as having powerful anti-inflammatory and especially anti-NF-κB effects; known as the pleiotropic effect of statins. Encouraged by this pleiotropic effect of statins, we administered Pitavastatin, one of the statins, to our rat model of IA and demonstrated that Pitavastatin treatment effectively prevented the growth of IAs in rats [3]. Pitavastatin treatment remarkably suppressed the inflammatory responses in IA walls, characterized by NF-κB activation and subsequent induction of the expression of NF-κB-regulating genes, such as MCP-1, VCAM-1, and IL-1β [3]. Furthermore, Pitavastatin treatment effectively inhibited the degenerative change of IA walls, suggesting a preventive effect of Pitavastatin against the rupture of IAs [3]. Other kinds of statins, Simvastatin and Pravastatin, also successfully prevented IA growth through inhibition of inflammation in IA walls, suggesting that statins are potential therapeutic drugs for IAs [2, 9].

Because of these findings from experimental animals, we examined the preventive effect of statins for the rupture of human IAs in a case-controlled clinical study in Japan. As a result, we clarified the inverse relationship between the usage of statins and the occurrence of aneurysmal subarachnoid hemorrhage in the Japanese population. Statins were administered in 9.4 % of cases with ruptured IAs and 26.0 % of cases with unruptured IAs. The usage of statins, therefore, significantly prevented the rupture of preexisting IAs with a relative odds ratio of 0.3 [12].

These studies suggest the potential of statins as therapeutic drugs to prevent the growth and rupture of IAs.

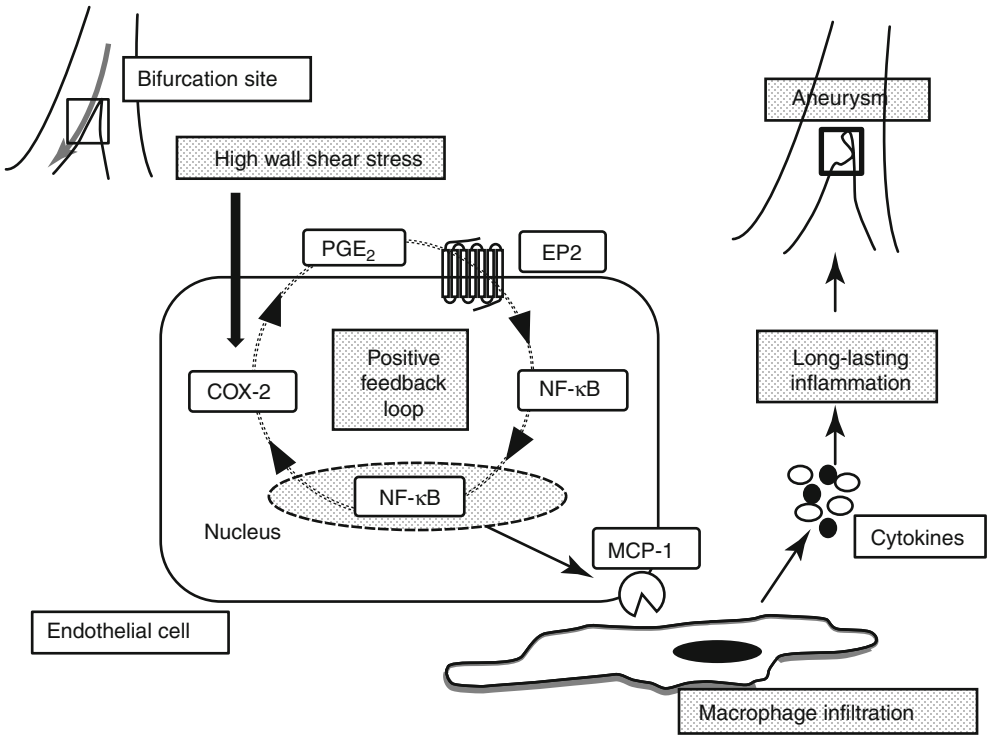

Fig. 1 Schema demonstrating our hypothesis for the potential mechanisms underlying the chronicity of inflammation contributing to intracranial aneurysm formation. Note the positive feedback loop consisting of PGE_2 – NF-κB signaling under hemodynamic stress and macrophage infiltration via NF-κB-mediated MCP-1 induction

Conclusion

Recent experimental studies using an animal model of IA have revealed the crucial role of long-lasting inflammation in its pathogenesis. In this process, prostaglandin-mediated NF-κB activation plays the role to trigger and amplify the inflammatory responses in IA lesion suggesting the potential of NF-κB as a therapeutic target for IA treatment. Indeed, recent case-control study has demonstrated the suppressive effect of statins on rupture of IAs in human cases through their potent anti-NF-κB effect. In near future, a medical treatment of IA is supposed to be established.

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Conflict of Interest Statement We declare that we have no conflict of interest.

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Aneurysm Wall Thickness Measurements of Experimental Aneurysms: In Vivo High-Field MR Imaging Versus Direct Microscopy

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Abstract *Background:* Thin cerebral aneurysm wall thickness (AWT) is connected to high aneurysm rupture risk. MR imaging of AWT leads to overestimations. The aim of the present study was to quantify MR inaccuracy by comparison with accurate light microscopic measurements.

Methods: In 13 experimental microsurgical bifurcation aneurysms in rabbits, 3 Tesla (3 T)-MR imaging using contrast-enhanced T1 Flash sequences (resolution: $0.4 \times 0.4 \times 1.5$ mm^3) was performed. The aneurysms were retrieved immediately after MR acquisition, cut longitudinally, and calibrated photographs were obtained. AWT (dome, neck) and parent vessel thickness (PVT) were measured on the MR images and microscopic photographs by independent investigators. All parameters were statistically compared (Wilcoxon test, Spearman correlation).

Results: AWT and PVT could be imaged and measured in all aneurysms with good quality. Comparison with the "real" light microscopic measurements showed a progressive tendency of MR AWT overestimation with smaller AWT: AWT at the dome (0.24 ± 0.06 mm vs. MR 0.30 ± 0.08 mm; $p = 0.0078$; $R = 0.6125$), AWT at the neck (0.25 ± 0.07 mm vs. MR 0.29 ± 0.07 mm; $p = 0.0469$; $R = 0.7451$), and PVT (0.46 ± 0.06 mm vs. MR 0.48 ± 0.06 mm; $p = 0.5$; $R = 0.8568$).

Conclusion: In this experimental setting, 3 T-MR imaging of cerebral AWT showed unacceptable inaccuracies only below the image resolution threshold. Theoretically, AWT for clinical usage could be classified in ranges, defined by the maximum image resolution.

Keywords Aneurysm • Wall thickness • High-field MR • Risk

Introduction

The risk assessment and treatment indications of unruptured aneurysms remain controversial and additional predictive parameters are clinically needed. A potential parameter could be aneurysm wall thickness (AWT). Although we know that thin aneurysm walls are correlated with higher rupture risks [3], few studies have focused on MR image-based

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