From rupture to haemorrhage

From intracranial aneurysm rupture to the consequences of subarachnoid haemorrhage, the CABMM investigates

Rupture of an intracranial aneurysm (IA) causes subarachnoid haemorrhage (SAH), a devastating condition leading to stroke, permanent neurological damage and death. In Switzerland, an estimated 250,000 Swiss are harbouring IAs and about 700 Swiss patients suffer from SAH every year. The disease has a significant socioeconomic impact as SAH often affects relatively young patients. Despite major improvements in surgical techniques, diagnosis, intensive care and interventional treatment, the average fatality rate remains between 40-50%, and only 60% of surviving patients will return to work. These figures underline the need for a better understanding of the natural course of IA and, in case of IA rupture, the need for improved therapies to alleviate the consequences of SAH.

Intracranial aneurysms

An IA is an outpunching of the cerebral artery most often at the base of the brain. The number of diagnosed incidental unruptured IAs parallels the number of increasing brain imaging studies. Many of these aneurysms, however, do not rupture during a person's lifetime. Hence, the decision to treat or not represents a dilemma for the surgeon: do the risks of preventive treatment outweigh the risk of death or severe disability through spontaneous IA rupture? While robust data on treatment risks exists (either via craniotomy and clipping or endovascular occlusion), sensitive and specific indicators for rupture-prone IA are missing. Our research group has recently started to study IA wall biology, which most likely holds the key to understanding the natural course of unruptured IA. We use a rat sidewall aneurysm model of different wall types to elucidate mechanisms of intraluminal thrombosis, aneurysm growth, and vessel wall remodelling.

Once the anticipated rupture risk outweighs the risk of treatment, the decision on whether the aneurysm is to be treated by open surgery or endovascular treatment (EVT) must be made. This decision should consider the increased risk of open surgery including superior IA repair *versus* the ease of access of EVT with the drawback of inferior IA repair. IA recurrence is a distressing clinical problem that occurs in approximately 20-35% of patients and necessitates retreatment in half of reopened IAs. The mechanisms required for reopening after EVT are poorly understood. We are currently examining new concepts for IA reopening and developing EVT approaches focused not only on the visible IA lumen but also the IA wall.

Subarachnoid haemorrhage

SAH occurs when the IA wall bursts outside of the brain parenchyma. The subarachnoid space rapidly fills with arterial blood until the rupture site is occluded by a blood clot. Delayed cerebral vasospasm (DCVS), and subsequent inadequate blood supply leading to tissue hypoxia, is one of the most feared complications after IA rupture. Despite half a century of research, no effective treatment for DCVS has been found. More recently, promising results from clinical studies using a selective endothelin receptor antagonist demonstrated significant reduction of DCVS, but failed to achieve an effect on vasospasm-related morbidity, mortality or functional outcome. It became evident that pathophysiological consequences other than DCVS after SAH play an important role in the overall outcome. However, the strong association between angiographic vasospasm and cerebral infarction still warrants efforts to reduce DCVS. Our research team has extensive experience with *in vivo* DCVS, and we continue to explore the pathophysiology of DCVS and potential substances and interventions reducing DCVS.

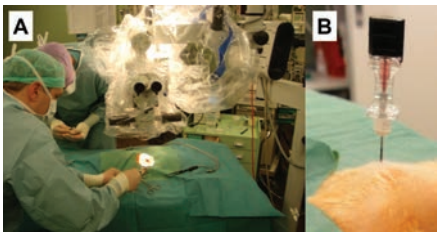

Fig. 1 Shunt model of acute subarachnoid haemorrhage. The subclavian artery is cannulated (A) with a spinal needle placed in the cerebromedullar cistern (B) to allow blood stream under arterial pressure into the subarachnoid space in a closed cranium. The bleeding stops when levels of intracranial and arterial pressure are equal. Further details and step by step description of the shunt model of acute subarachnoid haemorrhage can be found at: http://www.jove.com/video/52132/the-rabbit-blood-shunt-model-for-study-acute-late-sequelae

Clinical and experimental research has long been pointing to the importance of factors other than DCVS after SAH. Early brain injury (EBI) has been coined as an umbrella term to describe consequences of the complex pathophysiological mechanisms following the initial bleed and are responsible for early ischaemic damage. It is assumed that the bleeding itself, including initial increase in intracranial pressure during aneurysm rupture, triggers processes which ultimately result in EBI after SAH. In order to recreate EBI, we developed a novel acute SAH model that allows us to investigate the biological mechanisms early in the disease course after SAH.

Models for the study of subarachnoid haemorrhage

Different models have been developed in various animal species in the hope of a better understanding of SAH pathophysiology. Rabbits have become one of the most popular species for DCVS research, not least because of the readily applicable digital

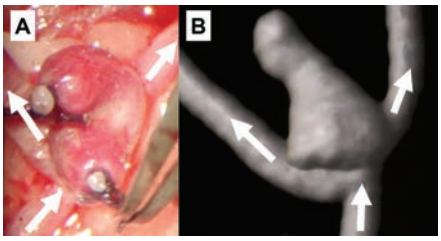

Fig. 2 Microsurgical bifurcation aneurysm model. Complex aneurysms in true haemodynamic bifurcation lesion are created by a venous pouch sutured into the end-to-side anastomosis of the proximal right and distal left common carotid artery. Intraoperative situs (A) and three-dimensional magnetic resonance image (B) of an experimental bilobular aneurysm. Solid white arrow demonstrates direction of flow. Further details and step by step description of the microsurgical bifurcation aneurysm model can be found at: http://www.jove.com/video/2718/microsurgical-venous-pouch-arterial-bifurcation-aneurysms-rabbit

subtraction angiography for the monitoring of intracranial basilar artery vasoconstriction. Injecting autologous blood into the *cisterna magna* is the standard technique of SAH induction but unfortunately produces only mild vasoplasm and does not reflect acute events or the key pathogenic mechanisms of clinical SAH. We recently introduced an acute SAH model that closely reflects pathophysiological sequences of IA rupture. The closed-cranium ICP-controlled model uses an extra-intracranial blood shunt from the subclavian artery into the *cisterna magna* to enhance DCVS and to provoke EBI after SAH (Fig. 1).

Experimental aneurysm models

Experimental work using animal models of IA are needed to delineate the biological mechanisms of IA formation and growth, and to establish new endovascular and medical therapies to prevent IA rupture. Today's models can be divided into two main groups according to the subject under examination: 1) models to evaluate induction, growth and rupture of IA and 2) aneurysm models as tools to test novel endovascular devices (biological interaction of EVT), evaluate the basic biological concepts and haemodynamics of IA, and to train neurointerventional radiologists and endovascular neurosurgeons.

None of the preclinical aneurysm models for testing endovascular devices currently available combine all the ideal characteristics. The rabbit bifurcation aneurysm model includes the following: 1) Size of aneurysm and parent artery similar to larger cerebral arteries (enables realistic microcatheter interventions); 2) Long term patency without spontaneous thrombosis; 3) Healing responses similar to those in humans; 4) Good reproducibility; 5) Haemodynamics (high shear stress at the neck of the aneurysm), coagulation profiles (clotting and thrombolytic system) and tissue and immunologic reactions similar to those of human IA. The use of various shapes and sizes of venous pouches allows generation of complex aneurysm angioarchitecture (Fig. 2).

In addition to the opportunity to vary aneurysm angioarchitecture there is also a demand for a model to create highly standardised aneurysms. Such standardised and reproducible aneurysm creation is ideal for early preclinical assessment of novel endovascular devices. To date, the most standardised aneurysm model in terms of graft origin, aneurysm shape and dimensions,

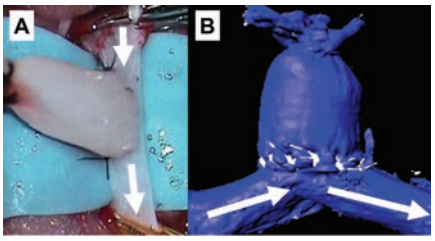

Fig. 3 Microsurgical sidewall aneurysm model. Highly standardised aneurysms in terms of size, shape, and haemodynamic conditions are created by end-to-side suturing of a thoracic aortic graft to the abdominal aorta. Intraoperative situs (A) and three-dimensional optical projection tomography (B) of an experimental sidewall aneurysm. Solid white arrow demonstrates direction of flow. Further details and step by step description of the microsurgical sidewall aneurysm model can be found at: http://www.jove.com/video/51071/the-helsinki-rat-microsurgical-sidewall-aneurysm-model

volume-to-orifice ratio and parent vessel to aneurysm long axis angle is the rat arterial sidewall aneurysm model. Most recently, this rodent model has been used to test basic biological concepts in different wall conditions and therefore to create links between models for evaluation of IA biology and models for testing endovascular devices (Fig. 3).

Summary and outlook

Understanding biological processes in aneurysm wall remodelling will allow us not only to better predict the natural course of IA but also to design endovascular treatment modalities with increased healing response after IA embolisation. Highly standardised aneurysm models for multicentre preclinical trials are just as necessary as models that enable realistic testing of endovascular devices. In SAH, research models that reflect early events will be of the utmost importance to evaluate pathophysiological concepts of EBI and hence to find DCVS-independent treatment approaches.

The broad infrastructure of the CABMM platform with excellence in imaging modalities and histopathology, combined with the ability to conduct studies in compliance with the principles of good laboratory practice (GLP), will allow us to achieve our research goals in a high quality surrounding.

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