Shape? Shape. Shape!

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SVEN HIRSCH AND PHILIPPE BIJLENGA ON THE ANEUX PROJECT – MODELLING SHAPE AS A BIOMARKER FOR INSTABILITY OF INTRACRANIAL ANEURYSMS

Shape? Shape. Shape!

AN aneurysm is a disease of the blood vessel wall resulting in the deformation and enlargement of the vascular lumen. If the process of deformation remains active, the vessel wall may either rupture, and produce a haemorrhage, or thrombosis and ischaemia may occur. All vessels may be affected by this degenerative disease, but systemic and intracranial aneurysms are separate entities with different underlying causes and management.

The AneuX project focuses entirely on intracranial aneurysms (IAs), which are weak spots on brain arteries that balloon out (see Fig. 1). The aneurysm formed becomes a part of the circulation and will usually remain quiescent and asymptomatic. The lesion is similar to wounded skin that will normally heal and scar.

The initial event to form an IA is usually related to excessive blood flow; less frequently mycotic aneurysms are induced by intraluminal biochemical injuries or triggered by bacteria or cancer cells. Most IAs will heal without further symptoms. Only if the natural repair mechanism fails will the wound remain active and become inflamed. An active aneurysm is unstable; it grows and might rupture eventually. A ruptured aneurysm is potentially lethal or is the cause for severe disabilities and should be avoided by all means.

Frequent but usually benign

From the epidemiological data, the occurrence of the disease is estimated to be around 3% of the population. More precisely, the prevalence of intracranial aneurysms in the western world is estimated at 2.8% (95% confidence interval [CI] 2.0% to 3.9%).[1]

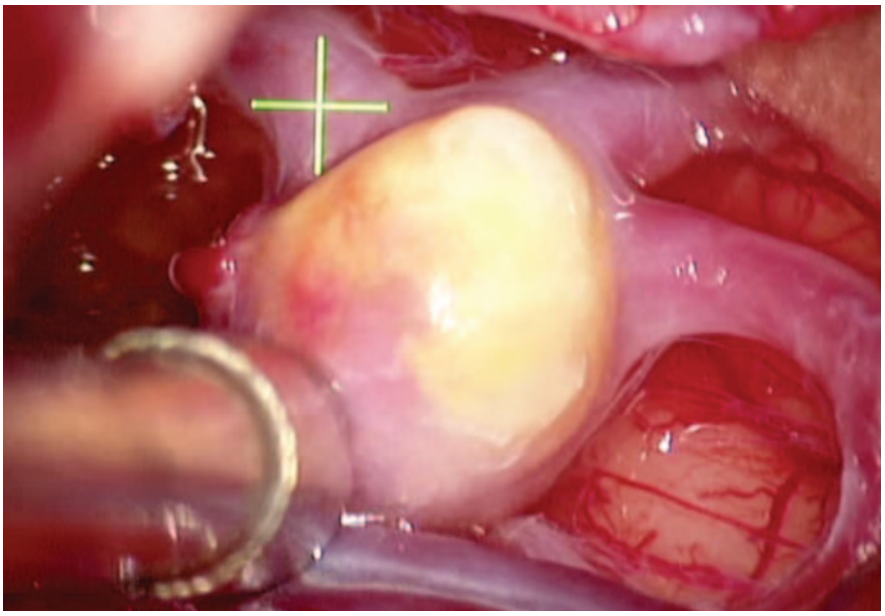

Fig. 1 An intracranial bifurcation aneurysm as presented to the neurosurgeon. The white part is a focal thickening of the aneurysm wall (hyperplasia)

The major danger with IAs is their rupture, which results in a subarachnoid haemorrhage (SAH). In Switzerland, the incidence of SAH is 4.61/100,000 inhabitants per year.[2] It peaks at 7.6/100,000 per year in the age group 55-59 years. The impact in terms of death, disability, and loss in workforce is approximately half the burden of road traffic accidents. Less than 10% of the patients suffering an SAH fully recover.

Since the beginning of the century, it has been demonstrated that most of the incidentally diagnosed IAs remain stable and represent a small threat in comparison to the risks associated with even the safest intervention procedure.[3] Statistics on large populations clearly show that the disease is frequent and threatening, but they also reveal that intervention is often even more dangerous than leaving the aneurysm untreated.

Diagnostic imaging

Another game changer in the equation is diagnostic imaging. Increasingly, asymptomatic dormant intracranial aneurysms are being detected. Radiologists often incidentally diagnose IAs when head imaging is prescribed by general practitioners in the context of headaches, by neurologists or ENT (ear, nose and throat) specialists in the case of vertigos or ill-defined spells, or by any physician in the context of a significant trauma.

Polycystic kidney disease (PKD) patients and patients with a positive familial history of IAs are systematically screened and approximately 10% are diagnosed with IAs. Most, if not all, SAH patients are diagnosed in neurovascular centres. As image-based diagnostics is increasingly being prescribed, the number of patients diagnosed with incidental IAs is likely to grow.

IA is a heterogeneous disease that results from the combination of multiple factors over time. Despite considerable effort, the understanding of the disease remains limited because of the disparate approaches adopted in basic, applied,

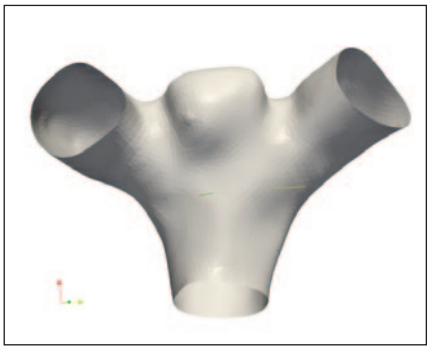

Fig. 2 A typical small bifurcation aneurysm. Of all IAs 70% are bifurcation type, 27% side-wall, the remaining are dissecting or ecstasies. Some aneurysms reveal features of all of these types

and clinical research, and the management of patients, in particular in low-incidence high risk subgroups (giant aneurysms, dissecting intracranial aneurysms, blister-like aneurysms), is contingent on the sharing of experience and data between multiple high volume centres. Overcoming these limits and significantly improving the management of patients, decision support, research, knowledge dissemination, and resource allocation requires a more integrative systems biology and precision medicine methodology, and the establishment of a disease-specific infrastructure.[4]

The biology of an aneurysm

The biology of initiation, development, and rupture of aneurysms is complex. It involves a cascade of physiological and pathophysiological events that involve actors as diverse as signalling molecules and mechanical forces.[5] Those actors intervene at all levels of biological organisation, from the molecular (signalling) to the subcellular extra cellular matrix (ECM), cellular (EC, SMC, T-cells, monocytes, macrophages), tissue (mechanical properties, flow) and organ scale. These interactions create a highly complex, multi-scale system facilitating the emergence of specific behaviours and properties, such as endothelial cells (EC) and smooth muscle cells (SMC) division and migration, ECM remodelling, inflammation, and clotting resulting in the healing or destruction of the vessel wall. The aetiology of vascular degeneration can therefore only be understood by studying those players in their interaction, i.e. by applying a systems biology approach.

It is known that shear forces induced by the blood on the vessel wall and cyclic stretching by pulse waves drive the vascular remodelling. The ability of a blood vessel to respond to haemodynamic stimuli is mainly mediated by the endothelium that forms the innermost layer of the vascular wall, and is in direct contact with blood flow.

The general consensus is that IAs progress through different stages. Each stage is associated with specific predisposing factors, injuries, repair mechanisms and treatments that all influence the balance between healing and progression.[6] Although the disease is most probably a continuum, the following disease milestones can been identified: 1) Disease initiation; 2) aneurysm growth; 3) aneurysm increase in shape heterogeneity; 4) aneurysm rupture; 5) bleeding; 6) cerebral ischaemia; 7) vasospasm; 8) hydrocephalus; and 9) recurrence.

The aneurysm disease reveals resemblances with atherosclerosis.[7] Extensive research has linked athero-prone blood flow conditions to atherosclerotic plaque development and stability.[8] While there is clear evidence relating abberant blood flow to aneurysm formation[9] only limited and incomplete information has been reported concerning blood flow conditions associated with growth and rupture. It is observed that biological reactions of the vessel wall result in shape modifications that are visible using modern routine imaging procedures and can be analysed and modelled.

To treat or not to treat

Some physicians have dubbed it a 'ticking bomb' that demands an aggressive treatment. This wording implies that rupture is inevitable and the 'bomb' needs to be secured by any means. Today, we know that this over-simplification is untrue and possibly hazardous. Treatment comes at significant risk and the outcome may very well be similarly devastating as a spontaneous rupture. Most aneurysms remain stable and the spontaneous rupture is the exception rather than the rule.

Although statistically safe, some IAs do rupture. The physician thus needs to decide what to do for the individual patient. Obviously, an aneurysm should only be treated if the treatment is less risky than the aneurysm itself. So far, no accepted criteria exist for individual assessment of aneurysm stability and there are no clear treatment guidelines. Studies suggest evidence for blood flow and pressure-related reasons, for genetic causes and for biological mechanisms. There is no consistent overall picture and no universal landmarks have yet been identified. Consequently, there is currently no validated tool to help predict development or treatment outcomes for an individual aneurysm and physicians rely solely on their personal judgement.

Today, more and more aneurysms are left untreated, which in turn implies that these patients require regular follow-up monitoring. The decision to intervene preventively requires an assessment by a specialised team in a high volume and certified centre to minimise the associated risks.

The selection of an invasive, complex, skill and resource intensive, and technically rapidly evolving procedure or endovascular treatment needs to be carefully evaluated. Most patients suffer associated chronic comorbidities and present risk factors, of which arterial hypertension and smoking are the most relevant that need to be managed by appropriate specialists in the long term.

All patients need a regular clinical and imaging follow-up. The prediction of both the threat and the risks is based on an assessment of a growing list of factors. Oversimplification, i.e. ignoring certain factors, either results in: an increased threat as a consequence of a failure to predict SAH; in

overuse of medical resources; or in increased risks as a consequence of inadequate case selection and patient exposure to invasive procedures.

The complexity of decision making regarding IA management has significantly increased since the last century. During the 1980s, all diagnosed aneurysms were considered high risk and treated by microsurgical clipping. Since then, technical innovations provide new, non-competing, complementary treatment options. So today we are in the situation where selecting the optimal treatment becomes increasingly complex. A systematic review reported that the use of flow-diverter devices is advisable mainly for unruptured intracranial aneurysms (UIAs) located in particular locations, for fusiform aneurysms, or for dissecting and saccular aneurysms with a large dome-to-neck ratio.[10]

Prior to rupture, most patients are totally asymptomatic and aneurysm rupture represents a major insult. Existing disease models integrate six to 28 factors and either estimate a five year absolute risk of rupture ranging from <1% to 15% or balance risks between observation and intervention based on expert consensus.[11] These models need prospective validation of clinical usability, safety and accuracy.

AneuX

The AneuX consortium collects a comprehensive number of patient data sets to estimate the disease status of intracranial aneurysms. The starting point is the hypothesis that vessel 3D shapes can be used as an image biomarker. Research and development in the field require massive information integration realised by a diverse community of scientists, physicians, and engineers involved in better understanding the biological processes, and the development of new tools to manage and treat patients.

The neurosurgeon Philippe Bijlenga from the Hôpitaux Universitaires de Genève (HUG) is leading the project, with modelling expert Sven Hirsch from Zürich University of Applied Sciences (ZHAW) being the co-lead. Additional partners are the vessel biologist Brenda Kwak (University of Geneva); the veterinarians Katja Nuss and Brigitte von Rechenberg from the VetSuisse faculty of the University of Zürich; Niels Kuster with joint affiliation from ETH Zürich, IT'IS foundation and the SwissNeuroFoundation represented by the neuro-interventionalist Daniel Rüfenacht. The project is funded by the Swiss systems biology initiative SystemsX.ch.

The partners involved follow a dual strategy centered on shape characterisation and biological pathway identification:

- The clinical track collects and organises clinical evidence, using machine learning techniques to consider shape descriptors; and
- The biological track integrates the basic biological findings of mechano-biological transduction into a vessel-remodelling simulator. The simulations are validated with an experimental animal model of growing aneurysms.

Combined, these approaches will improve both the prediction of disease progression and clinical decision making. The long term goal is to generate an integrated mathematical model able to predict disease trajectory and treatment outcomes.

Clinical track

The clinicians involved collect and provide high quality information and biological samples from patients. They are responsible for evaluating the clinical relevance and use of tools and information provided by other project partners, and will design a clinical trial to assess the predictive power of the final disease model. The team aims to verify the PHASES score prediction[12] and assessment of treatment risk using a continuously extended data based on the multi-centric international @neurIST cohort.

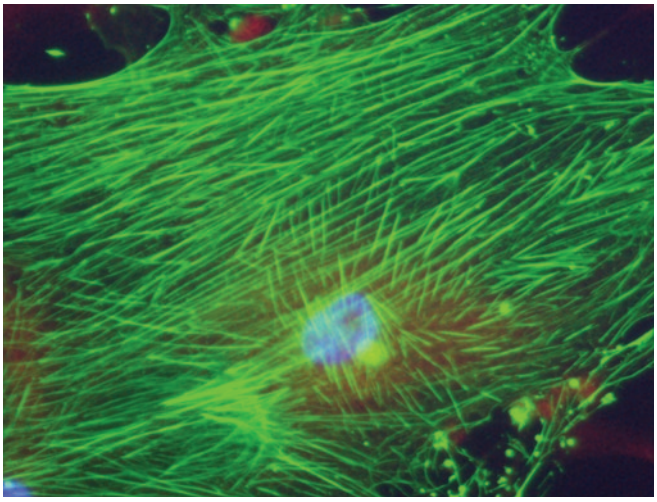

Fig. 3 Human carotid artery smooth muscle cells (Elchrom Scientific AG, Switzerland) cultured on a flexible membrane (FlexCell, Dunn Labortechnik GmbH, Germany) and immunostained for alpha-smooth muscle actin (in green). Cells are counterstained with Evans Blue (in red) and nuclei are stained with DAPI (in blue). Courtesy of: MR Diagbouga and BR Kwak, University of Geneva.

The team of clinicians and modelling experts will devise a statistical disease model. For this we will first understand how the aneurysm can be best represented with shape descriptors using the established 3D Zernike invariant moments as a starting point. We will then develop metrics to compare different aneurysm shapes. The last step is to set up a machine learning-based Bayesian framework to explore statistical associations within the database. This exploratory tool will be handed to the clinicians to further improve the disease model. The main outcome will be an holistic disease model to better balance benefit/risk of clinical decisions and an infrastructure to continuously collect high quality information from the bedside.

The available cases are collected in a unified database containing imaging and clinical patient information on intracranial aneurysms. The AneurysmDataBase (ADB) hosted by the Swiss Neuro Foundation[13] aspires to establish the standard for collecting and characterising intracranial aneurysms. The team develops web-based applications to inspect, analyse and display the AneurysmDataBase for various users: clinicians, patients and industry. The SwissNeuroFoundation will host the AneurysmDataBase, thus ensuring economical sustainability and accessibility of the information platform after the funding period.

Using available data and tools acquired and developed in the context of the European FP6 @neurIST project,[14] a second generation information platform will be developed and later disseminated across medical and academic centres in Switzerland using the Swiss Subarachnoïd Outcome Study (Swiss SOS) working group.

The information infrastructure and disease model will be harmonised to serve as an information backbone, bridging with other systems in the field of cardiovascular diseases, neurovascular diseases, and neuro-oncology using vessel biology as the common denominator.

Biological track

The second strand performs *in vitro* biological experiments and formulates mathematical models to represent these. In particular, the biologists study the effects of biomechanical factors on the structure and composition of the aneurysm wall. As mechanical stimuli, different shear stress, and circumferential stretch are considered and the molecular responses of vascular wall cells observed *in vitro* (Fig. 3). Layered (immuno-)histochemical characterisation is used to reconstruct human aneurysm domes. The modelling team produces a dynamic mechano-biological transduction model of the disease.

Next to the purely biological experiments, the team establishes and performs the computational fluid dynamics and structural mechanical simulations. This generates gender-specific estimations of the pathological flow conditions encountered at different disease stages (WSS, pressure, intramural stress). Those conditions are applied in the *in vitro* experiments to investigate the cellular reaction to gender specific pathological conditions.

The simulations are performed with the Sim4Life multi-physics framework and couple fluid flow with an established structural wall model from the Paul Watton (University of Sheffield). Considerable simulation functionality is needed for this project to couple fluid-solid interactions with the wall biology model. In this work stream, ZurichMedTech (ZMT) contributes basic framework functionalities.

The last step links the mechanically-related biological findings with the fluid and structure mechanical model. Known and new information across observation scales and time are integrated to generate a dynamic model of the disease. In this way, we can predict the altered composition of the aneurysm wall needed to simulate the structural changes. The local modification in wall mechanics will inevitably alter the three-dimensional shape of the IA. This fundamental tool will be validated against observation in growing side-wall aneurysms in animal experiments following the Helsinki rat model.

Understanding vessel wall remodelling and degenerative vascular diseases on a purely scientific level requires the collaboration of experimentalists and theoreticians (mathematicians, physicists and computer scientists). Exploiting this knowledge to develop predictive tools for personalised medicine, which can be embedded into the daily clinical practice, requires active participation of clinicians and the expertise of engineers. This interdisciplinary approach, which is a landmark of systems biology, is a prerequisite to reaching the targets of AneuX.

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