Travis C. Valentine Memorial Aneurysm Research Fund
George Mason University
2023 Annual Research Report Research Update

During the past year (2023) we continued to make significant progress in the identification and understanding of conditions that predispose aneurysms for destabilization and rupture which can be used to improve current clinical evaluation of cerebral aneurysms. We also made progress in understanding healing mechanisms after treatment with flow diverting stents.

Selected Research Studies:

Quantifying Flow Stagnation in Cerebral Aneurysms
Blood flow stagnation (slow recirculation within the aneurysm) is thought to be a risk factor for aneurysm growth and rupture. However, the degree of flow stagnation in a given aneurysm has not been quantified and analyzed. We have recently developed a simple computational tool (i.e. a Matlab code) to quantify the degree of contrast retention in aneurysms based on digital subtraction angiography image sequences routinely gathered in the clinics. This tool will enable studies relating flow stagnation to aneurysm characteristics (e.g. rupture) as well as other clinical and patient characteristics. These studies are conducted in collaboration with our colleagues from UCLA and the University of Pittsburgh.

Fibrin Deposition Modeling
We continued studying fibrin accumulation on flow diverting devices in collaboration with the Mayo Clinic. Flow diverting devices (stents) are becoming more and more commonly used to treat cerebral aneurysms (especially the most problematic ones) because they are easy to deploy. However, whether the aneurysm will occlude fast or remain open for a long time is not well understood. Fibrin deposition on the device wires and progressive occlusion of the device cells seems to be an important mechanism which leads to aneurysm occlusion. As such, we are investigating fibrin production and adhesion to the device and simultaneous alteration of the flow and progressive occlusion of the aneurysm. For this purpose, our colleagues at the Mayo Clinic have developed in-vitro models of stented aneurysms and assessed the fibrin deposition on the devices. This work has resulted in a paper accepted for publication: Bilgin et al. “In vitro evaluation of flow diverter performance using a human fibrinogen-based flow model”, J. Neurosurg. (JNS), 2024 - accepted. In parallel, at Mason, we are developing complex computational models to understand these mechanisms in detail. These models couple the flow dynamics to transport (convection and diffusion) and reactions between the different species involved in the clotting process. Current results indicate that fibrin is produced when fibrinogen is exposed to high levels of shear stress as blood flows through the stent cells and adheres to the device wires which then alters the flow though the device and into the aneurysm. Understanding these processes is important to assess the outcome of flow diverting treatment as well as developing the next generation of devices (e.g. those that stimulate fibrin deposition and thus rapid aneurysm occlusion). A second paper describing the computational models and results is under preparation.

Quantification of Flow Features in Different Regions of the Aneurysm
We developed a strategy to subdivide the aneurysm sac into different regions and characterize the local flow conditions in each region. In particular, we detect critical points of the wall shear stress vector field

which is thought to have a detrimental effect on the cells of the aneurysm wall. This work enabled studies of the prevalence of different pathologic conditions of the aneurysm wall such as thinning or thickening, growth, and failure and the relationship to the underlying hemodynamic conditions. A paper describing this strategy has been submitted: Karnam et al. "Description of the local hemodynamic environment in intracranial aneurysm wall subdivisions" Int. J. Num. Methd. Biomed. Eng. (IJNMBE), 2024 – under review.

Analysis of Rupture Site Locations

By inspection of intra-operative videos, we identified the rupture site in 30 aneurysms that were treated surgically and characterized the rupture location with respect to the neck, body or dome of the aneurysm as well as the inflow, central or outflow location along the flow streamlines. We found that most ruptures occur in association with blebs, but thin blebs tend to develop in regions exposed to high flow conditions (high wall shear stress and its gradient typically in the inflow zone), while thick atherosclerotic blebs tend to occur towards the dome of the aneurysm where flows are slow and more oscillatory. These findings are important to advance our knowledge of the relationship between local flow conditions and changes to the wall structure that result in wall fragility and eventually rupture. A paper describing these results has been submitted: Karnam et al. "Distribution of rupture sites and blebs on intracranial aneurysms" Int. J. Num. Methd. Biomed. Eng. (IJNMBE), 2024 - under review.

Analysis of Aneurysm Growth Regions

In this work, we examined the location where aneurysms enlarged (i.e. growing regions) and related them to the underlying flow conditions. The results suggest that aneurysms at different anatomical locations may be subject to varying flow conditions that predispose their walls to progress in different manners, for example by inflammation and thickening when exposed to low flow conditions and vortex flows, and by thinning and decellularization when exposed to high flow conditions and impingement. A paper reporting these results has been produced: Karnam et al. "Competing pathways of intracranial aneurysm growth: linking regional growth distribution and hemodynamics", JNS 2024 – in submission.

This study was conducted in collaboration with researchers from the University of Pittsburgh, and used data from our clinical collaborators from University of Illinois at Chicago, Allegheny General Hospital (Pittsburgh), Northwell Hospital (New York), and Helsinki and Tampere Medical Centers (Finland).

Assessment of Intramural Stress in Heterogeneous Aneurysm Walls

In intra-operative videos, we have identified regions of the aneurysm wall that correspond to thin walls (observed as red translucent walls) and thick atherosclerotic walls (that appear opaque white or yellow). Using this information, we are developing computational models to estimate the intramural stress (internal forces in the aneurysm wall) that are responsible for aneurysm rupture. We are creating these models for approximately 130 aneurysms with identified wall regions and will subsequently investigate the effects of these heterogeneous walls on the concentration or diffusion of intramural stresses and their relationship to aneurysm rupture.

Future Research Plans:

Our future efforts will aim at improving the understanding of both the disease process and the mechanisms of healing for enhancing aneurysm evaluation, clinical management, and minimally invasive treatment. In particular we will focus on the following studies:

Fibrin deposition modeling
We will continue to develop and evaluate the computational models of fibrin accumulation and use it to understand the effects of vascular geometries, concentrations of different species such as thrombin, as well as anti-coagulation agents such as heparin and calcium.

Understanding effects of flow stagnation
Using our previously developed approach based on synthetic angiograms as well as recently developed tools for quantifying contrast retention in aneurysms, we will study the relationship between the degree of flow stagnation in aneurysms and their likelihood of rupture, growth, and becoming symptomatic. This is important for making the aneurysm evaluation process more precise and personalized.

Categorizing aneurysm walls and analyzing their relationship to flow
We are developing categories of aneurysm walls by inspection of intra-operative videos and identification of thin and thick regions and will subsequently associate these wall categories to aneurysm flow conditions. This work is quite advanced, and we expect to produce a journal paper soon.

Assessment of Intramural Stress in Heterogeneous Aneurysm Walls
We will continue to develop and automate solid mechanics models of aneurysms to understand the distribution of stresses on the aneurysm wall, and the effects of heterogeneous walls.

Linking flow structures and endothelial cell responses
In collaboration with our colleagues at UCLA we are investigate how endothelial cells respond to different flow conditions, including flow impingement, vortex flows, and flow stagnation. For this purpose, we have conducted computational simulatitons and identified different flow features which are now been analysed with endothelializad in vitro models at UCLA.

Understanding MRI wall enhancement through computational models
A recent imaging approach called MRI wall enhancement has been developed which has been claimed to depict aneurysm wall inflammation. However, the mechanism responsible for this imaging effect if poorly understood. We intend to develop a computational model that incorporates the transport, diffusion, and retention of the injected contrast agent to explain the current observations of wall enhancement.

Develop models of endothelialization after endovascular treatment
We intend to develop models of device endothelialization (i.e. coverage of device wires by endothelial cells that migrate from the parent artery) to further understand the healing process after treatment (endothelialization occurs after occlusion of the aneurysm neck by either thrombus formation or fibrin deposition).

Develop models of inflammatory cells infiltration and migration within the aneurysm wall
We are developing novel computational techniques to model macrophage activity to better understand their collective motion and effects on the vascular walls.

Grants:

The last year has been year three of our three current NIH grants to our Laboratory for Computational Hemodynamics for studying cerebral aneurysms. Part of this successful research is thanks to the generous funds that allow us to focus on producing important preliminary studies to support the grant proposals.

Current Awards:
1-Title: *Improving cerebral aneurysm risk assessment through understanding wall vulnerability.* Collaborators: University of Pittsburgh, Allegheny General Hospital (Pittsburgh), University of Illinois at Chicago, Northwell Hospital (New York), Helsinki Medical Center (Finland), Tampere University (Finland). Duration: 5 years. Funding: National Institutes of Health (National Institute of Neurological Disorders and Stroke).

2-Title: *Bridging the gap from hemodynamic stress to intracranial aneurysm instability*. Collaborators: University of California Los Angeles, University of Pittsburgh, Allegheny General Hospital (Pittsburgh). Duration: 5 years. Funding: National Institutes of Health (National Institute of Neurological Disorders and Stroke).

3-Title: *Computational and biological approach to flow diversion*. Collaborators: Mayo Clinic. Duration: 5 years. Funding: National Institutes of Health (National Institute of Neurological Disorders and Stroke).

Use of Valentine Memorial Funds:

During the last year funds from the Valentine Memorial Fund were used to:
1) Support Graduate Research Assistants (GRAs) during the summer, which allowed these PhD students (Mr. Alireza Chitzas) to focus on some of the research activities described above
2) Support faculty research over the summer.

Support from the Valentine Memorial Funds is extremely valuable because of its flexibility which allows us to focus on otherwise unfunded efforts that we believe will have an important impact on the clinical practice and management of aneurysms. In order to advance the research efforts mentioned above, we plan to continue using the Valentine Memorial Funds to:

a) Support Graduate Research Assistants.
b) Support faculty effort during summer.
c) Cover publication costs.
d) Cover conference costs (domestic and international).
e) Cover research visits to collaborators and other colleagues Laboratories to learn from their experiences and develop a unified theory of aneurysm disease.
f) Buy new / update equipment (laptop for new student, workstation, data server) as needed.