Travis C. Valentine Memorial Aneurysm Research Fund

George Mason University

Research Update – 2022

During the past year (2022) we made significant progress in the identification of conditions that predispose aneurysms for destabilization and rupture which can be used to improve current clinical evaluation of cerebral aneurysms. Additionally, we made progress in understanding healing mechanisms after treatment with flow-diverting stents.

Selected Research Studies:

Analysis of Fibrin Deposition on Flow Diverting Devices

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. Aneurysm occlusion after stenting is thought to occur because of thrombus formation within the aneurysm sac after stent deployment. However, fibrin deposition on the device wires and progressive occlusion of the device cells seem to be another mechanism that may be even more important for aneurysm occlusion. As such, we are investigating fibrin production and adhesion to the device and subsequent alteration of the flow and progressive occlusion of the aneurysm. For this purpose, our colleagues at the Mayo Clinic are developing in-vitro models of stented aneurysms and assessing the fibrin deposition on the devices, while in parallel, we at Mason are developing corresponding computational models to understand these mechanisms in detail. Preliminary results indicate that fibrin is produced in association with shear stress and adheres to the device wires preferably at the inflow location, which then alters the flow through the device and into the aneurysm. This information 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). A first paper describing these results is under preparation.

Assessment of 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. Therefore, we develop a technique based on a “virtual-angiogram” (i.e., a simulation of the transport of contrast along the arteries and the aneurysm) that can be used to detect and assess the level of flow stagnation in cerebral aneurysms. We validated this approach by comparing it with actual X-ray angiograms of aneurysm patients evaluated by an expert neurosurgeon. We demonstrated that flow stagnation can be automatically detected with a precision of over 90%. This is important because it enables studies aiming at connecting flow stagnation and clinical outcomes as well as understanding why these flow conditions are detrimental to the aneurysm wall (which is the focus of current studies).

These results were published in the following paper: Hadad S, Karnam Y, Mut F, Lohner R, Robertson AM, Kaneko N, Cebral JR, “CFD-based virtual angiograms for the detection of flow stagnation in intracranial aneurysms”, IJNMBE, 2023 (DOI: 10.1002/cnm.3740). This study was conducted in collaboration with our colleagues from UCLA and the University of Pittsburgh.

Prediction of Aneurysm Growth

We trained machine learning (ML) models with hemodynamic, geometric, clinical, and demographic data of over 2,500 aneurysms to identify which aneurysms are likely to grow focally and develop blebs which significantly increases their rupture risk (and thus should be recommended for early treatment). These models were validated with a longitudinal dataset of 174 aneurysms that had been followed in time without treatment. We found that the best ML model was able to identify 85% of aneurysms that grew during observation and it misclassified 20% of the stable ones that did not grow. We concluded that these models could be used as early indicators of future risk in clinical practice.

The results have been published in the Journal of Neuro-Interventional Surgery: Hadad S, Mut F, Slawski M, Robertson AM, Cebral JR, "Evaluation of predictive models of aneurysm focal growth and bleb development using machine learning techniques", JNIS, 2023 (DOI: 10.1136/jnis-2023-020241). This study was conducted in collaboration with researchers from the University of Pittsburgh and used data from our clinical collaborators from the University of Illinois at Chicago, Allegheny General Hospital (Pittsburgh), Northwell Hospital (New York), and Helsinki and Tampere Medical Centers (Finland).

Analysis of Aneurysm Rupture Modes

Previous studies (including ours) have shown that the presence of blebs or secondary outpouchings in the aneurysm wall is associated with an increased risk of rupture. However, it is poorly understood how these blebs develop and how they affect the vulnerability of the aneurysm wall. We conducted a study that compared the blood flow and geometric characteristics of aneurysms that ruptured while harboring blebs against those that ruptured without developing blebs. We found that aneurysms at different locations are likely to develop different shapes and thus be exposed to different flow conditions that may predispose them to follow different pathways towards rupture either with or without bleb development. This finding could explain the different rupture rates and bleb presence observed in aneurysms at different locations.

These results were reported in the following paper: Salimi Ashkezari SF, Mut F, Robertson AM, Cebral JR, "Differences between ruptured aneurysms with and without blebs: mechanistic implications", Cardiovasc Eng Tech (CVET), 14, 92-103, 2023 (DOI: 10.1007/s13239-022-00640-4). This study was conducted in collaboration with our colleagues from the University of Pittsburgh.

Preliminary 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. This in turn is valuable to enhance

the current evaluation of aneurysms and support clinical treatment decisions. These results will be published in a paper that is currently under preparation.

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 model evaluation and validation
We will further develop the fibrin deposition model and compare it with the in-vitro models developed at the Mayo Clinic to tune in the parameters and validate the results.

Understanding effects of flow stagnation
Using the newly developed approach based on synthetic angiograms, we will identify aneurysms with flow stagnation in our database and study their association with aneurysm rupture, growth, and other clinical characteristics.

Categorizing aneurysm walls and analyzing their relationship to flow
We will develop categories of aneurysm walls by inspection of intra-operative videos and identification of thin and thick regions, and subsequently associate these wall categories to aneurysm flow conditions.

Linking flow structures and endothelial cell responses
In collaboration with our colleagues at UCLA, we will investigate how endothelial cells respond to different flow conditions, including flow impingement, vortex flows, and flow stagnation.

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).

Understanding MRI wall enhancement through computational models
A relatively new 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.

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.

Grants:

The last year has been year two 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 Ph.D. students (Mr. Alireza Chitsaz and Ms. Sara Hadad) to focus on some of the research activities described above Ms. Hadad successfully defended her Ph.D. thesis and graduated in the Spring of 2023.
2) Support faculty research over the summer.
3) International conferences: Due to the COVID-19 pandemic, all conferences we attended this year have been conducted online. Thus, we did not spend funds as expected.

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. To advance the research efforts mentioned above, we plan to use the Valentine Memorial Funds to:

a) Support Graduate Research Assistants
b) Support faculty efforts during the summer
c) Cover publication costs

d) Cover conference costs (domestic and international)
e) Buy new / update equipment (laptop for new student, workstation, data server) as needed