Travis C. Valentine Memorial Aneurysm Research Fund
George Mason University
2021 Annual Research Report

During the past year 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.

Selected Research Studies:

Preliminary Analysis of Small and Regularly Shaped Aneurysms

Although aneurysm size as well as shape irregularity are the most commonly used factors to evaluate the rupture risk of cerebral aneurysms, it is well known that many incidentally detected aneurysms (approximately 30% of all aneurysms) are small (<7mm) and have regular shapes (without blebs or secondary outpouchings). As such, current evaluations would consider these to be low-risk aneurysms even though approximately 20% of them go on to rupture. Over the past year, we analyzed a sample of over 700 small and regularly shaped aneurysms and found significant differences in the hemodynamics, shape, and anatomical location between ruptured and unruptured aneurysms in this important sub-population. We then used these aneurysm characteristics to build statistical and machine learning models that can predict the rupture of small regularly shaped aneurysms.

These results were reported in a paper which has recently been accepted for publication in the American Journal of Neuroradiology [Salimi Ashkezari SF, Mut F, Slawski M, Jimenez CA, Robertson AM, Cebral JR, “Identification of small and regularly shaped cerebral aneurysms prone to rupture”, AJNR 2022]. In addition, these findings were used as preliminary studies in a grant proposal entitled “Enhancing the evaluation of small and regularly shaped cerebral aneurysms” submitted to the NIH, which is currently under review.

Preliminary Analysis of Aneurysm Rupture Modes

Previous studies (including ours) have shown that the presence of blebs or secondary outpouchings in the aneurysm wall are associated with increased risk of rupture. However, it is poorly understood how these blebs develop and how they affect the vulnerability of the aneurysm wall. Recently, we conducted a study that compared the hemodynamic and geometric characteristics of aneurysms that ruptured while harboring blebs against those that rupture without developing blebs. We found that aneurysms at different locations are likely to develop into different morphologies and thus be exposed to different flow conditions that may predispose them to follow different pathways towards rupture 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 a paper that is currently under review [Salimi Ashkezari SF, Mut F, Robertson AM, Cebral JR, “Differences between ruptured aneurysms with and without blebs: mechanistic implications”, submitted to Cardiovascular Engineering and Technology (CVET), 2021].

Prediction of Bleb Formation in Cerebral Aneurysms

Since the development of blebs in cerebral aneurysms represents a loss of stability and an important increase in their risk of rupture, identifying early on which aneurysms are prone to develop blebs is important for improving the management of these aneurysms. Using a large database of over 2,500 cerebral aneurysm models that provide detail hemodynamic, geometric and anatomical information, we developed statistical and machine learning models to estimate the likelihood that an aneurysm will develop a bleb and possibly rupture.

The results have been published in the Journal of Neuro-Interventional Surgery [Salimi Ashkezari SF, Mut F, Slawski M, Cheng B, Yu A, White T, Koch MJ, Amin-Hanjani S, Charbel F, Rezai Jahromi B, Niemela M, Koivisto T, Frosen J, Tobe Y, Maiti S, Robertson AM, Cebral JR, "Prediction of bleb formation in intracranial aneurysms using machine learning models based on aneurysm hemodynamics, geometry, location, and patient population", JNIS 2021 (DOI: 10.1136/neurintsurg-2021-017976]. This study was conducted in collaboration with Bioengineering researchers from the University of Pittsburgh, and clinical collaborators from University of Illinois at Chicago, Allegheny General Hospital (Pittsburgh), Northwell Hospital (New York), and Helsinki and Tampere Medical Centers (Finland).

Evaluation of Outcome Prediction after Treatment with Flow Diverting Devices

In previous studies, we have proposed the use of patient-specific computational models to predict the outcome of minimally invasive endovascular procedures that consist in implanting a flow diverting device (stent) to treat cerebral aneurysms. This is important because not all aneurysms are obliterated by these devices and remain patent for a long time after treatment, and thus it is important to identify aneurysms that are prone to remain incompletely occluded and alter the treatment plans to personalize and optimize the procedure. In collaboration with researchers from the Mayo Clinic, we recently conducted a validation study to compare model-based predictions and outcomes using animal models developed at the Mayo Clinic. We showed that computational models are indeed capable of predicting outcomes with approximately 80% accuracy.

These results were recently published in the American Journal of Neuroradiology [Hadad S, Mut F, Ding Y, Kadirvel R, Kallmes D, Cebral JR, "Evaluation of outcome prediction of flow diversion for intracranial aneurysms", AJNR 2021 (DOI: 10.3174/ajnr.A7263)].

<u>Grant Awards and Proposals:</u>

The past year has been extremely successful in terms of grant awards for our Laboratory for Computational Hemodynamics for studying cerebral aneurysms. Part of this success is thanks to the generous funds that allow us to focus on producing important preliminary studies to support the grant proposals.

Grants Awarded:

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).

Proposals Pending:
4-Title: *Enhancing the evaluation of small and regularly shaped cerebral aneurysms*. Collaborators: Mayo Clinic. Duration: 5 years. Funding: National Institutes of Health (National Institute of Neurological Disorders and Stroke).

5-Title: *Mechanistic understanding of healing response to novel intrasaccular therapies*. Collaborators: Mayo Clinic. Duration: 5 years. Funding: National Institutes of Health (National Institute of Neurological Disorders and Stroke).

Future 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:

Evaluation and validation of predictive models of bleb development
We will use longitudinal data of cerebral aneurysms followed without treatment to evaluate and validate predictive statistical and machine learning models of bleb development. For this purpose, we will classify aneurysms into a stable group (no change during observation), focal growth (growth in a small portion of the aneurysm with bleb formation), and global growth (uniform enlargement of the aneurysm) and compare these outcomes to the model predictions based on hemodynamic, geometric and anatomical characteristics.

Aneurysm wall categorization and relationship with flow
We will classify aneurysm walls into different categories depending on their visual appearance in intra-operative videos. In particular this will consider atherosclerotic changes to the wall, wall thinning, and bleb formation in order to stratify the vulnerability of different aneurysm walls. Subsequently, we will investigate possible associations between flow conditions and wall properties to understand what conditions predispose aneurysms for the different wall structural changes.

Inflammation and aneurysm wall enhancement
Based on the results of the previous study, we will develop models of aneurysm wall inflammation and subsequently aneurysm wall enhancement during contrast-enhanced magnetic resonance imaging. This

imaging modality is a promising approach for assessing the status of the aneurysm wall non-invasively, but it is poorly understood which processes are responsible for the wall enhancement. As such, we will test the hypothesis that wall enhancement can only be observed in thick and permeable aneurysm wall that contain significant numbers of inflammatory cells (macrophages) that can ingest and retain the Gadolinium contrast injected to image the walls. This is important because, if confirmed, this knowledge will provide support to the idea of using aneurysm wall enhancement images to visualize the inflammation of the aneurysm wall, which is presumably associated with increased risk of instability and rupture.

Healing mechanisms
Finally, we will focus on developing models of the different processes responsible for the healing of aneurysms after implantation of endovascular devices. These processes, which are modulated by the local flow conditions, include clotting and thrombus formation, fibrin deposition, and endothelial cell coverage by cell migration and proliferation. We will develop computational models based on transport and reaction equations to simulate these processes on patient-specific vascular models with implanted endovascular devices. This is important to improve current endovascular devices and procedures, personalize the treatment, and enable the development of non-invasive management strategies to stabilize the aneurysms without surgery.

Use of Funds:

During the last year funds from the Travis Fund were used to:

1) Support two Graduate Research Assistants (GRAs) during the summer, which allowed these PhD students (Ms. Sara Hadad and Ms. Setareh Salimia) to focus on some of the research activities described above (specifically analysis of aneurysm evolution and aneurysm wall enhancement). Ms. Salimia graduated in the Summer of 2021. Ms. Hadad made substantial progress towards their PhD Dissertation.
2) Cover publication costs of a paper in American Journal of Neuroradiology.
3) International conferences: due to the Covid-19 pandemic, all conferences we attended this year have been conducted online. Thus, we did not spend fund as expected.

Support from the Travis C. Valentine Memorial Aneurysm Research Fund 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 use the Travis C. Valentine Memorial Aneurysm Research Funds to:

a) Support current Graduate Research Assistants during the summer
b) Support a new Graduate Research Assistant during the academic year
c) Support faculty effort during both academic year and summer
d) Cover publication costs
e) Cover conference costs
f) Buy new / update equipment (workstation, data server) if needed