

## Travis C. Valentine Memorial Aneurysm Research Fund

### George Mason University

#### 2020 Annual Research Report

During the past year, we have made significant progress towards better assessment of cerebral aneurysm rupture risk and understanding the disease process. In particular, we have completed the following studies:

- a) Analysis of bleb prevalence and association with clinical factors: blebs are a secondary outpouching located on the aneurysm sac and have been identified as a risk factor for aneurysm rupture. However, the prevalence in the aneurysm population as well as the mechanisms responsible for their development and rupture are not well understood. In this first study, we focused on characterizing the prevalence of blebs and investigating possible associations with patient and clinical factors. We found that blebs are common (they are present in 30-40% of aneurysms) and tend to occur more often at certain anatomical locations such as the anterior communicating artery. We also found that aneurysm patients with dental infections are more likely to harbor blebs, and that hormone replacement therapy seems to be protective against the formation of blebs. This study is important because it has identified a clinically controllable factor associated with risk of aneurysm instability. This study was published in the Journal of Neuro Interventional Surgery (JNIS).
- b) Analysis of hemodynamics and bleb formation: in a second study focusing on blebs, we compared the hemodynamic (blood flow) characteristics of aneurysms that developed blebs and aneurysms without blebs. We found that aneurysms that develop blebs tend to have blood flow patterns characterized by larger wall shear stress and gradients than aneurysms less likely to develop blebs. These results are important because they suggest that it could be possible to identify patients with aneurysms that are more likely to develop blebs (early risk indicator). This study was also published in the Journal of Neuro Interventional Surgery (JNIS).
- c) Analysis of hemodynamics and bleb walls: in a third study, we identified two distinct types of blebs by inspection of intra-operative videos, one type has thin translucent walls while the other thick atherosclerotic walls. We then compared the hemodynamic conditions that favor the formation of these different types of blebs. We found that thin blebs are associated with stronger flows, while atherosclerotic blebs are associated with slow / stagnant flows. These results are important because they indicate that not all blebs are equal and should not be analyzed as a single group. This study was also published in the Journal of Neuro Interventional Surgery (JNIS).
- d) Analysis of aneurysm wall enhancement and hemodynamics: recently it has been proposed that changes in the aneurysm wall permeability and subsequent inflammation can be observed in so called aneurysm wall enhancement sequences in magnetic resonance images. We collaborated with a group at the University of Iowa that has obtained such MRI images at high field strengths (7T) in patients with cerebral aneurysms. We analyzed the association between local flow conditions and aneurysm wall enhancement to understand the effects of these flow conditions, as well as to better interpret the significance of these imaging techniques. Similarly, to our blebs study, we found that not all regions of aneurysm wall enhancement are equal. Some are located near the aneurysm inflow and are exposed to high flow conditions, while others are far from the inflow and are exposed to slow flows. This suggests different mechanisms that affect the wall differently in these distinct regions. This study was published in the American Journal of Neuroradiology (AJNR).

- e) Analysis of hemodynamic evolution from aneurysm inception to rupture: we finalized our investigation how flow conditions change from the time of aneurysm formation to the final stages of aneurysm rupture or stabilization. This information is important for improving our understanding of mechanisms responsible for aneurysm wall degeneration and weakening and for enabling new therapeutic strategies targeting specific pathways involved in aneurysm wall degradation. We found that flow conditions evolve differently if the aneurysm neck grows as the aneurysm enlarges instead of staying unchanged. In particular, we believe the aneurysm progresses towards a more adverse environment if the neck enlarges as the aneurysm grows. This work has been published in the International Journal for Numerical Methods in Biomedical Engineering.

In addition, we have made progress with our two NIH projects, one focusing on combining data from multiple sources to identify different aneurysm wall characteristics and relate them to the local hemodynamic environment (in collaboration with University of Pittsburgh, Allegheny General Hospital, University of Illinois at Chicago Medical Center, and Helsinki University Hospital, Finland); the other focusing on developing computational models to understand the effects of intra-aneurysmal flow diverting devices (such as the Woven Endo Bridge or WEB device) being under development for the treatment of wide-necked aneurysms located at arterial bifurcations. These studies resulted in three additional journal papers over the last year.

### **Future Plans**

Our research plans for the next year include:

- a) Prediction of bleb formation in aneurysms: Based on our previous studies we plan to develop predictive models of bleb formation in cerebral aneurysms. These statistical models will identify aneurysms that are more likely to develop blebs and undergo instabilities that could result in their rupture. This is an important objective since it could be used as an early indicator of aneurysm risk.
- b) Analysis of rupture of aneurysm without blebs: Typically, small aneurysms with regular shapes (i.e. no blebs) are considered relatively safe. However, we have found many ruptured aneurysms that are small (<7mm) and have regular shapes (no blebs). Therefore, we will analyze the differences between ruptured and unruptured aneurysms in this sub-population with the aim of determining distinguishing characteristics that can help identify aneurysms at higher risk of rupture even though they are small and smooth. This is an important clinical question to understand how to best manage small aneurysms discovered incidentally (the majority), which are currently managed purely on the physician's intuition and experience rather than on objective quantitative data.
- c) Analysis of aneurysm growth modes: In series of aneurysms followed longitudinally in time without treatment, we have observed two main types of aneurysm enlargement: a) global enlargement, and b) focal enlargement with bleb development. We plan to investigate what local flow conditions predispose aneurysms to one or the other type of growth. This is important to further understand the different mechanisms of aneurysm wall degeneration and instability.

### **Use of Funds**

During the last year funds from the Valentine Memorial 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). They have made substantial progress towards their PhD Dissertations, and one of them (Ms. Salimia) is expected to graduate Spring or Summer 2021.

- 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.

In the near future, we plan to continue using these funds to cover summer support for PhD students and faculty, publication costs, and when the situation allows travel to international and domestic conferences, and research visits to collaborating institutions (e.g. University of Pittsburgh).

The funds provided by the Valentine Memorial Fund are very valuable and greatly appreciated because they allow us to focus immediately on research issues that are not currently supported by other grants or projects, which have a high potential impact and could also lead to future funding from NIH.