Research Highlights – 2024

Summary
During the past year (2023) we studied the hemodynamic conditions that are associated with aneurysm progression and subsequent rupture with the objective of improving aneurysm management decisions. In parallel, we studied the effects of endovascular interventions and devices to better understand the healing process and potential complications. These efforts resulted in 8 published journal papers, 4 papers under review, 13 conference presentations, 4 invited talks, as well as an article in Forbes Argentina magazine.

In addition, we hosted the Computational and Mathematical Bioengineering Conference (CMBE 2024) at the Mason Arlington Campus June 24-26, 2024, and organized a mini-symposium on Cerebral Aneurysms. Finally, in collaboration with our colleagues from the Departments of Mathematics and Physics of the College of Science at Mason, we co-organized a conference on Digital Twins and delivered a talk on digital twins in the biomedical field.

Understanding Mechanisms of Aneurysm Progression and Rupture
We conducted a series of studies to determine the flow conditions that favor aneurysm growth, bleb (secondary outpouching) development, and wall failure or rupture [papers 1,3,4,7, and one more under review]. We found that low flow conditions characterized by low wall shear stress (frictional force on the aneurysm wall), vortex swirling flows, and stagnant flows are associated with wall thickening and atherosclerotic wall remodeling, thick bleb development, aneurysm growth. In contrast, high flow conditions characterized by high wall shear stress, flow impingement against the aneurysm wall, and high spatial gradients are associated with thinning of the wall and thin bleb development. Both flow conditions can co-exist simultaneously in the same aneurysm, but aneurysms at the anterior communicating artery (a high risk aneurysm location) are more commonly exposed to high flow conditions, while aneurysms of the middle cerebral artery (a lower risk location) are more commonly exposed to low flow conditions. Both conditions can result in wall failure and aneurysm rupture, but these studies suggest that there may be different pathways towards rupture. These findings are important to better understand the specific conditions that lead to rupture and hopefully help improve aneurysm management by personalizing treatment decisions. These studies have been conducted in collaboration with Bioengineers from University of Pittsburgh, and Neurosurgeons from University of California Los Angeles (UCLA), Allegheny General Hospital (AGH, Pittsburgh), University of Illinois at Chicago (UIC), Northwell Hospital (New York), and University Hospitals Cleveland (UHC).

Understanding Healing Processes and Interventions
We developed computational models of fibrin accumulation and clot formation after implantation of endovascular devices (flow diverting stents) in order to understand the effects of these devices and assess their likelihood of success or potential for complications. The computational models were guided by and compared to in-vitro models developed by our collaborators at the Mayo Clinic. It was found that fibrin fibers, can be produced by exposure of fibrinogen (a protein dissolved in blood plasma) to high shear stress as blood flows through the flow diverting device cells and subsequently adheres to the device wires and eventually alters the flow into the aneurysm when enough fibrin has accumulated. Fibrin accumulation rates increase with increasing flow rates, vessel curvature, and in the presence of thrombin

(another protein produced during thrombus formation). These results are important to better understand the relative importance of clot formation inside the aneurysm cavity and fibrin accumulation at the device wires, both of which alter the blood flow and progressively result in aneurysm occlusion. Better understanding of these processes in turn is important to improve current devices and treatment outcomes. These findings have been reported in [paper 5, and 2 more papers under review].

In addition, we studied the effects of catheter insertion during endovascular interventions [papers 2 and 5], the effects of using a patch to close carotid arteries after surgical removal of atherosclerotic plaques [2 papers under review], and the sensitivity of boundary conditions in computational models [paper 8].

Future Plans

Our immediate research plans include: a) further investigation of the effects of flow stagnation on aneurysm wall and rupture, b) study effects of heterogeneous walls on the distribution of intramural stresses that ultimately result in wall failure, c) further investigating the association of flow structures including vortices, jet impingement, and flow stagnation and changes in the wall structure and strength, d) studying occlusion of side branches jailed (crossed) by flow diverting stents which is a problematic complication of these interventions, e) understanding the mechanisms of magnetic resonance wall enhancement which could be potentially used to assess the status of the aneurysm wall, and f) developing models of endothelial cell coverage of devices, which is an important process involved in the healing response to the implantation of endovascular devices.

Journal papers

1. Karnam Y, Mut F, Robertson AM, Cebral JR, "Competing Pathways of Intracranial Aneurysm Growth: Linking Regional Growth Distribution and Hemodynamics," Journal of Neurosurgery, 2024 – accepted.
2. Pradhan AM, Mut F, Sosale M, Cebral JR, “Flow Reduction Due To Arterial Catheterization During Stroke Treatment – A Computational Study Using a Distributed Compartment Model”, IJNMBE 2024 (DOI: 10.1002/cnm.3853) – in press.
3. Karnam Y, Mut F, Yu AK, Cheng B, Amin-Hanjani S, Charbel FT, Woo H, Niemela M, Tulamo R, Rezai Jahromi B, Frosen J, Tobe Y, Robertson AM, Cebral JR, "Description of the local hemodynamic environment in intracranial aneurysm wall subdivisions", *IJNMBE*, 40(8):e3844, 2024 (DOI: 10.1002/cnm.3844).
4. Karnam Y, Mut F, Yu AK, Cheng B, Amin-Hanjani S, Charbel FT, Woo H, Niemela M, Tulamo R, Rezai Jahromi B, Frosen J, Tobe Y, Robertson AM, Cebral JR, “Distribution of Rupture Sites and Blebs on Intracranial Aneurysm Walls Suggests Distinct Rupture Patterns in ACom and MCA Aneurysms”, *IJNMBE*, 40(8): e3837, 2024 (DOI: 10.1002/cnm.3837).
5. Pradhan AM, Mut F, Cebral JR, “A one-dimensional computational model for blood flow in an elastic blood vessel with a rigid catheter”, *IJNMBE*, 40(7): e3834, 2024 (DOI: 10.1002/cnm.3834).
6. Bilgin C, Bayraktar EA, Oliver AA, Li J, Ericson D, Cebral JR, Kallmes D, Kadrivel R, “In vitro evaluation of flow diverter performance using a human fibrinogen-based flow model”, *J NeuroSurg* (JNS), 2024 (DOI: 10.3171/2024.4.JNS232567) – in press.
7. Tobe Y, Robertson AM, Ramenzanpour M, Cebral JRC, Watkins SC, Charbel F, Amin-Hanjani S, Yu AK, Cheng B, Woo H, “Co-mapping cellular and extracellular matrix with hemodynamics in intact arterial tissues using scanning immunofluorescent multiphoton microscopy”, *Microscopy and Microanalysis*, 30(2): 342-358, 2024 (DOI: 10.1093/mam/ozae025).

8. Lohner R, Harbir A, Mut F, Cebral JR, “Adjoint-based estimation of sensitivity of clinical measures to boundary conditions for arteries”, *J. Comp. Phys.*, 497: 112-619, 2024 (DOI: 10.1016/j.jcp.2023.112619).

Conference Presentations

1. Karnam Y, Mut F, Robertson AM, Cebral JR, “Characterizing Local Hemodynamics and Wall Features in Intracranial Aneurysms Walls”, BMES, Baltimore, MD, Oct 23-26, 2024.
2. Aryan, Marsh L, Cebral JR, Kaneko N, “The Role of Contrast Stagnation in Identifying Ruptured Cerebral Aneurysms through Digital Subtraction Angiography”, WFITN, New York, Oct 6-10, 2024.
3. Abou-Mrad T, McGuire L, Marsh L, Cebral JR, Charbel F, “Hemodynamic changes and restenosis risk in carotid endarterectomy: the patching dilemma”, SNIS, 2024-A-28-SNIS, Colorado Springs, CO, July 22-26, 2024.
4. Kaneko N, Selim O, Cebral JR, Komuro Y, Tateshima S, Guo L, Villablanca JP, Tobe Y, Robertson AM, Duckwiler G, Hinman J, “Endothelial Inflammation Induced By Vortex Flow In Patient-derived 3d Intracranial Aneurysm Models” SNIS, 2024-A-434-SNIS, Colorado Springs, CO, July 22-26, 2024.
5. Bilgin C, Cebral JR, Kallmes D, Kadirvel R, “In Vitro Evaluation of Flow Diverter Performance Using a Fibrinogen Based Flow Model”, SNIS, Colorado Springs, CO, July 22-26, 2024.
6. Antil H, Lohner R, Mut F, Cebral JR, “Role of PDE Constrained Optimization in Evaluating Sensitivity of Clinical Measures in Arteries”, CMBE, Arlington, VA, June 24-26, 2024.
7. Cebral JC, Marsh L, Chitzas A, Mut F, Bilgin C, Kadirvel R, Kallmes D, “modeling fibrin deposition in flow diverting devices for cerebral aneurysm treatment”, CMBE, Arlington, VA, June 24-26, 2024.
8. Cebral JR, Marsh L, Karnam Y, Mut F, Kaneko N, “Understanding aneurysm flow features and their influence on what happens to the wall”, CMBE, Arlington, VA, June 24-26, 2024.
9. Karnam Y, Mut F, Robertson AM, Cebral JR, “What flow conditions predispose ACOM & MCA intracranial aneurysms to grow & rupture?”, CMBE, Arlington, VA, June 24-26, 2024.
10. Marsh L, Abou-Mrad T, Charbel, Cebral JR, “Hemodynamics of the carotid bulb: CEA with patch versus primary closure”, CMBE, Arlington, VA, June 24-26, 2024.
11. Pradhan A, Mut F, Sosale M, Cebral JR, “A Computational Study of Flow Alteration in Realistic Arterial Networks During Stroke Treatment”, CMBE, Arlington, VA, June 24-26, 2024.
12. Ramezanpour M, Robertson AM, Cebral JR, “The role of adventitial collagen fibers in modulating the mechanical environment of cerebral bifurcations”, CMBE, Arlington, VA, June 24-26, 2024.
13. Kaneko N, Samarage M, Kawaguchi R, Selim O, Guo L, Villablanca JP, Marsh L, Komuro Y,Tobe Y,Robertson AM, Cebral JR, Hinman J, “Impact of vortex flow on endothelial cells in Cerebral aneurysms”, CMBE, Arlington, VA, June 24-26, 2024.

Invited talks

1. Cebral JR, “Where do aneurysms grow and rupture? (and what are the prevalent flow conditions)”, Semana de Intervencionismo Minimamente Invasivo (SIMI2024), Buenos Aires, Argentina, Sep. 10-12, 2024.
2. Cebral JR, “Study of fibrin accumulation on Flow diverters”, Semana de Intervencionismo Minimamente Invasivo (SIMI2024), Buenos Aires, Argentina, Sep. 10-12, 2024.
3. Cebral JR, “Flow conditions that affect the aneurysm wall”, Semana de Intervencionismo Minimamente Invasivo (SIMI2024), Buenos Aires, Argentina, Sep. 10-12, 2024.
4. Cebral JR, “Cerebral aneurysm research using image-based computational modeling”, Grand Rounds, Neurosurgery Department, University of Louisville, Louisville, Kentucky, May 16, 2024.

Press Releases

"Un físico Argentino se instaló en Washington y logro desarrollar un modelo personalizado pare predecir la rotura de aneurismas cerebrales", Forbes Argentina, Jul 30, 2024 (in Spanish) (https://www.forbesargentina.com/innovacion/un-fisico-argentino-instalo-washington-logro-desarrollar-modelo-personalizado-predecir-rotura-aneurismas-cerebrales-n56888)

Use of Velentine Memorial Funds:

During the last year, funds were used to:

a) Support Graduate Research Assistants (GRAs) during the summer:
   Alireza Chitzas: research on intramural stress modeling
   Yogesh Kranam: research on flow and wall structure
b) Support faculty research over the summer:
   Prof. Juan R. Cebral: research on flow stagnation, fibrin accumulation modeling
c) Cover publication costs (paper by GRA Yogesh Karnam)
d) Cover conference costs for GRAs (Yogesh Karnam, Aseem Pradhan, Alireza Chitzas), postdoctoral fellow (Dr. Laurel Marsh), and faculty (Prof. Juan R. Cebral)
e) Cover costs to repair/upgrade hardware, including hard drives, graphic cards, network cards, and monitors.

Support from the Valentine Memorial Fund is extremely valuable (and highly appreciated) 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.