The Hemodynamics and Genetic Contributions to Aneurysm Pathology and Treatment Outcomes

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Background

Cerebral Aneurysm: Weakening of brain blood vessel wall

- **Unruptured aneurysm** in the general population
  - Cause: Multi-factorial, including hemodynamics and genetics

- **Unruptured aneurysms** in families with two or more members with aneurysms

- **Ruptured aneurysm** symptoms:
  - Onset Headache
  - Stiff Neck
  - Nausea
  - Motor Deficits
  - Photophobia
  - Coma/Death

- **Unruptured aneurysms in the general population**
  - 97%
  - 3%

- **Unruptured aneurysms in families with two or more members with aneurysms**
  - 19%
  - 81%

- **20-30% of patients have more than one aneurysm**
Hypothesis & Aims

• Different areas of hemodynamic stresses in cerebral aneurysm directly drive the quantifiable expression of key vascular remodeling factors in aneurysm endothelial cells

• Create patient-specific CFD simulation and 3D-printed models of cerebral aneurysms

• Quantify the relationship between hemodynamic forces and endothelial expression of key factors implicated in aneurysm pathology.
Methods: Volcano/3DRA

Obtain patient-specific hemodynamic anatomy and patient-specific measurements.

- Utilize 3D-rotational angiography to obtain patient-specific pre- and post-treatment imaging.
- Use Volcano-Philips Combowire to obtain patient-specific measurements of blood pressure and velocity in 4 perianeurysmal locations.
Methods: CFD

Computational Fluid Dynamics

- Use patient-specific boundary conditions to conduct blood flow simulation using supercomputing to solve the Navier-Stokes equation.
  - Input: Petrous velocity
  - Output: Distal pressure

What it is:
- Wall Shear Stress (WSS)
- WSS Gradient (WSSG)
- Flow (Q)
- Generates heatmap of hemodynamic regions of interest

Outcomes
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- Input: Extravasation of interest
- Output: Distal pressure
Methods: Virtual Modeling

Programs

- MeshLab
- SolidWorks
Methods: 3D-Printing

> Filaments Vs Resins
  > Stereolithography Apparatus (SLA) (~10 hrs)
  > Fused Deposition Modeling (FDM)
    > Polylactic Acid (>12hrs)
> Intermediate Mold (<24hrs)
> Soluble Wax (Varies)
> Final Cast in silicone (PDMS) (3 Days)
Methods: Model Seeding, Biopsy

- Seed model with human carotid endothelial cells.
- Place under patient-specific flow profile for 24 hrs.
- Use CFD hemodynamic heatmap to determine location for biopsy.
- Conduct genetic/proteomic analysis
The models were successfully populated with endothelial cells, which survived under flow for 24 hours.

Endothelial morphology showed alignment with flow in the proximal and distal parent vessel and aneurysm neck, but disorganization in the aneurysm dome. Genetic analysis of endothelial mRNA expression in the aneurysm dome and distal parent vessel was compared with the proximal parent vessels.

ADAMTS-1 and NOS3 were downregulated in the aneurysm dome, while GJA4 showed reduced levels of expression in distal parent vessel.

Disorganized morphology and decreased ADAMTS-1 and NOS3 expression correlated with areas of substantially lower wall shear stress and wall shear stress gradient in computational fluid dynamics simulations.
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