Biomathematical Analysis of Aneurysms

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Brain Aneurysms - Pathophysiology

- Medial Defects (Raphes)
- Intimal Cushions
  - SMC, Elastin & Collagen
- Atherosclerotic parent vessel
- Atrophic media
- None or little IEL
- Stiffer and thicker adventitia
Clinical Dilemma – Prediction

Ruptured

Non- Ruptured
The role of biomathematical modeling in the bigger picture
Complex Biology of Aneurysms
Mathematical Modeling of Flow Dynamics
Historical Example and a predecessor in the neurovascular realm

The Carotid Bulb
Morphological age-dependent development of the human carotid bifurcation

Axial velocity profiles in the carotid bifurcation model

Hydrogen bubble visualization in a glass model

3D-Numerical Analysis of Pulsatile Flow and Wall Shear Stress

- Peak systole
- Systolic deceleration
- Beginning diastole
- Diastole

Perktold, Resch, Peter. J Biomech 1991
Clinical Example: Lateral carotid angiogram in a 31-year-old male
## Asymptomatic & Symptomatic Plaque

<table>
<thead>
<tr>
<th></th>
<th>Stable Plaque (asymptomatic)</th>
<th>Unstable Plaque (symptomatic)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plaque rupture</td>
<td>32%</td>
<td>74%</td>
</tr>
<tr>
<td>Necrotic Core</td>
<td>22%</td>
<td>26%</td>
</tr>
<tr>
<td>Necrotic Core</td>
<td>0.5±0.5mm</td>
<td>0.27 ±0.3mm</td>
</tr>
<tr>
<td>Closer to Lumen</td>
<td>7%</td>
<td>6%</td>
</tr>
<tr>
<td>Calcification</td>
<td>7%</td>
<td>6%</td>
</tr>
<tr>
<td># Macrophages</td>
<td>385 ±622</td>
<td>1114 ±1104</td>
</tr>
<tr>
<td>Disruption of fibrous cap</td>
<td>+</td>
<td>++</td>
</tr>
</tbody>
</table>

Carr et al. 1996; Bassiouny et al. 1989; Bassiouny et al. 1997
Where are we today with atherosclerosis?


• Meta-analysis of genome-wide association studies from the CHARGE consortium identifies common variants associated with carotid intima media thickness and plaque. Nat Genet. 2011;43:940-7


• Carotid plaque and candidate genes related to inflammation and endothelial function in hispanics from Northern Manhattan. Stroke.2011;42:889-896
Brain Aneurysms
Proposed link between mathematical modeling and biology

If it would be that easy, most of the aneurysms would be located in the ICA terminus and basilar bifurcation.

Histology of Ruptured and Unruptured Human Aneurysms

- Aneurysm wall associated with rupture
  - EC lined wall with linearly organized SMC
  - Thick wall with disorganized SMC
  - Hypocellular wall with myointimal hyperplasia or luminal thrombosis
  - Thin thrombosis-lined, hypocellular wall

- IHC reveals ruptured aneurysms tend to exhibit:
  - Apoptosis
  - De-endothelialization
  - Luminal thrombosis
  - SMC proliferation
  - T-cell & macrophage infiltration

Remodeling of Saccular Cerebral Artery Aneurysm Wall Is Associated With Rupture: Histological Analysis of 24 Unruptured and 42 Ruptured Cases
Juhana Frösen, Anna Piippo, Anders Paetau, Marko Kangasniemi, Mika Niemelä, Juha Hernesniemi and Juha Jääskeläinen
Stroke 2004;35;2287-2293; originally published online Aug 19, 2004;
Where are we today with aneurysms?

- Differential effects of chromosome 9p21 variation on subphenotypes of intracranial aneurysm: Site distribution. *Stroke.* 2010;41:1593-8


Increasing evidence that gene expression may be playing the key role for vascular disease including atherosclerosis and some type of aneurysm (e.g., race, gender).

Association between atherosclerotic disease and aneurysm is compelling. This involves development, progression, and instability most likely associated with inflammation.

External factors impede reparative functions/inflammation (e.g., smoking, arterial hypertension, diet).
So what is the role of biomathematical modeling today in brain Aneurysms

- Design, development and refinement of devices and tools

- *In vitro* and *in vivo* validation prior to increment of complexity and implementation
Examples

Case # 1  coil compaction
Coil Compaction
Basilar apex aneurysm

Wakhloo, Gounis, Sandhu et al. AJNR 2007
Impulse Momentum Equation

\[ \sum F_x = \int \rho u_x u \, dA \]

Mean basilar flow waveform obtained with cine phase contrast MR pulse sequence (modified from Enzmann et al., 1994). Inset: Basal geometry, \( D_{\text{ane}} \) = aneurysm neck diameter, \( D \) = basilar artery diameter, \( \theta \) = bifurcation angle (180° and 70°)

*Lieber, Sadasivan, Gounis, Wakhloo (ASME 2003)*

Mean basilar flow waveform obtained with cine phase contrast MR pulse sequence (modified from Enzmann et al., 1994). Inset: Basal geometry, \( D_{\text{ane}} \) = aneurysm neck diameter, \( D \) = basilar artery diameter, \( \theta \) = bifurcation angle (180° and 70°)
Maximum force exerted on aneurysm neck, $D_{ane} = D = \text{basilar artery diameter}$. 

Maximum force exerted on aneurysm neck, $D_{ane} = D = \text{basilar artery diameter}$. 

*Lieber, Sadasivan, Gounis, Wakhloo (ASME 2003)*
Modeling Coil Interaction with Blood Flow after Coiling
Instantaneous velocity contours near peak flow rate

Dn/Dp = 1.0

Modeling Coil Interaction with Blood Flow after Coiling Instantaneous streamlines near peak flow rate

\[ \frac{Dn}{Dp} = 1.0 \]

Modeling for Evaluation of Aneurysm Treatment

- **Coil packing density**
- Porous media permeability $\kappa$ ;
- porosity $\varepsilon$; \( D_n \) aneurysm neck size
  - Darcy number $D_a = \frac{\kappa}{D_n^2}$
  - Outside aneurysm $\kappa = \infty$; $\varepsilon = 1$;

Average Pressure and Flow Rate in Aneurysm coiled same porosity but with different Permeability $\kappa$
Variation of the hemodynamic force on the coil during the pulse cycle – variation in aneurysm neck size

Fig. 8 Variation of the hemodynamic force on the coil during the pulsatile cycle. (----) Case 5 ($D_n/D_p = 1.0, \epsilon = 0.7, Da = 10^{-3}$); (---) Case 2 ($D_n/D_p = 1.0, \epsilon = 0.7, Da = 10^{-4}$); (-----) Case 7, ($D_n/D_p = 0.5, \epsilon = 0.7, Da = 10^{-4}$).

Aneurysm Flow and Permeability

• lower permeability “K” of the coil mass at a given packing density could also promote faster intra-aneurysmal thrombosis due to increased residence times.”


\[ PD_1 = PD_2 \]
\[ K_1 > K_2 \]
Histology in an Animal Model – Variability in Permeability $\kappa$

3 D - Complex Coils

Stroke, 2003, 34:2031
Examples

Case # 2  Flow diverters
FLOW DIVERTERS

INCORPORATE TWO PHENOMENA:

1. Disruption of the fluid momentum transfer into the aneurysm sac while preserving flow demand in side branches.

2. Scaffold that produces a progressive remodeling of vascular wall & endothelialial growth.
Step 1: INITIAL in vivo Observations

Side-Wall Aneurysm in the Canine Carotid Artery

Histology

Step 2: Mathematical analysis: Change in Hemodynamics?
PRE-STENT  POST-STENT
Step 3. Validation: PARTICLE IMAGE VELOCIMETRY
Side-wall aneurysm - Shear-driven Flow (I)

Pre Stent
Parent Vessel

Post Stent

Lieber, Nikolaidis, Wakhloo 1998
Vorticity contours
non-stented case, $\alpha = 2.54$, Re=175
Vorticity contours
stented case, $\alpha = 2.54$, Re=175
**Step 4: Increased complexity**

- An aqueous glycerol mixture of 41:59. 
  - To match a refractive index between the working fluid and the elastomer model.
- Viscosity was 4cP at working temperature 50 °C

Silicone replica of a rabbit elastase aneurysm model in a Plexiglas box

Silicone replica attached to pulse duplicator (“artificial heart”)
Step 5: Device Refinement

Bifurcation Aneurysm – Inertia-driven Flow (II)

No Device

Divertor #3

Lieber, Seong, Wakhloo    ASME 2005
Temporal Evolutions of Intra-aneurysmal Circulation
Final Step: Human Implementation

Post FD
(FD 4.4mm x 20mm)

6-mo fu
MATHEMATICAL MODEL – Use of Functional Angiography

Convection

$$f(t) = \rho_1 \int_0^t \frac{1}{\sigma\pi\sqrt{2}} e^{-\frac{(\eta-\mu)^2}{2\sigma^2}} \cdot \frac{1}{\tau_1} e^{-\frac{t-\eta}{\tau_1}} d\eta + \rho_2 \left[ \int_0^t \frac{1}{\sigma\sqrt{2\pi}} e^{-\frac{(\eta-\mu)^2}{2\sigma^2}} d\eta \right] - \left( 1 - e^{-\frac{t}{\tau_2}} \right)$$

Diffusion

$$\sigma, \mu = \text{Contrast injection related parameters.}$$

$$\rho_1 = \text{Relative magnitude of contrast convected out of aneurysm.}$$

$$\tau_1 = \text{Convection time constant.}$$

$$\rho_2 = \text{Relative magnitude of contrast diffused out of aneurysm.}$$

$$\tau_2 = \text{Diffusion time constant.}$$

MATHEMATICAL MODEL

Convection + Diffusion

Graphs showing the combined effects of convection and diffusion over time.
Fig 3. Images in patient 1.
A. Angiogram illustrates the selection of an ROI.
B. Final mask.

Fig 4. Gray-scale intensity curves before and after stent placement.
A. In vitro study.
B. Raw data curves in patient 1 (AP projection).

Sadasivan, Lieber, Gounis et al. AJNR 2002
Fusiform aneurysms of Posterior Circulation
Arterial Endothelialization – Reduction of Shear Forces?

Coil occlusion of contralateral VA to avoid inflow behind FD

FD 5.3mmx50mm

AICA

A

B

D

14 mo fu

Courtesy of Dr. Pedro Lylyk
Segmental disease

Pre-Procedure

6 month follow-up

Single FD 4.4mm x 20mm

Courtesy of Dr. Joost deVries
Flow reduction leads to Progressive Occlusion – Rabbit Elastase Aneurysm Model

Amorphous clot – Organizing clot

Collagen formation and Endothelialization

21 days

90 days

180 days

Sadasivan, Cesar, Seong, Rakian, Hao, Tio, Wakhloo, Lieber Stroke 2009
Remodeling of Dysplastic ICA and Progressive Aneurysm Occlusion

04.27.2010

10.20.2010

04.12.2011

Courtesy of Prof. von Kummer
No Change in Mean Flow Rate in Jailed Artery

Lieber, Seong, Wakhloo     ASME 2005
Patent Vertebral Artery Side Branch

Sadasivan, Cesar, Seong, Rakian, Hao, Tio, Wakhloo, Lieber  
*Stroke 2009*
Patent renal arteries – Rabbit aorta – Telescoping FDs
Complete incorporation of the device struts with a smooth endothelial lining. A small artery ostia with cross sectional area smaller than the flow diverter cell area.
Pre FD

Post FD 4.4mmx50mm

Courtesy of Prof. R. von Kummer
Flow Stagnation

Meningeo-hypophyseal trunk

Ophthalmic Artery (dorsal fetal variant)

Post FD

6 month fu
Limitations of Mathematical Modeling

- CFD is hampered by validation and findings of high WSS at areas of no pathology; WSS gradients subjected to changes by minor increase in BP, blood flow and HR
- Validation with in vitro experimental studies is difficult (PIV, LIF)
- Modeling of clot/device interaction and biological response is complex (vaso vasorum, inflammatory response, cellular signaling process, etc.)
Summary – Biomathematical Modeling

• Mathematics is a tool to describe the physics. Patient-specific computational models are capable of approximating *in vivo* hemodynamic conditions.

• In conjunction with Biology, Computational models may be helpful to test hypotheses about the natural history of cerebral aneurysms, i.e. to connect hemodynamic variables and clinical observations.

• Implantable devices can be evaluated for refinement.

• The complexity of biology is missing (genetic, vessel wall response, endothelial response, platelet function, etc.).
Thanks