Medicine, Biology and Engineering and their Integration in Endovascular Neurosurgery

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DISCLOSURES

- Stryker Neurovascular (Consultant)
- Codman J&J (Consultant)
- InNeuroco (Stockholder, CMO)
- Pulsar (Bridge loan)
- Medtronic (Stockholder)
- Philips (MAB, Research Grant, Equipment support)
- Postgraduate Course Harvard Medical School (Speaker)
- Baptist Hospital, Miami, Florida (Speaker)
- NIH (R01 NS45753-01A1; 1R21EB007767-02;
- 5R01 NS045753-02; 1R21NS061132-01A1; 1R01NS091552-01A1)
- R01 NS45753-01A1

Requirements

1. Multidisciplinary team building across all disciplines
2. Observation and description of clinical problem and need
3. Development and validation of methodology
4. Generation of preliminary data
5. Funding
6. Return to clinical setting and validation of research

INTRODUCTION

In the current EVT world Flow diverters for Brain Aneurysms and Thrombectomy for Ischemic Stroke are perfect demonstration of how *basic science, engineering and clinical medicine experts* share their knowledge and cooperate to solve an important health care problem

CLINICAL OBSERVATION

selection of a few topics currently important and of concern in *hemorrhagic and ischemic stroke* realm

Hemorrhagic Disease

1. Size and location on rupture risk (AcomArt-aneurysm vs Ophthalmic Art aneurysm)

2. Placement of FD: highest early and delayed ruptured seen in Ophthalmic art aneurysm > 12 mm

3. Role of coiling prior to placement of FD for selected areas and sizes such as Ophthalmic art aneurysms >12 mm???

PHASES Score

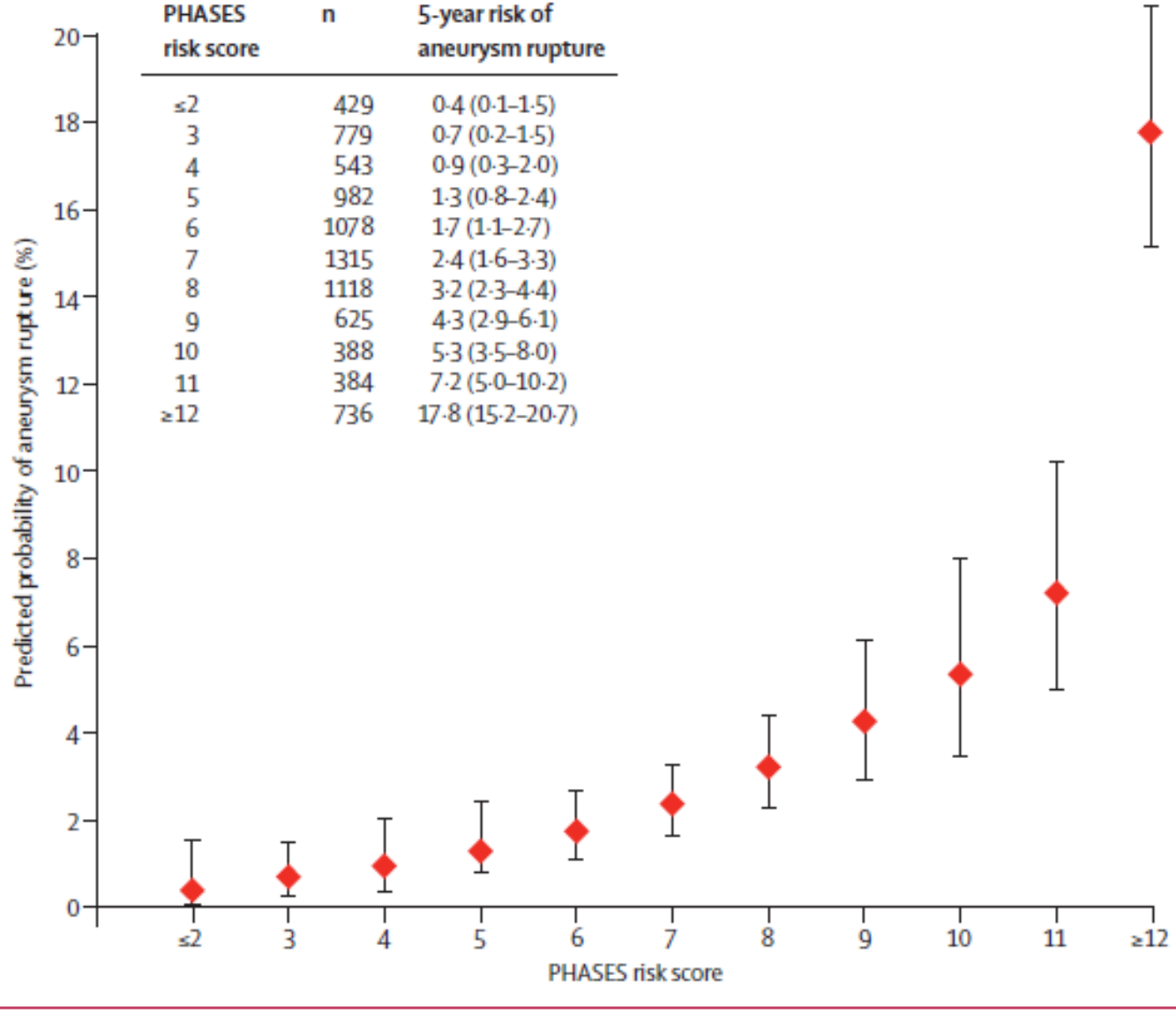
- Review studies (ISUIA, UCAS, etc…): 8,382 pts with 10,272 unruptured aneurysms
- 230 ruptures in 29,166 person-year
- Limitations
  - No detailed data on smoking, HTN Tx,
  - No data on growth
  - Aneurysm classification simplified

PHASES aneurysm risk score	Points
(P) Population	
North American, European (other than Finnish)	0
Japanese	3
Finnish	5
(H) Hypertension	
No	0
Yes	1
(A) Age	
<70 years	0
≥70 years	1
(S) Size of aneurysm	
<7·0 mm	0
7·0–9·9 mm	3
10·0–19·9 mm	6
≥20 mm	10
(E) Earlier SAH from another aneurysm	
No	0
Yes	1
(S) Site of aneurysm	
ICA	0
MCA	2
ACA/Pcom/posterior	4

Lancet 2014

PHASES Score

PHASES risk score	n	5-year risk of aneurysm rupture
≤2	429	0·4 (0·1–1·5)
3	779	0·7 (0·2–1·5)
4	543	0·9 (0·3–2·0)
5	982	1·3 (0·8–2·4)
6	1078	1·7 (1·1–2·7)
7	1315	2·4 (1·6–3·3)
8	1118	3·2 (2·3–4·4)
9	625	4·3 (2·9–6·1)
10	388	5·3 (3·5–8·0)
11	384	7·2 (5·0–10·2)
≥12	736	17·8 (15·2–20·7)



Case Observation

Ruptured Anterior Communicating Artery Aneurysm

Clinical presentation

- 69 y/o f with a past history of headaches.

  CT/CTA work up read negative for aneurysm

- Recently a 3 day history of posterior cervical pain and headaches.

- On 8/13/15 at 2:30 PM she presented with sudden severe worsening of her pain, reported as 10/10 with some photophobia and dizziness

- Patient brought to the ER

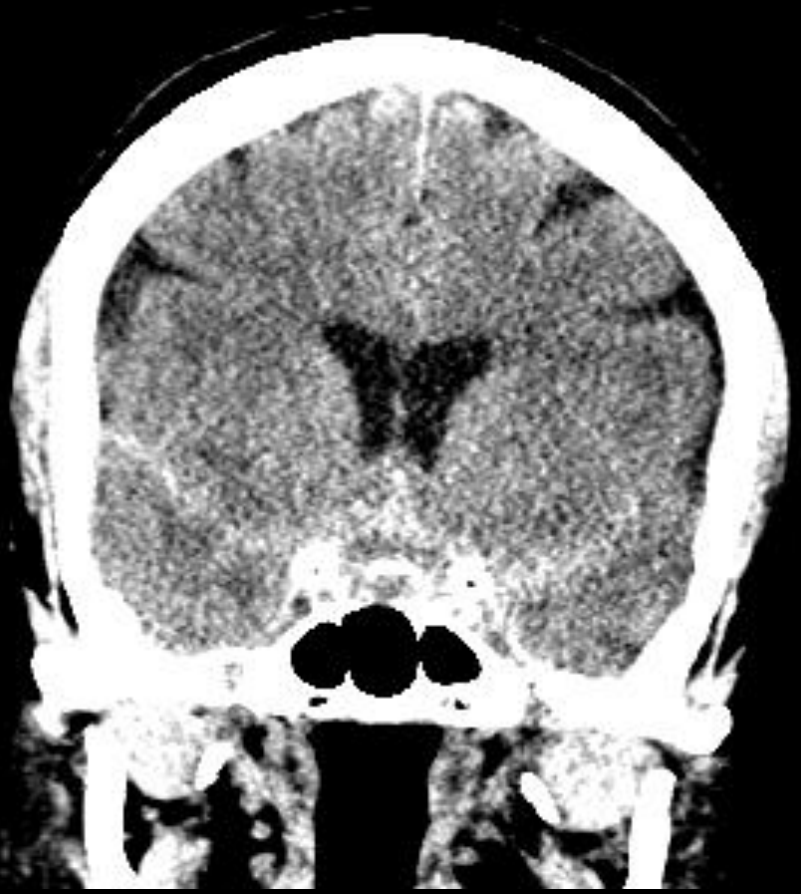
CT of the head from 3 years prior to current admission

Axial CT image of the head demonstrated a bulbous appearance of the anterior communicating artery
CT read negative

Coronal CT reconstructed image demonstrates bulbous appearance of the anterior communicating artery

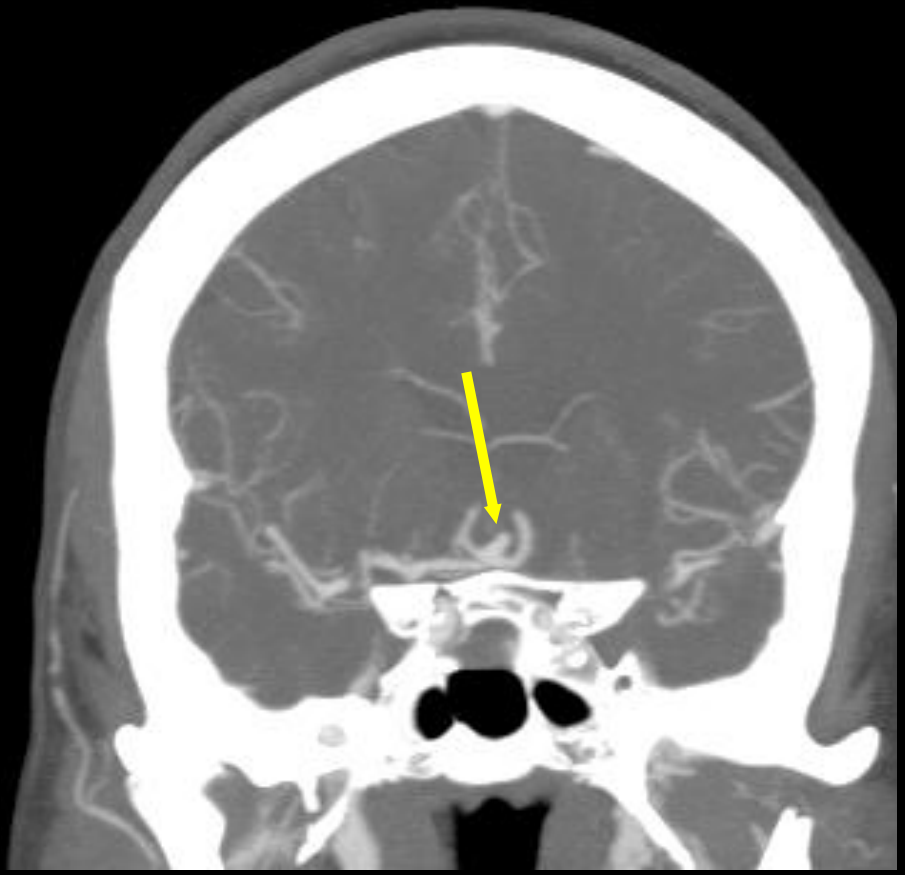
Admission Noncontrast CT of the head

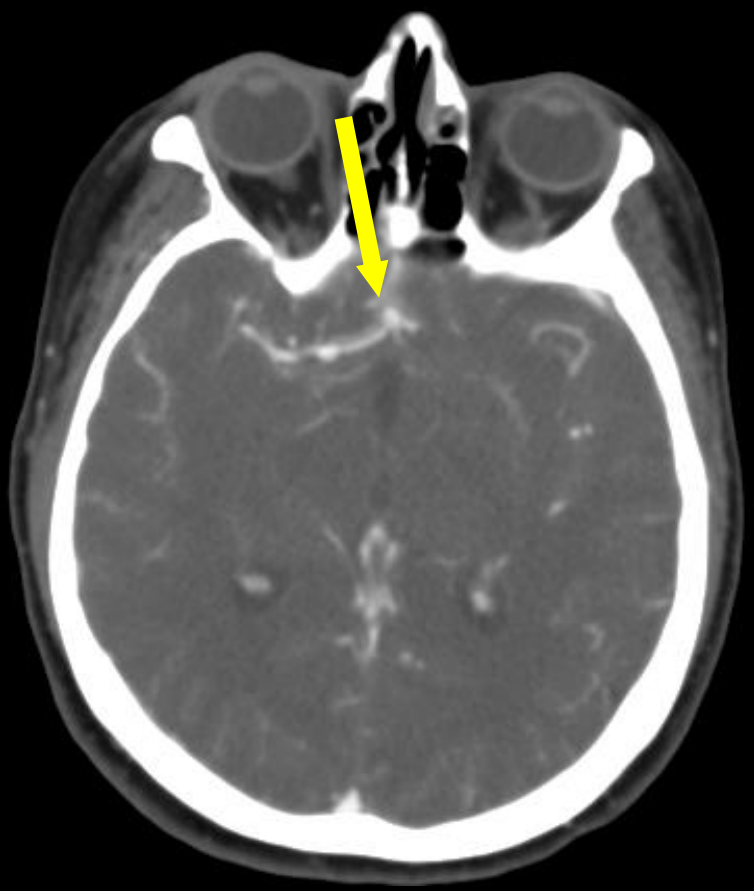
Axial CT image of the head demonstrating diffuse subarachnoid hemorrhage



Coronal CT reconstructed image of the head demonstrating the SAH

Admission CTA of the head

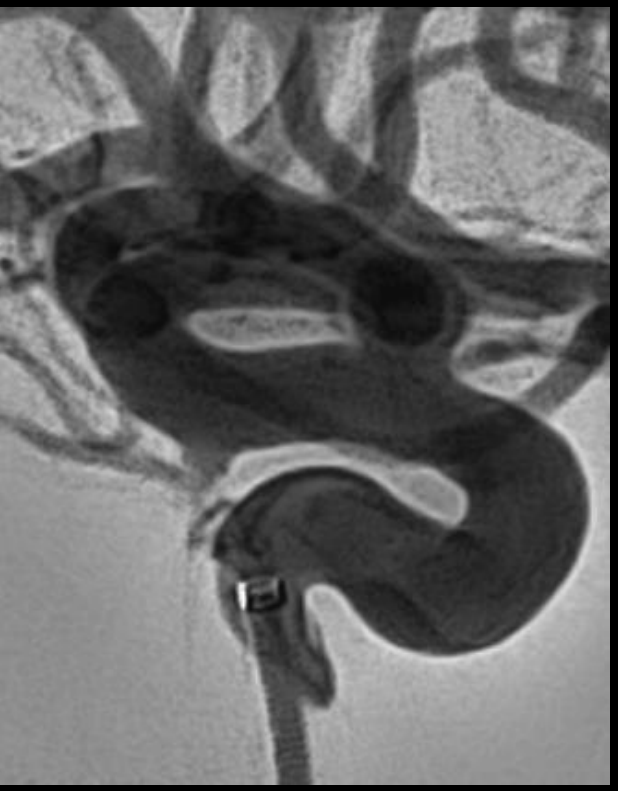


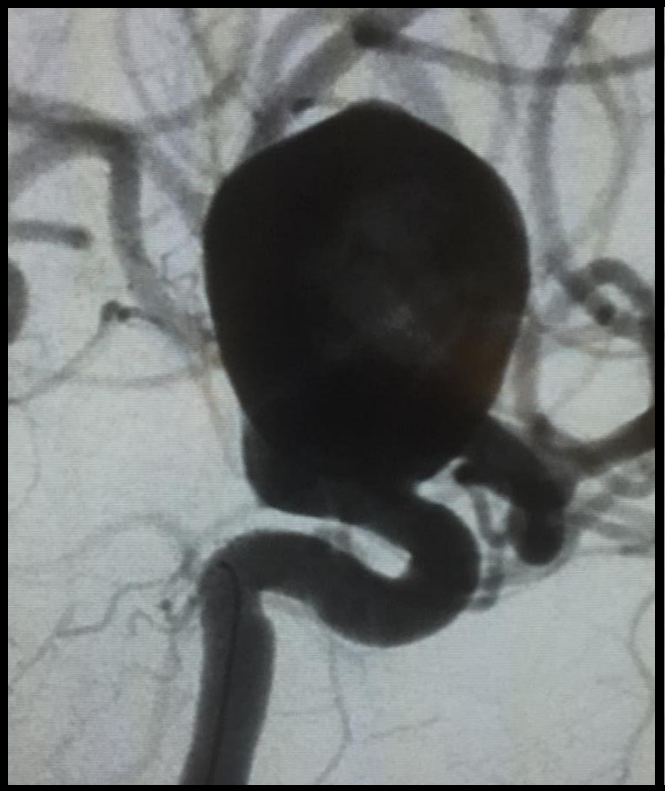


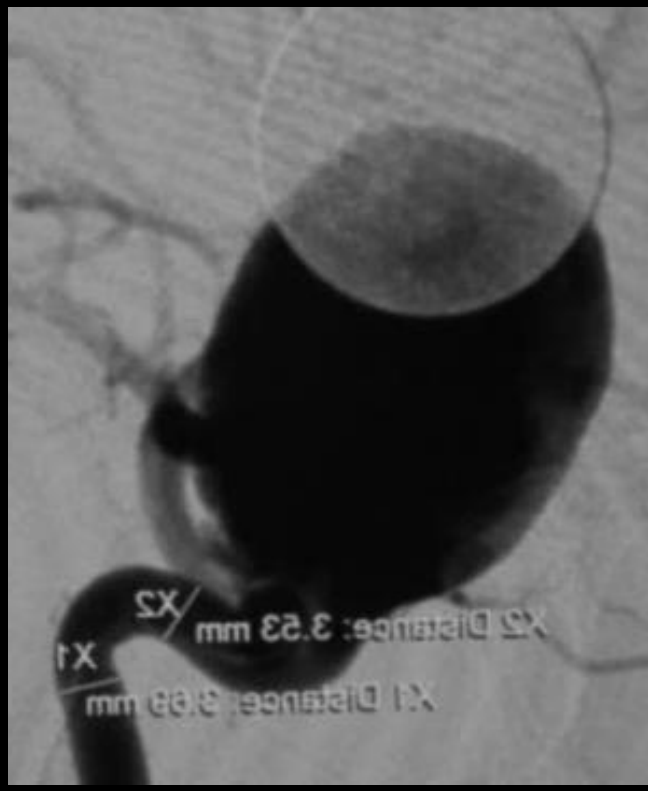
A 4 mm anterior communicating artery aneurysm

When compared to the prior CT of the head from 3 years ago, there has been significant interval growth of this aneurysm

Ophthalmic Artery Aneurysm – Low risk of rupture

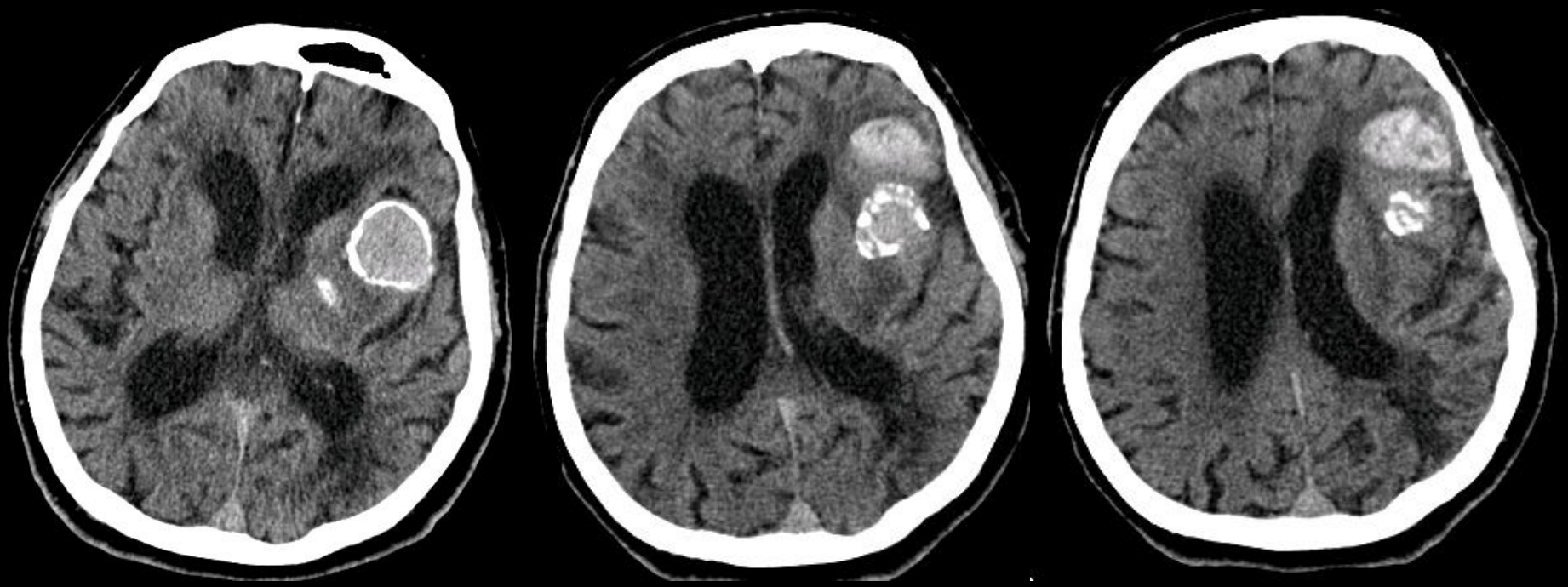




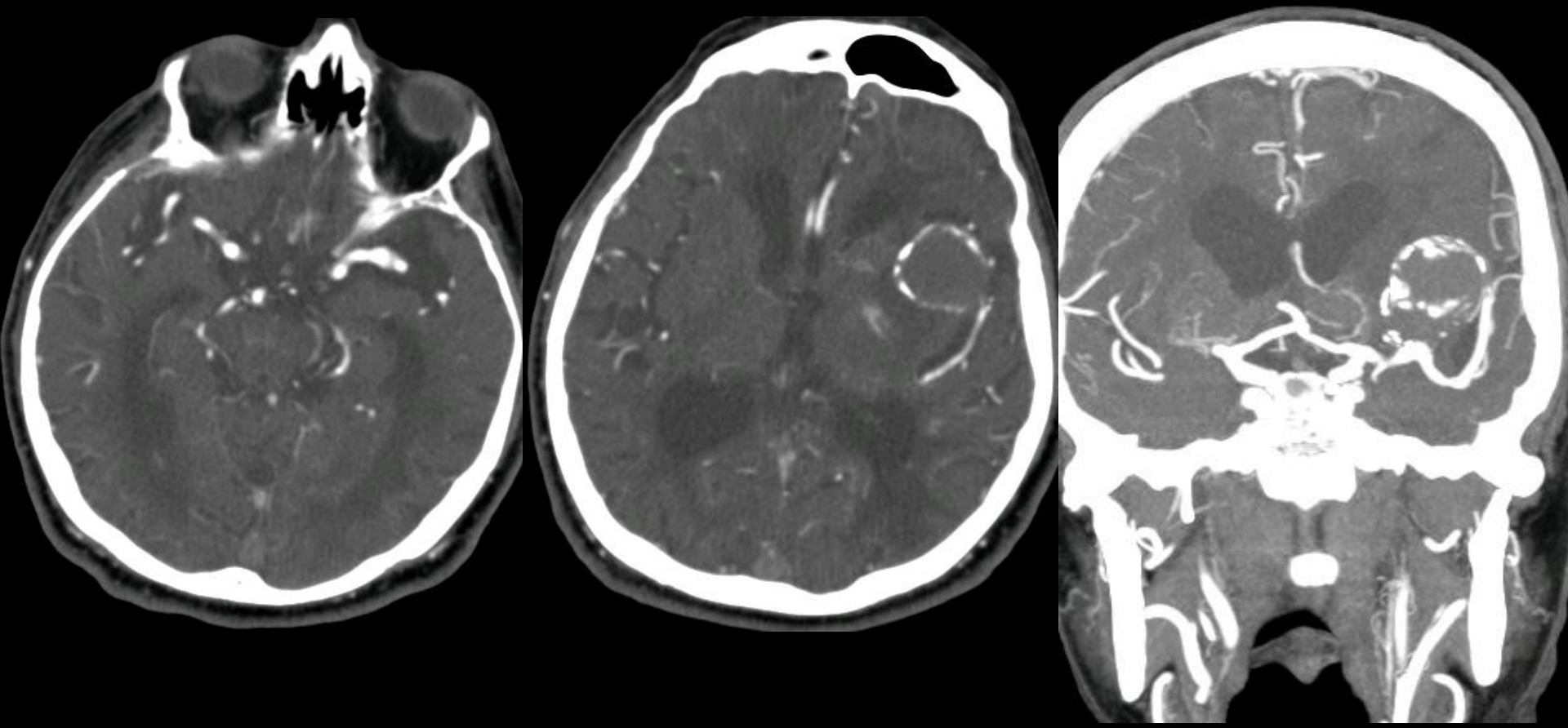


Are we dealing with different diseases?
Is really only the size and location important?

Spontaneous Hemorrhage from completely thrombosed Aneurysm



Spontaneous Hemorrhage from completely thrombosed Aneurysm



Question

What changed the aneurysm to grow and become instable/rupture ?

Is this predictable ?

Hemorrhagic Stroke

Model System: Brain Aneurys

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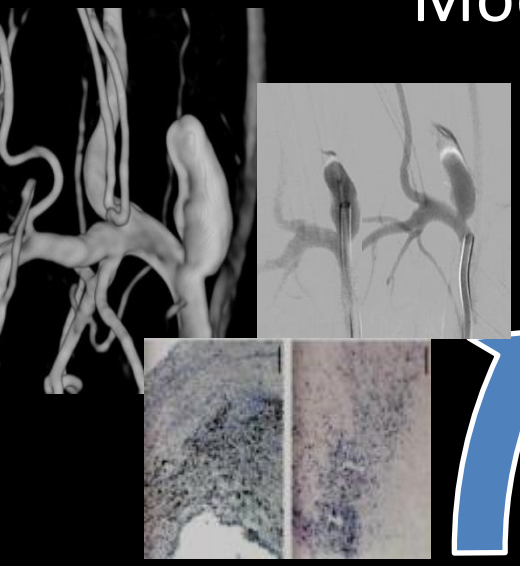
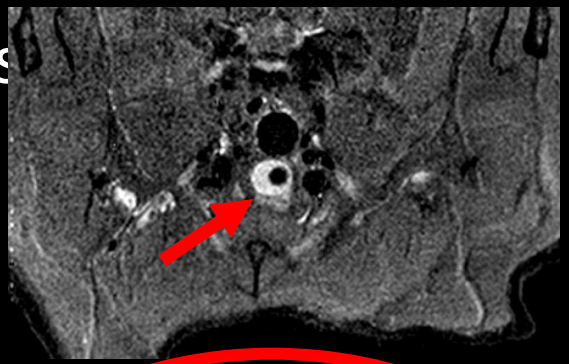
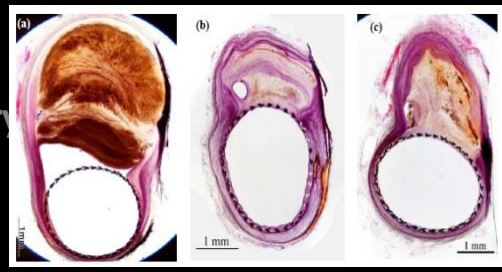


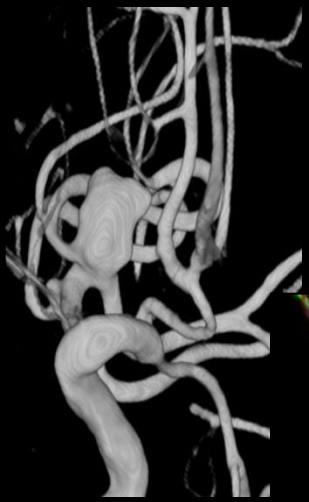
In Vivo Model

Molecular Imaging

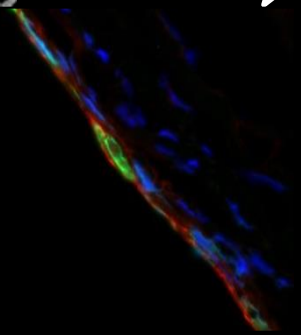


Imaging/ Medical Device/ Drug Delivery

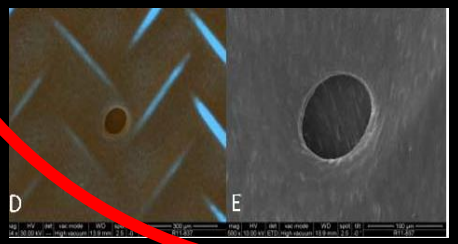




Human Tissue Analysis



Treatment Optimization



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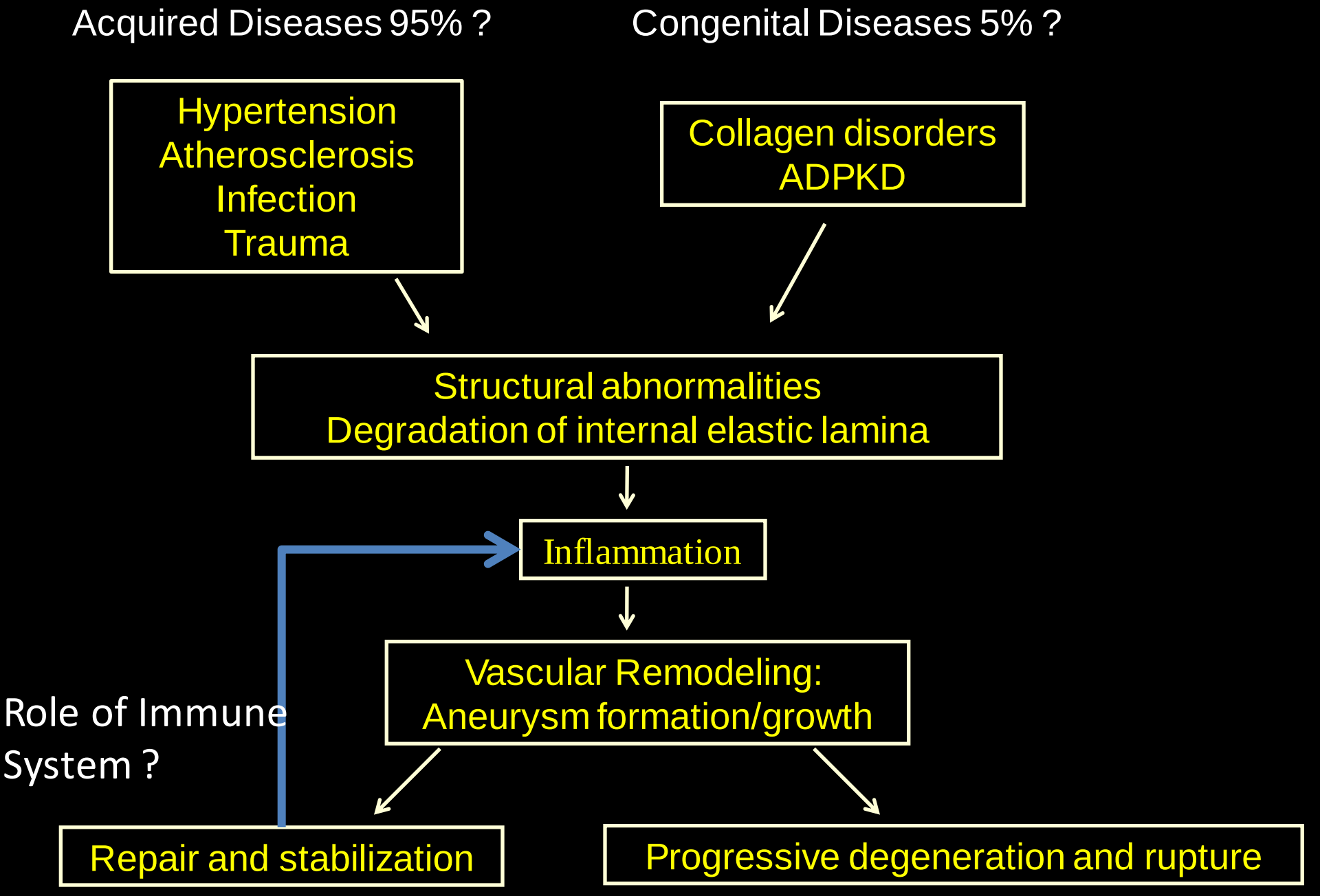
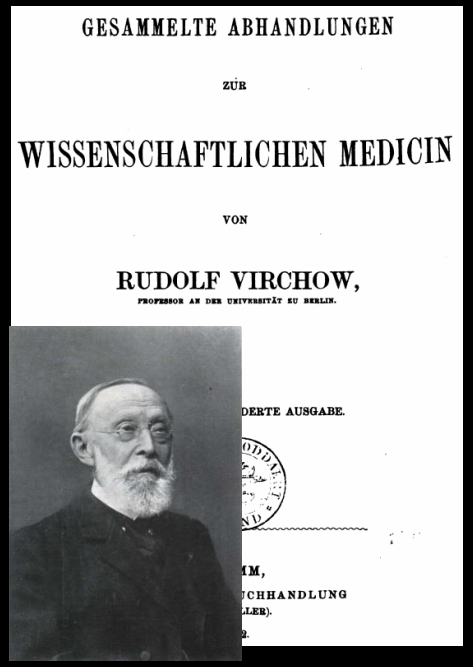

Acquired Diseases 95% ?
Congenital Diseases 5% ?
Hypertension
Atherosclerosis
Infection
Trauma
Collagen disorders
ADPKD
Structural abnormalities
Degradation of internal elastic lamina
Inflammation
Vascular Remodeling:
Aneurysm formation/growth
Role of Immune System ?
Repair and stabilization
Progressive degeneration and rupture

Inflammation in Aneurysm Pathophysiology

1. Virchow, 1847: Suggested the role of inflammation as the cause of intracranial aneurysms
2. Stehbens, 1972: “The presence of leukocytic infiltration and some fibrin deposition is not infrequent in unruptured aneurysms.”
3. Chyatte, 1999: “Extensive inflammatory and immunological reactions are common in unruptured intracranial aneurysms and may be related to aneurysm formation and rupture.”


GESAMMELTE ABHANDLUNGEN

ZUR

WISSENSCHAFTLICHEN MEDICIN

VON

RUDOLF VIRCHOW,

PROFESSOR AN DER UNIVERSITÄT ZU BERLIN.

DERTE AUSGABE.

M,

CHHANDLUNG

LER).

Pathophysiology

- Histology of Ruptured and Unruptured Human Aneurysms

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;

- Hypocellular wall w/ myointimal hyperplasia or

Basic science

Inflammatory changes in the aneurysm wall: a review

Riikka Tulamo,[1,2] Juhana Frösen,[1,3] Juha Hernesniemi,[1,3] Mika Niemelä[1,3]

leurosurgery Research Group, omedicum Helsinki, Finland
epartment of Bacteriology and mmunology, Haartman stitute, University of Helsinki, nland
epartment of Neurosurgery, elsinki University Central spital, Helsinki, Finland

ABSTRACT

Rupture of a saccular intracranial artery aneurysm (IA) causes subarachnoid hemorrhage, a significant cause of stroke and death. The current treatment options, endovascular coiling and clipping, are invasive and somewhat risky. Since only some IAs rupture, those IAs at risk for rupture should be identified. However, to

pathogen. Moreover, inflammation occurs in many diseases as a reaction to tissue injury caused by any mechanism, and as part of wound healing and scar formation.

Inflammation was first suggested to occur in IAs by Virchow in 1847.[9 10] Further evidence comes from the 1930s when Maass[11 12] described round

Molecular Imaging of Intracranial Aneurysms (IA)

- The pathophysiology of symptomatic unruptured IAs resembles ruptured aneurysms, generally showing significant endothelial cell damage, structural changes of the wall and inflammatory cell infiltration

- Early reports that investigated inflammation-induced antigens (VCAM-1, C3b) expression in aneurysmal tissues established also the elevated presence of CD68 and CD3+ cells in unruptured IA (versus normal basilar arteries) pointing to an existing link between IA progression and inflammation

  Heiss J Nuc Med 2014

Penn DL et al. J Clin Neurosci 2014; Zhang J et al. PLoS One. 2011 Krischek B et al. Neuroscience 2008; Yasuno K et al. Proc Natl Acad Sci USA 2011; Walmsley JG et al. Stroke 1983; Monson KL et al. J Biomech 2005; Heiss D. J Nuc Med 2014

Pro-inflammatory cytokines (TNF-alpha, INF-gamma, IL-6) secreted by brain resident mast cells, recruited neutrophils, and macrophages potentially up-regulate the expression of adhesion molecules in endothelium resulting in leukocyte recruitment essential to the pathogenesis of vascular inflammation[40].

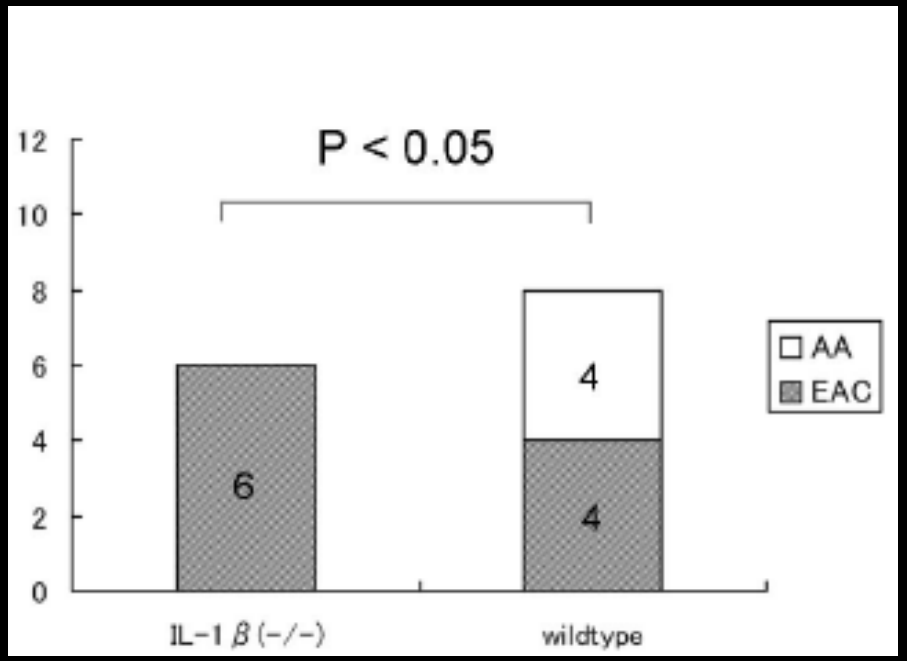
Abundant evidence already gathered by several independent research groups suggests that imaging of molecules associated with local inflammation would greatly assist in determining active remodeling and progression of IA to rupture

Penn DL et al. J Clin Neurosci 2014; Zhang J et al. PLoS One. 2011 Krischek B et al. Neuroscience 2008; Yasuno K et al. Proc Natl Acad Sci USA 2011; Walmsley JG et al. Stroke 1983; Monson KL et al. J Biomech 2005; Heiss D. J Nuc Med 2014

Pathophysiology

Impaired Progression of Cerebral Aneurysms in Interleukin-1β–Deficient Mice

Takuya Moriwaki, MD; Yasushi Takagi, MD, PhD; Nobutake Sadamasa, MD, PhD; Tomohiro Aoki, MD, PhD; Kazuhiko Nozaki, MD, PhD; Nobuo Hashimoto, MD, PhD



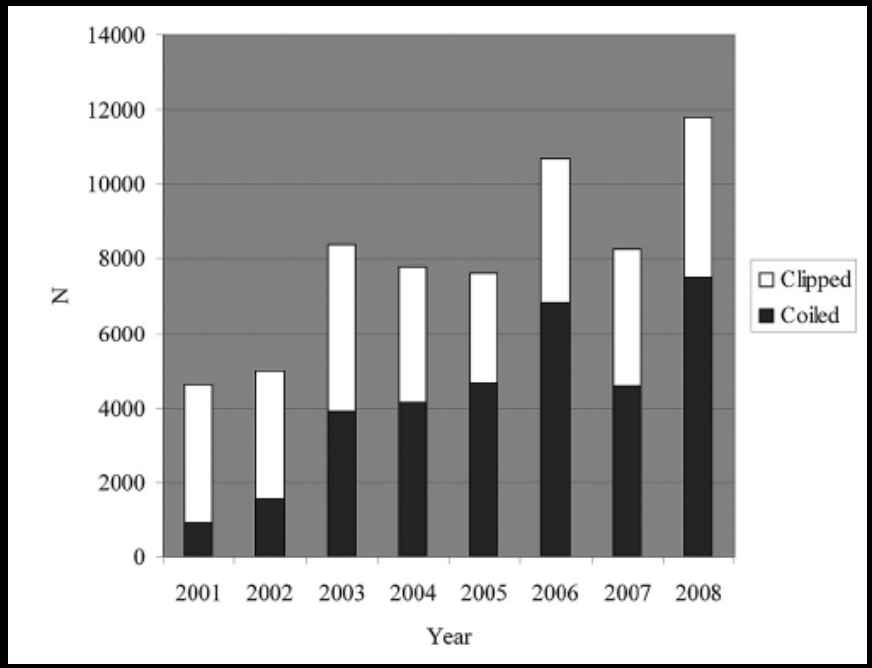
- Conclusions
  - IL-1β is important in the progression and maturation of cerebral aneurysms in this model
  - IL-1β appears from this data to be a key regulator of inflammation and immune response

Stroke 2006

Motivation

1. Largest growth in aneurysm treatment is incidentally found, unruptured aneurysms.
2. Cost: ~$6B per year**
3. Mortality: 0.6-1.2%
4. Morbidity: 4.9-14%
5. Risk of treatment might exceed natural history

NIS: 20% Inpatient Sample



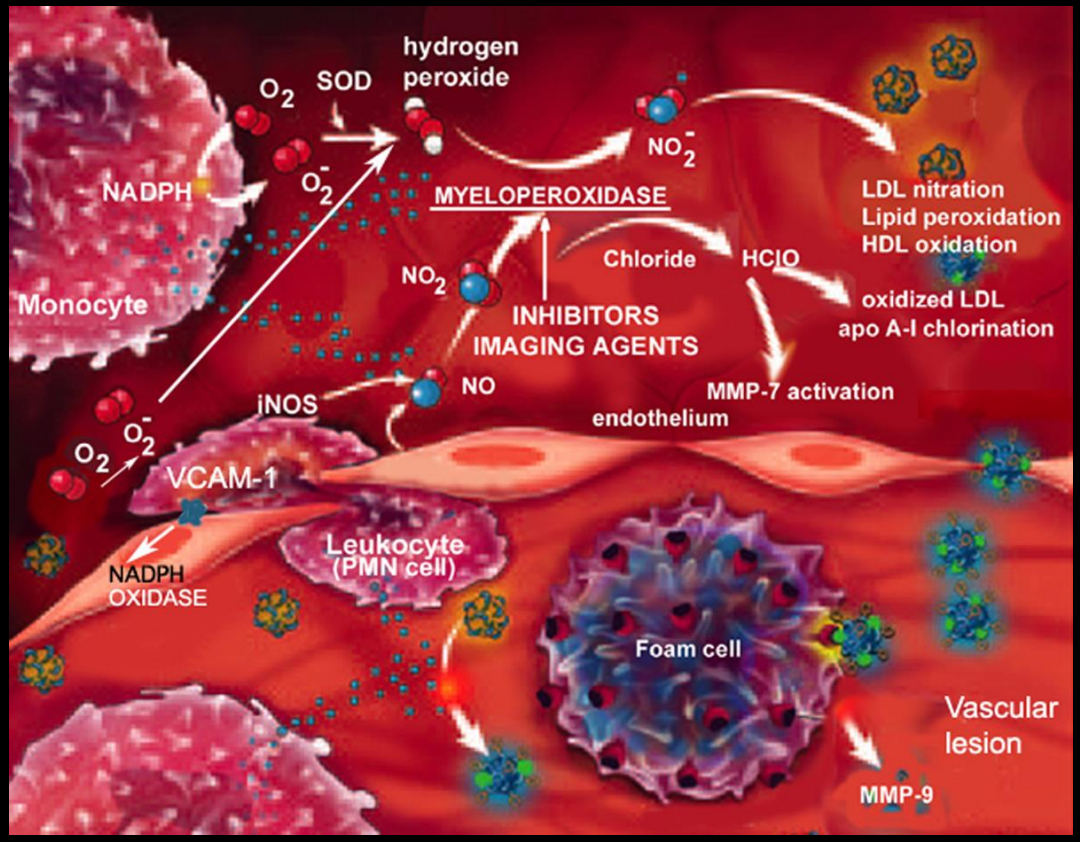
Brinjiki et al. AJNR 2011

*** Hoh et al, Stroke 2010*

Myeloperoxidase (MPO)

- Potent anti-microbial (respiratory burst)
- Implicated in atherogenesis (instable plaque)
- ↑ MPO levels correlated with adverse CV outcomes

Promise as a marker of inflammation in the vascular wall



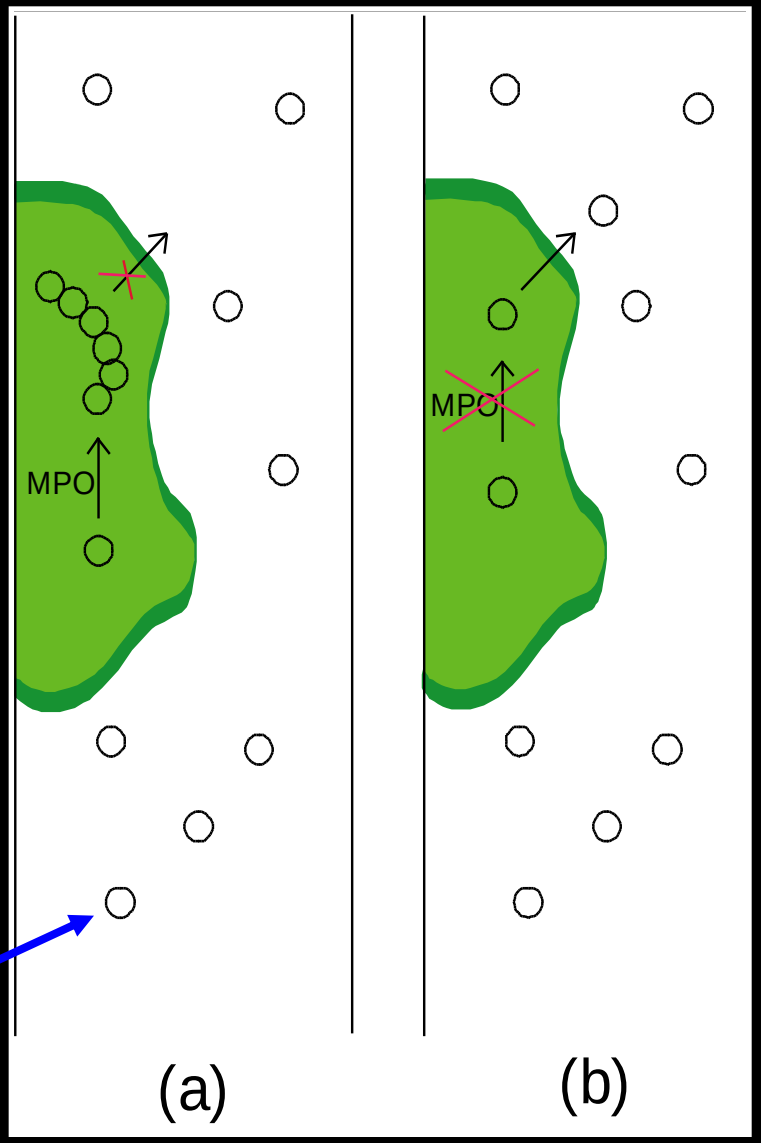
Naruko et al. *Circulation*. 2002.
Brennan et al. *N Engl J Med*. 2003.

Nicholls et al. *Arterioscler Thromb Vasc Biol*. 2005

Targeting Contrast Agents

di-5-hydroxytryptamide GdDTPA

- Enzyme-mediated structural changes
- Site-specific accumulation upon activation

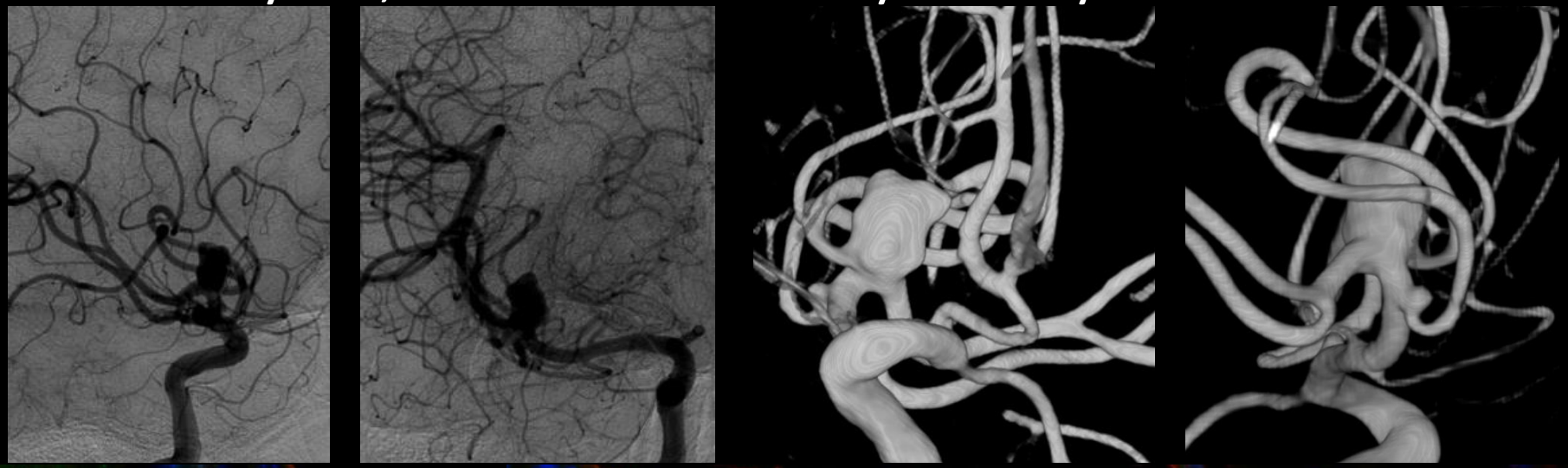


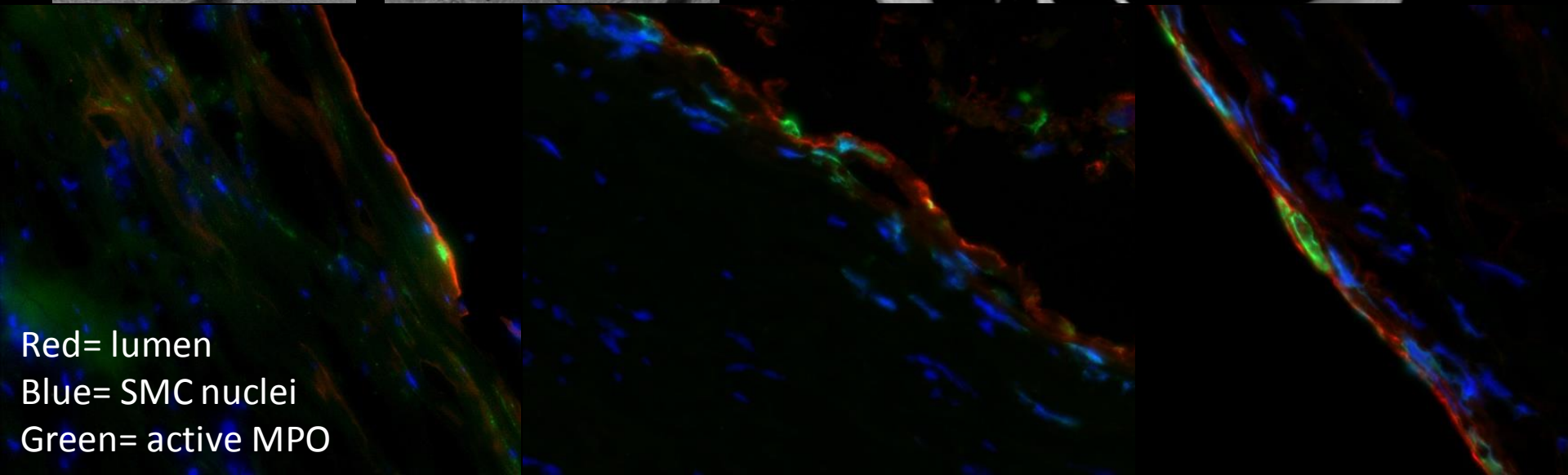
Querol et al. *Org Lett*. 2005.
Querol et al. *Org Biomol Chem*. 2006.

MPO in Human Brain Aneurysms

MPO Measurements from Human Specimens

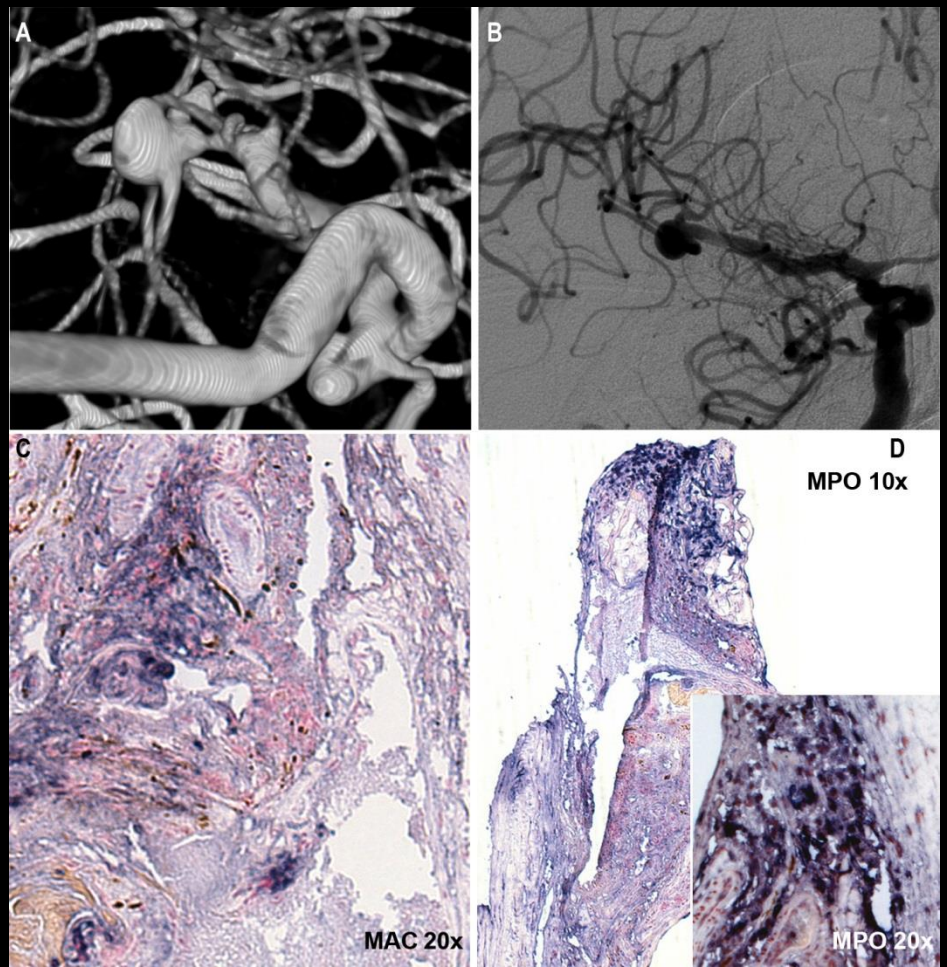
- 54 y-o F, Incidental + Family History SAH



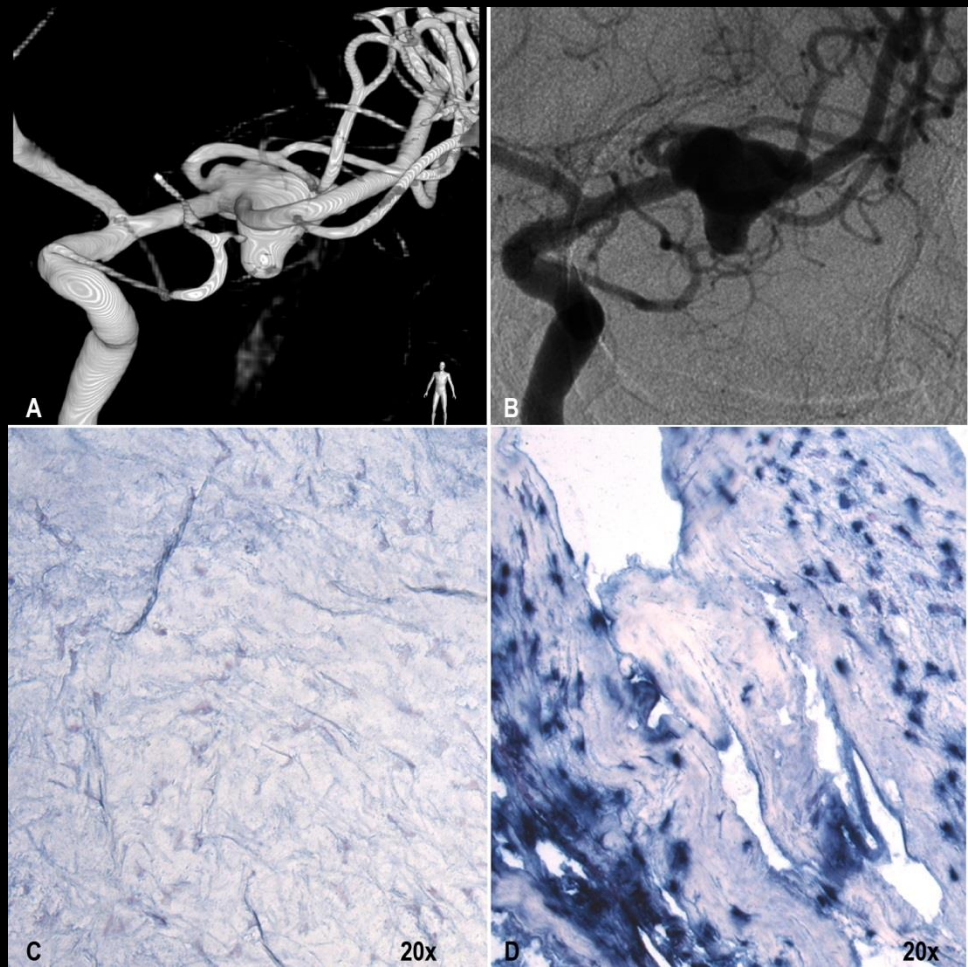


MPO Measurements from Human Specimens

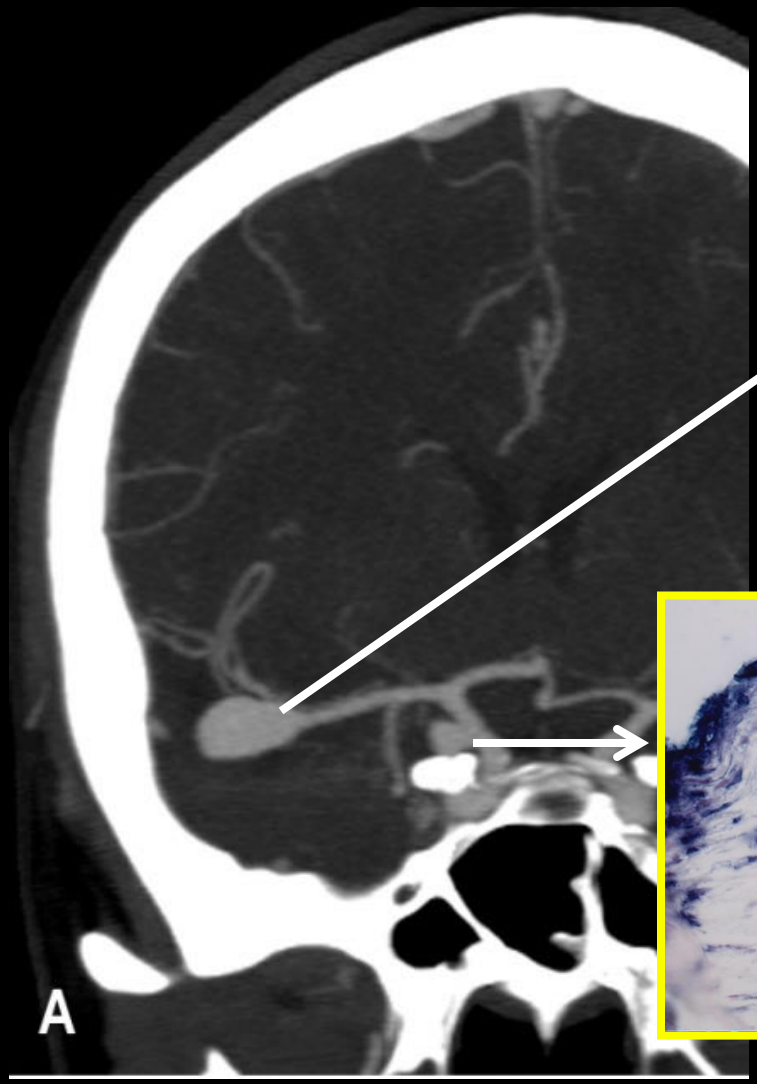
- 75 y-o F, SAH, Ruptured 7mm RT MCA IA

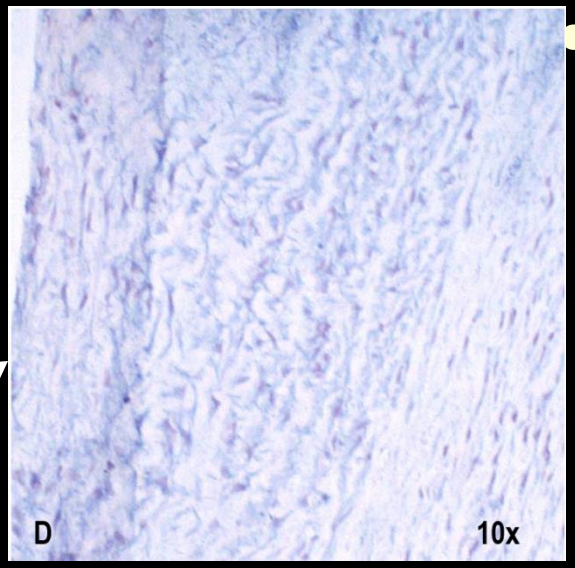


- 46 y-o F, Incidental, 10 mm LT MCA IA

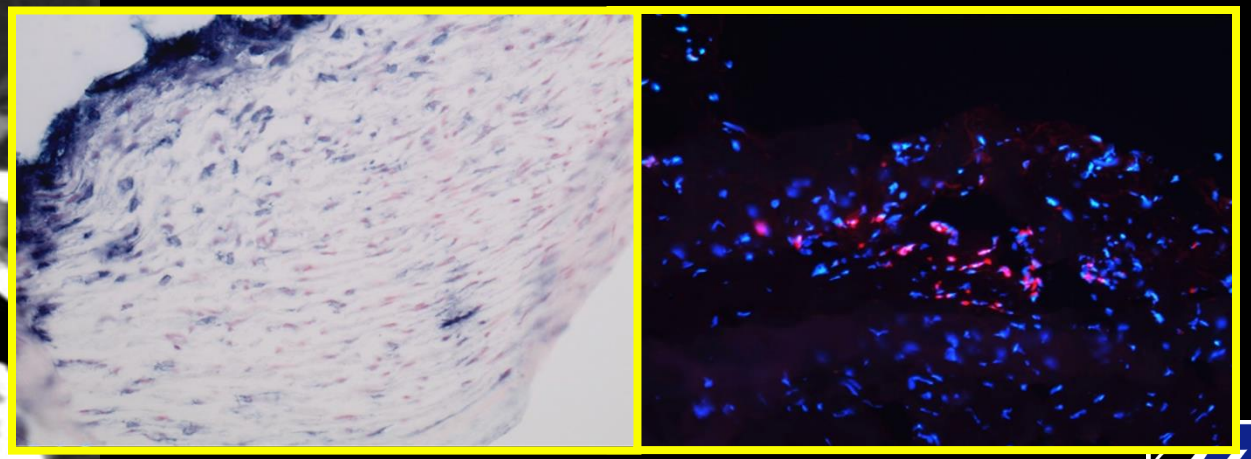


MPO Measurements from Human Specimens





- 29 y-o F, Incidental 14mm R MCA, Ruptured 5 mm Rt PCOM



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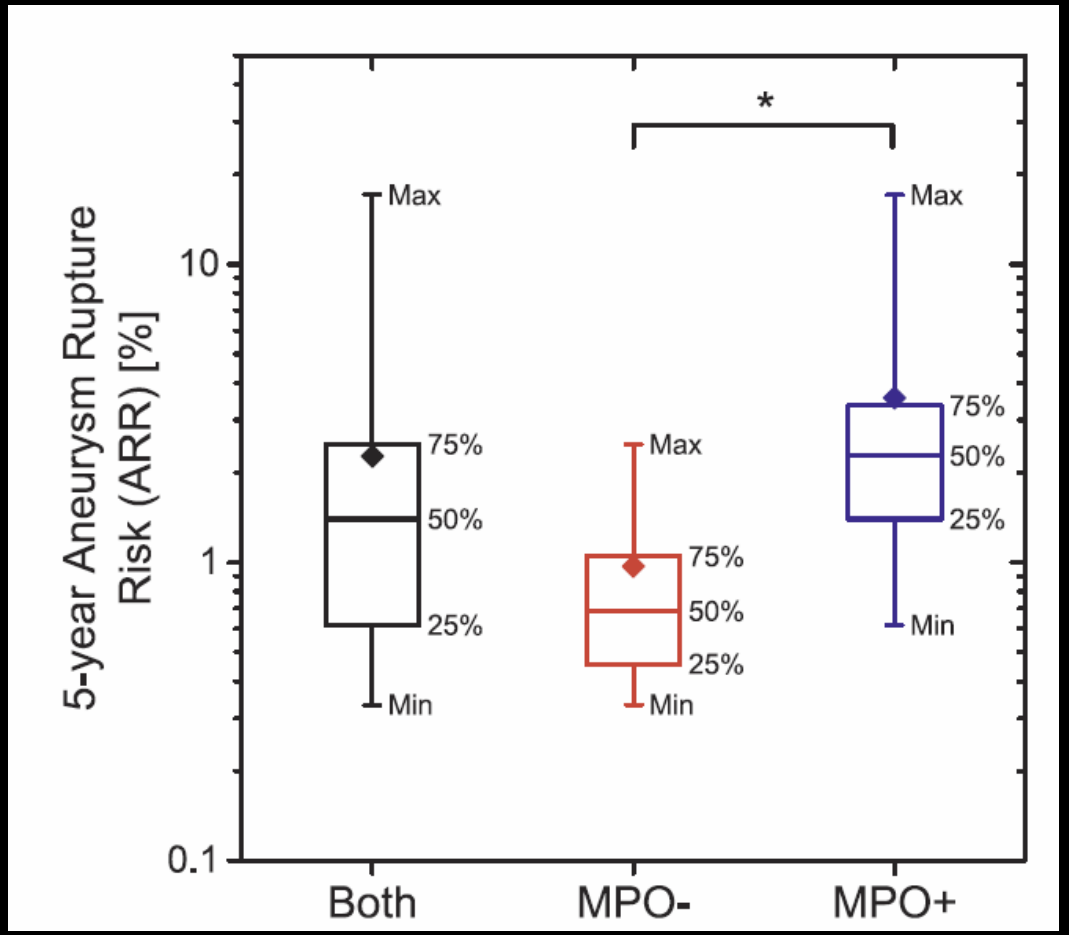
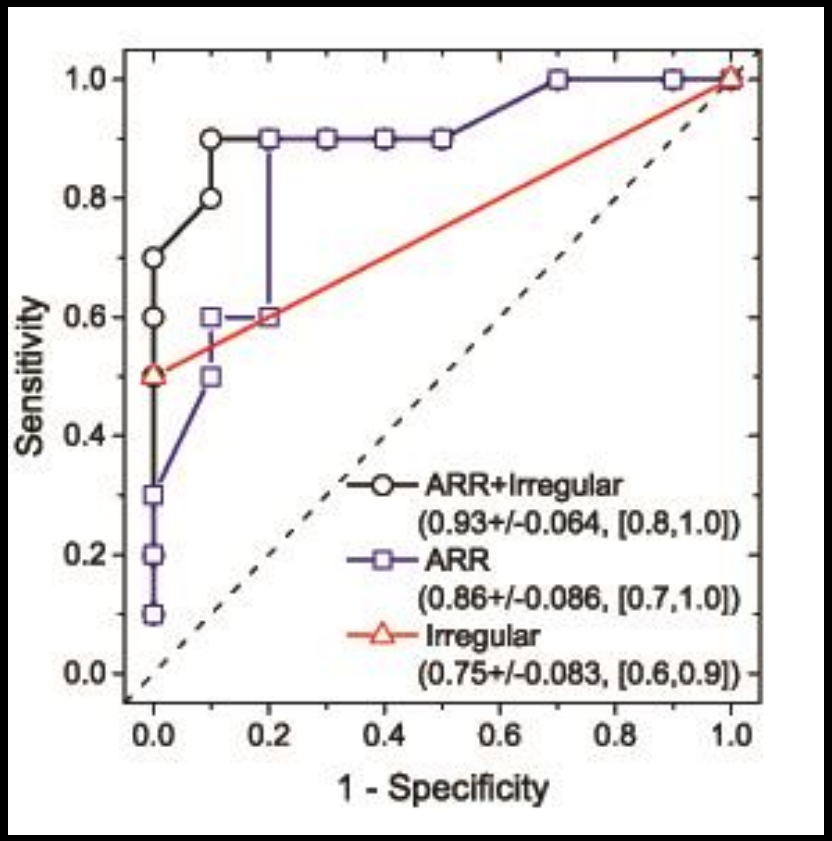
MPO and 5 Year Annual Rupture Risk Assessment (PHASES*)

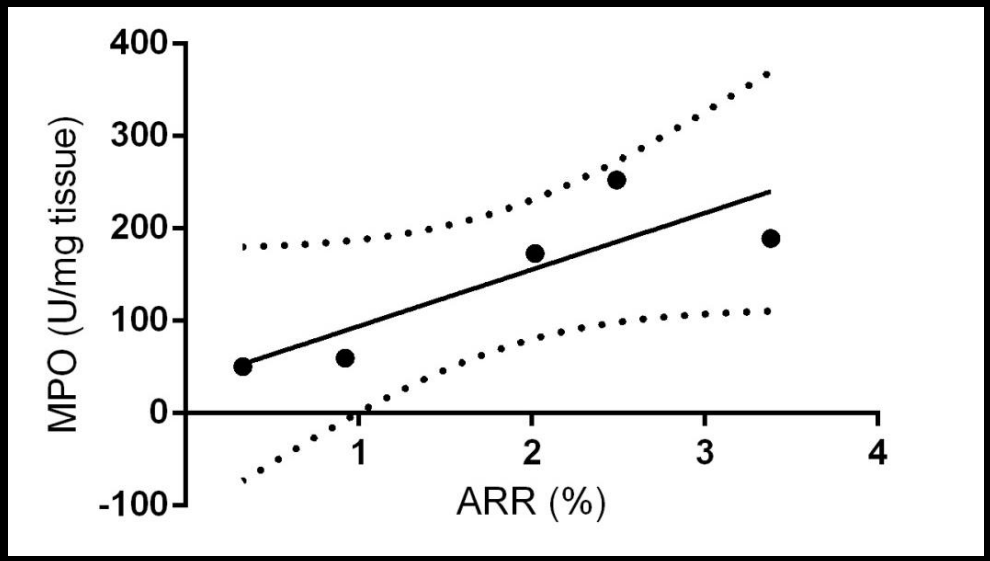
- 23 aneurysms from 19 pts collected
- 3 ruptured, 20 unruptured, mean diameter = 8.0mm
- 10 UIA MPO+ (212 vs. 55 U/mg)



* Greving et al. Lancet Neurol 2014, 13:59
Gounis et al, Stroke 2014, 45:1474

MPO as a Biomarker?



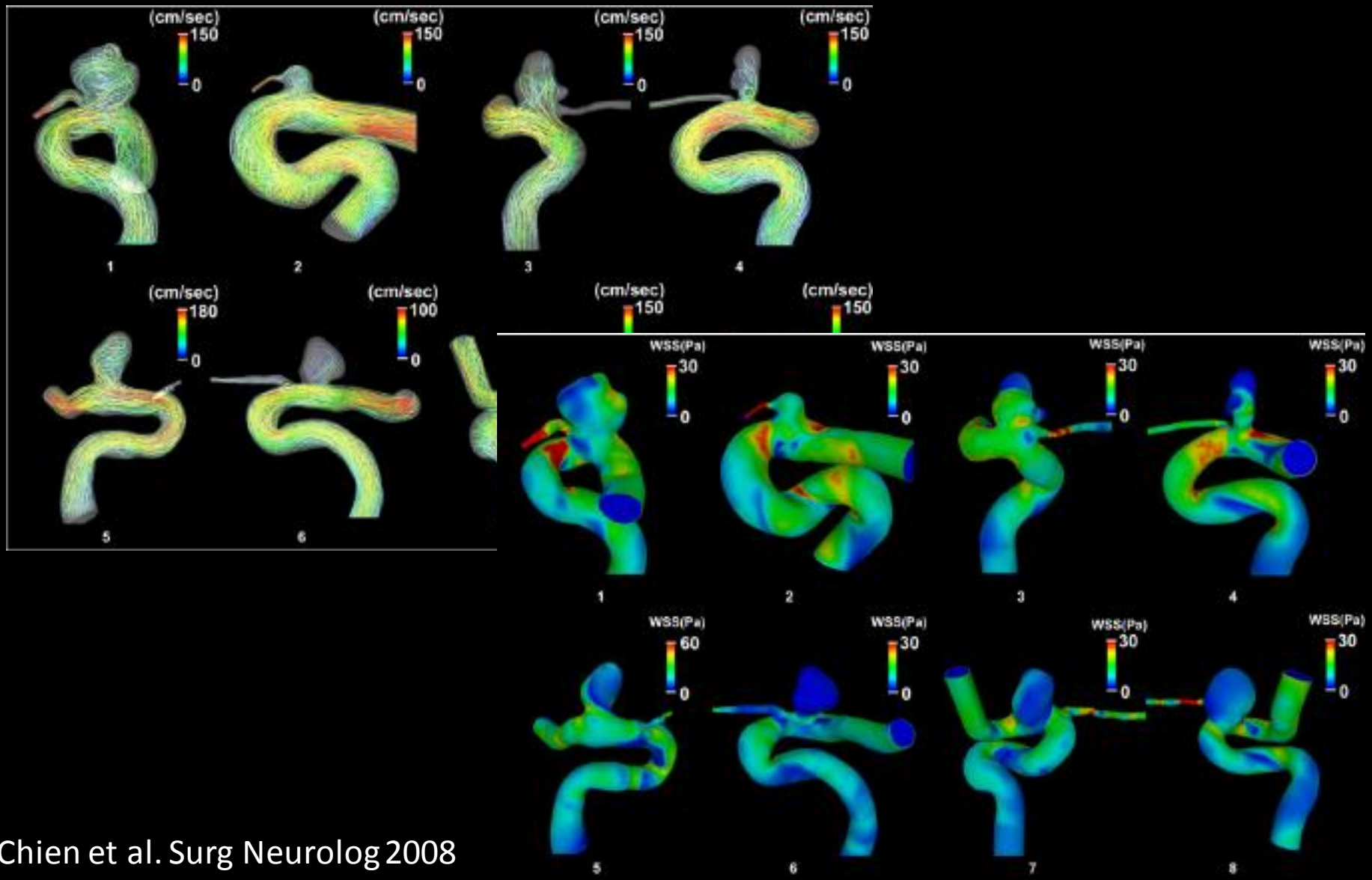


$n=5$, $p=0.06$, $R^2 = 0.73$

Receiver operating characteristics curves (ROC)
5-year aneurysm rupture risk and irregular aneurysm shape as predictors of MPO presence

Gounis et al, Stroke 2014, 45:1474

What is then the role of CFD?



Chien et al. Surg Neurolog 2008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Flow Diverters

1. Currently available FDs are Silk, PED, P64, Surpass, Fred
2. Trend in use of single devices.
3. Clinical results and occlusion rates in larger studies show similar occlusion rates at 12 months of 80-90%

Question

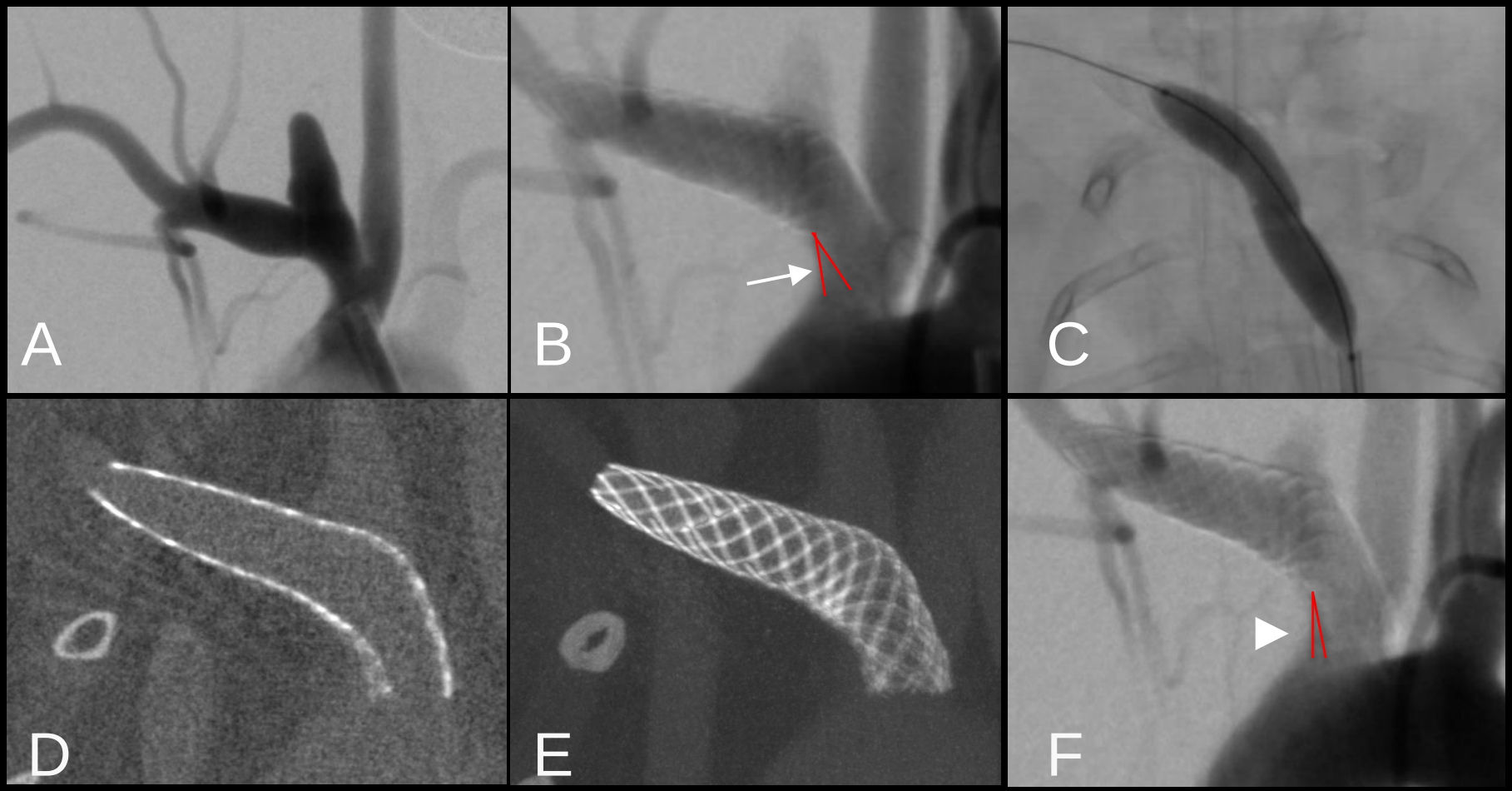
Does FD design matter for time of aneurysm occlusion ?

Is occlusion predictable ?

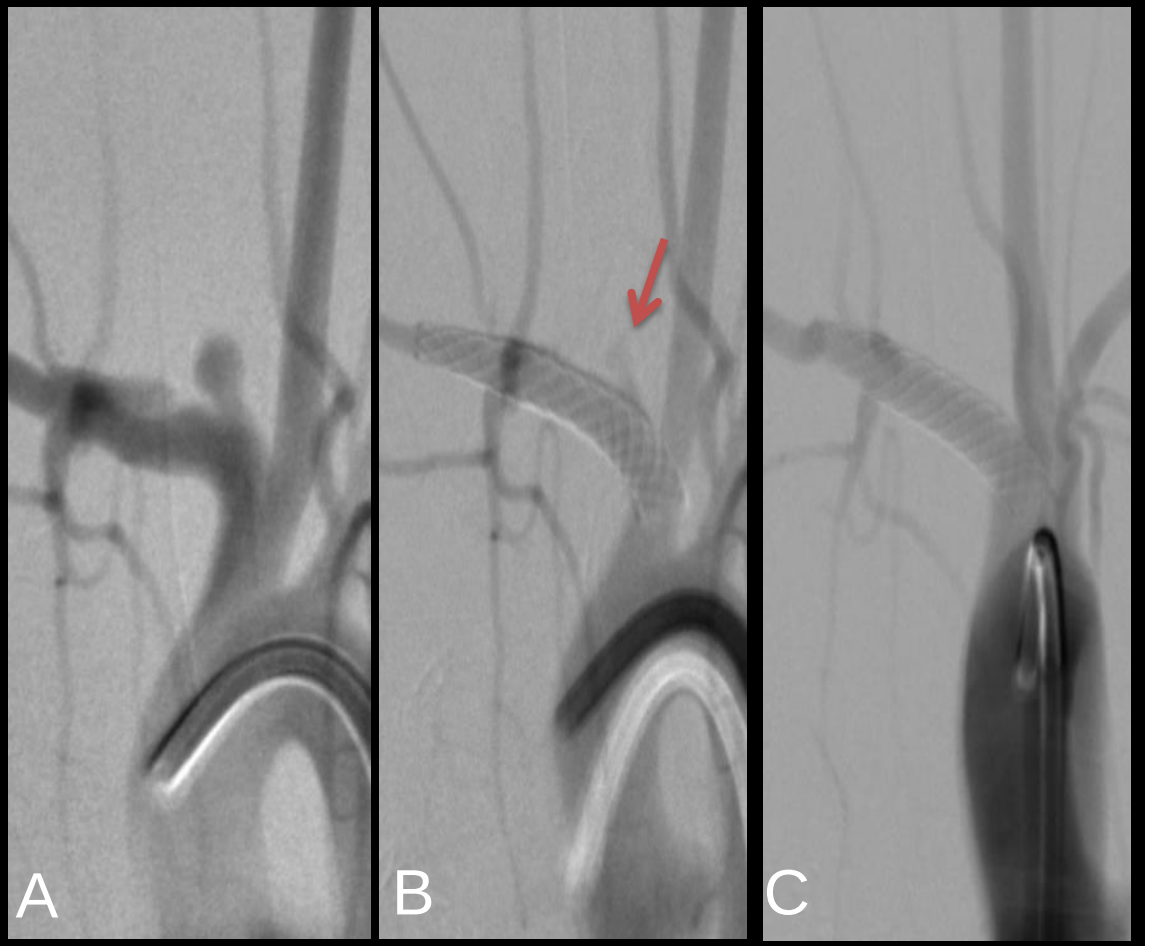
In Situ Tissue Engineering

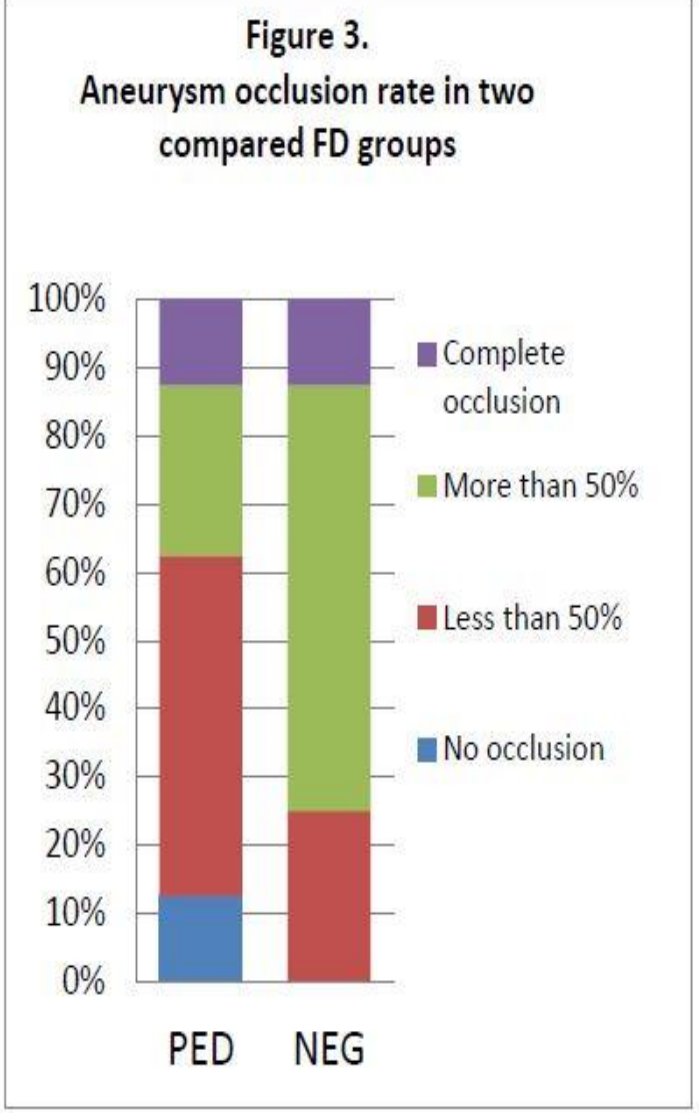
- **The objective of this study:**
  - to demonstrate formation of the basement membrane and subsequent endothelialzation rates after flow diverter stent implant

Development of in vivo models



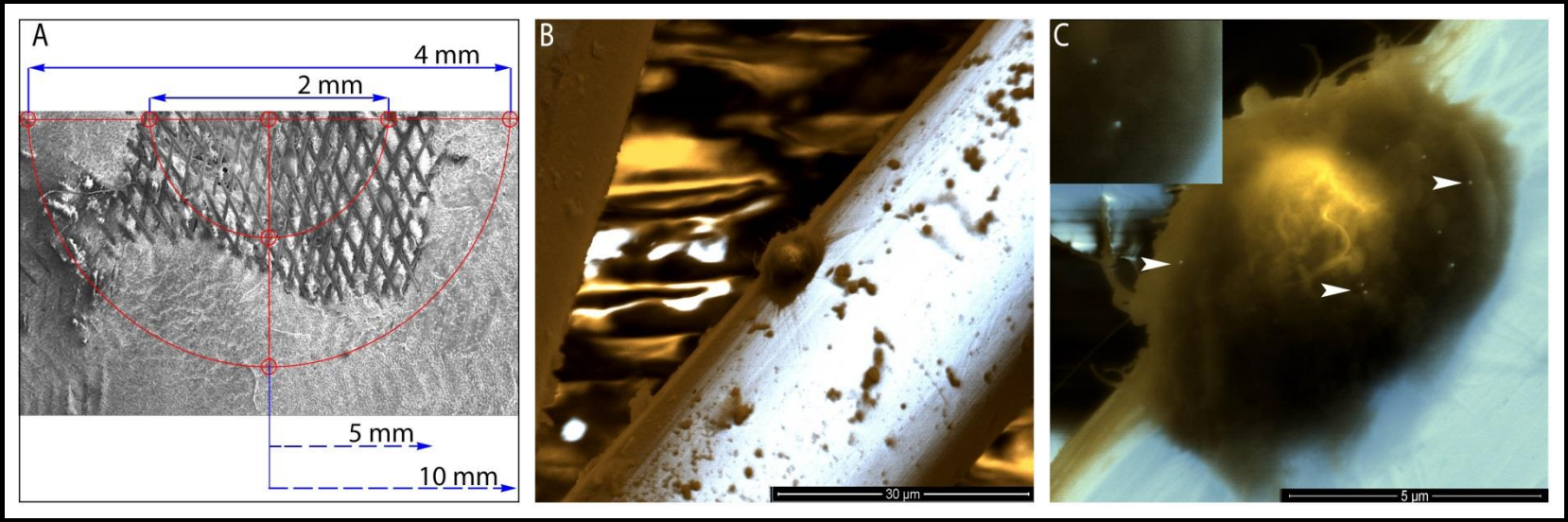
Defining study design and time frame

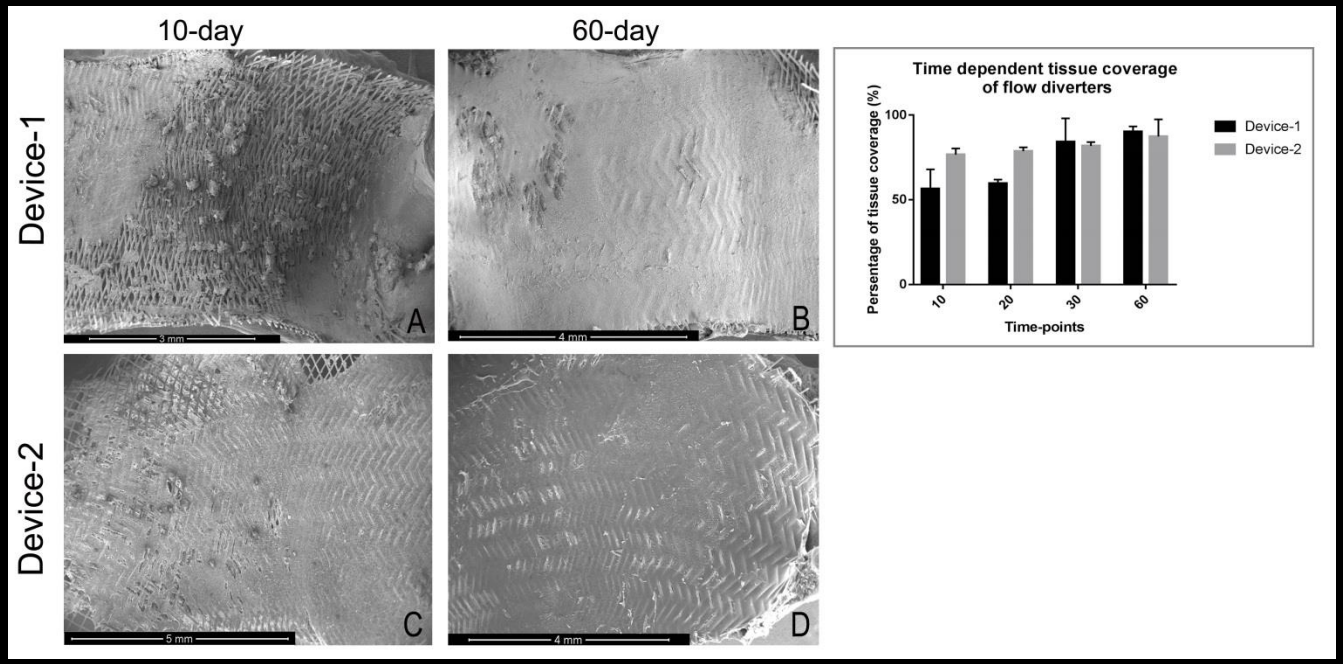




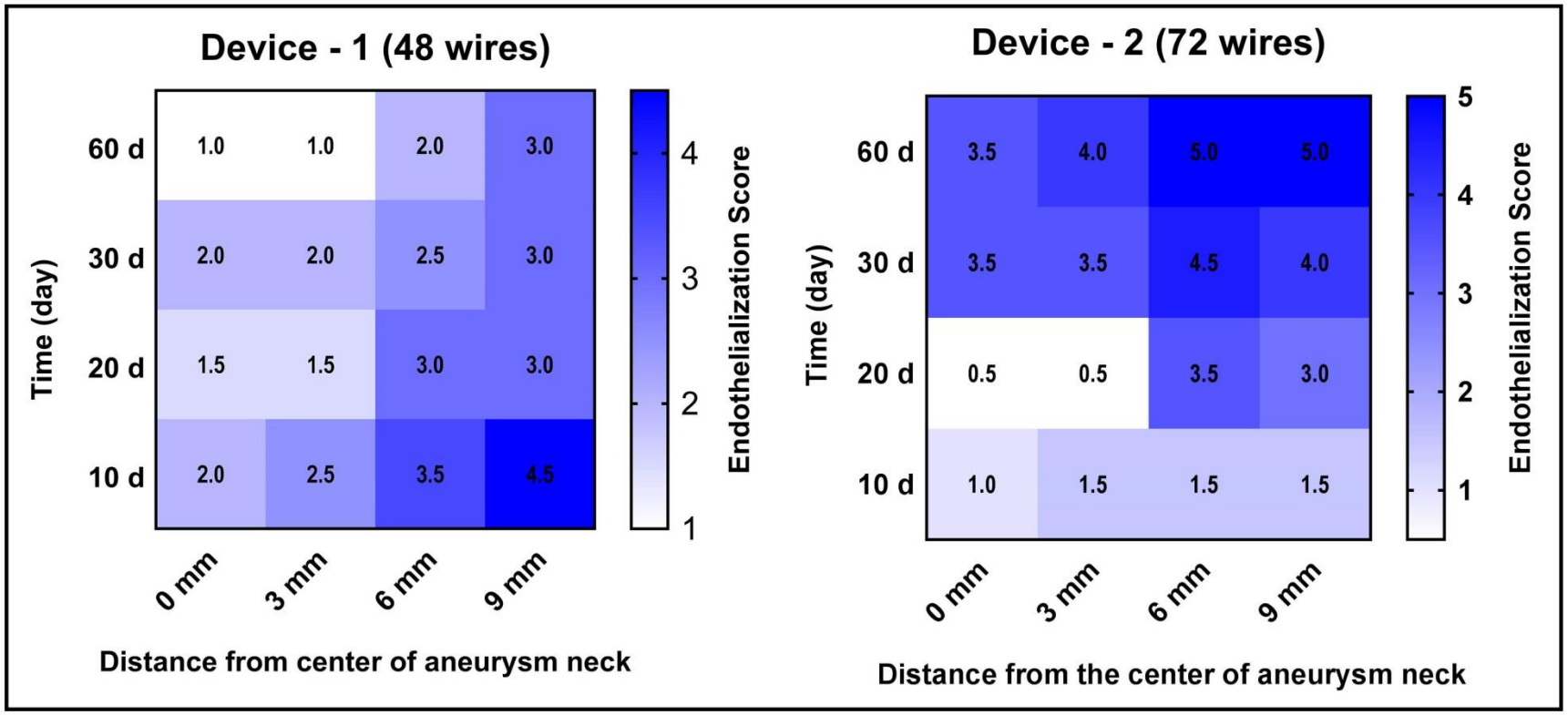
A.) DSA prior FD implant shows a small neck aneurysm with a distally dilated parent-vessel
B.) After NEG implant, some contrast inflow is still present on DSA (arrow),
C.) 30 days follow up DSA indicates complete aneurysm occlusion.

Biologic Response





Quantification



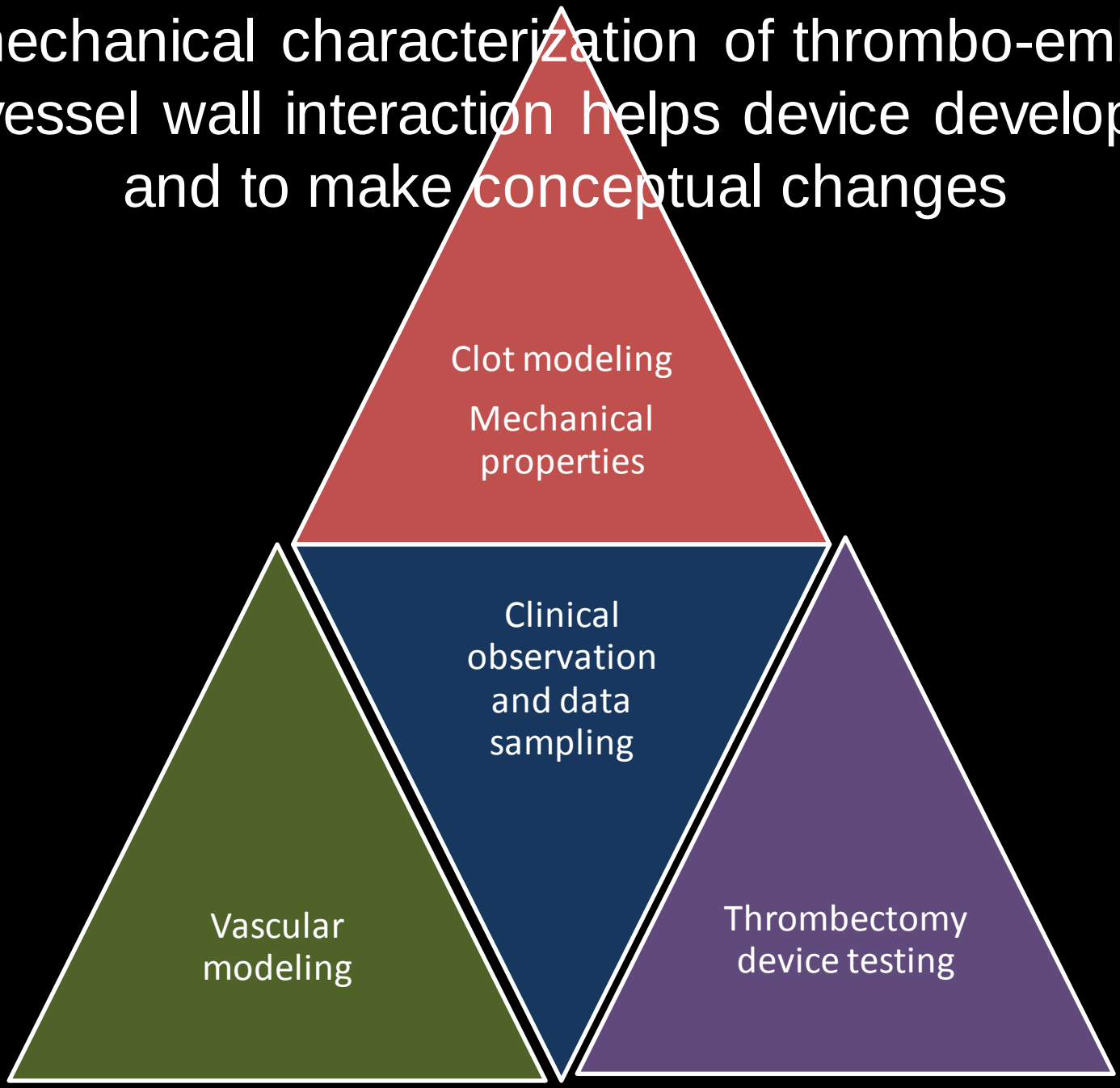
Ischemic Disease

1. Are we going to replace iv TPA with IA approach (e.g., thrombectomy) ?

2. Major problems with IA treatment – distal emboli (10-15%)

3. Are we moving away from stentrievers to clot suction?

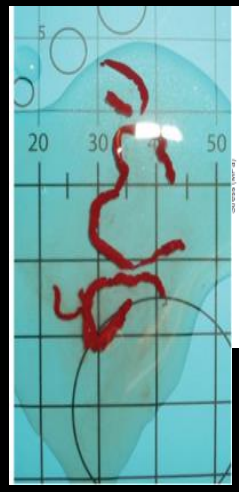
Biomechanical characterization of thrombo-embolus and vessel wall interaction helps device development and to make conceptual changes

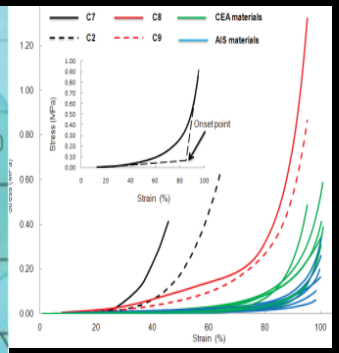


Ischemic Stroke

CLOT & Cerebrovascular ANALOGUE SYSTEMS

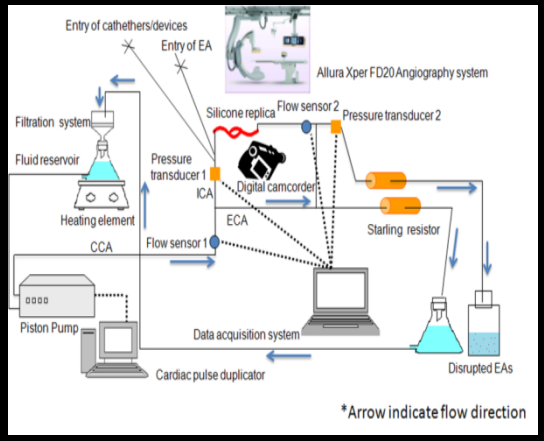
NEW ENGLAND CENTER FOR STROKE RESEARCH



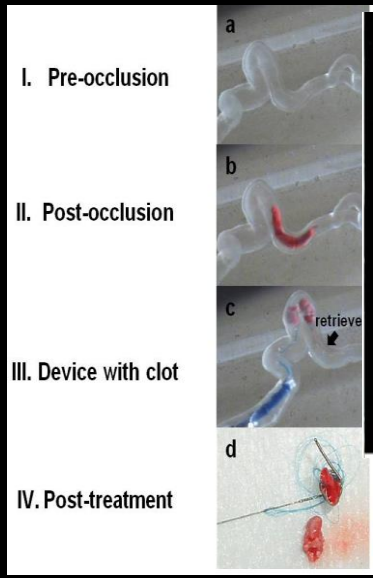


Clot Model

Circulation Loop



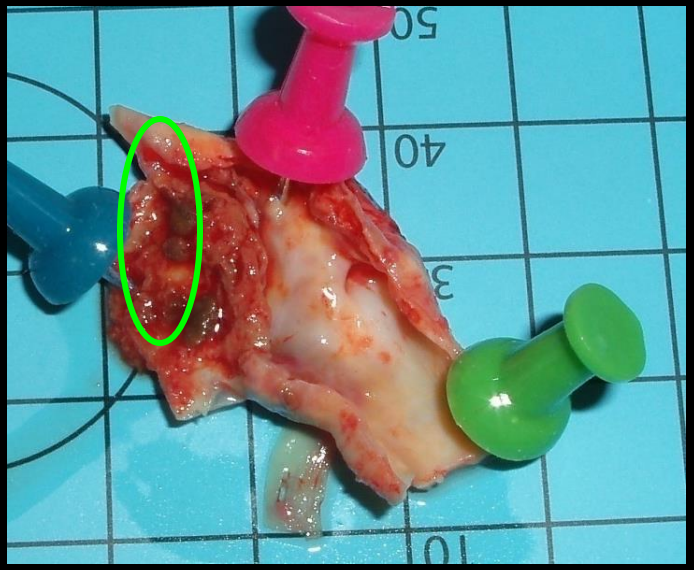
Imaging/ Medical Device

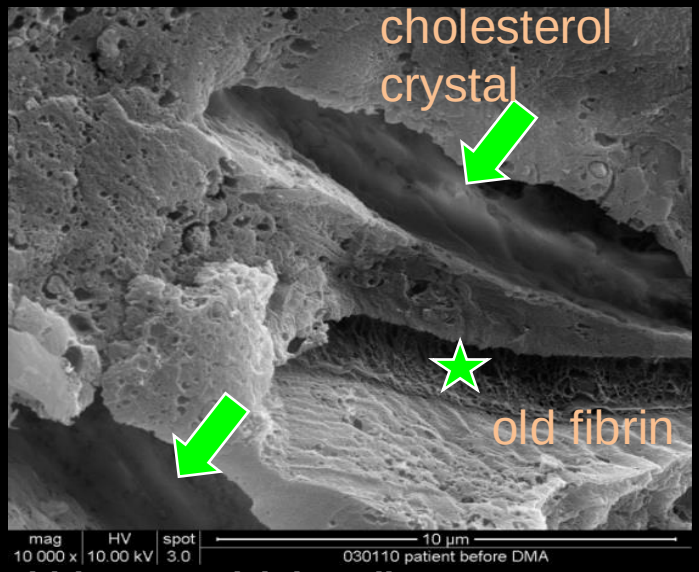


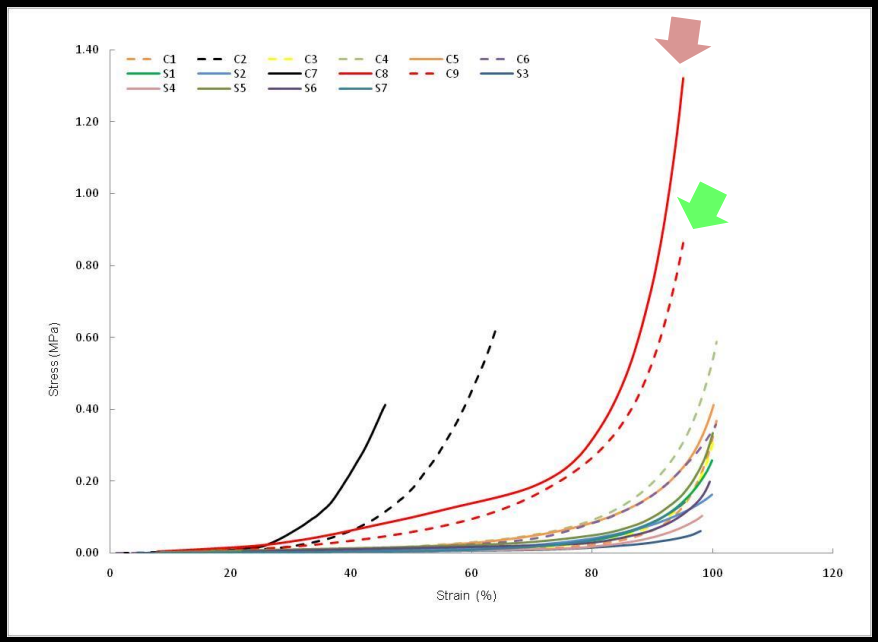
Bench-top Treatment Optimization

Vascular Model

Clot sampling from Patients and mechanical testing

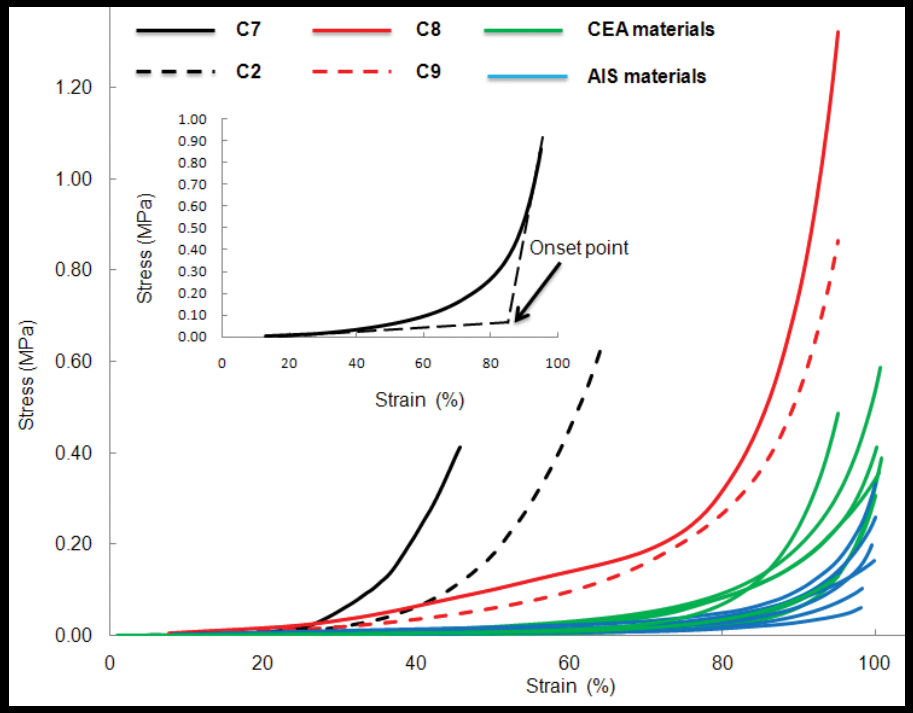




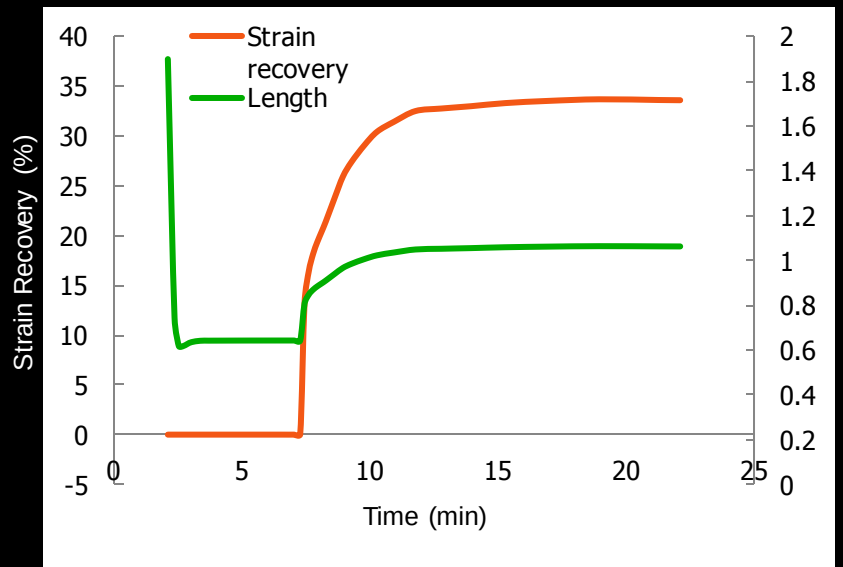


Chueh, Wakhloo, Hendricks, Silva, Gounis. AJNR 2011 32:1237

Mechanical Analysis of Clot



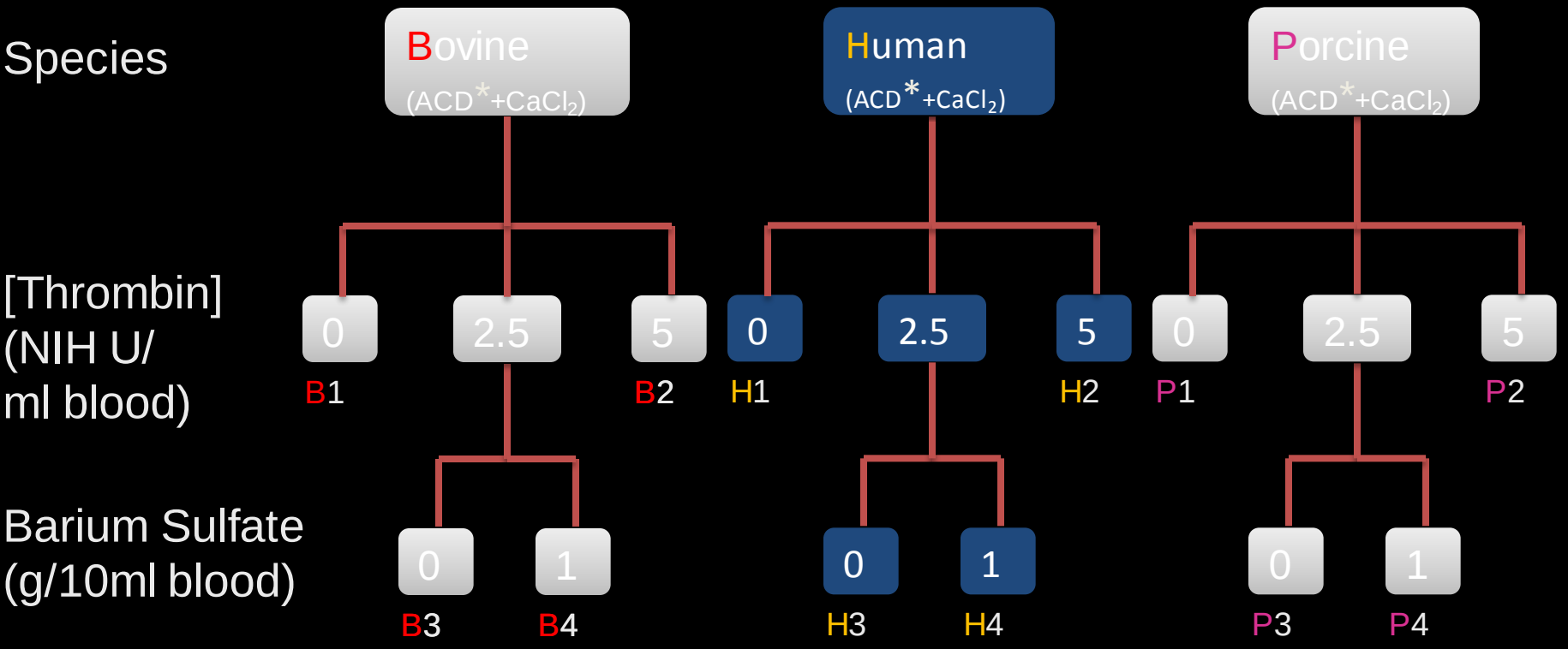
- Clot modeling – Need to know bulk mechanical properties
  - Stress-Strain: DMA compression test
  - Stress relaxation: Propensity for fragmentation



Chueh, Wakhloo, Hendricks, Silva, Gounis. AJNR 2011 32:1237

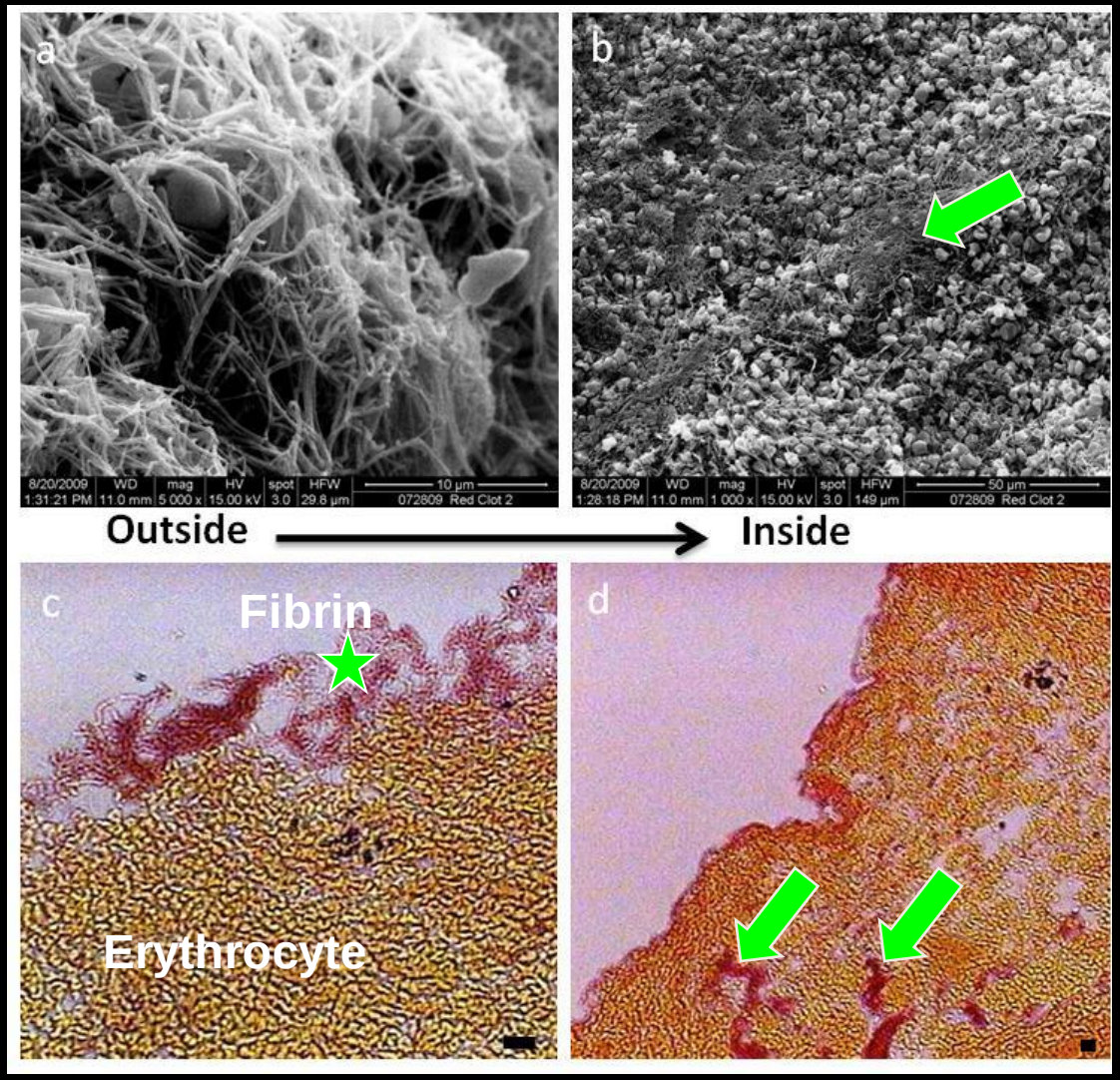
Preparation of In-Vitro Clots

Embolus analogue (EA)



* ACD: anticoagulant citrate dextrose solution

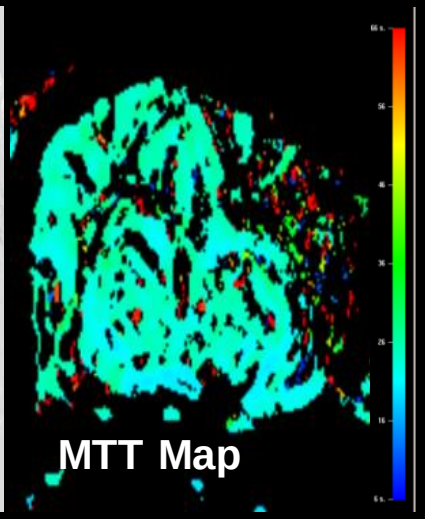
Structure and Composition of In-Vitro Clot

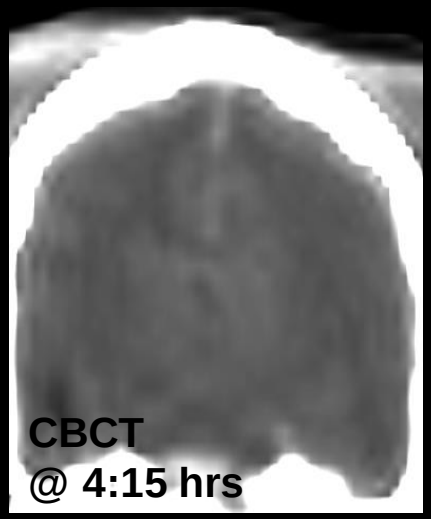


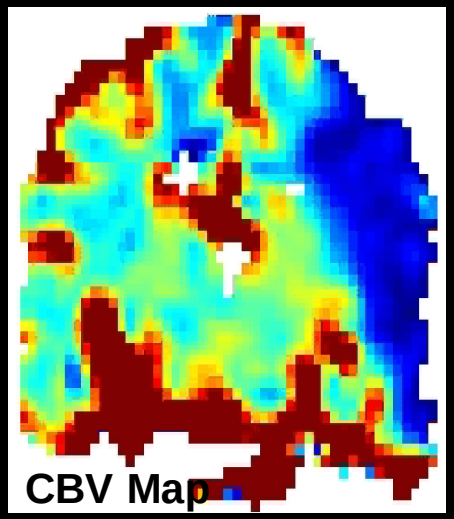
NEW ENGLAND CENTER FOR STROKE RESEARCH

Ischemic Stroke

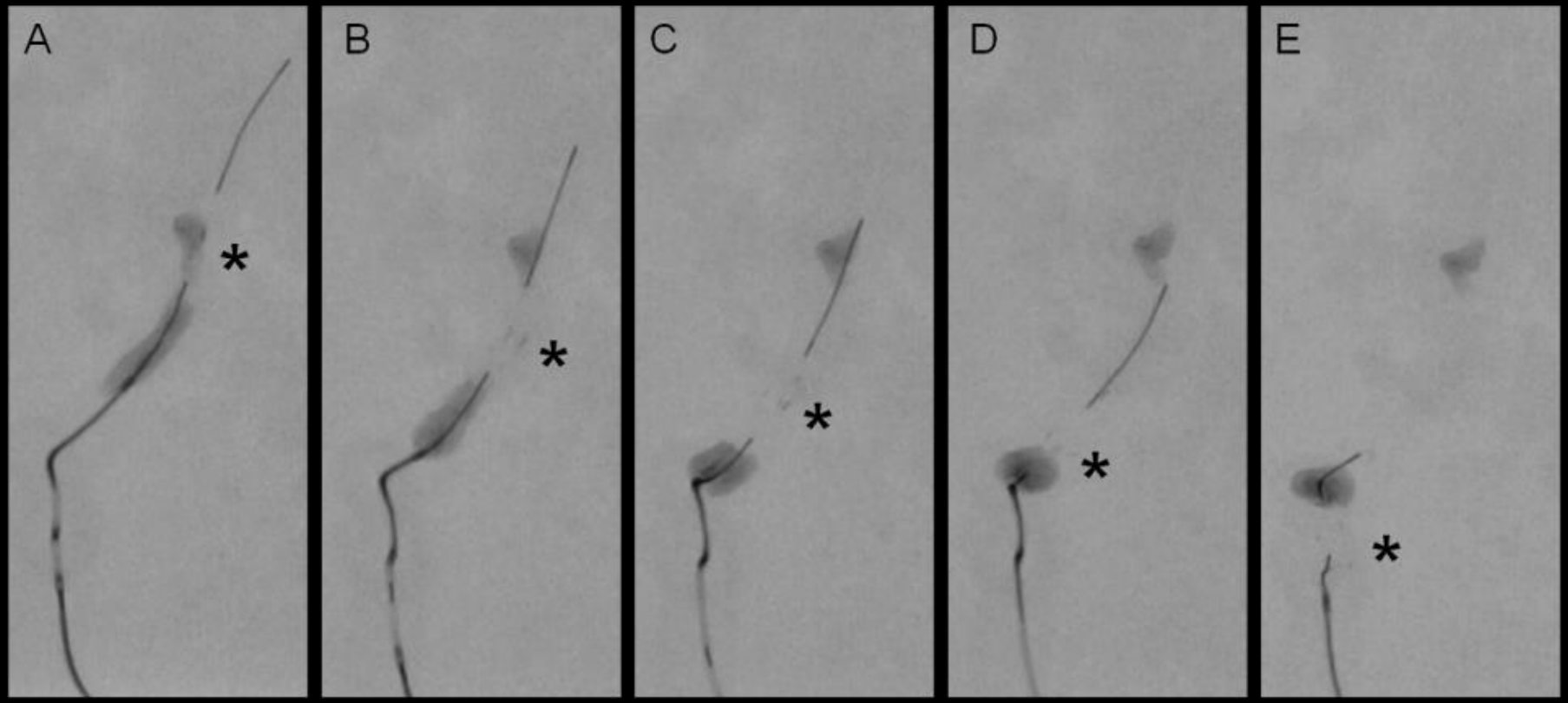
In Vivo surrogate Systems





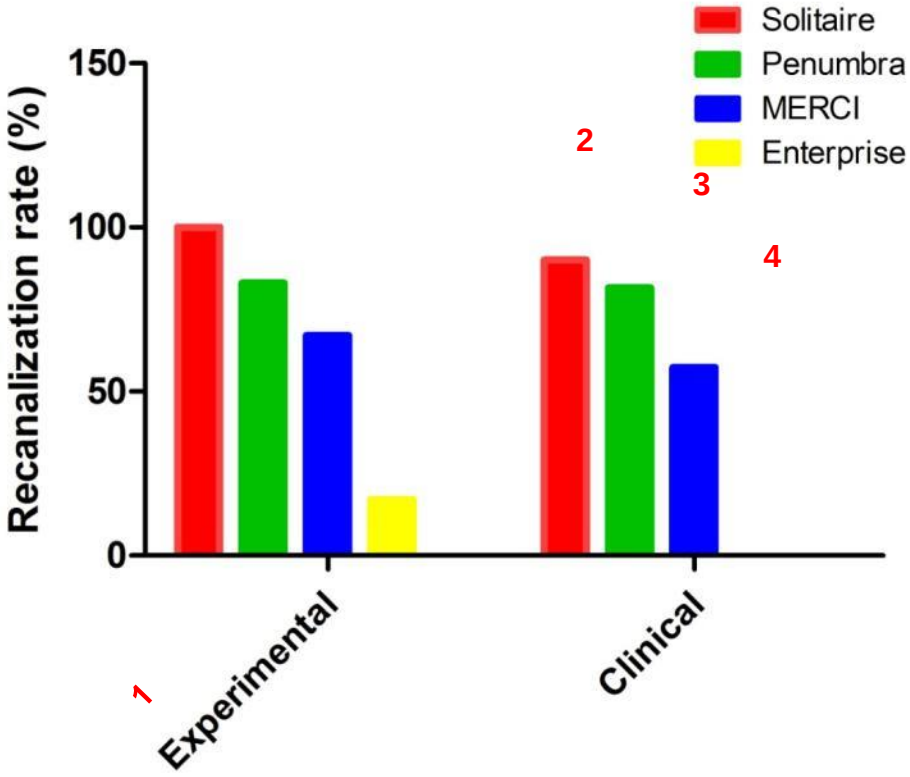


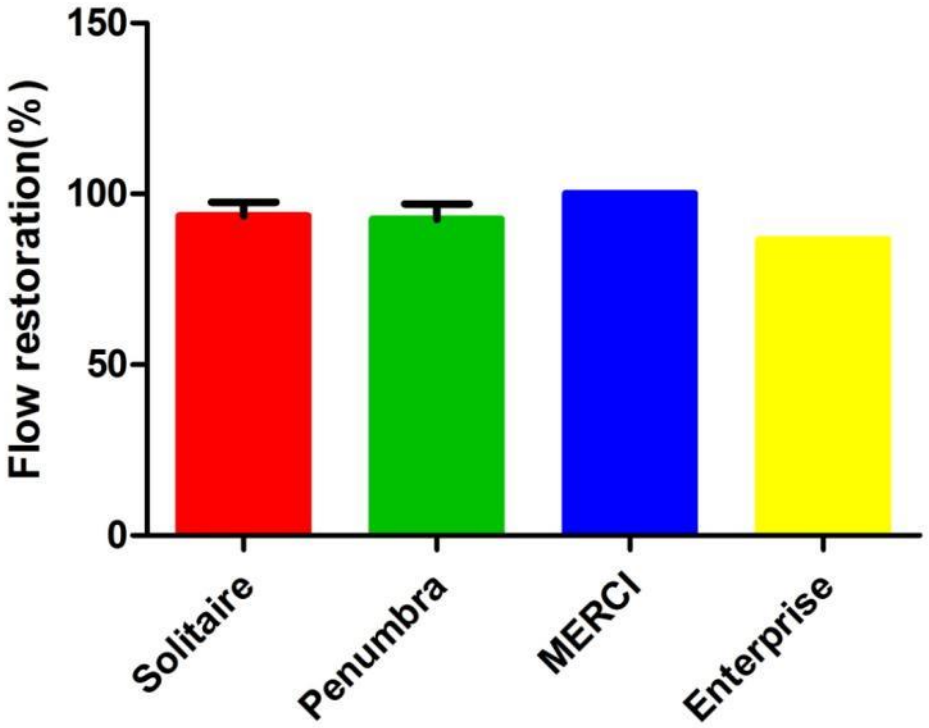
Device development and testing



Primary Efficacy Metrics

Recanalization and Flow restauration



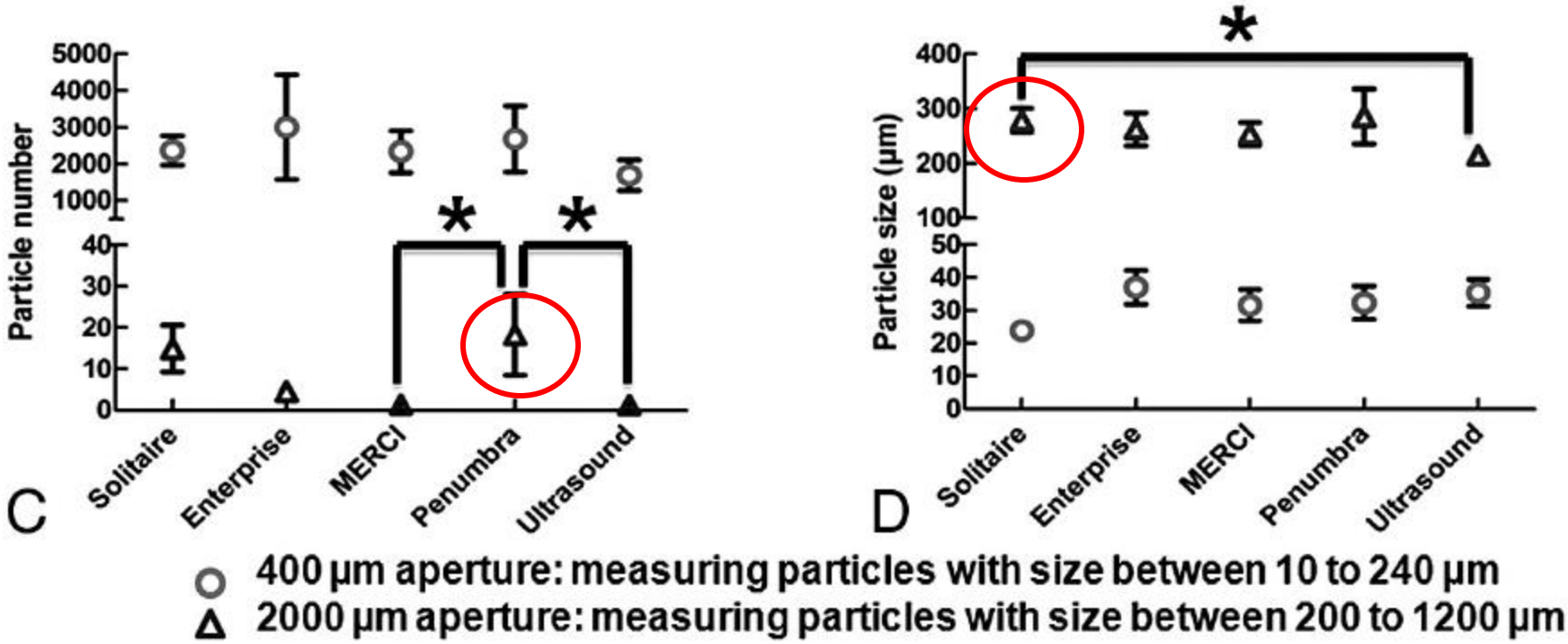


Waveguide failed to restore flow

1. *Chueh, Wakhloo, Gounis. AJNR 2012*
2. *Castaño C, Dorado L, Guerrero C, et al., Stroke 2010,41(8):1836*
3. *Penumbra Pivotal Stroke Trial Investigators. Stroke. 2009;40:2761–2768.*
4. *Smith WS, Sung G, Saver J, et al., for the MERCI Trial Investigators. Stroke 2008, 39: 1205*

Primary safety end point

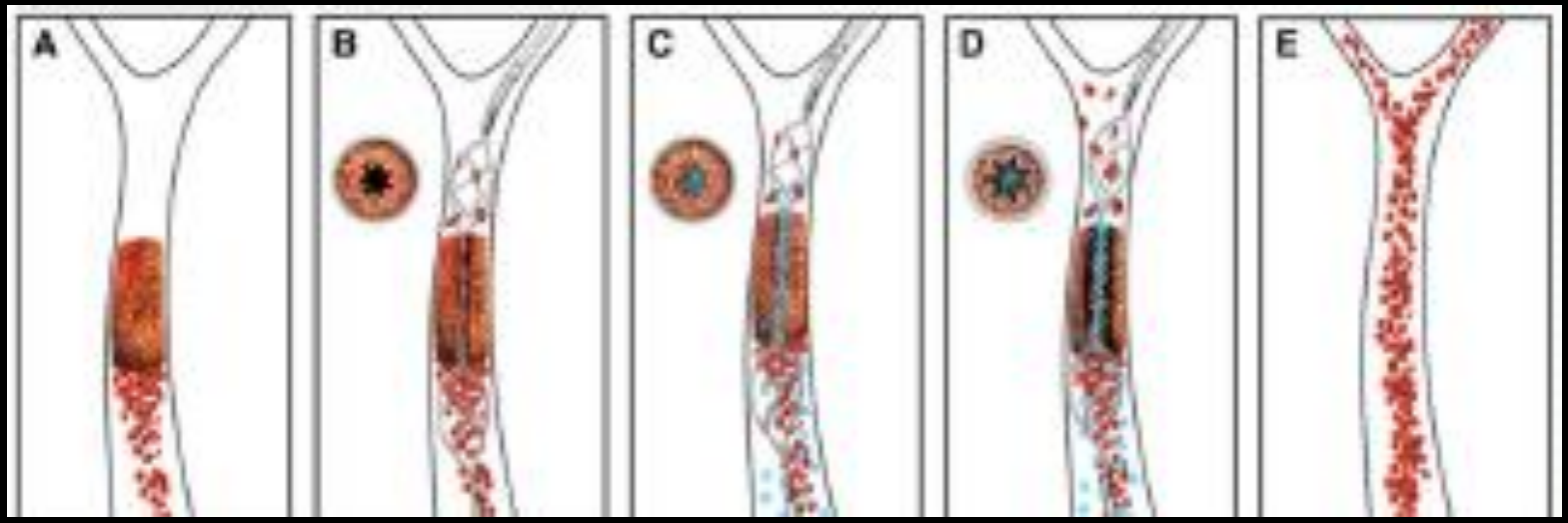
Particle Number and Size



Chueh, Wakhloo and Gounis, AJNR 2012

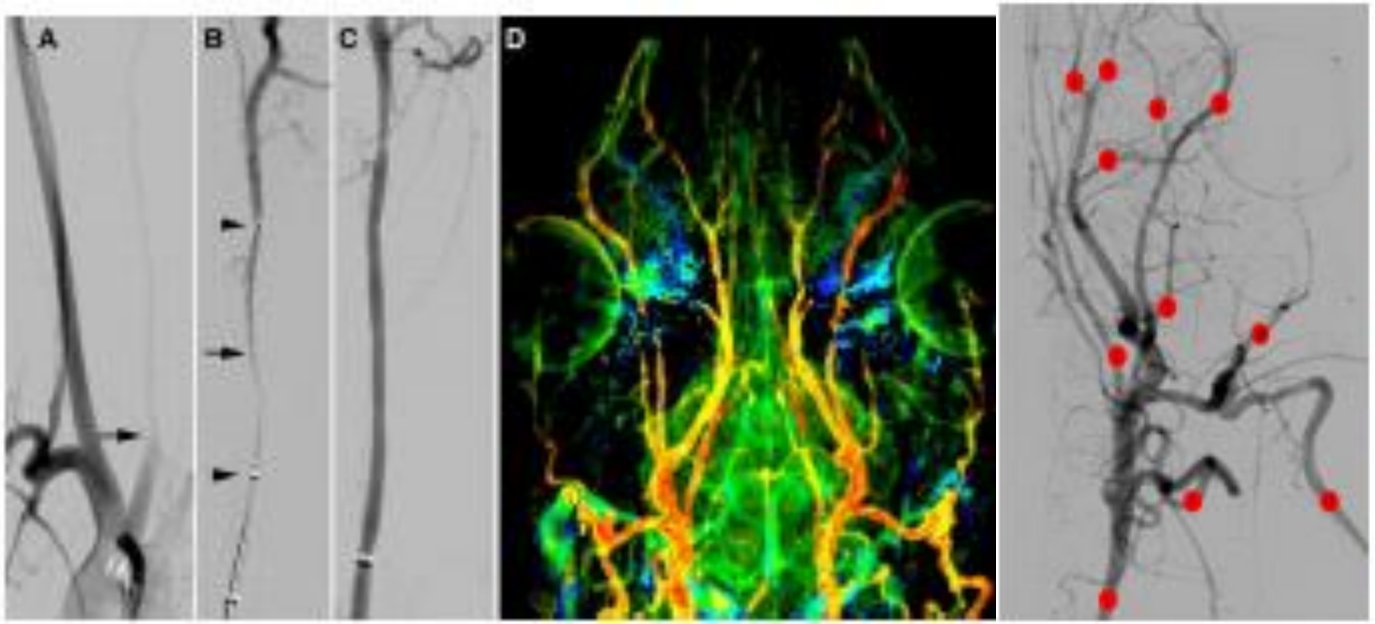
Shear-Activated Nanoparticle Aggregates Combined With Temporary Endovascular Bypass to Treat Large Vessel Occlusion

Miklos G. Marosfoi, MD*; Netanel Korin, PhD*; Matthew J. Gounis, PhD*; Oktay Uzun, PhD; Srinivasan Vedantham, PhD; Erin T. Langan, BS; Anne-Laure Papa, PhD; Olivia W. Brooks; Chris Johnson, BS; Ajit S. Puri, MD; Deen Bhatta, MS; Mathumai Kanapathipillai, PhD; Ben R. Bronstein, MD; Ju-Yu Chueh, PhD; Donald E. Ingber, MD, PhD†; Ajay K. Wakhloo, MD, PhD†



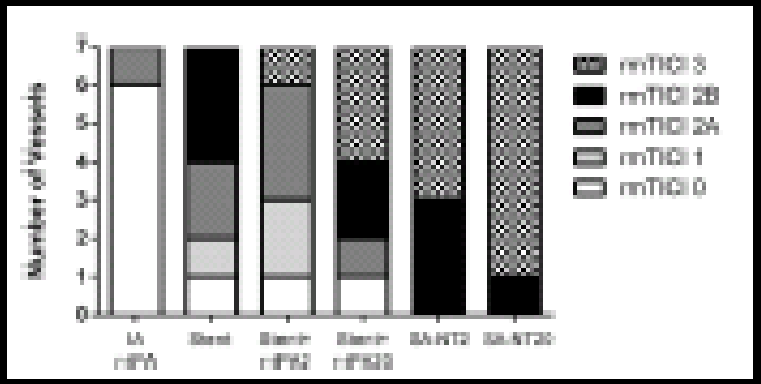
Stroke 2015

Development of in vivo models



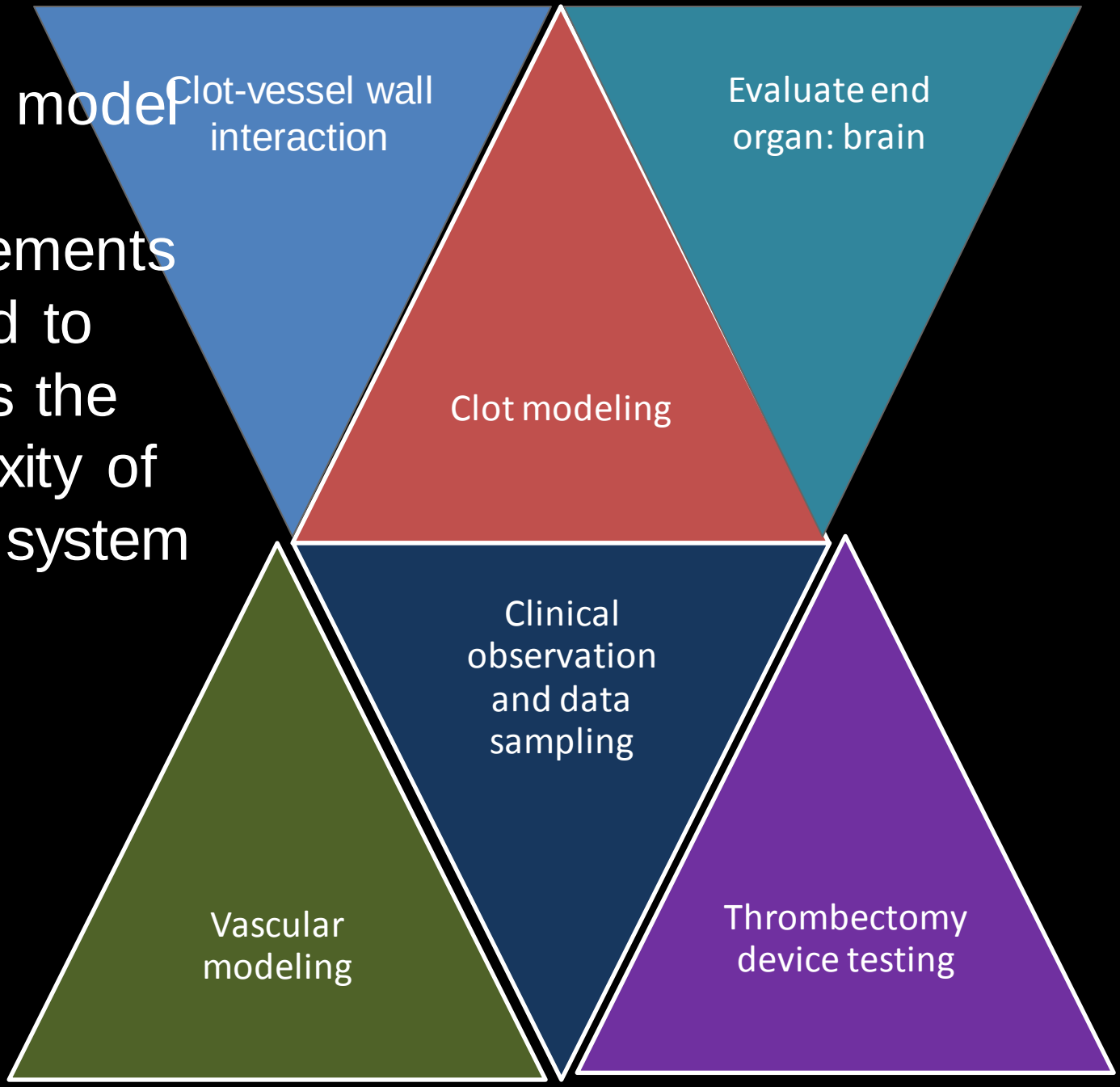
	number of distal vessels	*rmTICI score*
0% reperfusion	0	0
Partial recanalization, but no distal perfusion	0	1
less than 50%	1-5	2A
more than 50%	6-10	2B
100% perfusion	11	3

Supplemental Figure I: Left common carotid artery angiography, AP view: common carotid artery (1), occipital artery (2), lingual artery (3), descending palatine artery (4), infraorbital artery (5), buccal artery (6), mandibular alveolar artery (7), lower labial artery (8), distal part of facial artery (9), transversal facial artery (10), auricular artery (11)



Stroke 2015

Further model system improvements required to address the complexity of human system



Final Goal

Clinician is striving for *individualized medicine* with detection and inclusion of patient specific markers to better understand the system response and tailor treatment


3T MR

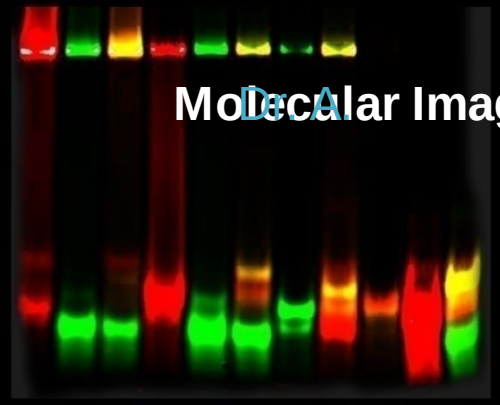
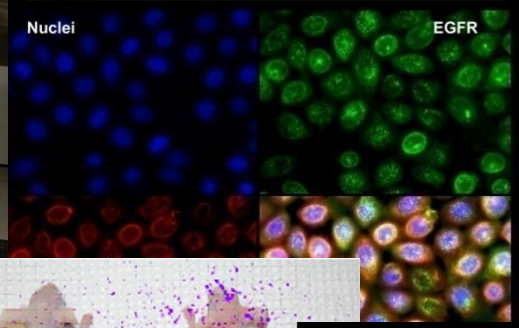
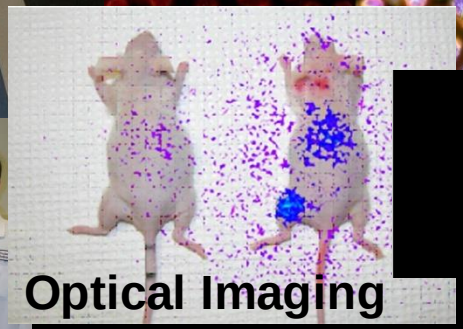
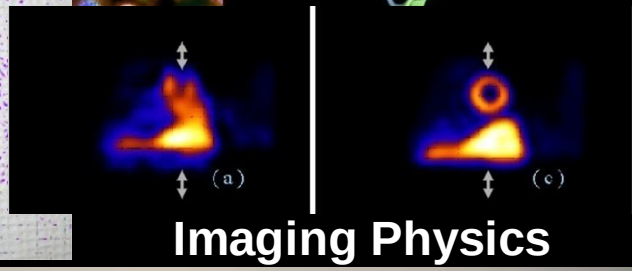

Molecular Imaging


Image Guided Therapy


Nuclei
EGFR


PET


Optical Imaging


(a)
(c)
Imaging Physics


Radiochemistry/Biomarkers


MicroCT

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  - Alexei Bogdanov, PhD
  - Greg Hendricks, PhD
  - Guanping Gao, PhD
  - Miguel Esteves, PhD
  - Rick Moser, MD
  - John Weaver, MD
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