Shear stress: Computer simulation of coagulation and blood trauma

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SCORE: 4

Clinical Problem

- Strokes and heart attacks
- Arterial thrombosis
- Intravascular devices

- Plaque builds up for decades
- Why is the acute attack only 30 minutes?
- -> Thrombotic Occlusion in artery

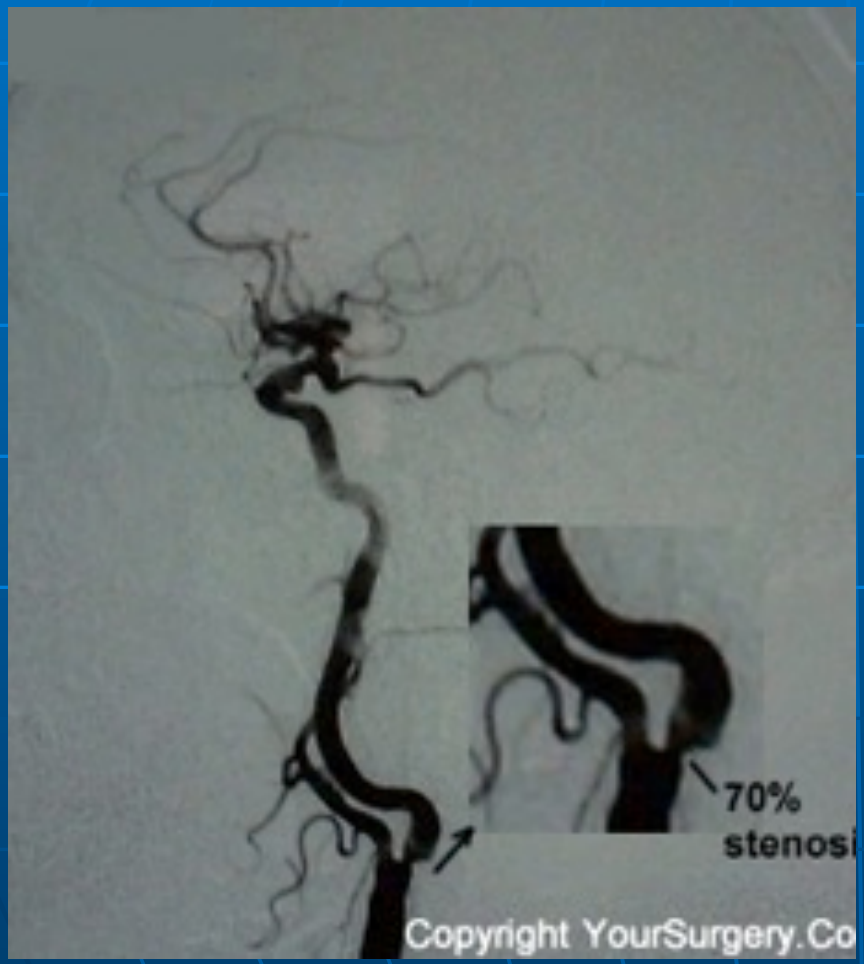
Controversy

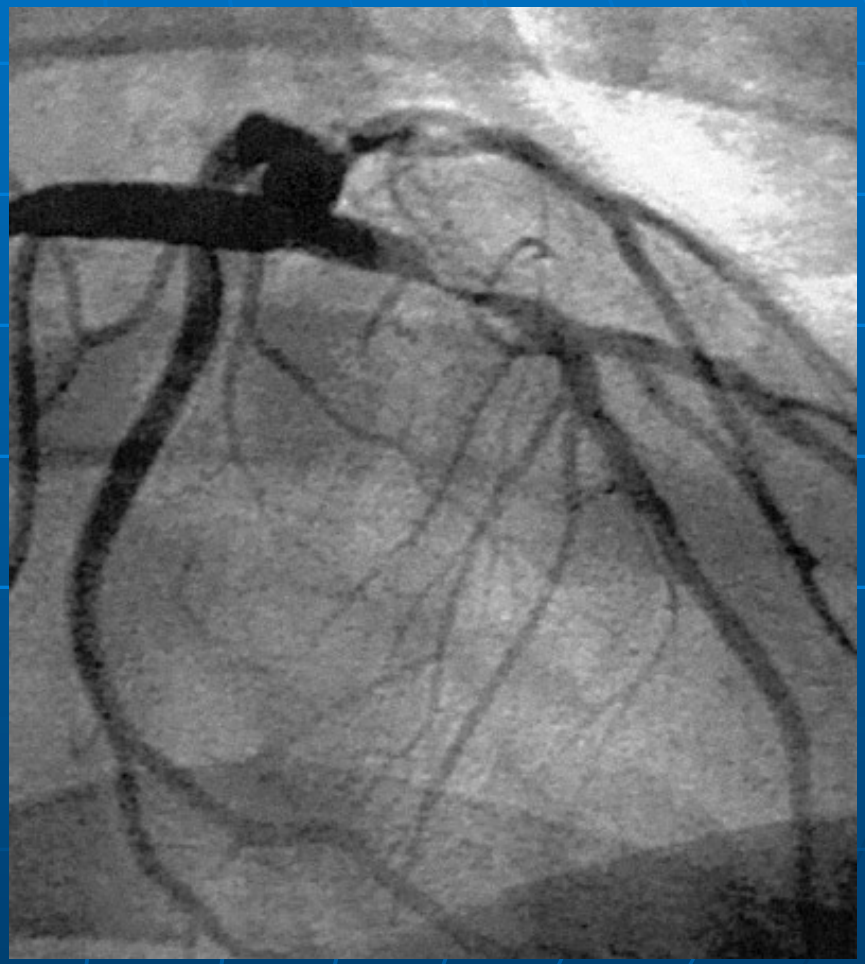
Thrombosis from Virchow's triad?

1. Stasis – Arterial flow is not static,
   but very high shear rates
2. Coagulation – Not coagulated red clot,
   but white from platelets
3. No EC – Surface covered within first minute

Thus, textbook science says we should not have heart attacks or strokes!

Disease causes stenosis

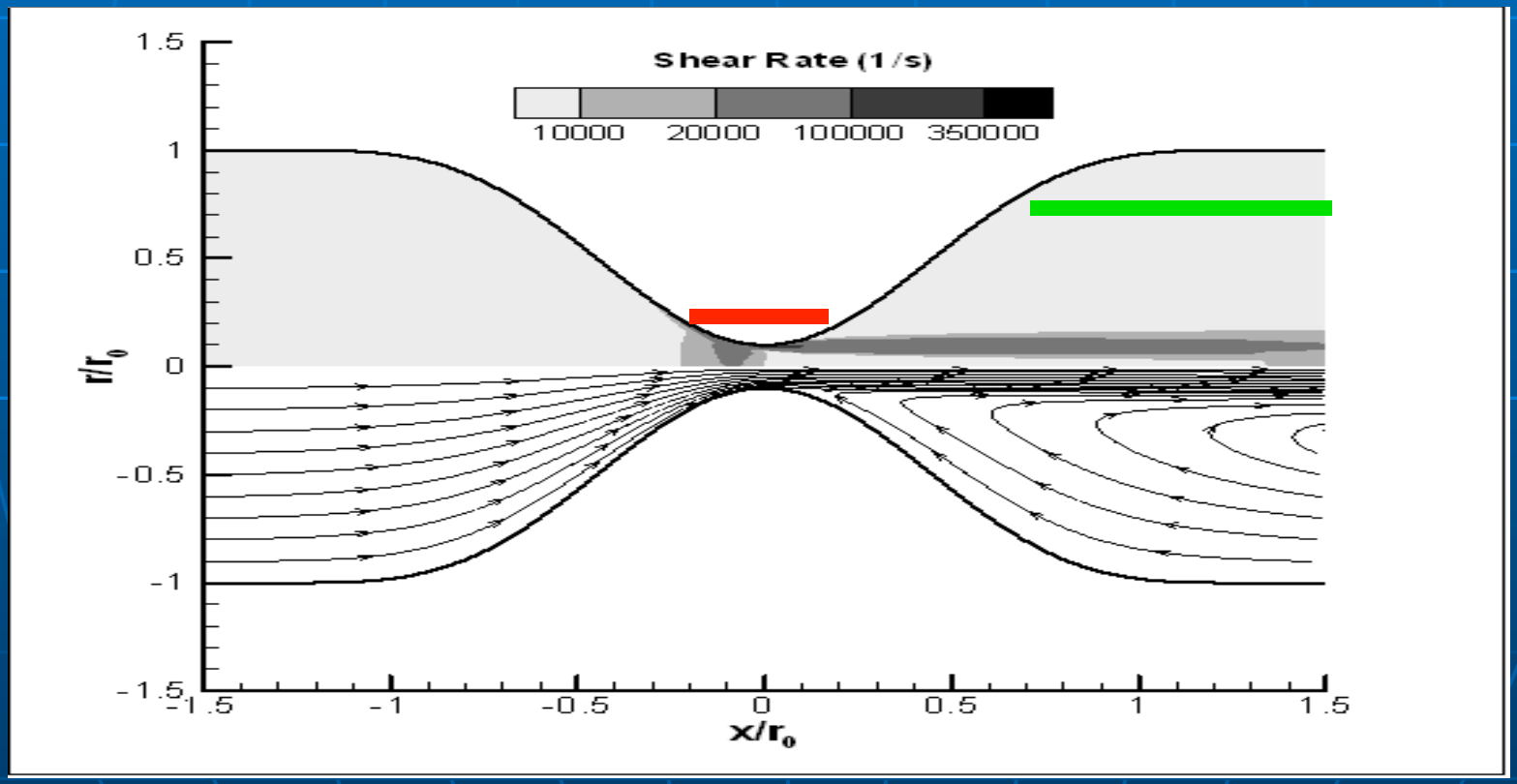




Shear rate is the change in velocity at the wall - varies 800x

Recirculation downstream – low shear

Apex – very high shear



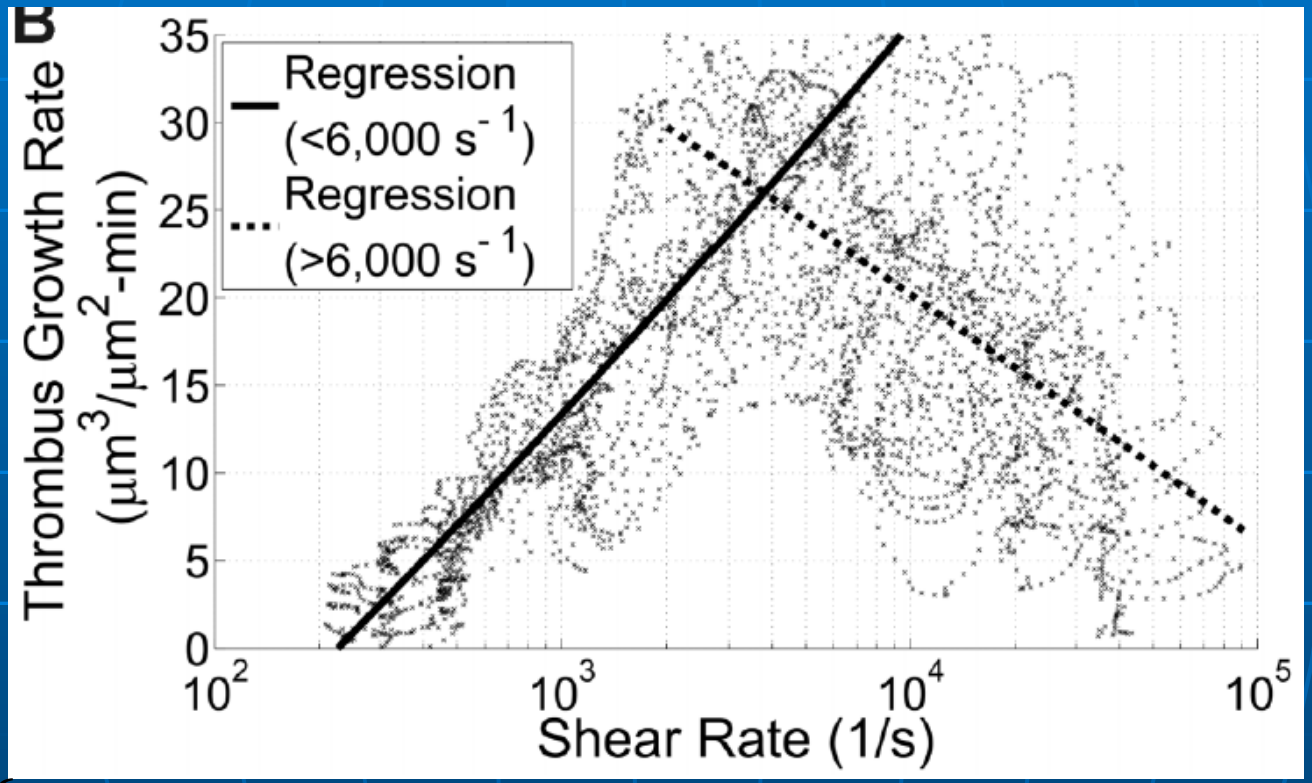
Where does thrombus occur?

- Tubular stenosis with high shear at throat
- Collagen coating
- Optical visualization – clear tubes
- Endpoint is Thrombus, not activated plts or hemolysis

Thrombosis to Occlusion

Para, Ku ABME 2011

Growth rate is shear dependent
(r=0.94, p<0.0001, n=5000)

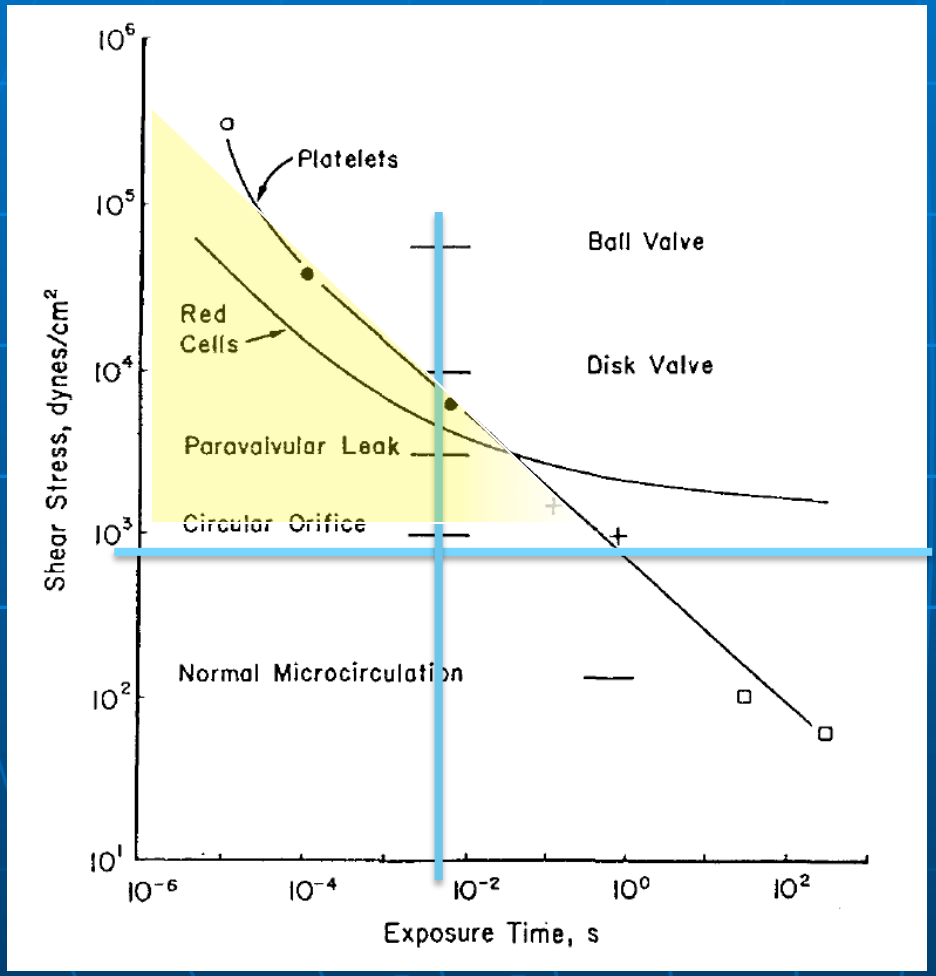


$$J = \begin{cases} 186\dot{\gamma}^{0.0382} - 229, & \dot{\gamma} < 6000\ \mathbf{s}^{-1} \\ 506 - 434\dot{\gamma}^{0.0124}, & \dot{\gamma} > 6000\ \mathbf{s}^{-1} \end{cases}$$

$$\text{□}\mathbf{m}^3\ /\text{□}\mathrm{m}^2 \cdot \mathbf{min}$$

Bark, Para, Ku Biotech Bioeng 2012

Occlusive Thrombosis Far Below Platelet Activation/Hemolysis Threshold

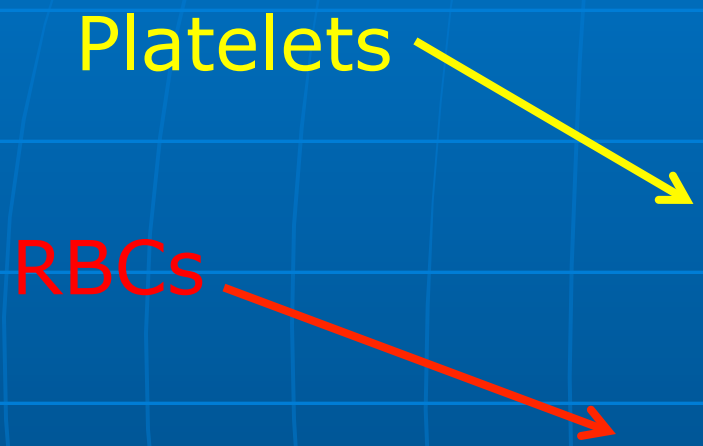


Shear Stress = 175 dyn/cm^2 ≈ 5000 s^{-1}

Transit Time ≈ 5 × 10^{-3} s

Hellums *Ann Biomed Eng* 1994

High shear thrombus is mainly platelets



Histology of whole blood thrombus with Carstairs staining method

0.5 mm

1. How do a billion platelets get to the wall?

Blood particles create strange behavior

RBCs have flexible membranes that can tank-tread

Causes RBCs to move to the middle of a blood vessel

Margination of platelets

Reasor, Ku *ABME* 2012

Endview of Margination

Effective diffusivity increases with shear rate
Migration stimulated by rigid, small, spheroids

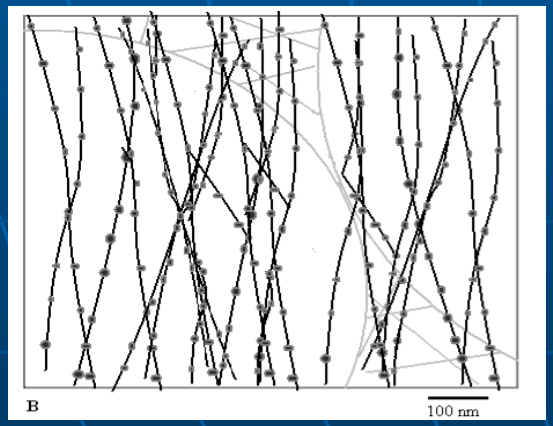
Reasor, Ku *ABME* 2012

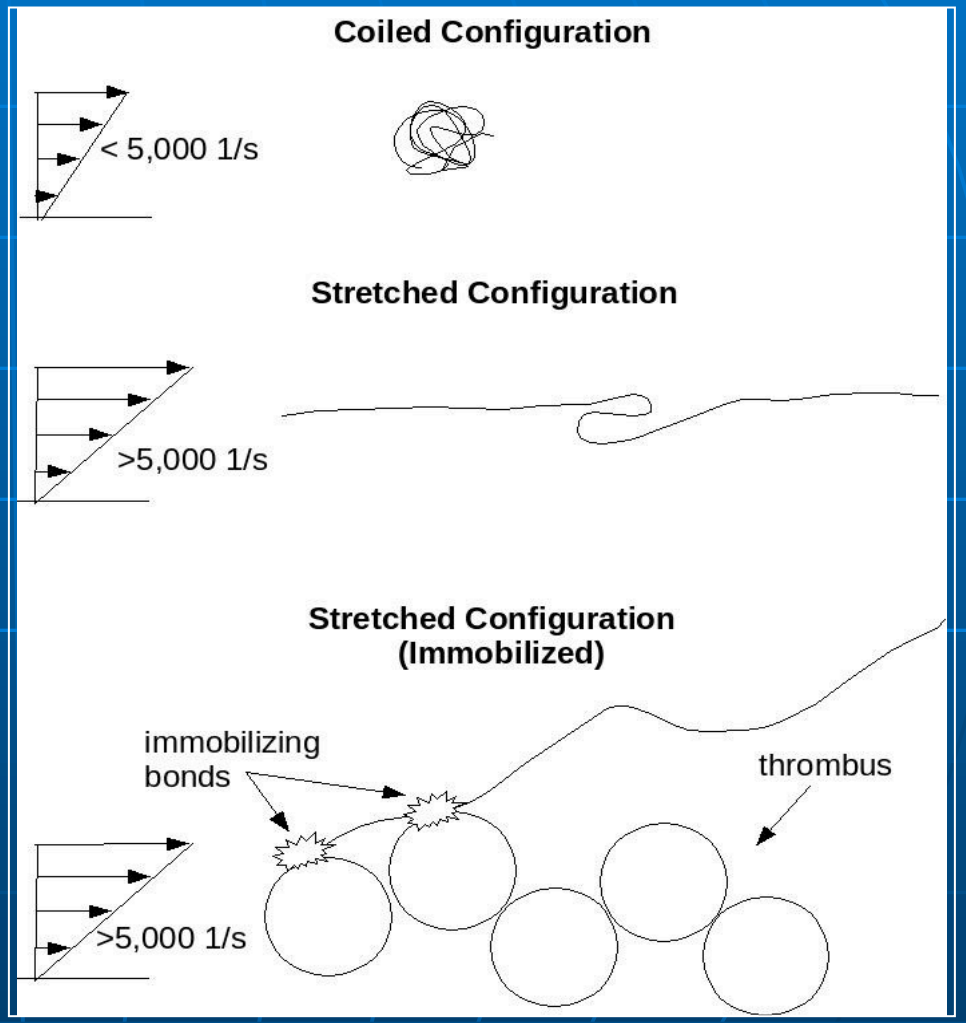
2. Platelets accumulate very fast under high drag forces.

How do platelets stick
so fast
and strong?

vWF elongation with shear

- GPIb – 25,000 per platelet
- Low shear - globular
  - Low receptor density **10 receptors/μm²**
- High shear – elongates exposing A1's
- Large release from platelets



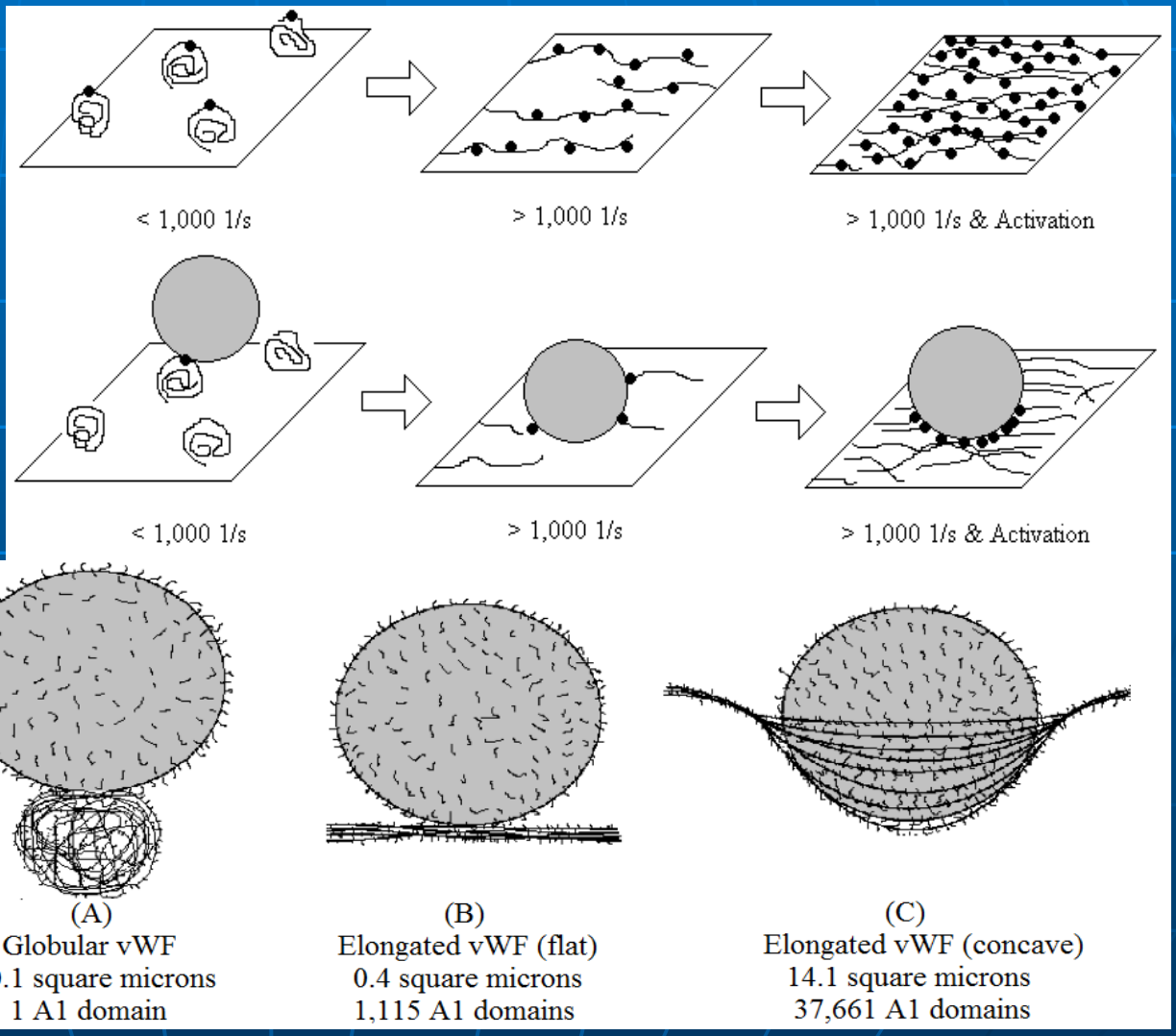


Schneider PNAS 2007 Wellings Ku CVET 2012

VWF nets catch platelets

- Nets of vWF strands
- Strand form can have high contact area
- Up to **37,000 A1** per platelet at high shear

- **Fastest, Strongest bond in biology**



Arterial Thrombus

A. High shear enhances margination of platelets to get to the wall
B. High shear unfolds vWF to make a long fishing line with many A1 hooks
C. High shear activates captured platelets to release 50x vWF to make strong nets

-> Thrombus grows big super fast to occlusion

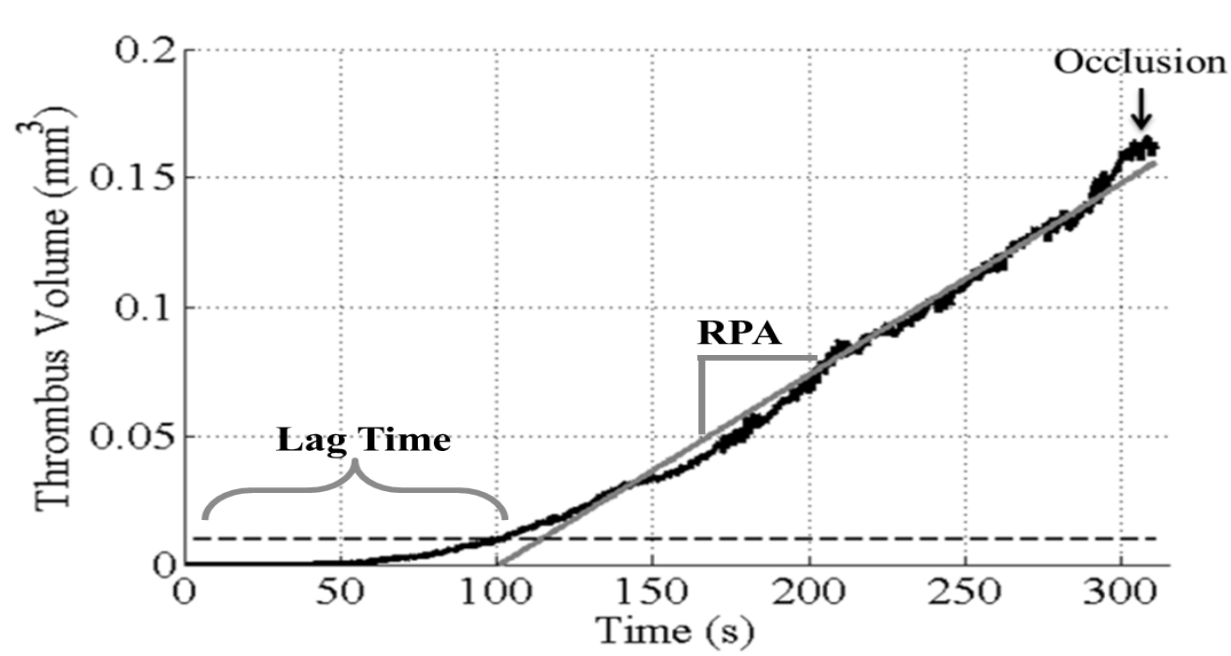
Mathematical model predicts occlusion

- Geometry sets the shear rate
- Growth rate = f (shear rate, plts, vWF, surface)
- Get location and growth rate of thrombus

- Use model to predict and design optimum

Predict Thrombus as a product of shear rate and time

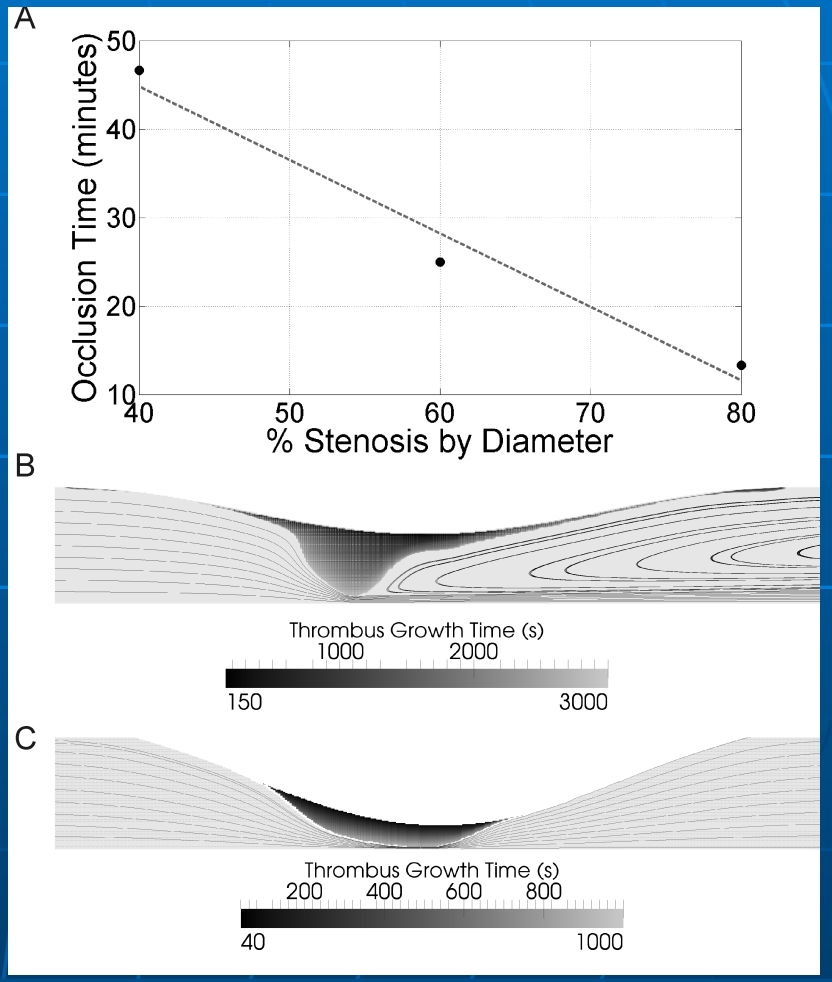
$$V_{thromb} = \sum_{i=1}^{n} J_i(\dot{\gamma})\Delta t_i$$



Bark et al. *Biotechnol Bioeng* 2012

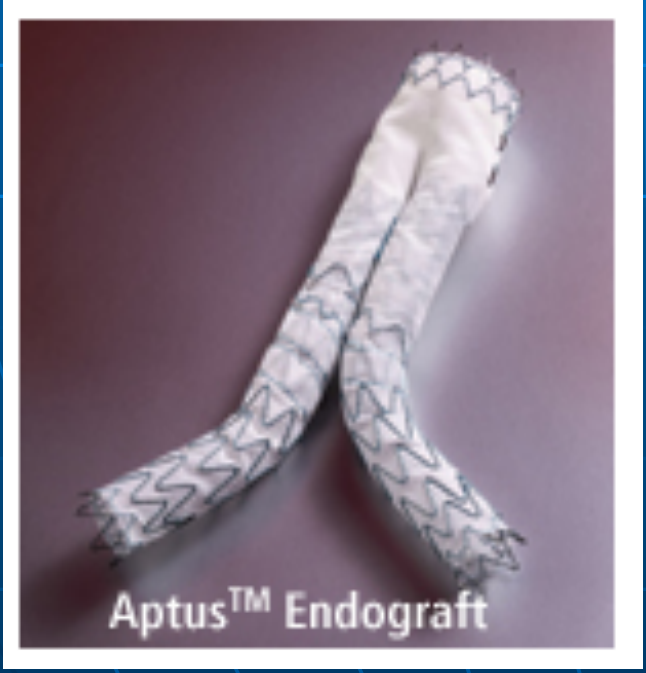
Validation 1

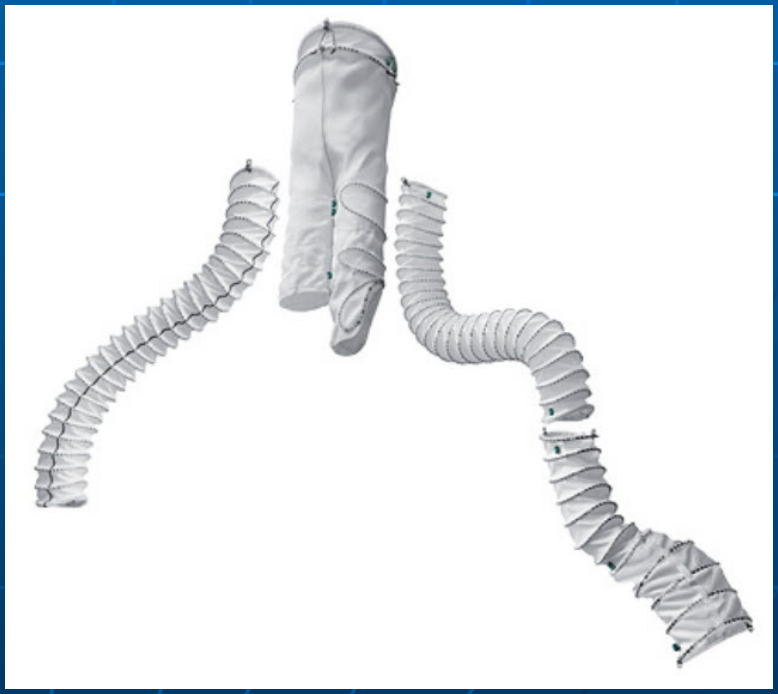
- 2 mm hour-glass stenoses
- Predict occlusion in 10 min
- Actual is 10+/- 2 min



Validation 2

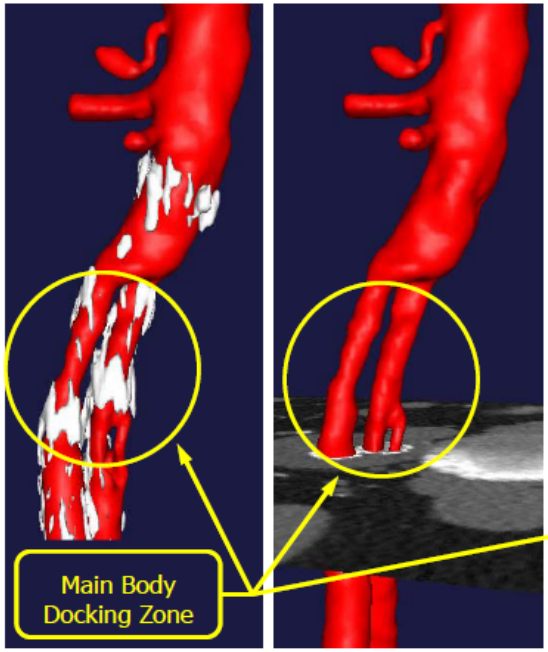
- **Aortic vascular grafts, EVAR (10 mm)**
- Long term exposure in patients

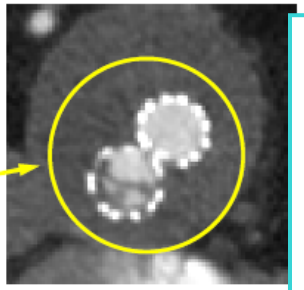




Surprise clinical thrombosis

Thrombus Formation Location

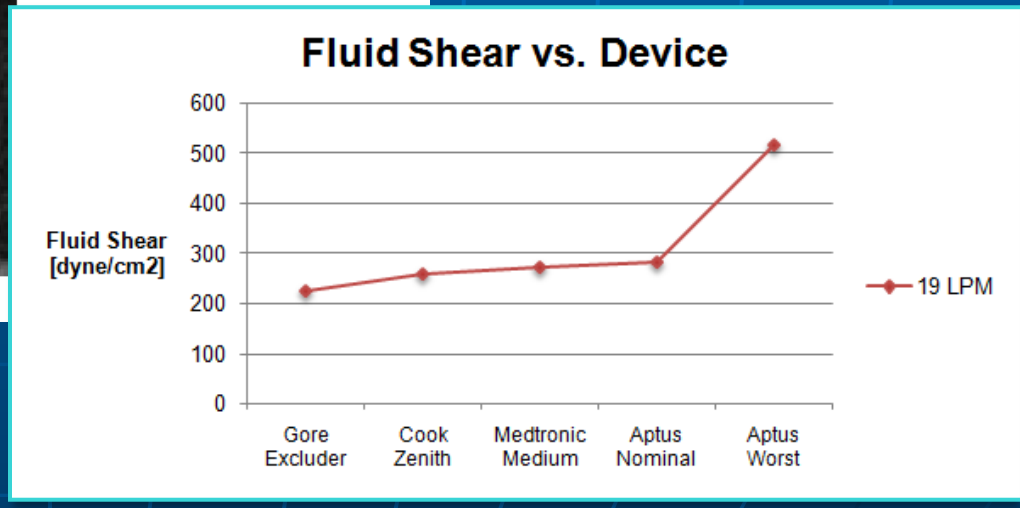




CT Reconstruction and Image of Irregular Thrombus

CT Film Analysis Demonstrate:

- Irregular thrombus in the Main Body docking zone
- Thrombus loosely connected and extending downstream
- Small diameters and rough surface in the docking zone



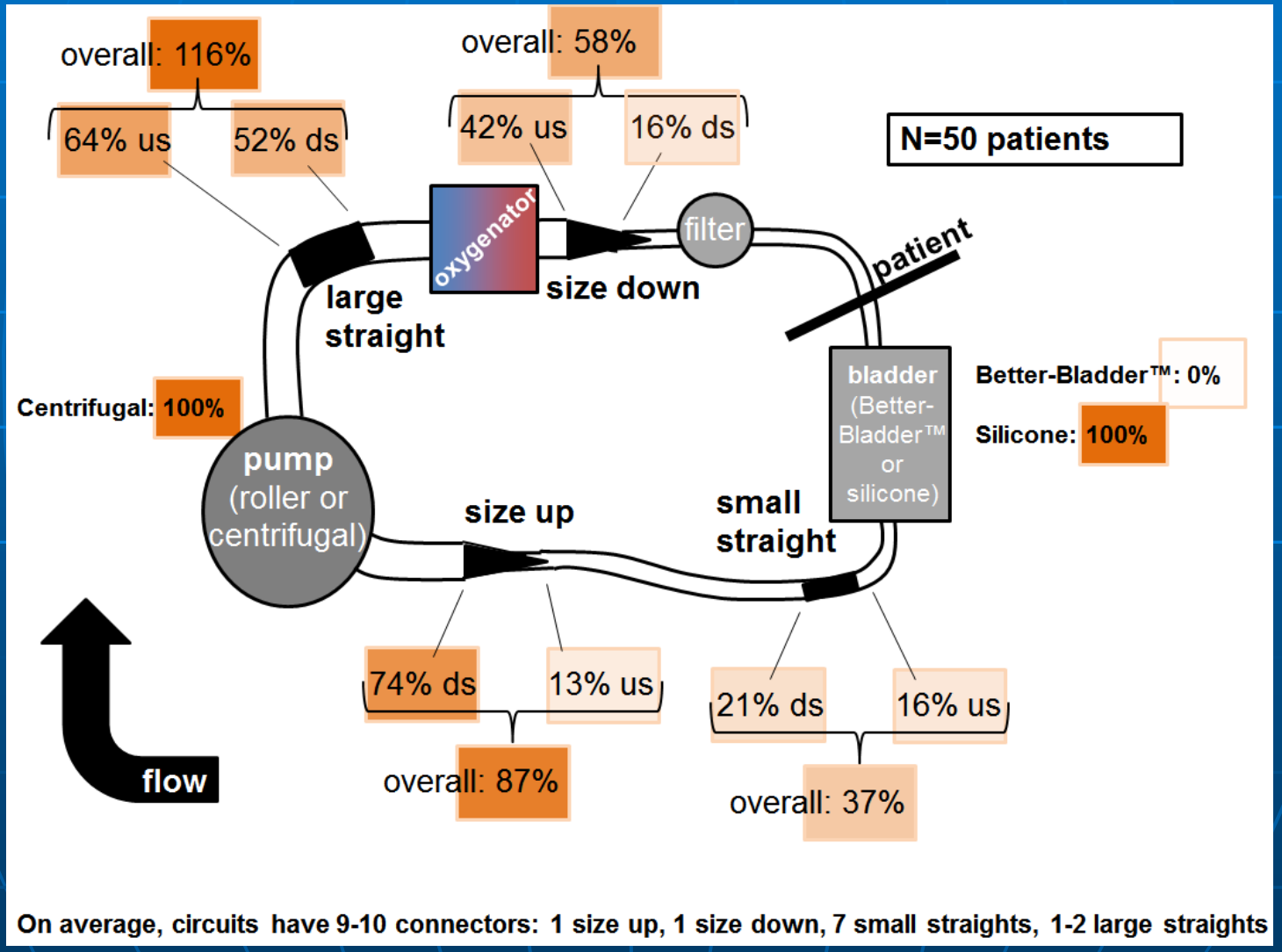
Vascular graft / PTFE EVAR
Clinical thrombosis duplicated *in vitro*

Thrombosis predicted: 161 min
Thrombosis actual: 155 min
Redesign eliminates clinical thrombosis

Validation 3:
Clinical ECMO Circuits

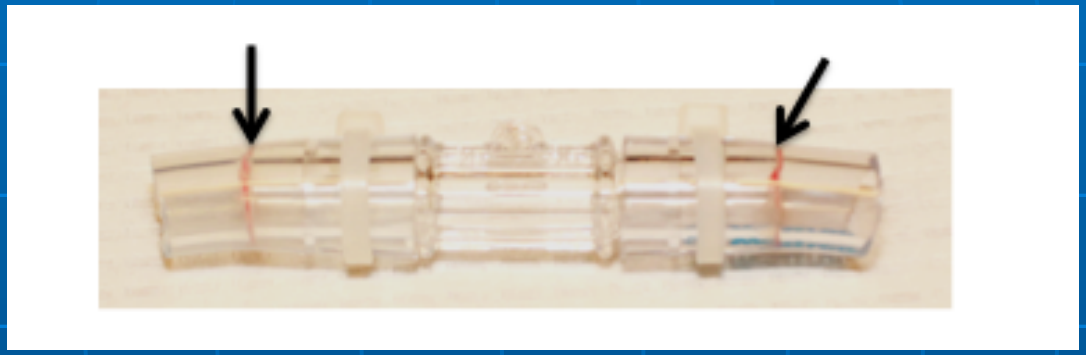
- Examined for adherent thrombi post patient removal
- Light rinse with saline
- 50 circuits in sample
- -> Location and frequency of clots

Clots at the Connectors



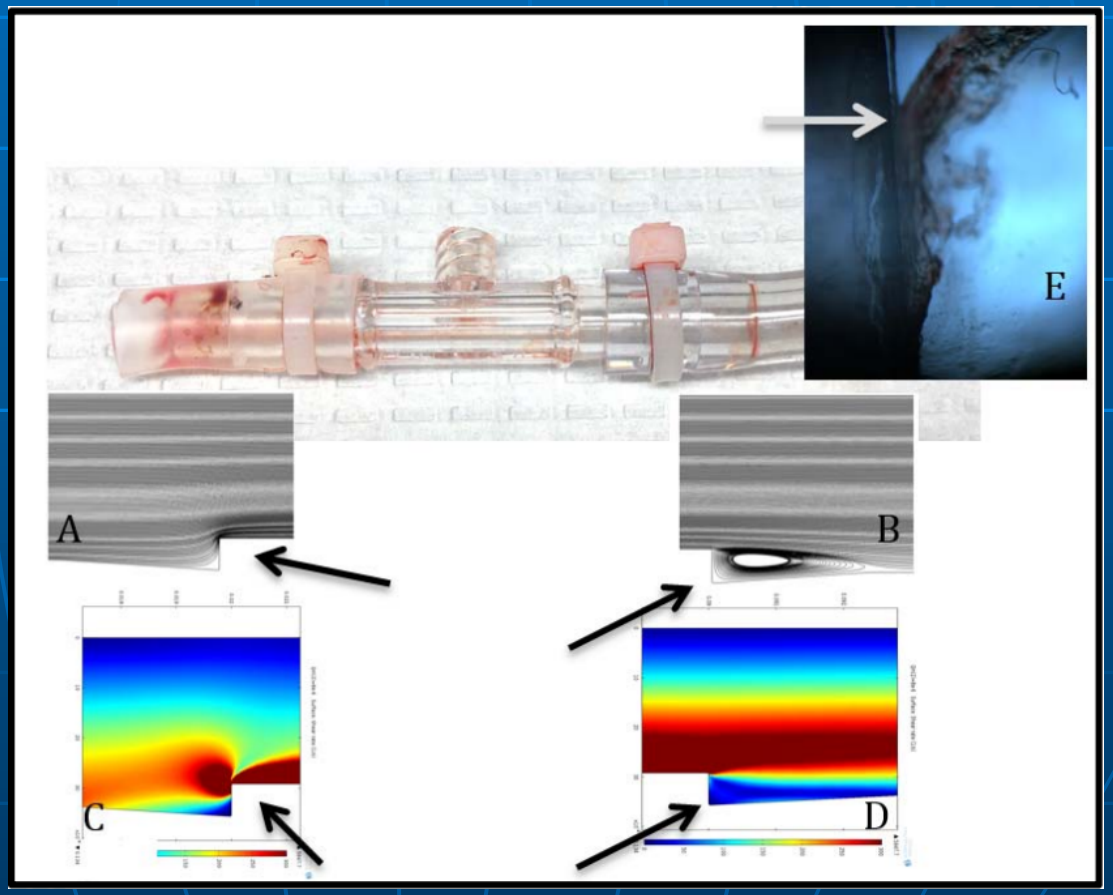
ECMO Connectors

- Thrombi at connectors in all cases, Large > small
- Capable of growing downstream



ECMO Connectors

- Adherent to connector edge
- Analysis revealed low shear region, almost stagnant



ECMO Study: *in vitro* Formation

- Clots formed at connector junctions
- Capable of downstream growth
- Fibrinous composition

→ Consistent with clinical samples

ECMO Redesign of Connectors

- Elimination of low shear zone with no material differences

  -> **elimination** of connector clot, $p<0.005$

  (paired control created clot)

unpublished

Predictive Device Design

- Shear at the intersection of surface adsorption and bulk thrombosis
- Reduce patient risk
- Treatment protocols for existing devices
- **Goal: Nonthrombogenic devices**

Centrifugal Pump Study

- Recent shift to centrifugal pumps in ECMO
- Approach: clinical analysis followed by *in vitro* replication

Centrifugal Pump Study: Clinical Analysis

- Roller pumps: 0/34 thrombus
- Sorin centrifugal pumps: 16/16 $p<0.001$
  - With more adherent thrombi in circuit ($p<0.01$)
- Stainless steel bearing is the nidus

IJAO, 2016 in press

Centrifugal Pump Study: *in vitro* formation

- Simplified *in vitro* loop run for 48 hrs
- Grows from bearing
- Platelet rich → Reproduces clinical samples

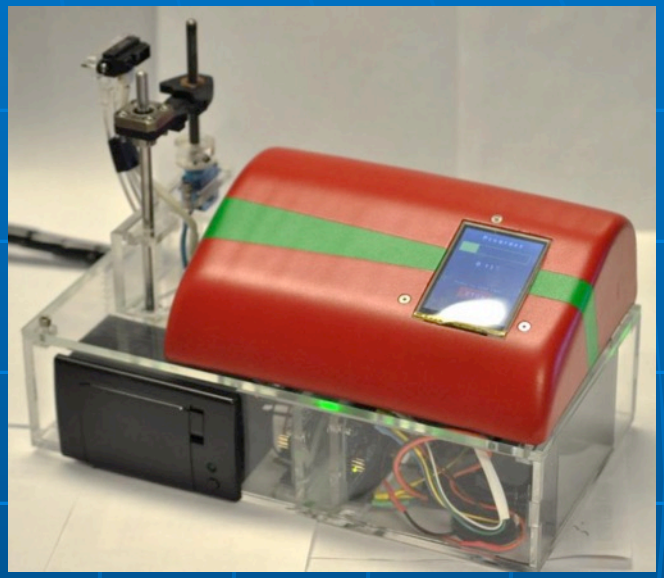
Centrifugal Pump Study: Future Redesign

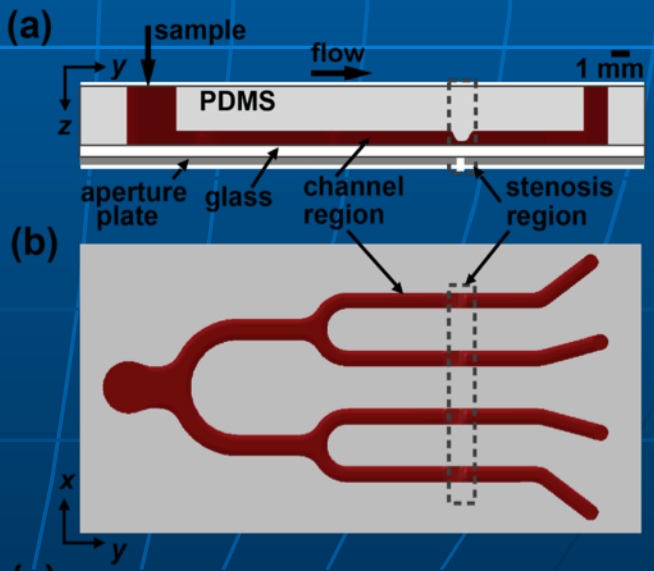
- Eliminate bearing steel pin (material)
- Use computational models to reduce extreme high shear
- HM3 MagLev eliminates steel and Reduces shear 20x

TAVR clots: high or low shear?

Pt-specific Thrombus Assay

- POC Microfluidics high and low shear (vacutainer blood)
- Endpoint – Thrombus formation
- Titrate anticoagulants/ antiplatelets
- Guidance for Rx that are patient specific

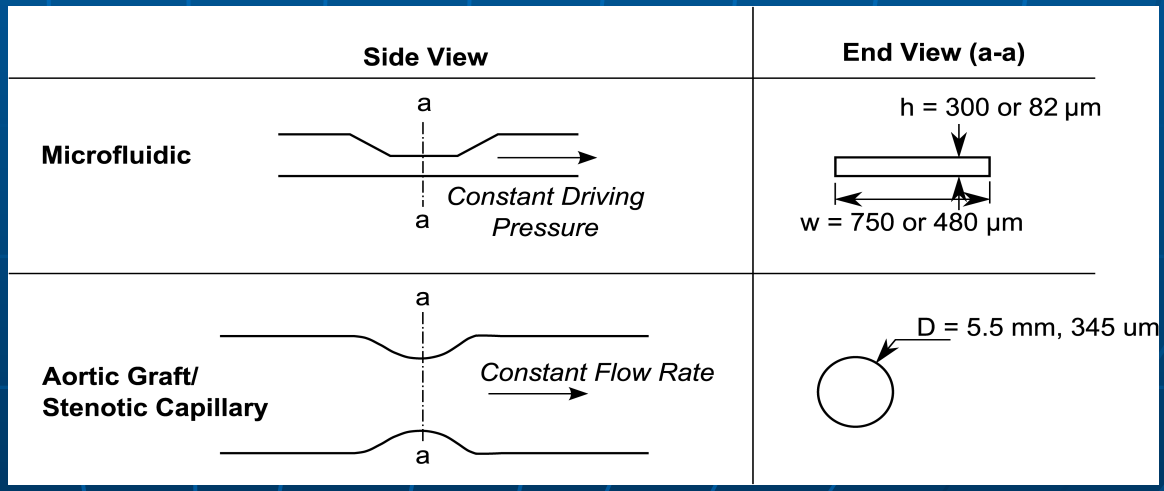




Li, Ku Lab on a Chip 2012
Li, Ku PLOS 2014

Validated PoC test

- **Microfluidic channels:** 82 microns
- Predict occlusion in 5.4 min
- Actual: 5.2 +/- 2.2 min
- Uses only 5 ml of vacutainer blood
- Identifies High on Aspirin/Plavix with high shear



Conclusions, Part I

1. Very High Shear Rates > 10,000 s^{-1}
   - Rapid Platelet Accumulation
   - Margination of platelets
   - vWF elongation nets capture platelets
   - Heparin does not prevent, Use antiplts?
2. **Low Shear Rates < 50s^{-1}**
   - Coagulation clots can form
   - Coagulation proteins, thrombin, fibrinogen
   - Not vWF/platelet, Use anticoagulants

Conclusions, II

3. New device design should optimize wall shear rates to reduce propensity for thrombosis

4. Point-of-Care assay may help titrate blood Rx (Anticoags / antiplatelets) – **not** one size fits all

Shear stress: Computer simulation of coagulation and blood trauma

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