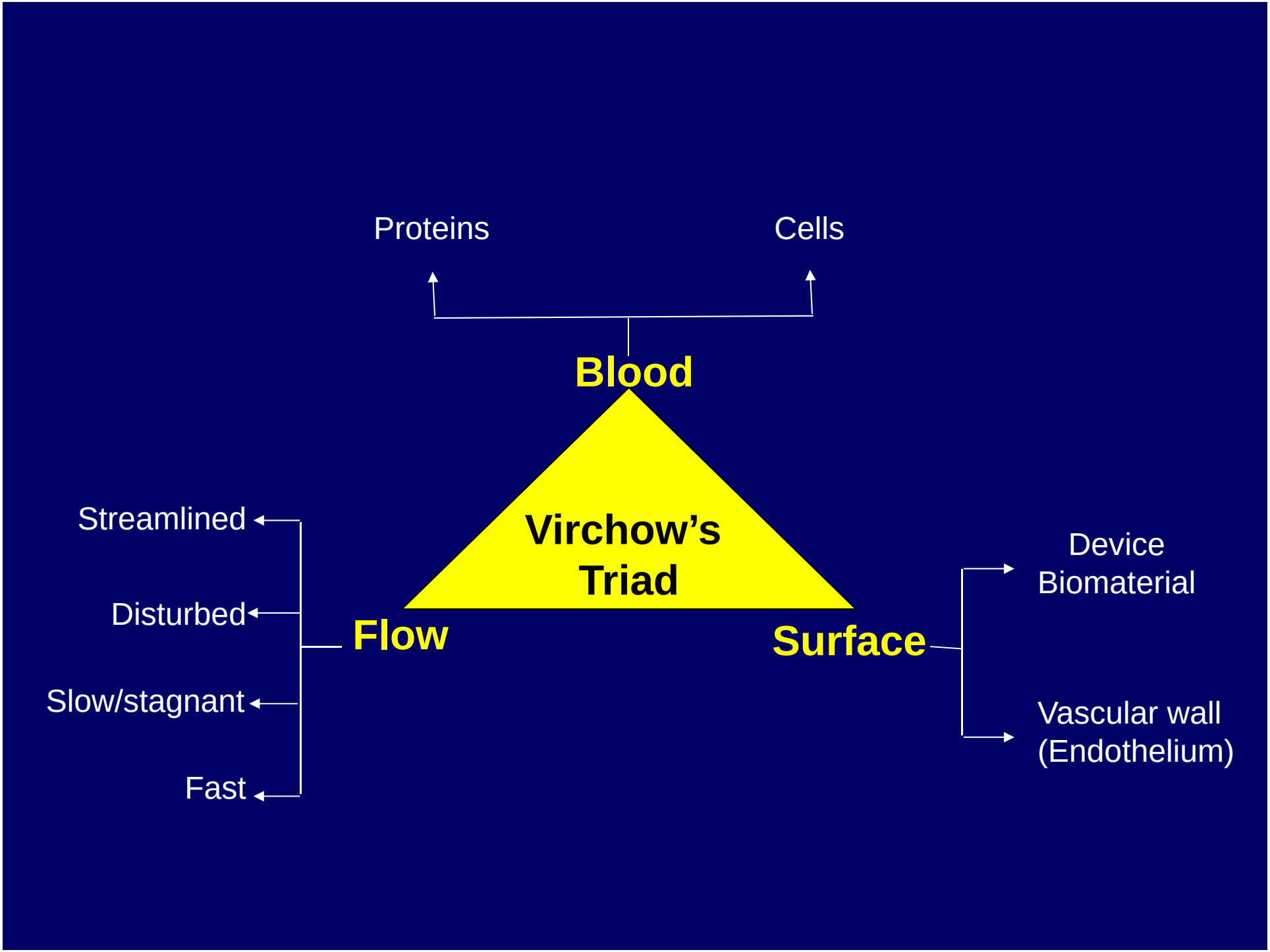
# In-vitro Blood Flow Models for the Assessment of Device Thrombosis

Sivaprasad (SP) Sukavaneshvar, Ph.D.
Vice President, Thrombodyne, Inc.

Research Faculty
Department of Pharmaceutics
University of Utah

Salt Lake City, UT


Proteins
Cells
Blood
Virchow's Triad
Flow
Surface
Streamlined
Disturbed
Slow/stagnant
Fast
Device Biomaterial
Vascular wall (Endothelium)

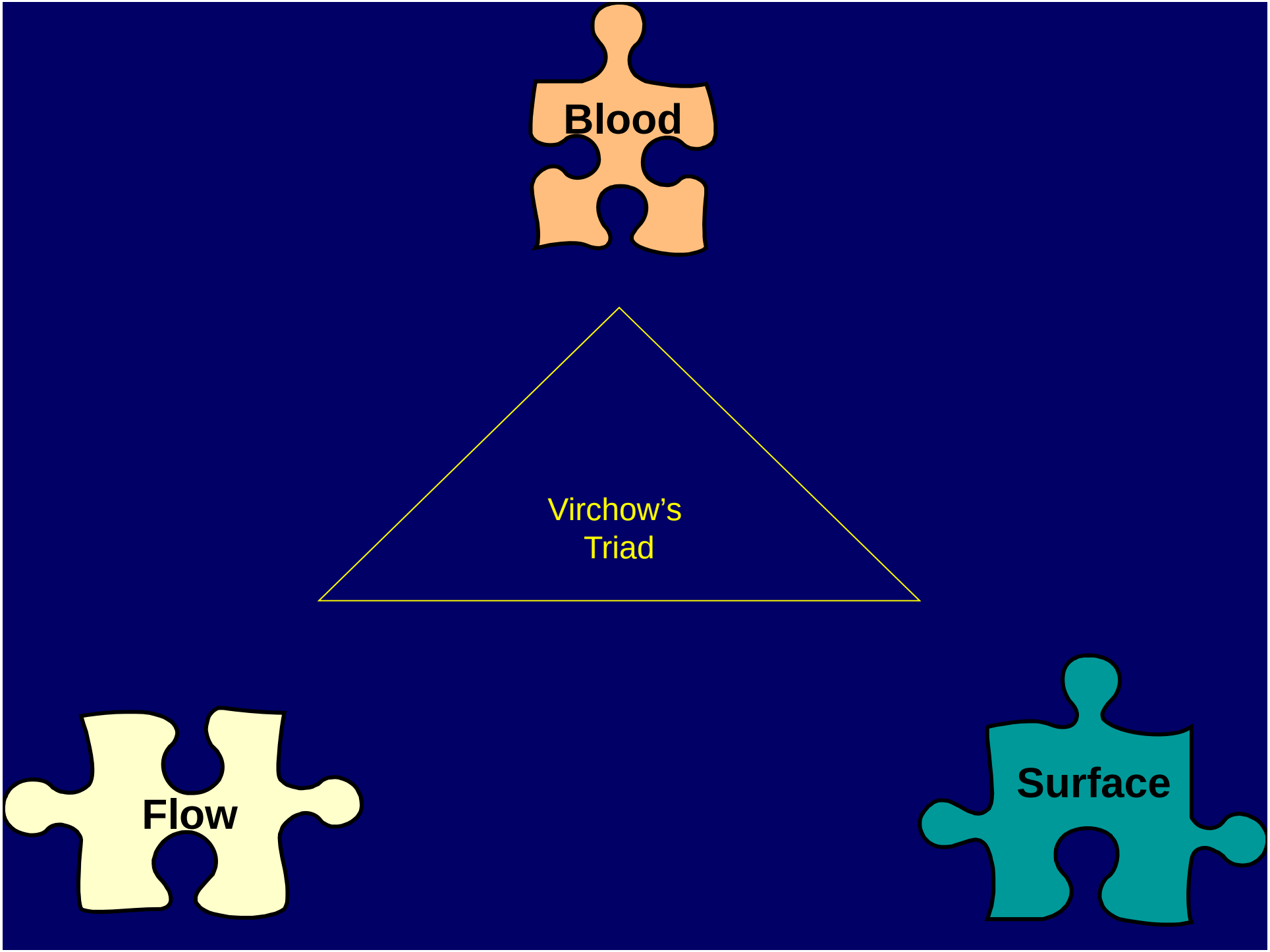
# Fluid Dynamics

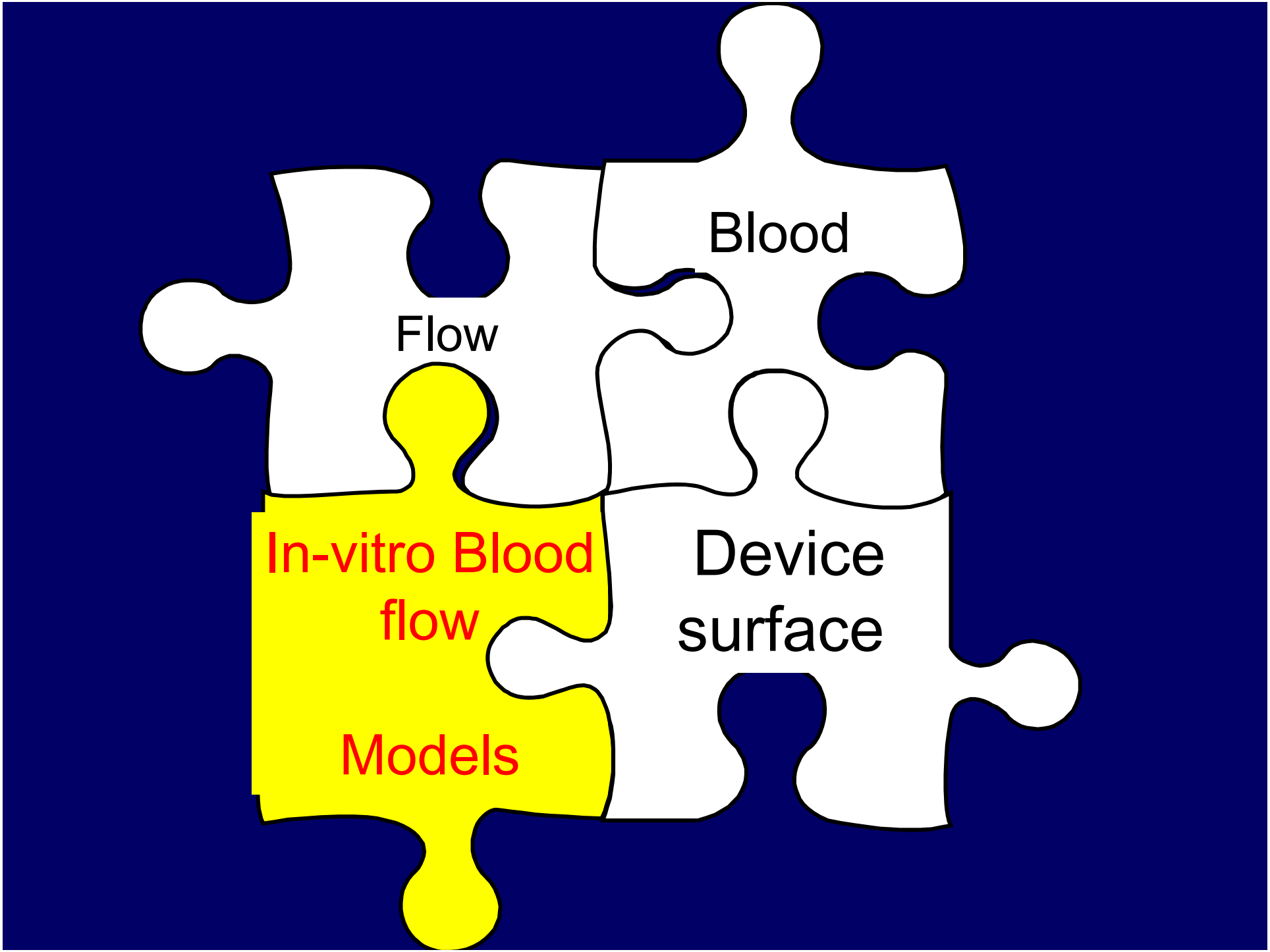
Shear Stress
- Platelet activation

Normal velocity
- Platelet adhesion & aggregation

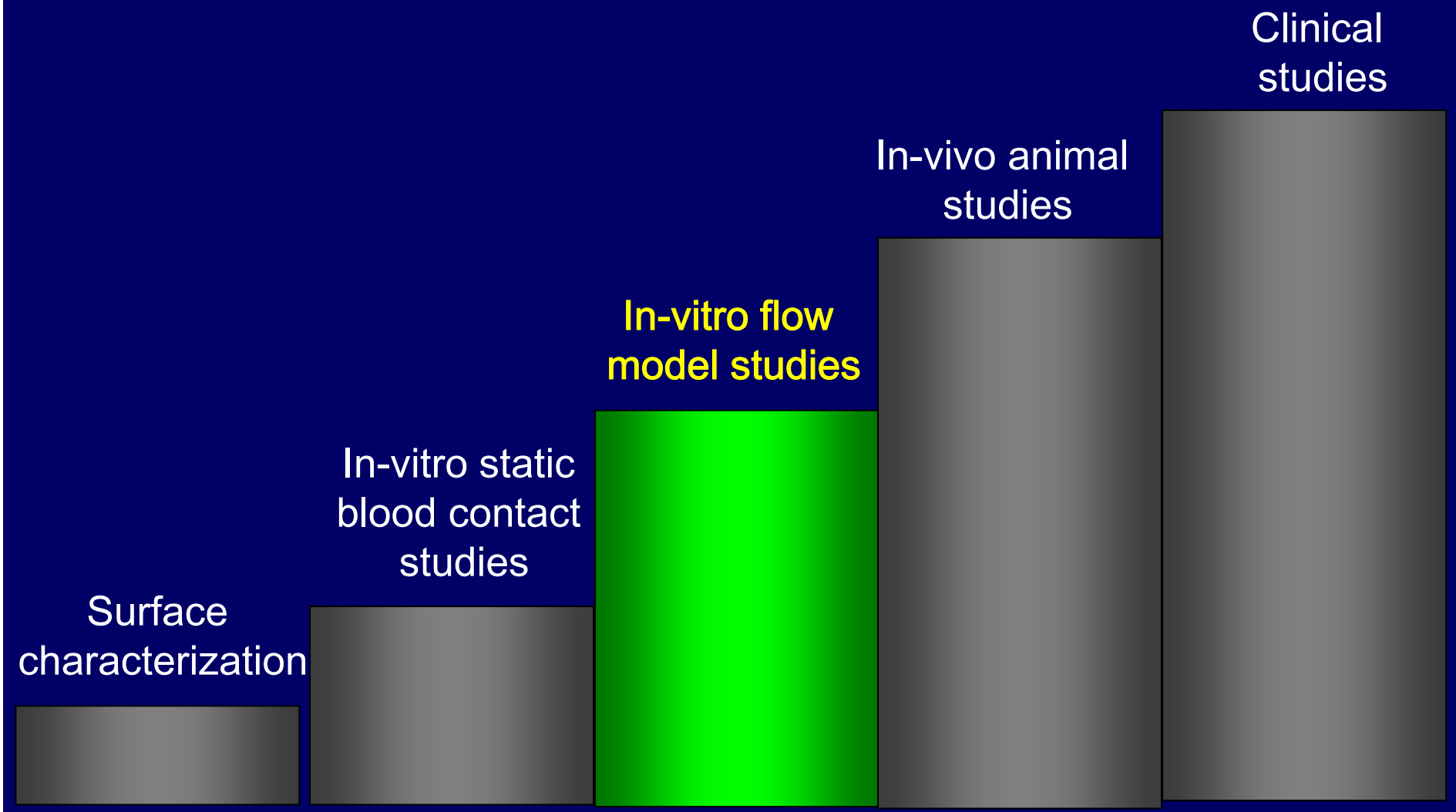
Vorticity
- Platelet aggregation (fluid phase)

Residence time
- Coagulation and consolidation

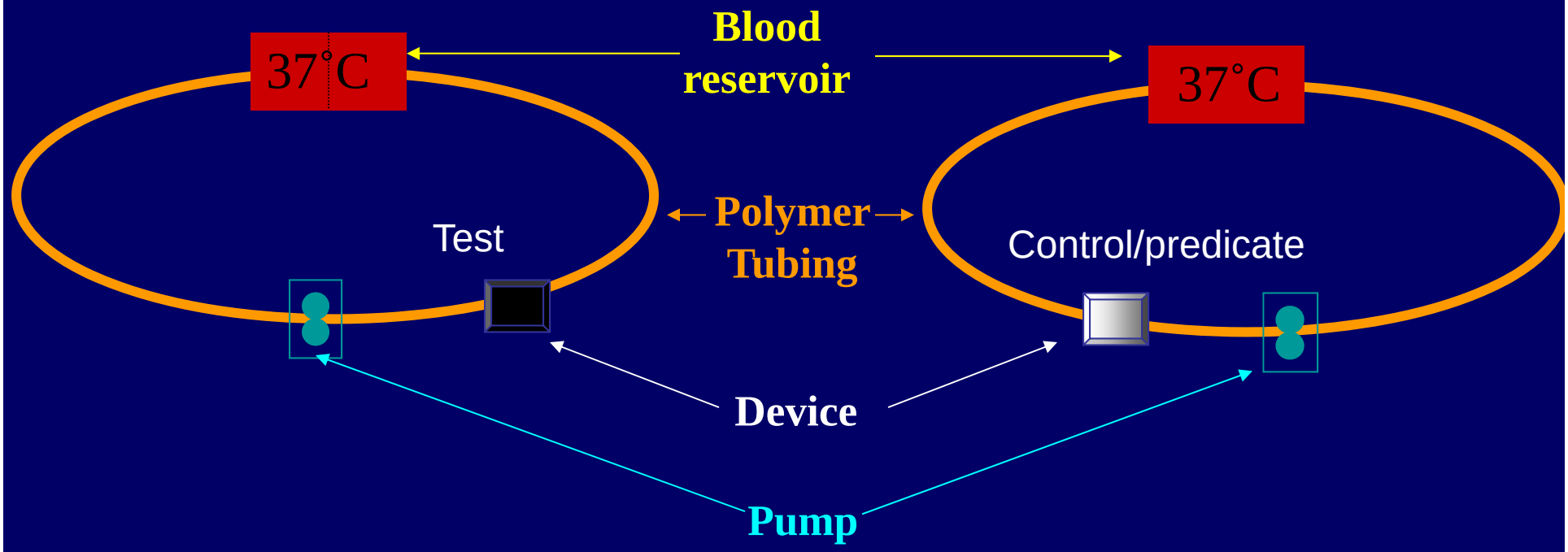

Blood
Virchow's
Triad
Flow
Surface


Blood
Flow
In-vitro Blood flow
Models
Device surface

# Assessment of Device Thrombosis



# In-vitro Blood Flow Model Configuration




Variations: Branched flow, Single pass, Chandler loop, etc.

# In-vitro Blood Flow Models: Key Features

- Relative assessment of thrombosis and related processes
- Fresh, anticoagulated whole blood
  - Heparin, citrate (recalcified), hirudin
- Blood flow conditions approach clinical use
  - Flow rate and conduit size
- Experiment time: ~hours

# In-vitro Blood Flow Models: Key Features

- Measured output
  - Macroscopic thrombus (Weight, Visual analysis, Radiolabeling)
  - Microscopic components (SEM)
  - Fluid phase biomarkers
  - Thromboemboli
  - Device dysfunction caused by thrombus (occlusion)
- Test conditions selected to focus on the device and minimize the impact of other model components
  - Surface/Volume ratio
  - Edge effects

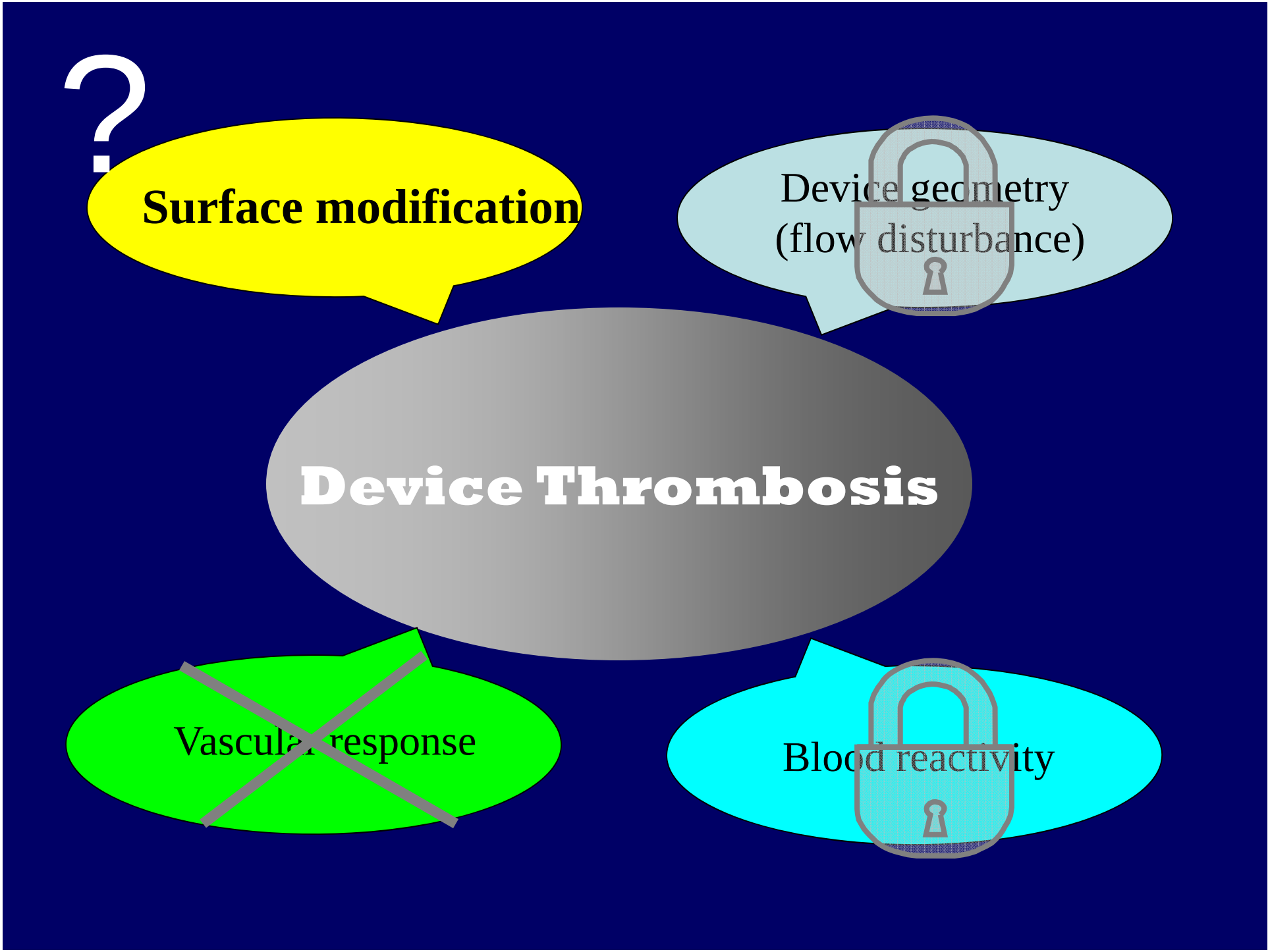
# MERITS OF IN-VITRO FLOW MODELS

- Useful template for comparing device thrombosis under similar conditions
- Some control over blood parameters
- Control of other important parameters (e.g. flow)*
- Quantification of thrombosis

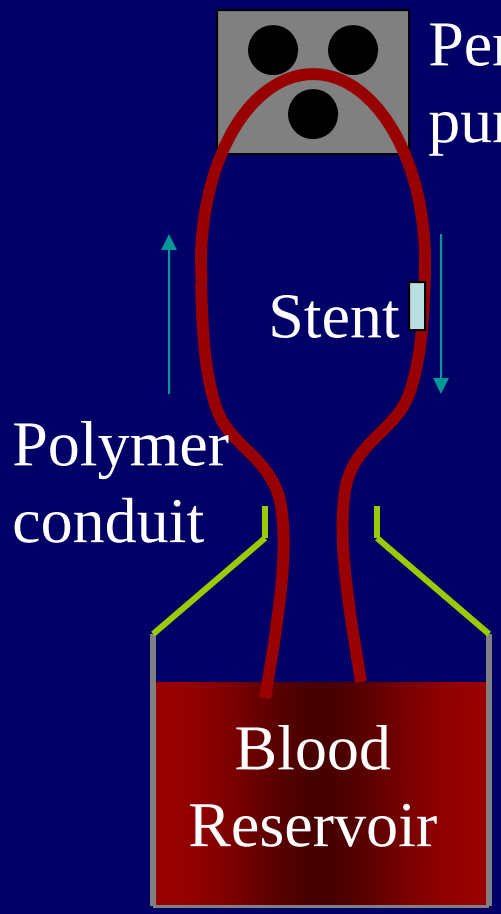
# LIMITATIONS OF IN-VITRO FLOW MODELS

- Experiment duration
- Absence of long-term effects
  - Blood vessel wall-device interactions
  - Comprehensive hemostatic pathways (e.g. lytic pathway)
  - Inflammatory and foreign body response
- Need anticoagulation
- Control of other parameters (e.g. flow)!

# EXAMPLES

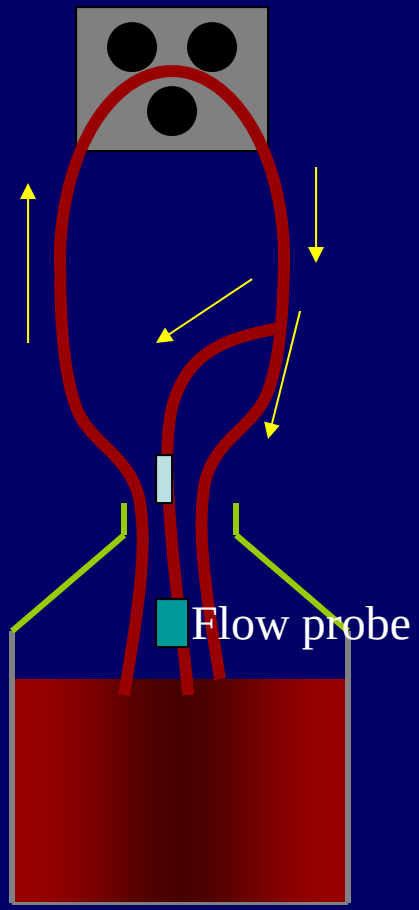

?
Surface modification
Device geometry
(flow disturbance)
Device Thrombosis
Vascular response
Blood reactivity

# Coronary Stents
# Model Configuration(s)




Conventional model

Initial flow rate: 75 ml/min
Heparin: 1 U/ml
Expt. Time: 60-90 min
Conduit: 3.2 mm ID
111-In labeled platelets




Branched flow model

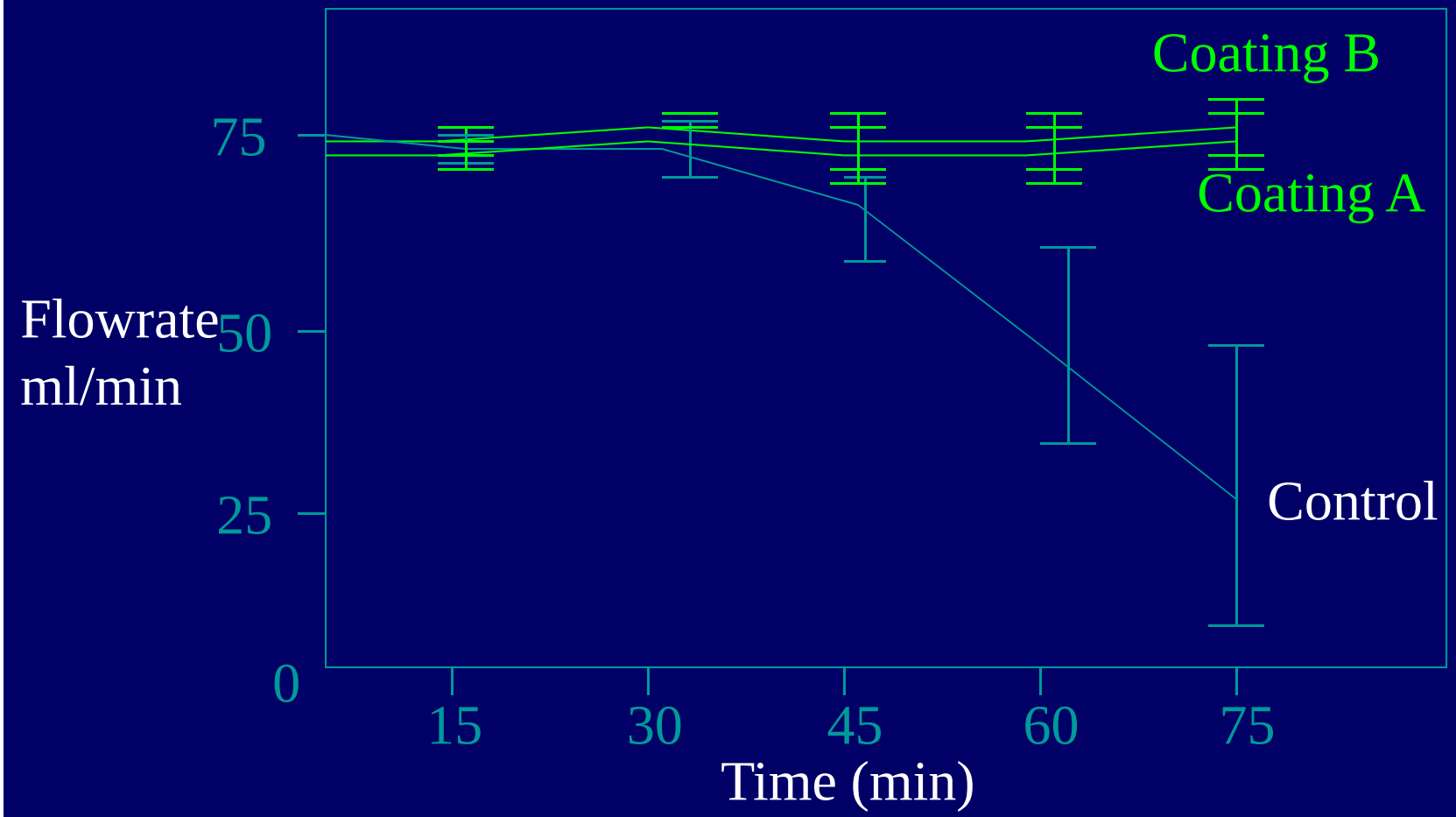
# THROMBUS ON STENTS

Uncoated (control)

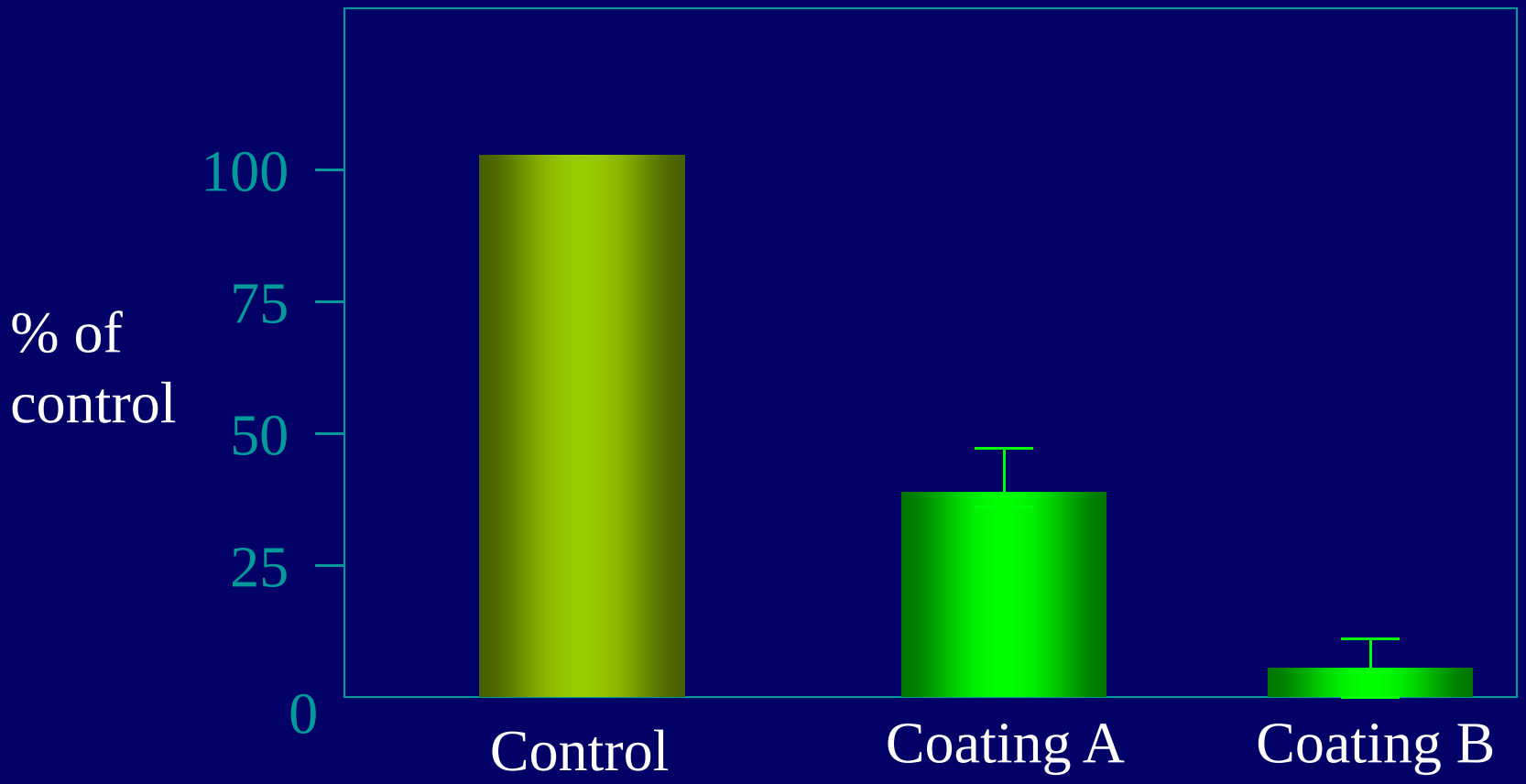
Coating A

Coating B

# Thrombotic Occlusion



# Thrombus Accumulation



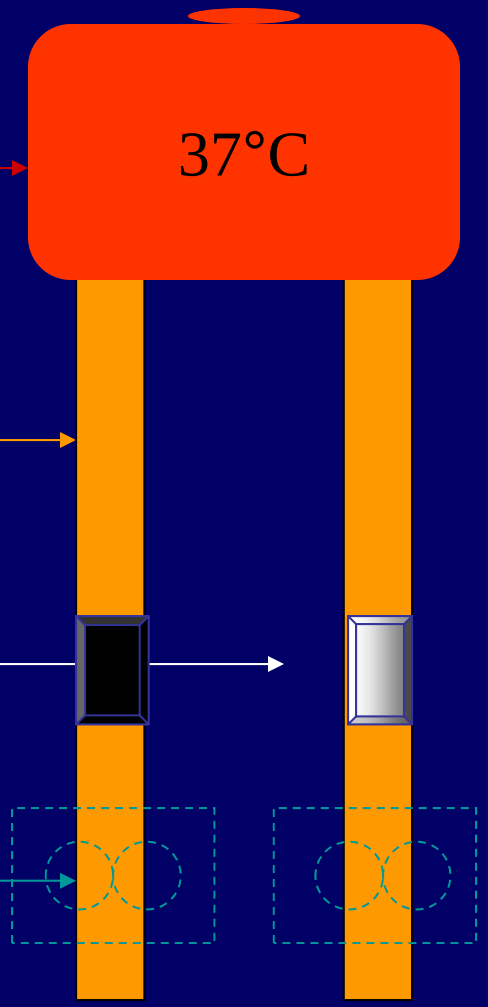
# ONE PASS CONFIGURATION

**Blood reservoir**

**Polymer Tubing (1/8” ID)**

**Devices**

**Pump**



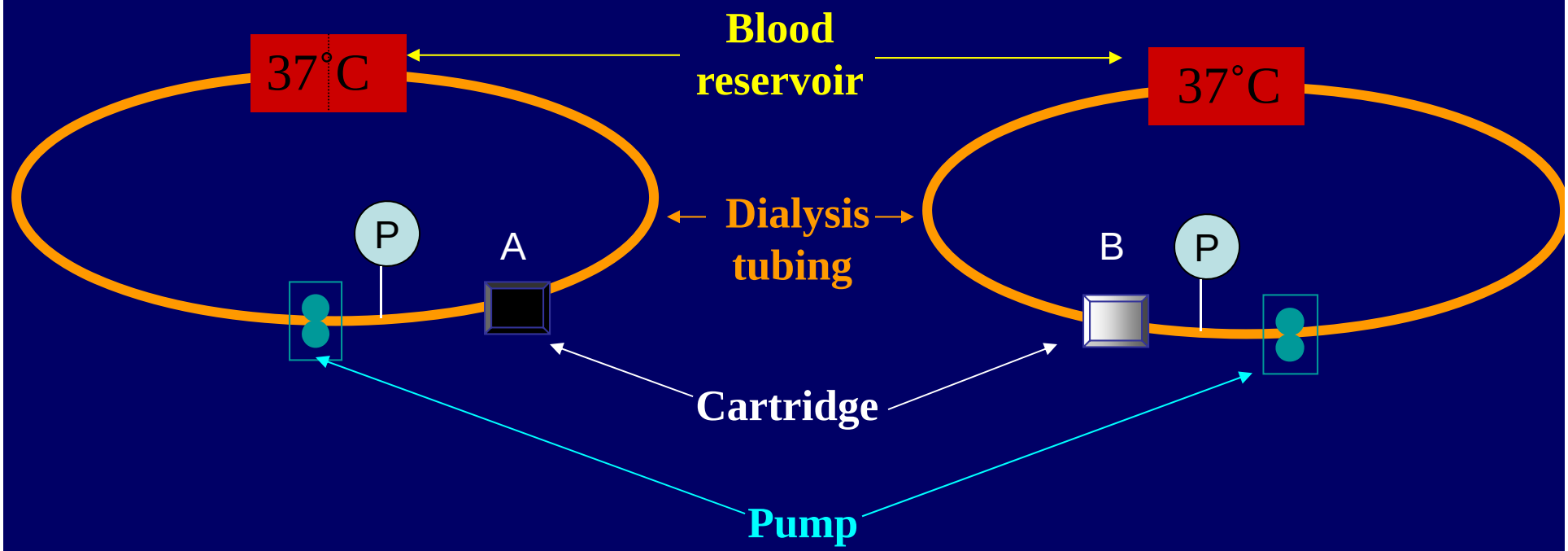

Useful for assessing thrombosis and embolism on small devices: Stents, distal embolic protection …

Circumvents recirculation & recounting of released emboli

Less extraneous blood activation

Limited range of flow rate, time, and number of simultaneous devices to be tested due to blood volume constraints

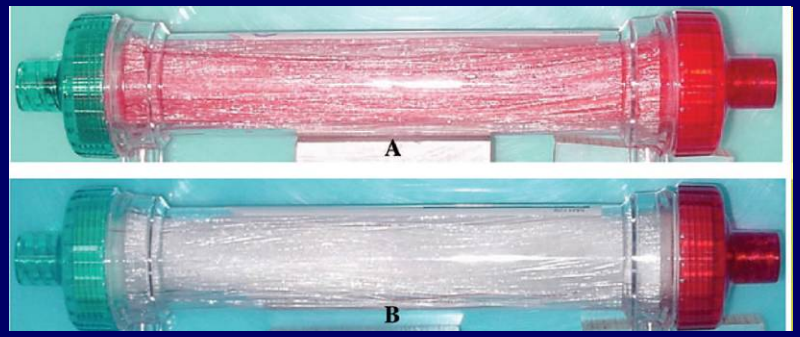
# Hemodialysis Cartridge

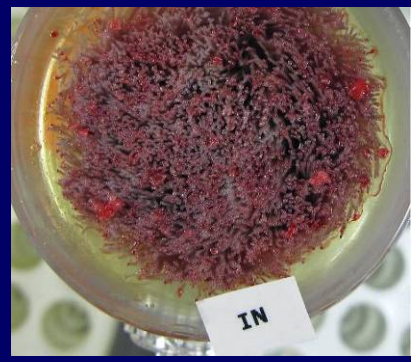


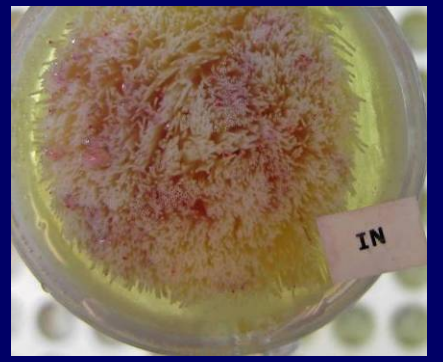

Flow rate: 300-400 ml/min
Heparin: 2-3 U/ml
111-In labeled platelets

# Hemodialysis Cartridge

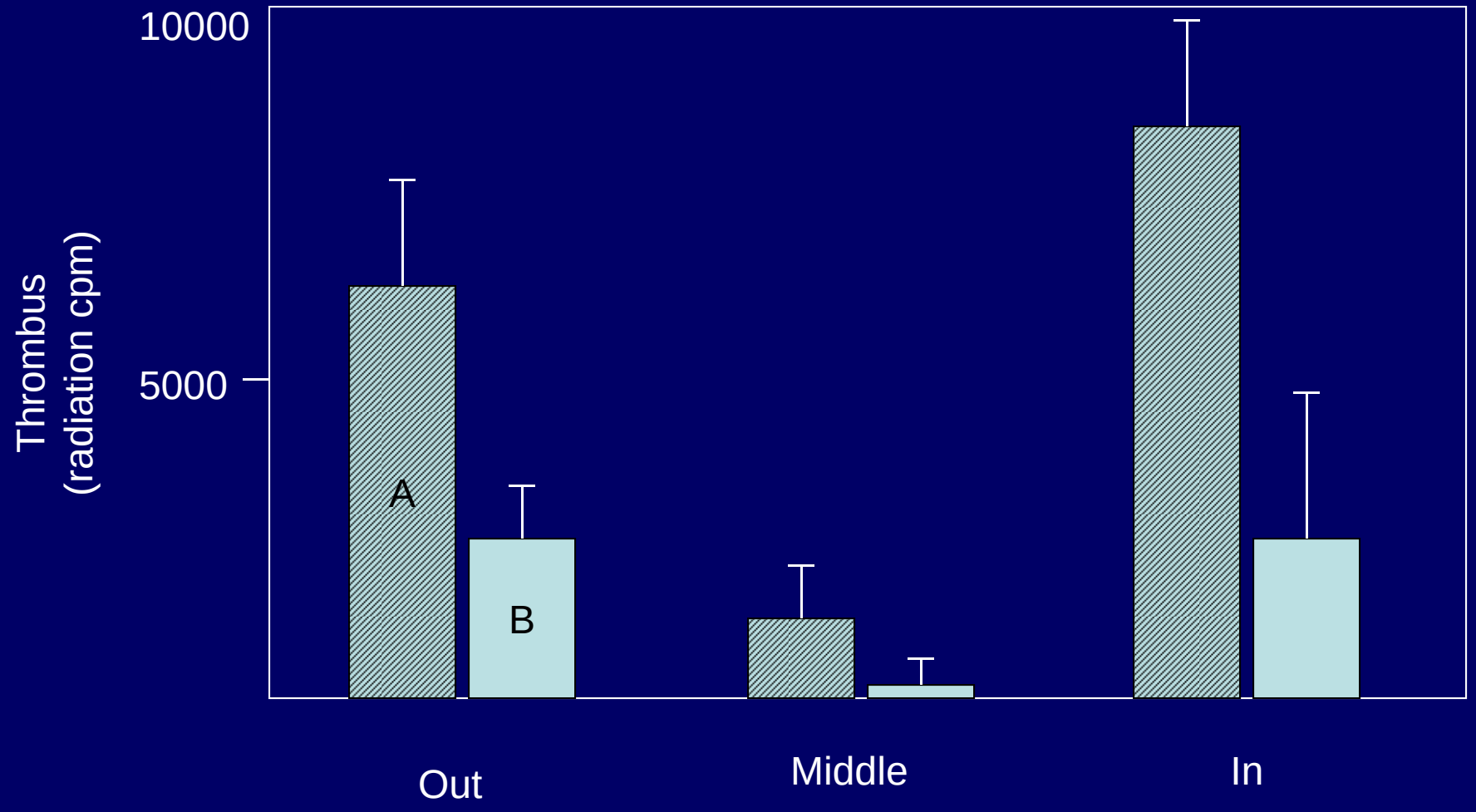




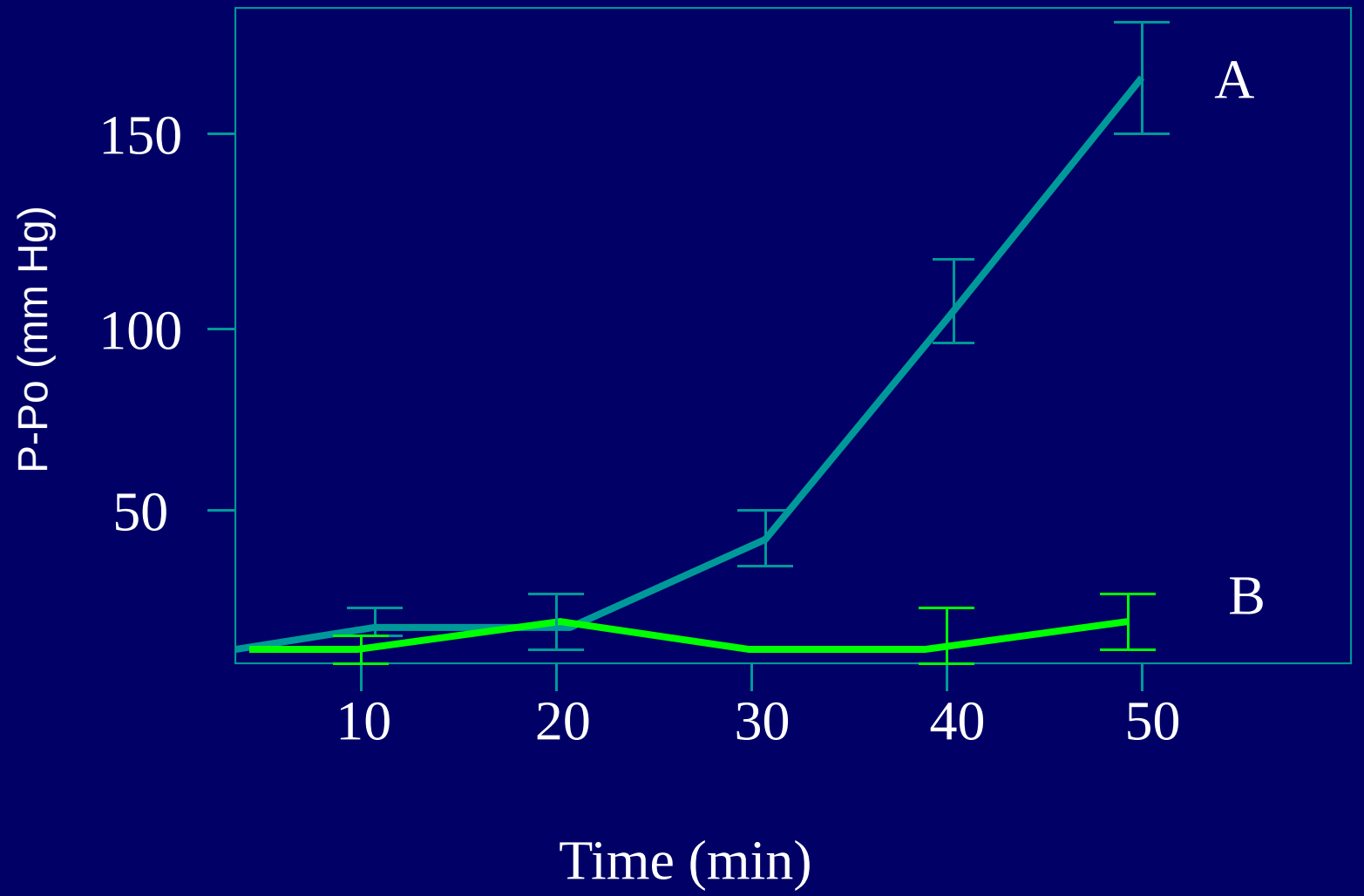



# Thrombus Accumulation

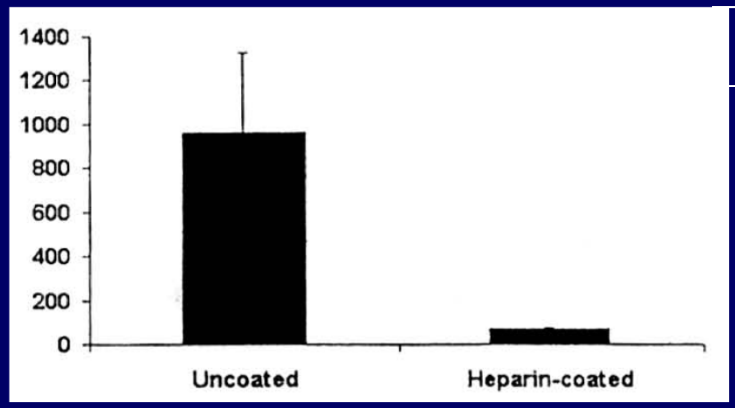


# Thrombotic Occlusion



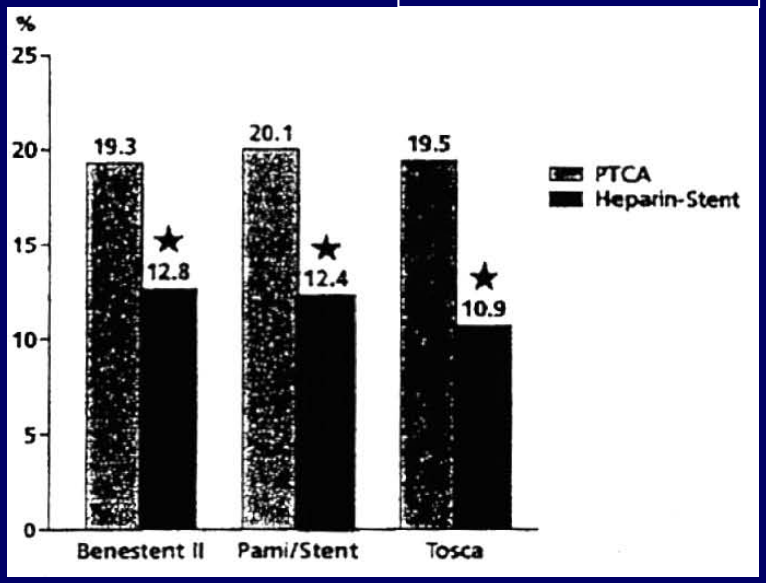
# Relative Device Thrombosis Assessed In-vitro and In-vivo

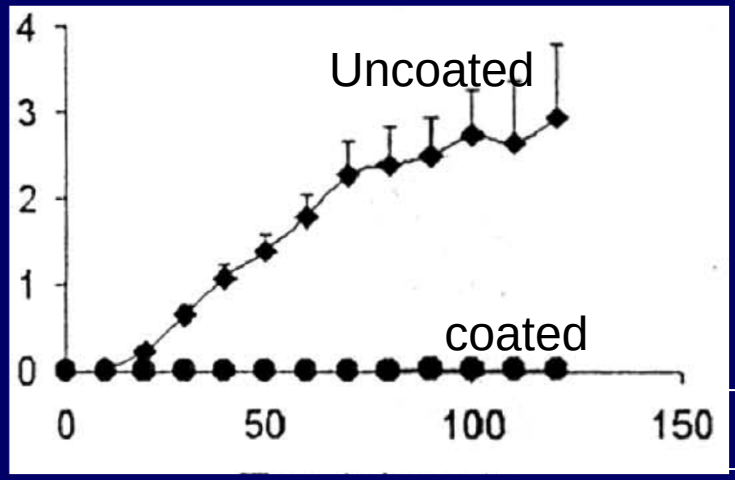
# Coronary Stents




In-vitro flow model

Clinical studies

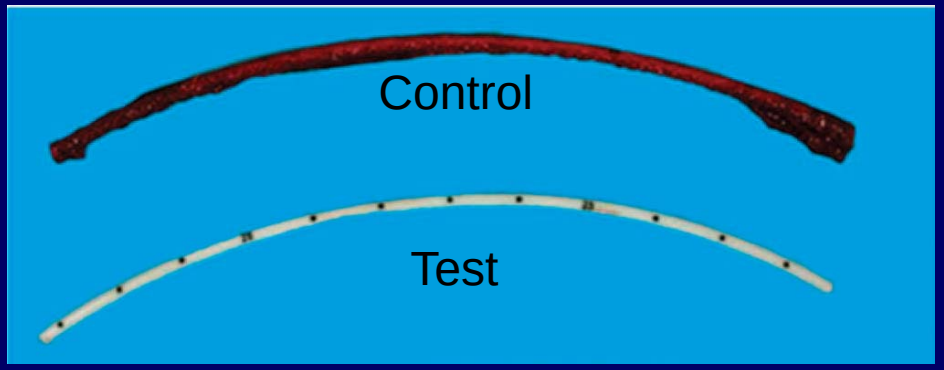


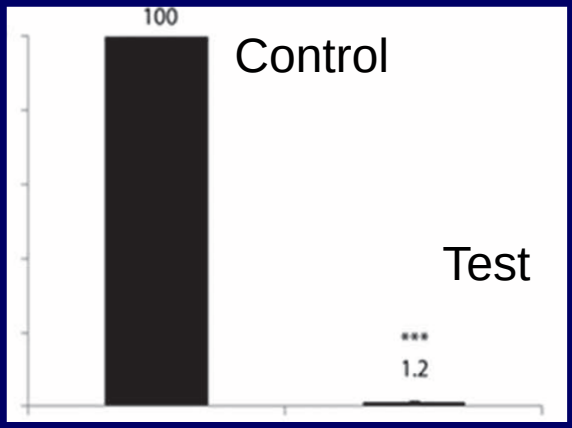




Baboon 2 hr ex-vivo shunt

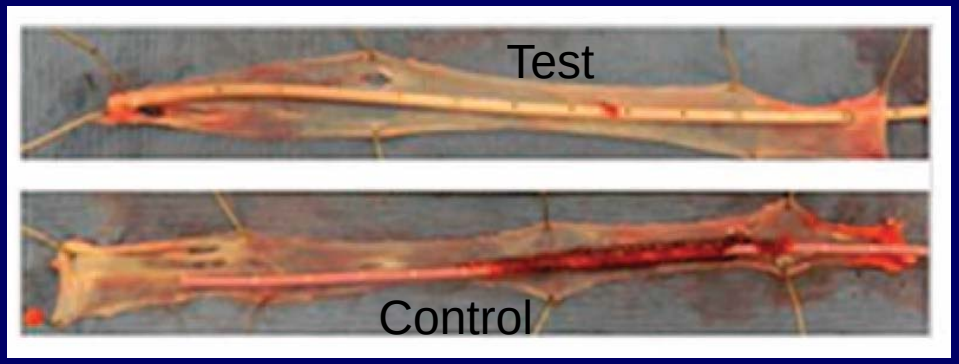
From Kocsis, et al. Journal of Long Term effects of Medical Implants 2000

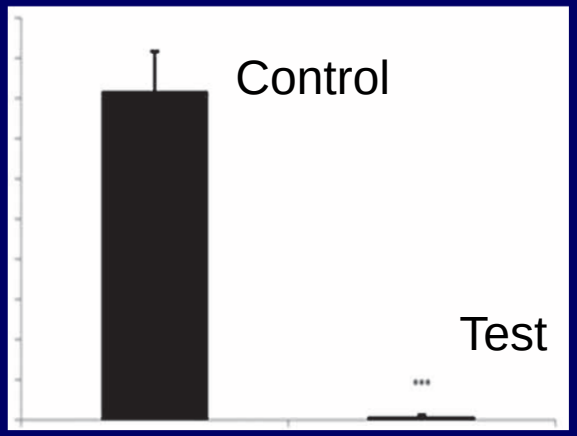
# Catheters (PICCs)




IN-VITRO FLOW MODEL

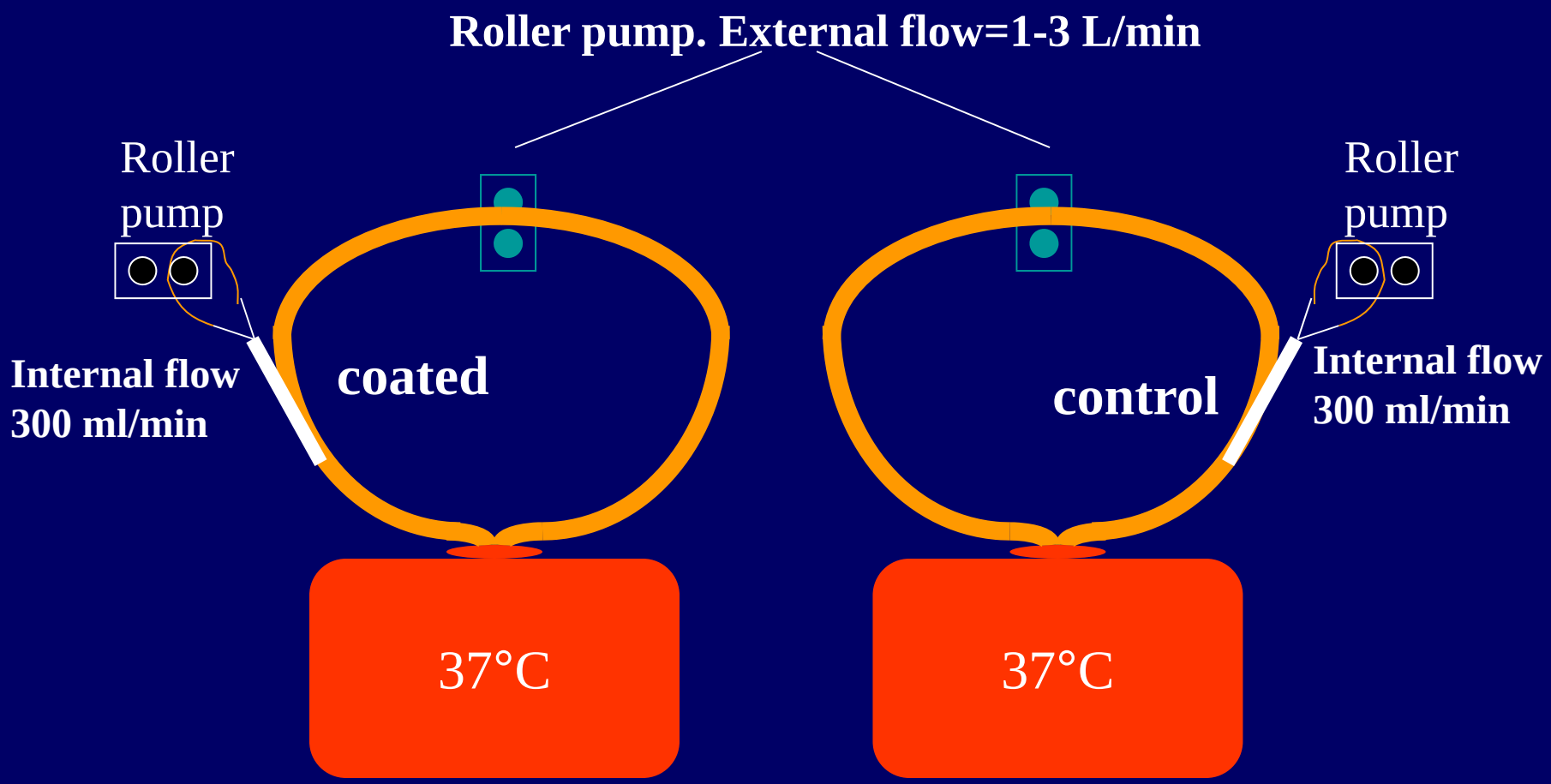


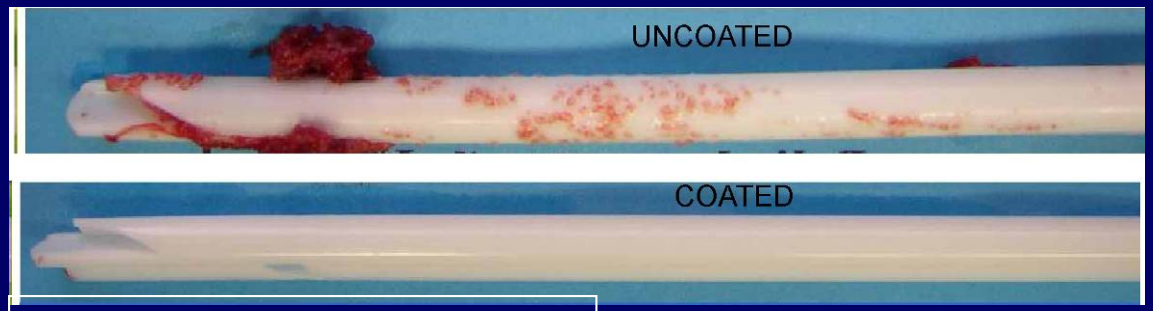

CANINE IN-VIVO JUGULAR IMPLANT (~4 hours)

From Smith, et al., Sci Transl Med 2012

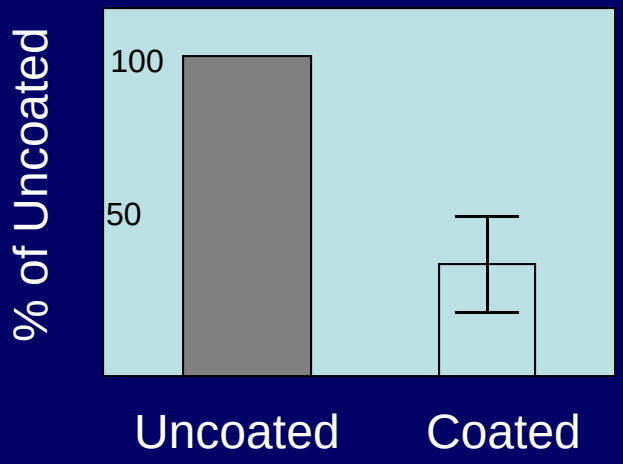
# Hemodialysis Catheters

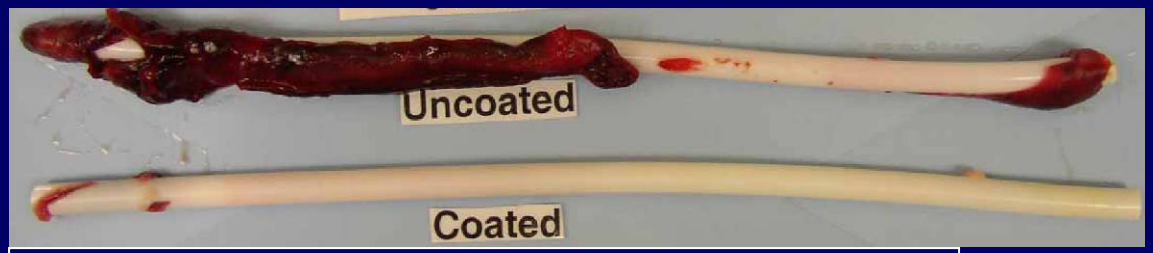


# Hemodialysis Catheters

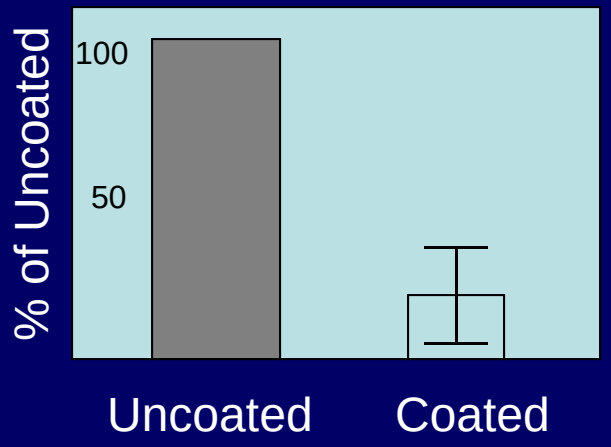



IN-VITRO FLOW MODEL




SHEEP IN-VIVO IMPLANT (up to 30 days)




From Lotito, et al. ASN 2006

# In-vitro Blood Flow Models Summary

- Useful template for comparing device thrombosis under similar conditions
  - Relative Assessment
  - Universal/absolute acceptance criteria elusive
- Has Limitations
  - Long-term biological processes
  - Pre-conditioning?
- Model Configuration
  - Clinical conditions and in-vitro framework
  - Anticoagulation, flow conditions, time, objective