III

Flow Effects on Thrombogenesis: Insights from Computational Models

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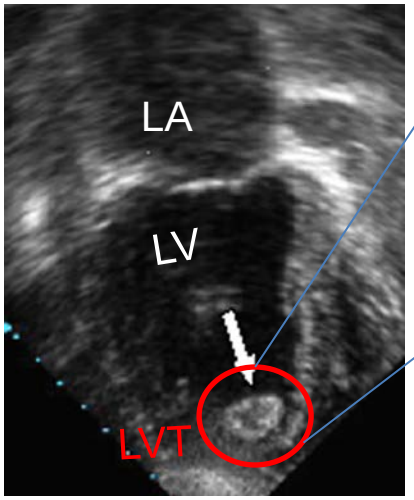
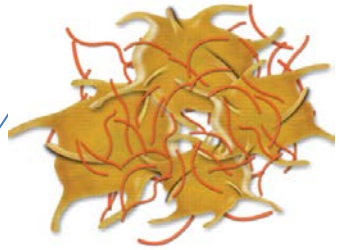
Division of Cardiology

Formation of Blood Clots in the Heart

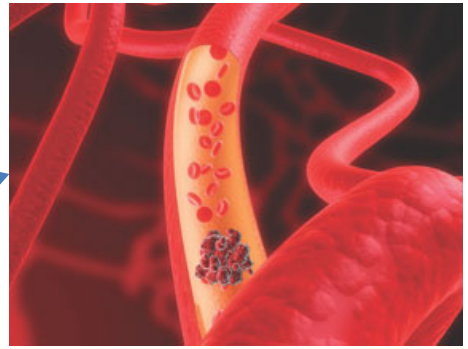
- Clot (thrombus) formation ➔ flow statis
- Normal ventricles
  - Ejection fraction ~55%
  - Avoids flow statis (How???)
- Conditions associated with cardiac thrombus formation
  - Myocardial infarction (MI)
  - Heart failure
  - Arrhythmias
  - Cardiomyopathies
  - …
- Clinical significance
  - Thomboembolic risk

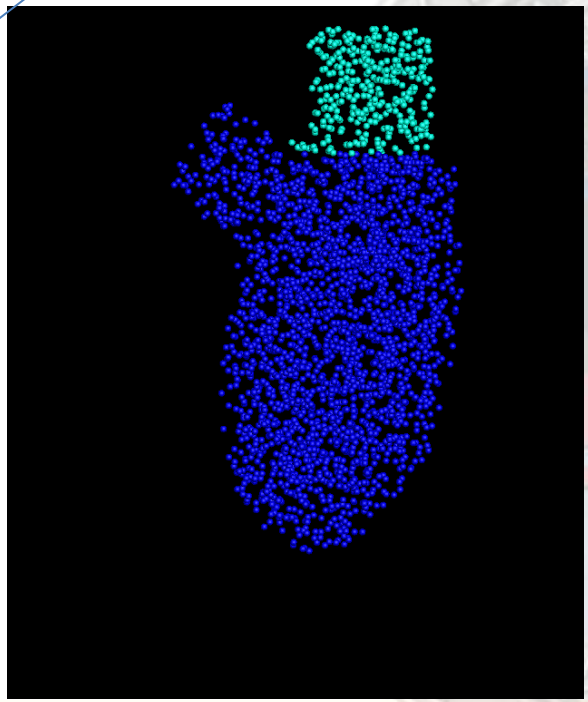


(Rehan et al. *Cardiovascular Ultrasound*, 2006)



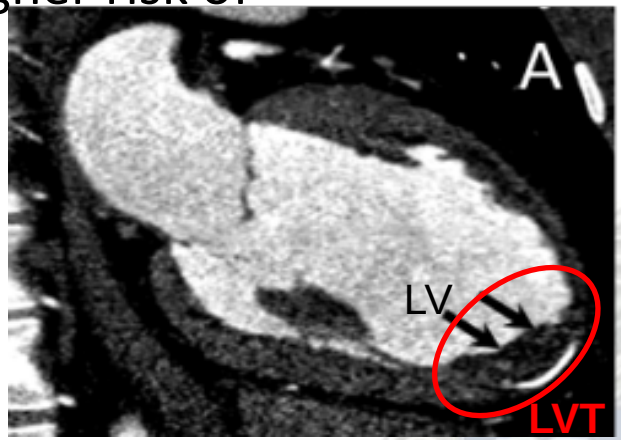
Platelets
+ Fibrin
+…

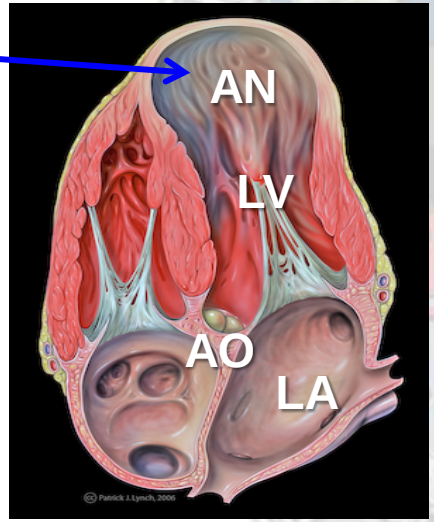


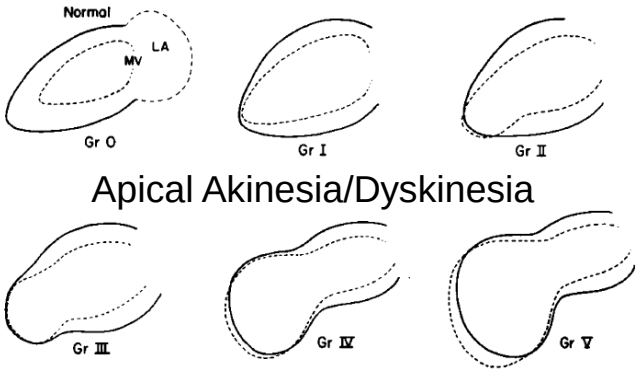


Post MI Thrombus Formation

- Patients recovering from MI are generally at higher risk of LVT formation
  - 720K MIs/yr in the US
  - Thrombus located in apical region
- Reduced ejection fraction (<40%)
- Apical Akinesia/Dyskinesia
- Ventricle remodeling
- Hypercoagulable endothelium – Tissue factor pathway



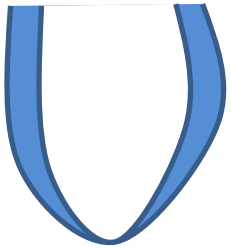




+Apical Aneurysm

LVT Risk Stratification & Therapy

- Risk criteria
  - Antero-apical STE-MI (250K/yr)
  - EF < 30%

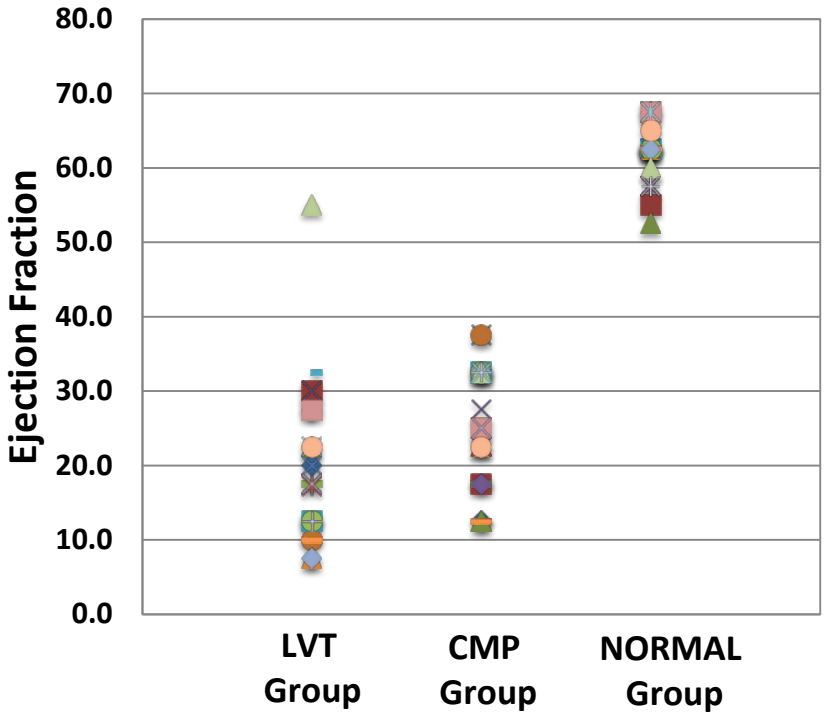


$$EF = \frac{\text{Stroke Vol}}{\text{End Dias. Vol}}$$

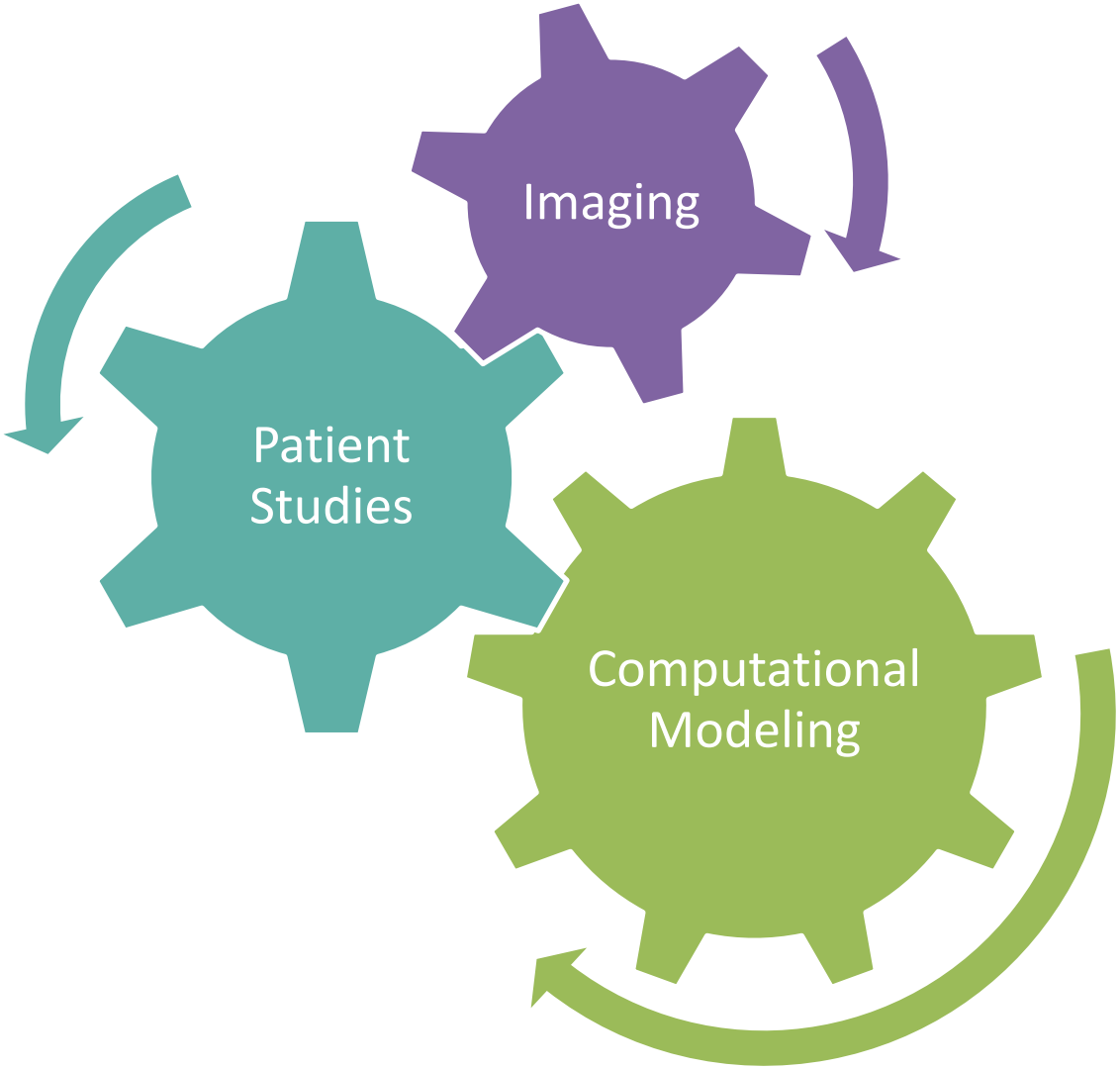
- Antithrombotic Therapy
  - Anticoagulants
  - Anti platelet
  - Blood thinners
- Implication
  - Only 1/10 people who currently receive 'triple' therapy in US are actually at risk of LVT formation
  - ½ patients receiving triple therapy are at high risk of bleeding.
- Better risk stratification metrics are needed.
- LVT risk determined by a complex coupling between flow dynamics and coagulation biochemistry.

Stratification of LVT Risk?

Group	N	Description
LVT	25	Patients with diagnosed LVT
CMP	25	Severe cardiomyopathy; no LVT
NORMAL	25	Normal



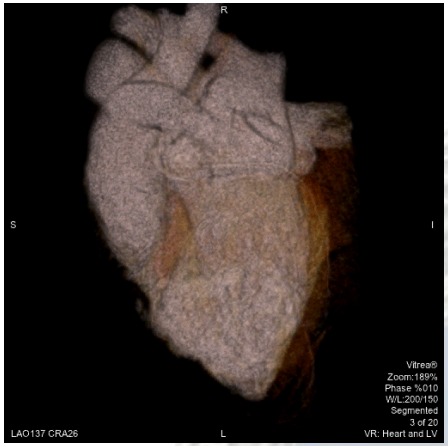
Approach



Modeling Approach

Understand how flow mediates coagulation in infarcted LVs

- EF, Stroke Volume
- LV Geometry & Kinematics
- Infarct Size & Location

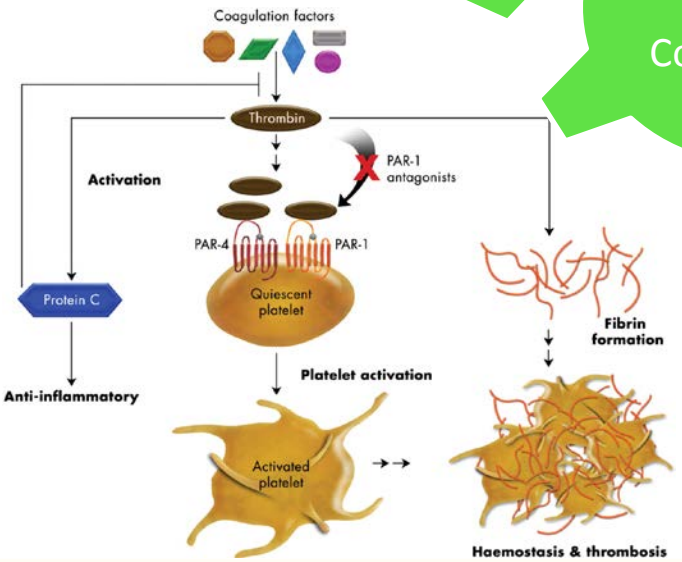


Patient Physiology

Biochemistry of Coagulation

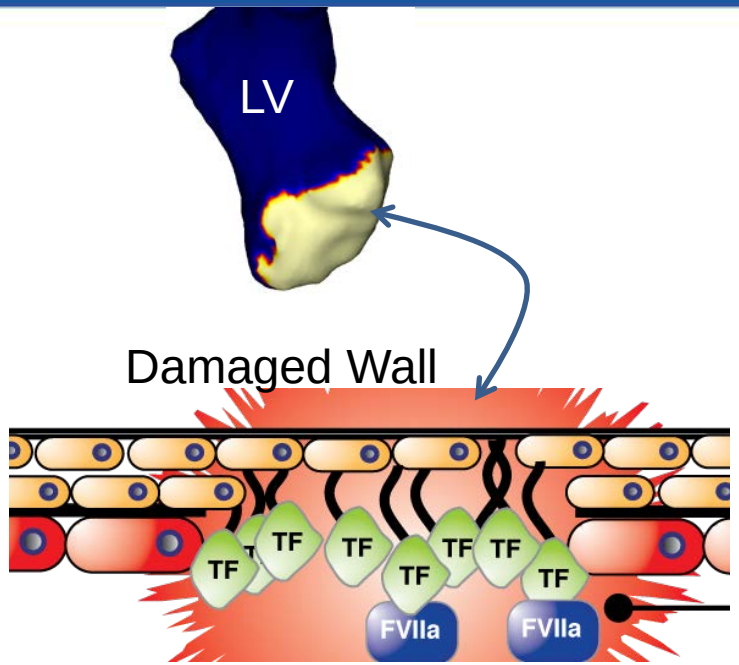
Computational Hemodynamics

- Tissue Factor Release
- Thrombin Production
- Platelet activation
- Fibrin polymerization

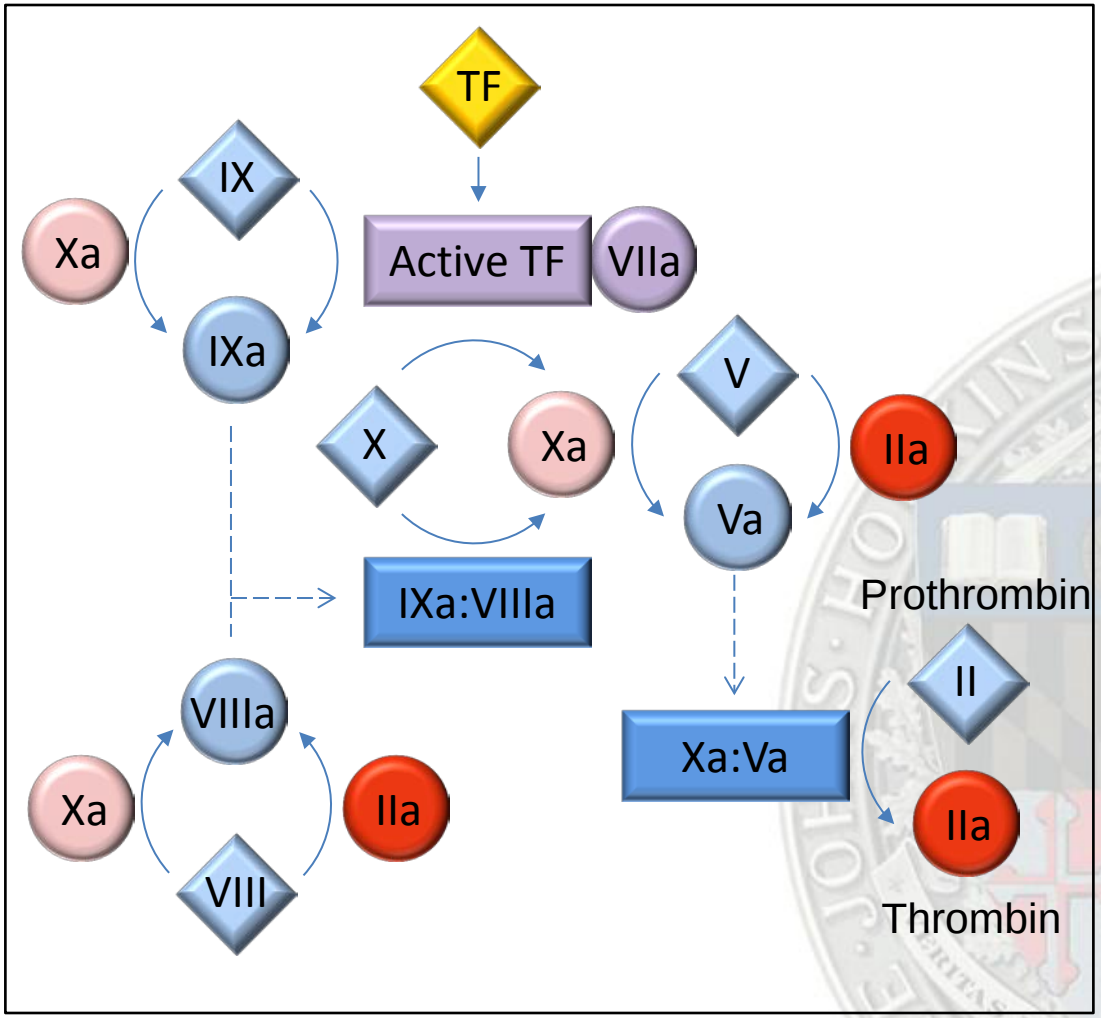


- LV Flow Patterns
- Flow Stasis
- Transport of CC biomolecules

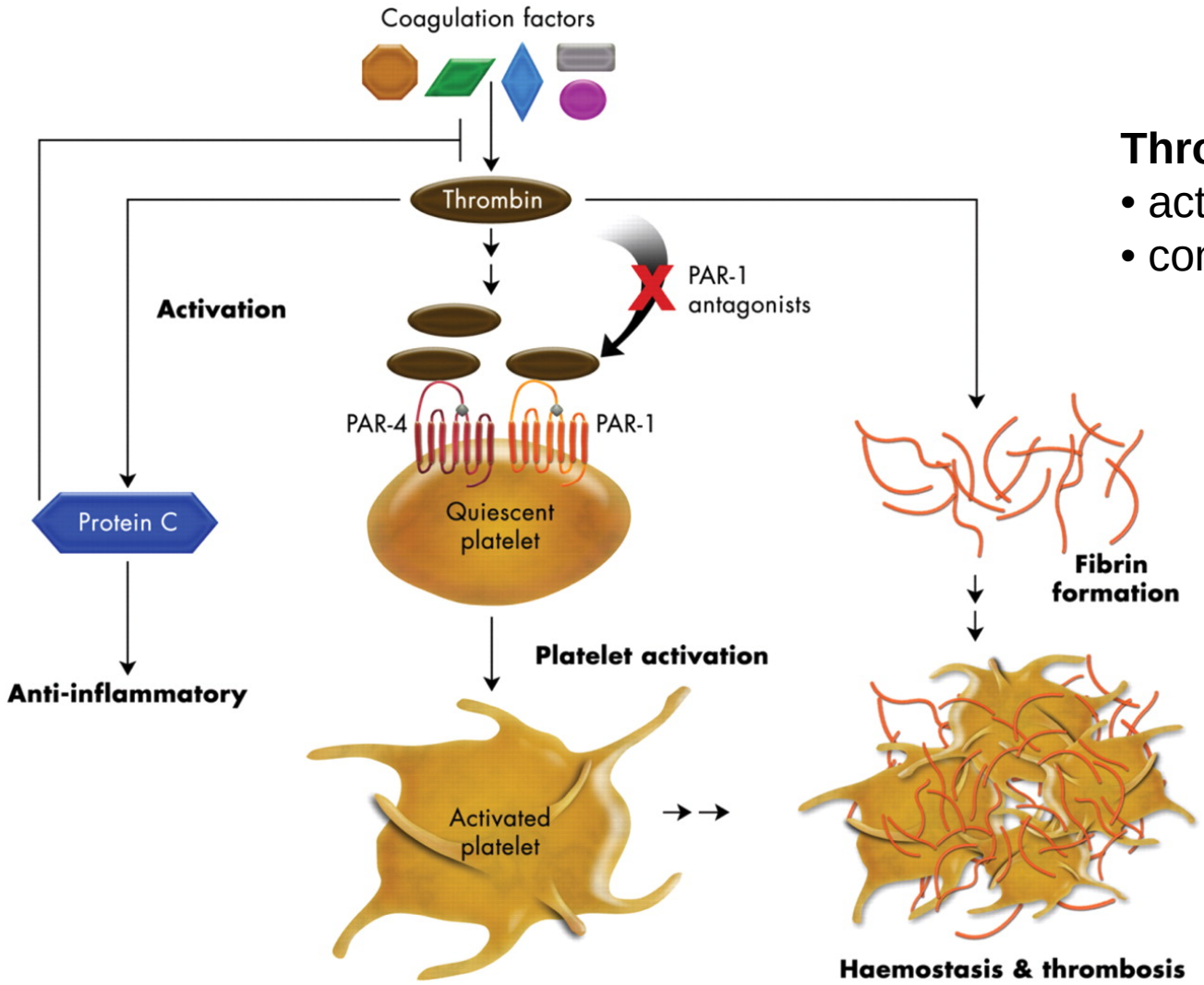
Coagulation Cascade



- Extrinsic (Tissue-factor) Pathway
- Damaged wall expose tissue factor (TF)
- TF-VIIa initiates reactions
- Produce Thrombin
- Thrombin activates other factors
- *Burst of Thrombin Production*



Role of Thrombin



Thrombin

- activates **platelets**
- converts fibrinogen to **fibrin**

(Angiolillo et al, European Heart J, 2009)

TF → Thrombin Coagulation Cacade (CC)

18 Species

- IX
- TF : VIIa
- IX : TF : VIIa
- IXa
- X
- X : TF : VIIa
- Xa
- VIIIa : IXa
- X : VIIIa : IXa
- V
- Va
- VIII
- VIIIa
- IIa (Thrombin)
- II (Pro-thrombin)
- Va : Xa
- II : Va : Xa
- mIIa

Reactions

$$IX + TF:VIIa \underset{k_{16}}{\overset{k_6}{\rightleftarrows}} IX:TF:VIIa \xrightarrow{k_{11}} TF:VIIa + IXa$$

$$X + TF:VIIa \underset{k_{17}}{\overset{k_6}{\rightleftarrows}} X:TF:VIIa \xrightarrow{k_{12}} TF:VIIa + Xa$$

$$X + VIIIa:IXa \underset{k_{18}}{\overset{k_6}{\rightleftarrows}} X:VIIIa:IXa \xrightarrow{k_{13}} VIIIa:IXa + Xa$$

$$IX + Xa \xrightarrow{k_{15}} Xa + IXa$$

$$V + Xa \xrightarrow{k_1} Xa + Va$$

$$VIII + Xa \xrightarrow{k_3} Xa + VIIIa$$

$$V + IIa \xrightarrow{k_2} IIa + Va$$

$$VIII + IIa \xrightarrow{k_4} IIa + VIIIa$$

$$II + Va:Xa \underset{k_{19}}{\overset{k_6}{\rightleftarrows}} II:Va:Xa \xrightarrow{k_{14}} Va:Xa + mIIa$$

$$mIIa + Va:Xa \xrightarrow{k_9} Va:Xa + IIa$$

$$VIIIa + IXa \underset{k_9}{\overset{k_7}{\rightleftarrows}} VIIIa:IXa$$

$$Va + Xa \underset{k_{10}}{\overset{k_8}{\rightleftarrows}} Va:Xa$$

(Biasetti et al, 2012)

$D \approx 1e^{-8}$ (m^2/s)

S: Stoichiometric Matrix

r_j: Reaction rate

$$\frac{\partial C_i}{\partial t} + (\vec{U} \cdot \nabla) C_i - D\nabla^2 C_i = R_i$$

(18 Eqs.)

$$R_i = \mathbf{S} \cdot r_j$$

Initial concentrations (mol/m^3)

$$C_{IX} = 9e-5;\ C_X = 1.7e-4$$

$$C_V = 2e-5;\ C_{VIII} = 7e-7$$

$$C_{VIIIa} = 1e-11;\ C_{II} = 1.4e-3$$

(Pro-thrombin)

$C_{TF:VIIa,wall}$: Prescribed on infarct

Platelet Activation and Deposition

Inactivated, mobile

Activation by Thrombin

$$\frac{\partial}{\partial t}PT_{m,u} = -(\vec{U}\cdot\nabla)PT_{m,u} + D_P\nabla^2 PT_{m,u} - A_1(IIa)PT_{m,u}$$

Activated, mobile

Activation by Thrombin

$$\frac{\partial}{\partial t}PT_{m,a} = -(\vec{U}\cdot\nabla)PT_{m,a} + D_P\nabla^2 PT_{m,a} + A_1(IIa)PT_{m,u}$$

$$A_1(IIa) = k_{IIa}\frac{C_{IIa}}{C^* + C_{IIa}}$$

$$-k_{adh,a}\cdot h(\vec{x})(PT_{\max} - PT_b)PT_{m,a} - k_{coh}\cdot g(PT_b)PT_{m,a}$$

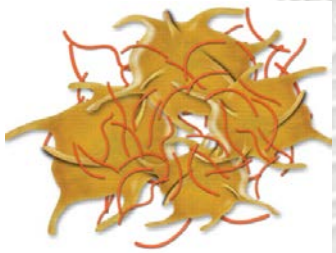
Adhesion to wall — Cohesion to bound platelets

⇩ ⇩

Bound

$$\frac{\partial}{\partial t}PT_b = k_{adh,a}h(\vec{x})(PT_{\max} - PT_b)PT_{m,a} + k_{coh}\cdot g(PT_b)PT_{m,a}$$

Adhesion to wall — Cohesion



$D_P \approx$ 1e-9 (m²/s)

(Leiderman and Fogelson, 2011)

Polymerization of Fibrinogen → Fibrin

Fibrinogen

$$\frac{\partial}{\partial t}C_f = -(\vec{U}\cdot\nabla)C_f + D\nabla^2 C_f - k_t C_f$$

Conversion by Thrombin

$$k_t = \frac{k_{cat} C_{IIa}}{K_m + C_f}$$

Fibrin (Monomer)

$$\frac{\partial}{\partial t}C_m = -(\vec{U}\cdot\nabla)C_m + D\nabla^2 C_m + k_t C_f + k_p C_m{}^2$$

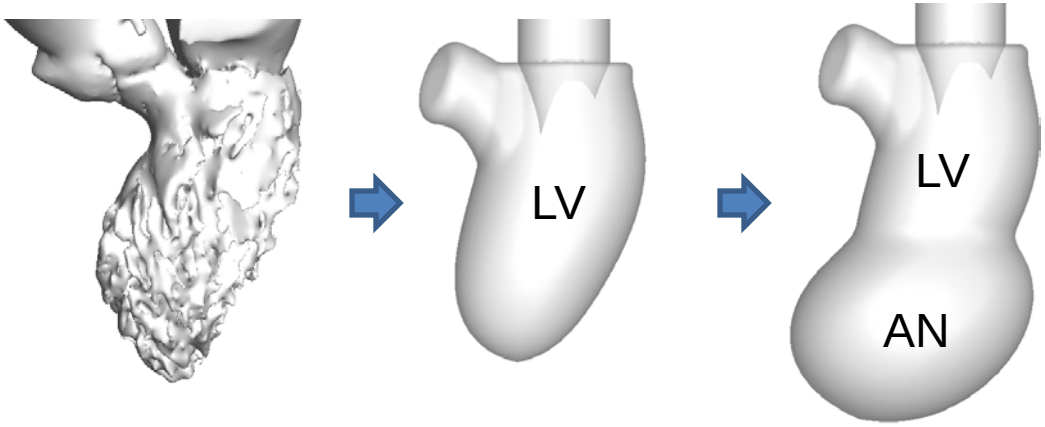
$$k_{cat} = 84\,\mathrm{s}^{-1}$$
$$K_m = 7.2\times10^{-3}\ \mathrm{mol/m^3}$$
$$k_p = 8.2\times10^{2}\ (\mathrm{mol/m^3})^{-1}\mathrm{s}^{-1}$$
$$C_{f,0} = 9\times10^{-3}\ \mathrm{mol/m^3}$$

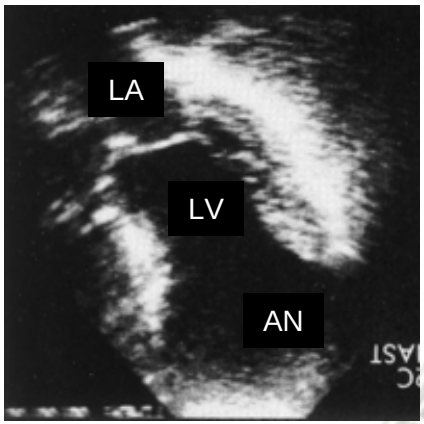
(Neeves et al. 2010, *Biophysics J*)

Canonical Models- Comparative Study Design

Normal

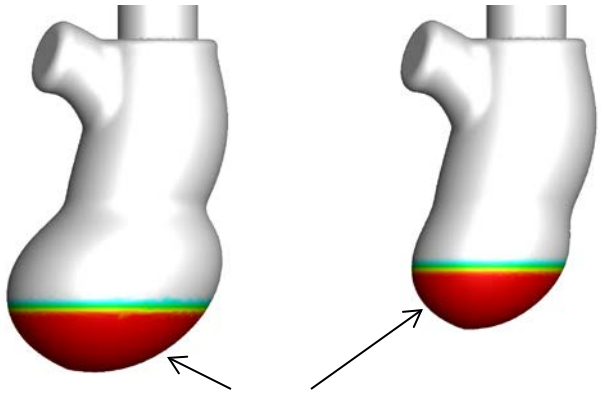
Infarcted/Aneurysm





Large Aneurysm

Small Aneurysm



Damaged wall due to the acute infarction

E/A=1.2, HR=60 BPM

Case	ESV (mL)	EDV (mL)	SV (mL)	EF (%)	AN
A	105	167	62	37	L
B	105	146	41	28	L
C	70	111	41	37	S
D	70	97	27	28	S

Clinical Translation?

- What *flow metric* can be used for the LVT risk prediction
  - Quantified correlation between flow metrics and coagulation
  - Could be obtained from echo PI or CMR

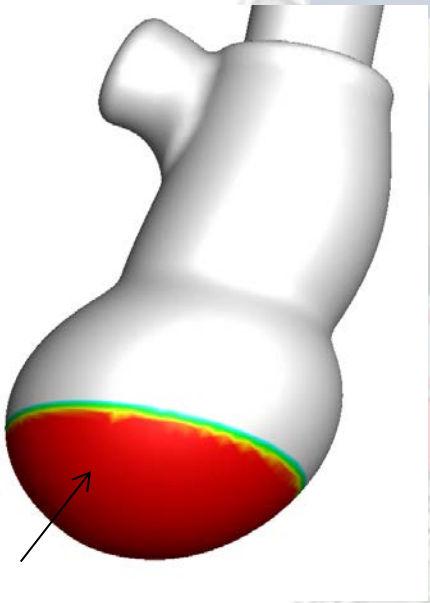
Residence Time (RT)

-How long blood volume stays in ROI

-Near damaged Wall Residence Time (**NWRT**)

-Decreased flow strength leads to high NWRT

$$\frac{d}{dt}\tau_{NW} = \left(\frac{\partial}{\partial t} + \vec{U}\cdot\nabla\right)\tau_{NW} = H(d_0 - d_w)$$



Marsden et al.

Predicted Thrombogenic Risk

SV=62 mL, EF=37%

Peak:1e-5
Mean:3e-7

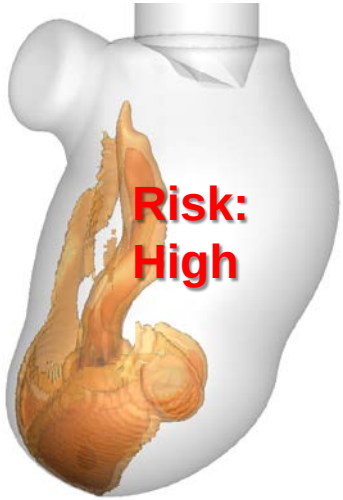
SV=41 mL, EF=28%

Peak:15
Mean:0.016

SV=41 mL, EF=37%

Peak:0.05
Mean:3e-4

SV=27 mL, EF=28%



Peak:0.5
Mean:0.012

Fibrin concentration (μmol/m^3)

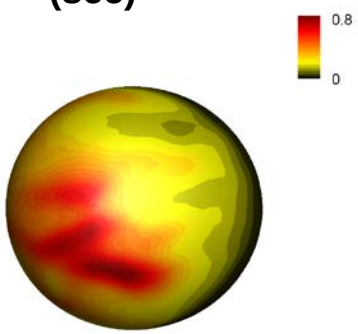
Average Surface Distributions

Small Aneurysm Cases

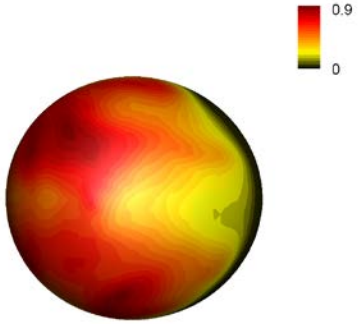
Hemodynamic

NWRT (sec)

SV = 41 mL
EF = 37 %

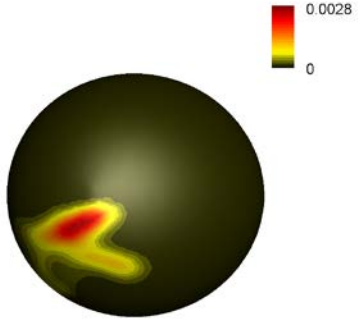


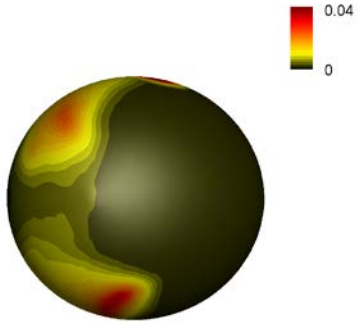
SV = 27 mL
EF = 28 %



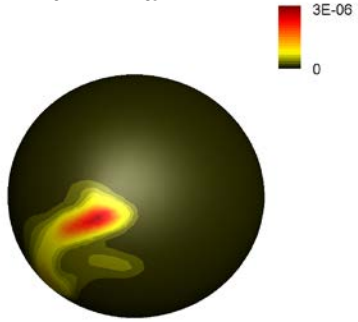
Coagulation

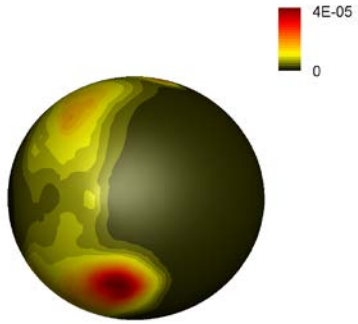
Thrombin ($\mu mol/m^3$)





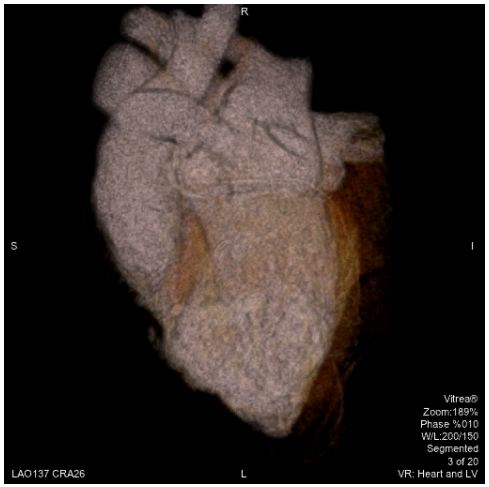
Bounded Platelet (PT_b/PT_{max})



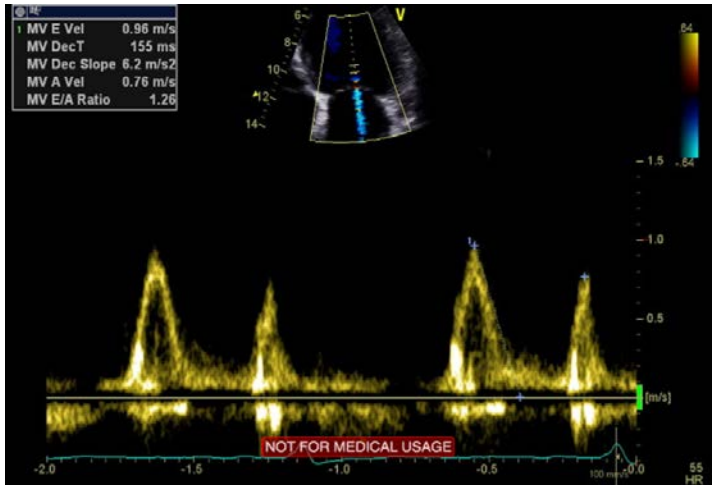


Distributions on the (damaged) aneurysm wall

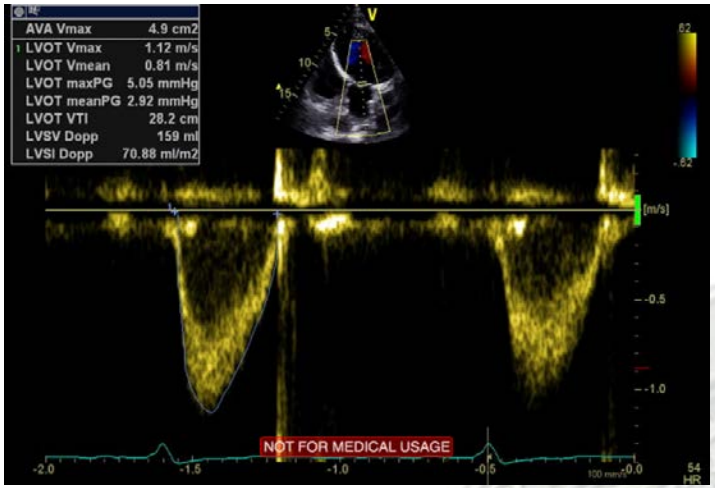
Patient-Specific Model from Multimodal Data Registration



Dynamic 4D CT scan



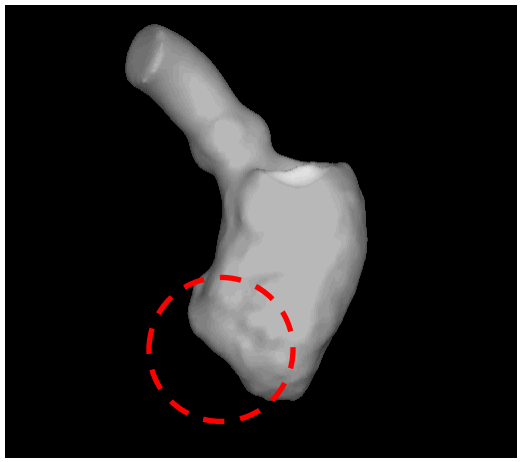
Mitral inflow Doppler



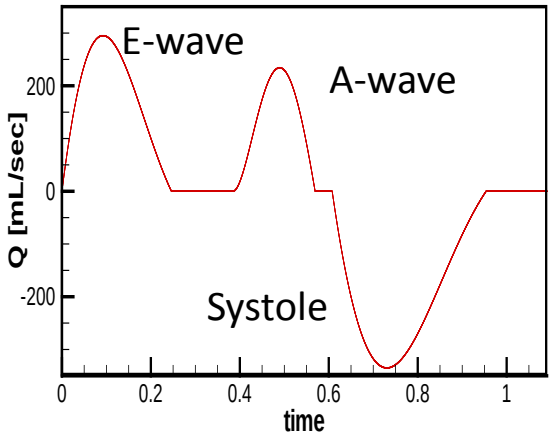
Outflow tract Doppler

Patient:
SV=84 mL, EF=47%
Apical Aneurysm
Apical Akinesia

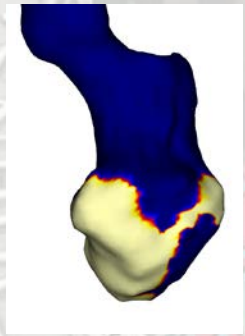
Nearly automated Procedure!



Segmented/Reconstructed Model



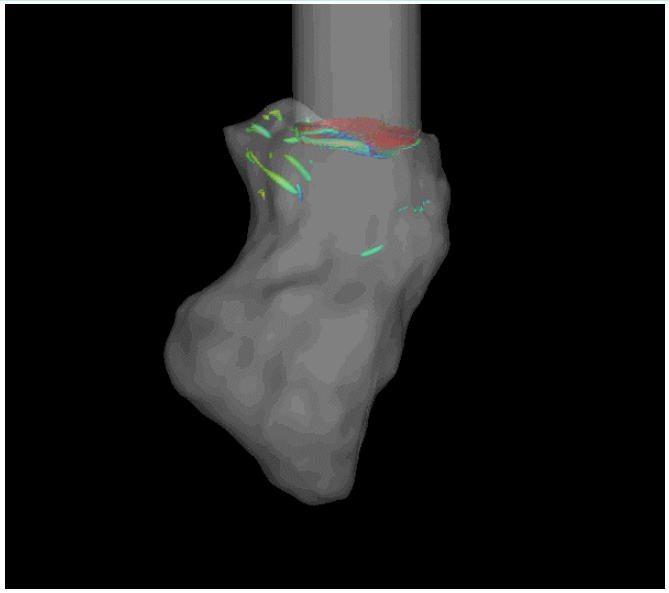
Reconstructed LV Flow Profile



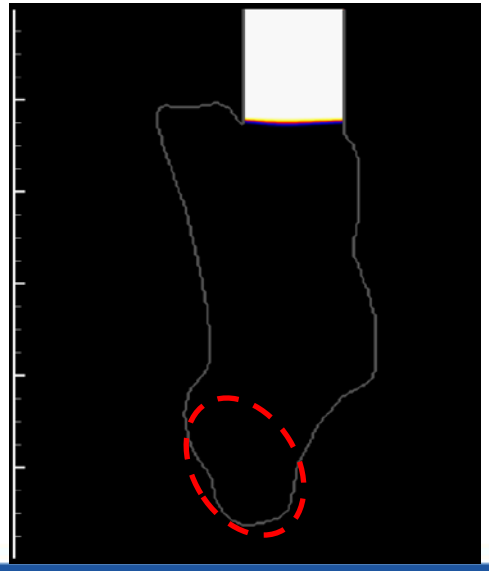
Infarct Indentification

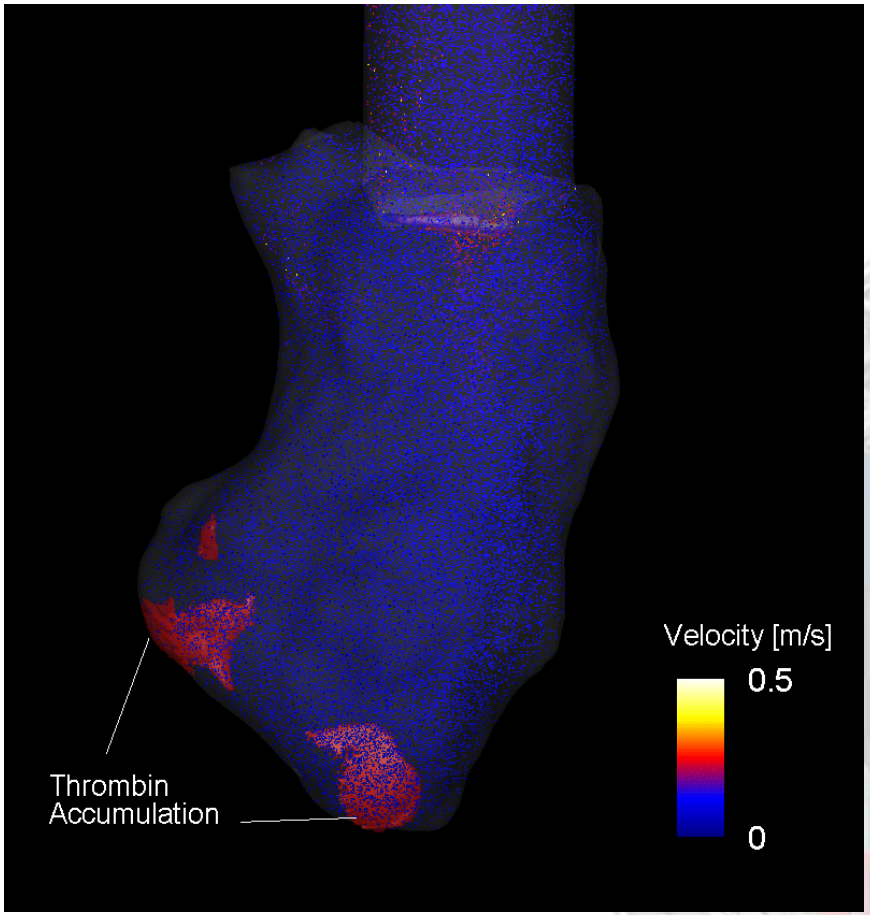
Chemo-Fluidic Interaction

Vortex Dynamics



Mixing and Washout





Evolution of flow and thrombin

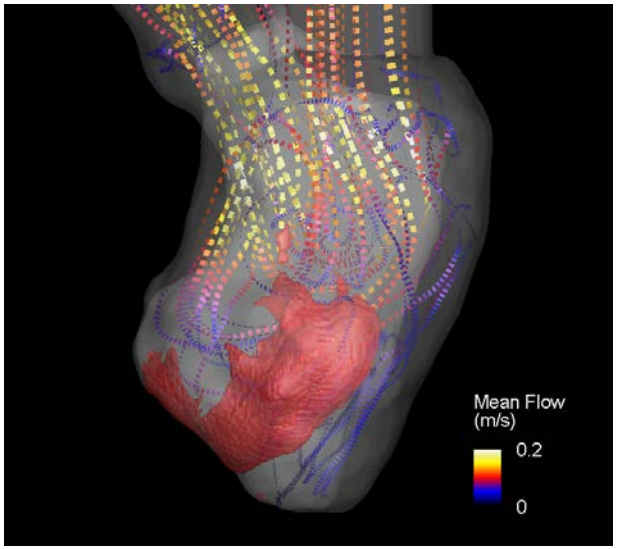
Time averaged flow and thrombin accumulation

192x192x256 (9.4M) grid points

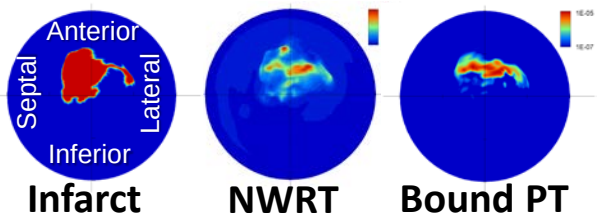
Hemodynamics and Coagulation

Averaged flow and thrombin accumulation

LVT01
EDV=178 mL, EF=47%

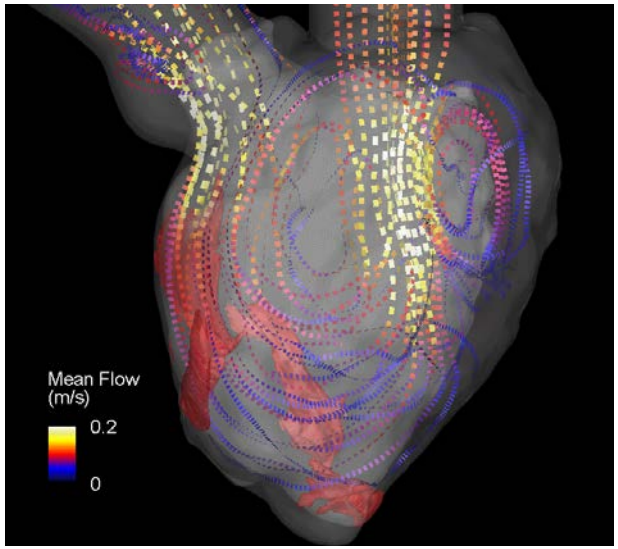


Thrombin: **5e-4** µmol/m^3

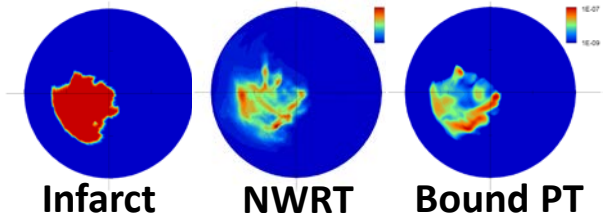


Infarct **NWRT** **Bound PT**

LVT02
EDV=334 mL, EF=40%

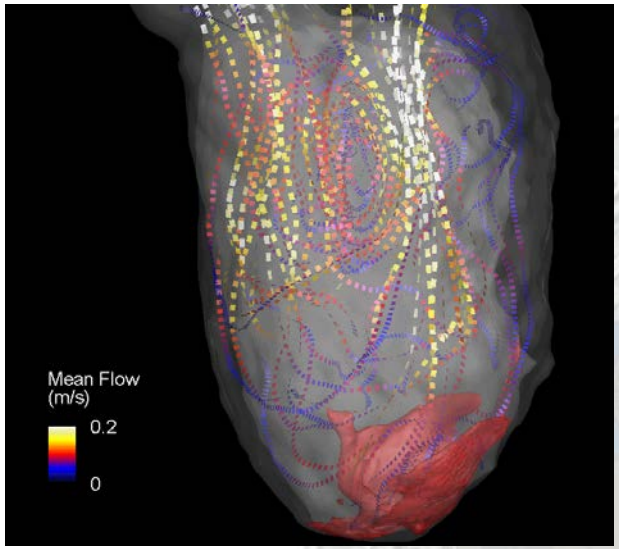


Thrombin: **1e-5** µmol/m^3

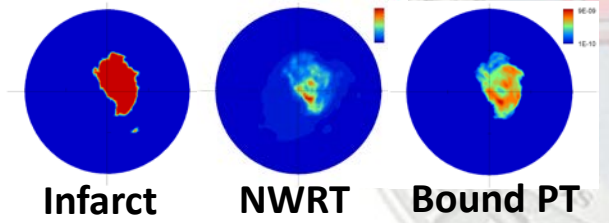


Infarct **NWRT** **Bound PT**

LVT09
EDV=417 mL, EF=39%



Thrombin: **1e-6** µmol/m^3

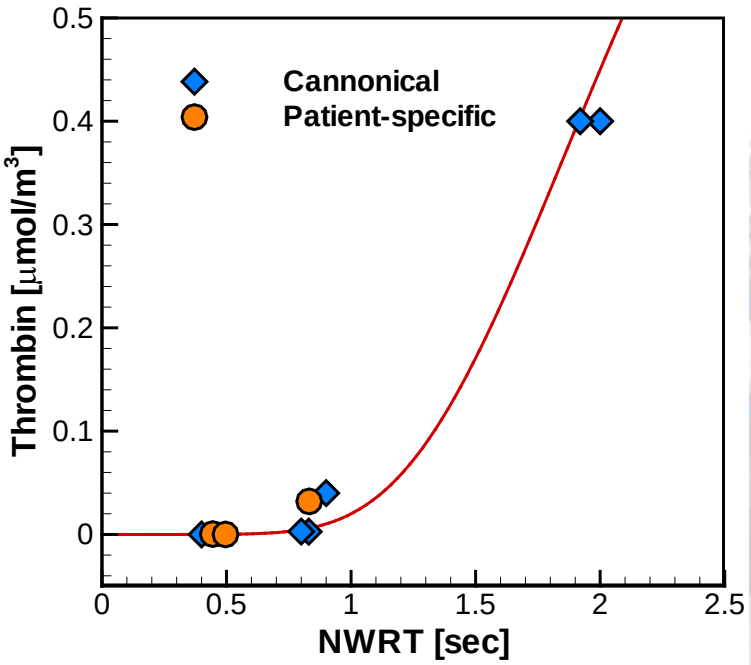


Infarct **NWRT** **Bound PT**

NWRT as a Predictor for Thrombosis?

Correlation between NWRT and Bound PT

Case	Correlation
SV=62 mL; EF=37%	0.61
SV=41 mL; EF=28%)	0.75
SV=41 mL; EF=37%	0.55
SV=27 mL; EF=28%	0.58

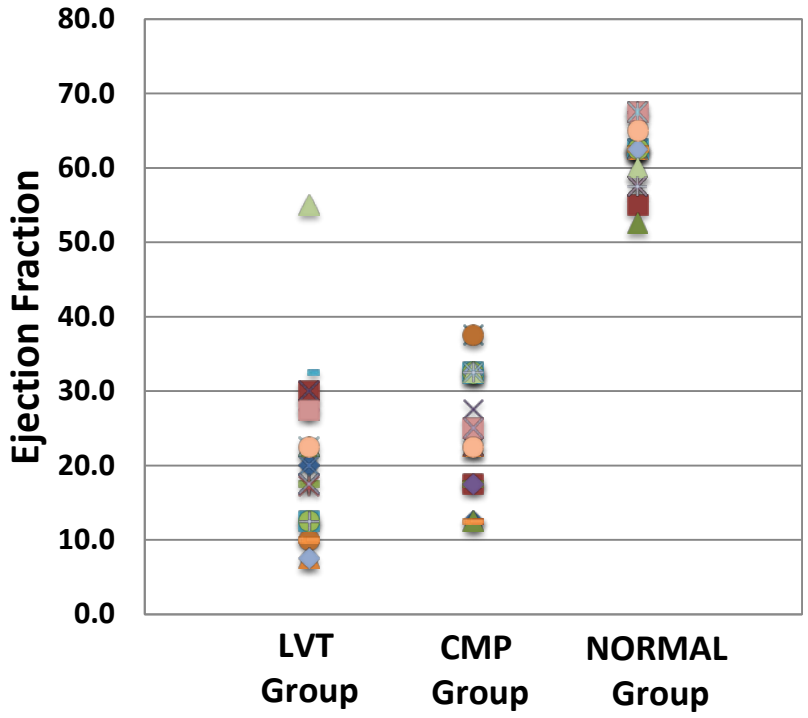


Residence time of flow in the vicinity of the infarct is a key indicator of LVT risk.

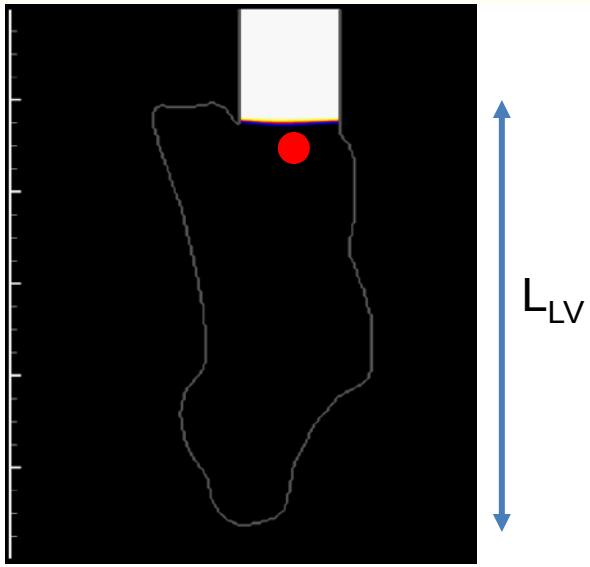
How to obtain a clinical measure of NWRT??

Stratification of LVT Risk?

Group	N	Description
LVT	25	Patients with diagnosed LVT
CMP	25	Severe cardiomyopathy; no LVT
NORMAL	25	Normal



A New Metric for LVT Risk



Normal LVs
High mixing and washout
<1% of blood cells stay in ventricle for >5 cycles

Cited Papers

- Seo, Jung Hee, Thura Abd, Richard T. George, and Rajat Mittal. “A Coupled Chemo-Fluidic Computational Model for Thrombogenesis in Infarcted Left Ventricles.” *American Journal of Physiology-Heart and Circulatory Physiology* (2016): ajpheart-00855. Published 25 March 2016 Vol. no. , DOI: 10.1152/ajpheart.00855.2015.