BIOMECHANICS OF VULNERABLE PLAQUE

Jacques Ohayon, Professor of Mechanics

Laboratory TIMC-DynaCell, UJF, CNRS UMR 5525, In^{3}S, Grenoble, France
University of Savoie, Engineering School Polytech Savoie, Chambéry, France

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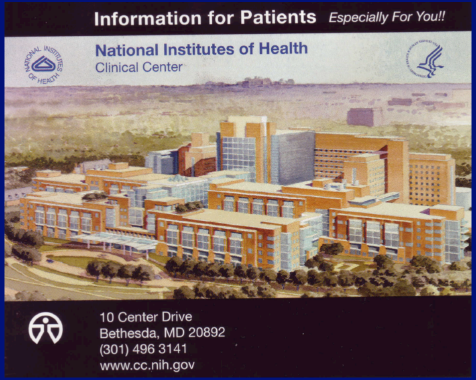
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Group of Structural Mechanics and Materials Modelling

LBUM

Ohayon et al., Am. J. Physiol 2007
Ohayon et al., Am. J. Physiol 2008
Le Floc'h et al., IEEE, 2009

Collaborators

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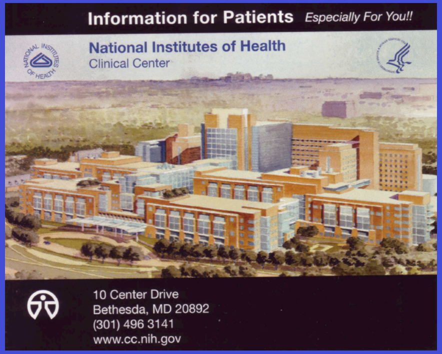
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France

Gérard Finet, MD, PhD

Philippe Tracqui, PhD

Simon Le Floc'h, PhD

Nicolas Mesnier, PhD Std

USA

Roderic I. Pettigrew, MD

Ahmed M. Gharib, MD

Julie Heroux, MSc, PhD Std

CANADA

Guy Cloutier, PhD

Roch Maurice, PhD

ESPAGNE

Manuel Doblare, PhD

Miguel-Angel Martinez, PhD

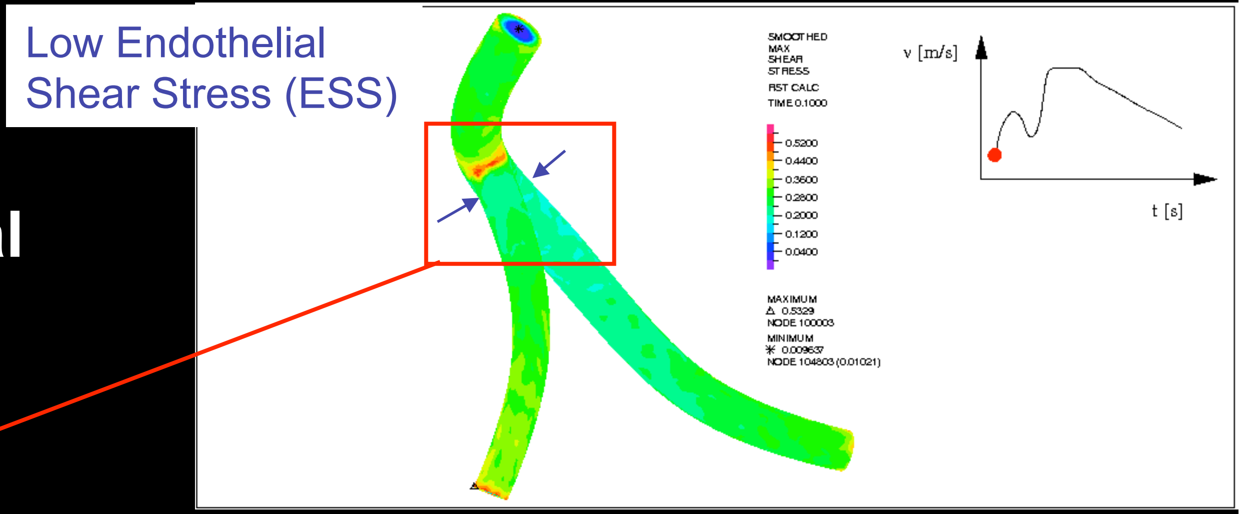
Estefania Pena, PhD

Biomechanics of Atheroma Plaque

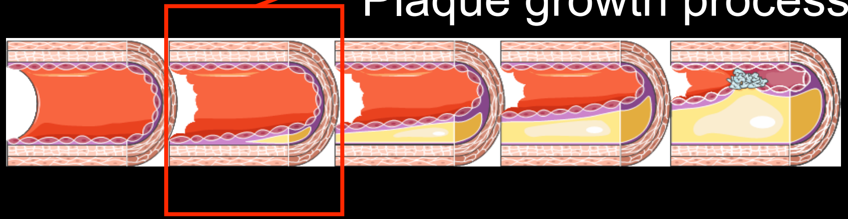
- 1st Remarkable Finding -

Fluid Biomechanical Simulations

Left main coronary bifurcation



Plaque growth process



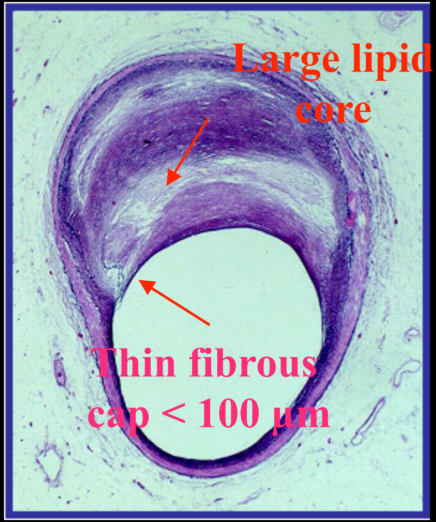
Low Endothelial Shear Stress is a strong local risk factor for **atherosclerosis**

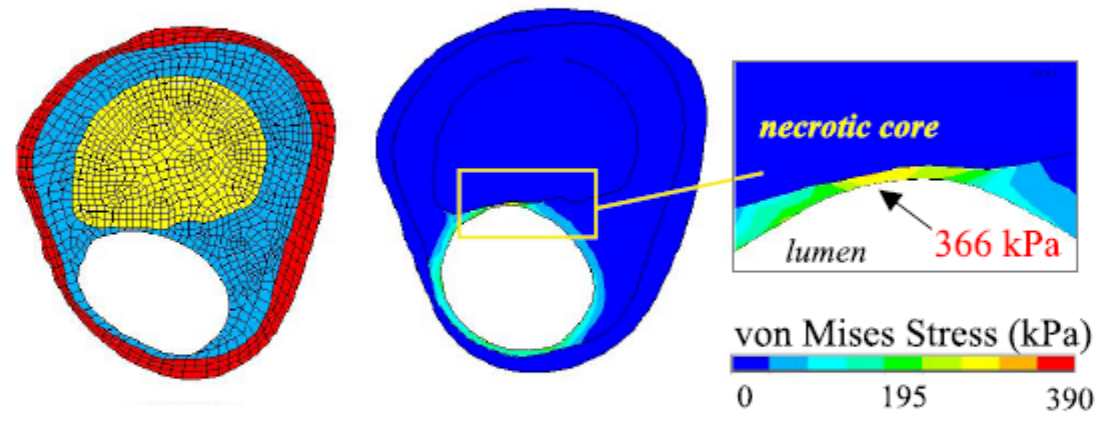
***Fry** , Circ Res 1968 – **Caro** et al., Proc. R Soc London B Biol Sci, 1971 - **Malek** et al., JAMA, 1999*

Biomechanics of Atheroma Plaque

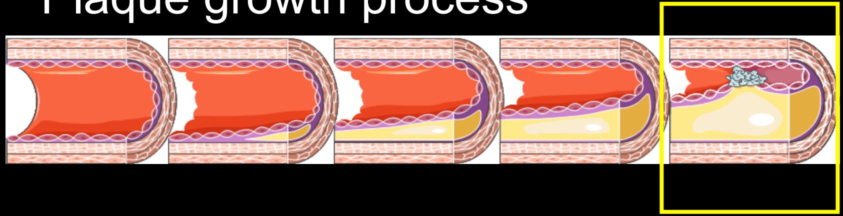
- 2nd Remarkable Finding -

Solid Biomechanical Simulations





Plaque growth process



Peak cap stress can predict **plaque rupture**

***Richardson** et al., Lancet 1989 – **Loree** et al., Circ Res, 1992 - **Cheng** et al., Circulation, 1993*

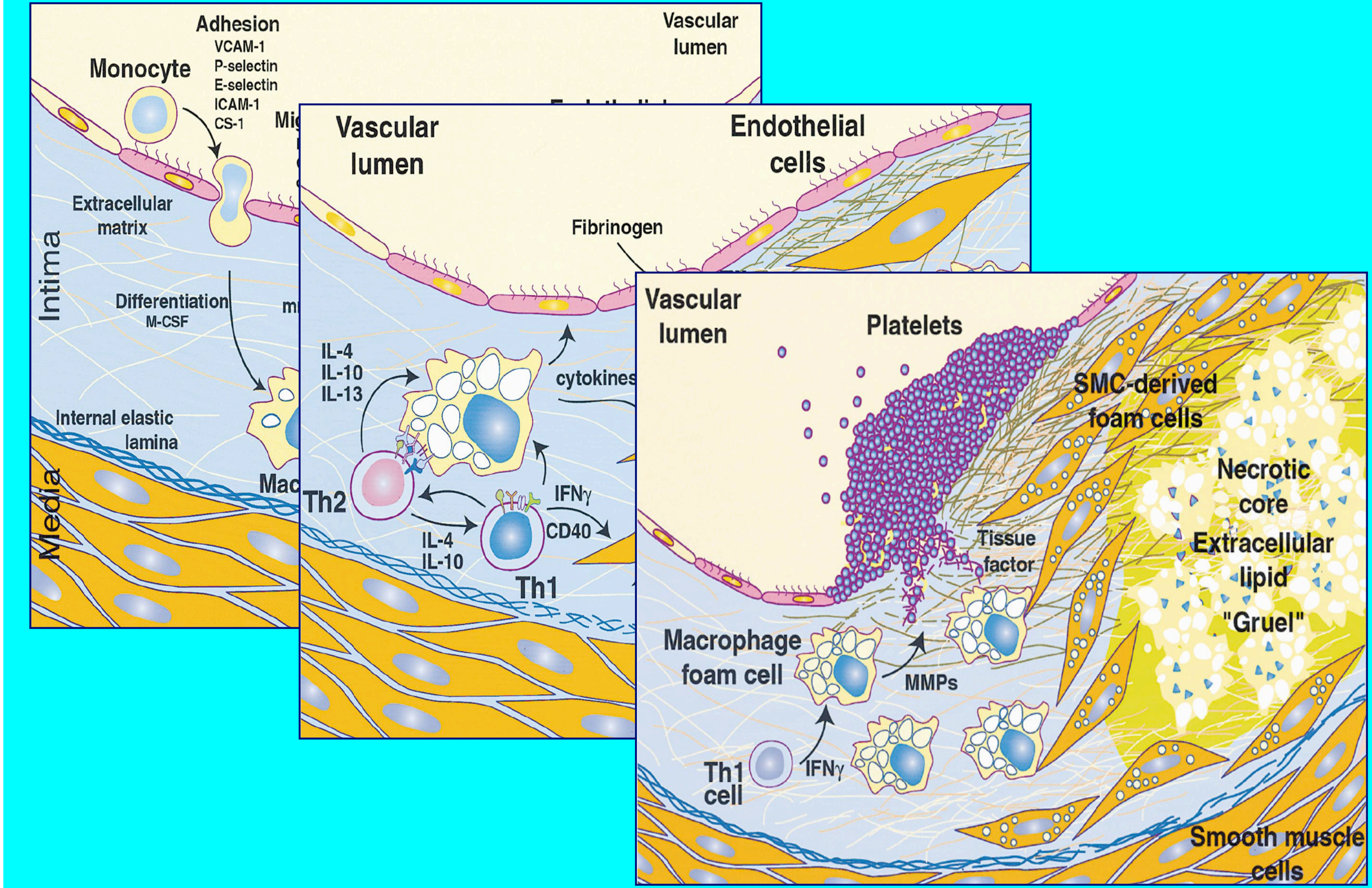
Investigations of the Biomechanics of Vulnerable Plaque

Biomechanics can help define vulnerable plaque morphology and critical parameters

Key Questions:

1. What are morphologic determinants of vulnerability?
2. What is the elasticity of plaque-wall constituents ?

Atheroma – Biological Processes



(Glass CK. *Cell* 2001)

BACKGROUND

A Cascade of Events Leads to Plaque Rupture

Lipid accumulation
(decades)

Inflammation
(Probably years)

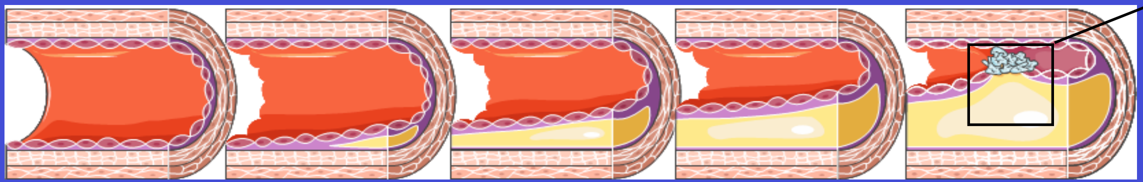
Increased
stress

Increased
degradation

Decreased
synthesis

fibrous cap

Plaque rupture



- **Peak cap stress a good predictor of rupture**

Arroyo et al., Cardiovascular Research, 1999

PART II

Peak cap stress depends on:

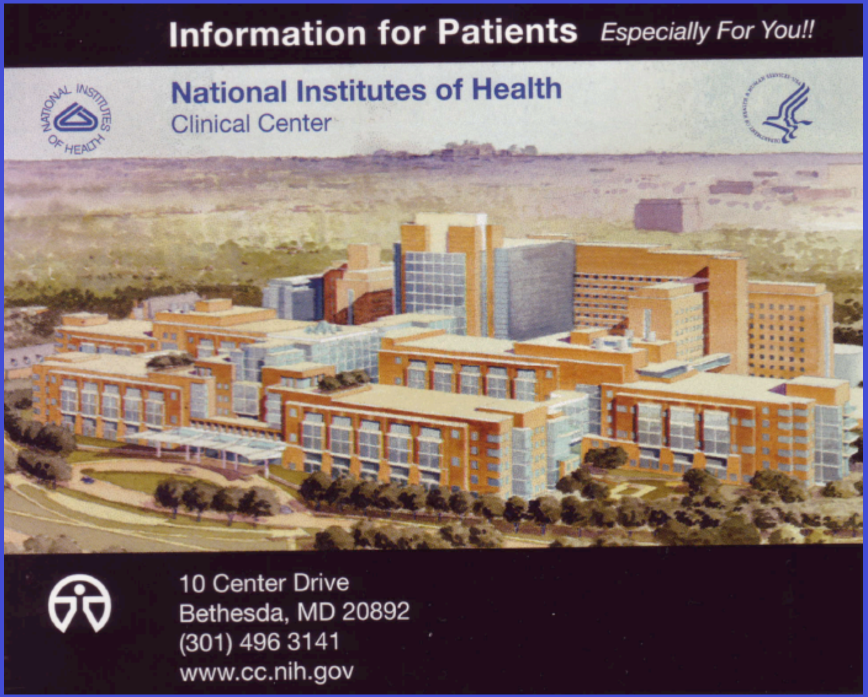
a) Spatial Residual Stress Distribution

b) Plaque Morphology

c) Mechanical Properties of Plaque Constituents

Ohayon et al., Am. J. Physiol 2008

Necrotic Core Thickness and Arterial Remodeling Index: Emergent Biomechanical Factors for Evaluating the Risk of Plaque Rupture



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Ohayon et al., Am. J. Physiol 2008

Jacques Ohayon, PhD, France

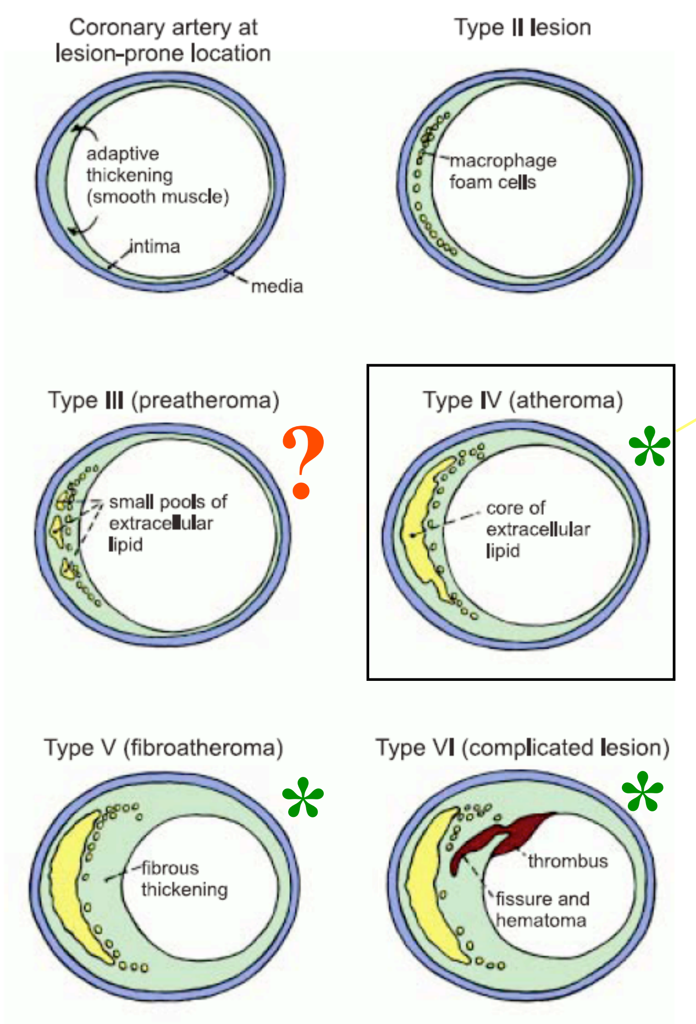
Gérard Finet, MD, PhD, France

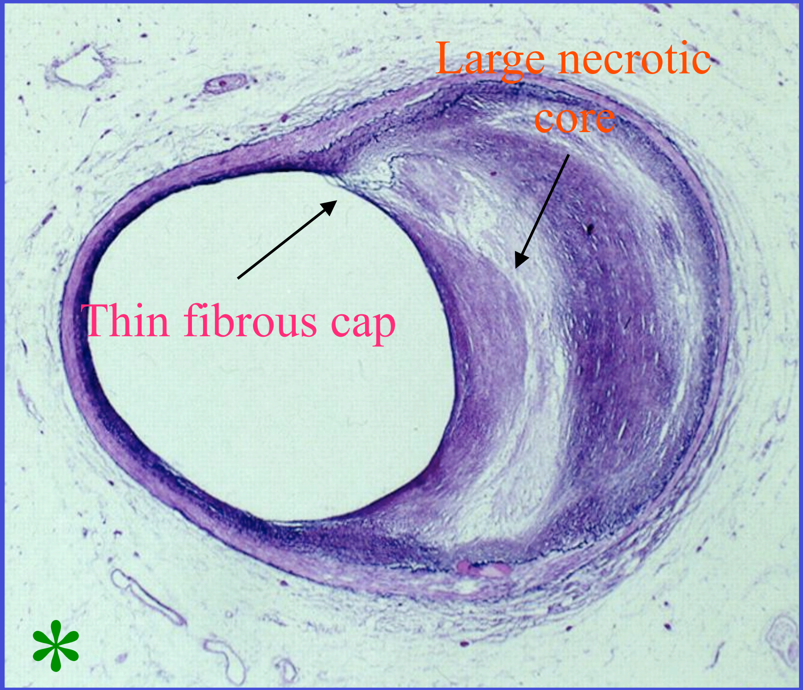
Roderic I. Pettigrew, MD, PhD, USA

BACKGROUND

Criteria for Defining Vulnerable Atherosclerotic Plaques

Illustration of the usual sequence in the development of the coronary atherosclerosis





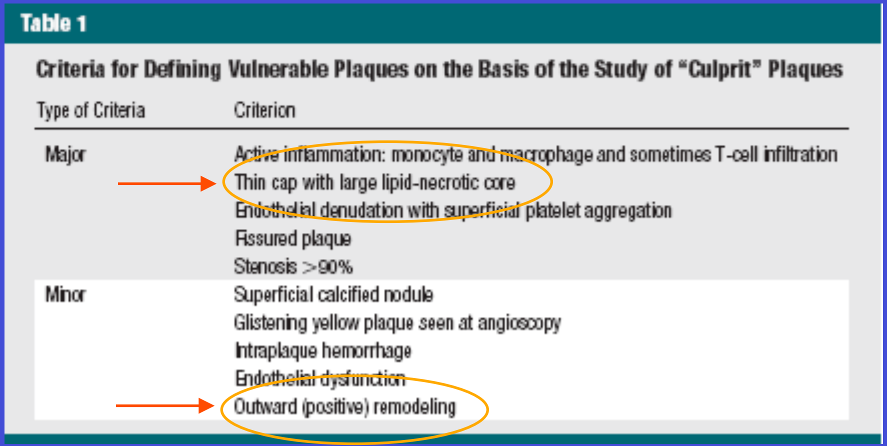


Table 1

Criteria for Defining Vulnerable Plaques on the Basis of the Study of "Culprit" Plaques

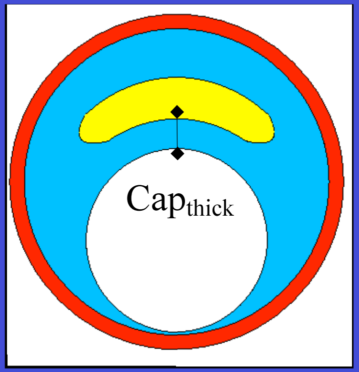
Type of Criteria	Criterion
Major	Active inflammation: monocyte and macrophage and sometimes T-cell infiltration
	Thin cap with large lipid-necrotic core
	Endothelial denudation with superficial platelet aggregation
	Fissured plaque
	Stenosis >90%
Minor	Superficial calcified nodule
	Glistening yellow plaque seen at angioscopy
	Intraplaque hemorrhage
	Endothelial dysfunction
	Outward (positive) remodeling

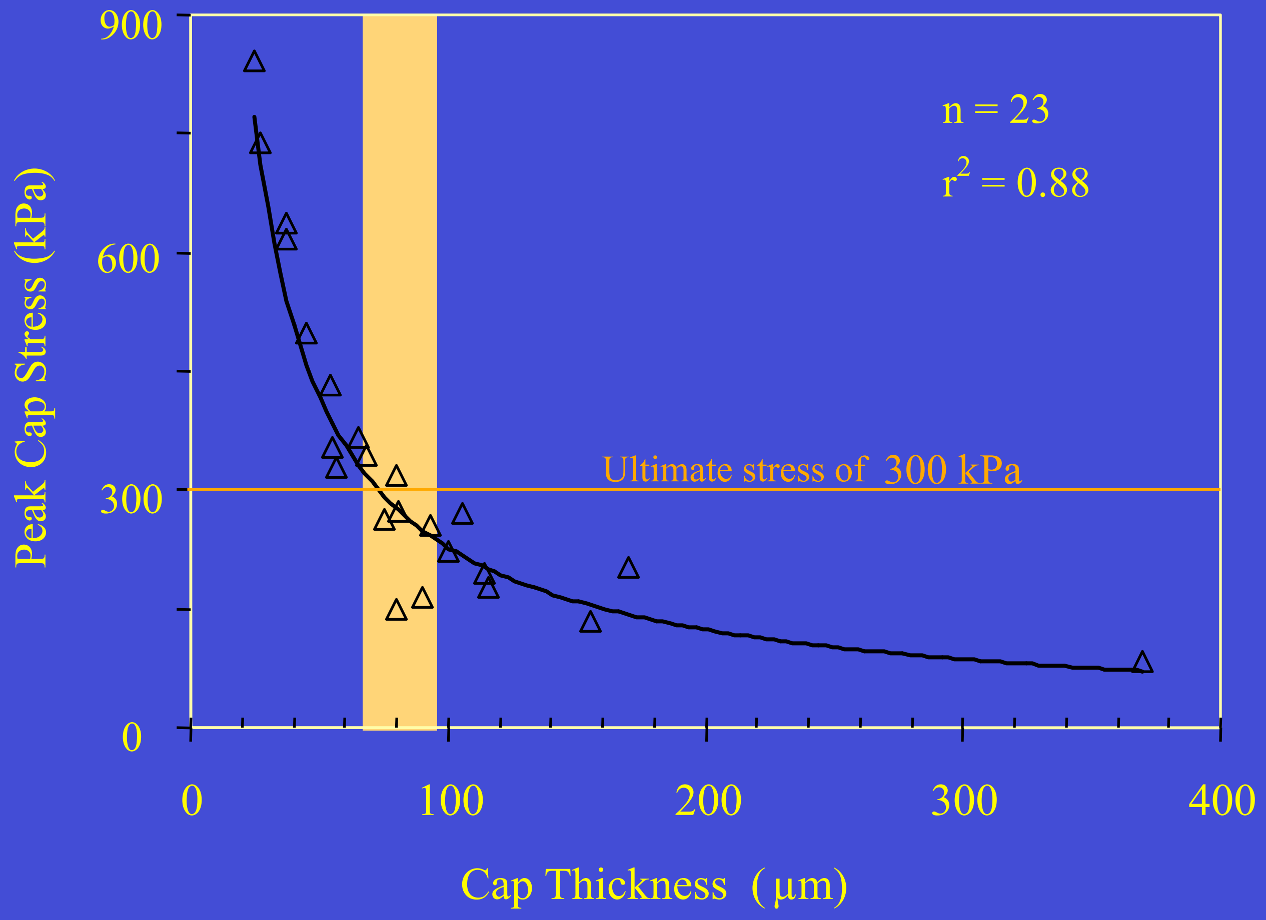
H.C. Stary, Atlas of Atherosclerosis, 2nd edition, 2003.

Naghavi et al., Circulation 2003.

BACKGROUND

I. Plaque Vulnerability and Cap Thickness





Critical Cap Thickness:

65 – 100 µm

Naghavi et al., Circulation, 2003
Virmani et al., ATV, 2000
Finet et al., Coro. Art. Dis., 2004

From Ohayon et al., 2008

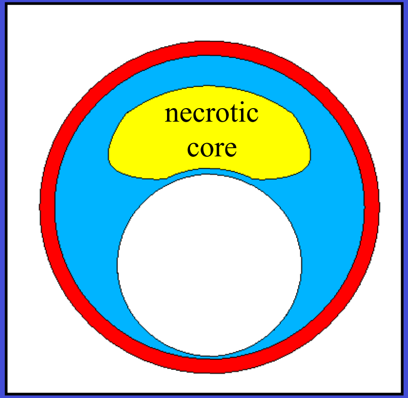
BACKGROUND

II. Plaque Vulnerability and Necrotic Core Size

- **Large lipid-necrotic core :** But what is the critical necrotic core size ?

Large Variation, between **10%** and **50%** of plaque area

- ***Fujii et al., Circulation, 2003***
- ***Gertz et al., Am. J. Cardiol, 1990***
- ***Kolodgie et al., Curr Opin Cardiol , 2001***
- ***Naghavi et al., Circulation, 2003***
- ***Rioufol et al., Circulation, 2004***

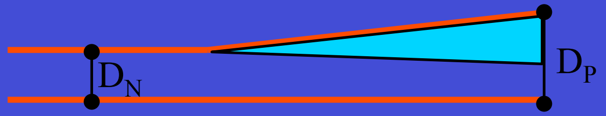


III. Plaque Vulnerability and Remodeling Index (RI)

- **Few is known about the** effect of remodeling index on plaque vulnerability

Plaque rupture often occurs often at sites with relatively small luminal stenosis

(Varnava et al., Circulation, 2002)



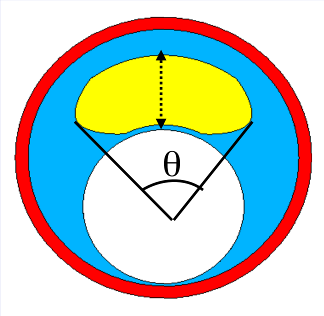
$$RI = D_P/D_N$$

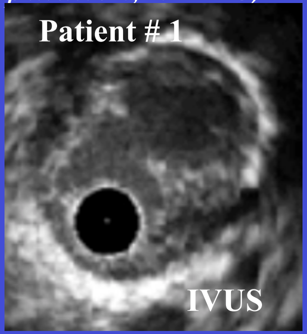
Thus, it still remains unclear how both, necrotic core size and plaque-growth process affect the peak cap stress – a predictor of rupture.

METHOD : Strategy 1

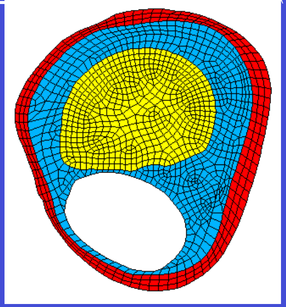
Structural Analysis Performed on Real Plaque Morphologies

Clinical Measurements (Population, n = 24)

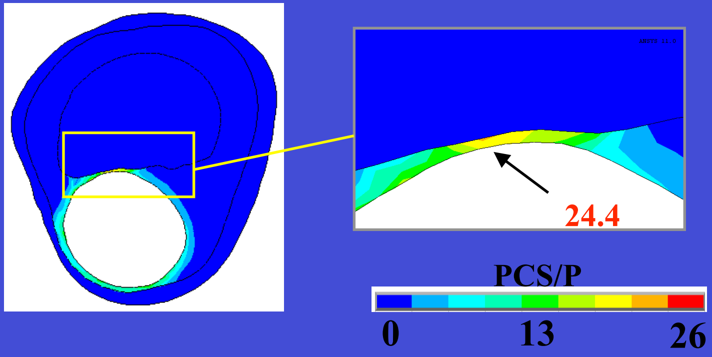




Structural Analysis (n = 24)



Finite element analysis

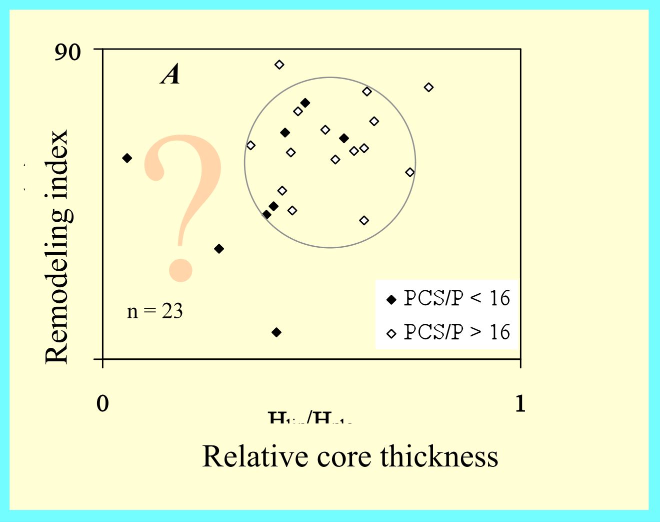


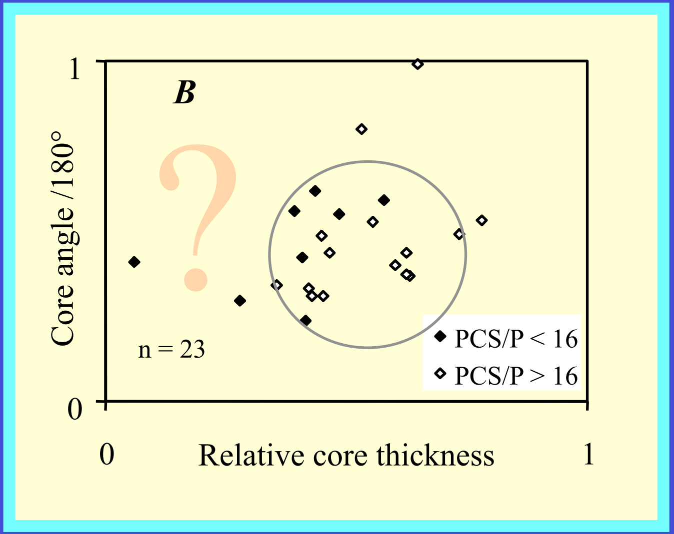
- Core area
- Core angle
- Core thickness
- Remodeling index
- Cap thickness

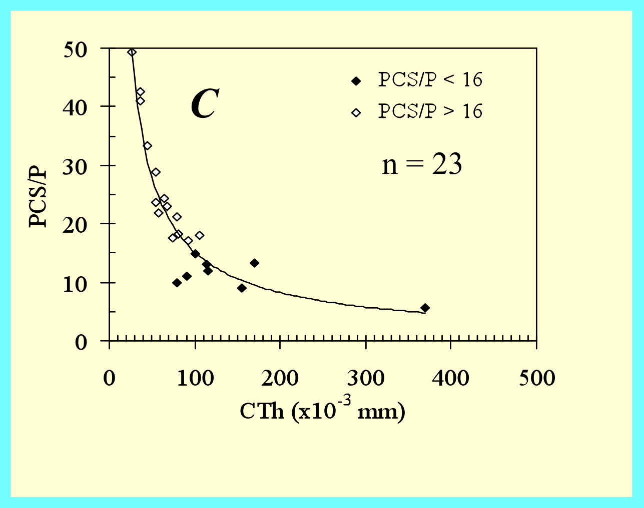
Peak cap stress

Correlations ?

RESULTS : Correlations Between Peak Cap Stress and Plaque Morphology







Unfortunately, 70% of our IVUS population had similar Remod$_{\text{index}}$ and Core$_{\text{area}}$, so that **statistical analysis failed** to disclose any influence on plaque stability of such parameters.

RESULTS : Clinical Study (n =24 patients)

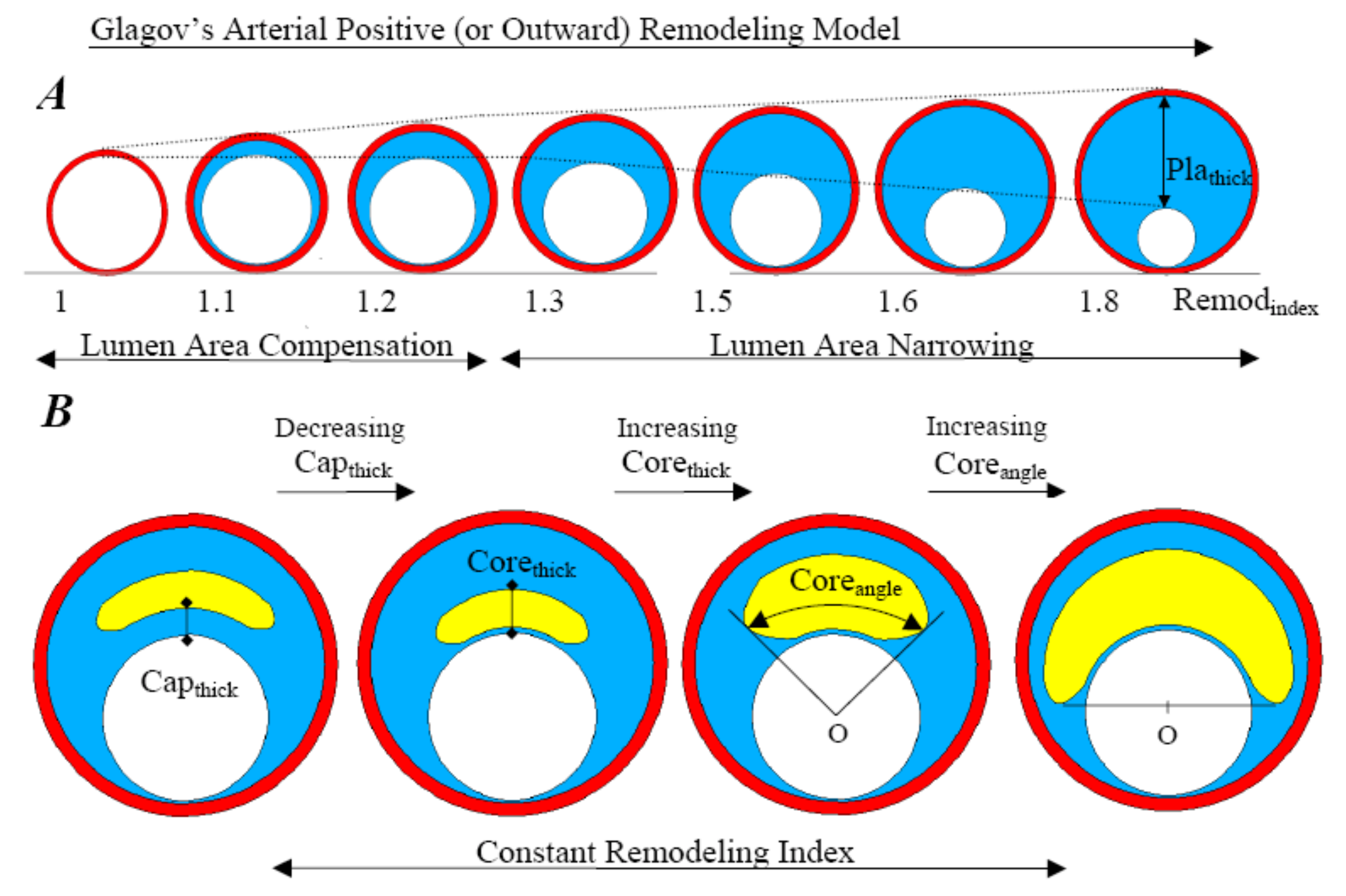
Description of Plaque Characteristics Detected by IVUS

Patient # and Sex (n = 24)	Age (years)	Coronary Artery	Remodeling Index	External Elastic Membrane Area (mm^2)	Lumen Area (mm^2)	Core Area (mm^2)	Relative Core Area (%)	Plaque Burden (%)	Core Arc Angle (degrees)	Relative Core Thickness (%)	Cap Thickness (x 10^{-3} mm)
1-M	67	LAD	1.52	19.93	3.24	5.69	44.0	83.8	96	77.92	< 90 (65)
2-M	69	LAD	1.22	15.95	6.01	1.15	15.5	62.3	67	62.50	< 90 (37)
3-M	52	OMA	1.35	19.16	5.34	2.48	25.0	72.1	95	55.56	< 90 (45)
4-M	56	OMA	1.54	21.47	3.61	2.10	15.0	83.2	67	63.16	< 90 (81)
5-M	59	LAD	1.33	20.32	6.06	2.04	18.5	70.2	88	73.53	< 90 (37)
6-M	71	OMA	1.46	21.5	5.72	1.77	15.2	73.4	88	45.00	< 90 (54)
7-M	72	LCX	1.24	19.85	4.27	4.41	38.8	78.5	178	64.86	< 90 (80)
8-M	68	RCA	1.32	23.32	5.94	4.59	31.6	74.5	61	35.56	93
9-M	49	RCA	1.70	34.62	4.34	2.72	10.5	87.5	60	42.22	< 90 (27)
10-M	65	LAD	1.22	26.22	6.80	1.97	15.7	74.1	79	62.50	< 90 (57)
11-M	65	LAD	1.29	20.31	4.06	2.95	24.7	80.0	79	46.67	< 90 (25)
12-M	65	LAD	1.34	25.73	8.44	1.33	10.4	67.2	55	42.86	< 90 (55)
13-M	76	LAD	1.47	28.91	7.67	1.87	11.2	73.5	72	60.00	106
14-M	52	RCA	1.16	19.13	10.63	0.46	6.7	44.4	42	41.67	116
15-M	59	LCX	1.12	14.73	5.30	0.80	11.1	64.0	56	45.24	< 90 (75)
16-M	45	RCA	1.37	17.71	6.26	0.70	7.4	64.7	76	40.91	100
17-M	61	RCA	1.30	25.22	10.63	0.88	8.0	57.8	53	28.00	< 90 (80)
18-M	68	RCA	1.43	17.86	4.18	2.88	26.1	76.6	111	43.48	155
19-M	79	LAD	1.46	24.46	6.75	1.70	11.8	72.4	74	6.00	90
20-M	65	LAD	1.20	19.73	4.53	3.54	32.8	77.1	144	53.13	< 90 (68)
21-M	60	LAD	1.20	11.44	2.79	1.36	20.7	75.6	106	57.89	114
22-M	60	LAD	1.24	20.16	7.41	1.97	19.9	63.3	101	39.29	170
23-M	57	RCA	1.36	14.67	2.75	1.81	20.5	81.2	99	48.48	370
Mean	62.61		**1.34**	20.97	5.77	2.22	**19.17**	72.06	84.65	49.41	
SD	8.49		**0.14**	5.06	2.17	1.32	**10.16**	9.63	30.78	15.59	
24 -M	63	LAD	1.40	25.10	6.86	1.92 / 0.47	12.8 / 3.1	68	79 / 31	57.20 / 24.12	90 / 90

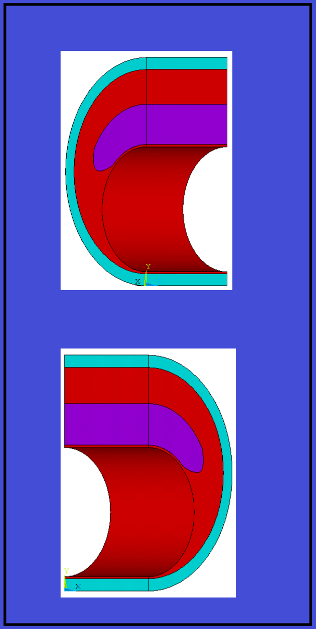
In order to test the model's performance, cap thicknesses were randomly assigned (values in brackets) when found to be under the limit of the IVUS resolution (i.e., < 0.090mm). A 10 -months' follow-up IVUS was performed on patient # 24, who interestingly presented a vulnerable plaque with two necrotic cores. *Column 1:* M = male. *Column 3:* LAD = left anterior descending artery; OMA = obtuse left marginal artery; LCX = left circumflex artery.

METHOD : Strategy 2

Structural Analysis Based on a Dataset of Idealized Plaque Geometries Mimicking Atherosclerotic Lesion Growth (5,500 morphologies)



Plane strains

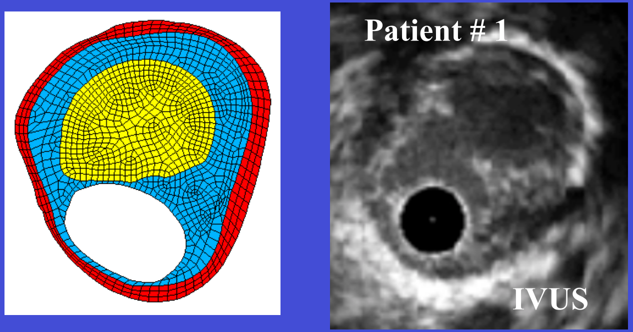


For a given Stenos$_{deg}$ (N=14), all topologically admissible blunt crescent-shaped necrotic cores were investigated (n=393)

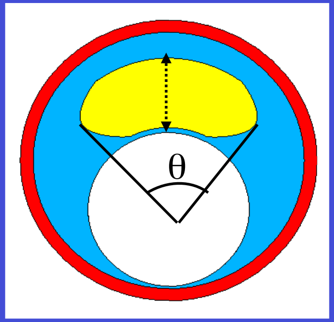
METHOD : Validation

Structural Analysis

Real Plaque Morphologies (n = 24)



Associated Idealized Plaque Morphologies



- Core area
- Core angle
- Core thickness
- Remodeling index
- Cap thickness

Finite Element Simulation

'Real' peak cap stress

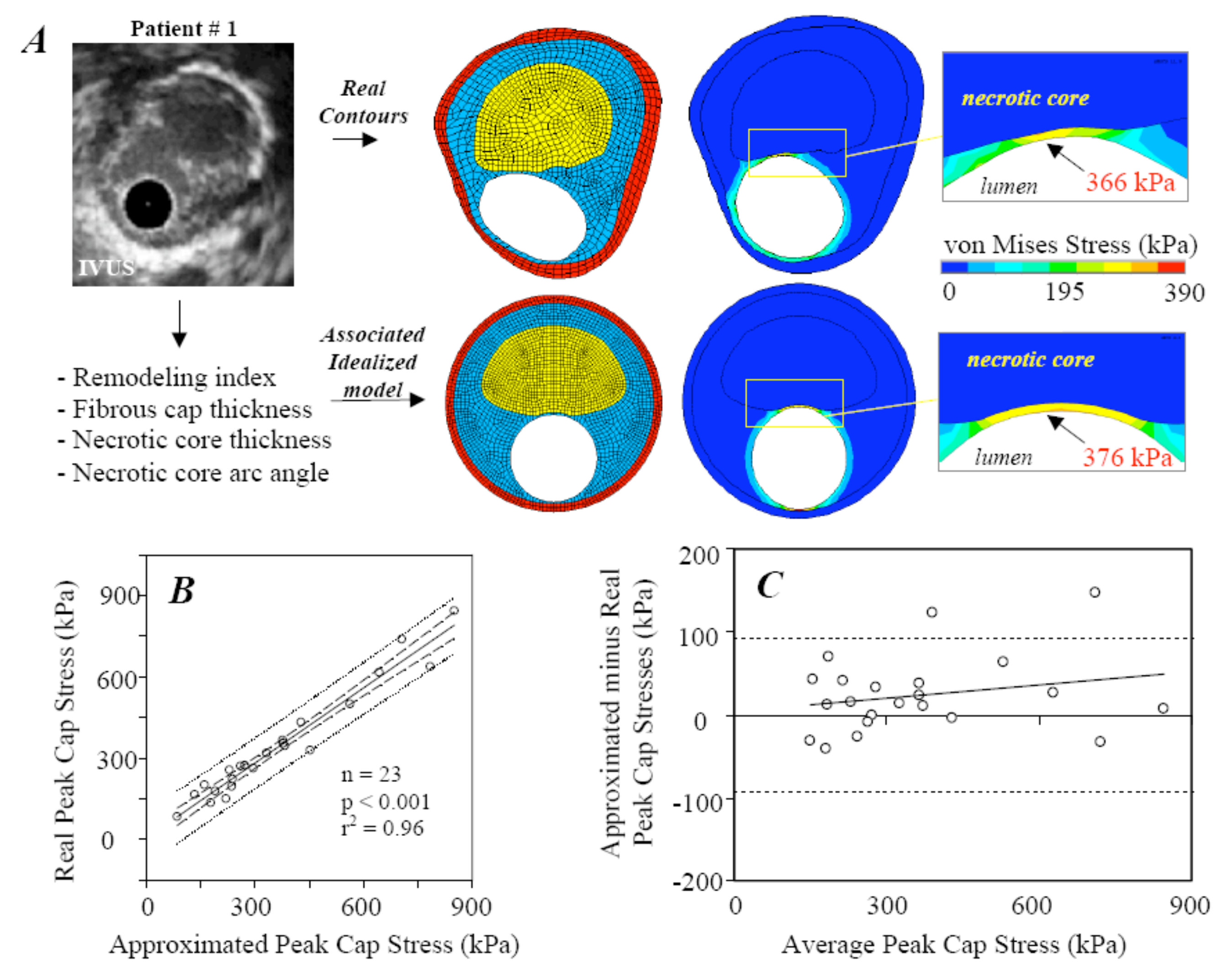
Finite Element Simulation

'Approximated' Peak cap stress

Comparison

RESULT :

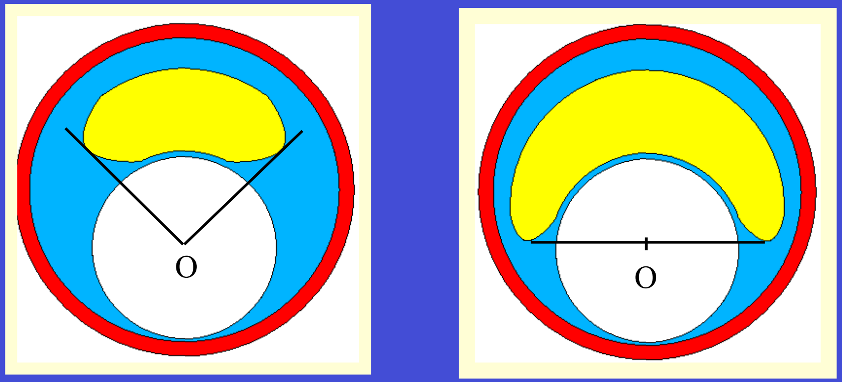
Model Validation

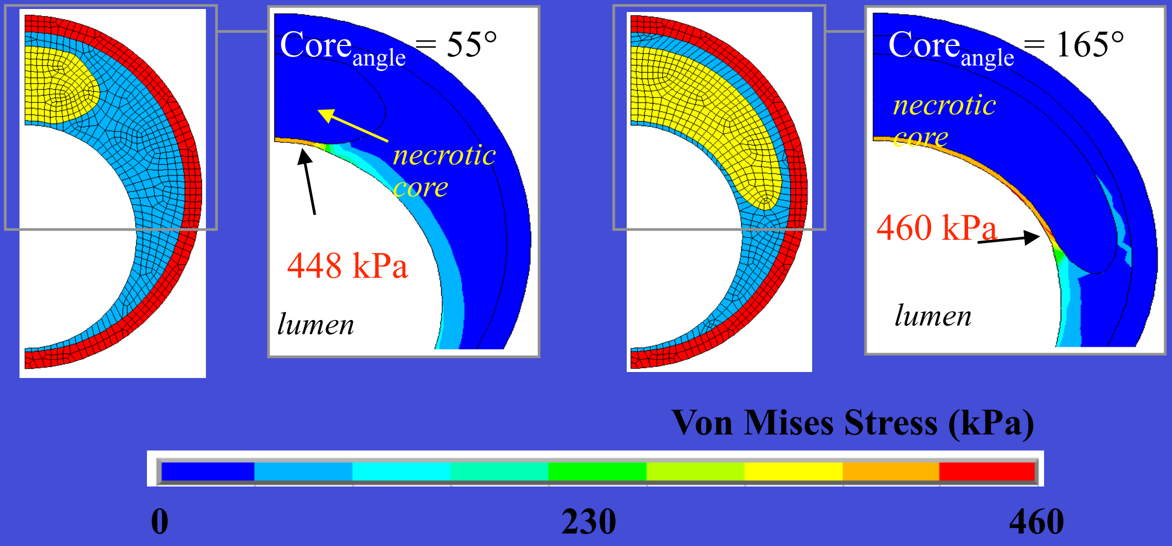


RESULT : Non Significant Influence of Necrotic Core Angle on Peak Cap Stress

Increase of core area inducing only by a **variation of core angle**

- Fixed cap thickness
- Fixed remodeling index

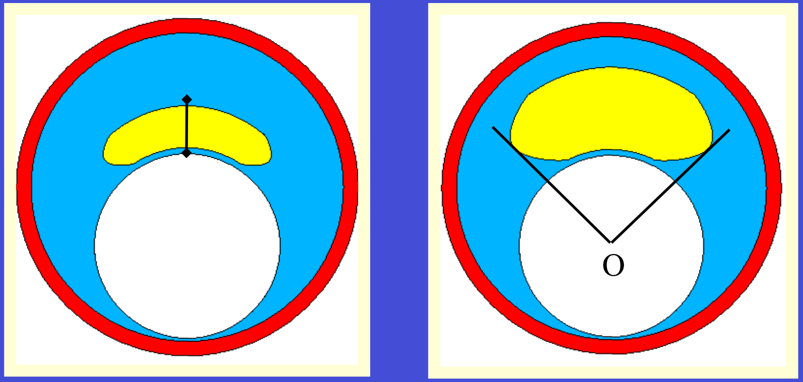


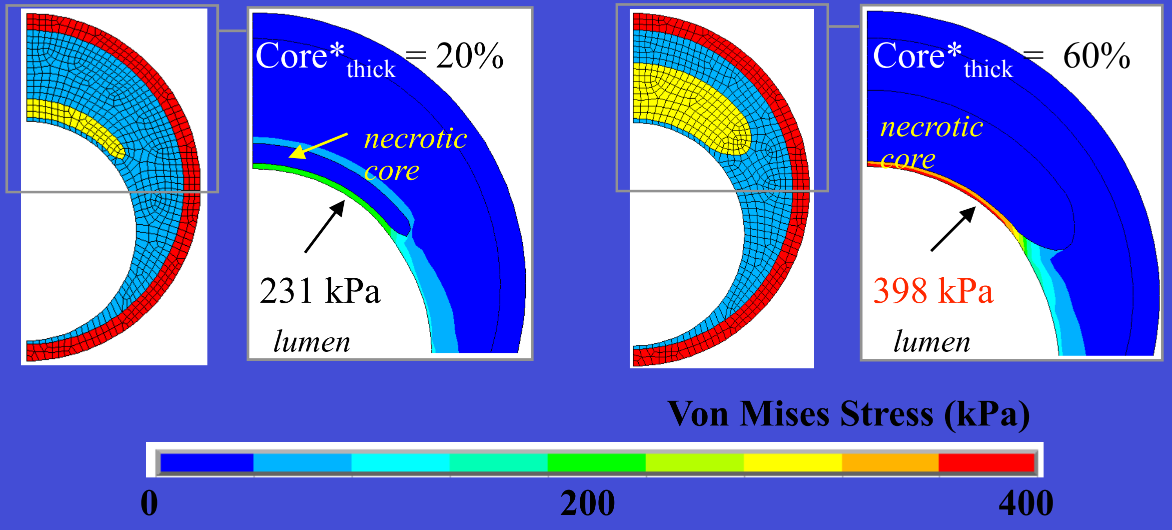


RESULT : Importance of Necrotic Core Thickness when Evaluating Peak Cap Stress

Increase of core area inducing only by a **variation of core thickess**

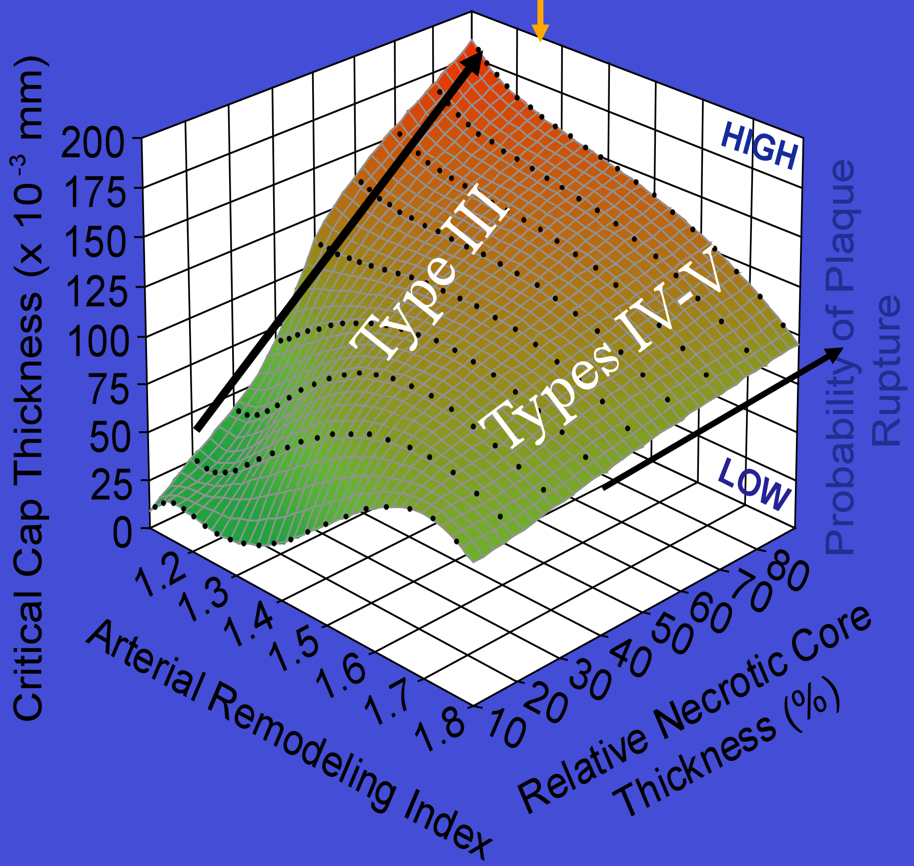
- Fixed cap thickness
- Fixed remodeling index





RESULT : Combined Effects of Remodeling Index and Necrotic Core Thickness on Critical Cap Thickness

Even with a large $\mathrm{Cap}_{\mathrm{thick}}$ (>150 µm) the plaque may be vulnerable to rupture



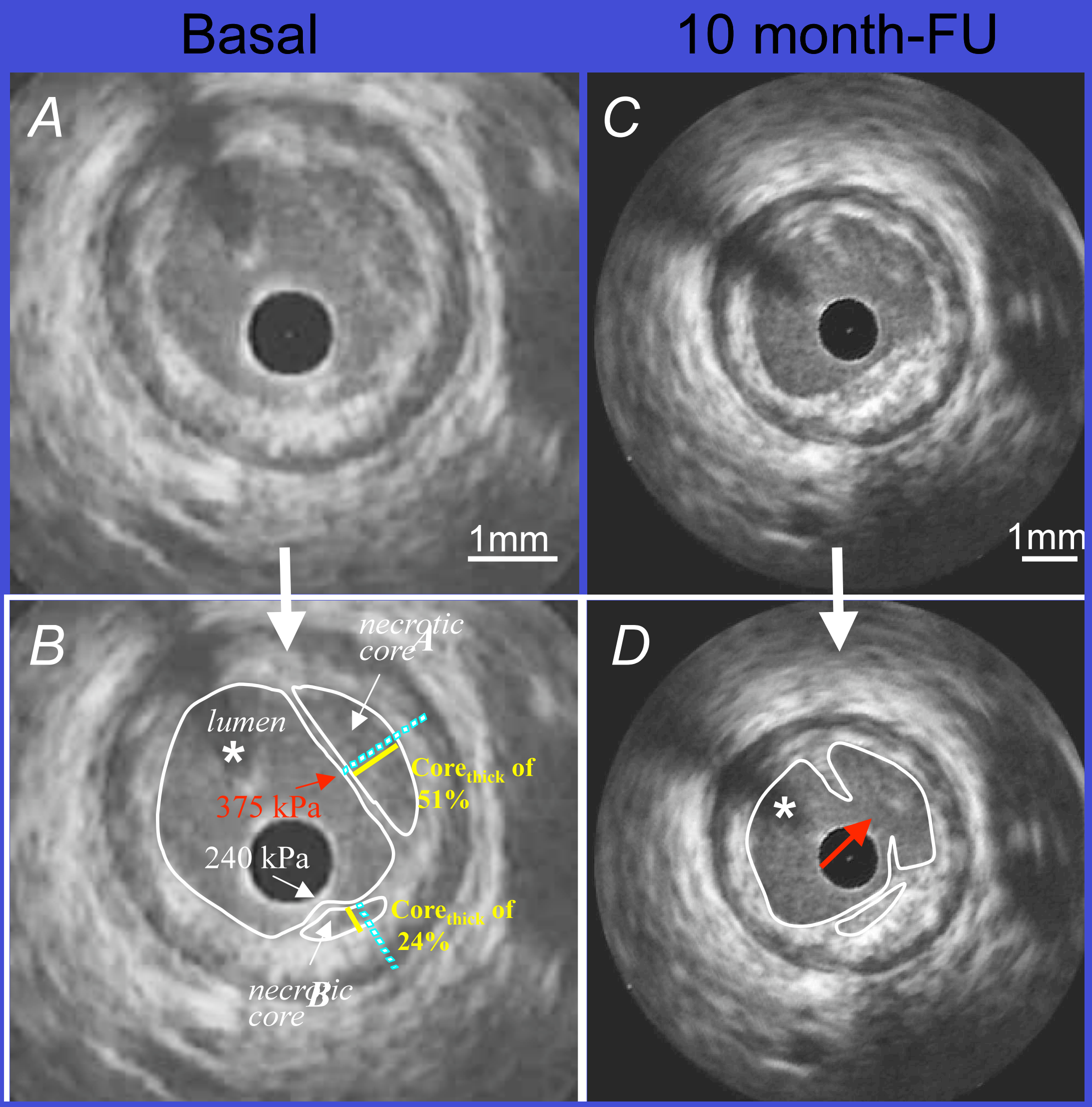
From Ohayon et al., 2008

Definition:

Critical $\mathrm{Cap}_{\mathrm{thick}}$ was defined as the value of $\mathrm{Cap}_{\mathrm{thick}}$ at which $\mathrm{Cap}_{\mathrm{stress}}$ reached the ultimate tensile stress of 300 kPa

Plaque with large relative necrotic $\mathrm{Core}_{\mathrm{thick}}$ and small $\mathrm{Stenos}_{\mathrm{deg}}$ were found more liable to rupture.

RESULT : **Potential Clinical Implications :** Plaque Rupture Prediction



From Ohayon et al., 2008

*: wire echo

Both cores had same:

- $\text{Cap}_{\text{thick}} = 100\ \mu\text{m}$
- $\text{Remod}_{\text{index}} = 1.40$

CONCLUSIONS

Necrotic core thickness - rather than area – appears to be critical in determining plaque stability.

At the early stages of positive remodeling, atherosclerotic lesions were more prone to rupture, which could explain the progression and growth of clinically silent plaques.

Biomechanical plaque instability is not a consequence of cap thickness alone, but rather of a subtle combination of cap thickness, necrotic core thickness and arterial remodeling index.

PART III

Peak cap stress depends on:

a) Spatial Residual Stress Distribution

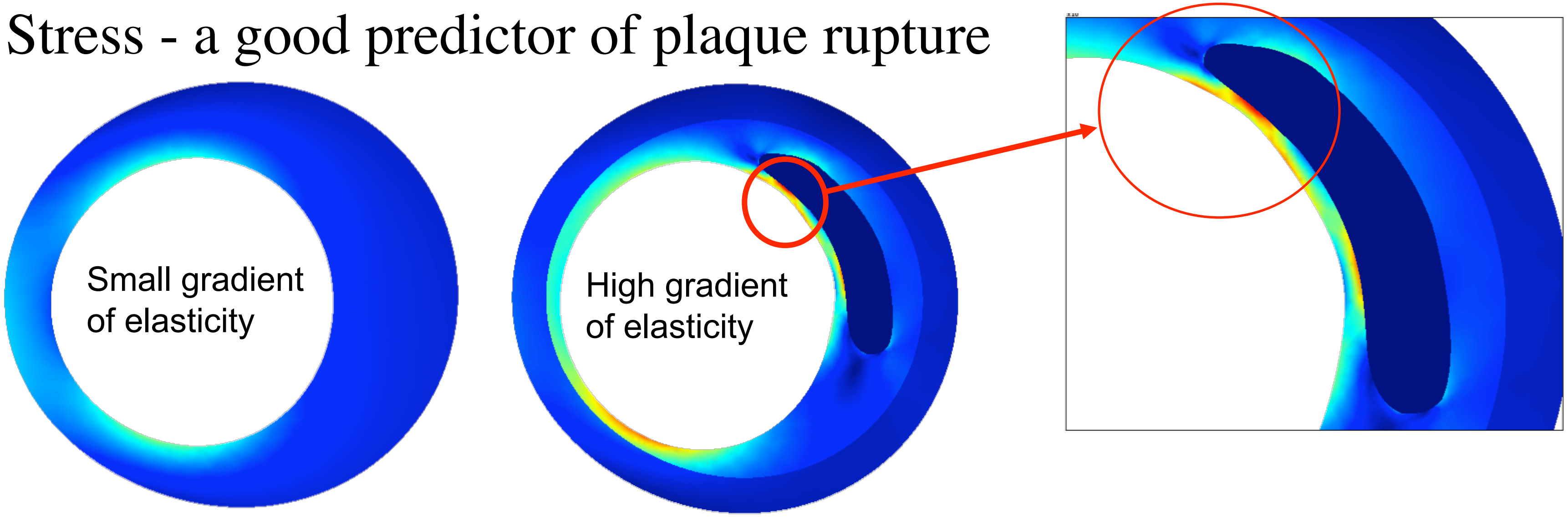
b) Plaque Morphology

c) Mechanical Properties of Plaque Constituents

Le Floc'h, Ohayon et al., IEEE 2009

Why do we need a modulography's tool ?

The knowledge of mechanical properties allows an accurate estimation of Peak Cap Stress - a good predictor of plaque rupture

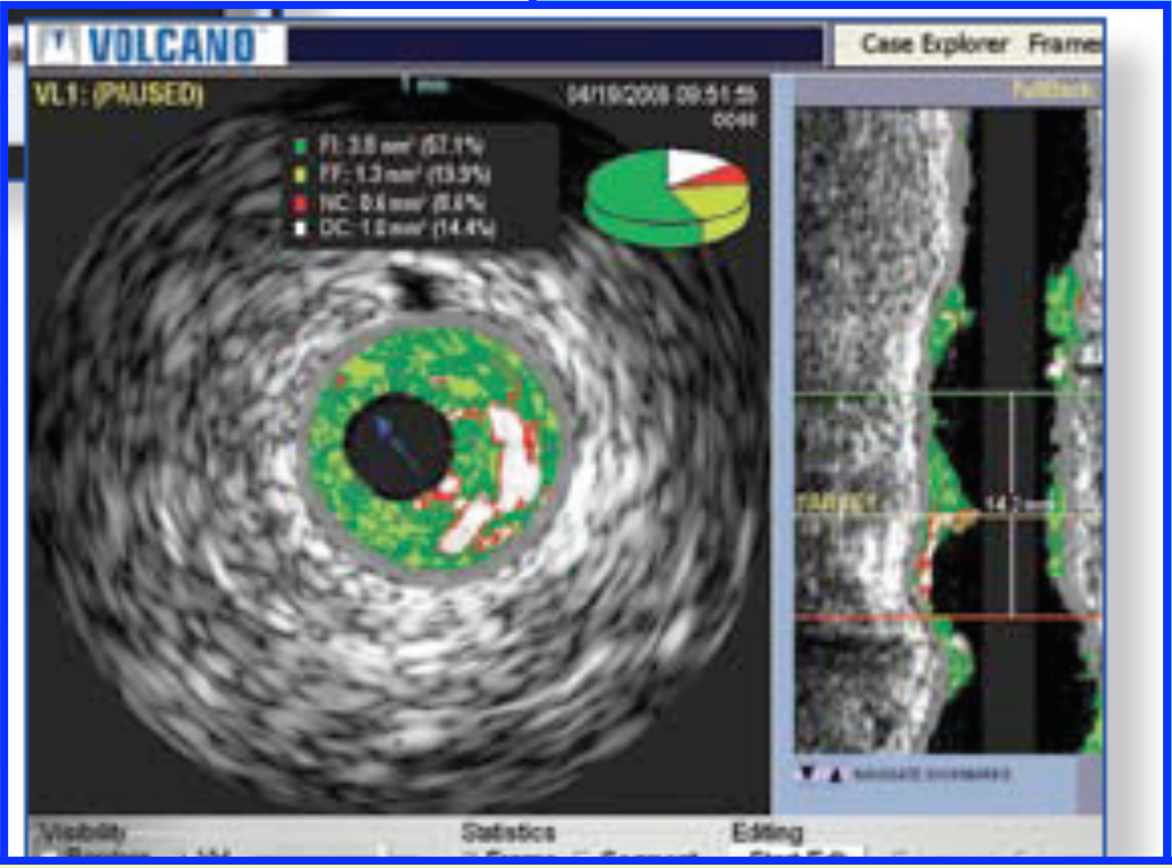


A essential tool also for Pharmacologists :

- Allows to explore non invasively the effects of any drug on Plaque Stability

- **Challenge :** WE NEED A TOOL TO ESTIMATE *IN-VIVO* THE MECHANICAL PROPERTIES

IVUS Virtual Histology



Limitations:

. Parametric Signal analysis – based

(Spectral analysis of ultrasound RF data), don't allow any stiffness quantification

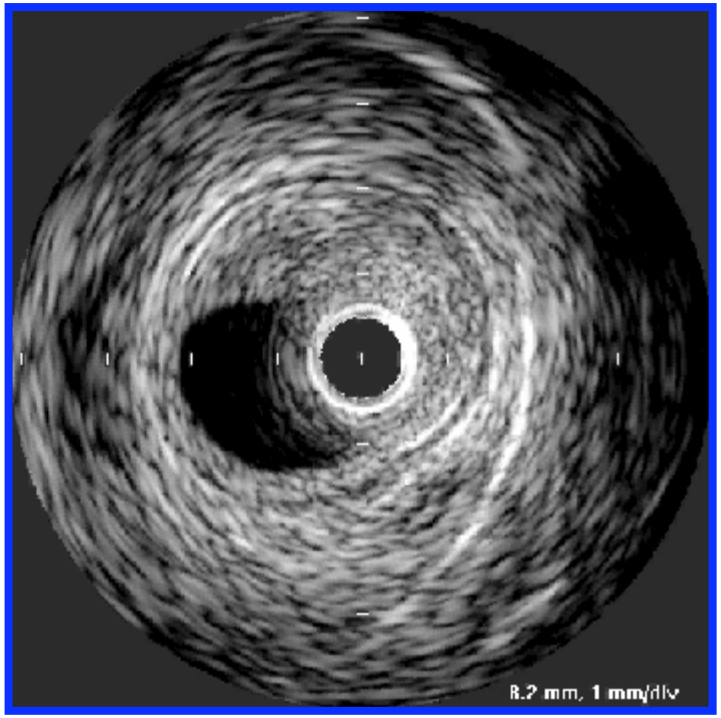
. Don’t satisfy the cardiologists

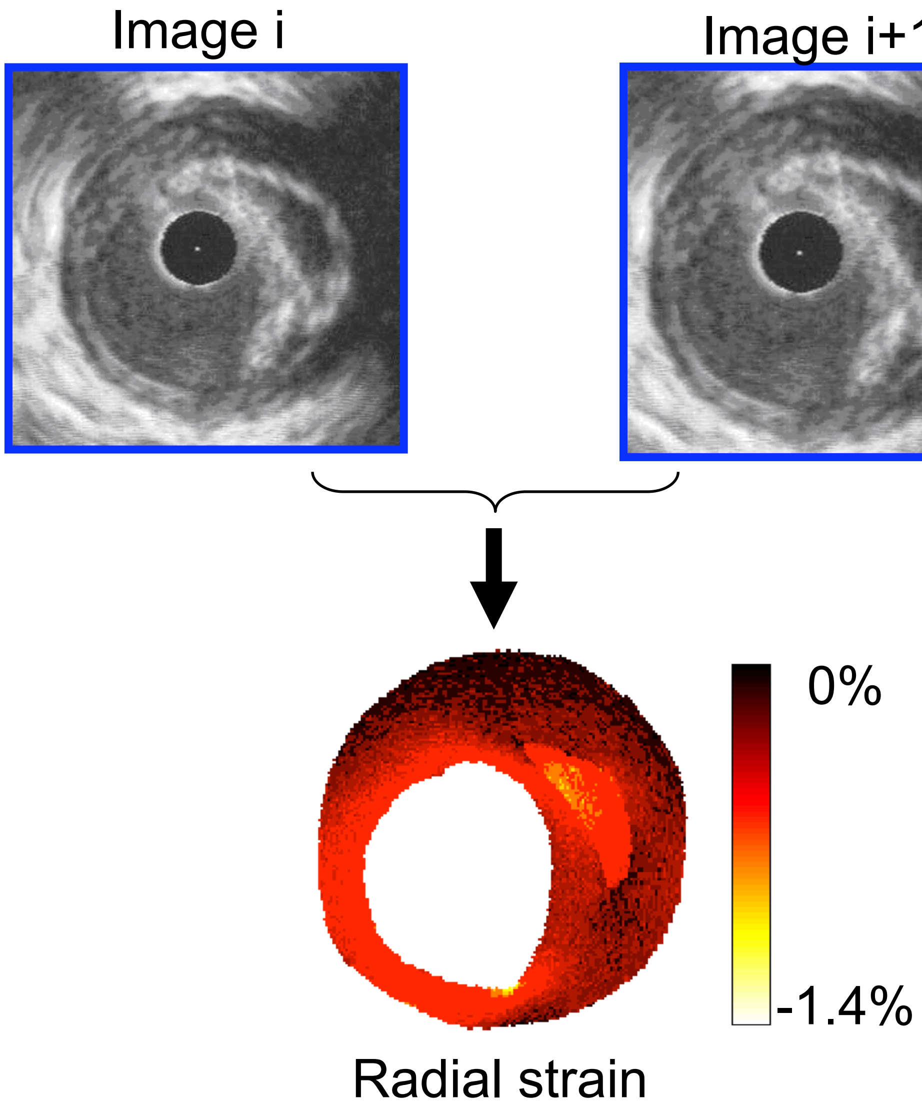
(not accurate enough to highlight cap thickness close to 100 µm)

Starting Point: *Strain Fields (clinical measurement)*

- Estimation of strain using two successive images

(Optical flow approach, Maurice et al., 2004)

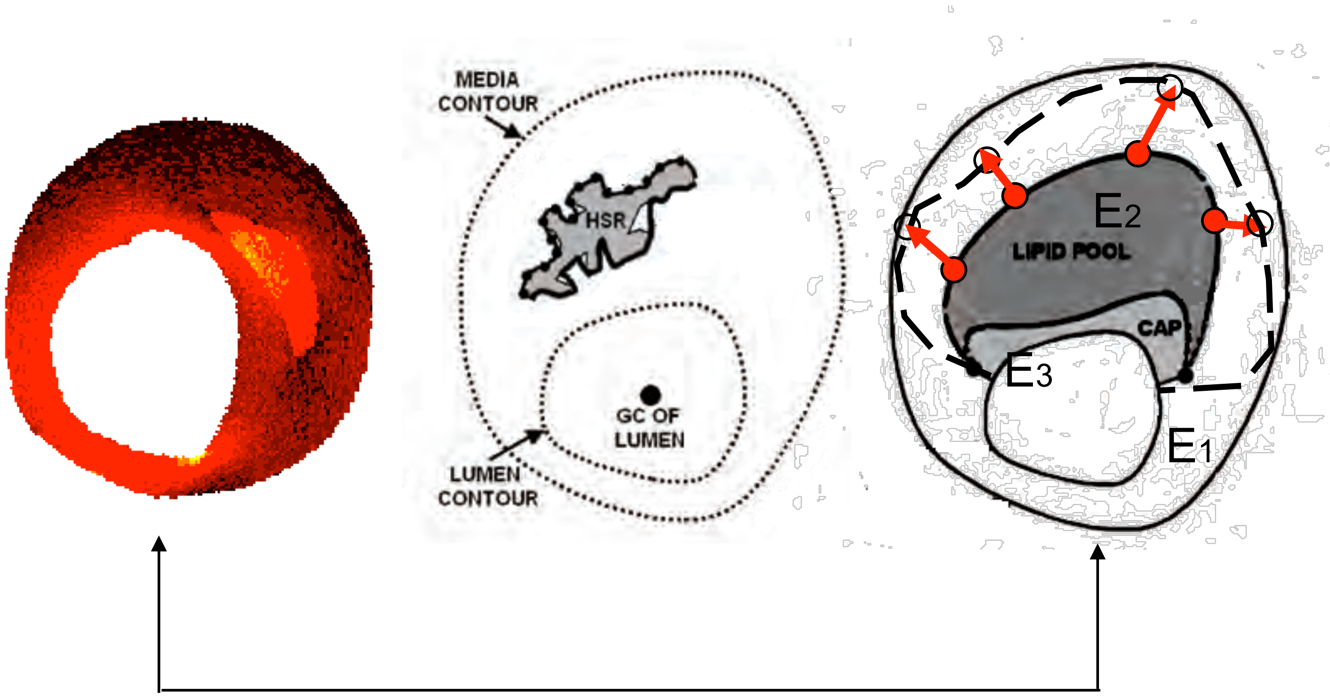




State of the Art in R&D:

Parametric FE Model of Baldewsing (2001-2008)

- Initialization of necrotic core shape using High Strain Regions
- Update of the geometry during the optimization process

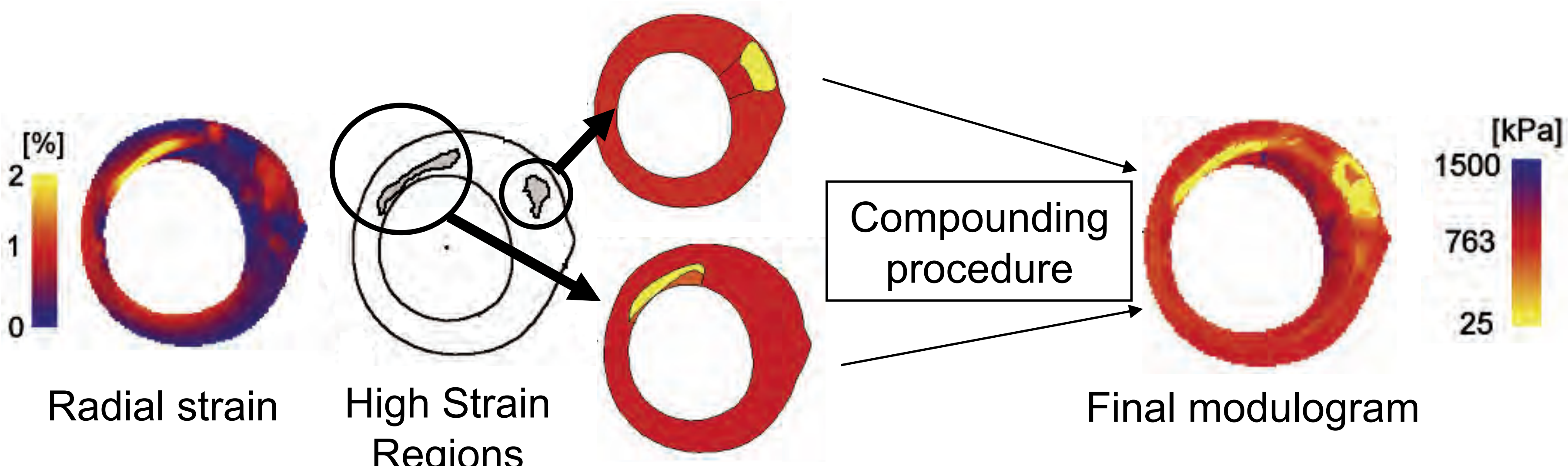


2 unknowns by points

3 unknows for the material properties (Ei)

State of the Art in R&D :

Parametric FE Model of Baldewsing (2001-2008) - Limitations



Radial strain

High Strain Regions

2 independant modulograms

Compounding procedure

Final modulogram

LIMITATIONS

- Complex Plaques (neglects the interaction between inclusions)
- Initialization of the inclusion (Lipid far from the lumen may be omitted)
- Not able to detect calcium inclusions

Parametric FE Model : i-MOD

Mechanical Segmentation Criterion

- Local equilibrium equation $\nabla . \left[\sigma\right] = \vec{0}$

- Linear elasticity, incompressible medium : $\left[\sigma\right] = -p[I] + E(x)\,\frac{2}{3}\left[\varepsilon\right]$

- Substitution of Eq.(2) into Eq. (1) leads to : $\frac{\nabla E}{E} = \frac{3}{2}[\varepsilon]^{-1}\frac{\nabla p}{E} - [\varepsilon]^{-1}\nabla . \left[\varepsilon\right]$

- **Lagrange multiplier p cannot be measured**

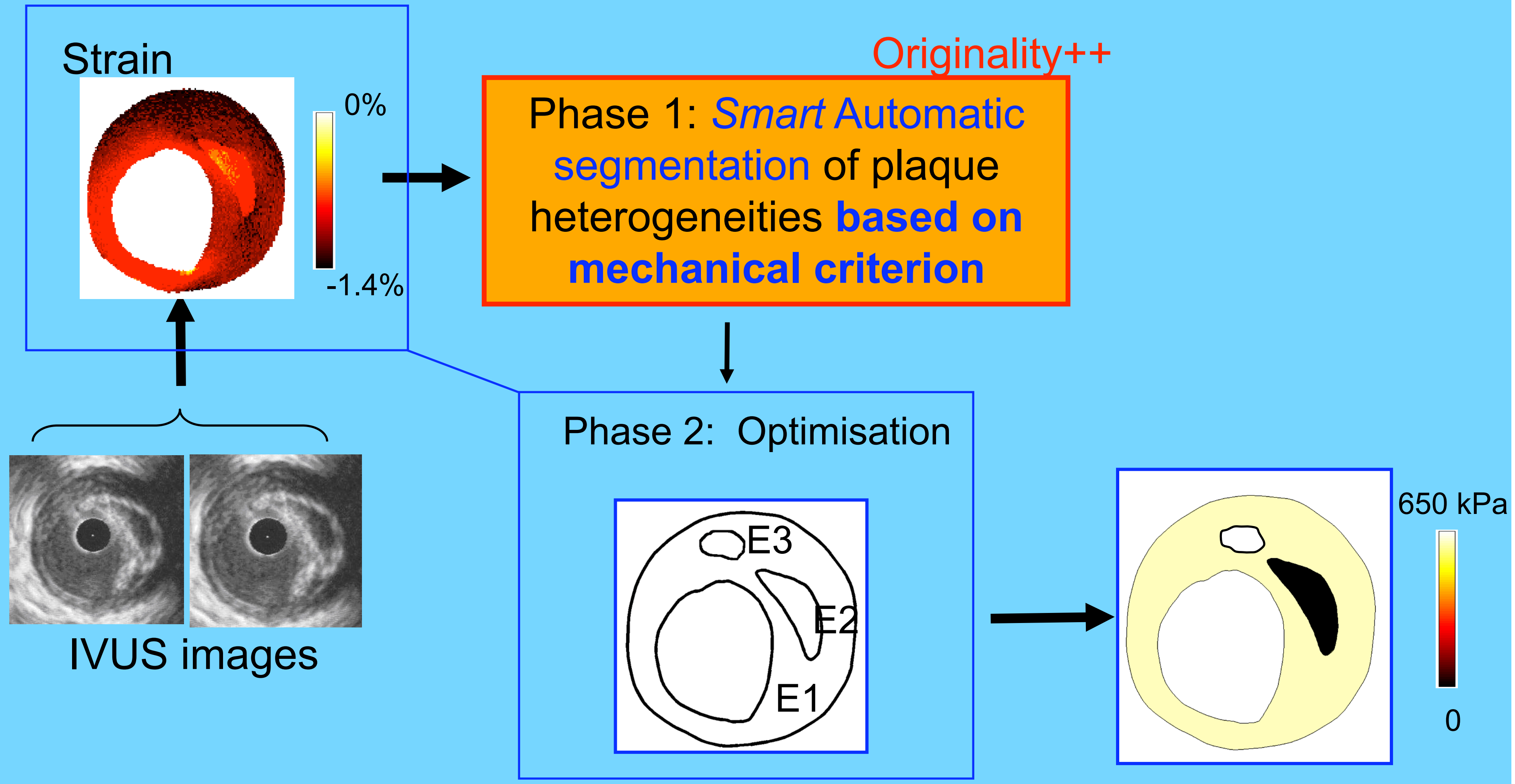
2nd term

- luckily, **the second term** appears to be sensitive enough to highlight the modification of the material properties

Our criterion

$$\boxed{\vec{H} = -\,[\varepsilon]^{-1}\,\nabla . \left[\varepsilon\right]}$$

Our Original Parametric FE Tool « i-MOD »
(imaging MODulography)



Strain

IVUS images

Originality++

Phase 1: *Smart* Automatic segmentation of plaque heterogeneities **based on mechanical criterion**

Phase 2: Optimisation

++ Approach Based on Continuum Mechanics

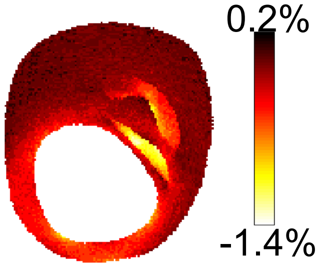
Parametric FE Model : i-MOD

Iterative Watershed Segmentation Procedure

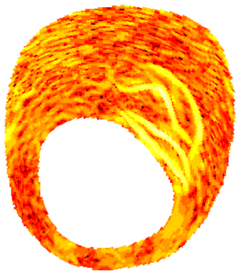
Images

IVUS (Coronary)

MRI (Carotid)



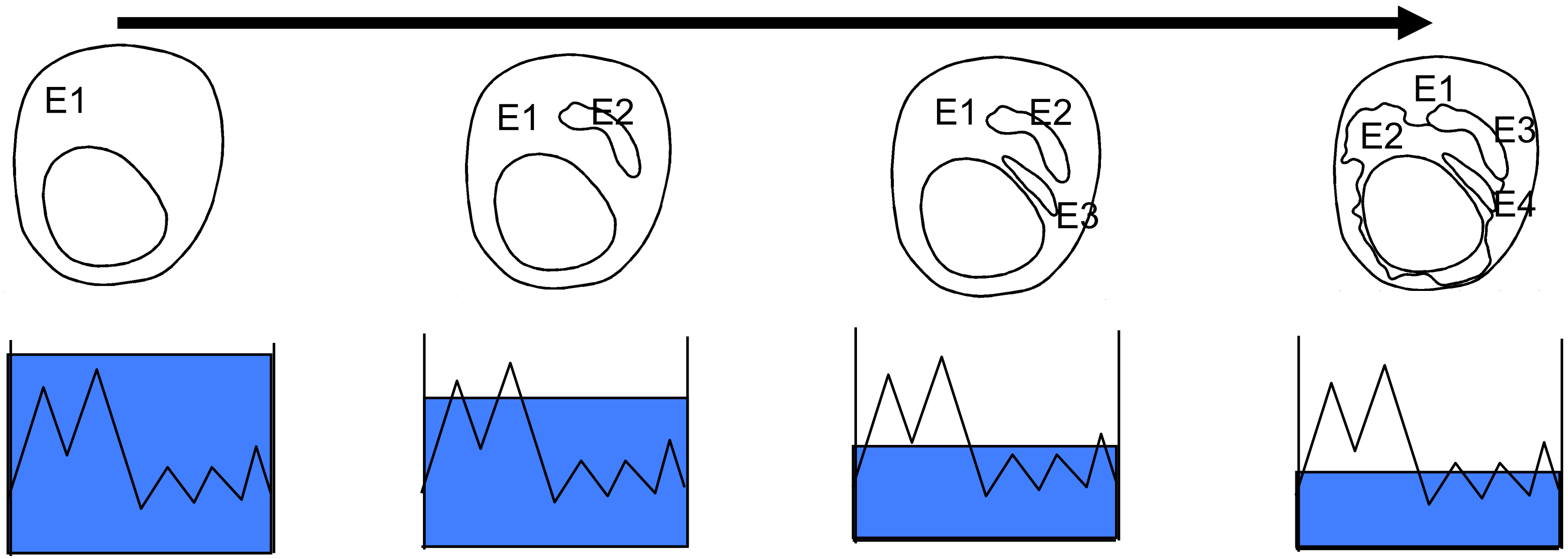
Radial strain



Criterion

Iterative watershed segmentation

Iterative Watershed segmentation

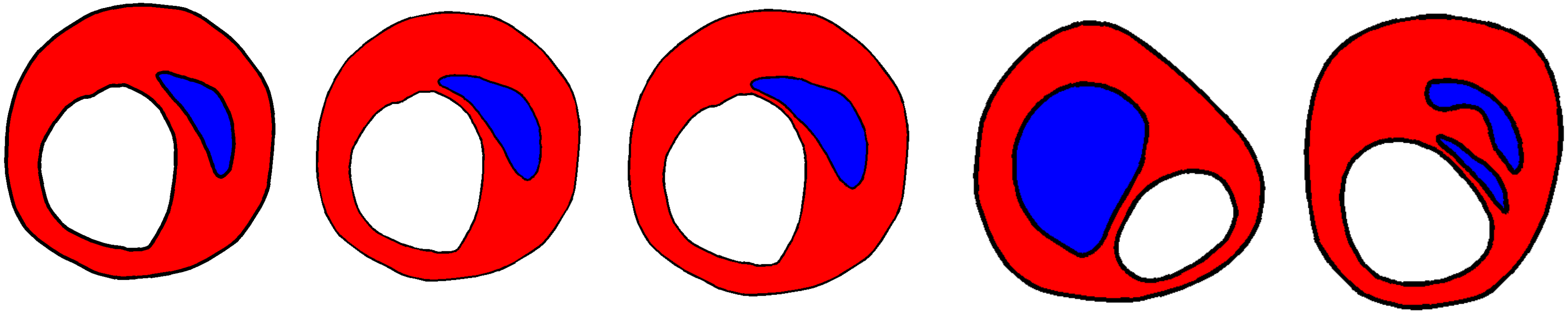


Determination of Ei with classical optimisation method

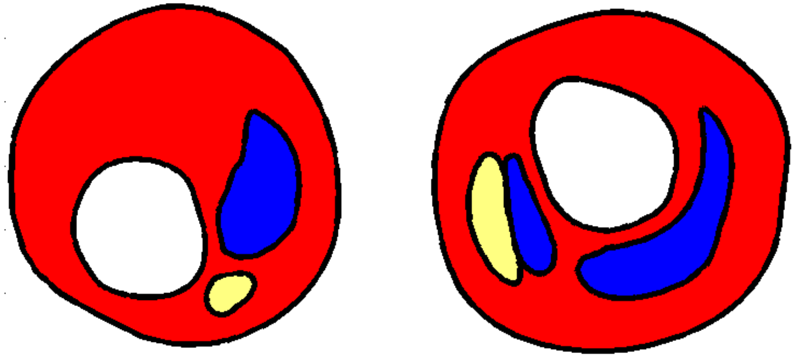
Successful Validation of i-MOD: Theoretical Framework

Plaque Morphologies and Mechanical Properties

- With necrotic cores



- With necrotic cores & calcium



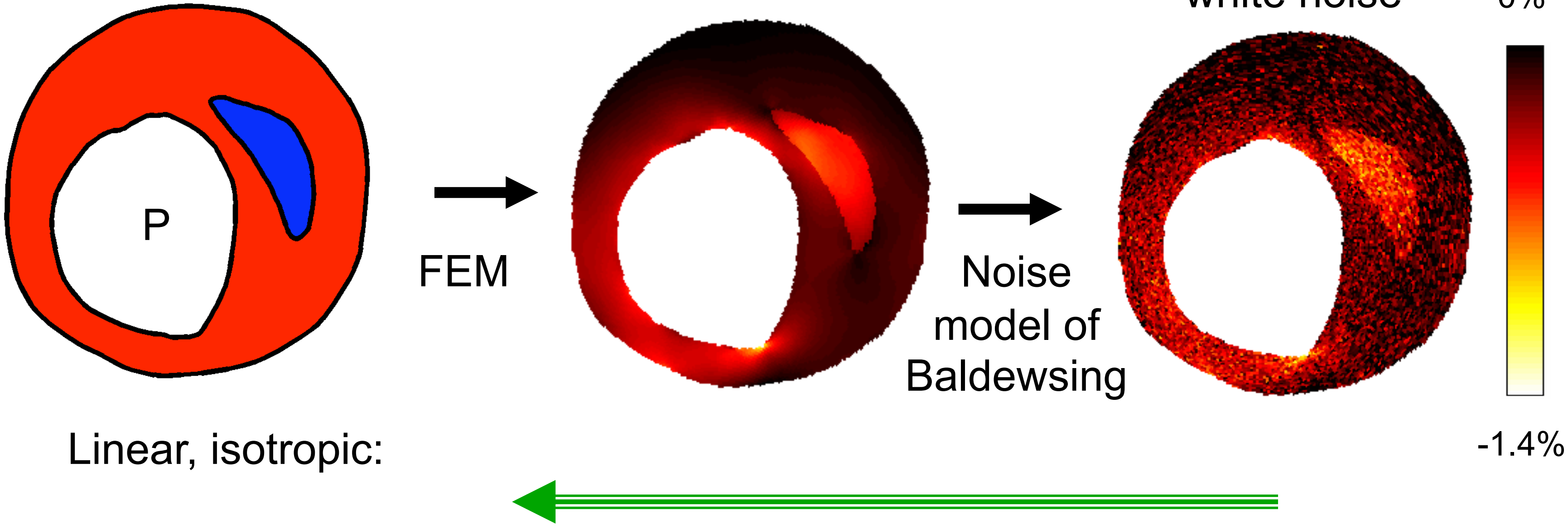
🟨 **Calcium, E = 5,000 kPa**

🟦 **Lipid, E = 10 kPa**

🟥 **Fibrosis, E = 600 kPa**

Successful Validation of i-MOD : Theoretical Framework

Forward and Inverse Problem: FEM Simulations (Strain)



Radial strain,
no noise

Radial strain,
white noise

FEM

Noise
model of
Baldewsing

Linear, isotropic:

Solving the Inverse Problem

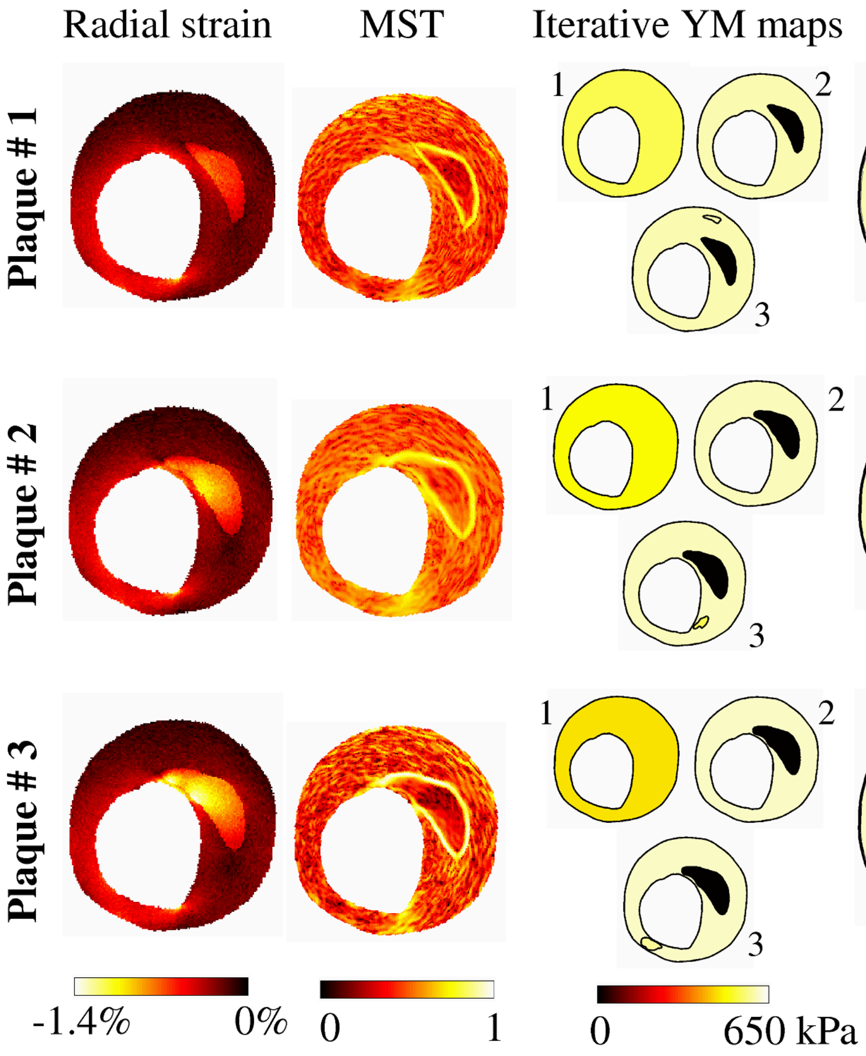
Poisson’s ratios $\nu = 0.49$

E- fibrosis = 600 kPa

E-lipid = 10 kPa

i-MOD A Promising Tool for Vulnerable Plaque Detection

Accurate detection of cap thickness



Plaque # 1

■ 11.1 kPa *(10 kPa)*
🟨 601 ± 0.1 kPa *(600 kPa)*

$\text{Cap}_{\text{thick}} = 376\ \mu\text{m}$ *(369)*
$\text{Core}_{\text{area}} = 1.59\ \text{mm}^2$ *(1.60)*

Plaque # 2

■ 11.8 kPa *(10 kPa)*
🟨 605 ± 8 kPa *(600 kPa)*

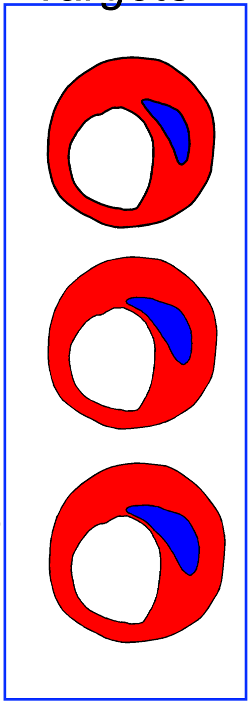
$\text{Cap}_{\text{thick}} = 147\ \mu\text{m}$ *(174)*
$\text{Core}_{\text{area}} = 2.30\ \text{mm}^2$ *(2.29)*

Plaque # 3

■ 10.4 kPa *(10 kPa)*
🟨 614 ± 4 kPa *(600 kPa)*

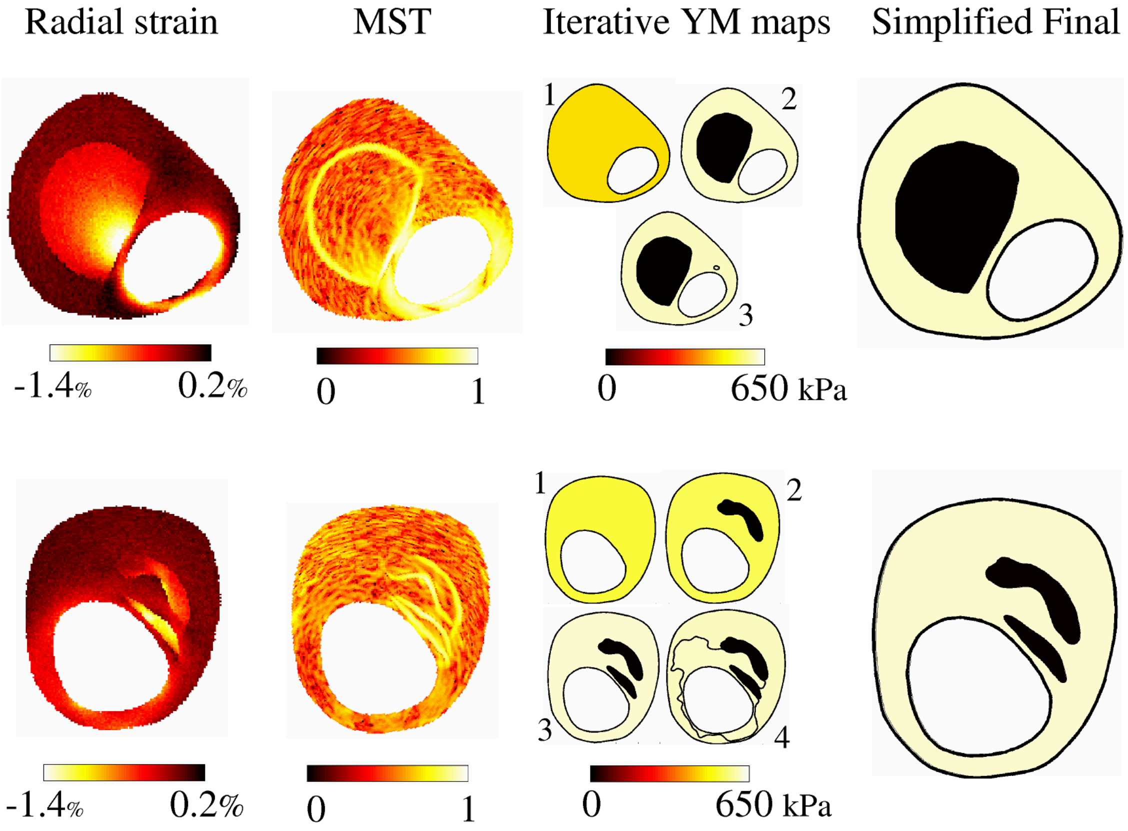
$\text{Cap}_{\text{thick}} = 92\ \mu\text{m}$ *(103)*
$\text{Core}_{\text{area}} = 2.38\ \text{mm}^2$ *(2.37)*

Targets

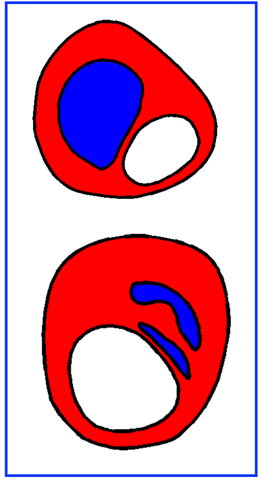


i-MOD A Promising Tool for Vulnerable Plaque Detection

Accurate detection of intra-plaque structure



Targets



■ 11.5 kPa
□ 611 ± 0.1 kPa

$\text{Cap}_{\text{thick}}$ = 201 µm *(204)*
$\text{Core}_{\text{area}}$ = 5.56 mm² *(5.56)*

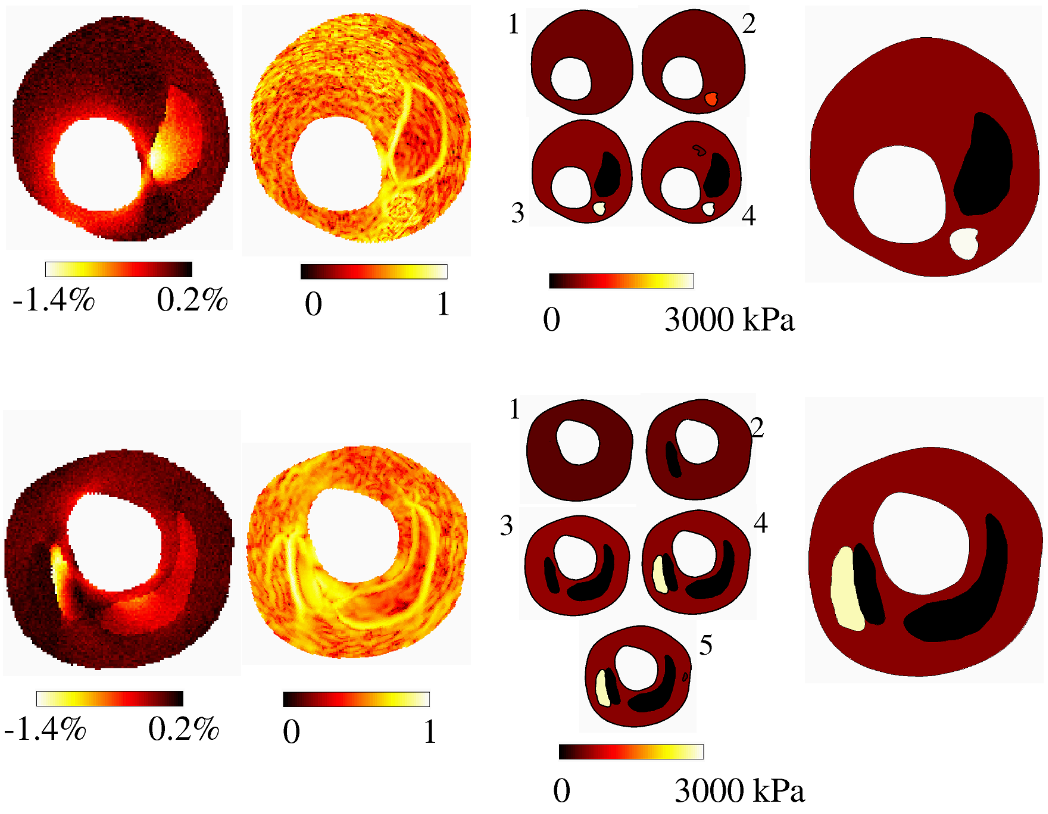
■ 15.6 ± 0.1 kPa *(10 kPa)*
□ 612 ± 1 kPa *(600 kPa)*

$\text{Cap}_{\text{thick}}$ = 101 µm *(147)*
$\text{Core}_{\text{area1}}$= 0.56 mm² *(0.51)*
$\text{Core}_{\text{area2}}$= 1.34 mm² *(1.20)*

i-MOD A Promising Tool for Vulnerable Plaque Detection

Accurate detection of calcium inclusions

Radial strain MST Iterative YM maps Simplified Final YM maps



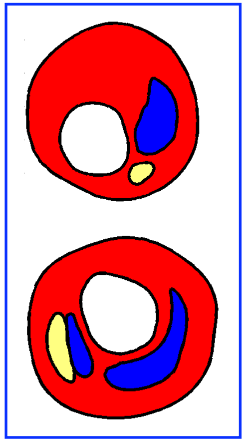
■ 15.0 kPa
🟥 608 ± 14 kPa
□ 2968 kPa

$\text{Cap}_{\text{thick}} = 214\ \mu\text{m}$ *(199)*
$\text{Core}_{\text{area}} = 2.07\ \text{mm}^2$ *(2.00)*
$\text{Cal}_{\text{area}} = 0.353\ \text{mm}^2$ *(0.356)*

■ 17.1 ± 0.7 kPa *(10 kPa)*
🟥 610 ± 10 kPa *(600 kPa)*
□ 2784 kPa *(5000 kPa)*

$\text{Cap}_{\text{thick}} = 184\ \mu\text{m}$ *(214)*
$\text{Core}_{\text{area1}} = 2.33\ \text{mm}^2$ *(2.15)*
$\text{Core}_{\text{area2}} = 0.761\ \text{mm}^2$ *(0.701)*
$\text{Cal}_{\text{area}} = 0.890\ \text{mm}^2$ *(0.891)*

Targets



Next Research Program

- Phase 1 : ***in vitro* study** : **PVA Phantoms Study**
  - * Invasive Ultrasound Modulography
  - * Non Invasive MRI Modulography

- Phase 2 : ***in vivo* study : Animal Study**
  - * Invasive *in vivo* Ultrasound Carotid Modulography
  - * Non Invasive *in vivo* Ultrasound Carotid Modulography

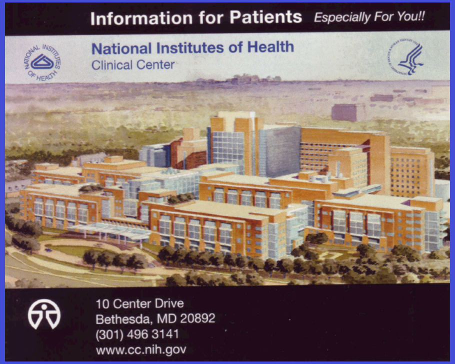
- Phase 3 : ***in vivo* study : Clinical Study**
  - * Patients with Coronary Disease (Invasive Ultrasound)
  - * Patients with Carotid Disease (Non Invasive Ultrasound)
  - * Patients with Carotid Disease (Non Invasive MRI)*

Collaborators

UNIVERSITE JOSEPH FOURIER
SCIENCES TECHNOLOGIE MEDECINE

cnrs

TIMC
DynaCell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National Institutes of Health
Clinical Center

10 Center Drive
Bethesda, MD 20892
(301) 496 3141
www.cc.nih.gov

LBUM

GEMM
Group of Structural Mechanics
and Materials Modelling

France

Gérard Finet, MD, PhD

Philippe Tracqui, PhD

Simon Le Floc'h, PhD
Patrick Clarysse, PhD
Pierre Croisille, MD, PhD

Creatis

Nicolas Mesnier, PhD Std

USA

Roderic I. Pettigrew, MD

Ahmed M. Gharib, MD

Julie Heroux, MSc, PhD Std

CANADA

Guy Cloutier, PhD

Roch Maurice, PhD

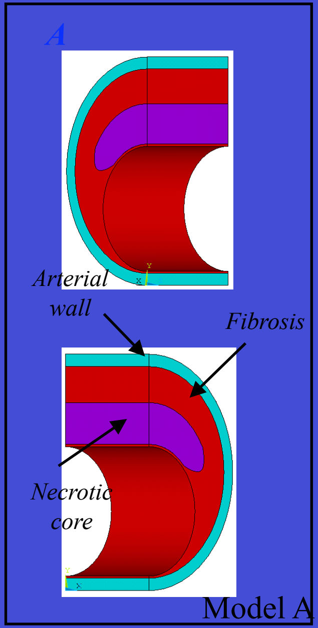
ESPAGNE

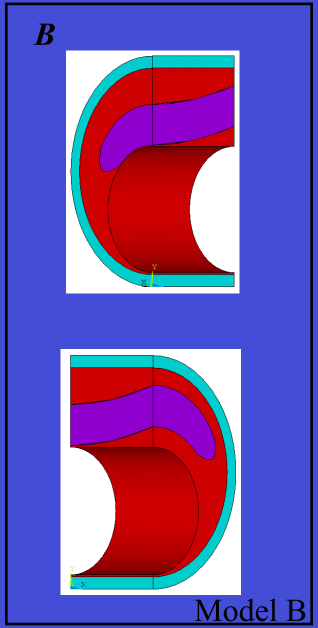
Manuel Doblare, PhD

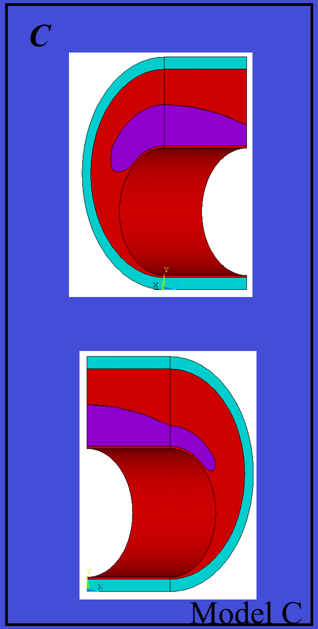
Miguel-Angel Martinez, PhD

Estefania Pena, PhD

Thank you


A
Arterial wall
Fibrosis
Necrotic core
Model A


B
Model B


C
Model C