Pathologic Insights into Vulnerable Plaque

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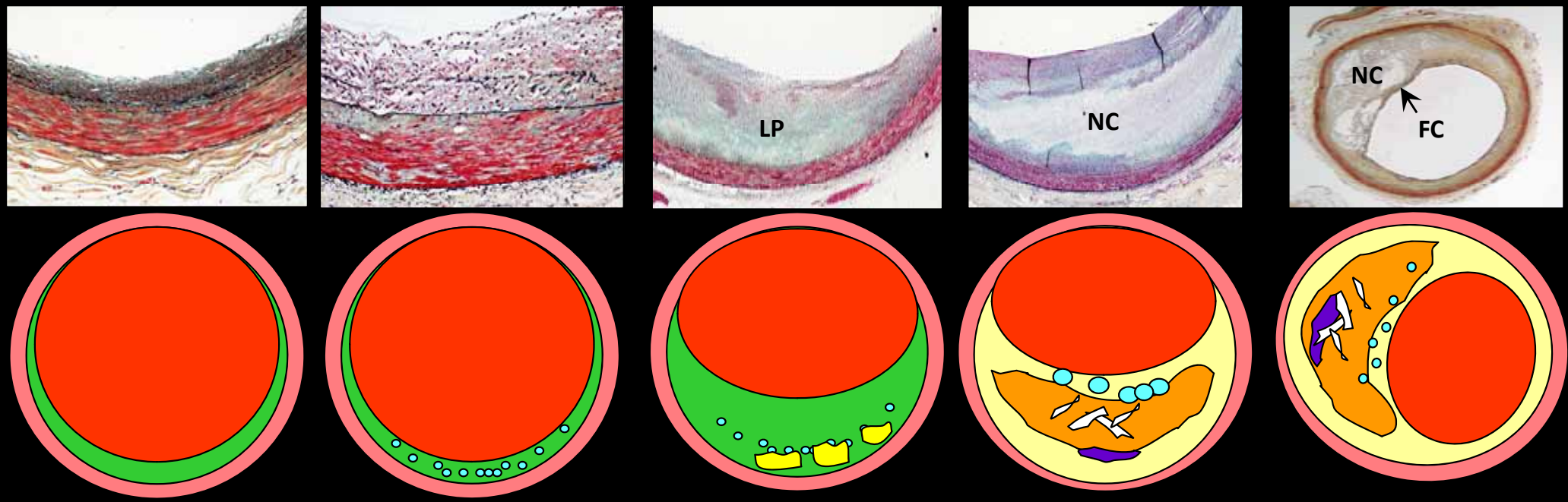
Tokai Univ.

Development of Human Coronary Atherosclerosis

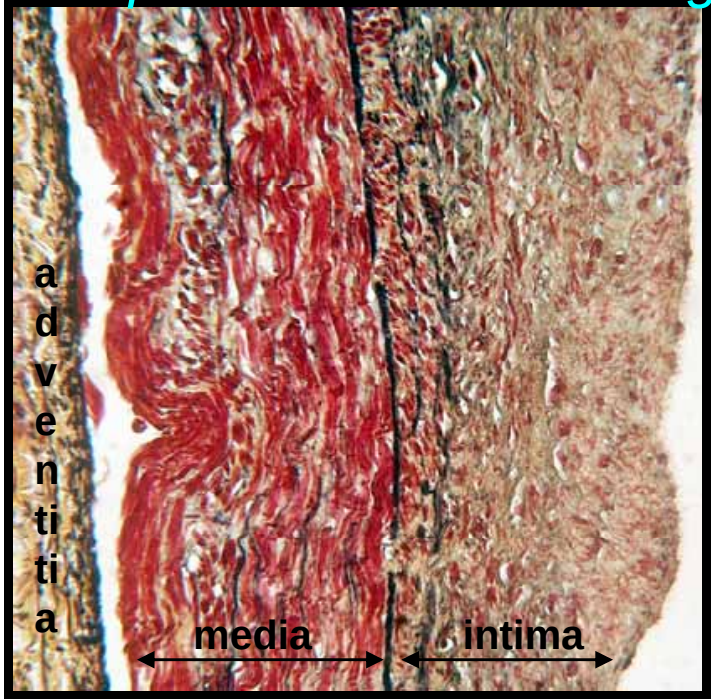


- Smooth muscle cells
- Macrophage foam cells
- Extracellular lipid
- Cholesterol clefts
- Necrotic core
- Calcified plaque
- Hemorrhage
- Thrombus
- Healed thrombus
- Collagen

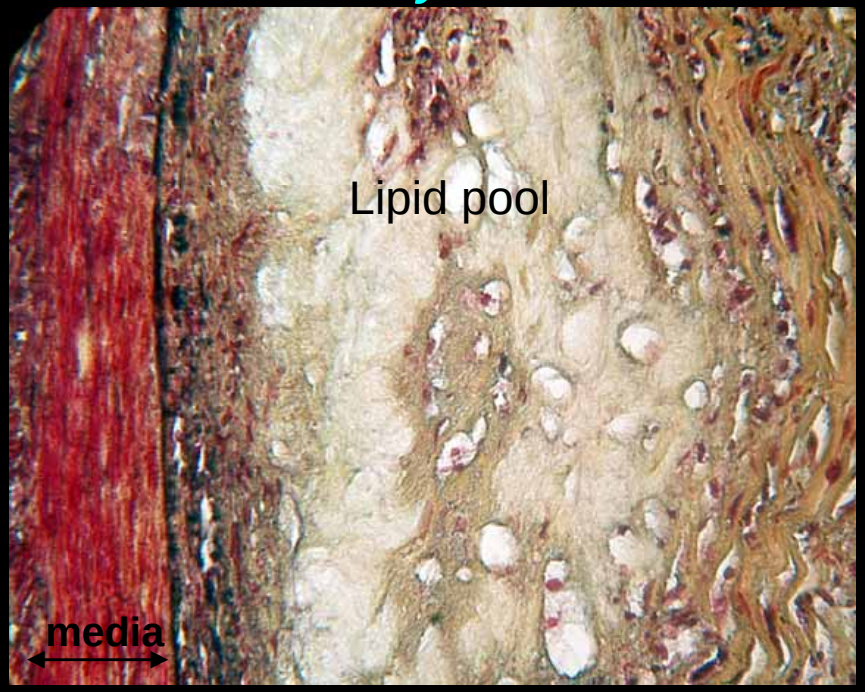
FC = fibrous cap
LP = lipid pool
NC = necrotic core

Conversion to Atherosclerosis

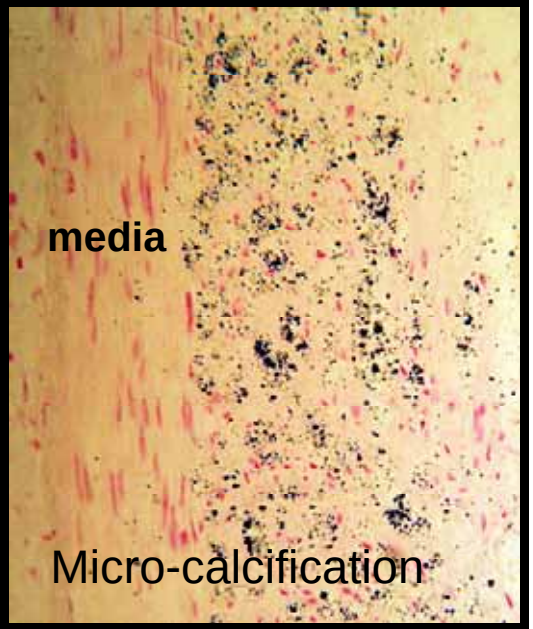
Adaptive intimal thickening → *Early atherosclerosis*



Adaptive IT



PIT



Von Kossa stain

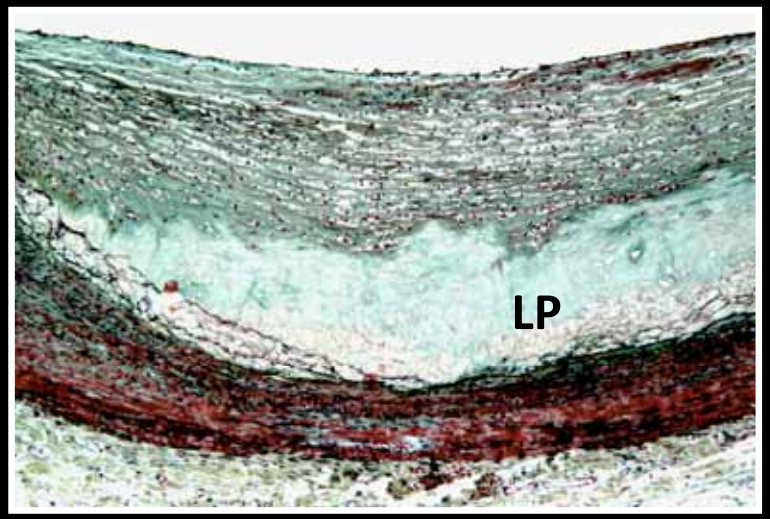
Intimal thickening (IT) → Pathologic intimal thickening (PIT)

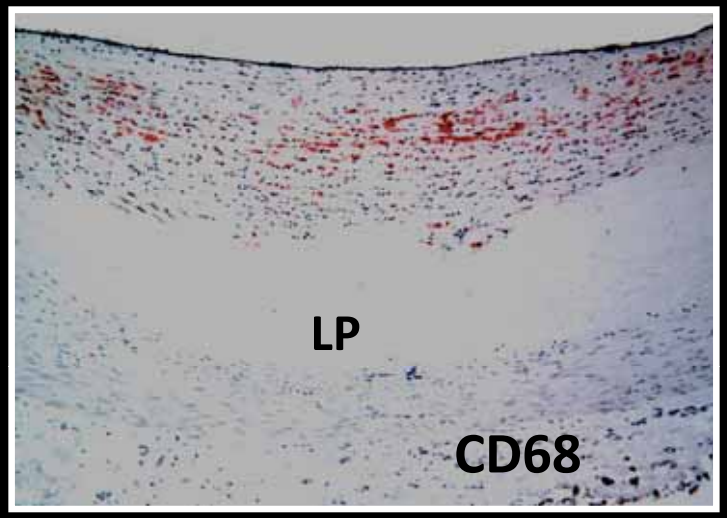
Smooth muscle cells + proteoglycans

Smooth muscle cell, apoptosis + lipid pool + proteoglycans + microcalcification

Pathologic Intimal Thickening to Fibroatheroma

PIT





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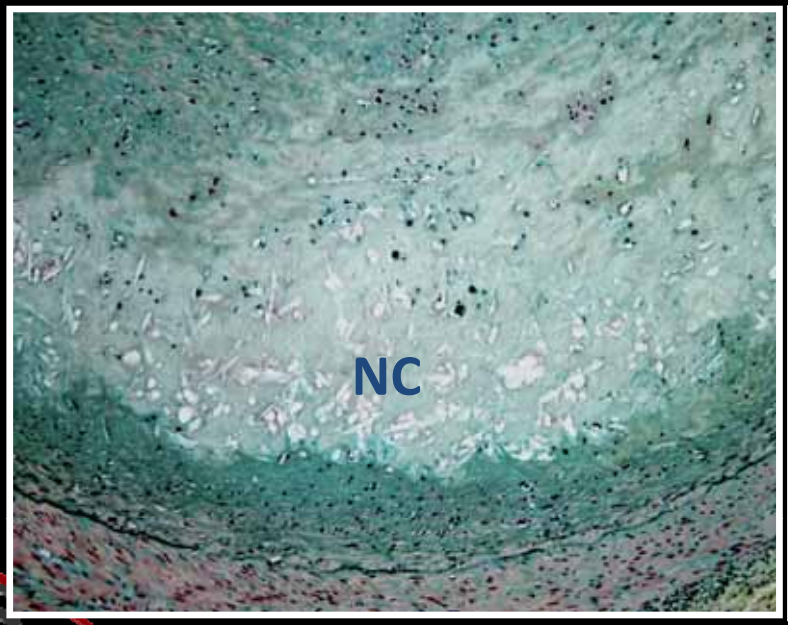
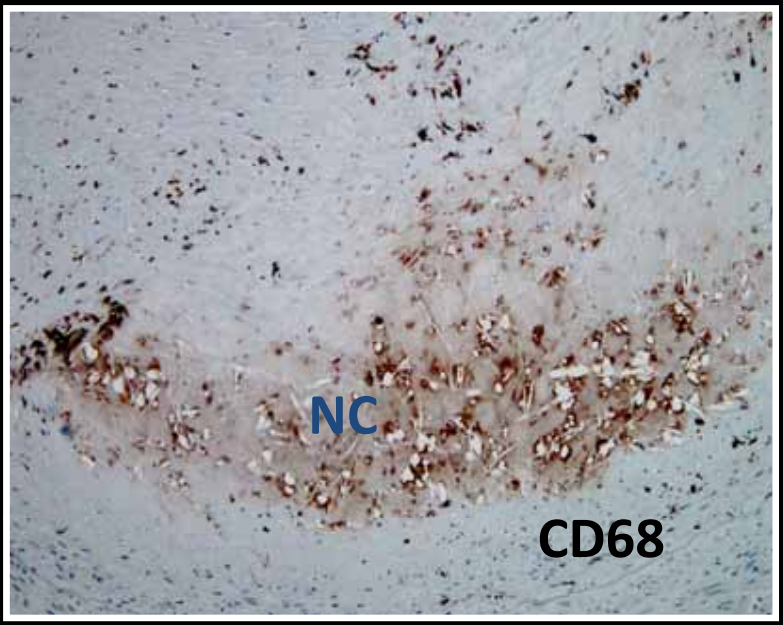
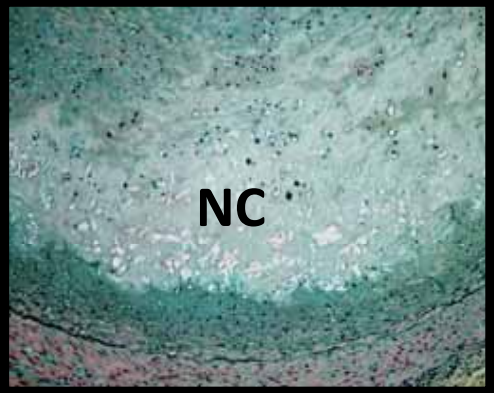


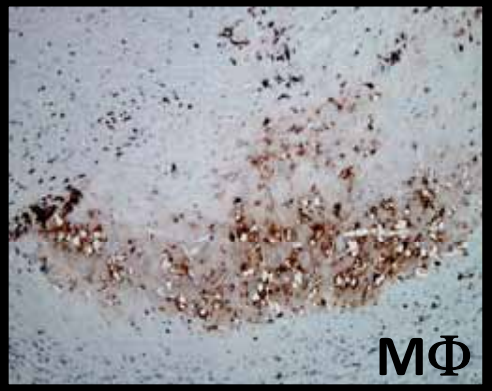


Abbreviations: LP = lipid pool; NC = necrotic core

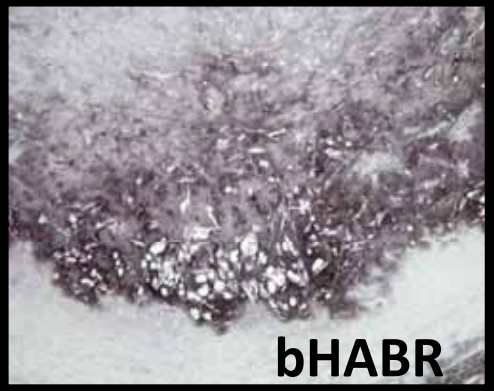
Differential Expression of Hyaluronan and Versican in the Developing Necrotic Core

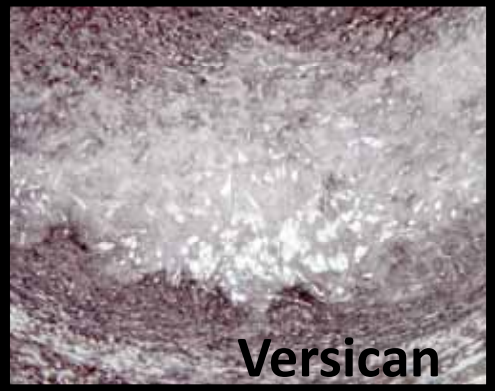
Fibroatheroma 'Early' Necrosis



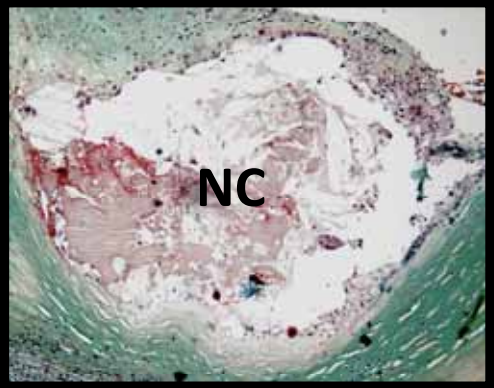


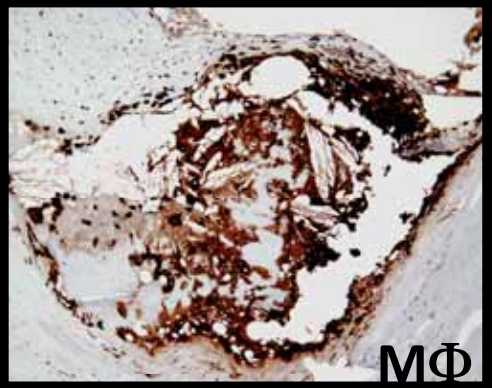
Presence of Extracelluar Matrix



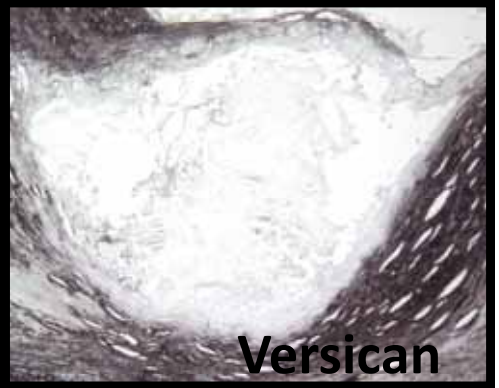


Thin-cap Fibroatheroma



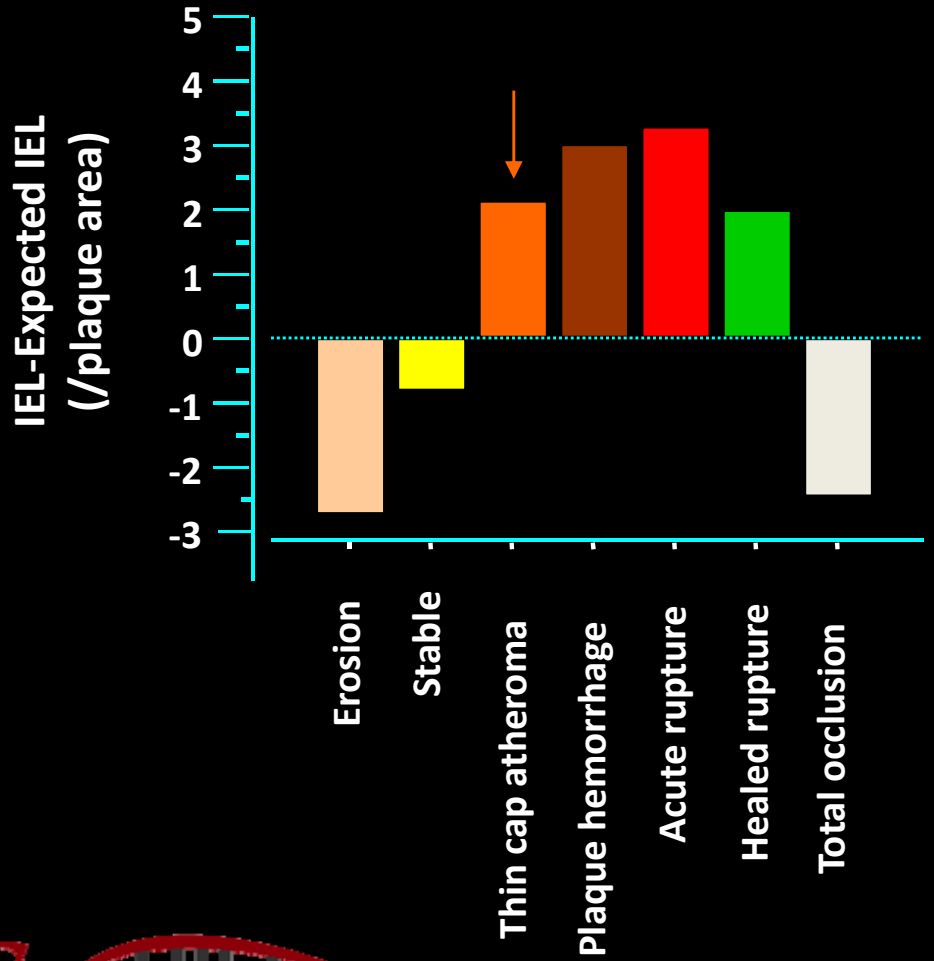


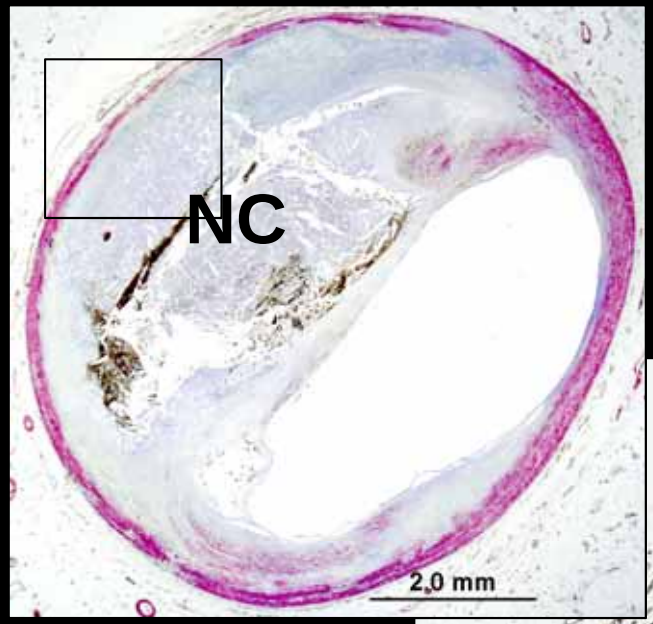
Loss of Matrix



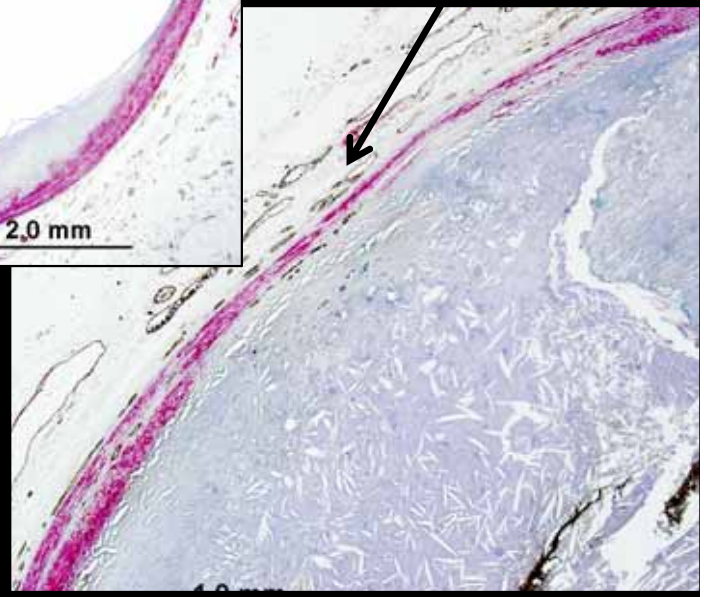
Remodeling in Varying Coronary Lesion Morphologies

A.

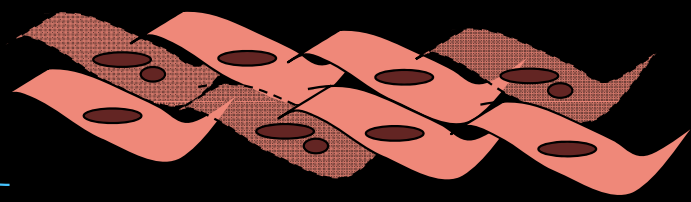




Medial SMC loss



Medial SMC apoptosis

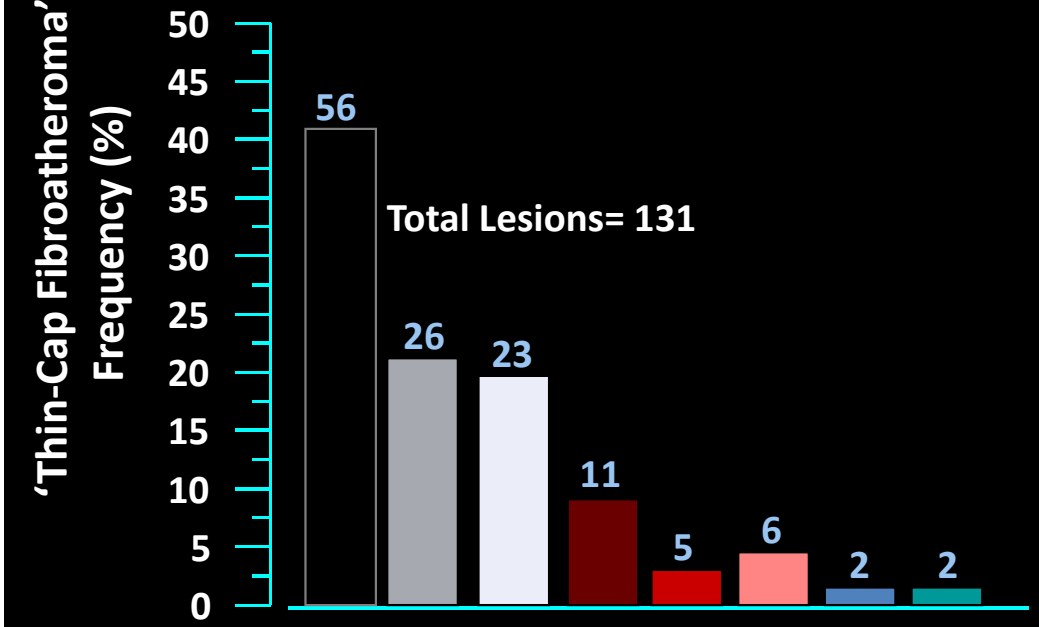


Morphometric assessment of plaques from 72 pts with SCD

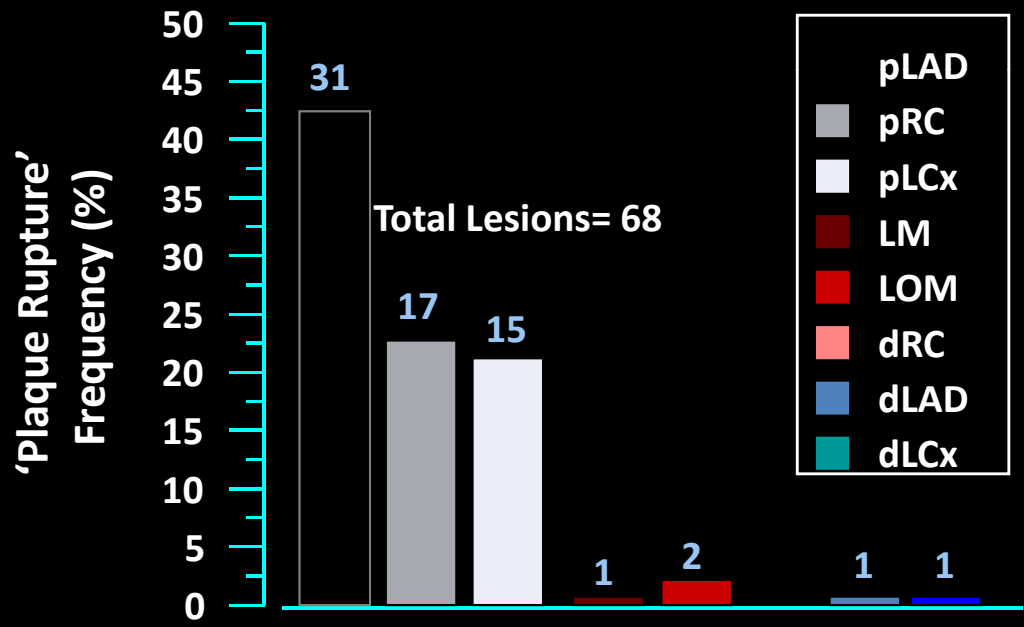
Plaque Type	IEL mm^2	Stenosis %	Necrotic core %	Macrophage (%CD68)
Pathologic intimal thickening (n=125)	6.5+4.0	43.0±16.1	0.1±0.4	0.1±0.2
Fibroatheroma (n=262)	9.2±4.9	64.5±17.8	11.2±13.2	1.1±1.5
Thin-cap Fibro-atheroma (n=46)	12.8±7.9	67.0±15.5	21.6±23.7	2.0±1.9
Plaque rupture (n=55)	13.2±6.4	79.8±14.4	29.0±19.0	5.3±5.4
P value	<0.0001**	<0.0001*	<0.0001***	<0.0001*

Frequency and Location of Unstable Lesions in the Coronary Circulation

Thin-cap Fibroatheroma

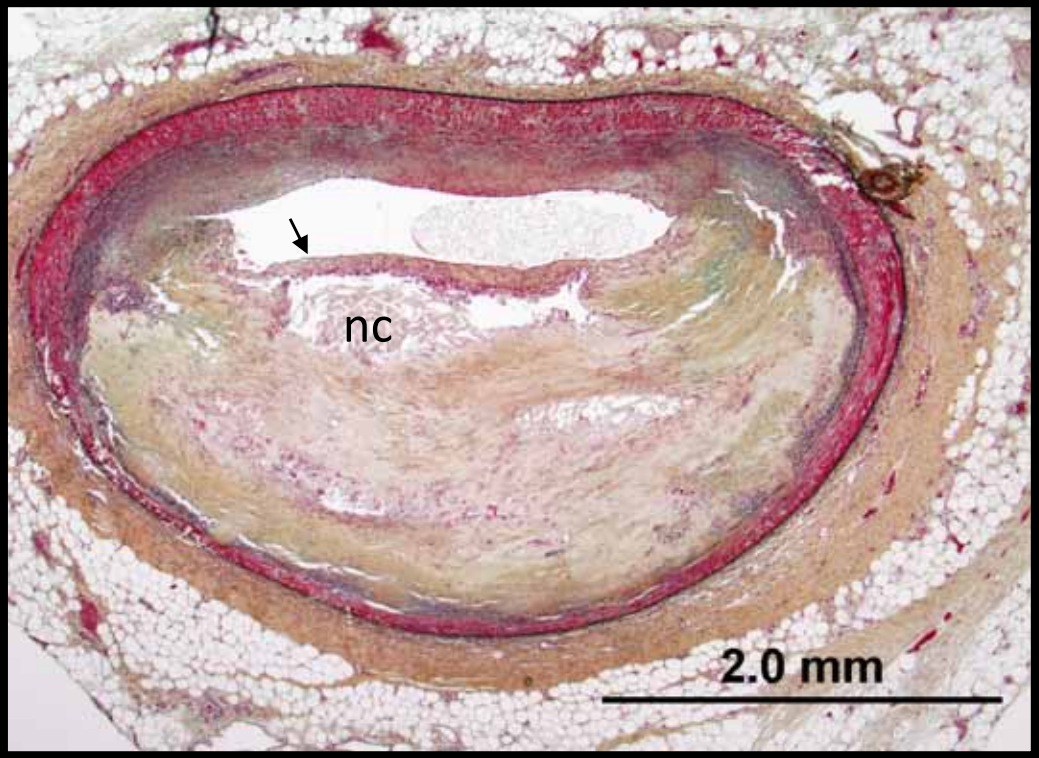


Acute Plaque Rupture



Kolodgie F, et al. Current Opinion in Cardiology 2001;16:285

Do thin cap fibroatheromas (vulnerable plaques) go on to Rupture?



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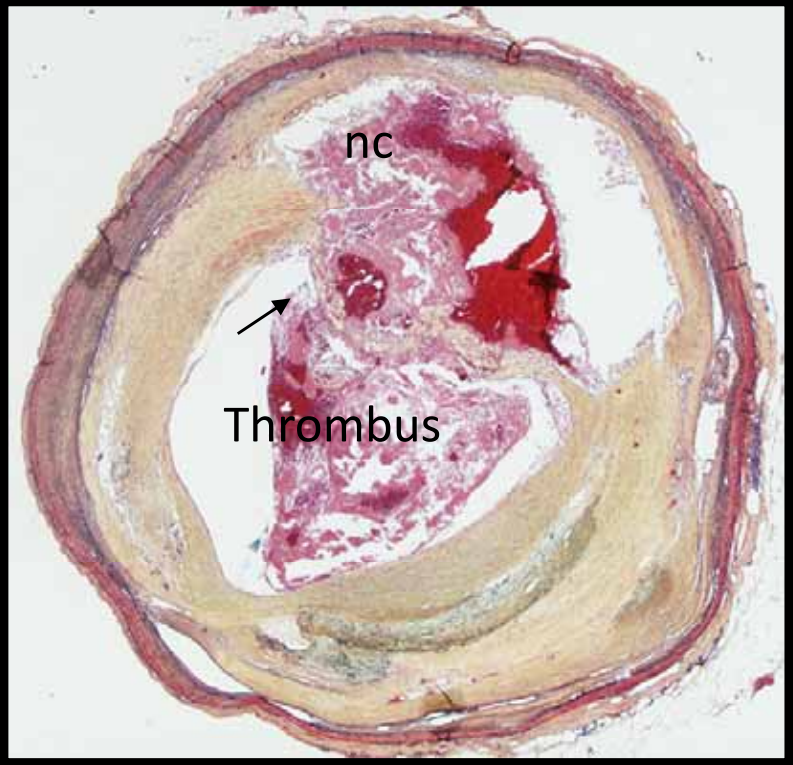


Thin cap fibroatheroma

- Necrotic core
- Thin fibrous cap (< 65 μm)
- Cap infiltrated by macrophages and lymphocytes
- Cap composition – type 1 collagen with few or absent smooth muscle cells

Plaque Rupture

- Discontinuous fibrous cap
- Underlying necrotic core
- Luminal thrombus

What can you detect now?

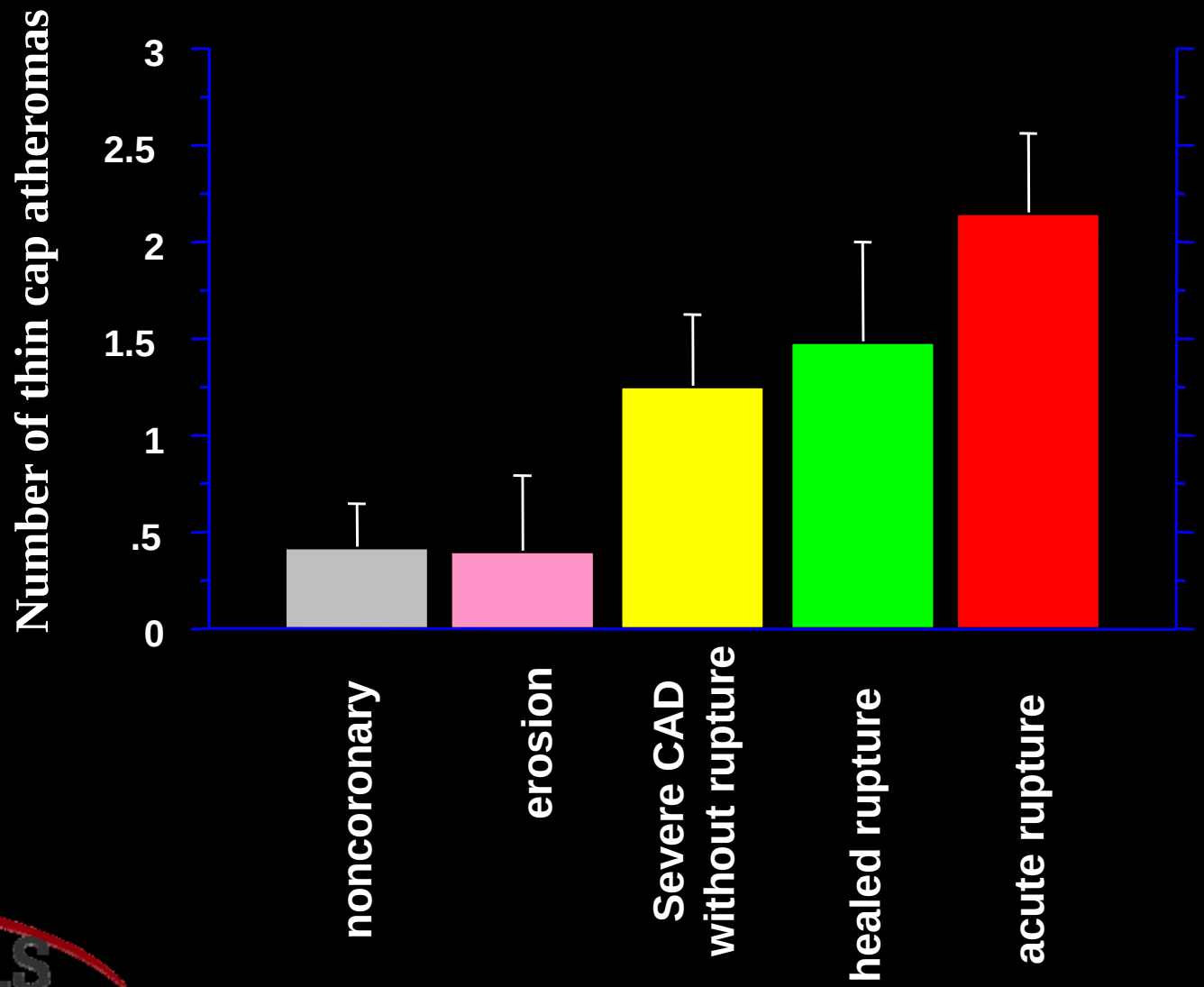
- Plaque detection → Definitely!
- Plaque size → Definitely!
- Plaque type → Probably
- Necrotic core size → Probably
- Fibrous cap thickness → Possibly

OK…

So, detect the “thin-fibrous cap” in the proximal epicardial coronary arteries and treat them!!!

Is it that simple?

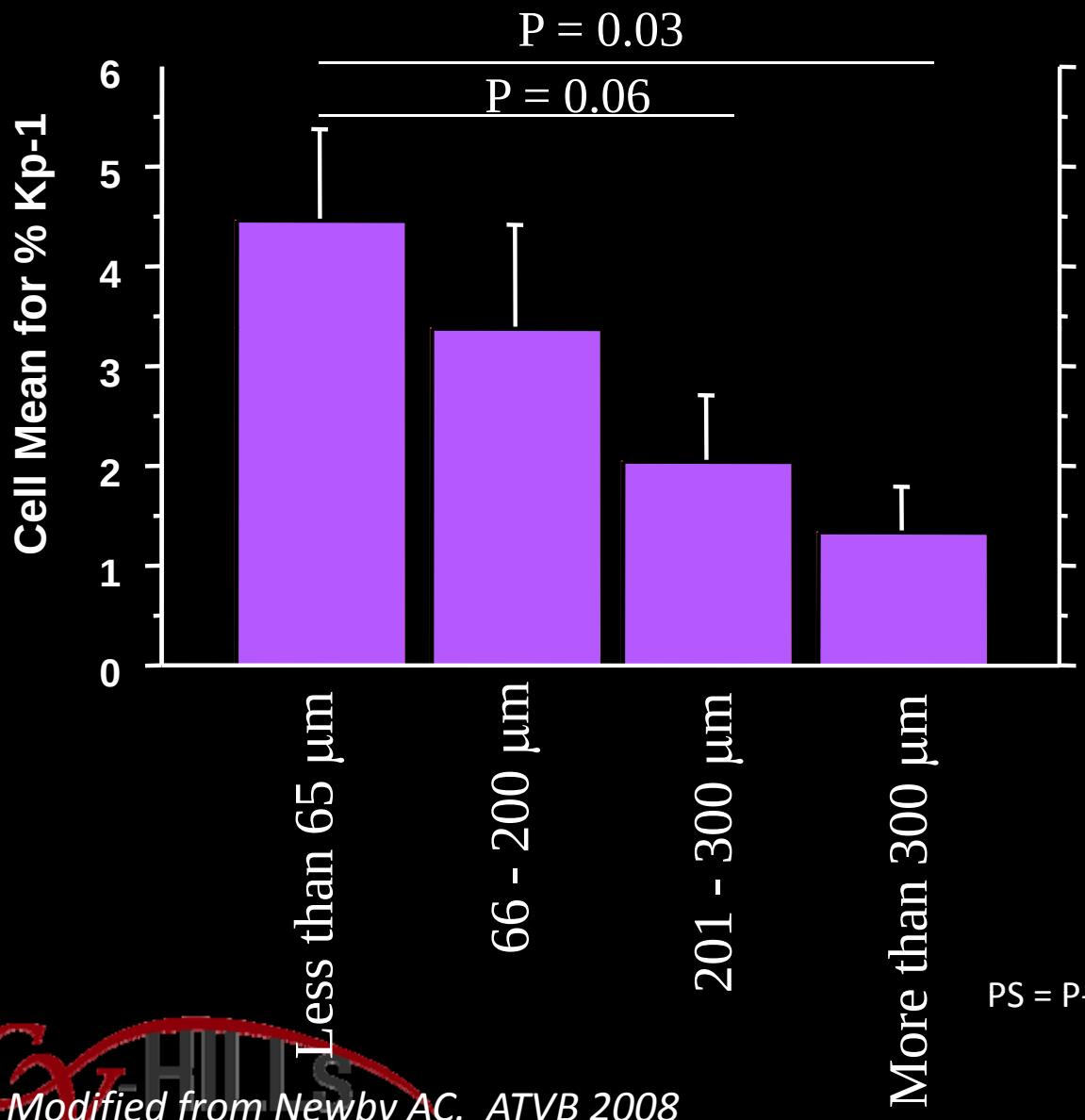
Frequency of TCFAs in various causes of death

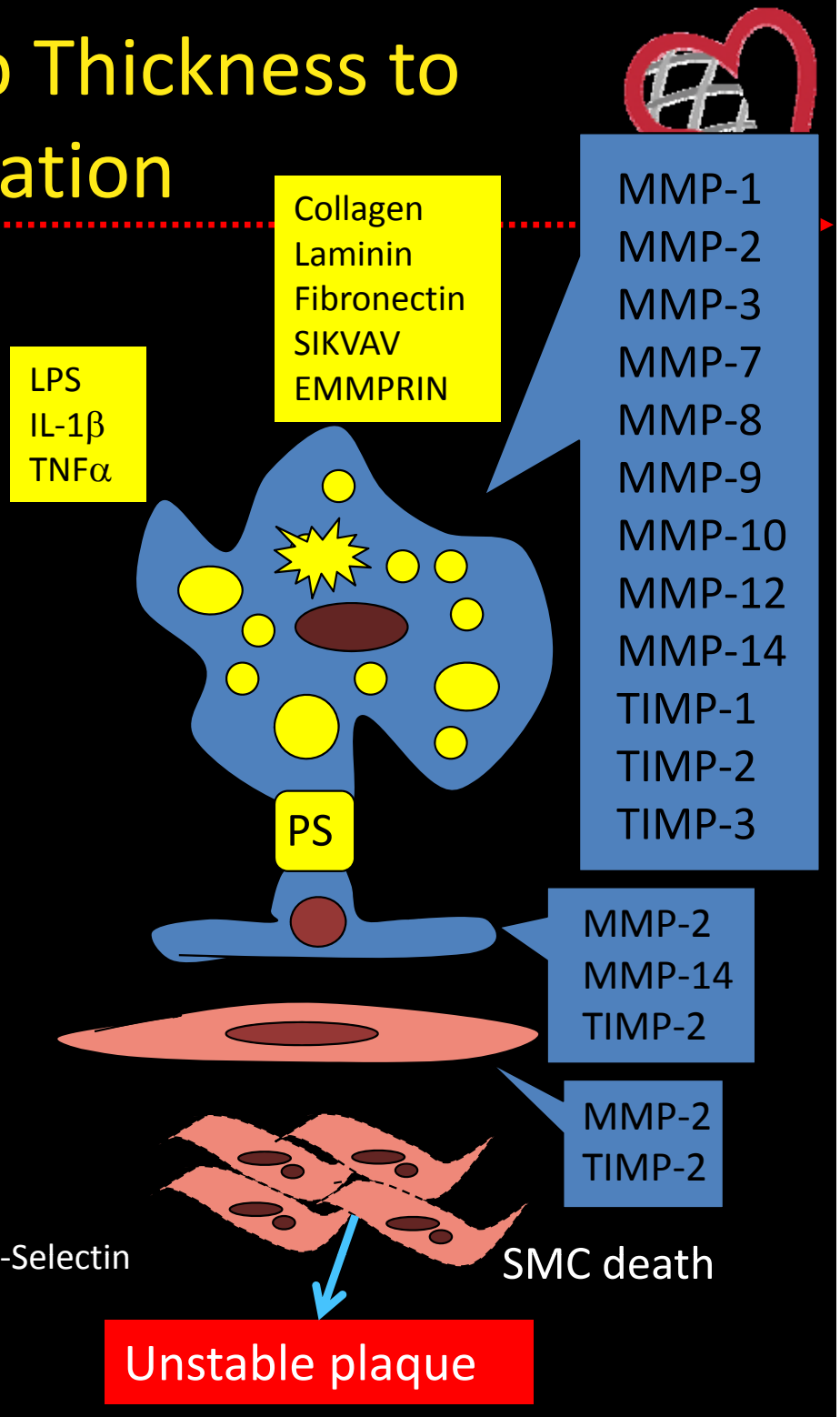


So… We need more information

Relationship of Fibrous Cap Thickness to Macrophage Infiltration

Virmani R, J Interv Cardiol 2002

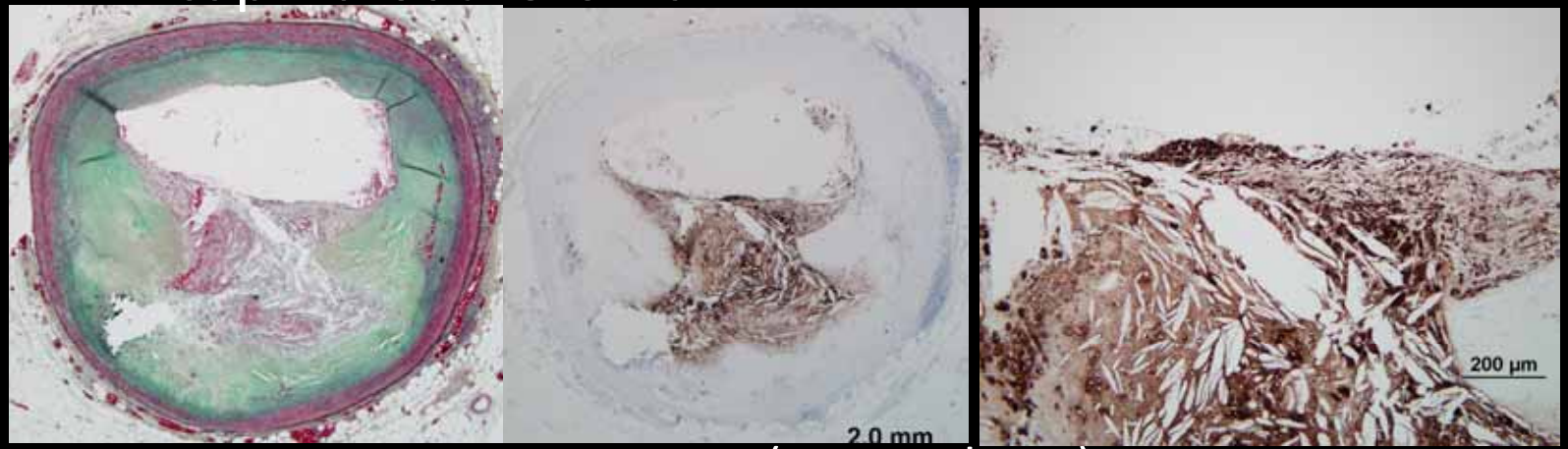




Modified from Newby AC. ATVB 2008

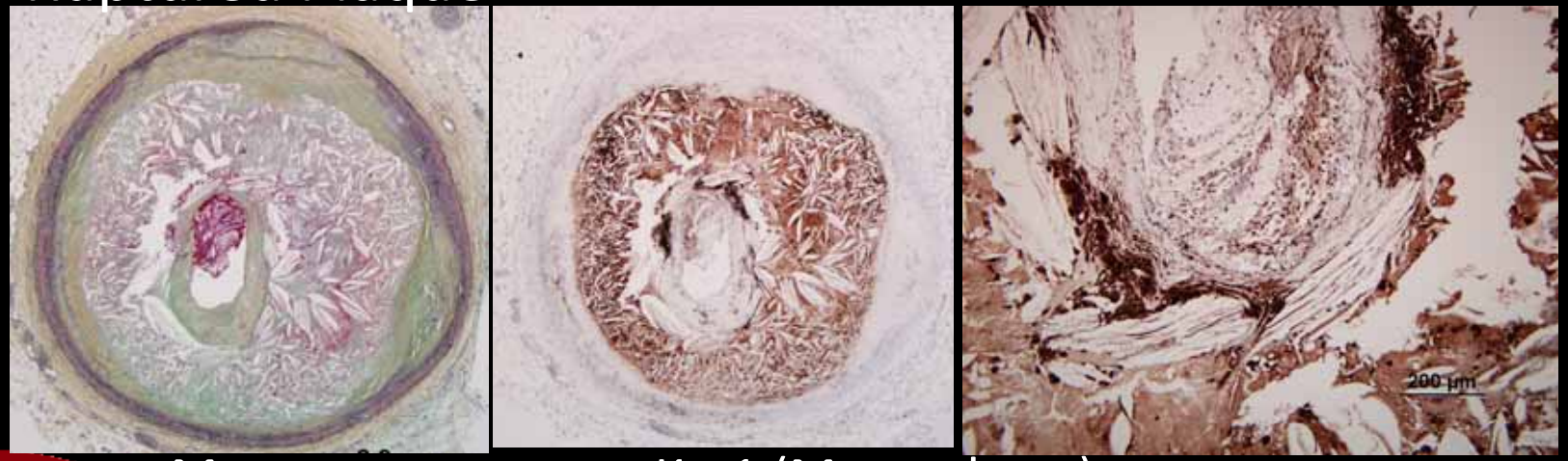
Macrophages in Vulnerable Plaque

Thin-cap fibroatheroma



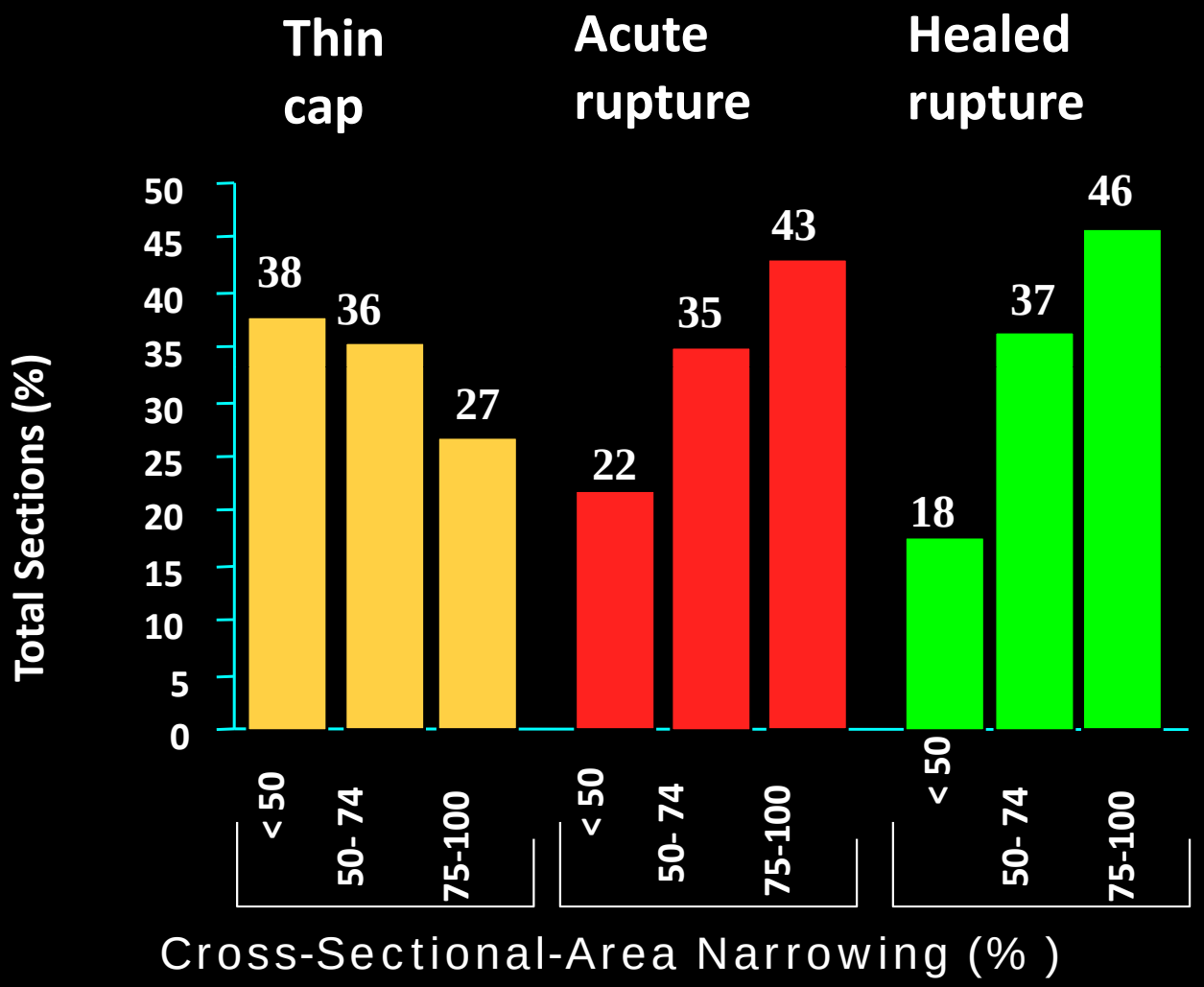
Movat Kp-1 (Macrophage)

Ruptured Plaque



Movat Kp-1 (Macrophage)

Percentage of Cross-Sectional-Area Narrowing by Plaque Morphology



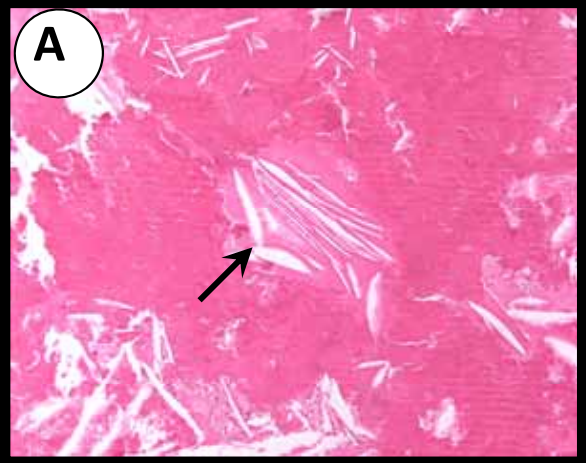
It is possible that TCFAs rapidly progress in terms of %stenosis before it ruptures

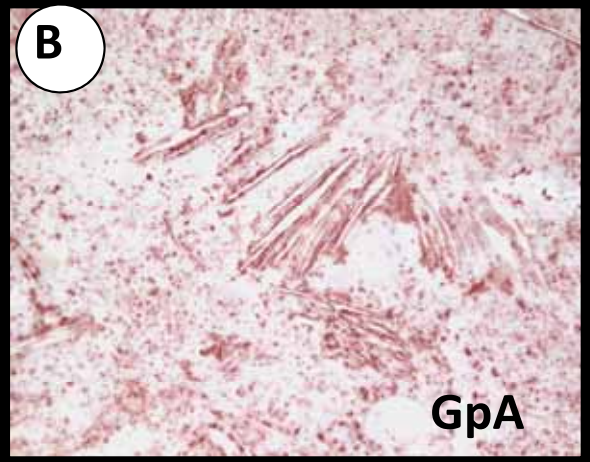
Rapid Necrotic expansion is definitely one of the important factors for plaque rupture!

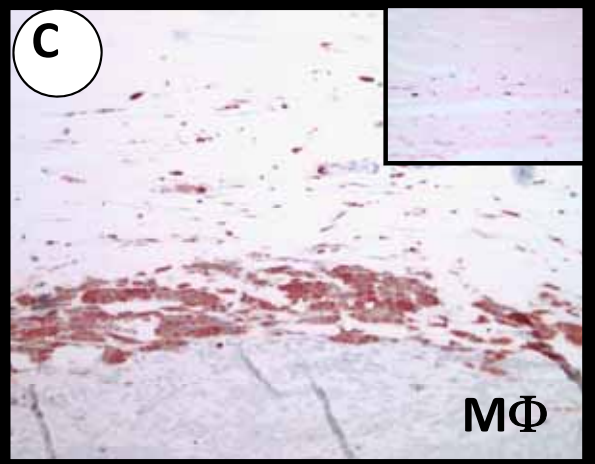
G-HILLS

Similarities between hemorrhagic pericarditis and Fibroatheroma

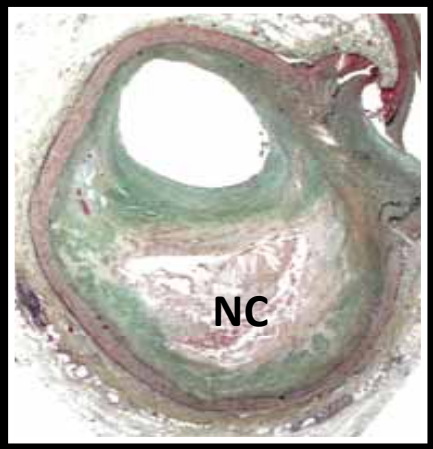
Hemorrhagic pericarditis

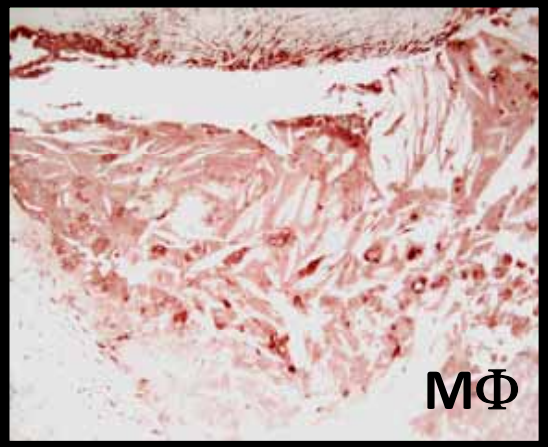


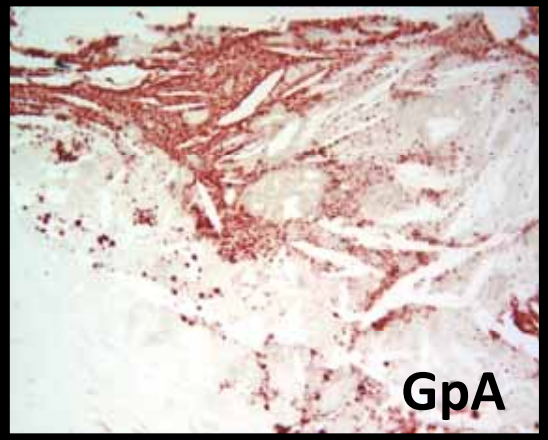


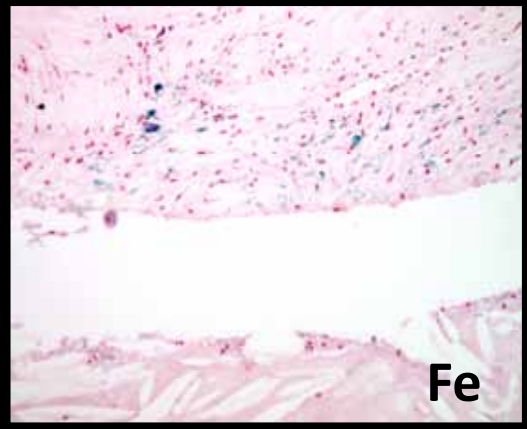


Late Fibroatheroma









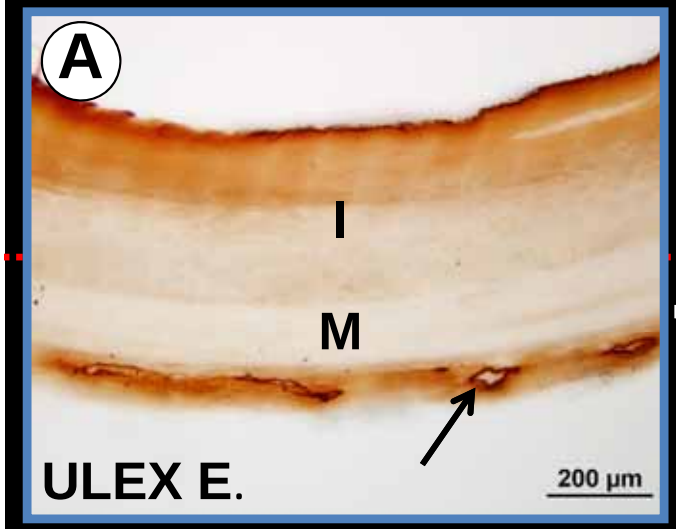
Morphometric Analysis of Hemorrhagic Events in Human Coronary Plaques from Sudden Death Victims

Plaque Type	GpA Score	Iron	Necrotic Core (mm^2)	MΦ (mm^2)
PIT *no* core *(n=129)*	0.09±0.04	0.07±0.05	0.0	0.002±0.001
FA *early* core *(n=79)*	0.23±0.07	0.17±0.08	0.06±0.02	0.018±0.004
FA *late* core *(n=105)*	*0.94±0.11	*0.41±0.09	*0.84±0.08	*0.059±0.007
TCFA *(n=52)*	*1.60±0.20	*1.24±0.24	*1.95±0.30	*0.142±0.016

Values are reported as the means±SE, *p<0.001 versus early core. The number in parenthesis represent the number of lesions examined;the total number= 365. MΦ = macrophages

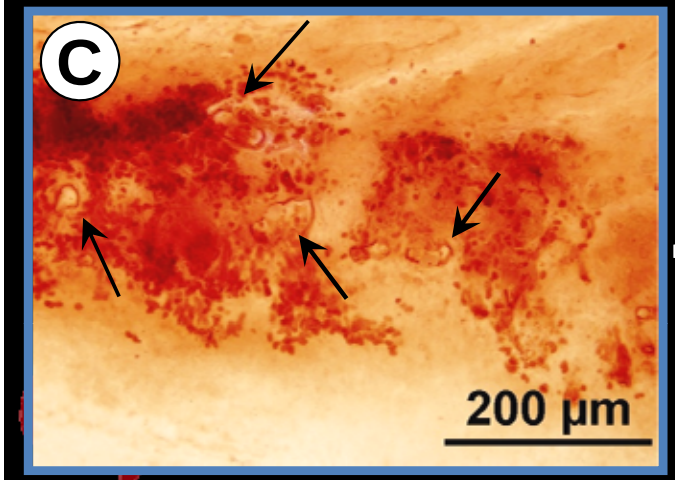
Kolodgie FD, et al. New Engl J Med 2003

Evidence that Human Coronary Plaques Express a Latent Proangiogenic Phenotype



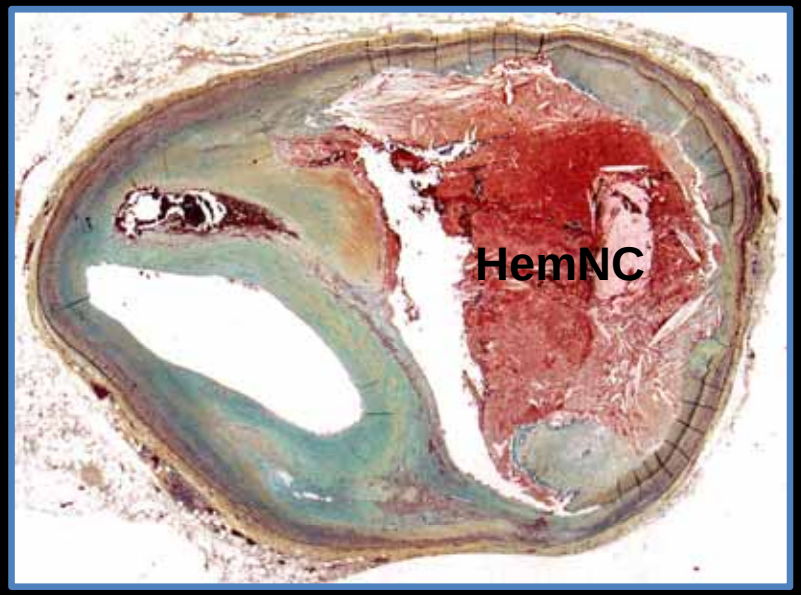
– Normal artery with adventitial Vv

– Fibroatheroma with Tortuous and Abnormal Vv



– Fibroatheroma with Leaky Vv (peri-vascular hemorrhage)

Fibroatheroma with severe Intraplaque hemorrhage

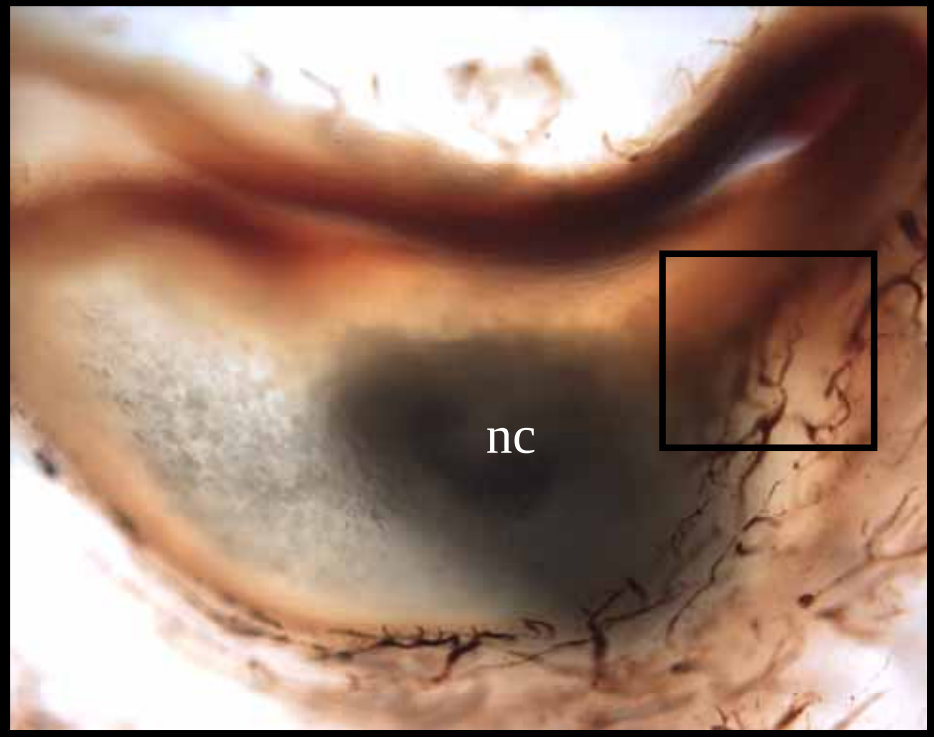


Modified from Jain et al., Nat Clin Pract Cardiovasc Med, 2007

Intraplaque Vasa Vasorum in Coronary Plaques with a Necrotic Core

150 μm thick sections stained with Ulex

A



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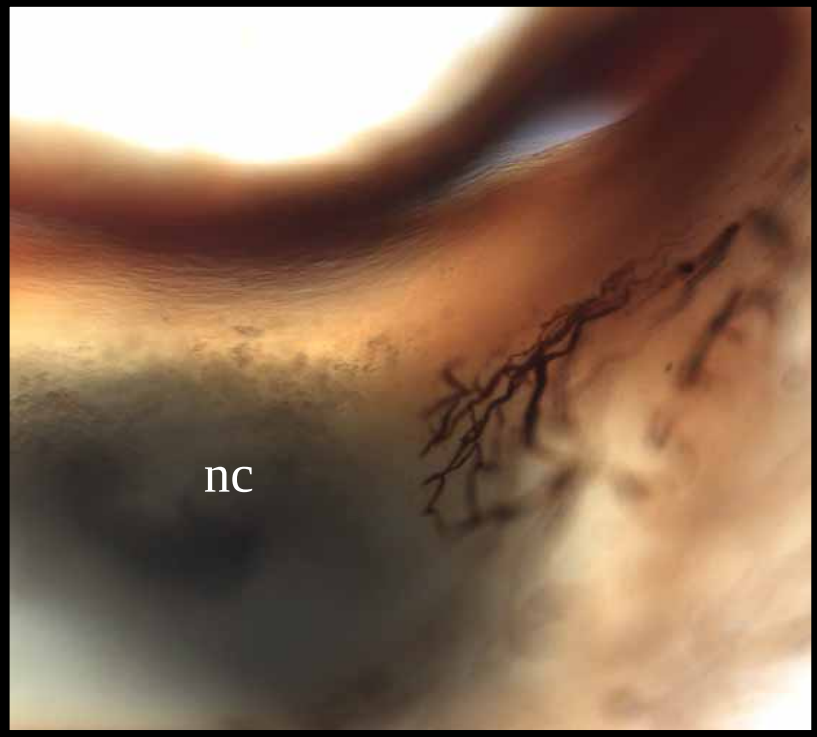
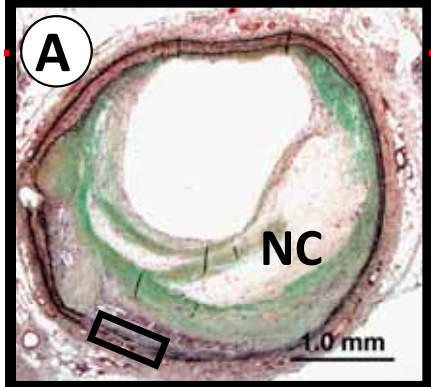
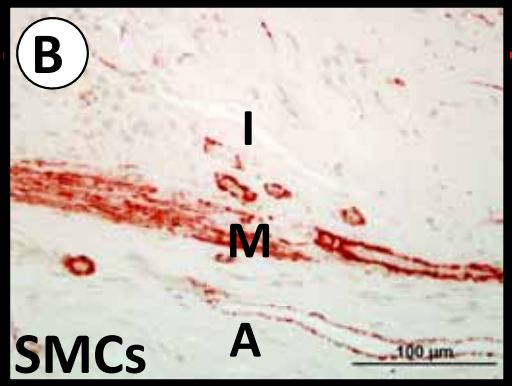


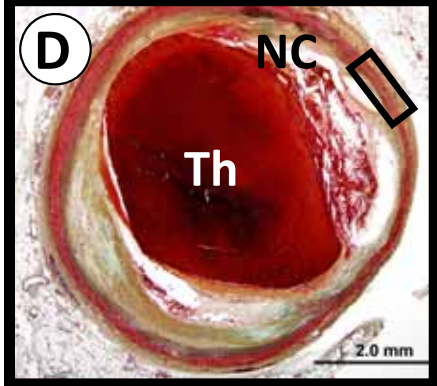
Vasa Vasorum by Plaque Type

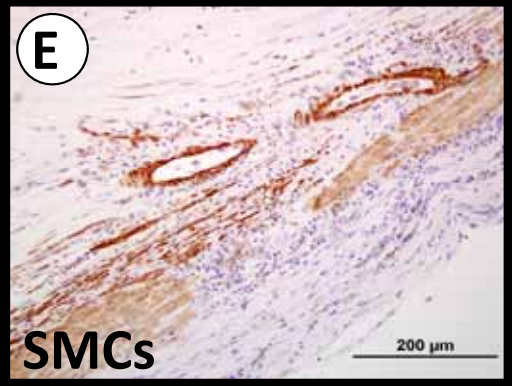
Thin-Cap Fibroatheroma

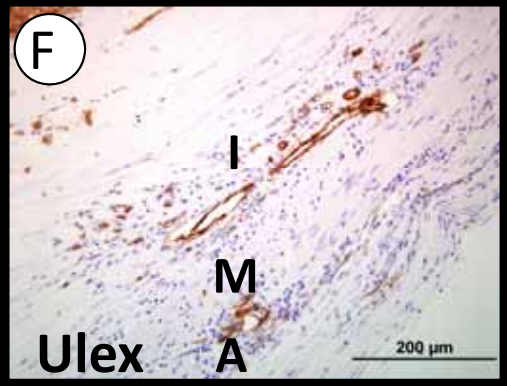




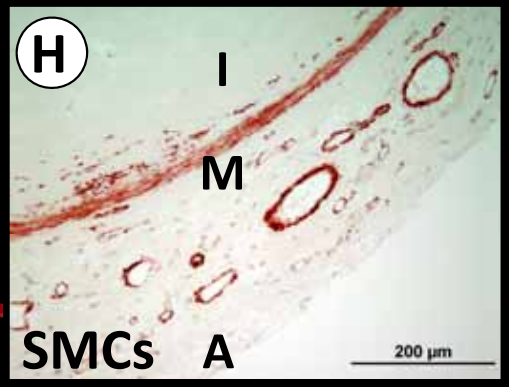
Plaque Rupture

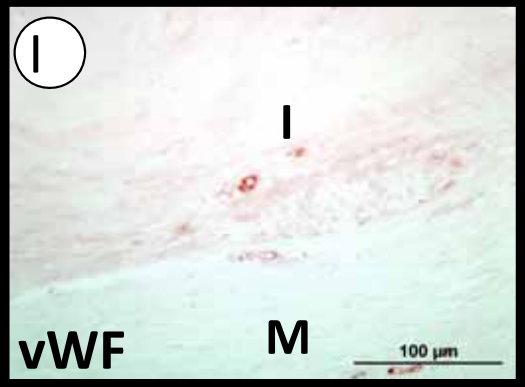


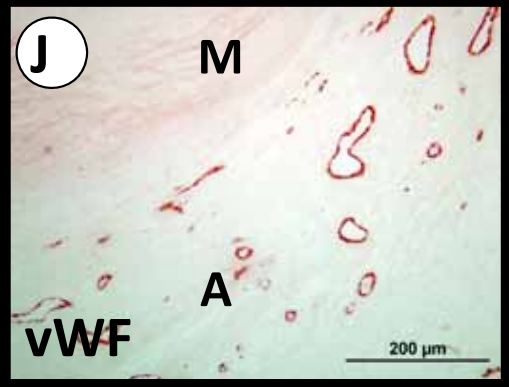


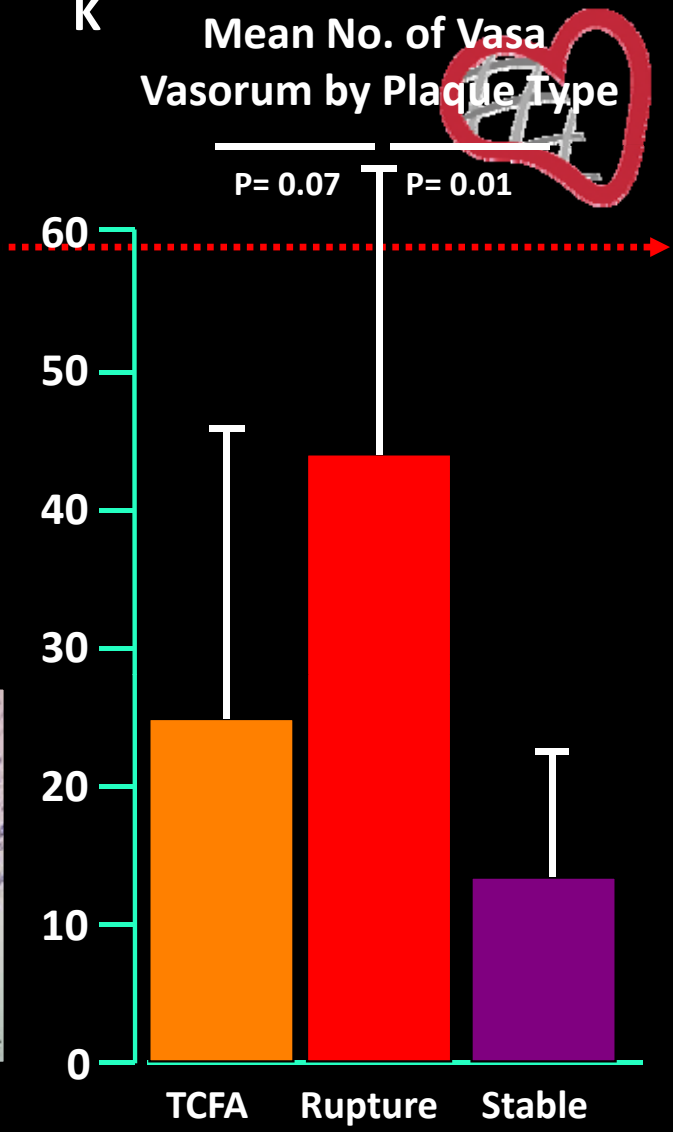


Stable Plaque

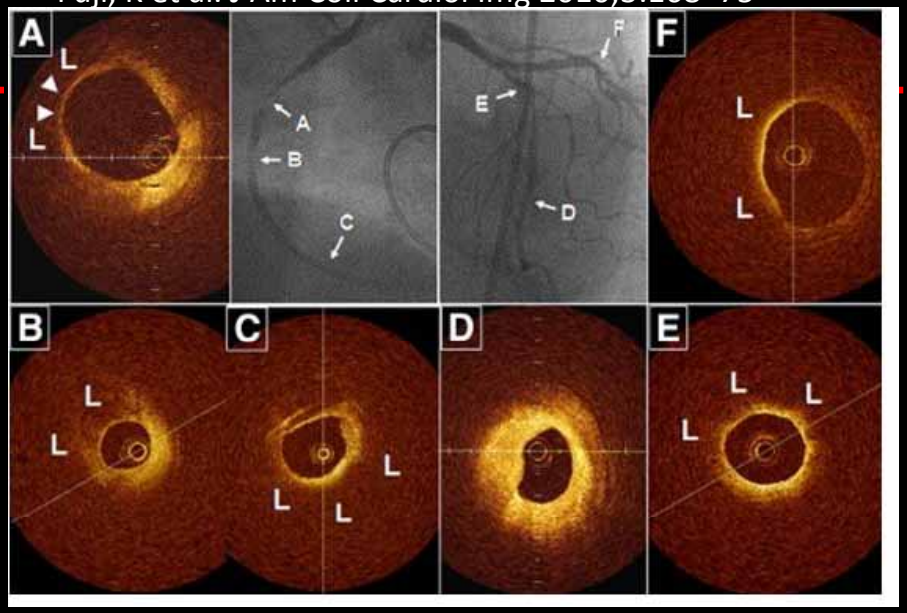




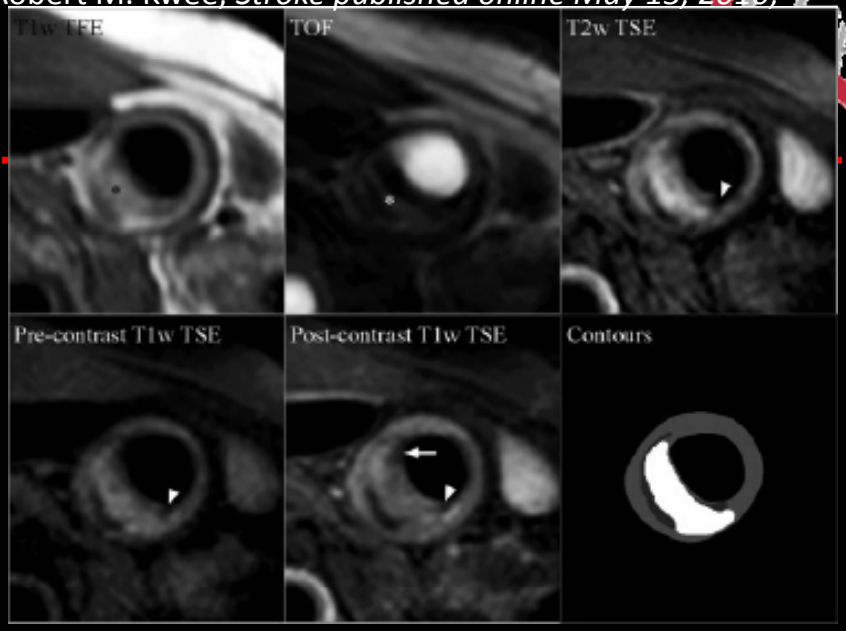


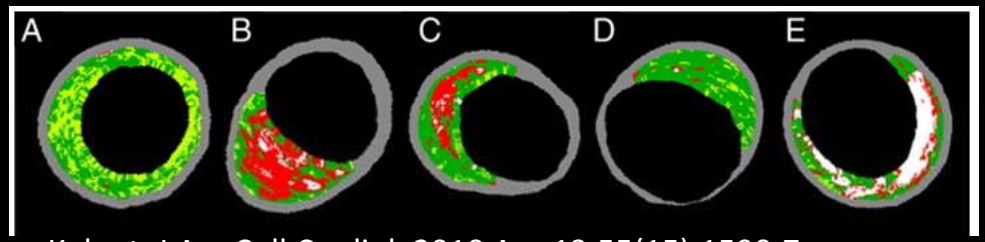


Fuji, K et al. J Am Coll Cardiol Img 2010;3:168–75

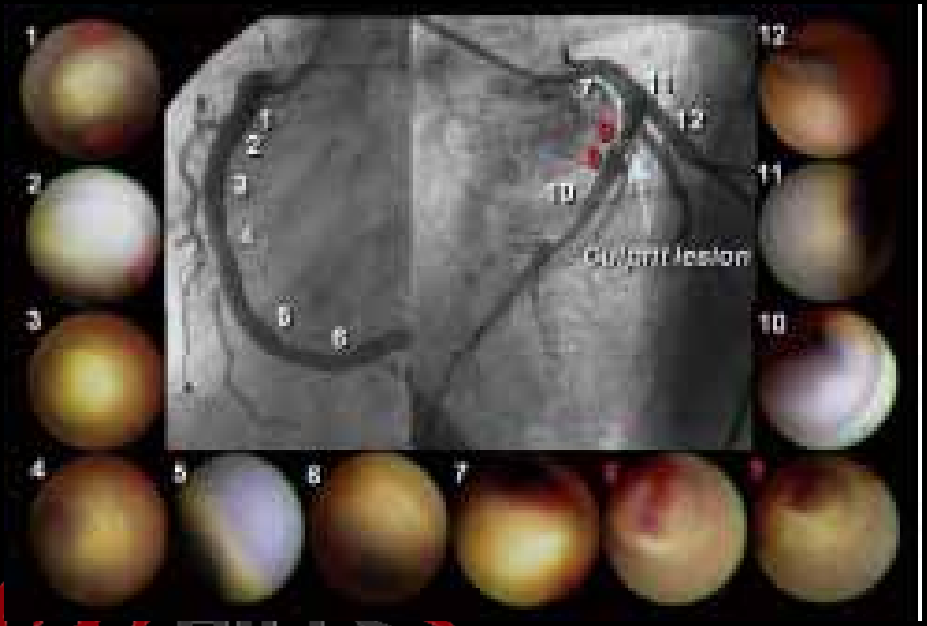


Robert M. Kwee, *Stroke published online May 13, 2010;*

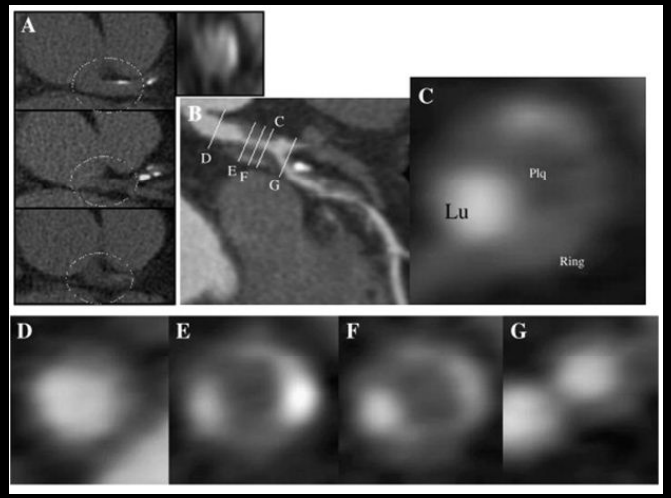




Kubo t, J Am Coll Cardiol. 2010 Apr 13;55(15):1590-7.



Asakura M, J Am Coll Cardiol. 2001 Apr;37(5):1284-8.



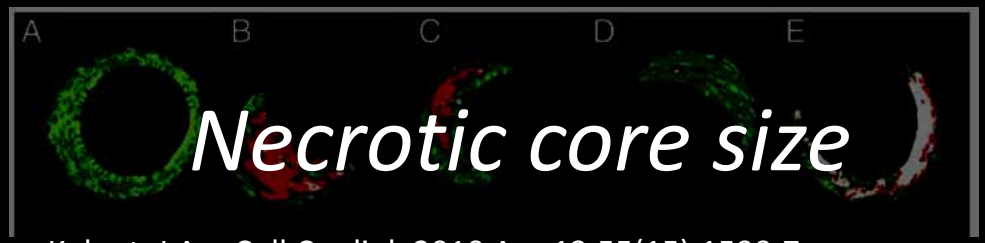
Nakazawa G, Am Heart J 2008

Fuji, K et al. J Am Coll Cardiol Img 2010;3:168–75

Fibrous cap thickness

Robert M. Kwee, *Stroke published online May 13, 2010;*

Intraplaque hemorrhage



Necrotic core size

Kubo t, J Am Coll Cardiol. 2010 Apr 13;55(15):1590-7.

Intramural thrombus

Asakura M, J Am Coll Cardiol. 2001 Apr;37(5):1284-8.

Plaque density /Vasa Vasorum

Nakazawa G, Am Heart J 2008

We are close!!!

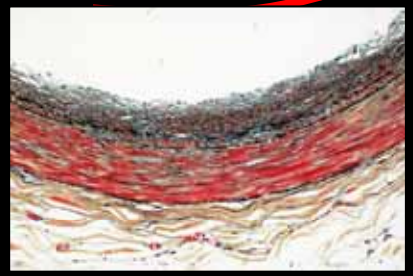
But Close Enough?

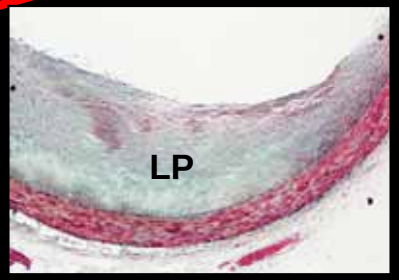
Catch me if you can!

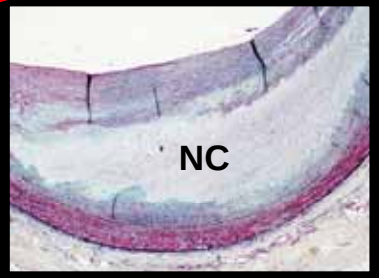
Physiological markers

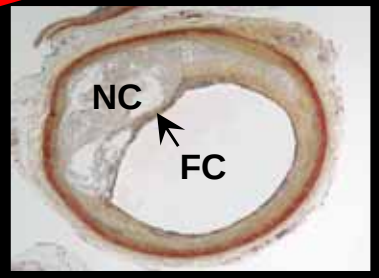
Imaging

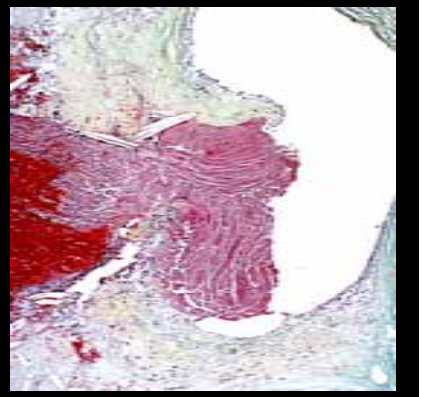
Biomarkers











Time

Summary

- Plaque progression and the concept of "vulnerable plaque" has been well-understood morphologically by pathology and imaging modalities
- However, the trigger of progression or plaque rupture remains unclear
- Therefore, we still need more information to detect "vulnerable patients" timely