Evidence and Future Perspectives for Vulnerable Plaque

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TCT Asia Pacific 2009

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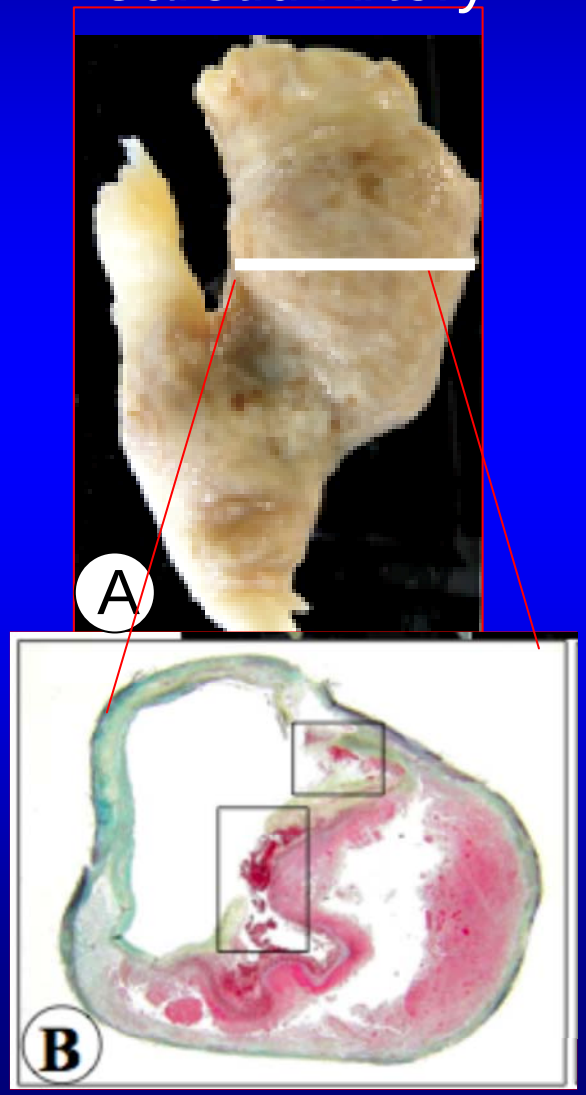
Conflict: Nothing to declare

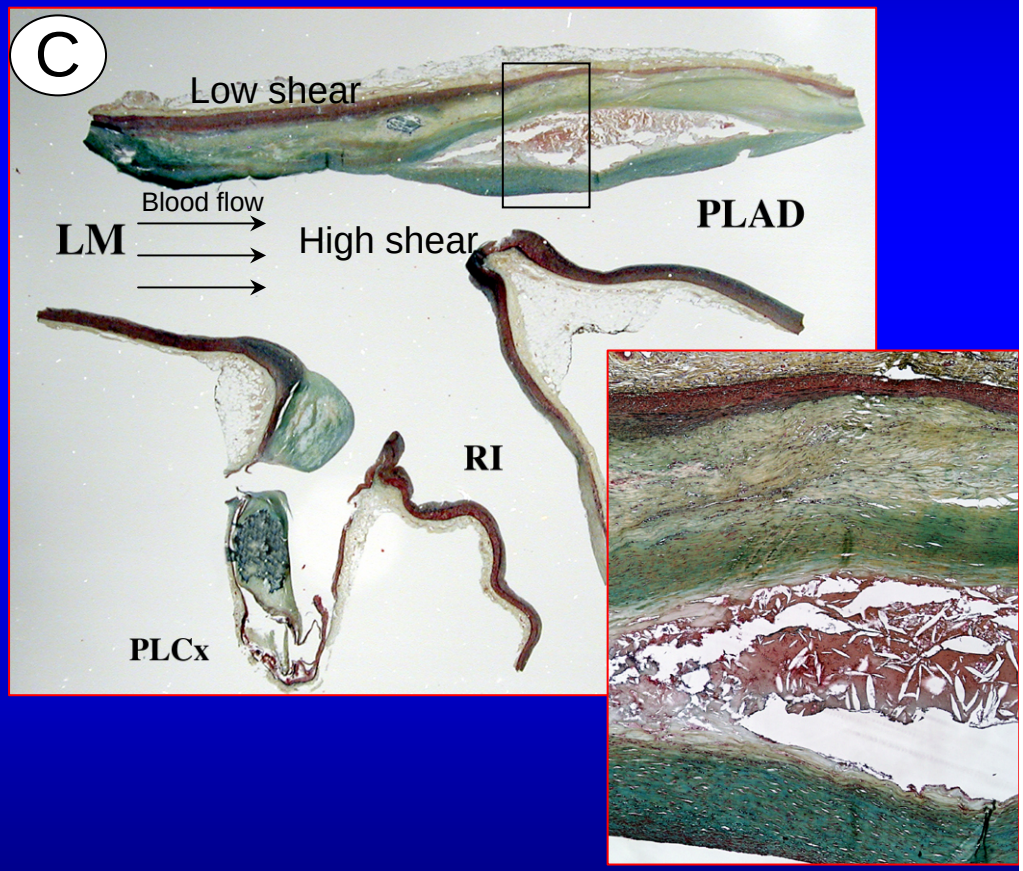
CVPath
CVPath Institute, Inc.

Branch points are the sites of atherosclerosis and occur in areas of low shear

Carotid Artery

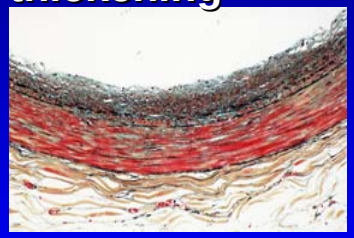


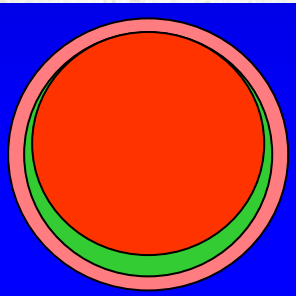
Left Coronary artery



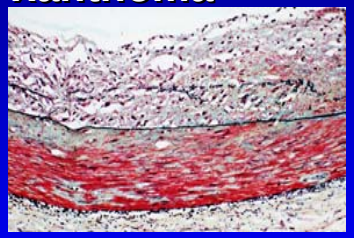
Progression of Human Coronary Atherosclerosis

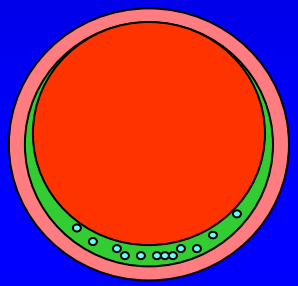
Intimal thickening



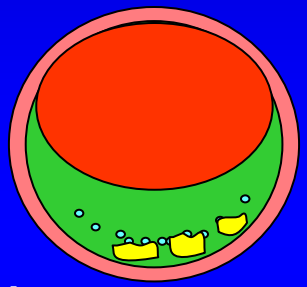


Intimal xanthoma

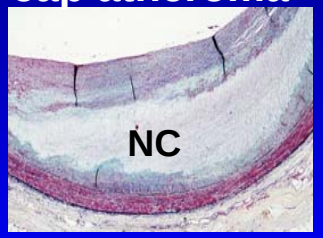


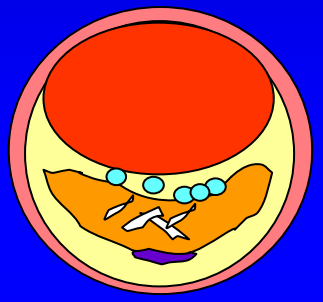


Pathologic intimal thickening

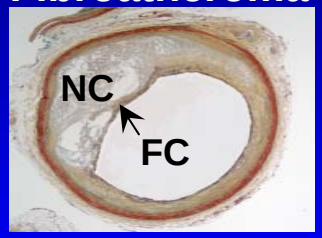


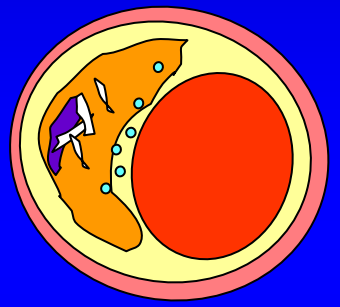
Fibrous cap atheroma



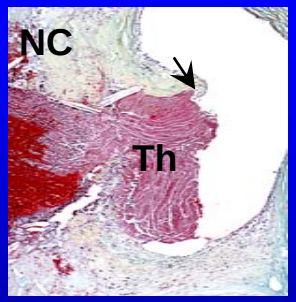


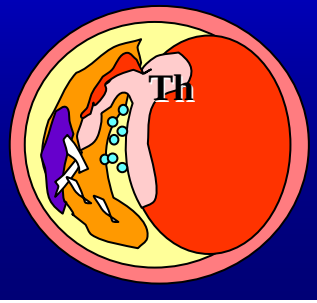
Thin-cap Fibroatheroma



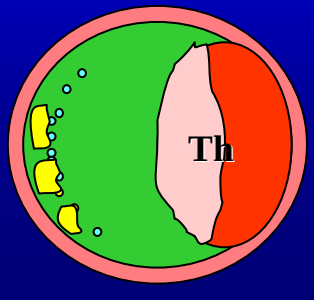


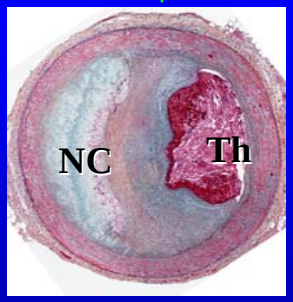
Rupture

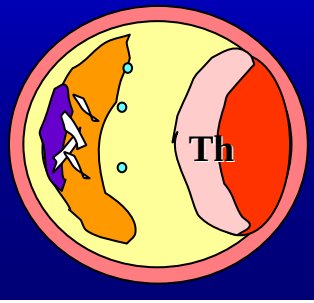




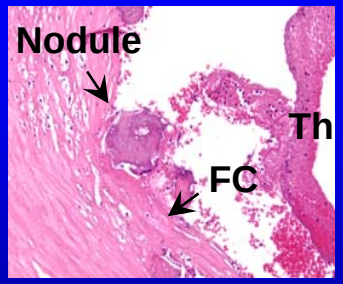
Erosion

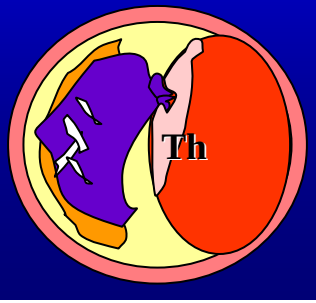




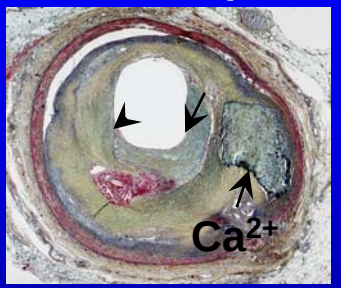


Calcified nodule



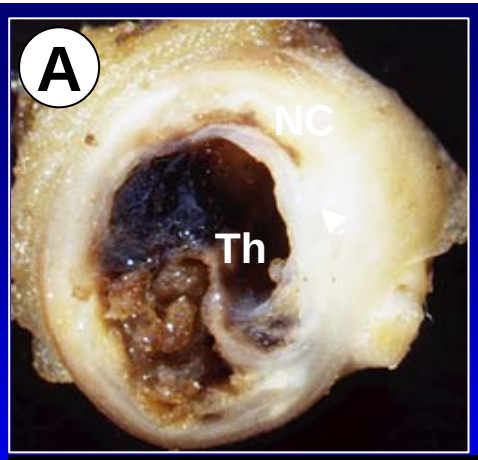


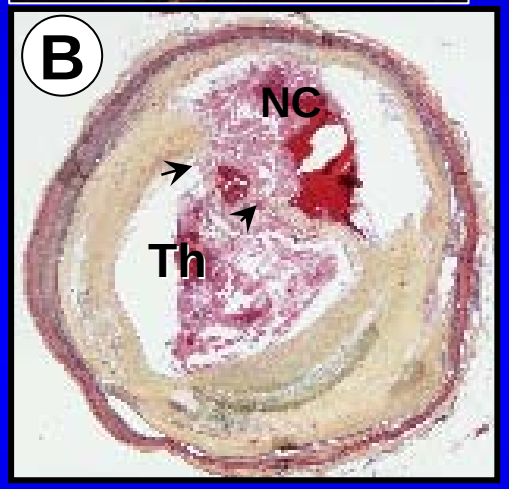
Healed Rupture

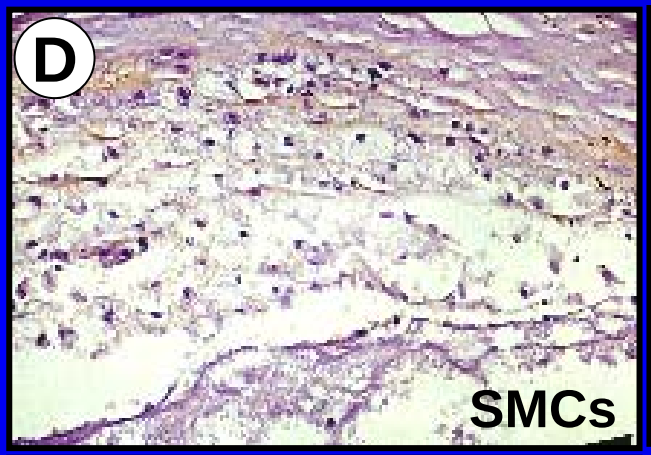


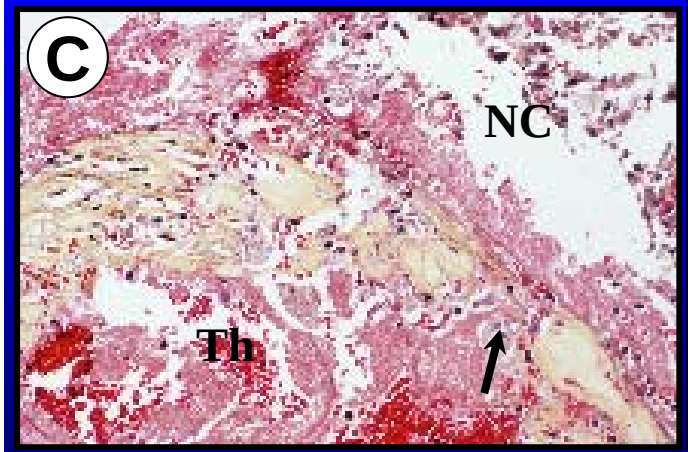
Gross and Light Microscopic Features of Plaque Rupture

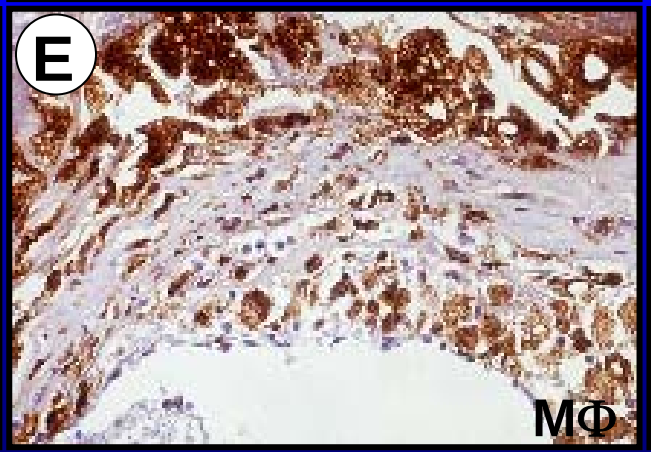
60% of Thrombi in Sudden Coronary Death occur form Plaque Rupture











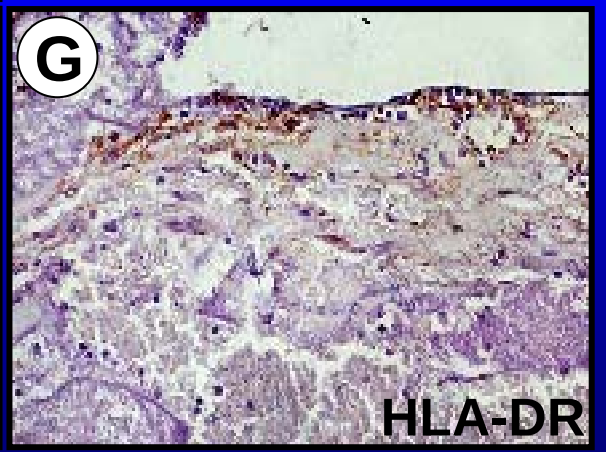
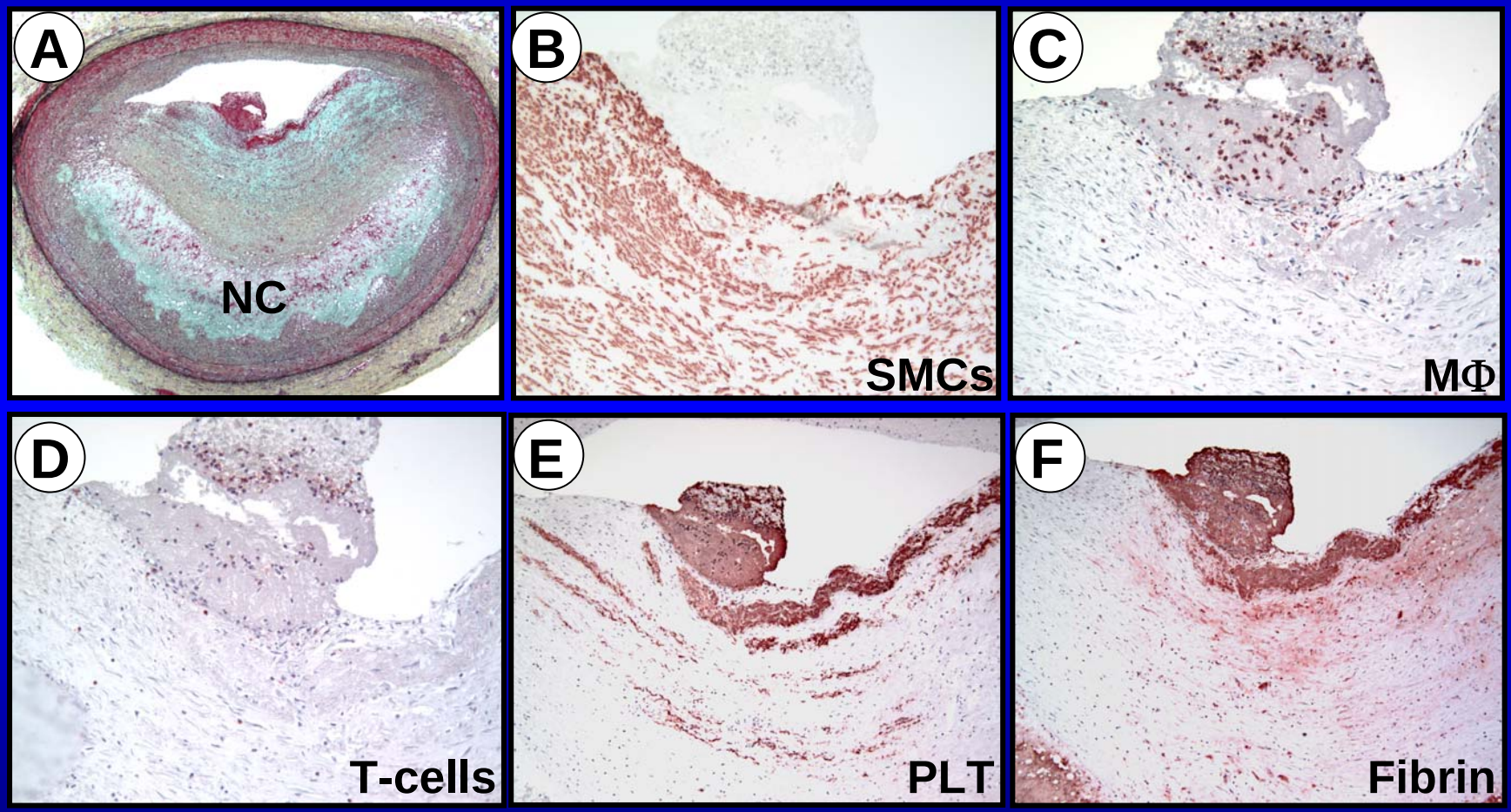
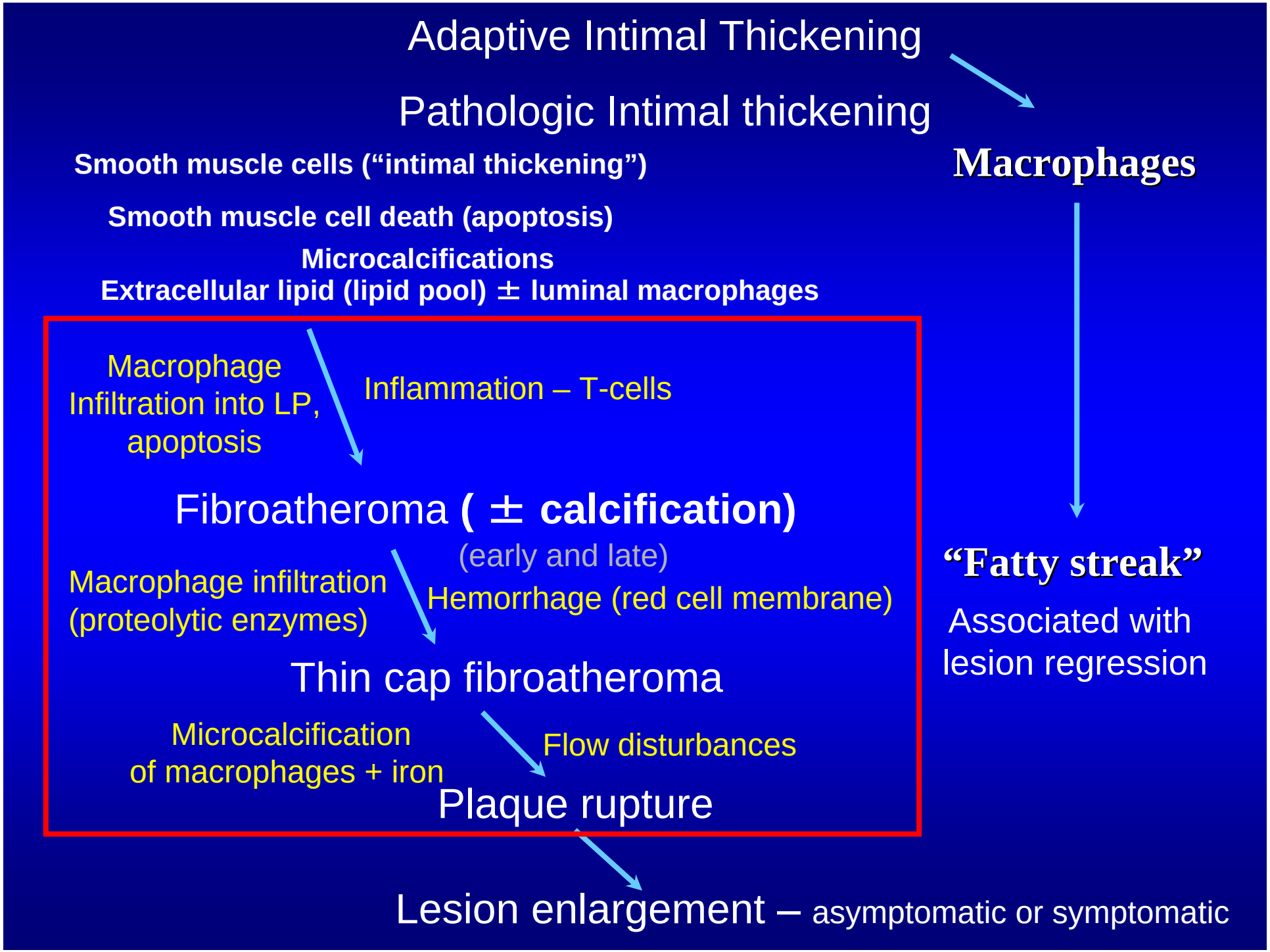


Fig 3-1

Plaque Erosion: 30-35% of thrombi in SCD

Plaque erosion in a 33 year-old female complaining of chest pain for two-weeks and discharged from the emergency room with a diagnoses of anxiety.




Adaptive Intimal Thickening
Pathologic Intimal thickening
Smooth muscle cells ("intimal thickening")
Smooth muscle cell death (apoptosis)
Microcalcifications
Extracellular lipid (lipid pool) ± luminal macrophages
Macrophages
Macrophage Infiltration into LP, apoptosis
Inflammation – T-cells
Fibroatheroma (± calcification)
(early and late)
Macrophage infiltration (proteolytic enzymes)
Hemorrhage (red cell membrane)
Thin cap fibroatheroma
Microcalcification of macrophages + iron
Flow disturbances
Plaque rupture
"Fatty streak"
Associated with lesion regression
Lesion enlargement – asymptomatic or symptomatic

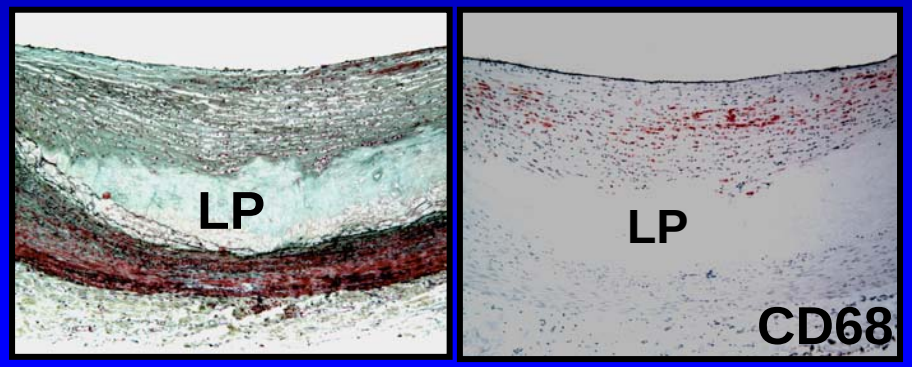
Morphometric assessment of vessel area, stenosis, necrotic core size, and macrophage density from 72 pts with SCD

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*

Plaque Progression

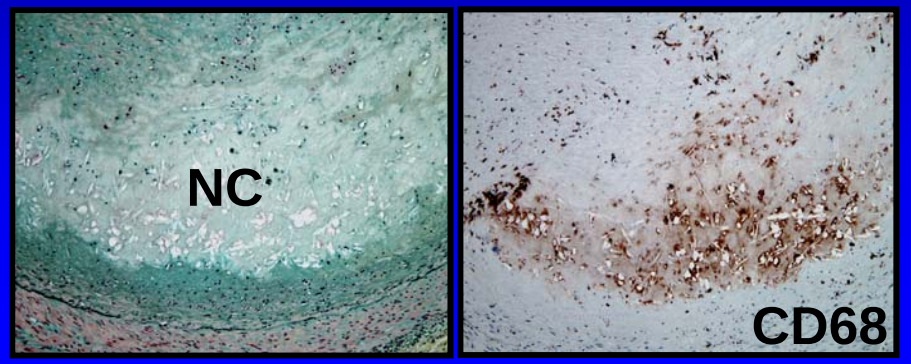
A.

Pathologic Intima Thickening



B.

Fibroatheroma ‘Early’ Core

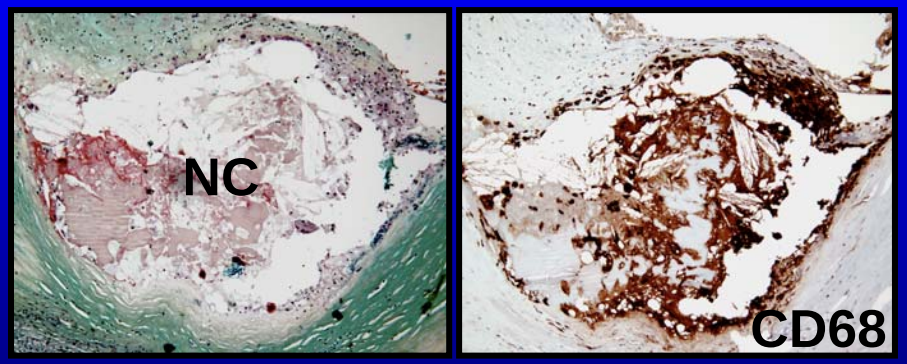


C.

Fibroatheroma ‘Late’ Core

D.

Thin Cap Fibroatheroma

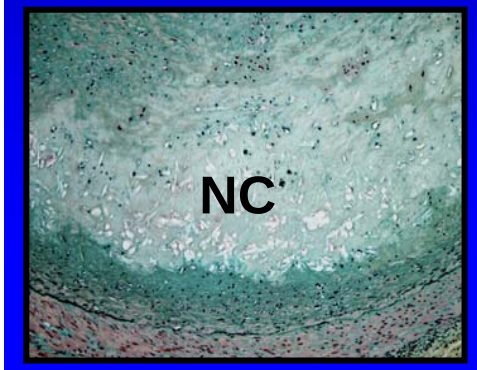


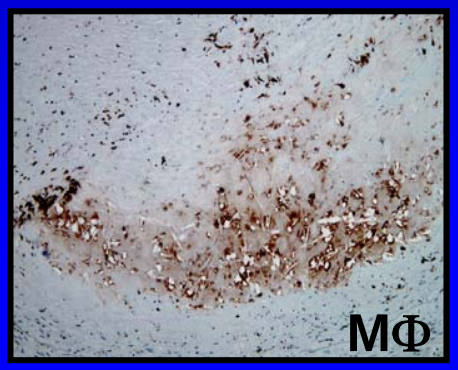
Differential Expression of Hyaluronan and Versican in the Developing Necrotic Core

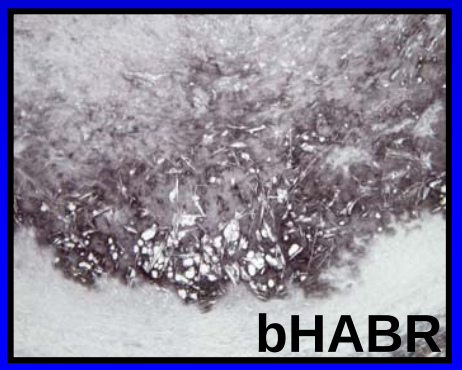
A

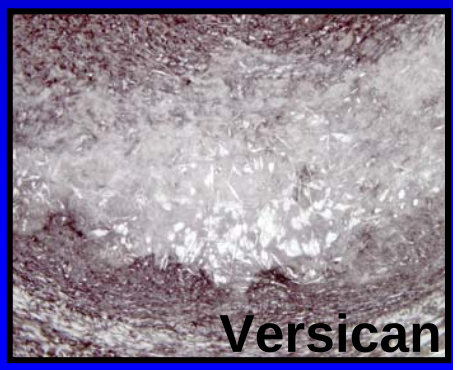
B

Fibroatheroma ‘Early’ Necrosis





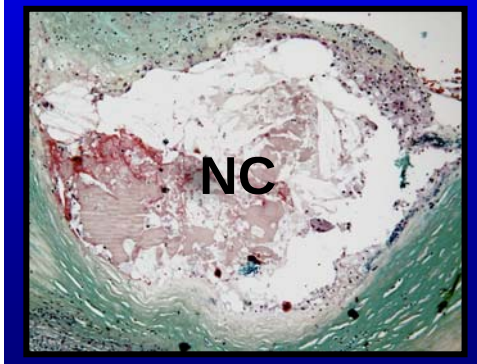


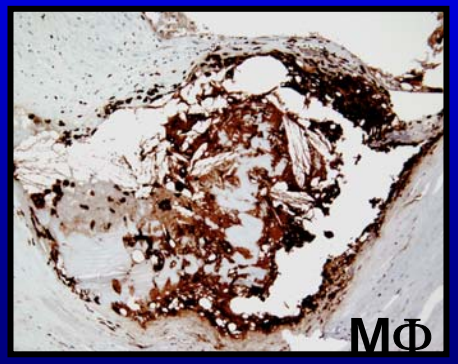


C

D

Thin-cap Fibroatheroma ‘Late’ Necrosis

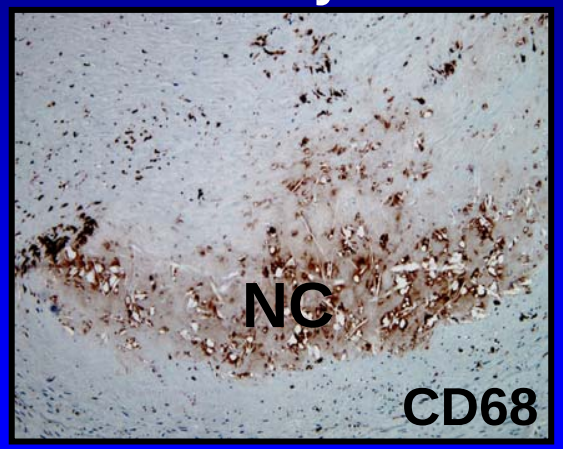




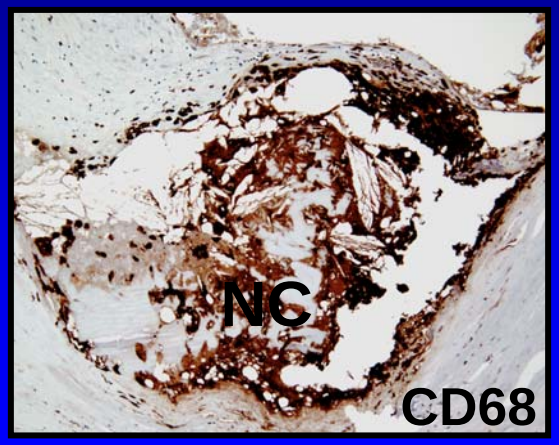
Defective Foam Cell Clearance and Necrotic Core Formation

A.

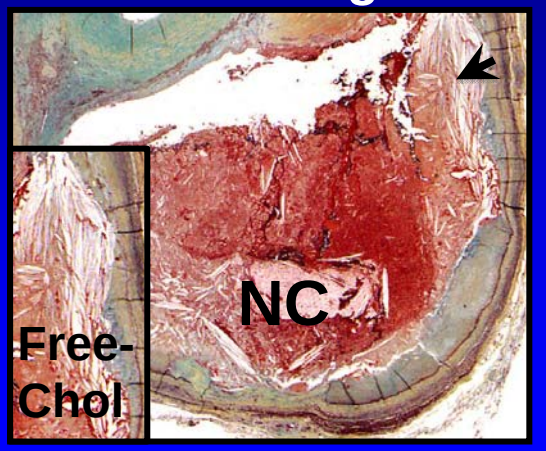
Early



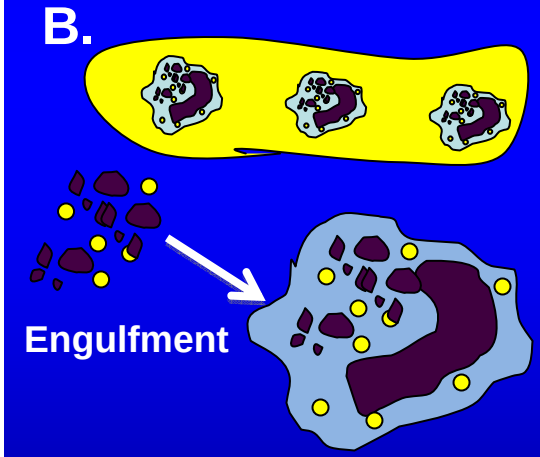
Late

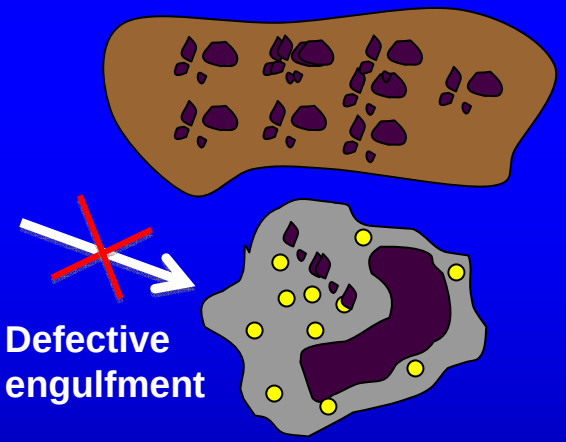


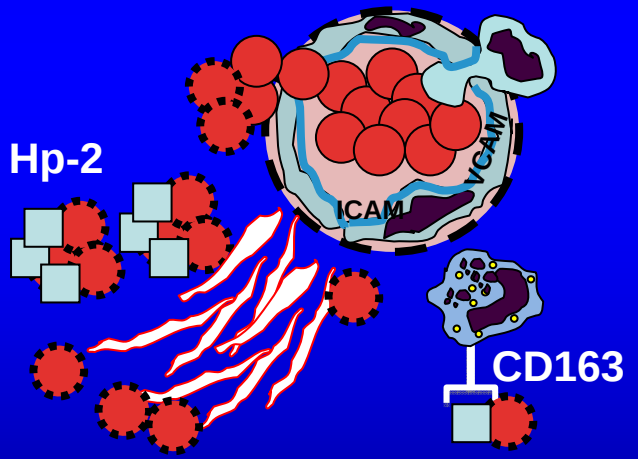
Hemorrhagic



B.







Early foam cell apoptosis
(via ER stress path)
Clearance by efferocytosis
(phagocytosis)

Excess foam cell apoptosis
Defective efferocytosis
1) Fas ligand (apoptosis stimulating fragment)
2) transglutaminase-2
3) lactadherin
4) Mertk (Mer receptor tyrosine kinase)

Excess
free cholesterol
free hemoglobin (Hb)
macrophages

efferocytosis

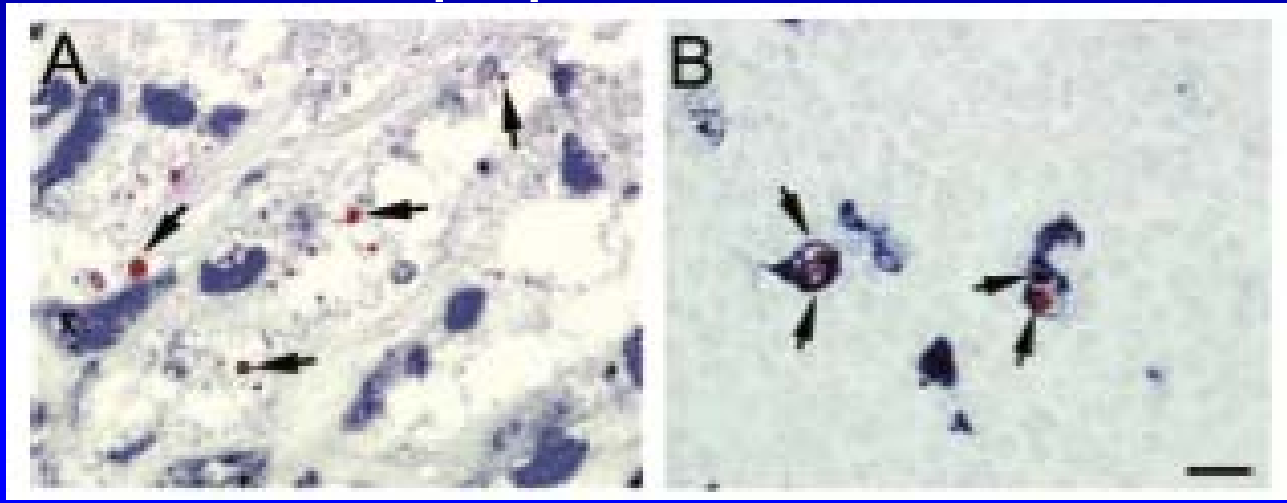
The Pathology of Transitional Human Coronary Plaques that Later Develop Necrosis

Lesion Type	Plaque Area	Stenosis %	Necrotic core area (mm2)	Macro-phages %	Apoptotic cells/mm2
PIT-M	3.3±1.9	42±10		0.7±0.7	1.8±1.3
PIT+M	2.5±1.1	46±14		1.8±1.5	2.4±1.6
Early Fibroatheroma	4.8±2.5	60±12	0.93±0.92	3.1±3.8	3.1±2.1
Late Fibroatheroma	5.8±2.7	70±13	1.34±0.70	4.3±3.7	5.4±3.3
P value	<0.0001	<0.0001	0.16	<0.0001	0.004

Kramer MC, et al.

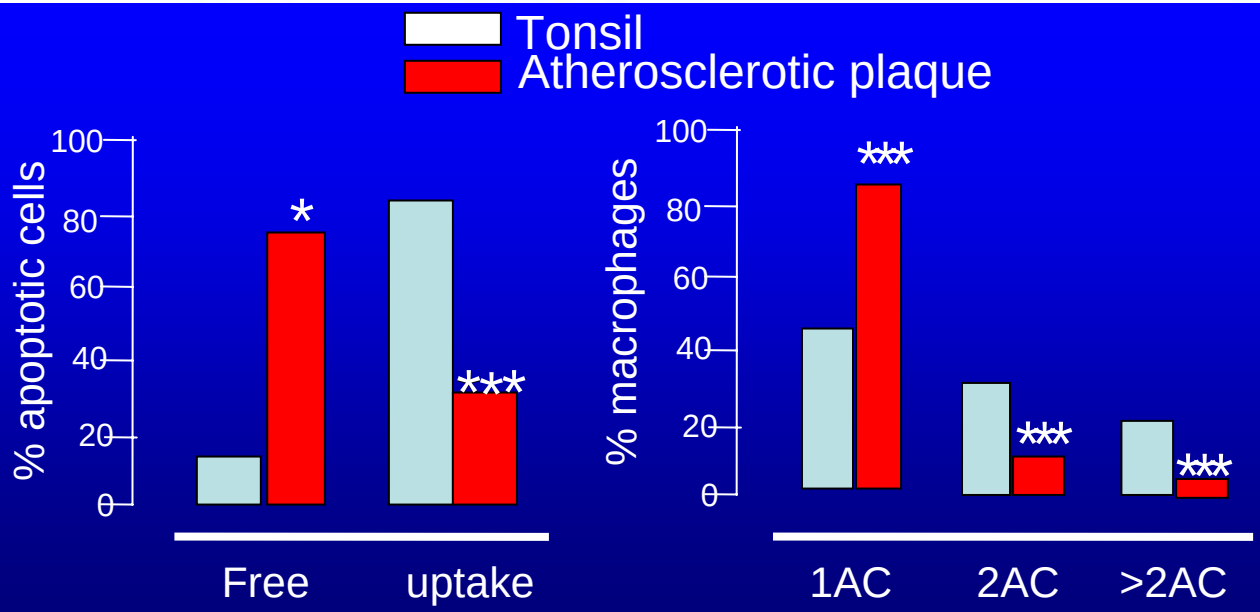
Phagocytosis efficiency of apoptotic cells (AC) in advanced atherosclerotic plaque and human tonsils

Atherosclerotic plaque **Tonsil**



TUNNEL (AC, red)

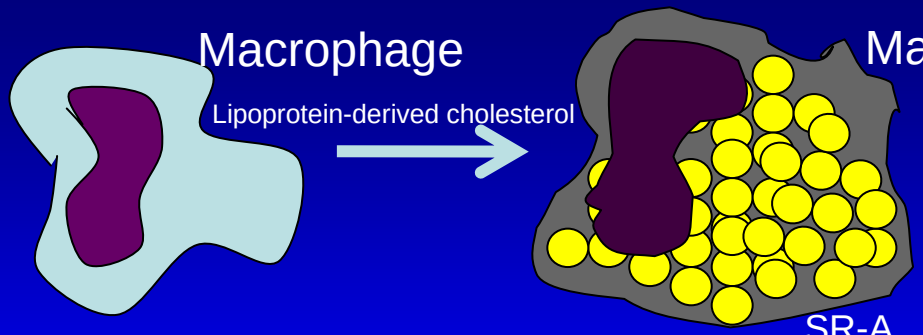
CD 68
(macrophages, blue)



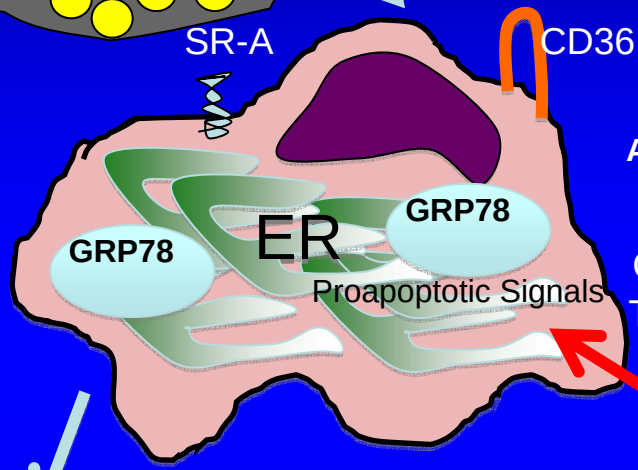
The radio of free AC versus phagocytized AC was 19 times higher in athero-sclerotic plaques as compared to human tonsil

Schrijvers DM et al. ATVB,2007

Potential Inducers of Macrophage Apoptosis



ER = endoplasmic reticulum plays an important role in intracellular calcium homeostasis, protein secretion and lipid biosynthesis.
UPR = Unfolded Protein Response

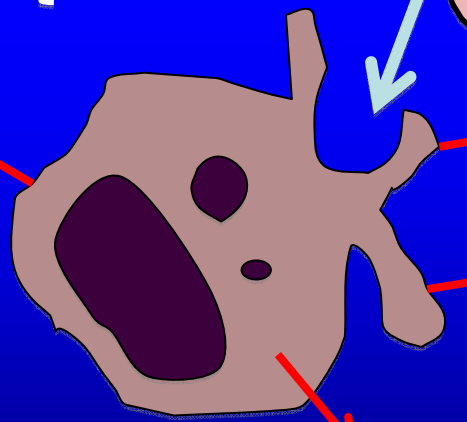


Anti-apoptotic
Bcl2

GRP = glucose regulated protein
TDGA = T-cell death-associated gene 51

Apoptosis Inducers

- **UPR**
- **CHOP**
- **TDAG51**
- **Caspase 12**



MMP's

IL -1 β

TNF α

IL-6

ER stressors

Free Cholesterol from Erythrocytes
Nitric oxide
Hypoxia
Oxidant stress
and others

Apoptotic macrophages are a source of proinflammatory cytokines and proteases

Seimon T and Tabas I. J Lipid Res 2008

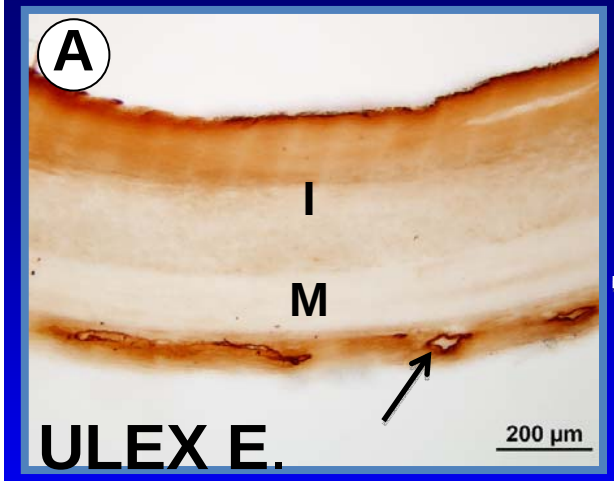
Intraplaque Hemorrhage and Progression of Coronary Atherosclerosis

- **Conversion of a stable, asymptomatic lesion to an unstable, ruptured plaque involves many processes, the most studied of which is inflammation.**
- **Commonly believed that death of macrophages, and in addition aggregation of lipoproteins, contribute to the accumulation of extracellular free cholesterol within unstable plaques.**
- **We have shown that red cell membranes in intraplaque hemorrhage also lead to expansion of the necrotic core. (***Kolodgie FD, et al. New Engl J Med 2003***)**
- **However, the role of angiogensis and the mechanisms that lead to angiogenesis remain unknown.**

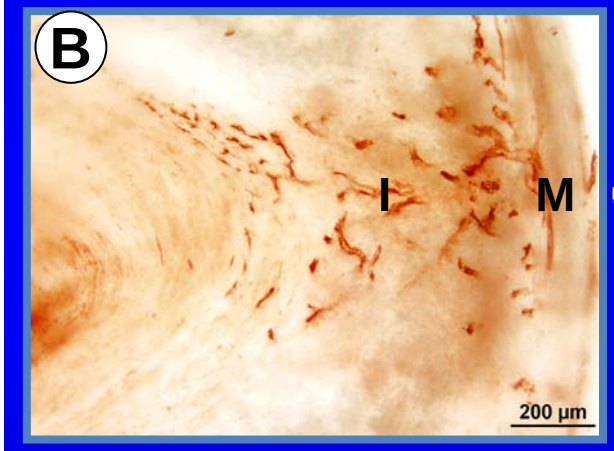
Plaque Vasa Vasorum

- Plaque capillaries are observed in atherosclerotic plaques with plaque thickness > 0.5 mm, suggesting that wall hypoxia may be a determinant of neovascularization.
- Heistead and Armstrong reported a 5 fold increase in intimal/medial blood flow from proliferating micro vessels in monkeys fed a high cholesterol diet for 17 months. (Arteriosclerosis 1986)
- Plaque Vv may be a potential source of inflammation within the plaque [expression of VCAM-1, ICAM-1 and E-selectin has been shown in plaque Vv (O'Brian, et al. AJP 1994).

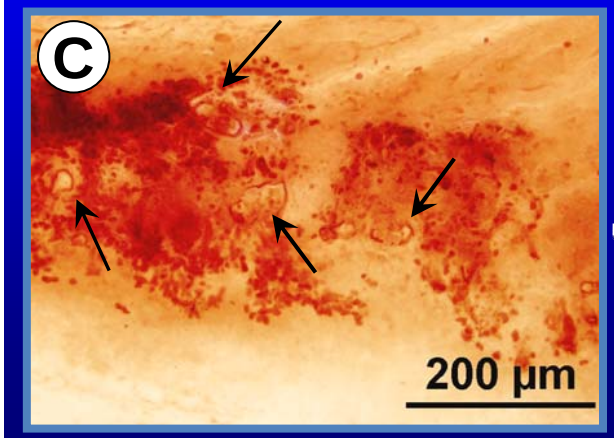
Evidence that Human Coronary Plaques Express a Latent Proangiogenic Phenotype



– Normal artery with adventitial Vv

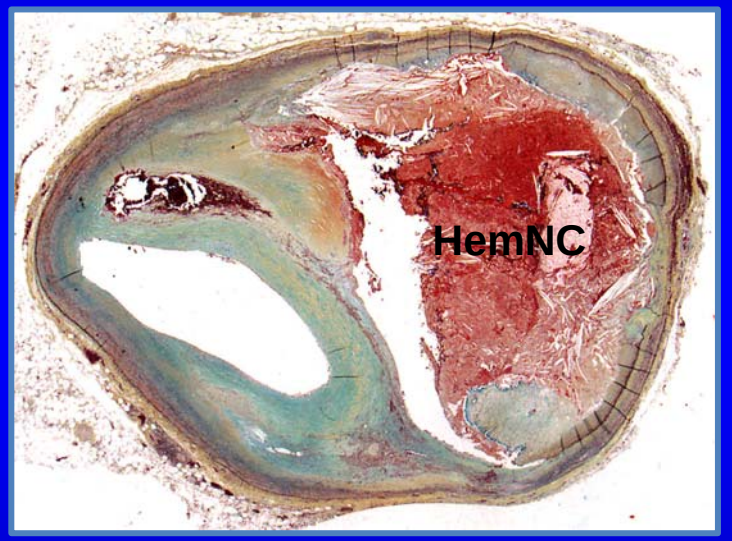


– Fibroatheroma with Tortuous and Abnormal Vv



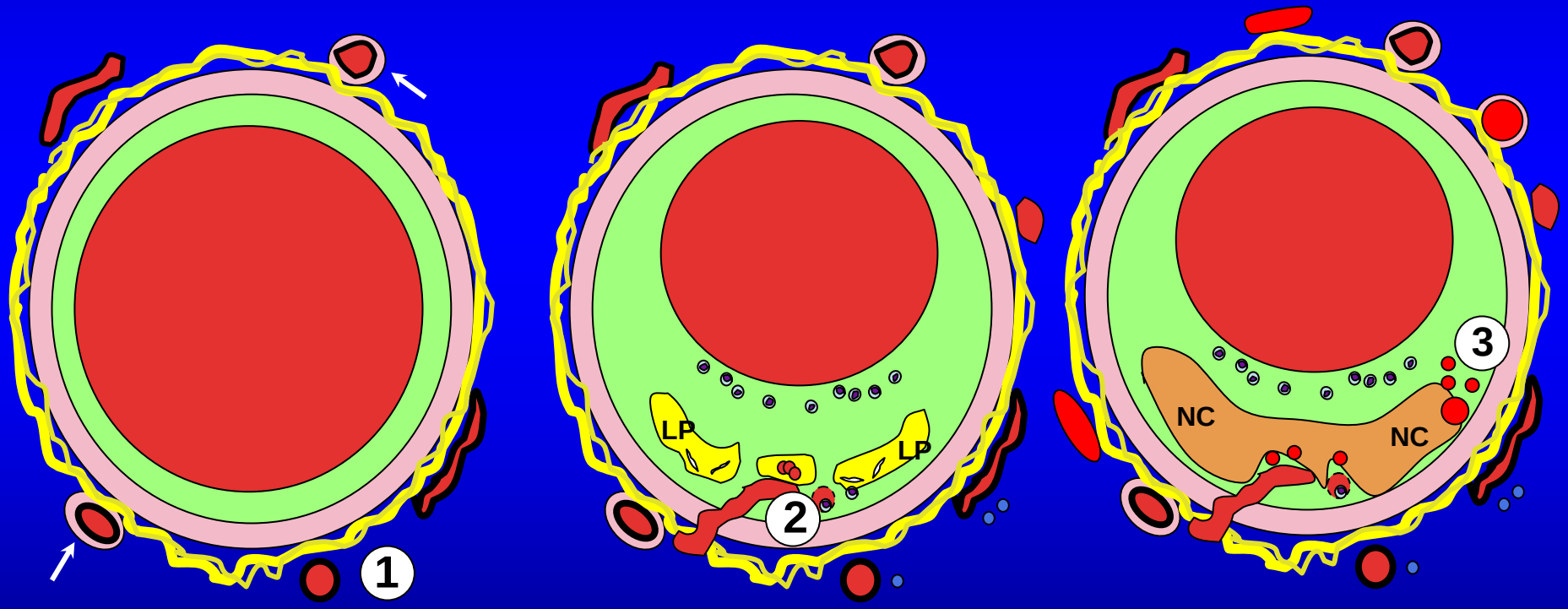
– Fibroatheroma with Leaky Vv (peri-vascular hemorrhage)

Fibroatheroma with severe Intraplaque hemorrhage



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

Vasa Vasorum Assessed at Three - different locations

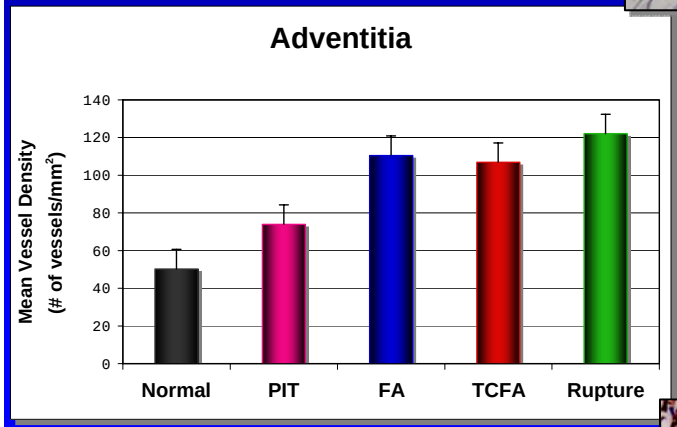


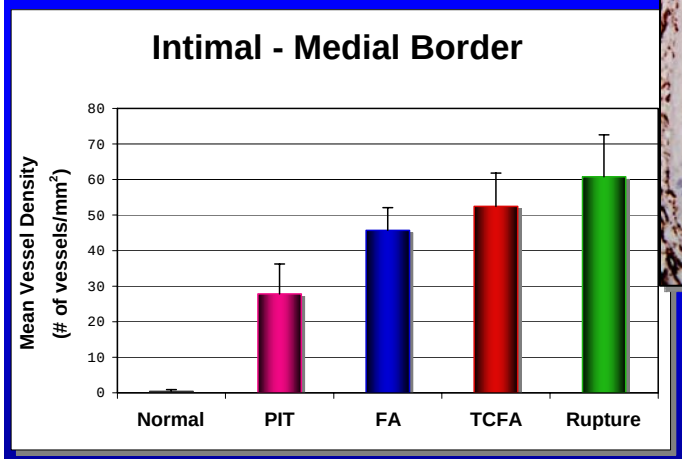
1. Adventitia

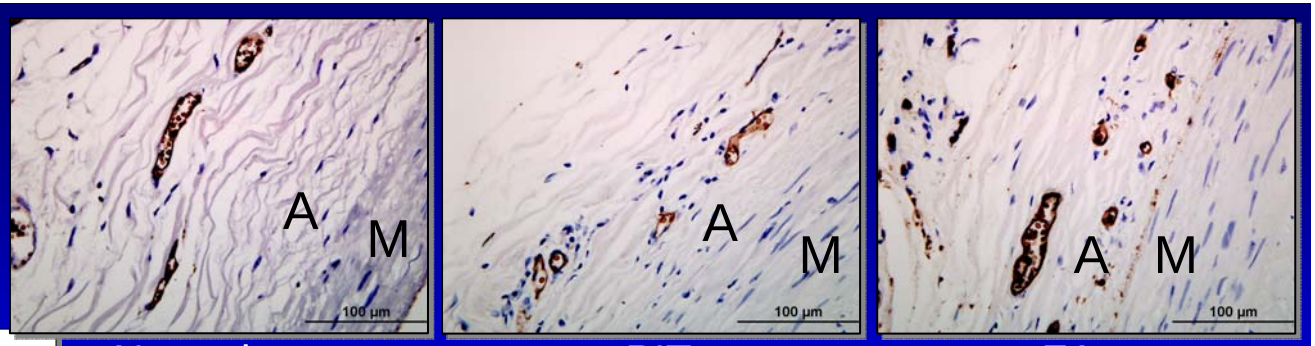
2. Intimal/ medial Border

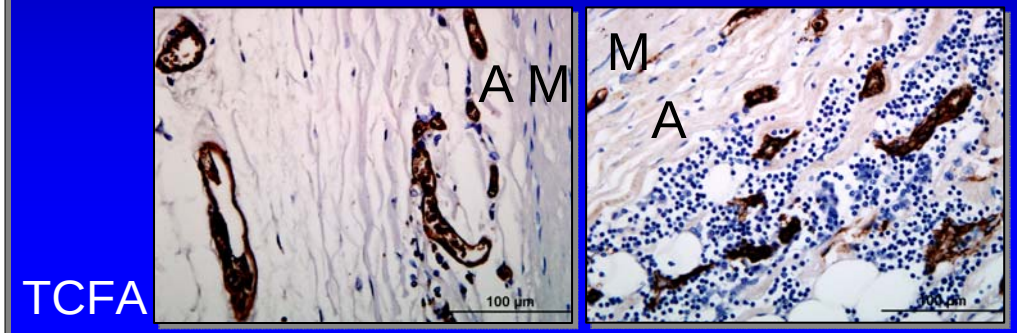
3. Pericore

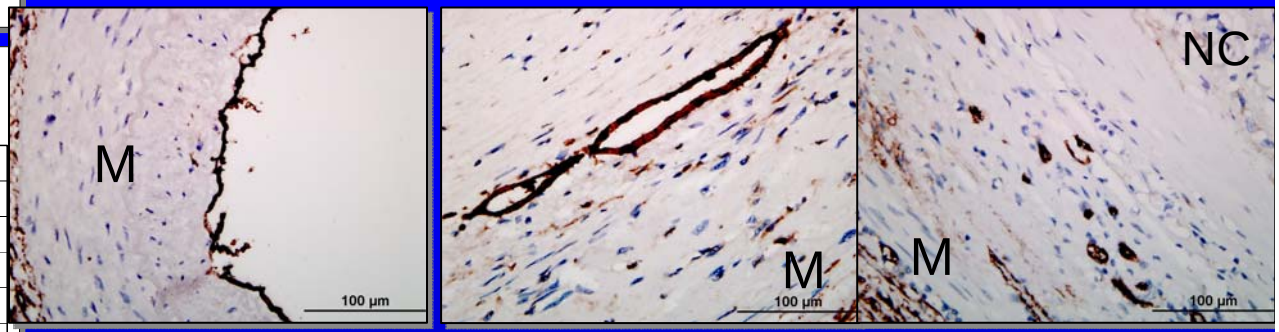
Adventitial Vasa Vasorum In Varying Plaque Morphologies (Ulex Europaeus)

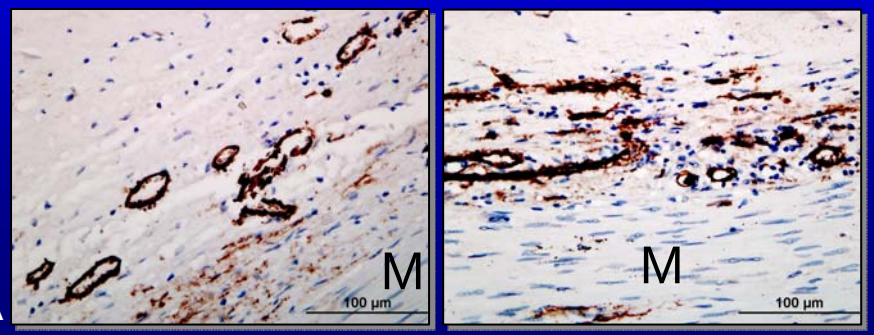






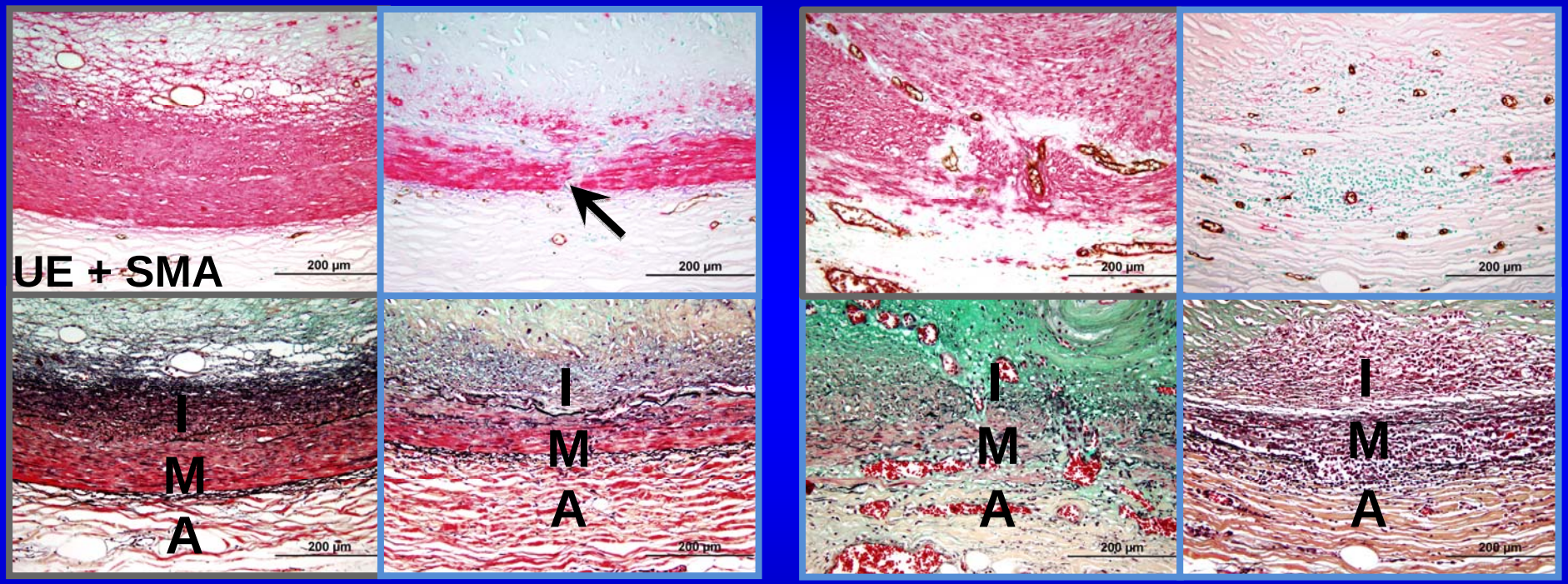






Intimal-Medial Border Vasa Vasorum in Varying Plaque Morphologies (CD31/CD34)

Natural Degradation of the Medial Wall Promotes Invasion of Vasa Vasorum from the Adventitia



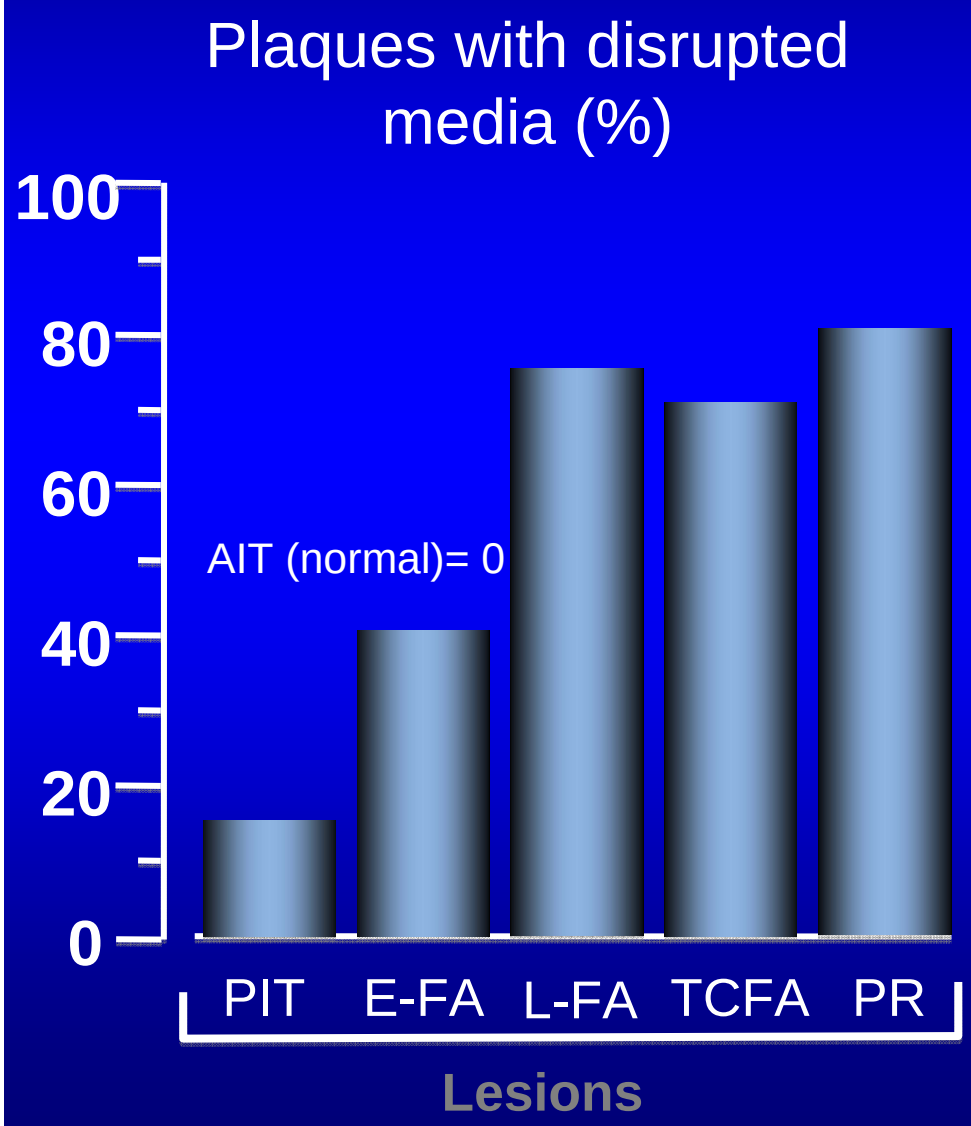
Intact

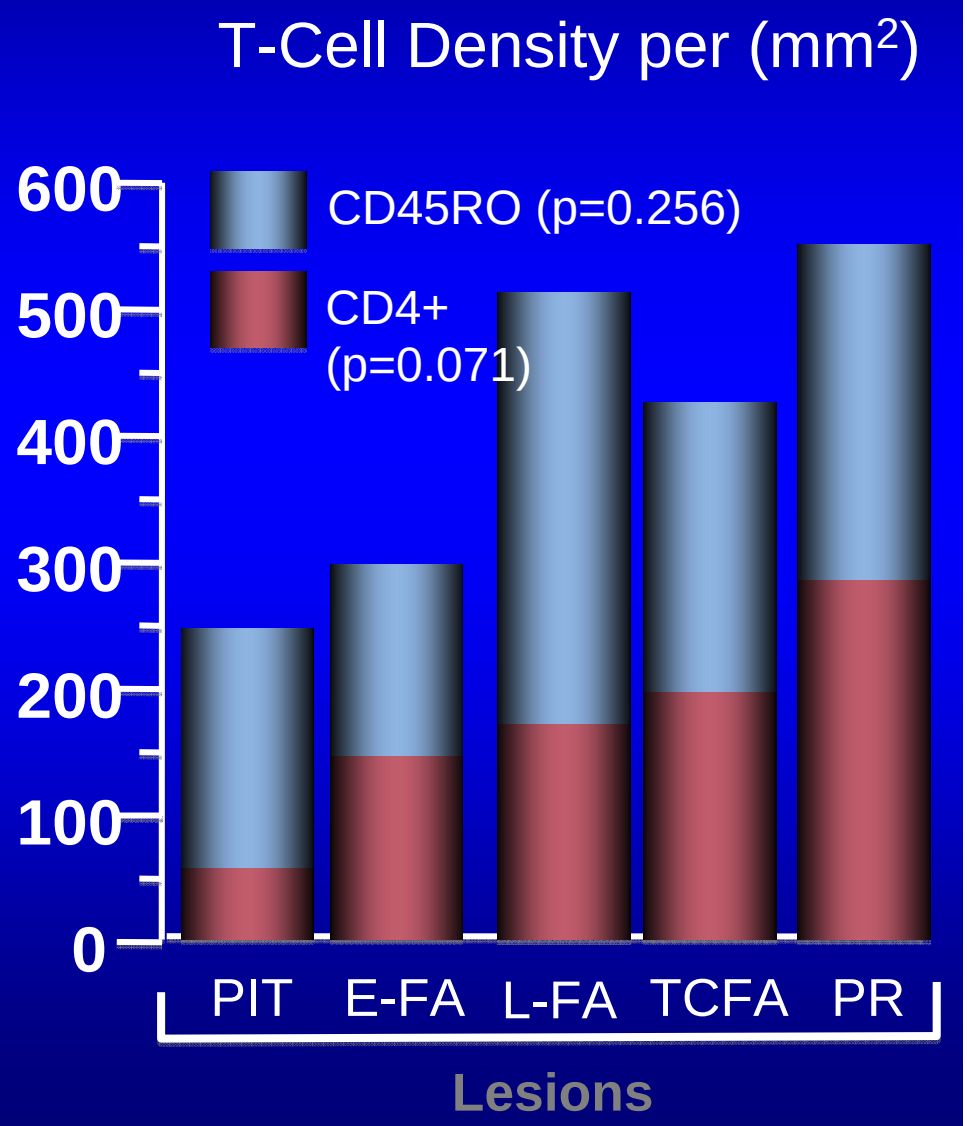
Focal Breaks without invading (Vv)

Focal Breaks with invading (Vv)

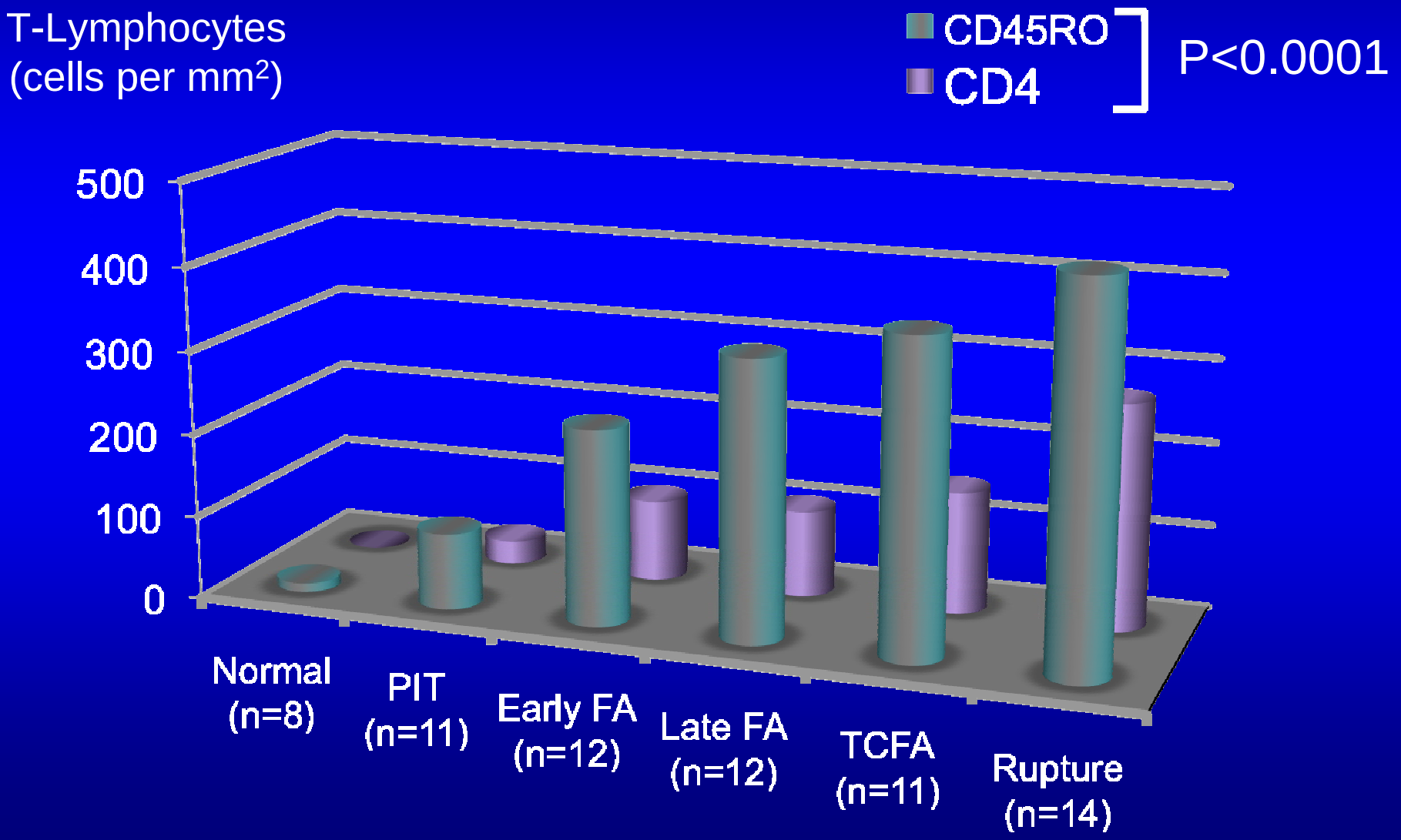
Fully degraded media

Medial Disruption in Human Coronary Plaques and Associated Lymphocytic Inflammation

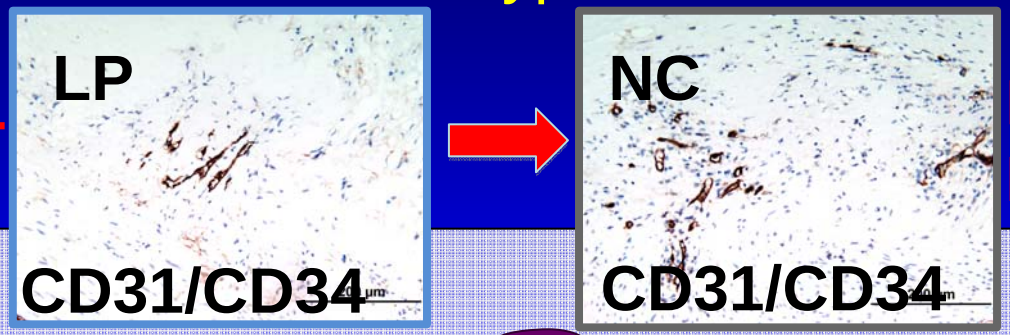




T Cell Densities of Vasa Vasorum at 'Hot-Spots' within the Intima of Progressive Human Coronary Atherosclerotic Plaques

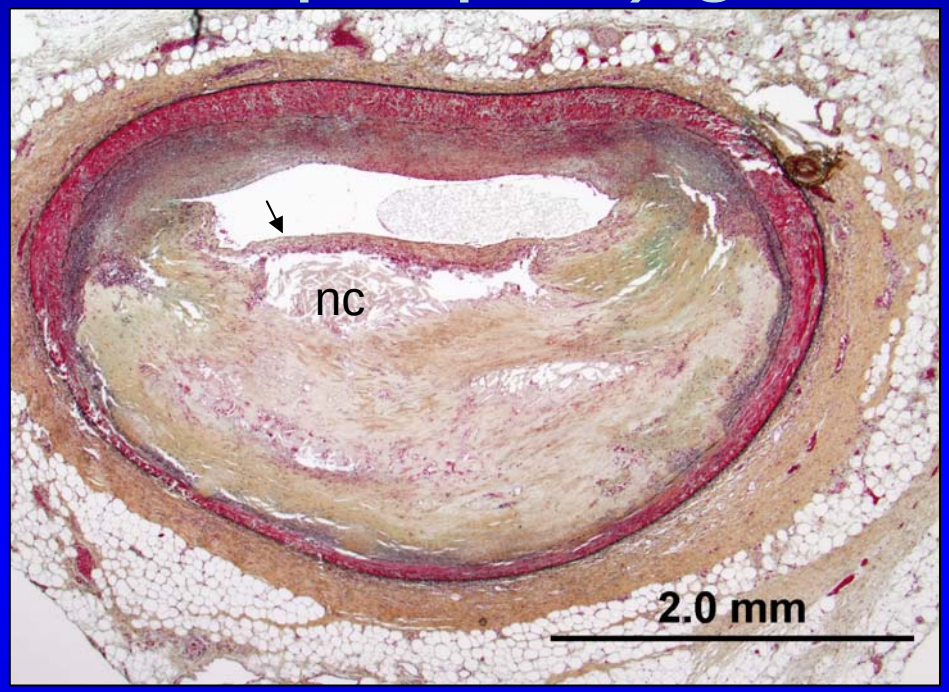


Potential Mechanism Underlying a Latent Pro-Angiogenic Phenotype in Human Coronary Atheroma

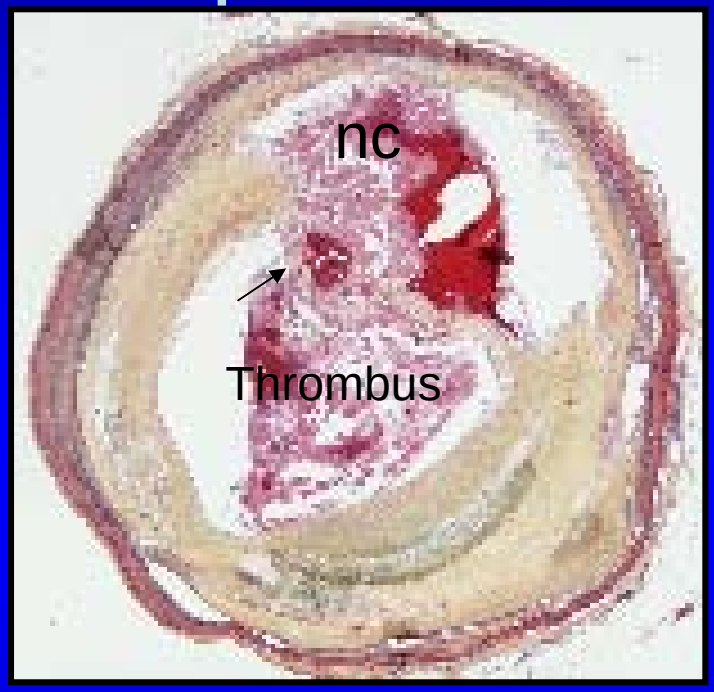


Modified from Imhof BA & Aurrand-Lions M Nat Med, 2006

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



?



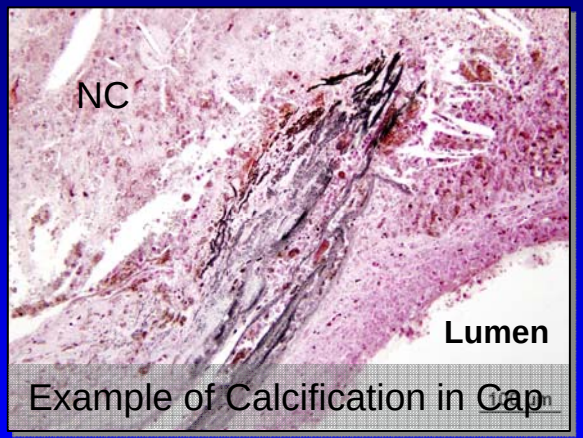
Thin cap fibroatheroma

- **Necrotic core (21.6±23.7%)**
- **Thin fibrous cap (< 65 μm)**
- **Cap infiltrated by macrophages and lymphocytes**
- **Cap composition – type 1 collagen with few or absent smooth muscle cells**

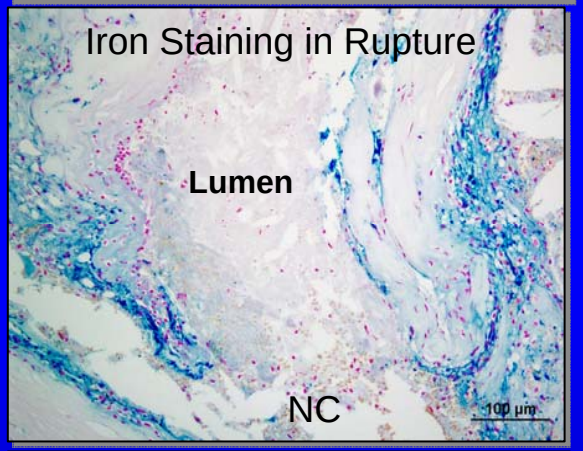
Plaque Rupture

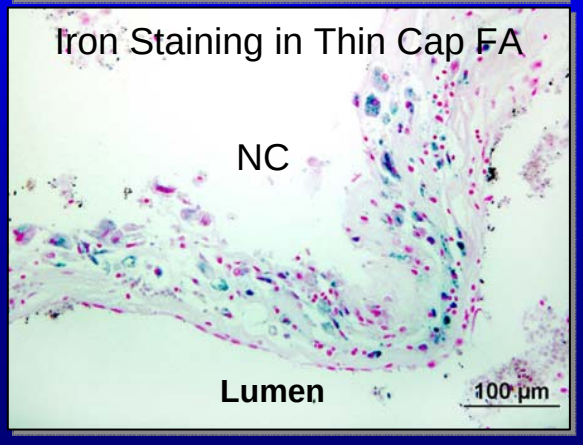
- **Discontinuous fibrous cap (23±19 μm)**
- **Underlying necrotic core (29.0±19.0%)**
- **Luminal thrombus**

Calcification and Iron in Caps of Thin Cap FAs and Ruptures

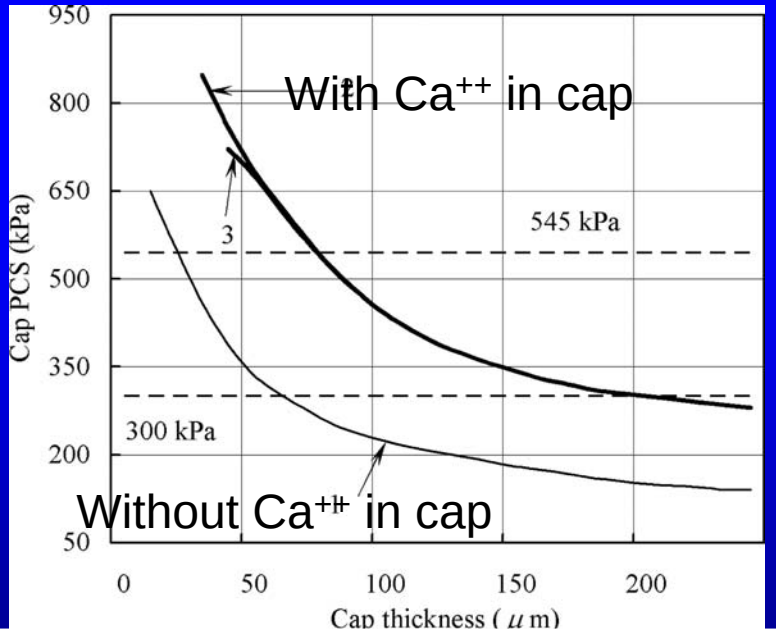


Example of Calcification in Cap





	TCFA (25)	Rupture (34)	P Value
Calcification in Cap	10	17	0.09
Iron in Cap	17	27	0.02

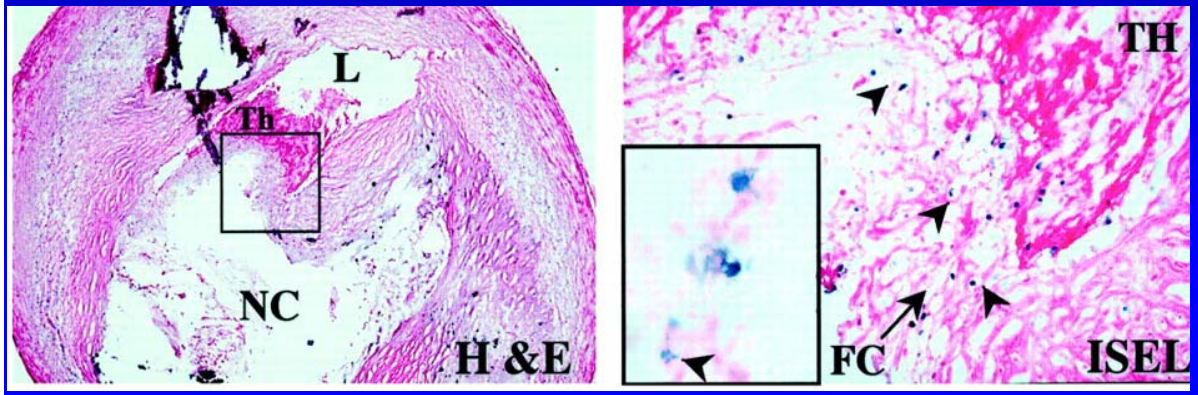


Vengrenyuk Y. et.al. PNAS 2006;103:14678-14683

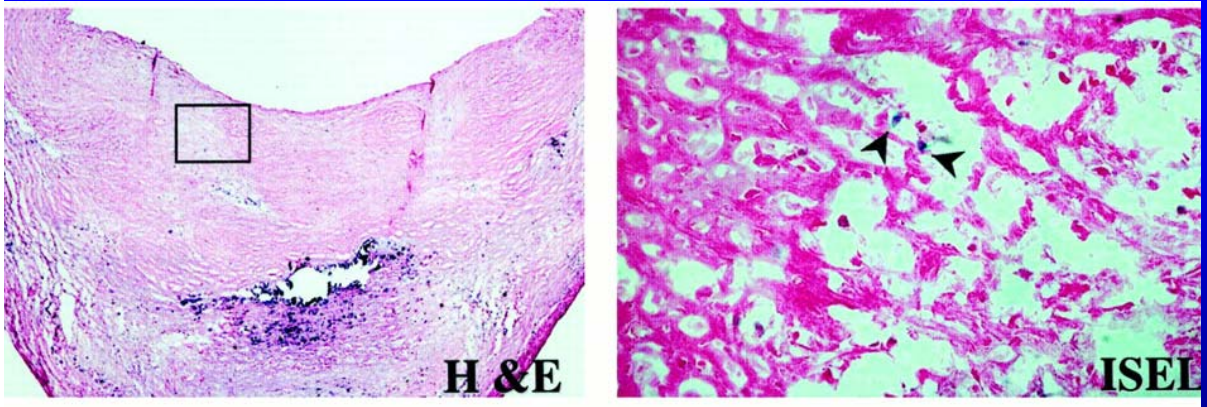
Peak Circumferential Stress is 2-times higher in cap with Ca++

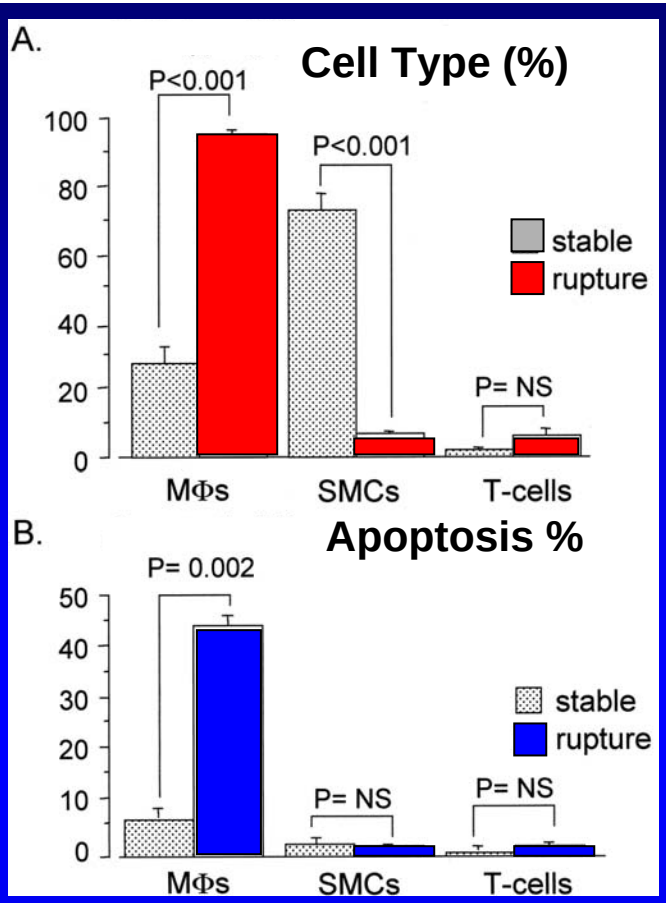
Apoptotic cells in Rupture versus Stable Plaques

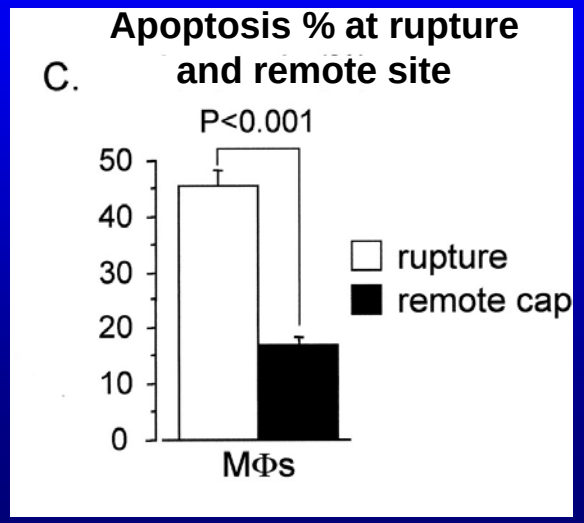
Rupture



Stable





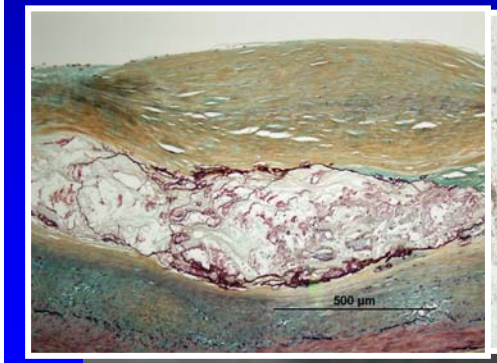


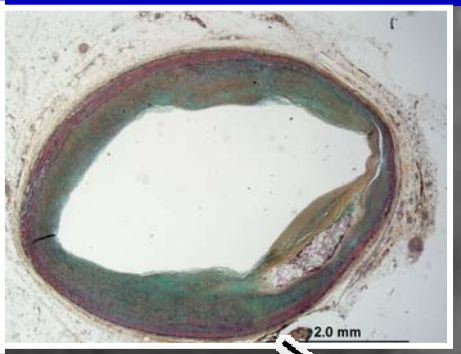
Kolodgie FD, Am J Pathol 2000; 157:1259

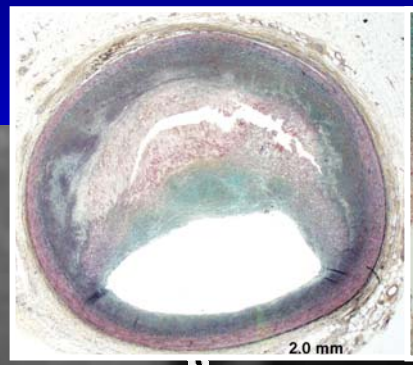
Multi-slice CT vs. Histology

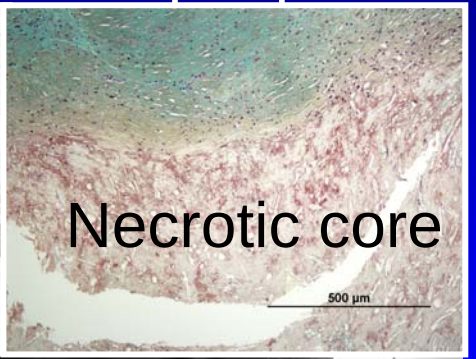
Non- calcified plaque

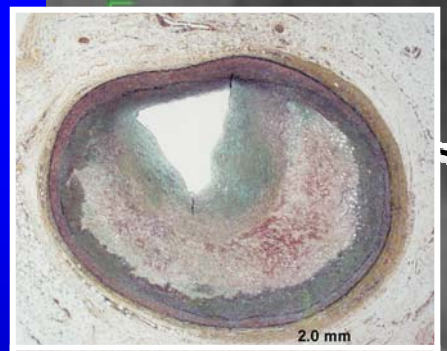
Spotty calcification







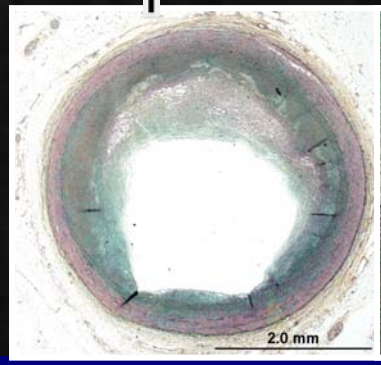


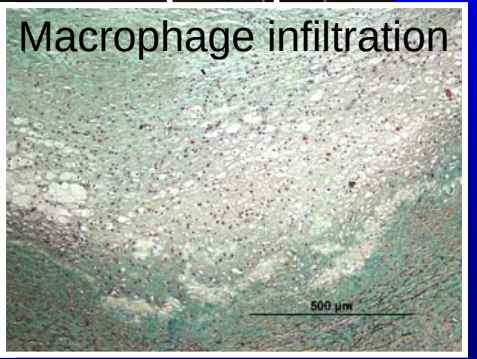


Non- calcified plaque

Courtsey Udo Hoffman M.D.

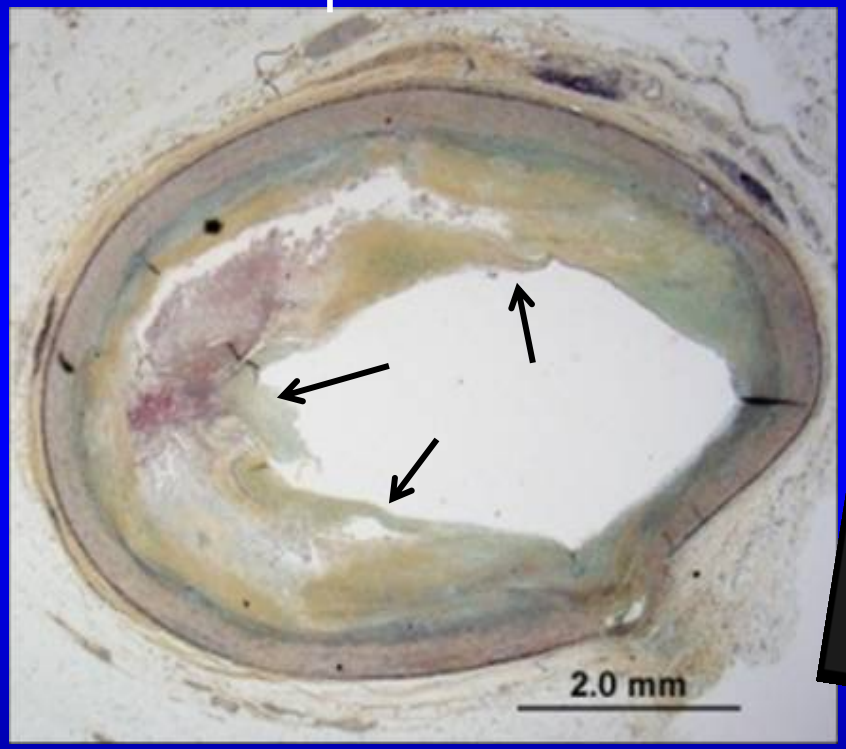
Non- calcified plaque

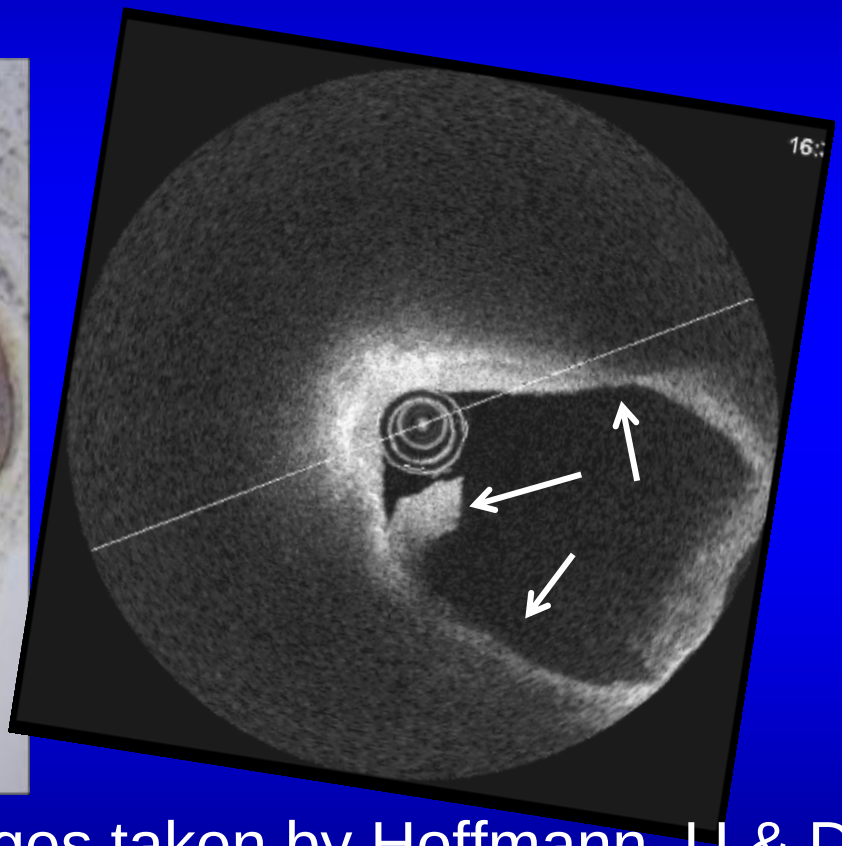




Possibility of OCT imaging Findings from Ex-Vivo Imaging

Thin-cap fibroatheroma





OCT images taken by Hoffmann, U & Donne

Summary

- Macrophage infiltration and apoptosis play a critical role in the early induction of necrotic core formation (occurring via triggering of apototic cell death in macrophages undergoing ER stress)
- Plaque angiogenesis from invading adventitial vasa vasorum is a major cause of intraplaque hemorrhage, which is partly responsible for necrotic core expansion and potential lesion instability.
- Degradation of the medial wall increases as lesions progress toward a more unstable phenotype where an attenuated media likely facilitates the invasion of adventital vasa vasorum.
- Although hypoxia is considered a major driving force for the induction of lesion vascularization, inflammation, in particular T- cell mediated immunity likely provides a potent stimulus for both medial degradation and plaque neoangiogenesis, in particular in ruptured plaques.

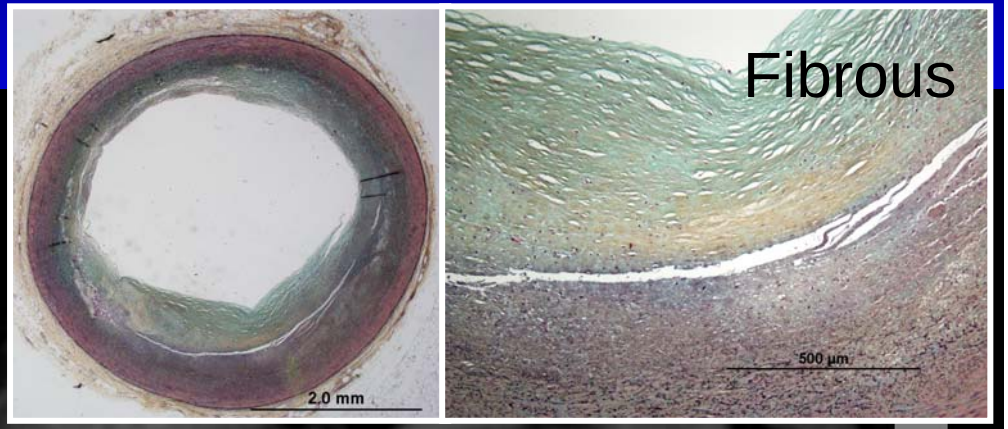
Conclusion

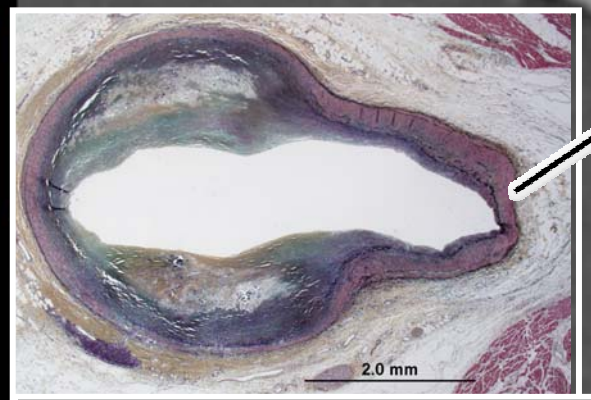
- *Future perspective:*
- What makes a necrotic core enlarge and at the same time cause the fibrous cap to thin is crucial to our understanding of plaque rupture.
- Angiogenesis and surrounding inflammation may also be critical to enlargement of the necrotic core.
- Fibrous cap areas of calcification and iron deposition may help in the understanding of the role of peak circumferential stress sites and rupture.

Multi-slice CT vs. Histology

Micro-calcification

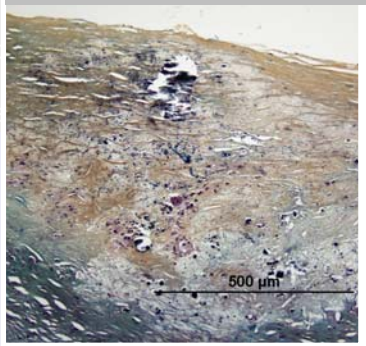
Non- calcified plaque

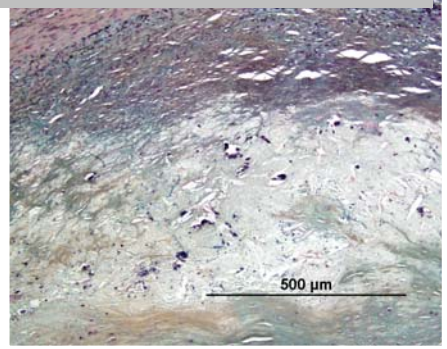




LAD

Micro-calcification (dark purple)





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Courtsey Udo Hoffman M.D.