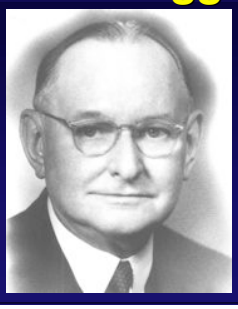
New Insights into the Pathophysiology of the Acute Coronary Syndromes

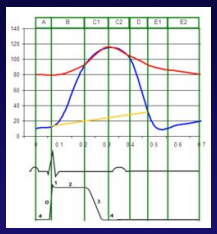
Peter Libby
Brigham & Women's Hospital
Harvard Medical School

Carl J. Wiggers Lecture
April 26, 2007

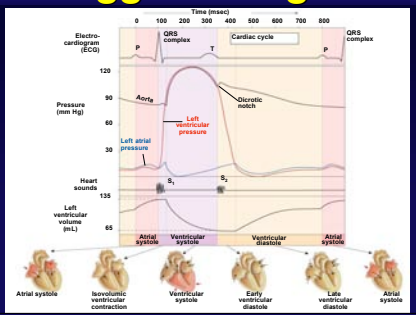
Carl J. Wiggers



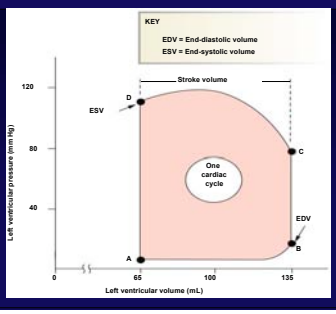
Carl J. Wiggers

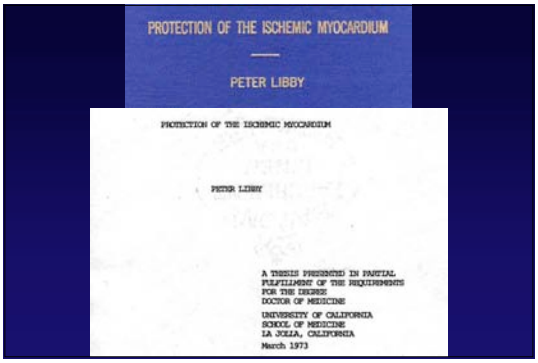


Wiggers' Diagram



Left ventricular pressure-volume loop





PROTECTION OF THE ISCHEMIC MYOCARDIUM

PETER LIBBY

43. Tennant, R., C.J. Wiggers: The effect of coronary occlusion on myocardial contraction. Am. J. Physiol. 112:351, 1935.

The First Description of Paradoxical Ventricular Motion During Acute Coronary Ischemia

THE EFFECT OF CORONARY OCCLUSION ON MYOCARDIAL CONTRACTION[1]

ROBERT TENNANT[2] AND CARL J. WIGGERS

From the Department of Physiology, Western Reserve University Medical School, Cleveland, O.

Received for publication March 22, 1935

3. Occlusion of a main coronary branch is followed by an evoluting series of myographic changes which indicate progressive enfeeblement of contraction to the extent that approximately within a minute the area stretches during isometric contraction, remains stretched during systolic ejection and shortens quickly during isometric relaxation; in short, the myogram is completely inverted.

Tennant and Wiggers *Am J Physiol* 1935;112:351.

Molecular Mechanisms of the Acute Coronary Syndromes



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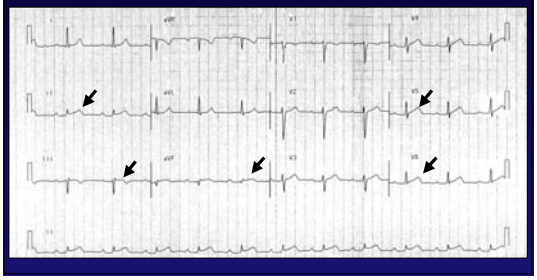
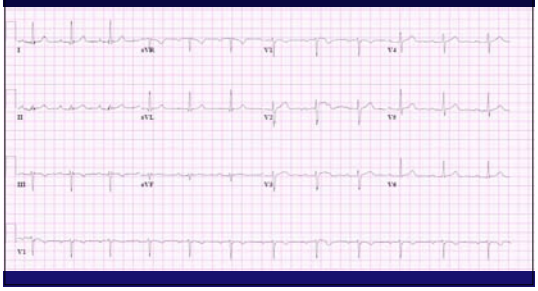
Case Presentation – "J.S."

- 61M who presents with epigastric pain.
- Generally healthy and active, runs 5 miles qod
- No DM, HTN, hyperlipidemia, tobacco use, or FHx
- Episode of abdominal / epigastric pain ~ 2 weeks before presentation while running, improved with rest and OTC proton-pump inhibitor
- Similar episode on day of presentation, with nausea, vomiting while running.

JS: Electrocardiogram @ Suburban Clinic



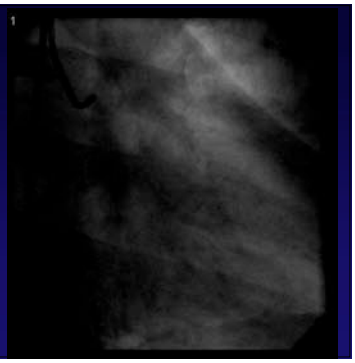
JS: Electrocardiogram @ BWH



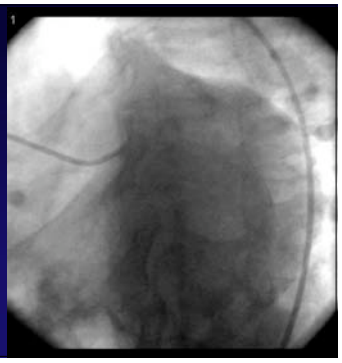
Case Presentation – "J.S."

- Cardiac TnI 1.18
- CK 234 / CK-MB 8.6

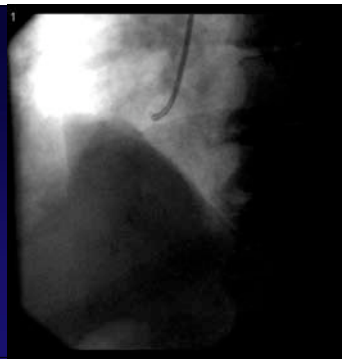
JS: Left coronary artery



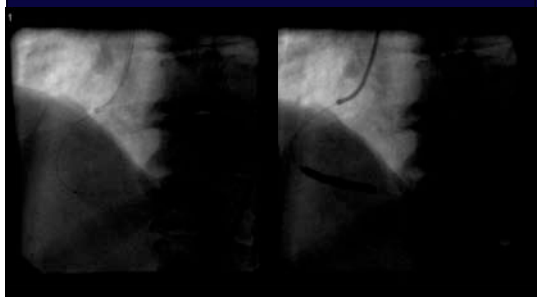
JS Left coronary artery



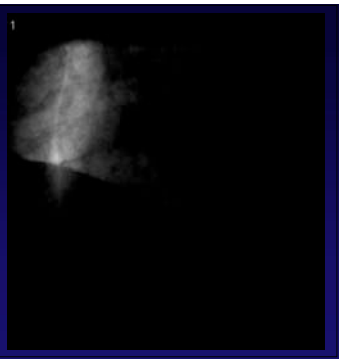
JS: Right coronary artery



JS: Right coronary intervention



JS: Right coronary artery



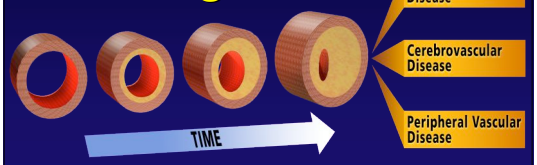
Case Presentation – "J.S."

- CK peak 688 / CK-MB 40.9 / cTnI 11.13

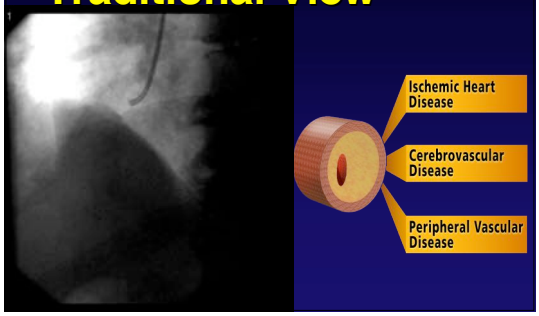
Case Presentation – "J.S."

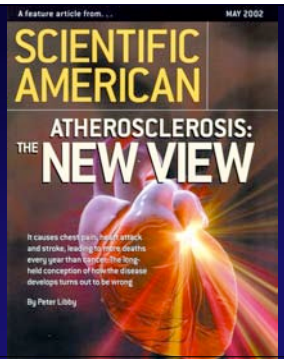
- He had an otherwise uneventful post-PCI course
- Discharged on Aspirin, clopidogrel, atorvastatin, lisinopril and metoprolol.
- Seen in follow up after 6 weeks without symptoms.

Traditional View of Human Atherogenesis



Traditional View





MIs often arise from non-critical stenoses

- Post-thrombolysis angiography
- Serial angiographic studies
- Intravascular Ultrasound studies

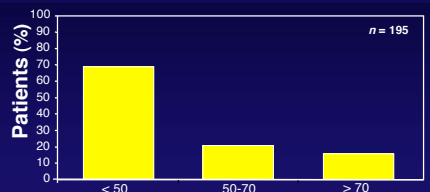
Stenosis and Coronary Thrombosis

- Studied 60 consecutive patients by QCA during 1st MI post-thrombolysis
- Residual stenosis < 60 % in 28 (47%)

'Pre-existing coronary stenoses in patients with first myocardial infarction are not necessarily severe.'

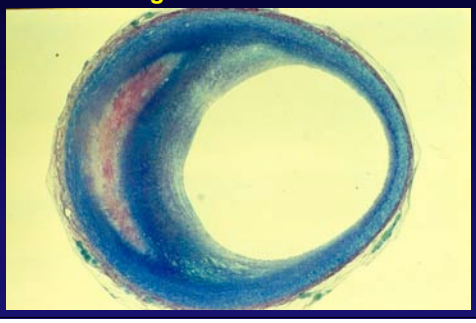
Hackett D, Davies G, Maseri A. European Heart J 1988

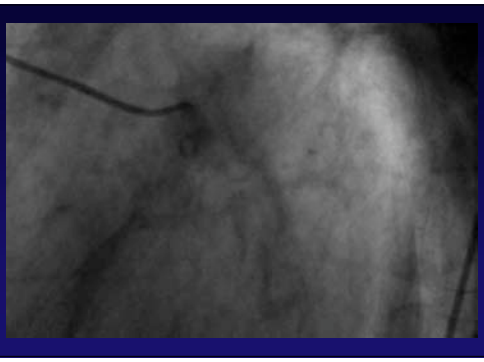
Severity of coronary artery stenosis before acute MI



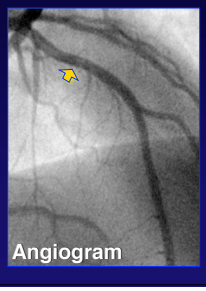
Data from four studies. *Smith SC. Circulation 1996*

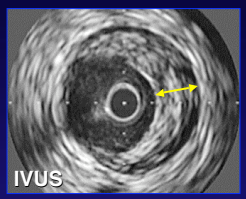
Remodeling in human atherosclerosis





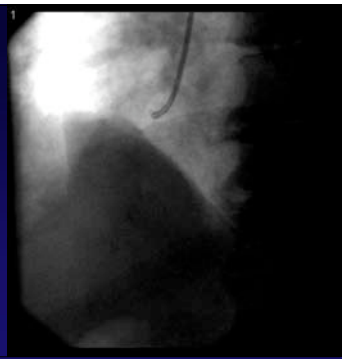
Angiography does not show eccentrically remodeled atheroma

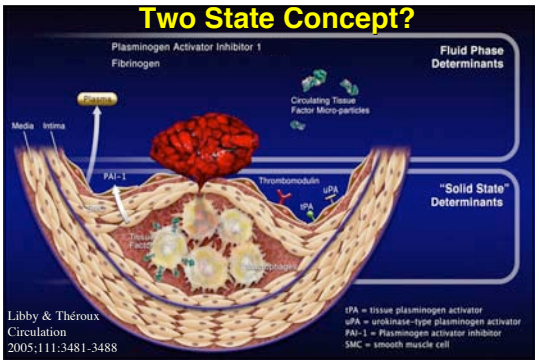


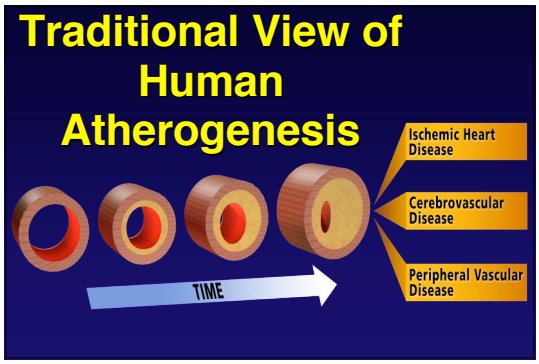


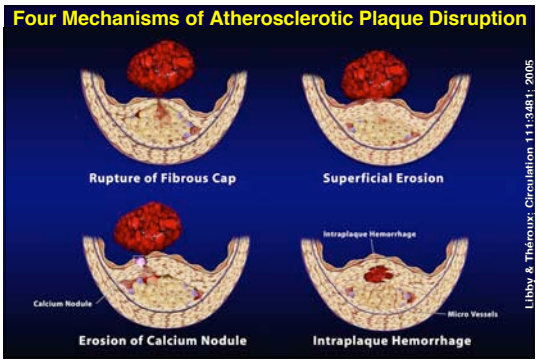
From Scott Kinlay, BWH, HMS

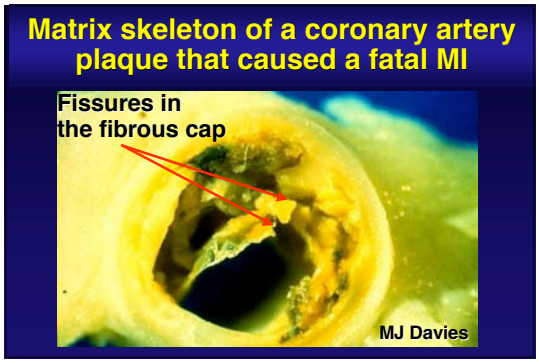
JS: Right coronary artery

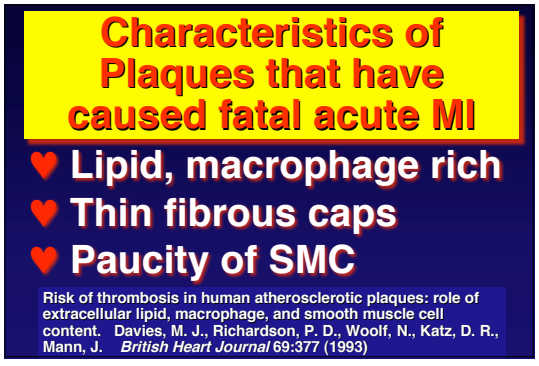


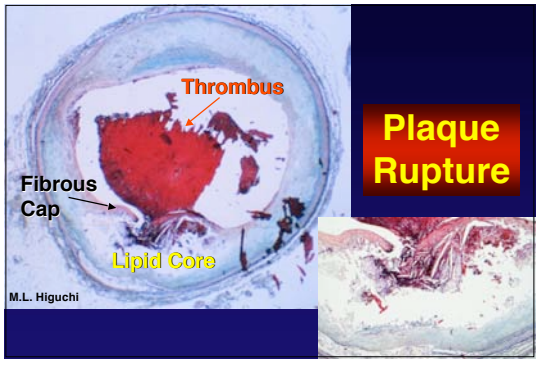

Two State Concept?
Plasminogen Activator Inhibitor 1
Fibrinogen
Fluid Phase Determinants
Circulating Tissue Factor Micro-particles
Platelet
Media
Intima
PAI-1
Thrombomodulin
uPA
tPA
"Solid State" Determinants
Tissue Factor
Macrophage
Libby & Théroux
Circulation
2005;111:3481-3488
tPA = tissue plasminogen activator
uPA = urokinase-type plasminogen activator
PAI-1 = Plasminogen activator inhibitor
SMC = smooth muscle cell


Traditional View of Human Atherogenesis
Ischemic Heart Disease
Cerebrovascular Disease
Peripheral Vascular Disease
TIME


Four Mechanisms of Atherosclerotic Plaque Disruption
Rupture of Fibrous Cap
Superficial Erosion
Calcium Nodule
Intraplaque Hemorrhage
Micro Vessels
Erosion of Calcium Nodule
Intraplaque Hemorrhage
Libby & Théroux. Circulation 111:3481. 2005

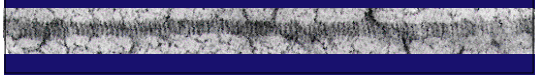

Matrix skeleton of a coronary artery plaque that caused a fatal MI
Fissures in the fibrous cap
MJ Davies


Characteristics of Plaques that have caused fatal acute MI
Lipid, macrophage rich
Thin fibrous caps
Paucity of SMC
Risk of thrombosis in human atherosclerotic plaques: role of extracellular lipid, macrophage, and smooth muscle cell content. Davies, M. J., Richardson, P. D., Woolf, N., Katz, D. R., Mann, J. British Heart Journal 69:377 (1993)


Thrombus
Plaque Rupture
Fibrous Cap
Lipid Core
M.L. Higuchi

Structural Integrity of the Plaque's Fibrous Cap

- Depends on interstitial collagen fibrils (types I & III) synthesized by smooth muscle cells

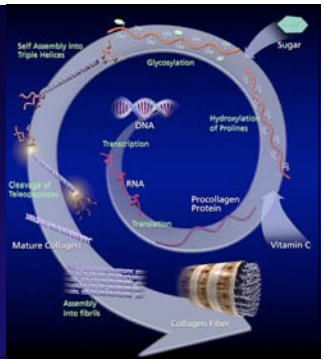


Plaque rupture

- Decreased synthesis of interstitial collagens

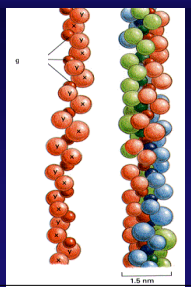
Interstitial Collagen Production

Libby & Aikawa
Circulation
2002;105:1396-1398



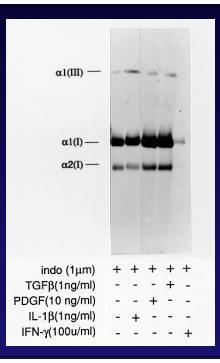
Collagen fibril organization into triple helices

Gly-X (pro)-Y (Hyp)



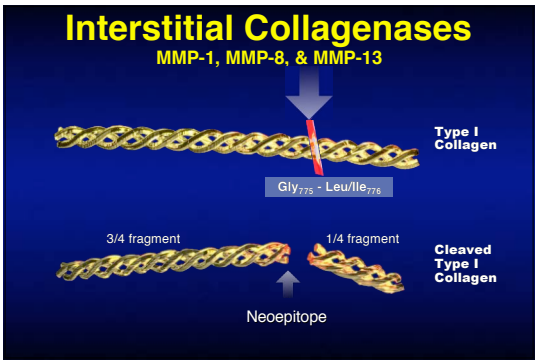
Cytokines positively and negatively regulate interstital collagen synthesis by human smooth muscle cells

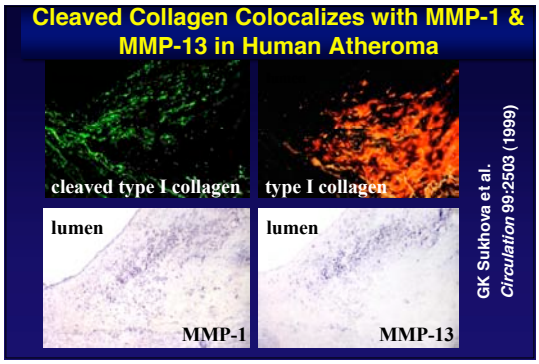
(Amento, Ehsani, Palmer, Libby *Arteriosclerosis* 11:1166, 1991)

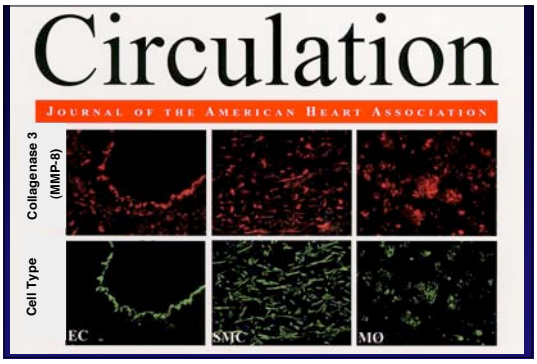


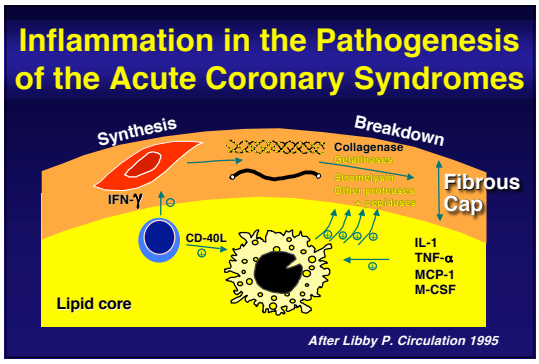
Plaque rupture

- Decreased synthesis of interstitial collagens
- Increased *degradation* of extracellular matrix

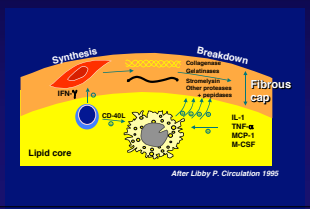








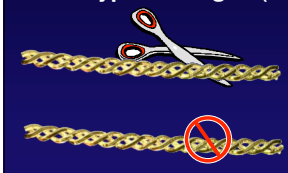
However, so far ***no direct evidence*** links collagenases with regulation of the collagen content of atheroma



Therefore, we tested directly the hypothesis that collagenolysis critically influences collagen accumulation in atheroma *in vivo* using genetically altered mice.

Collagenase-resistant mutant mice

•Mutation at the specific collagenase cleavage site on type I collagen ("knock-in")



collagenase cleavage site

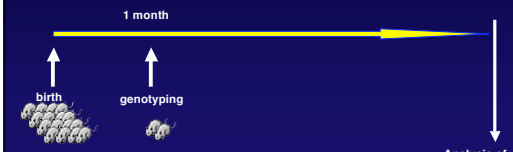
GLY (775) - ILE (776)

GLY (775) - PRO (776)

(Zhao W, Byrne MH, Boyce BF, Krane SM. JCI 1999)

Experimental protocol

Backcrossed >7 generations into C57BL/6.
Collagenase-resistant mutant (R/R) / apo E (-/-) mice
Wild-type collagen (+/+) / apo E (-/-) mice

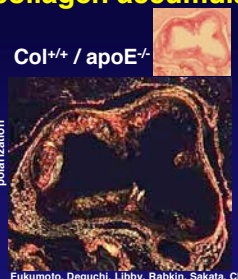


Experimental protocol

Collagenase-resistant mutant (R/R) / apo E (-/-) mice
Wild-type collagen (+/+) / apo E (-/-) mice

Does collagenolysis influence collagen accumulation in atheroma?

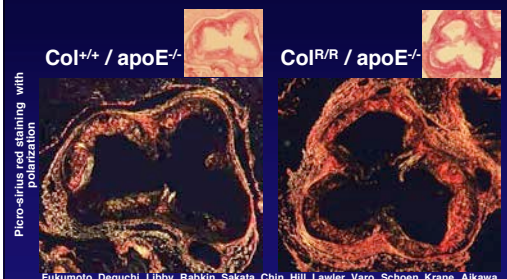
$Col^{+/+}$ / $apoE^{-/-}$



Fukumoto, Deguchi, Libby, Rabkin, Sakata, Chin, Hill, Lawler, Varo, Schoen, Krane, Aikawa
Circulation 2004;110:1953

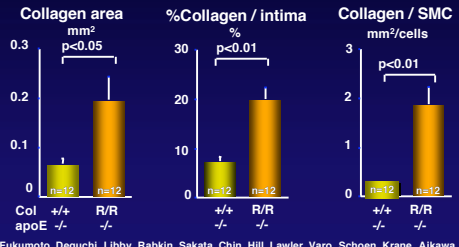
Collagenase-resistance promotes collagen accumulation in mouse atheroma

$Col^{+/+}$ / $apoE^{-/-}$ $Col^{R/R}$ / $apoE^{-/-}$



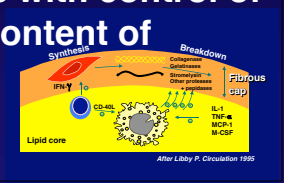
Fukumoto, Deguchi, Libby, Rabkin, Sakata, Chin, Hill, Lawler, Varo, Schoen, Krane, Aikawa
Circulation 2004;110:1953

Collagenase-resistance causes collagen accumulation in mouse atheroma



Fukumoto, Deguchi, Libby, Rabkin, Sakata, Chin, Hill, Lawler, Varo, Schoen, Krane, Aikawa
Circulation 2004;110:1953

This study in genetically altered mice provides the first *direct evidence* that links collagenolysis with control of the collagen content of atheroma



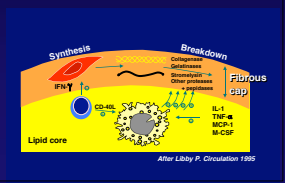
Which proteinases control the collagen content of atheroma?

MMP-1?

MMP-8?

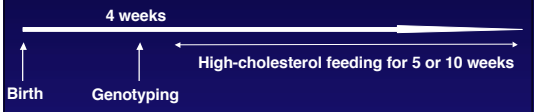
MMP-13?

MT-1-MMP…?



Experimental protocol

Mmp 13 -/- mouse backcrossed 7 generations into C57BL6 background, then crossed with atherosclerosis-susceptible *apoE*$^{-/-}$ mice

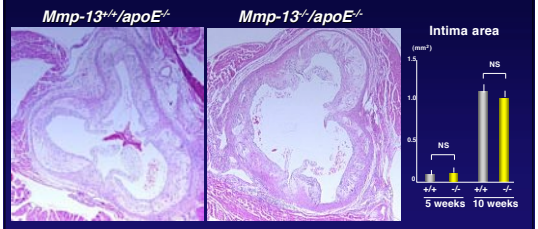


Mmp-13$^{+/+}$*/apoE*$^{-/-}$ male mice (n=17)

Mmp-13$^{-/-}$*/apoE*$^{-/-}$ male mice (n=17)

Deguchi *et al.* Circulation 2005; 112:2708

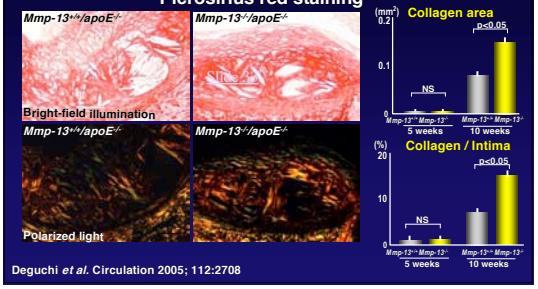
MMP-13/collagenase-3 deficiency does not affect atheroma burden in *apoE*$^{-/-}$ mice



Deguchi *et al.* Circulation 2005; 112:2708

MMP-13/collagenase-3 deficiency increases fibrillar collagen in mouse atheromata

Picrosirius red staining



Deguchi *et al.* Circulation 2005; 112:2708

Collagenases critically influence collagen accumulation in mouse atheromata *in vivo*

P Libby

Work in Progress

MMP-14 deficient / apoE$^{-/-}$ mice
MMP-8 deficient / apoE$^{-/-}$ mice
TIMP-3 deficient / apoE$^{-/-}$ mice
MMP-8 & 13 deficient / apoE$^{-/-}$ mice

P Libby

Clinical and Therapeutic Correlations

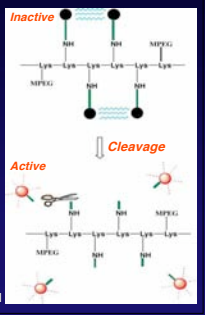
- Many matrix-degrading proteases particpate in atherogenesis
- Proteolysis may predispose to plaque disruption and thrombosis
- Can we monitor protease activity in vivo?

Near Infrared Fluorescent (NIRF) probes

The NIRF probes are optically inactive in their native, quenched state and produce very low background fluorescence.

Upon enzymatic cleavage of specific peptide sequences by the protease (e.g., MMP-2), the NIRF probe elaborates fluorescence (e.g., Cy5.5) with hundreds-fold amplification.

Bremer C, Bredow S, Mahmood U, Weissleder R, Tung CH. *Radiology* 2001



Inflammation in Atherosclerosis

Visualizing Matrix Metalloproteinase Action in Macrophages In Vivo

Jun-o Deguchi, MD, PhD*; Masanori Aikawa, MD, PhD*; Ching-Hsuan Tung, PhD; Elena Aikawa, MD, PhD; Dong-Eog Kim, MD; Vasilis Ntziachristos, PhD; Ralph Weissleder, MD, PhD; Peter Libby, MD

Background—Matrix metalloproteinases (MMPs) in inflamed atherosclerotic plaques may contribute to extracellular matrix remodeling and the onset of acute thrombotic complications.

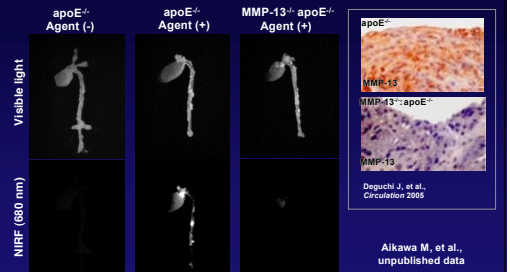
Methods and Results—To test the hypothesis that optical molecular imaging with the use of an activatable near-infrared fluorescence (NIRF) probe can detect enzymatic action of MMP in atherosclerotic plaques, we used a NIRF substrate for gelatinases (MMP-2/gelatinase-A and MMP-9/gelatinase-B) in apolipoprotein E–deficient (apoE$^{-/-}$) mice that consumed a high-cholesterol diet for 12 weeks and age-matched apoE$^{+/+}$ mice as control. The aortas of apoE$^{-/-}$ mice at 24 hours after probe yielded intense NIRF signals, as detected by NIRF reflectance ex vivo, compared with negligible signals in aortas of apoE$^{+/+}$ mice with/without probe administration or atherosclerotic apoE$^{-/-}$ aortas without probe. Gelatinase inhibitor treatment abolished NIRF signals in apoE$^{-/-}$ mouse aortas ex vivo. Sites of gelatinase activity visualized by NIRF colocalized with macrophage accumulation, immunoreactive MMP-2 and MMP-9, and gelatinolytic activity detected by in situ zymography. Furthermore, fluorescence molecular tomography indicated in vivo that atherosclerotic aortas of apoE$^{-/-}$ mice produced NIRF signals for gelatinase action, whereas aortas of apoE$^{+/+}$ mice injected with the probe or apoE$^{-/-}$ aortas with no probe exhibited negligible NIRF signals.

Conclusions—These results suggest the feasibility of noninvasively imaging the enzymatic action of MMPs in vivo, an approach that may gauge inflammatory foci in atherosclerosis, assess cardiovascular risk, and evaluate the effects of therapeutic interventions. (*Circulation*. 2006;114:55-62.)

Cleavage of an MMP-13-activatable agent *in vitro*

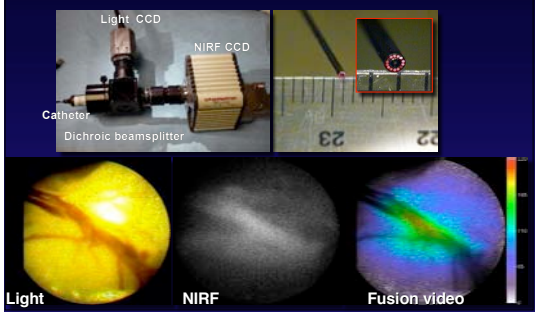
Aikawa M et al., unpublished data

Imaging of MMP-13 by Near Infrared Fluorescence in Mouse Atheromata

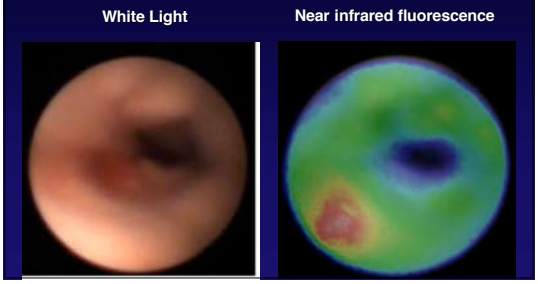


Aikawa M, et al., unpublished data

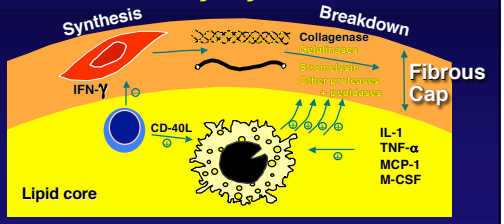
Near IR Fluorescence Catheter



Intra-arterial Protease (Cat B) Imaging in vivo in Watanabe Rabbits

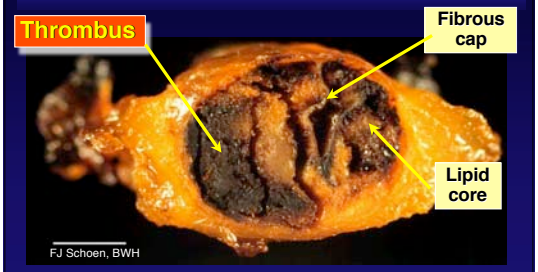


Proteinases Participate in the Pathogenesis of the Acute Coronary Syndromes

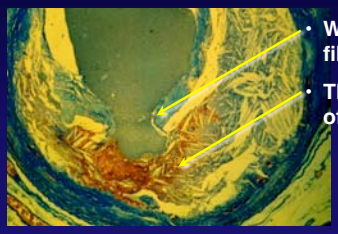


After Libby P. Circulation 1995

Plaque rupture with thrombosis

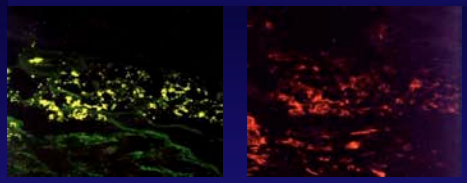


Thrombosis of a disrupted atheroma, the cause of most acute coronary syndromes, results from:



- Weakening of the fibrous cap
- Thrombogenicity of the lipid core

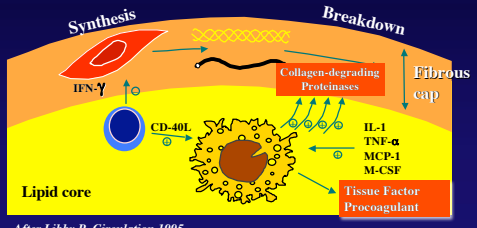
CD40 and tissue factor in atheroma



CD40 Tissue factor

After Mach F et al. Circulation 1997

Molecular Mechanisms of the Unstable Coronary Syndromes



After Libby P. Circulation 1995

The "New Biology" of Atherosclerosis

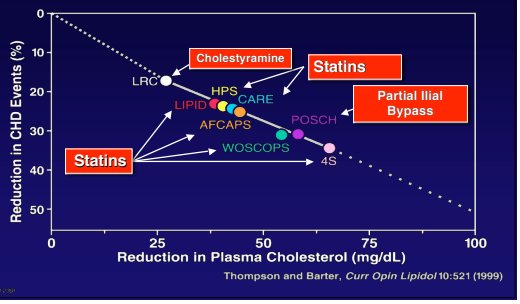
- Unstable coronary atheromata are often not the "tight" stenoses
- ***Stabilization of lesions, by medical therapy, provides a new therapeutic target beyond revasularization***

How do we "stabilize" atherosclerotic plaques?

How do we "stabilize" atherosclerotic plaques? :

- Smoking Cessation
- Diet
- Physical activity
- Choosing your parents wisely

Lipid-Lowering Prevents Clinical Events



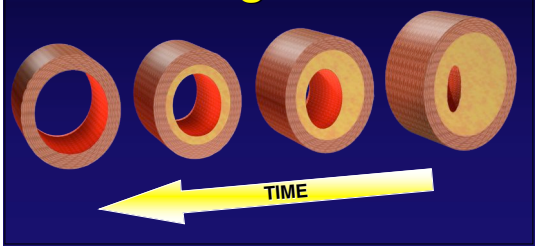
Thompson and Barter, *Curr Opin Lipidol* 10:521 (1999)

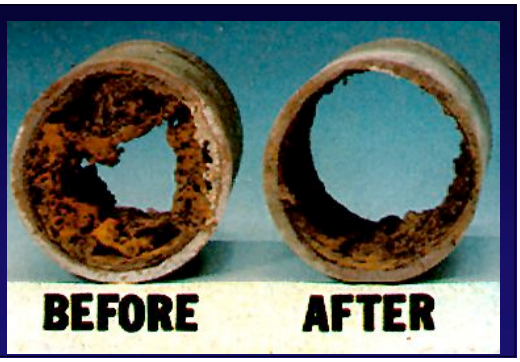
How does lipid-lowering improve patient outcome?

How does lipid-lowering improve patient outcome?

- Regression of fixed stenoses?

Regression of Human Atherogenesis?





Disproportionate reduction of coronary events and stenosis in lipid-lowering trials

Trial	Δ Stenosis	Δ Events
FATS (niacin + resin)	- 0.9 %	- 80 %
FATS (statin + resin)	- 0.7 %	- 70 %
STARS (diet)	- 1.1 %	- 69 %
STARS (diet + resin)	- 1.9 %	- 89 %

After Brown BG.

What accounts for the disparity between degree of coronary artery stenosis and producing the acute coronary syndromes?

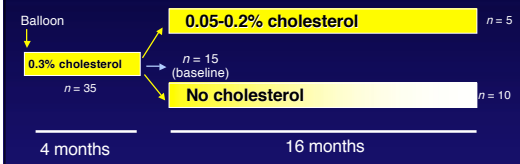
The functional state of the atheroma, not merely its size or the degree of luminal encroachment, determines the propensity for development of acute coronary syndromes

How does lipid-lowering improve patient outcome?

- ~~Regression of fixed stenoses?~~
- Anti-inflammatory effect?

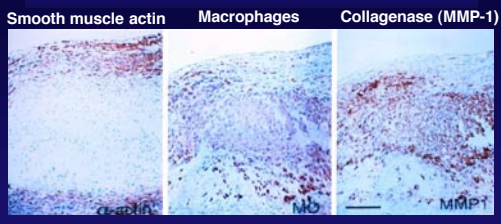
Does lipid lowering stabilize experimental atheroma?

Lipid lowering in rabbits

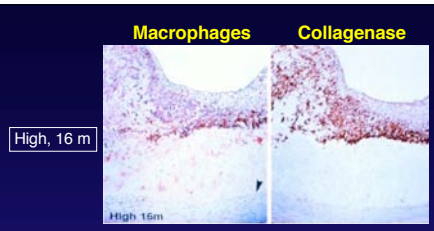


Aikawa M et al.

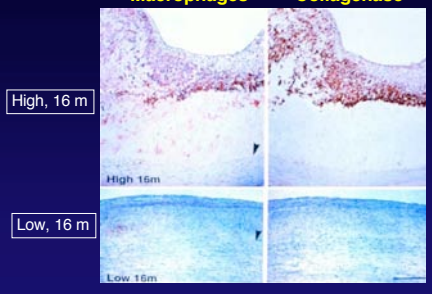
Baseline lesions



Aikawa M *et al. Circulation 1998*

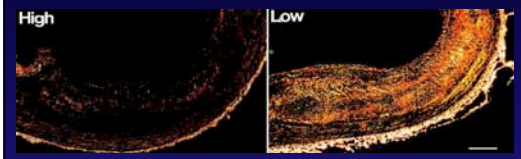


Aikawa M *et al. 1998*



Aikawa M *et al. 1998*

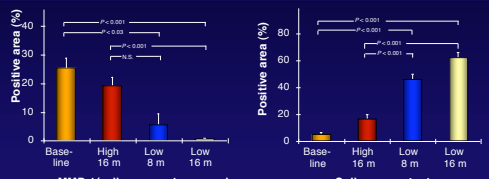
Dietary lipid lowering increases collagen content of rabbit atheroma



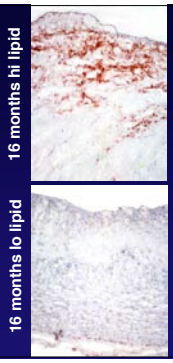
(Picrosirius-red staining after 16 months on a low-lipid diet)

Aikawa M *et al. Circulation 1998*

Inverse relationship between collagenase-1 expression and collagen content in rabbit atheroma during lipid lowering



Aikawa M *et al. Circulation 1998*



Dietary lipid lowering reduces tissue factor expression in rabbit atheroma

Aikawa, Voglic, Sugiyama, Rabkin, Taubman, Fallon, Libby.

Circulation 100:1215;1999

Dietary Lipid Lowering Reduces Inflammation in Atheromata

Lipid lowering by diet alone reduces ROS production, oxLDL accumulation, and VCAM-1 and MCP-1 expression in atheroma of cholesterol-fed rabbits.

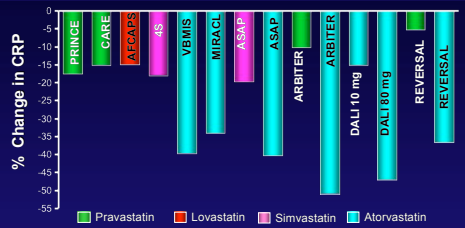
Aikawa, Sugiyama, Hill, Voglic, Rabkin, Fukumoto, Schoen, Witztum, Libby.
Circulation 2002;106:1390-1396

Lipid lowering stabilizes atheroma

In rabbits with diet-induced atherosclerosis, reduced cholesterol consumption:

- Limits inflammation in atheroma
- Improves features of plaques associated with stability
- Reduces plaque thrombogenicity
- Decreases oxidative stress and endothelial dysfunction

Statin Therapy Reduces C-Reactive Protein



Albert et al. *JAMA*. 2001;286:64-70; Crea et al. *Clin Cardiol*. 2002;25:461-466; Kinlay et al. *Am J Cardiol*. 2002;89:1205-1207; Ridker et al. *N Engl J Med*. 2001;344:1959-1965; Ridker et al. *Circulation*. 1998;98:839-844; Taylor et al. *Circulation*. 2002;106:2055-2060; van de Ree et al. *Atherosclerosis*. 2003;166:129-135; van Wissen et al. *Atherosclerosis*. 2002;165:361-366; Nissen et al. JAMA. 2004;291:1071-1080.

Mechanisms of benefit of lipid lowering therapy:

Experimental and human studies suggest that lipid-lowering may stabilize plaques and reduce events by limiting inflammation

The Vulnerable Plaque

- Local therapies relieve angina (PCI, CABG)
- Systemic therapies prevent MI, stroke, and prolong life

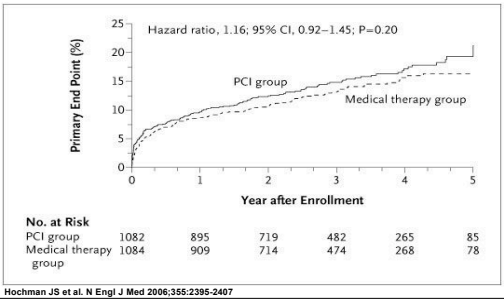
Coronary Intervention for Persistent Occlusion after Myocardial Infarction (OAT)

Judith S. Hochman, M.D., Gervasio A. Lamas, M.D., Christopher E. Buller, M.D., Vladimir Dzavik, M.D., Harmony R. Reynolds, M.D., Staci J. Abramsky, M.P.H., Sandra Forman, M.A., Witold Ruzyllo, M.D., Aldo P. Maggioni, M.D., Harvey White, M.D., Zygmunt Sadowski, M.D., Antonio C. Carvalho, M.D., Jamie M. Rankin, M.D., Jean P. Renkin, M.D., P. Gabriel Steg, M.D., Alice M. Mascette, M.D., George Sopko, M.D., Matthias E. Pfisterer, M.D., Jonathan Leor, M.D., Viliam Fridrich, M.D., Daniel B. Mark, M.D., M.P.H., Genell L. Knatterud, Ph.D., for the Occluded Artery Trial Investigators

N Engl J Med
Volume 355:2395-2407
December 7, 2006

The NEW ENGLAND JOURNAL of MEDICINE

Kaplan-Meier Curves for the OAT Primary End Point, According to the Intention-to-Treat Analysis



Hochman JS et al. N Engl J Med 2006;355:2395-2407

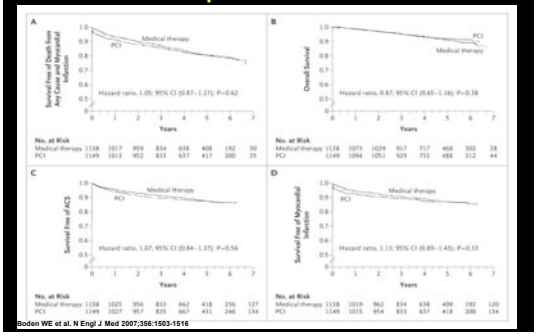
Optimal Medical Therapy with or without PCI for Stable Coronary Disease (COURAGE)

William E. Boden, M.D., Robert A. O'Rourke, M.D., Koon K. Teo, M.B., B.Ch., Ph.D., Pamela M. Hartigan, Ph.D., David J. Maron, M.D., William J. Kostuk, M.D., Merril Knudtson, M.D., Marcin Dada, M.D., Paul Casperson, Ph.D., Crystal L. Harris, Pharm.D., Bernard R. Chaitman, M.D., Leslee Shaw, Ph.D., Gilbert Gosselin, M.D., Shah Nawaz, M.D., Lawrence M. Title, M.D., Gerald Gau, M.D., Alvin S. Blaustein, M.D., David C. Booth, M.D., Eric R. Bates, M.D., John A. Spertus, M.D., M.P.H., Daniel S. Berman, M.D., G.B. John Mancini, M.D., William S. Weintraub, M.D., for the COURAGE Trial Research Group

N Engl J Med
Volume 356:1503-1516
April 12, 2007

The NEW ENGLAND JOURNAL of MEDICINE

COURAGE: Kaplan-Meier Survival Curves



Boden WE et al. N Engl J Med 2007;356:1503-1516

The Clinical "Bottom Line" of the "New Biology" of Atherosclerosis

- After revascularization patients should receive life style counseling and medical therapy to modify the *biology* of the underlying disease and prevent *future* events