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Frequency and Distribution of Microcalcifications in Vulnerable Plaque and Their Role in Fibrous Cap Rupture

Natalia Maldonado
The City College of New York

Adreanne Kelly
The City College of New York

Yuliya Vengrenyuk
The City College of New York

Luis Cardoso
The City College of New York

Sheldon Weinbaum
The City College of New York

FREQUENCY AND DISTRIBUTION OF μCALCS IN VULNERABLE PLAQUE AND THEIR ROLE IN FIBROUS CAP RUPTURE

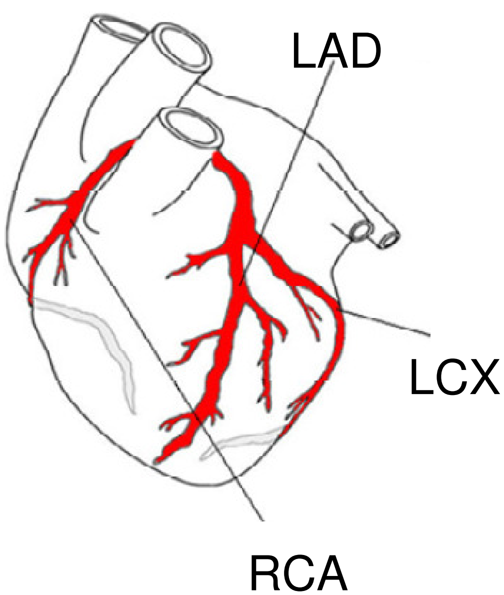
Natalia Maldonado, Adreanne Kelly, Yuliya Vengrenyuk, Luis Cardoso and Sheldon Weinbaum.

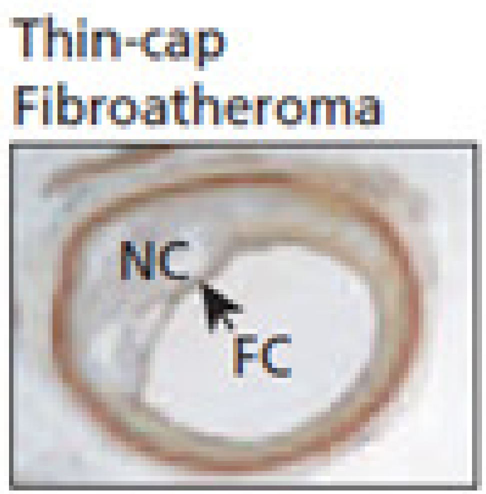
DEAD SEA CONFERENCE 2012

70th Birthday Shmuel Einav

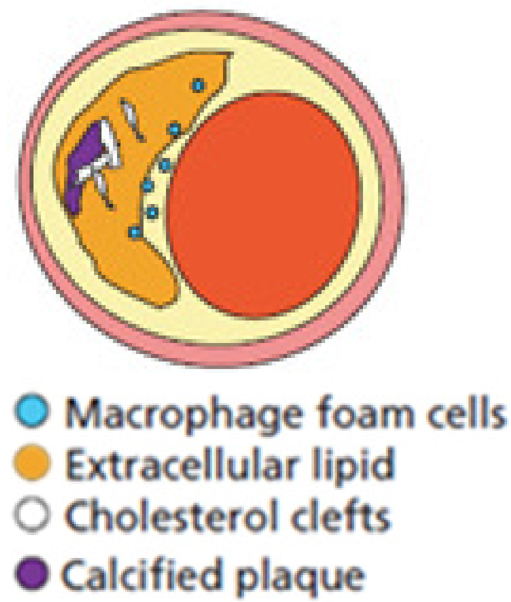
MYOCARDIAL INFARCTION AND VULNERABLE PLAQUE

More than 50% of Coronary deaths are caused by plaque rupture.





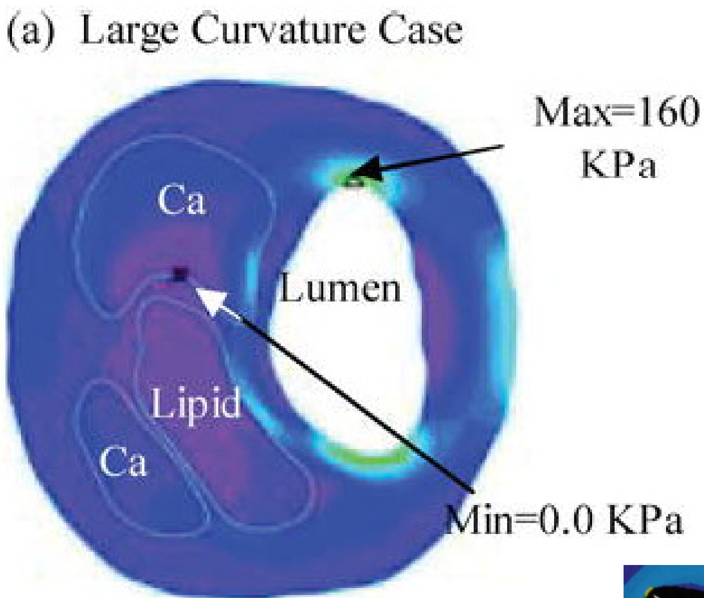
Virmani et al.(2007)



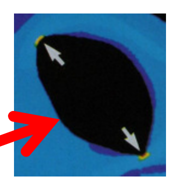
Common criterion for plaque vulnerability is fibrous cap <65µm.
Necrotic core size and cap stiffness also play a role.

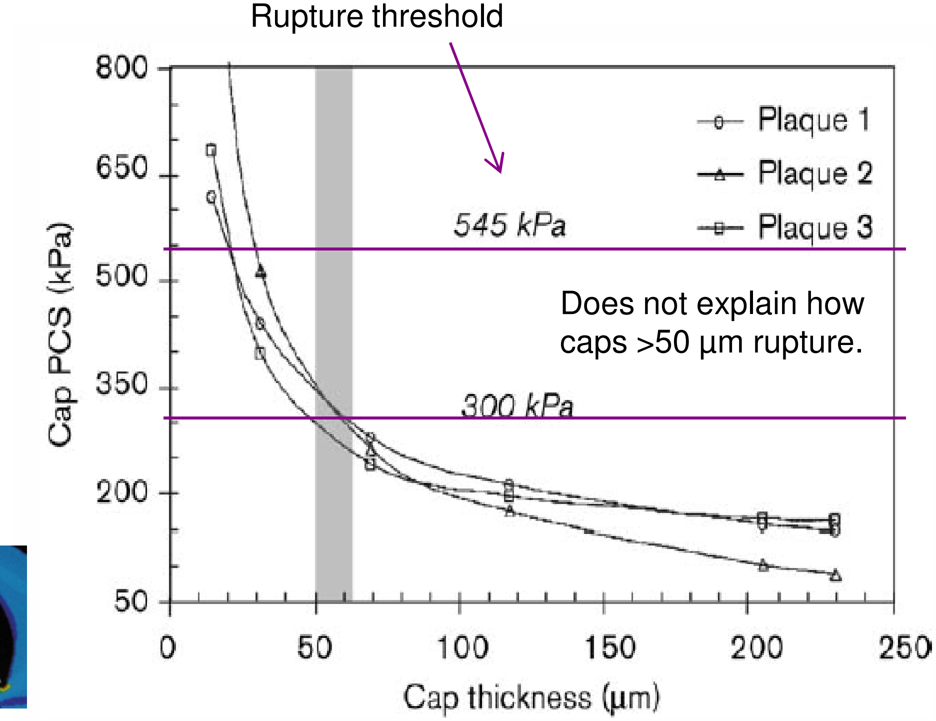
REGIONS OF HIGH CIRCUMFERENTIAL STRESS CORRELATE WITH RUPTURE SITES

Models predict rupture in the shoulders or regions of high curvature.



Tang et al. (2005)





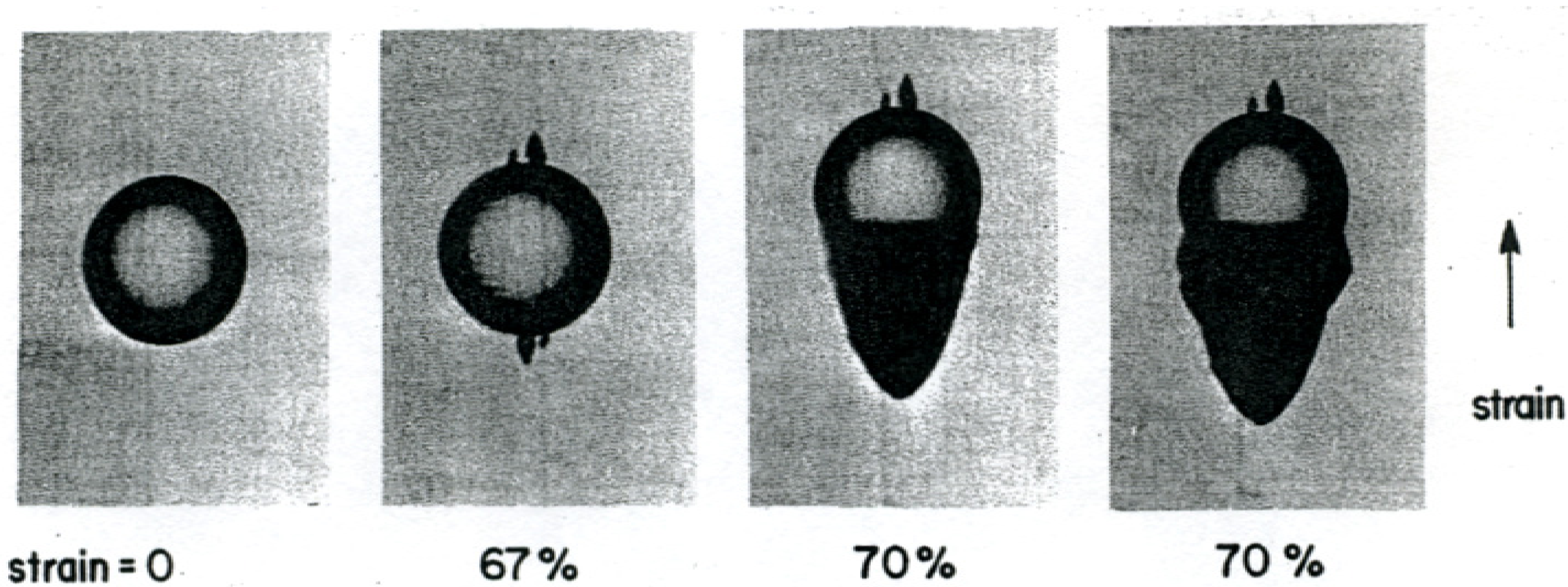
However, 40% of the ruptures are found in the center of the cap.

Maehara et al.(2002)

Finet et al. (2004)
Cheng et al. (1993)

EXPLOSIVE GROWTH OF SMALL VOIDS AT THE POLES OF A SPHERICAL INCLUSION IN AN ELASTOMERIC MATERIAL UNDER TENSION

Theory first proposed by Goodier (1933) to explain rupture due to solid impurities in rubber tires



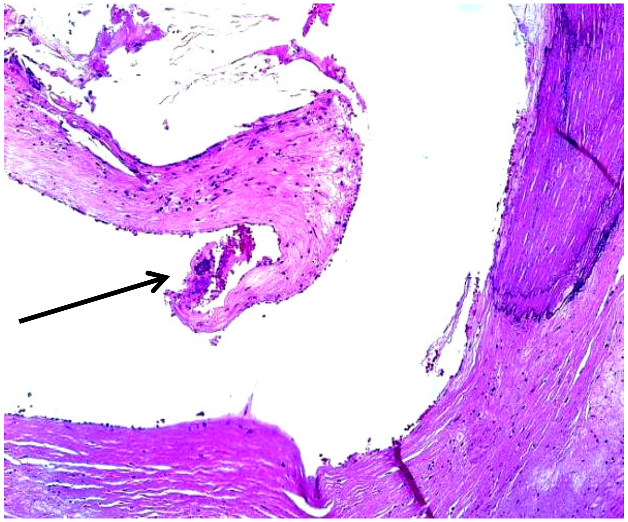
(Gent and Park, 1984)

Large particle: interfacial debonding
Small particle: cavitation near surface
Very small particle: surface energy too large

THE µ-CALC HYPOTHESIS

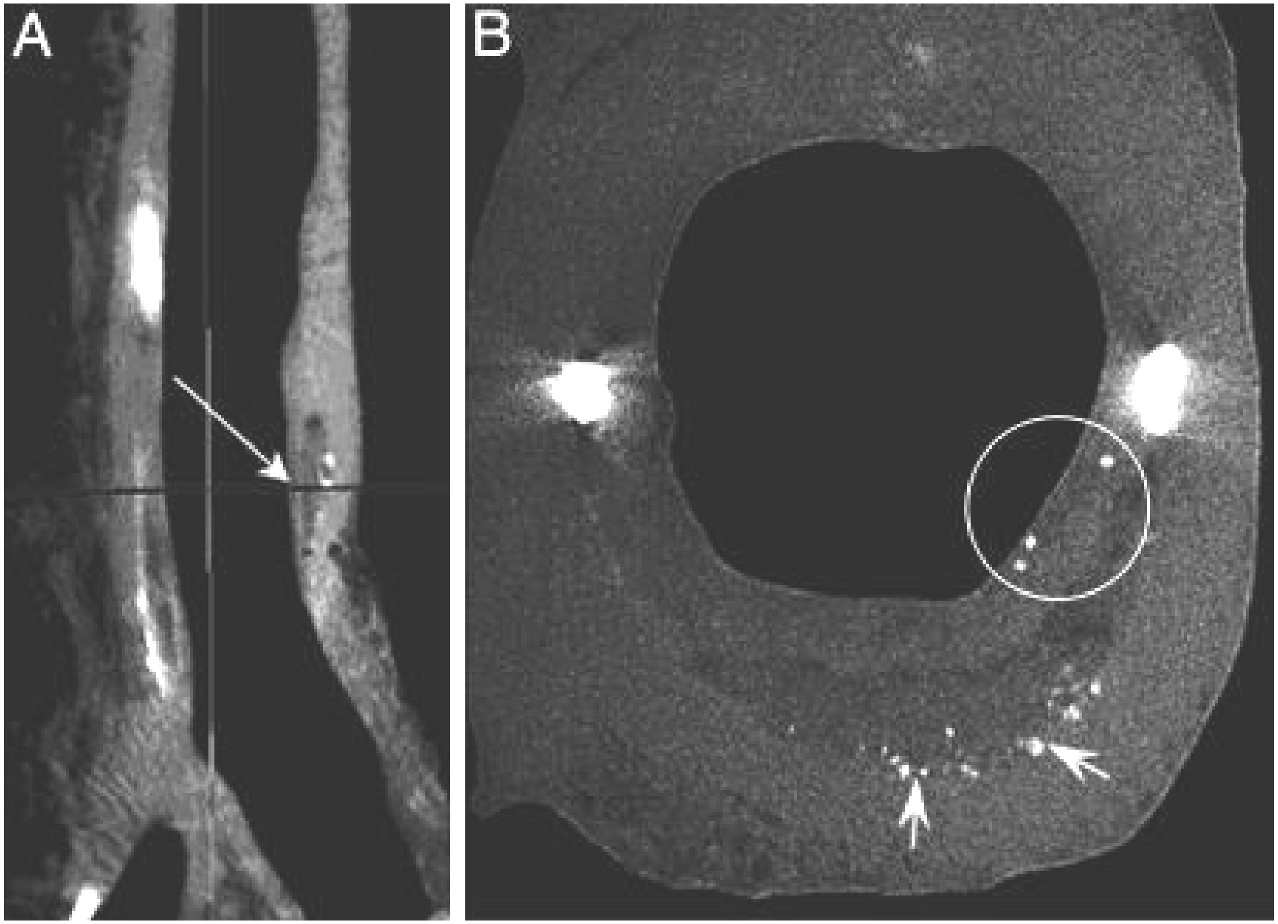
- Vengrenyuk et al. PNAS (2006) propose that rupture caused by either cavitation or interfacial debonding due to small cellular level microcalcifications in the fibrous cap proper.
- Such calcifications had not previously been seen in IVUS, OCT or MRI.
- Goodier (1933) infinite medium theory extended to thin fibrous caps.

Histological section of ruptured cap from Virmani showing µCalc at rupture site.
Burke et al. (1997) estimate cap thickness as 23±19 µm.
Virmani et al (2003) 95% of all ruptures Occur in caps < 65 µm.



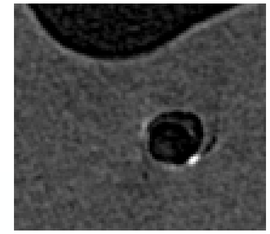
Ruptured cap stained with H&E

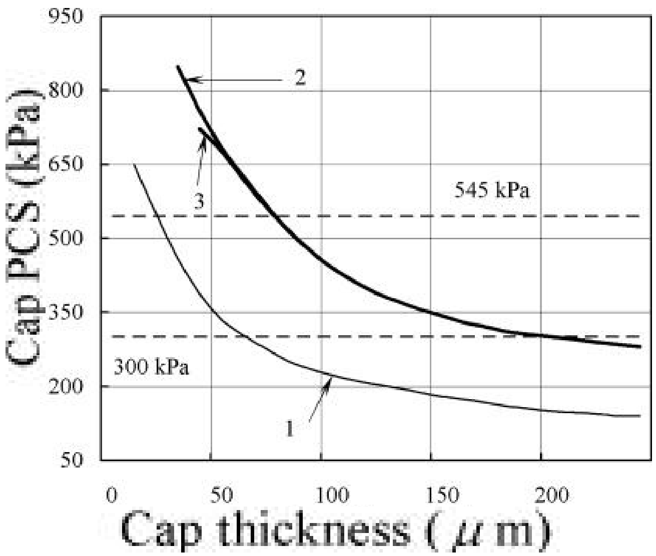
μ-CALCS ARE VISIBLE WITH μ-CT



Vengrenyuk et al. (2006)

STRESS CONCENTRATION PREDICTED AT TENSILE POLES OF THE μ-CALCS

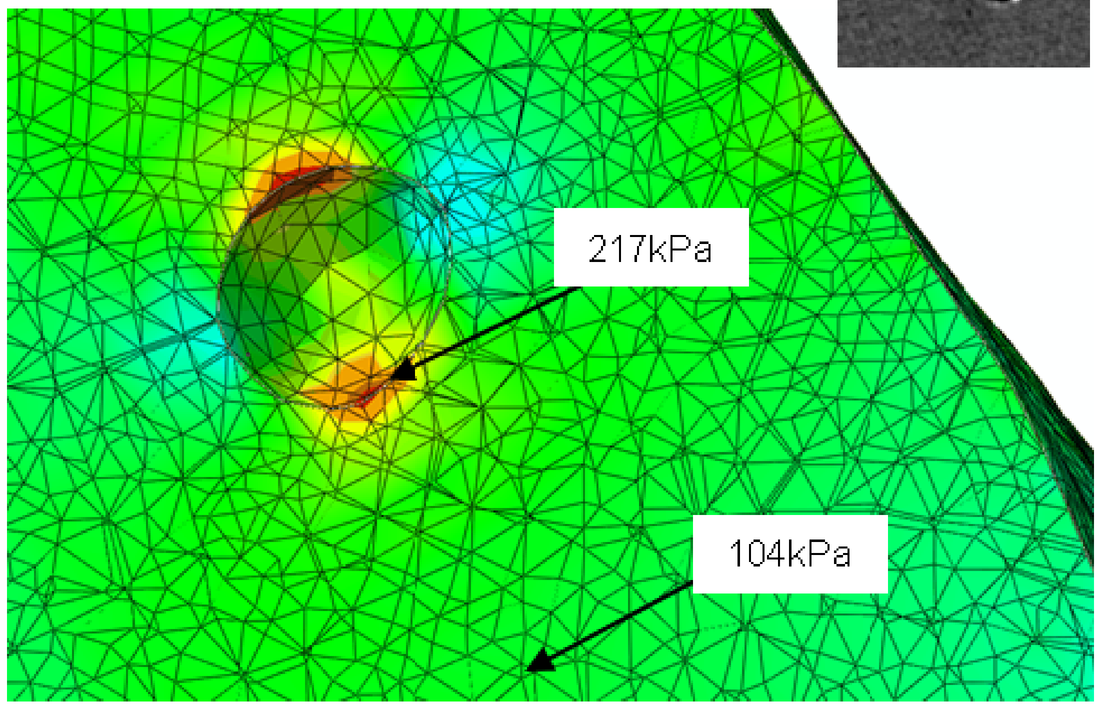




Spherical μCalc doubles PCS near interface at poles

Vengrenyuk et al. (2006)

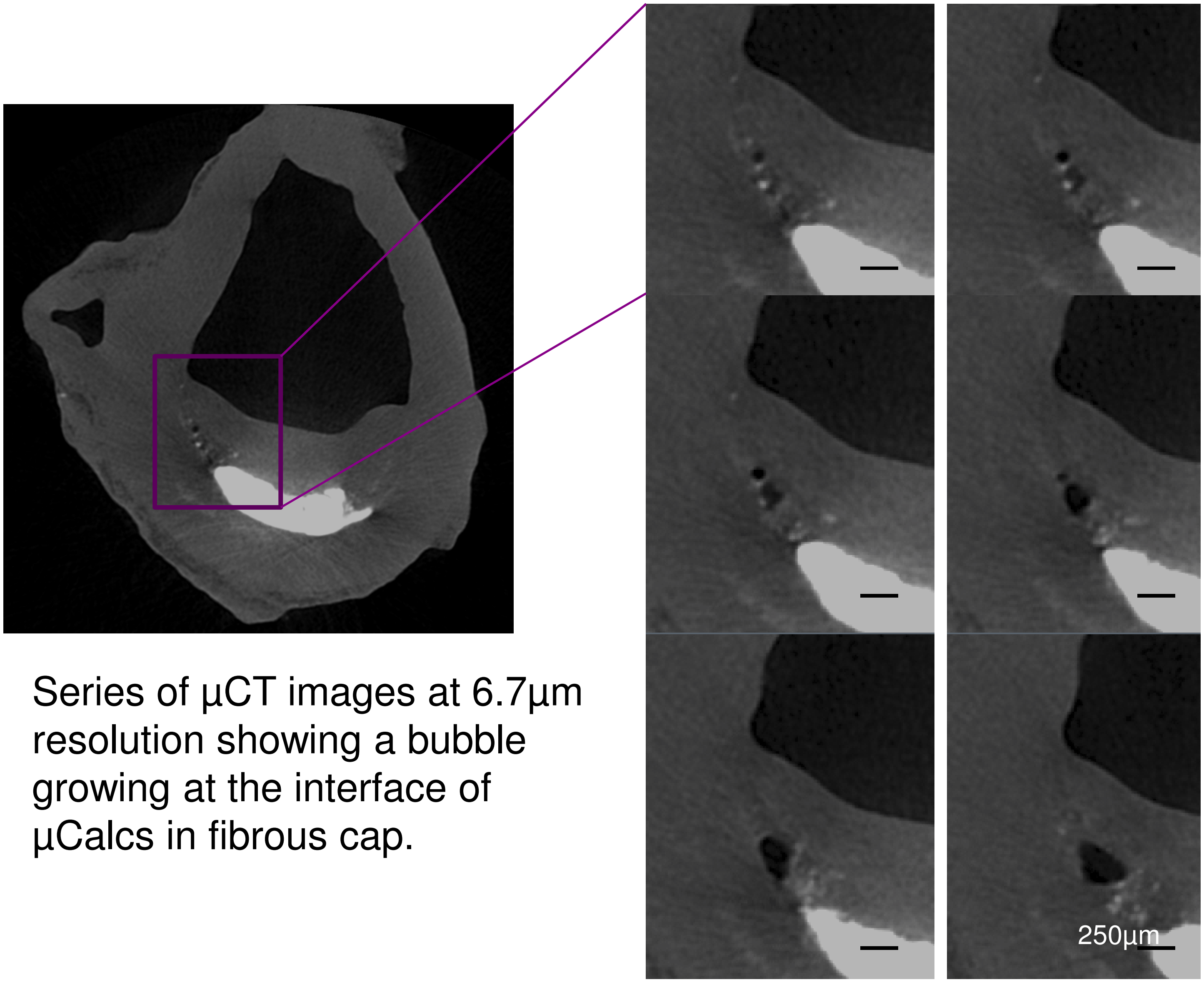
Key insight:
Cavitation σ=(E+P)/2
, E=500 to1000 kPa
300< σ < 550kPa



FEA stress calculations indicate stress concentration at the poles of the μ-calcs.

Vengrenyuk et al (2008)

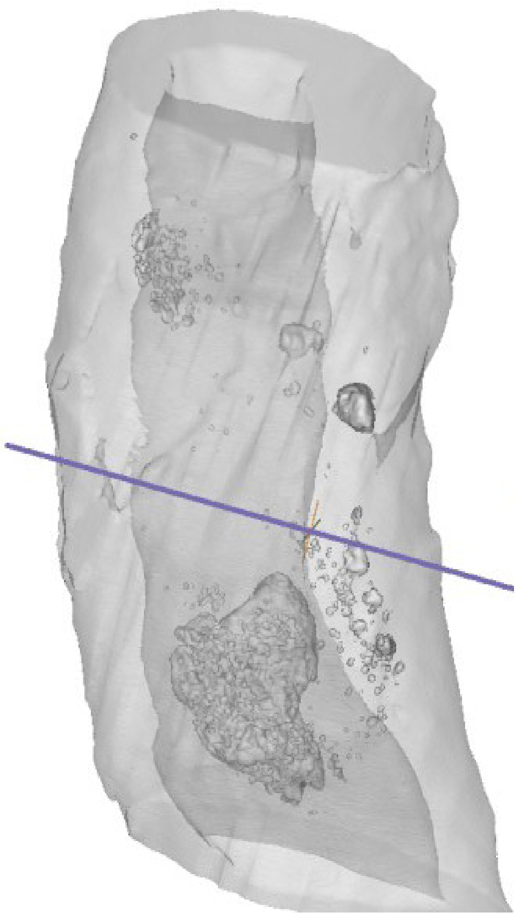
CAVITATION INDUCED DEBONDING

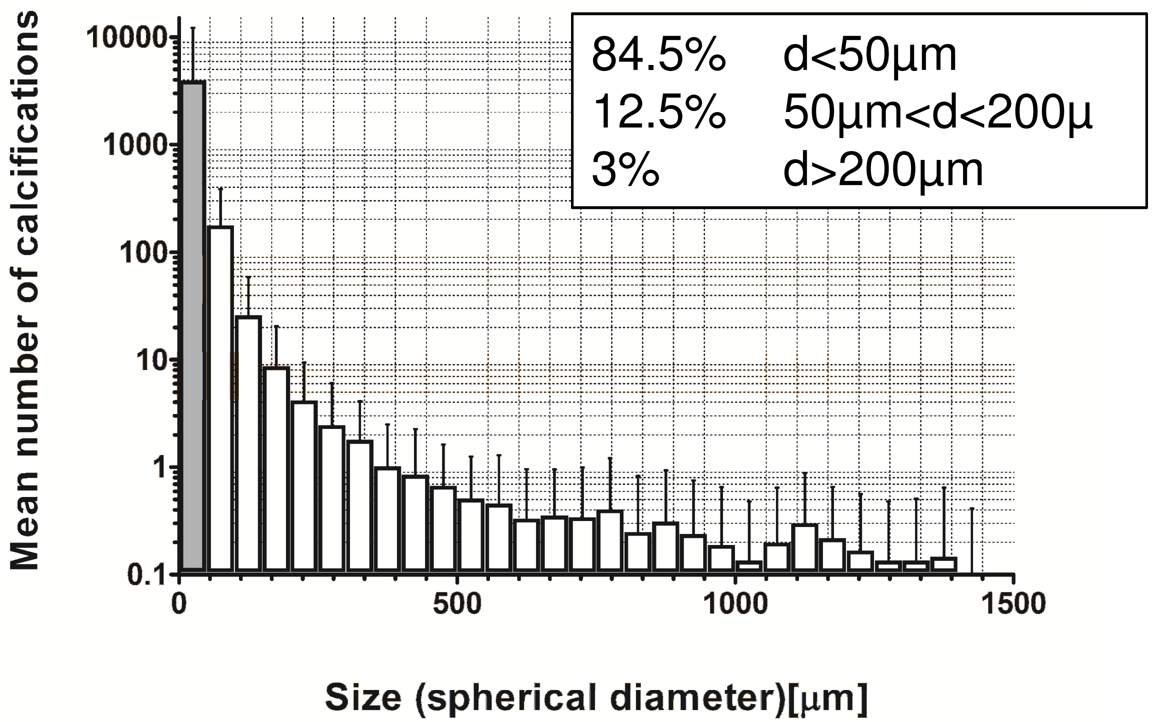


Series of µCT images at 6.7µm resolution showing a bubble growing at the interface of µCalcs in fibrous cap.

THOUSANDS OF CORONARY µ-CALCS

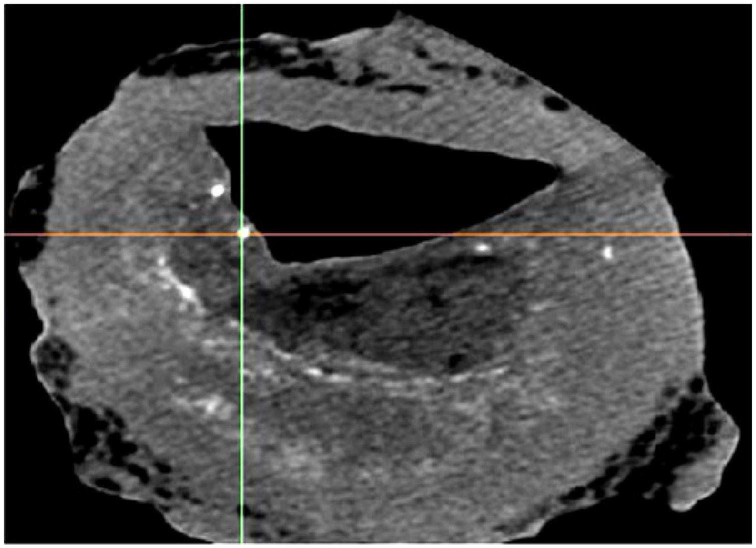
From 6.7µm micro-CT images of **92** human coronaries.



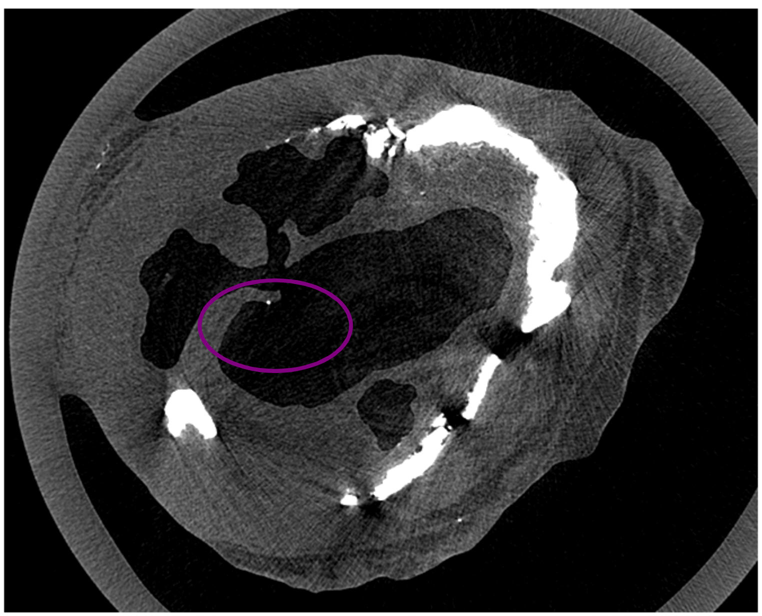


Samples came from patients with atherosclerosis, ages 51-80.

µ-CALCS IN THE CAP ARE RARE

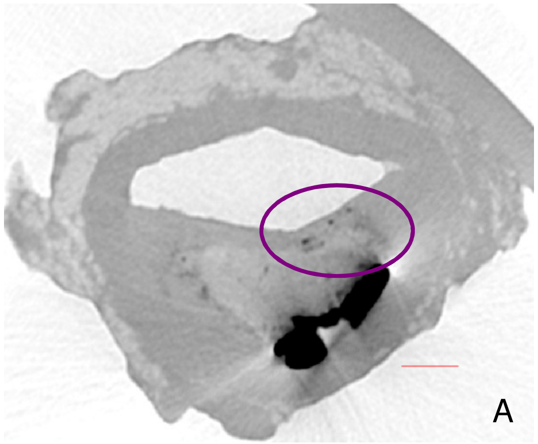


- Less than 0.2% of the calcifications are in the cap proper where they could be dangerous.
- 9 of 62 vulnerable lesions had µCalcs in cap, 81 µCalcs total.

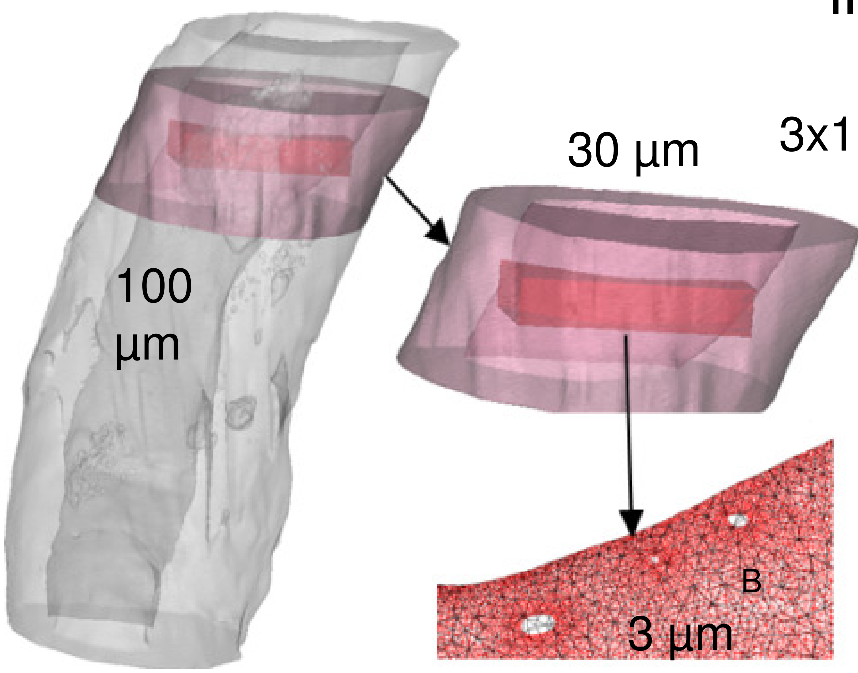


Rare case where 35µm µCalc localized at site of cap rupture and thrombus detached.

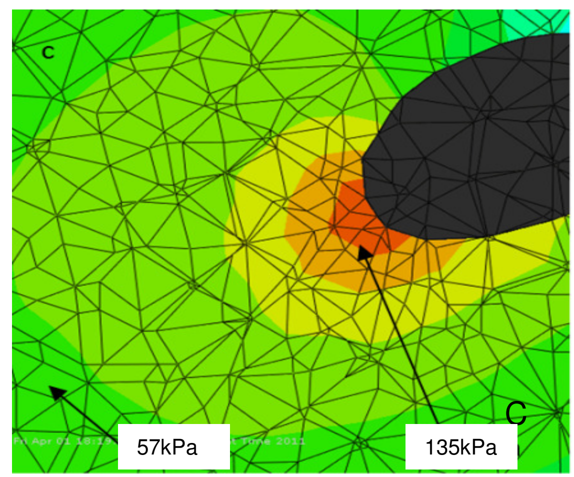
ARE µ-CALCS INCREASING STRESS IN FIBROUS CAPS?



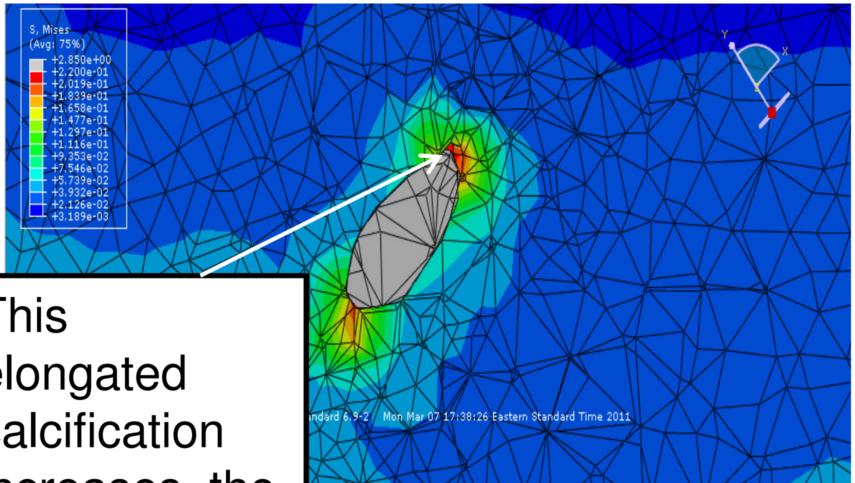
- Finite Element Analysis Submodeling allows us to greatly refine the stress calculations at the interface of the µ-calcs.



3x10^6 elements

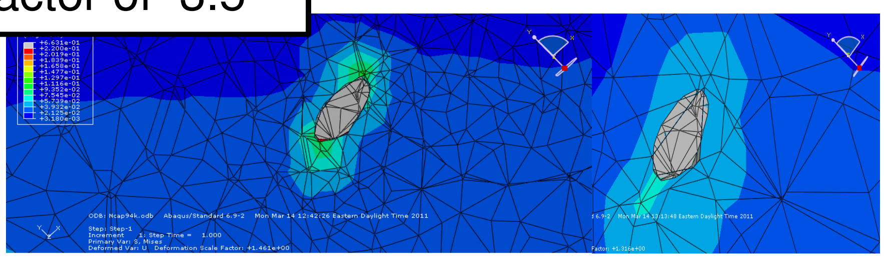


FINITE ELEMENT MODEL MESH OPTIMIZATION



This elongated calcification increases the PCS by a factor of 3.5

Edge size 3µm

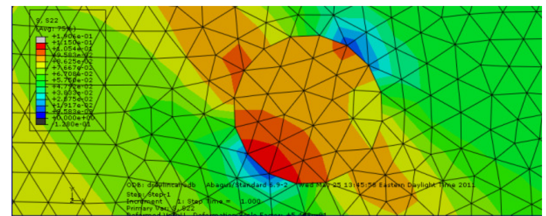


Edge size 5µm

Edge size 8µm

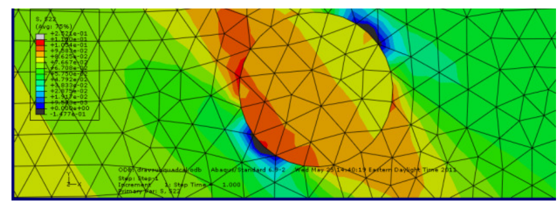
Results in stress concentration differ <5% but using linear elements reduces computational cost.

Nodes



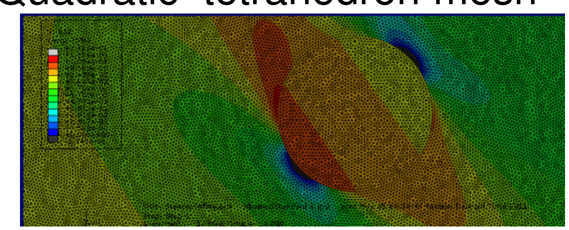
n

Linear tetrahedron mesh



4n

Quadratic tetrahedron mesh



100n

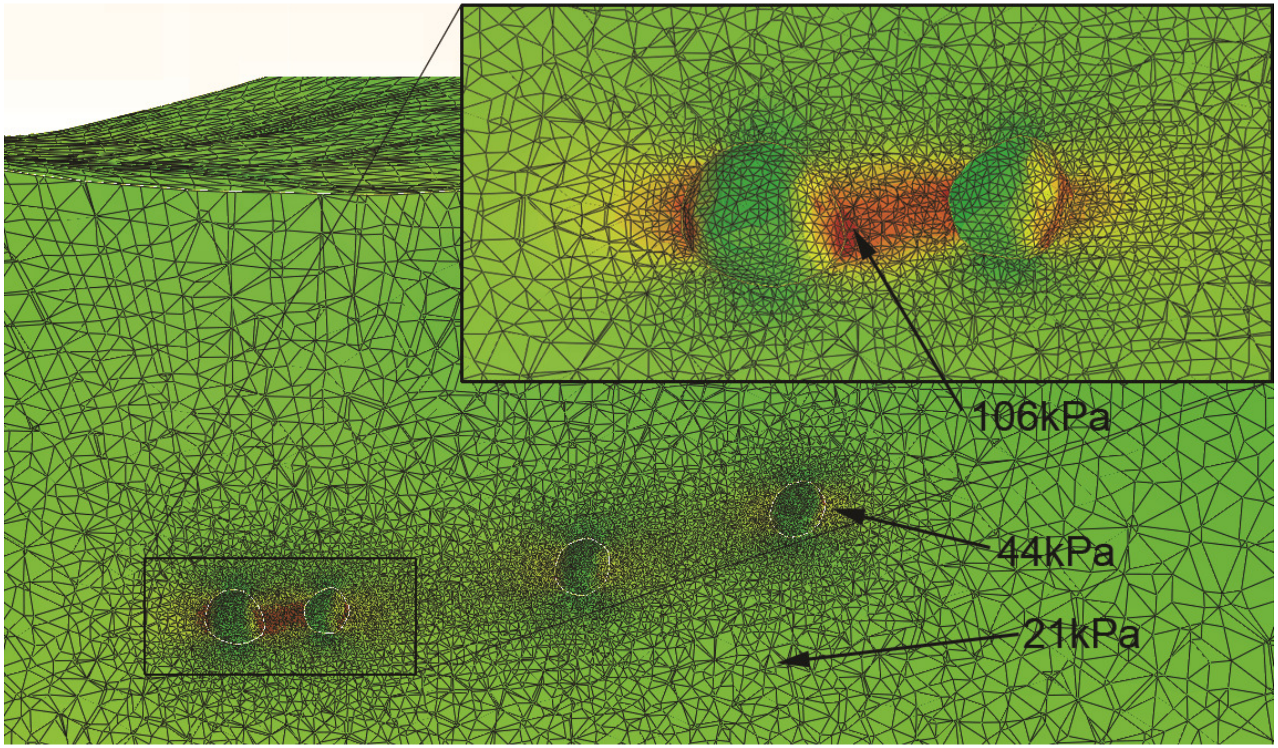
Refined linear mesh

Analysis of 81 μCalcs in fibrous caps

Sample	#μCalcs	Max. PCS concentration	PCS	#μCalcs shoulders	#μCalcs center
1	5	4.2	138	3	2
2	5	2.5	103	5	0
3	16	3.5	144	6	10
4	11	2.6	41	4	7
5	15	3.4	48	12	3
6	9	5	106	3	6
7	11	4.29	133	7	4
8	5	2.17	275	5	0
9	4	2	92	2	2
Total	81			58% 47	42% 34
Mean	9.00	3.30	120.00	5.22	3.78
SD	4.56	1.05	68.73	2.99	3.35

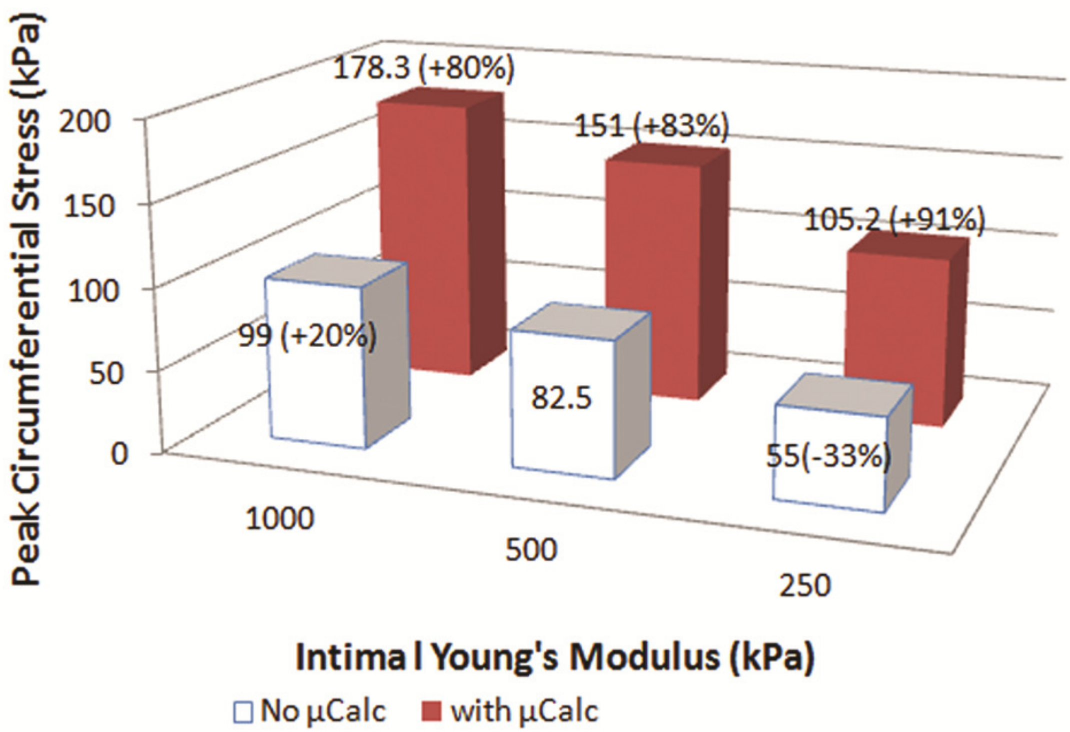
53 lesions no μcalcs in cap, thinnest cap 66 μm, PCS 107kPa << 300kPa
Basic paradox: Why are there no non-ruptured lesions between 30-66 μm

STRESS CONCENTRATION PREDICTED AT µ-CALCS



Tissue stress concentrations five times the background stress can result from the close clustering of µCalcs.

EFFECT ON PCS OF A µCALC EMBEDDED IN FIBROUS CAPS OF DIFFERENT TISSUE STIFFNESS



Changes in the E_{intima} increase PCS 30%, while the presence of a µCalc increases PCS >80%. 25µm µCalc in 120µm thick cap.

Conclusions

- μ-Calcs, invisible in current clinical techniques, were found to be abundant, but just a few of them, less than 0.2%, were present in the fibrous cap proper.
- At 6.7um resolution 9 out of 62 caps (15%) exhibited μ-Calcs. 81 μ-Calcs in total.
- μ-Calcs are present at the rupture site.
- A μ-Calc increases the PCS by a factor of 2 to 5 depending on shape factor and clustering.
- The presence of μ-Calcs in the cap is more important than variation in tissue properties.
- Size of μ-Calcs enters into the energy stored in interfacial debonding.

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