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

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FREQUENCY AND DISTRIBUTION OF $\mu$CALCS 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.

(a) Large Curvature Case

Rupture threshold

Does not explain how caps >50 µm rupture.

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

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

(Gent and Park, 1984)
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.
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 \( \sigma = (E+P)/2 \), \( E=500 \) to \( 1000 \) kPa
\( 300< \sigma < 550 \) kPa

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.

84.5% d<50µm
12.5% 50µm<d<200µ
3% d>200µm

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.

![Diagram showing stress calculations with µ-calcs interface highlighted.](image-url)
FINITE ELEMENT MODEL MESH OPTIMIZATION

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

This elongated calcification increases the PCS by a factor of 3.5
### Analysis of 81 μCalcs in Fibrous Caps

<table>
<thead>
<tr>
<th>Sample</th>
<th>#μCalcs</th>
<th>Max. PCS concentration</th>
<th>PCS</th>
<th>#μCalcs shoulders</th>
<th>#μCalcs center</th>
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<td>138</td>
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<tr>
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<td>41</td>
<td>4</td>
<td>7</td>
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<td>48</td>
<td>12</td>
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<tr>
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<td>106</td>
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<td>0</td>
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<tr>
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<td>4</td>
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<td>92</td>
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<td>2</td>
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<tr>
<td>Total</td>
<td>81</td>
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<td></td>
<td>58%</td>
<td>42%</td>
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#### Mean and SD

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<th>Mean</th>
<th>SD</th>
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<tr>
<td>Max. PCS</td>
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<tr>
<td>PCS</td>
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<td>68.73</td>
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<tr>
<td>#μCalcs shoulders</td>
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<td>2.99</td>
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<tr>
<td>#μCalcs center</td>
<td>3.78</td>
<td>3.35</td>
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</tbody>
</table>

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
Tissue stress concentrations five times the background stress can result from the close clustering of µCalcs.
Changes in the $E_{\text{intima}}$ increase PCS 30%, while the presence of a $\mu\text{Calc}$ increases PCS $>80\%$. 25$\mu$m $\mu\text{Calc}$ in 120$\mu$m 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 6.7μm 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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