Micro-calcifications Predict Plaque Vulnerability and Initiate Rupture of the Fibrous Cap

Andrea Corti[1]; An Dinh[1]; Annalisa De Paolis, PhD[1]; Elena Aikawa, PhD[2]; Sheldon Weinbaum, PhD[1]; Luis Cardoso, PhD[1]
[1]Department of Biomedical Engineering, The City College of New York, New York, USA
[2]Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA

Introduction: The mechanical stability of an atheroma fibrous cap (FC) is a crucial factor for the risk of heart attack or stroke in asymptomatic vulnerable plaques. Common determinants of plaque vulnerability are the cap thickness and the presence of micro-calcifications (μCalcs). Higher local stresses have been linked to thin caps(<65μm) and, more recently, our lab demonstrated how μCalcs can potentially initiate cap rupture [1-3]. When combined, these two factors can compromise to a greater extent the stability of the plaque. On this basis, we quantitatively analyzed both individual and combined effects of key determinants of plaque rupture using a tissue damage model on idealized atherosclerotic arteries. Our results were then tested against a diseased human coronary sample.

Methods: We performed 28 finite element simulations on three-dimensional idealized atherosclerotic arteries and a human coronary sample. The idealized models present 10% lumen narrowing and 1.25 remodeling index (RI)(**Fig.1A**). The FC thickness values that we considered were of 50, 100, 150 and 200μm. The human coronary presents a RI=1.31, with 31% lumen occlusion and a 140μm-thick cap(**Fig.1B**). The human model is based on 6.7μm high-resolution microcomputed tomography (HR-μCT) images. The μCalc has a diameter of 15μm and each artery was expanded up to a systolic pressure of 120mmHg. Layer-specific material properties were defined by the HGO model coupled with the hyperelastic failure description proposed by Volokh et al. [4] to replicate the rupture of the FC. We considered a max. principal stress for rupture of 545kPa[5]. The lipid core and the μCalc were considered as elastic materials (E_{core} = 5kPa, ν_{core} = 0.49; $E_{\mu Calc}$= 18,000 kPa, $\nu_{\mu Calc}$=0.3). To obtain a detailed analysis of the cap stresses and rupture progression, a sub-modeling approach was implemented using ABAQUS (Dassault Systemes, v.2019) (**Fig. 1**).

Results: We investigated the quantitative effect of cap thickness and μCalc by simulating tissue failure and deriving a vulnerability index (VI) for each risk factor. The VI coefficient was defined as the peak cap stress (PCS) normalized by the threshold stress for rupture (545kPa). The relationship between the risk factors and VI was determined by deriving the Pearson's correlation coefficient (PCC) followed by one-tailed t-test (SPSS, IBM, v.25). The null hypothesis was rejected if p<0.05.

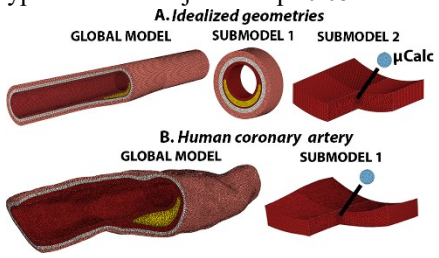

Figure 1. *Mesh view of the global model and submodels of the idealized geometry (A) and human coronary sample (B)*

The presence of the μCalc is the factor that manifests the greater impact on cap stability, leading to at least a 2.5-fold increase in VI and tissue rupture regardless of cap thickness (**Fig.2A,B**). One μCalc in the cap is the first predictor of vulnerability, with $PCC_{\mu Calc}$=0.59 and $p_{\mu Calc}$=0.001. Our results also confirm the substantial influence of cap thickness, with an exponential increase in stresses as the cap becomes thinner. The 50μm cap is the only phenotype that ruptures without μCalc (**Fig2A**).

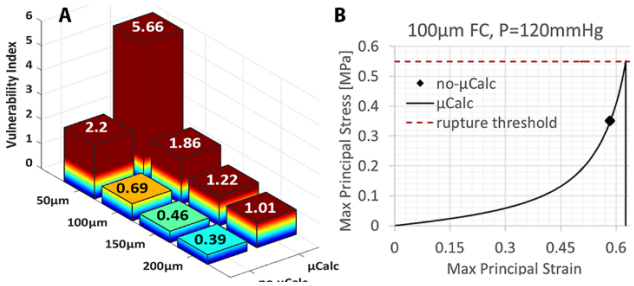

Figure 2*. (A) 3D-barplots of the change of VI based on cap thickness and the presence of the μCalc; (B) Comparison of the stress-strain response of a 100μm cap with and without one μCalc, under the same systolic pressure.*

The human sample exhibits PCS levels that are close to the idealized case with 150μm cap and it doesn't rupture in the absence of the μCalc (PCS_{human}=233kPa, PCS_{ideal}= 252kPa). Conversely, the phenotypes with the μCalc showed an increase in VI of about 2.5 and reached rupture under the same blood pressure regime.

Conclusions: Our results clearly show the multifactorial nature of plaque vulnerability and the significance of micro-calcifications on the cap mechanical stability. The presence of a μCalc strongly amplifies the stresses in the surrounding tissue, and it can provoke tissue failure even in thick caps that would otherwise be classified as stable. Clearly, plaque phenotypes with a thin cap and μCalcs in the tissue represent the most vulnerable condition. Finally, these observations are well validated by the case of the human atherosclerotic segment, which closely compares to its corresponding idealized model. The novel implementation of the tissue damage description and the definition of a vulnerability index allow one to quantitatively analyze the individual and combined contribution of key determinants of cap rupture, which precedes the formation of a thrombus and myocardial infarction.

References:

1. Vengrenyuk et al, PNAS, 103 (40) 14678-14683, 2006.
2. Kelly Arnold et al, PNAS110 (26) 10741-10746, 2013.
3. Kawakami et al, ATVB, 40(8):1838-1853, 2020.
4. Volokh et al, J. Biomech., 41(2), 447–453, 2008.
5. Cheng et al, Circulation, 87(4), 1179–1187, 1993.

Acknowledgements:

NSF grants CMMI-1662970 & MRI-2018485, NIH Grant 1R01HL136431