Atherosclerosis 236 (2014) 351–352

Contents lists available at ScienceDirect

Atherosclerosis

journal homepage: www.elsevier.com/locate/atherosclerosis

Invited commentary

Vulnerable plaque: The biomechanics of matter

Yiannis S. Chatzizisis [a,*], Antonios P. Antoniadis [a], Jolanda J. Wentzel [b], George D. Giannoglou [c]

[a] Cardiovascular Division, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA
[b] Department of Biomedical Engineering, Erasmus MC, Rotterdam, The Netherlands
[c] Cardiovascular Engineering and Atherosclerosis Laboratory, AHEPA University Hospital, Aristotle University Medical School, Thessaloniki, Greece

ARTICLE INFO

Article history:
Received 13 July 2014
Accepted 26 July 2014
Available online 4 August 2014

Keywords:
Coronary arteries
Atherosclerosis
Biomechanical forces
Strain

"…ειδέναι δε ου πρότερον οιόμεθα έκαστον πριν αν λάβωμεν το δια τί περι έκαστον, τούτο δ' εστι το λαβείν την πρώτην αιτίαν…"

"… we do not have knowledge of a thing until we have grasped its why, that is to say, its cause …"

Aristotle, *Physics 194 b17–20*.

Despite the considerable progress that has been made in cardiology over the last four decades through intensive risk-factor modification and life-style changes, cardiovascular disease prevalence, morbidity and mortality remain high [1]. One coronary event occurs every 34 s leading to one death every 83 s in the United States [2]. A significant proportion of these coronary events occur totally unexpectedly in previously asymptomatic individuals and are frequently catastrophic or lead to significant morbidity. In most of the patients with acute coronary events, the culprit lesion is a ruptured atherosclerotic plaque associated with complete or partial atherothrombotic occlusion of the coronary artery lumen. Eroded plaques and plaques with calcified nodules are less frequent causes of acute coronary syndromes [3]. Pathological studies have identified thin cap fibroatheromas as the precursor lesions of ruptured plaques [4]. Thin cap fibroatheromas feature a large necrotic core with abundant inflammatory cells, thin fibrous cap and paucity of smooth muscle cells and collagen [4]. Low endothelial shear stress, internal elastic lamina fragmentation, expansive vascular wall remodeling, increased neovascularization and microcalcifications are additional features of high-risk lesions (Fig. 1) [3,5,6]. The pursuit of high-risk (rupture-prone) plaques early in their natural history is the goal of intense basic and translational research, since their timely identification is anticipated to set the foundation for prevention of adverse coronary events.

The plaque mechanical properties are a field of rigorous investigation in biomechanical research given that structural disruption of plaque integrity is the principal pathophysiologic instigator of an acute coronary event. Strain is the mechanical response of vascular wall to the local hemodynamic forces imposed by blood pressure and is directly associated with the wall's structural composition (Fig. 1). Endothelial shear stress is another local hemodynamic force determined by the friction of the flowing blood on the arterial wall (Fig. 1) [7]. Both forces are in constant interplay with the vascular wall biology and constitute major determinants of atherosclerotic plaque stability [6,8,9].

Studies have shown that high radial strain is associated with vulnerable plaque phenotype and coronary events [10]. Recent developments in radiofrequency signal processing allowed for assessment of shear strain [11], which is the gradient of radial strain in the circumferential direction. In a recent issue of Atherosclerosis, Keshavarz-Motamed Z et al. reported a very interesting investigation of plaque shear strain based on intravascular ultrasound radiofrequency signal analysis in coronary artery plaques of 12 patients undergoing coronary atherectomy [12]. Shear strain elastography values decreased after direct coronary atherectomy. Excised lesions were histologically analyzed and fibrotic, thrombotic and fibrin content was found to be positively associated with high shear strain levels. Intriguingly, intensely inflamed plaques exhibited higher shear strain elastography values than moderately inflamed and non-inflamed plaques. This study enhances our current understanding on the association of plaque mechanical properties with histopathologic high-risk features and creates the

DOI of original article: http://dx.doi.org/10.1016/j.atherosclerosis.2014.04.022.
* Corresponding author. Cardiovascular Division, Brigham and Women's Hospital, Harvard Medical School, 75 Francis Street, Boston, MA 02115, USA. Tel.: +1 857 234 2604; fax: +1 857 307 2011.
E-mail addresses: joc@med.auth.gr, ychatzizisis@partners.org (Y.S. Chatzizisis).

http://dx.doi.org/10.1016/j.atherosclerosis.2014.07.032

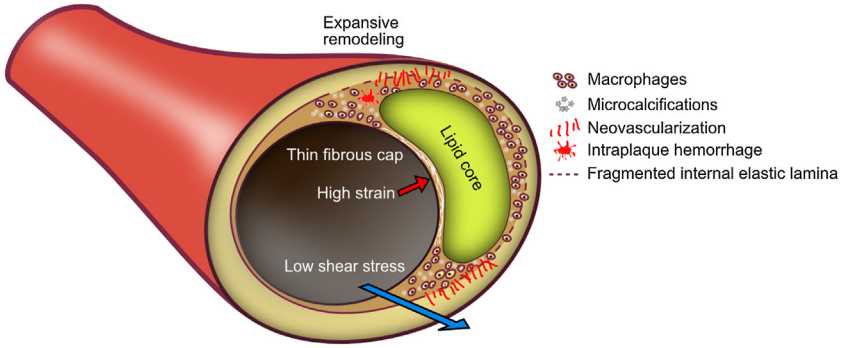

Fig. 1. Pathobiologic and local hemodynamic features of high-risk (rupture-prone) plaque.

perspective for further investigations concerning the association of plaque biomechanics with plaque rupture and acute cardiac events.

However, the study findings should be interpreted with caution. The exact matching of intravascular ultrasound frames with histological cross-sections was not straightforward due to methodological constrains. Intravascular ultrasound analysis was focused on the minimal lumen area segment of each plaque, thereby not taking into account the longitudinal variability of atherosclerosis [13]. On the other hand, atherectomy encompassed a wider area of plaque tissue, which was excised, fragmented and homogenized. Therefore, the histological indices of this study did not completely account for plaque heterogeneity along the length of the artery. More importantly, the basic concept underlying the assessment of plaque shear strain is to identify plaques likely to acquire high-risk phenotype and precipitate acute events. It is not clear, however, whether the patients enrolled in this study had clinical features attributed to ruptured plaques. It is conceivable that a thick-capped fibrous plaque in a patient with stable angina would have substantially different mechanical properties than a thin-capped, lipid-rich and highly inflamed plaque in a patient with an acute coronary syndrome. We should also not overlook that out of the total denominator of plaques with morphological and functional high-risk features, only a minority will progress to induce an acute event [5,6]. Plaque natural history is quite dynamic over time and the sole identification of high-risk plaque features in a single point in time is not necessarily a proof that the plaque will lead to future adverse outcomes. A larger clinical study assessing the plaque biomechanical properties at baseline with subsequent clinical follow-up to identify the subpopulation of plaques that will precipitate an acute coronary event would be of utmost importance. Such a study would provide more definite answers regarding the implication of biomechanics in plaque instability.

Collectively, the understanding and management of atherosclerosis has undergone evolutionary changes over the last two decades, as our insights into the underlying pathobiology have been enormously enhanced. It is necessary, however, to further understand the causative pathobiologic and biomechanical factors leading to high-risk plaque generation and rupture. Such an understanding of the actively evolving vascular biology processes, together with the advent of novel in vivo imaging modalities, may enable the early identification of high-risk plaque. As new information about vascular biology of atherosclerosis emerges, preemptive local and systemic treatments will likely emanate to reduce outcomes and increase efficacy, long-term safety and quality of life.

Conflicts of interest

None.

Funding sources

This work was supported by the Behrakis Foundation, Boston, USA (to YSC and APA), European Commission, Marie Curie International Reintegration Grant (SMILE, 249303, to YSC) and European Commission, ERC starters grant (BioCCora, 310457, to JJW).

References

[1] Fact book, fiscal year 2012. U.S. Department of Health and Human Services, National Institutes of Health, National Heart, Lung, and Blood Institute; 2012. p. 41.
[2] Go AS, Mozaffarian D, Roger VL, Benjamin EJ, Berry JD, Blaha MJ, et al., American Heart Association Statistics C, Stroke Statistics S. Executive summary: heart disease and stroke statistics – 2014 update: a report from the American Heart Association. Circulation 2014;129:399–410.
[3] Libby P. Mechanisms of acute coronary syndromes and their implications for therapy. N Engl J Med 2013;368:2004–13.
[4] Virmani R, Kolodgie FD, Burke AP, Farb A, Schwartz SM. Lessons from sudden coronary death: a comprehensive morphological classification scheme for atherosclerotic lesions. Arterioscler Thromb Vasc Biol 2000;20:1262–75.
[5] Chatzizisis YS, Baker AB, Sukhova GK, Koskinas KC, Papafaklis MI, Beigel R, et al. Augmented expression and activity of extracellular matrix-degrading enzymes in regions of low endothelial shear stress colocalize with coronary atheromata with thin fibrous caps in pigs. Circulation 2011;123:621–30.
[6] Wentzel JJ, Chatzizisis YS, Gijsen FJ, Giannoglou GD, Feldman CL, Stone PH. Endothelial shear stress in the evolution of coronary atherosclerotic plaque and vascular remodelling: current understanding and remaining questions. Cardiovasc Res 2012;96:234–43.
[7] Chatzizisis YS, Coskun AU, Jonas M, Edelman ER, Feldman CL, Stone PH. Role of endothelial shear stress in the natural history of coronary atherosclerosis and vascular remodeling: molecular, cellular, and vascular behavior. J Am Coll Cardiol 2007;49:2379–93.
[8] Gijsen FJ, Wentzel JJ, Thury A, Mastik F, Schaar JA, Schuurbiers JC, et al. Strain distribution over plaques in human coronary arteries relates to shear stress. Am J Physiol Heart Circ Physiol 2008;295:H1608–14.
[9] Teng Z, Brown AJ, Calvert PA, Parker RA, Obaid DR, Huang Y, et al. Coronary plaque structural stress is associated with plaque composition and subtype and higher in acute coronary syndrome: the BEACON I (Biomechanical Evaluation of Atheromatous Coronary Arteries) study. Circ Cardiovasc Imaging 2014;7:461–70.
[10] Schaar JA, Regar E, Mastik F, McFadden EP, Saia F, Disco C, et al. Incidence of high-strain patterns in human coronary arteries: assessment with three-dimensional intravascular palpography and correlation with clinical presentation. Circulation 2004;109:2716–9.
[11] Majdouline Y, Ohayon J, Keshavarz-Motamed Z, Roy Cardinal MH, Garcia D, Allard L, et al. Endovascular shear strain elastography for the detection and characterization of the severity of atherosclerotic plaques: in vitro validation and in vivo evaluation. Ultrasound Med Biol 2014;40:890–903.
[12] Keshavarz-Motamed Z, Saijo Y, Majdouline Y, Riou L, Ohayon J, Cloutier G. Coronary artery atherectomy reduces plaque shear strains: an endovascular elastography imaging study. Atherosclerosis 2014;235:140–9.
[13] Box LC, Angiolillo DJ, Suzuki N, Box LA, Jiang J, Guzman L, et al. Heterogeneity of atherosclerotic plaque characteristics in human coronary artery disease: a three-dimensional intravascular ultrasound study. Catheter Cardiovasc Interv 2007;70:349–56.