Editorial

Advances in Vulnerable Plaque Detection and Treatment: How Far Have We Gone?

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During recent years important developments have been made in the field of high-risk or vulnerable plaque. The advances in understanding the mechanisms of acute coronary syndromes have been impressive and have led to the formation of a new terminology for describing high-risk or vulnerable plaque. In addition, new detection modalities and therapeutic proposals for atheromatic plaque stabilisation, or even regression, have been presented. In this article we summarise recent important advances regarding the pathophysiology, the diagnosis and the therapy in this exciting area.

The terminology of high-risk atheromatic plaque, often referred to as vulnerable plaque, has been changed since the consensus of the first *International Vulnerable Plaque Meeting* held in Santorini, Greece, in 2003. During this meeting a first attempt was made by the community of scientists working on atherosclerosis, to adopt a common nomenclature for describing high-risk or vulnerable plaques.[1] The consensus was that a high-risk plaque should be described as thin-cap fibroatheroma (TCFA), based on retrospective pathological studies of plaque rupture with thrombosis. The main components of TCFA were as follows: lipid-rich atheromatous core, thin fibrous cap with macrophage and lymphocyte infiltration, decreased smooth muscle cell content and extensive remodelling of the arterial wall.[1] These characteristics were found in TCFAs, in which the incidence of rupture is increased and leads to acute coronary syndromes.[2-4] It was also recognized that plaque erosion or plaques with calcified nodules provoke thrombus formation.

Recently, the impact of *vasa vasorum* proliferation on atherosclerotic plaques in plaque vulnerability has been widely recognised.[4-6] During the *4th International Vulnerable Plaque Meeting* there was agreement by all participants that neovascularisation should also be included in the description of high risk plaques. Especially in ruptured plaques, the neovessel content is significantly increased compared to non-ruptured plaques of human aorta. The extent of neovascularisation is well correlated with the infiltration of inflammatory cells. Our group has also found that in atheromatic rabbit aortas the removal of *vasa vasorum* was associated with a decrease of vessel wall temperature, an indication that inhibition of *vasa vasorum* proliferation may stabilise the high risk plaques.

Another issue that has attracted the interest of researchers during recent years is the development of animal models for high-risk or vulnerable plaque investigation. Until now there are no animal models with plaque rupture resembling the human coronary arteries. The rabbit atheromatic model has been used in the majority of studies for vulnerable plaque investigation. However, this animal model has several limitations, as plaque rupture and an equal amount of

atheromatic burden are not consistently reproduced. A promising animal model was recently presented, in which a plaque with all the mentioned high-risk features is produced.[7] In this model the researchers developed a perivascular shear stress modifier that induces regions of lowered, increased, and lowered/oscillatory shear stresses in mouse carotid arteries, and studied plaque formation and composition. Lowered shear stress lesions were larger, contained fewer smooth muscle cells, less collagen, and more lipids. In addition, they showed more outward vascular remodelling than did oscillatory shear stress lesions. This animal model seems to have several advantages compared to other experimental models and hopefully future studies will evaluate this model.

Although genetics have contributed substantially to the diagnostic and therapeutic approach in other medical specialties, there have been no equivalent achievements in atherosclerosis because of the complexity of the disease. Recently, however, heritable patterns of myocardial infarction have been identified, such as variants of the gene ALOX5AP (also known as FLAP).[8,9] These variants are known to be associated with an increased risk of myocardial infarction, and the first studies of FLAP inhibitors showed significant and dose-dependent suppression of known biomarkers with proven prognostic value for myocardial infarction.[10] Many researchers mentioned that the genetics of atherosclerosis and myocardial infarction are different. The likely explanation is that, despite the numerous atheromatic plaques of variable size observed in individuals, only a limited number of them have particular susceptibility to plaque rupture or erosion. Of course, in order to understand the actual genes responsible for myocardial infarction, direct assessment of the genome of individuals is required. Thus, the genomic basis of myocardial infarction requires further investigation to expand our knowledge in the field of vulnerable plaque.[11]

During recent years several methods have been proposed for the invasive detection of vulnerable plaques *in vivo*. Imaging and functional methods, including intravascular ultrasound,[12,13] palpography,[14] virtual histology,[15-17] intracoronary thermography,[18-20] optical coherence tomography,[21-23] intravascular magnetic resonance imaging,[24,25] Raman spectroscopy,[26] low coherence interferometry,[27] and near infrared spectroscopy,[28] have advantages and disadvantages in the detection of vulnerable plaques. The combination of parametric, spatial, and temporal resolution required for the *in vivo* assessment of vulnerable plaques cannot be accomplished by a single method. The simultaneous structural and functional evaluation of atheromatic plaques seems to provide the most reliable information regarding plaque vulnerability. The impressive development of non-invasive methods for qualitative and quantitative analysis of coronary plaques, including multislice computed tomography[29,30] and magnetic resonance imaging,[25,31,32] still needs improvement in order to address the current shortcomings that prevent widespread clinical application.

Finally, the treatment of high-risk plaques is also an emerging field of research. By targeting specific components of vulnerable plaques, the incidence of acute coronary syndromes is expected to be dramatically reduced. Multiple approaches for plaque stabilisation have been adopted. Inhibition of local and systemic inflammatory activation is currently being tested in the clinical field. New pharmaceutical anti-angiogenic agents used in oncology are delivered locally for the inhibition of *vasa vasorum* proliferation within atheromatic plaques.[33] Long-term studies are required before safe conclusions can be drawn regarding the effectiveness of these approaches.

During the last decade there have been significant advances in understanding the pathophysiologic mechanisms of vulnerable plaque. Plaque rupture is the predominant feature leading to acute coronary syndromes. The field is eager for solutions that identify and assess the vulnerable plaques. In the near future we will have the results from the first studies evaluating new therapies specifically targeted at vulnerable plaques. We must hope that all this effort will result in a reduction of the incidence of acute coronary syndromes.

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