Interventional Cardiology

The challenge to detect and to treat vulnerable plaques and vulnerable patients

Submitted: 15 November 2016; Accepted: 17 November 2016; Published online: 22 November 2016

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Introduction

One of many "holy grails" of cardiology is to avoid the occurrence of acute coronary syndromes (ACS). It would be a remarkable improvement in the field if we could develop the capacity to identify the spots of the coronary vessels that are about to become unstable during the following weeks or months. This should be possible if we were able to prevent dissection, rupture or erosion of the coronary wall which usually causes an ACS [1-3]. It is said that this could possibly be realized by identifying those unstable coronary artery lesions that are more prone to result in future coronary events and, consequently, acute myocardial loss [4].

By searching for the above, we almost accomplished in recent years the ability to identify vulnerable coronary atheroma. Identifying a coronary plaque that is usually associated with a higher risk of rupture or erosion would possibly help us to establish more aggressive treatment to prevent the genesis of the pathophysiology of the ACS. However, the best way to establish this treatment (locally or systemically) still remains highly controversial [3,5].

The notion of the 'vulnerable plaque' arose from autopsy studies that disclosed two-thirds to three-fourths of fatal acute myocardial infarctions resulting from a rupture of the fibrous cap of the plaque that engendered thrombosis. Decades ago, some elegant post-mortem studies by pathologist pioneers redirected the cardiology community from confusion about the causality of thrombosis in ACS as well as a focus on vasospasm towards plaque rupture [1,2].

Loaded with lipid and inflammatory cells such as macrophages, covered by a thin fibrous cap, and considered perilously poised to rupture, the thin-capped fibro atheroma (TCFA) has become a target for imaging, possible intervention, model attempts in animals, and much discussion [6]. Over the last several decades, the quest to identify and treat the 'vulnerable plaque' has generated much interest [7,8]. Different imaging techniques have been touted as being able to identify vulnerable plaques: thermography, Near Infrared Spectroscopy (NIRS), intravascular ultrasound, virtual histology, intracoronary optical coherence tomography and the "noninvasive", but also contrast and radiation demanding: coronary tomography [5].

However, identifying a coronary atherosclerotic plaque in patients does not mean that they will develop an ACS [9-11]. We now know that identifying one or more vulnerable plaques is only an alert to the patient and to the cardiologist that a coronary event could happen. This certainly can help us to establish the patients we should concentrate on in our efforts to increase our treatment in order to avoid ACS. There are, however, several limitations in considering this finding as a perfect alert for possible future events. Actually, the vast majority of thin-capped, lipid-rich atheroma persists for years without causing any clinical event [9-11]. Another important topic to notice is

that thin-capped, lipid-rich atheroma are not always solitary, but are often multiple, and affect several arterial beds in the same individual. Besides all this, there is not an excellent clinical or anatomical feature that will predict which of these coronary plaques may rupture or erode [12].

In the Providing Regional Observations to Study Predictors of Events in the Coronary Tree (Prospect) study, only approximately 5% of thin-capped plaques as defined by virtual histology caused coronary events during a 3.4-year follow-up period [13]. As longitudinal intravascular imaging studies such as Prospect enrolled higher risk patients, thin-capped plaques in lower risk populations may cause even fewer thrombotic events. Thus, the vast majority of so-called 'vulnerable plaques' does not exhibit clinical 'instability' and indeed seldom provokes ACS. Moreover, the consequences of a plaque disruption depend not only on the 'solid state' of the atheroma itself, but also on the fluid phase of blood, for example the concentrations of fibrinogen, endogenous inhibitors of fibrinolysis, and pro-coagulant micro particles [9].

Thus, besides all this development in the capacity of detecting these dangerous spots in the coronary arteries, there is currently no significant evidence that treating these vessels locally (with coronary stenting, for example) could protect the patient from having an ACS. In other words, there is no evidence that finding a vulnerable plaque and treating it locally can lead to improved outcomes. In contrast, systemic therapies, with oral drugs like statins and antiplatelet, apparently can greatly improve outcomes in patients with vulnerable plaques. Identifying vulnerable patients (not only vulnerable plaques) and treating them aggressively, seems to bring more benefits than invasively investigating and treating vulnerable plaques locally. Besides, it is easier and cheaper to identify vulnerable patients than vulnerable plaques [14].

We still far from know if treating locally all vulnerable caps could promote any benefit. Some animal experiments suggested that the use of metallic stents or vascular scaffolds could reinforce fibrous caps and stabilize the plaque [15-17]. But, the disappointment with the results of the 3-year follow up of the ABSORB II trial population (recently presented at TCT 2016) brought up high concerns about the possible future intend to the use of vascular scaffolds to "stabilize" vulnerable plaques. The study showed that treatment with Absorb (Abbott Vascular) was associated with a two-fold increased risk of device-oriented clinical events (10 *vs.* 5%; p = 0.0425), specifically an increased risk of target-vessel MI (7% *vs.* 1%; p = 0.006), as well as an increased risk of late scaffold thrombosis compared with Xience (Abbott Vascular). So, using vascular scaffolds to treat a vulnerable plaque could actually increase the risk of a coronary event.

Animal studies show that lipid-lowering and/or statin treatment can reinforce the fibrous cap, decrease the lipid pool, and reduce inflammation [18]. Human imaging studies buttress the notion that statin therapy reduces the lipid content of plaques and augments the proportion of the plaque composed of fibrous tissue, a characteristic associated with resistance to rupture [19,20].

Other determinants that could alter plaque composition merit careful investigation, including improvement in the control of other risk factors, such as smoking, blood pressure, diabetes, metabolic syndrome and sedentary life style. Drugs that were recently associated with better cardiovascular outcomes (such as PCSK9 inhibitors, colchicine, semaglutide and empaglifosin) should also be tested for this purpose [2,21-24].

Other studies are still needed to determine whether the local treatment of vulnerable plaques (such as stenting the vessel or implanting vascular scaffolds) is superior to conventional management or to the intense control of conventional risk factors. Alteration in plaque composition and fibrous plaque thickening should also be tested by the use of other drugs recently associated with preventive benefits. The pathophysiological mechanism to explain the benefit of some drugs related to better cardiovascular outcomes could possibly be related to alterations in the coronary plaque composition and to the thickness of the fibrous cap.

In conclusion, despite all the latest advances in intra-coronary imaging that improve the identification of vulnerable plaques, current clinical decision making for the local management of coronary artery disease should remain based on the degree of luminal stenosis or on the degree of flow impairment to the distal vessel. Further studies are still needed to better understand the linkage between the findings suggesting vulnerability of the coronary wall and the development of future coronary events.

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