The visualization of the remodelling paradox

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Online publish-ahead-of-print 24 June 2008

This editorial refers to ‘In vivo association between positive coronary artery remodelling and coronary plaque characteristics assessed by intravascular optical coherence tomography’ by O.C. Raffel et al., on page 1721 of European Heart Journal (2008), 29, 1704–1705.

In the 1990s, significant efforts and investments were made in the development of imaging technologies with the objective of visualizing and characterizing the atherosclerotic plaque. Although angiography still is the indisputable first choice for the clinical diagnosis of coronary artery luminal narrowing, new imaging modalities are likely to stay to provide surrogate markers for disease progression and treatment efficacy.

Since its clinical introduction, an important role has been arrogated to intravascular ultrasound (IVUS) in the diagnosis of coronary artery disease. However, despite the superior information that is provided on plaque and vessel morphology, IVUS has never met the expectations that were raised more than a decade ago, i.e. that IVUS would be routinely used in the cathlab. IVUS did improve our understanding of the natural history of atherosclerotic disease and, more specifically, the impact of geometrical arterial remodelling on luminal stenosis.

Plaque formation has long been considered the only determinant of atherosclerotic luminal narrowing. The arterial wall, however, is an organ capable of overall reshaping in response to haemodynamic, mechanical, and biochemical stimuli. Glagov et al. were the first who raised the concept of ‘compensatory enlargement’. They described that the artery can partially or totally compensate for encroachment of atherosclerotic plaques upon the lumen by expansion of the arterial diameter. For a long time it was proposed that all arterial segments that suffered from atherosclerotic lesion formation underwent expansive remodelling and that luminal narrowing occurred when a maximal degree of arterial enlargement was reached. However, the arterial wall may also respond with constrictional remodelling, thereby aggravating the luminal narrowing response. In the same arterial segment one can observe lesions with an identical plaque area but with major differences in percentage luminal stenosis.

Scientific interest in the role of arterial remodelling in occlusive arterial disease soared with the upcoming use of the visualization technique of IVUS. The application of IVUS revealed how ubiquitously remodelling can prevent plaque from encroaching upon the lumen but also how failure of an expansive remodelling response accelerates luminal narrowing in de novo atherosclerosis. The variation of geometrical arterial remodelling in response to plaque formation is currently appreciated but has been traditionally underestimated as a causal factor for arterial occlusive disease. For instance, with IVUS studies it was demonstrated that in 5% of patients eligible for coronary intervention, the plaque mass at the culprit lesion is actually smaller than the plaque size located at the angiographically normal reference site. The latter emphasizes the role of geometry changes of the artery in atherosclerotic luminal narrowing and that the degree of luminal narrowing may be determined by inadequate compensatory enlargement rather than by the increase in plaque mass.

One would be easily inclined to think of arterial enlargement as a beneficial response and constrictive remodelling as a harmful response to atherosclerotic plaque formation. The increase in vessel size in response to plaque formation is considered a natural compensatory response to prevent downstream lack of oxygen supply. However, the remodelling response is a coin with two faces and hides a paradox. Histopathological studies clearly demonstrated that expansive remodelling is associated with infiltration of inflammatory cells, expression of pro-inflammatory cytokines, and increased protease activity. These features are recognized as major determinants of plaque destabilization. In addition, collagen and smooth muscle cell content is lower in plaques that undergo expansive remodelling. On the other hand, constrictive remodelling may aggravate narrowing of the lumen, but is associated with a stable fibrous plaque phenotype. The histopathological observations were soon followed by clinical IVUS studies that linked the clinical presentation of patients suffering from coronary artery disease with the mode of arterial remodelling. Different studies clearly revealed that unstable coronary syndromes often originated from lesions that revealed expansive remodelling while constrictively remodelled lesions were more frequently observed in patients suffering from stable angina.

The aforementioned observations gave rise to the concept that IVUS could be applied to assess plaque characteristics and
remodelling as prognostic measures for plaque destabilization, rupture, and subsequent thrombosis. Indeed, the mode of arterial remodelling and spectral analysis of IVUS radiofrequency data are reported as derivate of atherosclerotic plaque destabilization and are more frequently used as surrogate measures for progression of disease in longitudinal interventional studies.

The search for the vulnerable plaque and the patient at risk is ongoing and remains one of the major challenges in the research fields of biomarkers and imaging. Non-invasive visualization of the vulnerable plaque by identification of, for instance, an inflammatory molecular fingerprint is in an experimental phase but is unlikely to become widely applied in the clinical setting in the near future. The histological description of the vulnerable atherosclerotic plaque still is the most important lead for diagnostic imaging modalities. The classical definition of the vulnerable plaque encompasses histopathological features such as a large lipid core, the presence of inflammatory cells, and a thin fibrous cap. Thus far, IVUS has been the most widely applied imaging technology to visualize the aforementioned features of the vulnerable plaque. However, the use of IVUS for vulnerable plaque detection merits careful consideration. IVUS resolution is too limited to visualize thin fibrous caps, and reports on histological validation studies correlating between echolucency and the presence of lipids are conflicting.

Raffel et al. report a study in which two imaging modalities have been applied simultaneously in vivo that have significant added value: IVUS and optical coherence tomography (OCT).11 IVUS was used to grade the degree of arterial remodelling (expansive vs constrictive) whereas OCT revealed the prevalence of the three histological determinants of the vulnerable plaque: the thickness of the fibrous cap, the presence of lipid cores, and macrophage infiltration. A trade-off exists between resolution and penetration depth. Using the combination of IVUS and OCT integrates the strengths of both imaging technologies: penetration depth to assess remodelling mode and optimal resolution to assess the determinants of plaque vulnerability.

The message of the study, that expansive remodelling is associated with features of plaque vulnerability, is not surprising since the association has been revealed earlier in histopathological studies. However, this is the first time that a high-resolution technology is capable of verifying the post-mortem observations in vivo, demonstrating that expansive remodelling is associated with an unstable plaque phenotype. In addition, the authors should be complimented on the detailed analyses of images obtained using two imaging modalities in a relatively large number of patients.

After the first description of OCT images of coronary arteries in 1991,12 it took almost a decade before different atherosclerotic lesions were discriminated with this high-resolution technology.13 In this study, OCT and IVUS were applied to visualize arterial geometry and plaque phenotype in 40 patients. The study by Raffel et al. supports the concept that OCT may be ready for more widespread application in clinical studies. Even though basic technological challenges must be addressed prior to widespread use of this technology,14 the unique capabilities of OCT will facilitate the search for surrogate markers of atherosclerotic disease progression. Imaging technologies such as OCT may provide new insights into the natural history of atherosclerotic disease and provide markers of plaque destabilization.

**Conflict of interest:** none declared

**References**