Atheromatous plaque location and arterial remodelling

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Atherosclerosis is associated with a number of structural and functional changes in the arterial wall. Endothelial dysfunction, oxidised-LDL accumulation, increased concentrations of macrophages, neutrophils and T-cells as well as smooth muscle cell migration are some of the most relevant changes that take place during atherogenesis and coronary artery disease progression. It has been shown that the presence of a space-occupying plaque is commonly associated with the expansion of the arterial wall (‘vessel remodelling’). The mechanisms responsible for this phenomenon are speculative.

Positive and negative vessel remodelling

The majority of coronary artery atheromatous plaques are eccentric and tend to grow towards the adventitia before encroaching upon the lumen of the artery. This was shown initially by Glagov et al.1 in a pioneering study, which demonstrated that left main coronary arteries enlarge in response to atheromatous plaque growth, a phenomenon termed remodelling. Interest in arterial remodelling grew significantly in recent years with the advent of intravascular ultrasound (IVUS) imaging.2,3 Both ‘positive’ and ‘negative’ types of vascular remodelling have been identified. Positive arterial remodelling is described by pathologists as outward plaque bulging associated with the thinning of the arterial media. Positive remodelling is also defined by IVUS as the (positive) ratio: external elastic membrane (EEM) area measured at the lesion site/EEM measured at a control reference site. Negative remodelling, identified in IVUS studies, describes a ‘paradoxical wall shrinkage’ at the site of atheromatous plaques. This type of remodelling is more commonly found in peripheral arteries compared to coronary arteries.4–6

There is an apparently erratic behaviour of atheromatous coronary artery segments regarding wall expansion at atheromatous sites. Although vessel remodelling is commonly observed in coronary arteries bearing atheromatous plaques, a sizeable proportion of atherosclerotic arteries do not undergo remodelling. Recent observations suggest that arterial remodelling is lesion-specific, rather than a ‘programmed’ arterial response in a giving individual.7 IVUS, which enables the in vivo visualisation of atheromatous plaques and the assessment of plaque characteristics, has provided valuable information regarding anatomical variables that may condition arterial remodelling in the clinical setting.2,3,5–7 Factors affecting the expansion of arterial segments at atheromatous sites are likely to be multiple and complex. Remodelling appears to be influenced by dynamic changes in vessel diameter caused by changes in blood flow and shear stress forces as well as the release of endogenous substances that affect vasomotor tone.8 Inflammatory mechanisms and endothelial cell activation that lead to plaque fissuring in patients with acute coronary syndromes have been also postulated to play a role in arterial remodelling.9 Upon activation by interferon-gamma macrophages within atheromatous plaques release metalloproteinases that degrade both the connective tissue plaque matrix and the muscular media, weakening the plaque fibrous cap and favouring its rupture. Interferon

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gamma, produced by T-lymphocytes, may also contribute to the thinning of the fibrous cap by inhibiting vascular smooth muscle cell collagen synthesis. It may be therefore speculated that inflammation may represent a link between plaque fissuring and positive vessel remodelling. However, despite the attractive and apparently rational hypothesis linking both mechanisms, Smits et al.\textsuperscript{11} showed that less than 60% of patients with acute coronary syndromes exhibit positive remodelling at the culprit lesion site, while von Birgelen et al.\textsuperscript{12} found remodelling in only 34% of culprit lesions showing plaque rupture, as assessed by IVUS.

Other mechanisms have been also postulated to explain the occurrence of remodelling in certain arteries but not in others. In 2001, Ward et al.\textsuperscript{13} reported a significantly higher incidence of plaque remodelling in coronary artery segments with eccentric plaques facing the myocardium compared to those facing the pericardium. They suggested a splinting effect of the myocardium, which could prevent the occurrence of vessel remodelling. In this issue of the Journal, Prati et al.\textsuperscript{14} give further insight regarding this suggested relationship between different locations of atheromatous plaque within sections of the arterial circumference and the occurrence of vessel remodelling. They carried out elegant anatomical investigations in patients undergoing arteriography for the assessment of coronary artery disease. More stringent criteria were used in the Prati study\textsuperscript{14} compared to previous studies,\textsuperscript{13} to define both the location of coronary plaques within the vessel circumference and their relation to the pericardial and myocardial surfaces. Arterial segments selected for analysis were reconstructed with the use of three dimensional (3-D) IVUS imaging techniques. Two findings are relevant in the Italian study: (1) the confirmation of previous suggestions by Ward et al.\textsuperscript{13} that remodelling is affected by the transversal distribution of atherosclerotic plaques, possibly due to the splinting effect of myocardial mass and (2) the observation that plaque location in relation to the myocardial or pericardial surfaces does not affect remodelling in distal coronary artery segments. The results reported by Prati et al.\textsuperscript{14} provide a mechanical explanation to what appears to be an erratic incidence of vessel remodelling in the coronary tree of patients with angina pectoris.

The assessment of plaque distribution within the circumference of the coronary artery in vivo is problematic, particularly regarding the accurate identification of plaque location. Prati et al. have at least partially overcome this difficulty by using 3-D IVUS to reconstruct the coronary artery under scrutiny. The left anterior descending (LAD) coronary artery was specifically interrogated in the study and both proximal and distal segments were assessed. Evaluation of distal segments was carried out to ascertain whether findings in proximally located plaques could be extrapolated to plaques located in distal segments. In order to more accurately identify plaque location, the take-off of a septal branch emerging opposite to the pericardial surface was used as a marker to divide the vessel circumference into two semicircles. One of the semicircles thus faced the myocardium and the other the epicardium. A single, well-defined anatomical landmark was thus used in the study. Another important methodological point addressed by the authors was the selection of plaques appropriate for analysis. Prati et al. excluded lesions showing ‘an intermediate grade of remodelling’ and also eliminated stenoses with poor image quality and ostial lesions. These attempts by the authors to minimise error in plaque location are laudable but they may also introduce some bias, as only selected lesions were analysed in the study. Due to numerous exclusions, Prati and colleagues were able to study only 88 (60%) of the initial 147 stenoses. Calcified plaques, however, were not eliminated from the study and this also represents an important difference with previous investigations\textsuperscript{6} where heavily calcified plaques were excluded from analysis on the basis that they offered problems regarding the identification of the EEM by echocardiography. In a previous report by Mintz et al.\textsuperscript{6} calcified lesions (arc <60°) were found to be independent predictors of vessel remodelling.

Analysis of selected stenoses showed remodelling in 50% (44 stenoses) in the Prati study. Of these, 77% had pericardial distribution and 23% myocardial distribution, thus confirming previous suggestions that higher proportions of atherosclerotic segments with plaques facing the pericardial surface undergo remodelling compared to plaques with myocardial location. A permissive role of epicardial fat, favouring vessel expansion has been offered as an explanation for this finding.

Of interest, the pattern described for proximal LAD coronary artery segments was not present in the distal segments of the artery, where positive remodelling occurred irrespective of both plaque location and findings in proximal segments. In the Prati study, remodelling in distal segments was found in 16 plaques, eight with myocardial distribution and eight with pericardial distribution. It was therefore suggested that in the distal coronary segments, myocardial resistance may be lower and
thus unable to limit vessel expansion in response to plaque growth.

Although these mechanical hypotheses offer useful, practical explanations, the molecular mechanisms responsible for differential vessel expansion in plaques with different locations, are likely to be complex. The findings in the Prati study open interesting avenues for research in this area. Future technical advances in 3-D reconstruction techniques and improvement in the understanding of wall vessel biology will help to design studies aimed at investigating the roles of mechanical, haemodynamic and molecular factors in the genesis of vascular remodelling in patients.

References