Coronary artery remodelling in atherosclerosis: unfortunately unpredictable

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This editorial refers to ‘Relation between baseline plaque burden and subsequent remodelling of atherosclerotic left main coronary arteries: a serial intravascular ultrasound study with long-term (≥12 months) follow-up’ by M. Hartmann et al., on page 1778

Coronary heart disease is the main cause of mortality and morbidity worldwide, and occurs because of the growth and complications of coronary atherosclerosis. Therefore, efforts in the understanding of how atherosclerotic plaques grow and undergo complications, and in identifying predictors of such dramatic events are welcome and worthwhile. Atherosclerosis has long been considered a relentless process by which the accumulation of lipids and extracellular matrix leads to progressive lumen encroachment. Two notions in the past 20 years have dramatically altered this conception. One is that most cases of myocardial infarction (progressive lumen encroachment) and not from progressive lumen stenosis1. The other is that the growth of atherosclerotic plaques is not necessarily towards the lumen, but may also occur towards the outer vessel layers, leading to an actual overall enlargement of the vessel, contrary to the previous tenet that atherosclerosis is similar to the encrustation of metal pipes in a building. This second aspect, although less appreciated in current literature than the burgeoning plethora of investigations on mechanisms of plaque rupture, is also fertile of important clinical consequences.

In a series of human histopathological observations, Glagov et al.2 were the first to identify a significant direct correlation between the plaque area—calculated as the area defined externally by the internal elastic lamina (internal elastic membrane, IEM) and internally by the vessel lumen (intimal area) and the potential lumen area—i.e. the area circumscribed by the internal elastic lamina, taken as a measure of the area of the arterial lumen if no plaque had been present and the intima remained a virtual space. This finding indicated that, in general, the larger the plaque, the larger the vessel, and allowed the inference that plaques also grow towards the outside (‘positive remodelling’). These results have been subsequently validated in a number of investigations both by histopathology and by intravascular ultrasound (IVUS), clearly demonstrating that the evaluation of lumen area (and, by comparison with adjacent vessel segments, lumen stenosis, as routinely performed by angiography), may grossly underestimate the volume of the plaque, and that acute plaque complications (plaque rupture in most cases), may occur even in the total absence of any lumen reduction.

Another interesting part of Glagov’s original findings has spurred further research. In correlating lumen area with the plaque burden, calculated as the percent of plaque area out of the IEM area, the authors found that lumen area was not related to the plaque burden for a range of percent plaque areas between 0 and 40; but an important significant negative relationship existed for plaque areas >40%. The inference at that time was that early plaque growth occurs preferentially towards the outside, because of the occurrence of positive remodelling, whereas further growth of the plaque, beyond a value estimated at 40% of the total potential lumen area, leads to lumen encroachment, and therefore, potentially, to a limitation of the coronary reserve.3

Two important theoretical limitations of Glagov’s analysis, on which the hypothesis was based were that: (1) the estimate of the relationship between lumen area and plaque burden is biased by the fact that one term of the relationship (lumen area) is arithmetically related to the other (plaque burden = % plaque area/IEM area, with IEM area = lumen area + plaque area); and (2) Glagov’s original findings were correlations in a snapshot of a sample of coronary arteries, and not dynamic estimates or the actual progression of the two parameters (plaque burden and lumen area) over time.

The introduction of IVUS in the clinical routine has more recently allowed the in vivo imaging of the vessel area, as IVUS can identify the external elastic membrane (EEM) and may document the presence of atheromas otherwise undetectable by standard angiography. Lesions localized in the left main stem and detected by IVUS, but not by angiography have a clear clinical relevance, as they predict one-year clinical events5. Moreover, IVUS is repeatable and allows serial measurements. One example of such
elevations is presented in the current issue of this Journal by Hartmann et al.6. These authors performed serial (18 ± 8 months apart) IVUS examinations of 46 atherosclerotic left main stems with minor lumen stenoses at angiography, and analysed them by IVUS to assess the relation between baseline plaque burden (here defined as plaque + media area/ EEM area) vs. serial remodelling (=EEM area at baseline – EEM area at follow-up, Figure 1). In 25 plaques of the left main stem with baseline plaque burden <40% (group A) and 21 plaques with baseline plaque burden ≥40% (group B), the authors found no relation between baseline plaque burden and subsequent changes in vessel area, both overall and in the analyses restricted to group A or group B lesions. The frequency of positive serial remodelling (vessel area increase) vs. negative or intermediate serial remodelling (decrease or no change) were similar in group A and group B lesions. The authors were also not able to reproduce the differential relationship of plaque burden vs. lumen area for the two types of vessel segments (with plaque burdens <40 vs. ≥40%) even in the baseline evaluation, a condition comparable with that of the original Glagov’s report.

The study has limitations, acknowledged by the authors, in the fact that it included a relatively small number of patients, in a limited range of plaque burdens (from 17.4 to 64.7%), excluding severe left main diseases and heavily calcified lesions. Patients were also studied before and after intensive medical treatment (e.g. statins) that may influence remodelling. Yet, such limitations appear not to be substantial and the conclusions are in agreement with what obtained by Sipahi et al.7, who documented that plaque burden is not a predictor of positive remodelling during the progression of atherosclerosis in a series of 210 coronary lesions deriving from the cohort of the Reversal of Atherosclerosis with Aggressive Lipid Lowering (REVERSAL) trial. Other factors, including the geometrical plaque localization (in proximal segments, positive remodelling appears to occur preferentially in lesions facing the pericardium as compared with lesions facing the myocardium),8 may play a role in determining the occurrence of positive remodelling.

IVUS is, currently, the standard method to monitor lesion modifications over time, and has been used to document that aggressive statin therapy may halt and even induce regression of the plaque burden in human coronary arteries9,10. IVUS, however, can currently only delineate plaque size by allowing measurement of the plaque + media area (=EEM area – lumen area) (Figure 1), but not its content. Insight on plaque composition may derive from the analysis of back-scattered IVUS (virtual histology)11, from the analysis of physical characteristics of the vessel during systo-diastolic excursions (palpography),12 or likely better, from intravascular optical coherence tomography, another imaging technique that measures the intensity of back-reflected infrared light and provides high resolution cross-sectional images of tissue in situ.13 Such techniques are potentially powerful diagnostic tools, able to document qualitative modifications of the plaque content and to assess lesion vulnerability.

Thus, it appears that IVUS has been extremely helpful in clarifying the relationship of baseline plaque features with remodelling, indicating that plaque growth is substantially a random process, causing frank lumen reduction, vessel expansion, or both, independent from the baseline quantitative features of plaque burden. IVUS, however, falls short in finding its own practical role in the clinic for predicting the rate of lumen encroachment and, in its current status, the greater or lesser risk of plaque rupture. As it often happens in science, one advancement in our understanding is not accompanied by a parallel increase in our ability to decide what to do in an individual patient.

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References

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Neointimal proliferation around malapposed struts of a sirolimus-eluting stent: optical coherence tomography findings

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A 65-year-old man with hypercholesterolaemia and hypertension underwent elective percutaneous coronary intervention (PCI) because of exertional angina. Three sirolimus-eluting stents (Cypher; 3.0 × 33, 3.0 × 13, and 2.5 × 28 mm) were deployed in the left anterior descending artery. Three months after the PCI, follow-up studies were performed. An angiogram showed no in-stent restenosis. A coronary angiography showed the struts with a glimmer were detached from the vessel wall (black arrowhead in Panel A). Neither neointima nor intracoronary thrombi around this strut were visible. Both longitudinal and cross-sectional images by optical coherence tomography (OCT) clearly demonstrated protrusion of stent struts into the lumen (white arrowheads in Panels B–D) and existence of a lumen behind the struts (white arrows in Panels B–D). Surprisingly, neo-intimal proliferation around these malapposed struts (red arrows in Panels C and D) extended from the vessel wall to the strut like a polyp with a stalk (Panel D). Thin neo-intimal layer on the struts of drug-eluting stents is often difficult to detect, even with an intravascular ultrasound. Our images suggest that angiography also appears to have limitations in detecting very thin layer of neo-intima. OCT, with its high resolution, provides detailed information on intracoronary structure. OCT may be a useful tool to evaluate the process of neo-intimal proliferation after drug-eluting stents implantation.

Angioscopic and OCT findings of malapposed struts of a sirolimus-eluting stent.