Arterial remodelling: an independent pathophysiological component of atherosclerotic disease progression and regression. Insights from serial pharmacological intervention trials

Paul Schoenhagen¹,²* and Ilke Sipahi²

¹Division of Radiology and ²Department of Cardiovascular Medicine, The Cleveland Clinic, 9500 Euclid Avenue, Cleveland, OH 44195, USA

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This editorial refers to 'Effect of perindopril on coronary remodelling: insights from a multicentre, randomized study' by G.A. Rodriguez-Granillo et al., on page 2326

Rodriguez-Granillo et al.¹ report arterial remodelling data from the 'PERSPECTIVE' study,² an imaging substudy of the 'EUROPA' study.³ 'EUROPA' is a randomized, placebo-controlled, multicentre trial, which demonstrated that the angiotensin-converting enzyme (ACE) inhibitor perindopril reduced adverse clinical events in 12,218 patients with stable coronary artery disease (CAD). The EUROPA investigators suggested that the clinical benefit is related to anti-atherosclerotic effects of ACE inhibitors. However, the 'PERSPECTIVE' substudy, which examined the impact of perindopril on atherosclerosis in a subset of 118 patients, found neither an effect on plaque burden assessed by intravascular ultrasound (IVUS) nor an effect on angiographic luminal diameter. The lack of change in these imaging endpoints could indicate that the clinical benefit of ACE inhibition is not mediated by changes of atherosclerotic plaque anatomy. However, an alternative explanation is that ACE inhibition exerts other plaque-stabilizing effects including modification of plaque composition and arterial remodelling.

This hypothesis is examined in the current, serial IVUS study, which investigates the effect of perindopril on arterial remodelling and plaque composition. Remodelling was defined as a relative increase (expansive remodelling) or decrease (constrictive remodelling) of the mean vessel cross-sectional area (CSA) between baseline and follow-up. A total of 711 matched 5 mm segments from 118 IVUS examinations were available at baseline and after 3-year follow-up. There was no significant difference in the change of plaque burden between the perindopril and placebo groups. However, the change in vessel CSA was significantly different (P = 0.04), and constrictive remodelling occurred more frequently in the perindopril than in the placebo group (34 vs. 25%, P = 0.01). The perindopril group showed a non-significantly smaller mean remodelling index than the placebo group (1.00 ± 0.2 vs. 1.03 ± 0.2, P = 0.06). In summary, treatment with perindopril was associated with constrictive (negative) remodelling despite neutral effect on plaque burden and luminal dimensions.

Arterial remodelling was first described in human left main coronary arteries by Seymour Glagov in a seminal post-mortem study examining the relationship between vessel size and plaque burden.⁴ Glagov found compensatory expansion of the vessel area during early plaque progression. In clinical cardiology, the lumen-maintaining effect was seen as a distinct benefit of 'positive', expansive remodelling. This assumption was further enforced by the subsequent recognition of the opposite process, 'negative', constrictive remodelling, which was first observed in patients with restenosis after coronary angioplasty. However, subsequent studies demonstrated that expansive arterial remodelling is associated with inflammation, plaque progression, and unstable clinical presentation.⁵,⁶ Based on these findings, expansive remodelling is now recognized as a characteristic of unstable/vulnerable lesions.

These findings have generated the hypothesis that plaque-stabilizing, pharmacological interventions may in fact be associated with constrictive remodelling, which has been examined in serial IVUS trials during lipid-lowering therapy. In a subgroup analysis of the REVERSAL trial, progression in plaque area at focal, mildly stenotic lesion sites was associated with constrictive remodelling during 18 months of statin treatment.⁷ The results reported by Rodriguez-Granillo et al.¹ further support the association between constrictive remodelling and plaque stabilization, and provide insights into a potential mechanism of vascular protection related to ACE inhibition.

A particularly intriguing aspect is the relationship between changes in plaque burden, remodelling, and luminal dimensions during plaque progression/regression.
Serial angiographic studies demonstrate a correlation between changes in luminal size and clinical outcomes. However, in the current IVUS study, luminal size was unchanged in the perindopril group despite non-significant plaque regression because of the simultaneous constrictive remodelling. Paradoxically, the placebo group showed a non-significant increase of the lumen area as a result of a larger mean remodelling index with no change in plaque size. Other serial IVUS trials during statin treatment have also shown that progression of coronary atherosclerosis can be associated with a paradoxical increase in lumen CSA, whereas regression may not be associated with any change in lumen area.

The potential pathophysiological mechanisms linking plaque stabilization with different pharmacological interventions and constrictive remodelling are incompletely understood. Rodriguez-Granillo et al. discuss that statins and ACE inhibitors may have a common target in their modification of the inflammatory response. In fact, recent animal data in the peripheral circulation suggest that ACE inhibition modifies vascular injury by reversing the effect of proinflammatory mediators and vascular remodelling. Preliminary clinical data in the above-described analysis of the REVERSAL trial demonstrated a correlation between the change in remodelling and C-reactive protein, but not low-density lipoprotein cholesterol and high-density lipoprotein cholesterol. The relationship between remodelling and inflammation requires further evaluation.

A strength of the current study is its methodology, which allows the assessment of remodelling in entire vessel segments. Most previous studies have defined remodelling by comparing the vessels size at a focal lesion site and an adjacent reference. This approach is limited by imprecise matching and does not take into account that remodelling may vary among coronary segments. Rodriguez-Granillo et al. demonstrate a highly heterogeneous remodelling pattern along coronary segments. This finding is very important for future serial observation of remodelling in pharmacological intervention trials. Similar to plaque burden, volumetric assessment of remodelling may provide a more reliable representation of the overall change in a coronary vessel.

Another methodological aspect is the influence of plaque components and in particular vessel calcification. Similar to previous IVUS studies, segments with severe calcification were excluded from the final analysis. Previous studies suggest that these calcified segments are probably characterized by constrictive remodelling and are less prone to changes in plaque burden during pharmacological intervention. After excluding densely calcified segment, the authors did not find characteristic changes in plaque quantitative grey-scale composition during disease progression/regression. Results from ongoing and future studies utilizing more advanced plaque analysis systems, including radiofrequency analysis, are pending.

Finally, the authors describe discrepancies in comparison with previous histopathological studies, in particular Glagov's original finding, that expansive remodelling is limited beyond a cross-sectional plaque burden of ~40%. Similarly to recent data from statin trials, the current serial observation of coronary vessels demonstrates that the capacity for remodelling is maintained even in lesions with greater plaque burden. In this context it is important that contemporary clinical trial design requires baseline treatment with statins and other vasoactive medications. For example, in the PERSPECTIVE trial, ~70% of patients received lipid-lowering therapy and ~60% received a β-blocker. As these medications influence plaque progression and remodelling, comparison with previous 'statin-naive' data is biased.

The manuscript by Rodriguez-Granillo et al. further supports the concept that arterial remodelling is an independent component of atherothrombotic disease progression/regression, and suggests a strong relationship to the inflammatory response. It is increasingly obvious that observation of plaque, lumen, vessel size, and plaque composition together provides a more comprehensive understanding of disease progression/regression than changes in each single parameter alone. Using yet to be standardized methodology, inclusion of remodelling as an end-point in pharmacological progression/regression studies may provide an improved window into plaque vulnerability and stabilization.

References