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## EDITORIAL COMMENT

# Vascular Remodeling: Do We Really Need Yet Another Study?*

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More than 15 years have passed since Seymour Glagov published his seminal article describing the phenomenon of vascular remodeling which now bears his name (1). By meticulously examining finely sectioned left main coronary arteries from necropsy specimens, he observed a change in the arterial size that was proportional to the plaque burden. This simple observation had profound implications. The coronary arteries have always been viewed as conduits of blood flow similar to pipes in a house. But Glagov's observation suggests that coronary arteries are not inanimate pipes; instead arteries are living structures that change shape and size to adapt to plaque accumulation. This alteration in size, or remodeling, may effectively maintain the luminal orifice and therefore maintain blood flow to the myocardium despite the accumulation of plaque. From his and

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others' observations, the relationship between arterial size and plaque burden is maintained up to a plaque burden of 40% to 45% (on average), but thereafter the lumen becomes compromised due to the inability of the artery to expand further. The process of arterial enlargement to accommodate the plaque and maintain the lumen has been referred to as the Glagov phenomenon, compensatory enlargement, or positive remodeling.

Although the concept of vascular remodeling was revolutionary, it had little effect on clinical practice in the years immediately after its publication. By its nature (necropsy), it was observational. It is also very difficult for an autopsy study to discern cause from effect (i.e., was the plaque accumulation causing the artery to expand or was plaque accumulating in those areas because there was arterial enlargement?). Most importantly, this phenomenon could not be "seen" in clinical practice. Clinical assessment of coronary arteries utilizes angiography, which outlines the luminal contour and does not allow assessment of the plaque nor of the true arterial size (other than by inference from the luminal contours). If vascular remodeling could not be confirmed in vivo and if practicing angiographers were not able to "see" the remodeling for themselves, it would have been a slow uphill battle before final acceptance of these phenomena.

Intravascular ultrasound (IVUS) circumvents those limitations. It allows in vivo, real-time assessment of the lumen, plaque, and arterial (external elastic membrane [EEM]) areas. Most importantly, IVUS is performed by angiographers and allows side-by-side comparison of the angiographic and ultrasound images. Immediately after inception of IVUS in the clinical arena, it became apparent that there is significant angiographically silent atherosclerotic disease, in part because vascular remodeling itself is "angiographically silent." Early IVUS studies replicated Glagov's observations in peripheral and coronary arteries (2). In addition to assessing the relationship between arterial size and plaque accumulation across patients, IVUS allowed the examination of focal areas of arterial expansion associated with focal accumulation of plaque. A remodeling index was developed which compares the arterial area at the reference or references to the arterial area at the lesion (3).

Intravascular ultrasound also extended the concept of vascular remodeling beyond the Glagovian compensatory enlargement. By comparing arterial lesion sites to adjacent reference sites, focal luminal narrowing (or negative remodeling) was observed. This demonstrated that luminal stenosis can also be due to arterial shrinkage in addition to atherosclerotic plaque accumulation. A remodeling index (lesion arterial area/reference arterial area) $>1$ indicates positive remodeling (enlargement), and a remodeling index $<1$ indicates negative remodeling. Positive remodeling has been associated with acute (vs. stable) coronary syndromes, and negative remodeling has been associated with smoking, insulin-dependent diabetes, and fibro-calcific disease (4–7). Differential remodeling in distinct populations further reinforces the likelihood that this phenomenon is real.

Ultimately, seeing is believing. Intravascular ultrasound provides immediate, visual evidence to the interventional cardiologists indicating which lesions have an arterial area larger (or smaller) than the adjacent reference. Numerous publications have documented patient characteristics and clinical conditions associated with a particular type of remodeling (4–7). Remodeling has even been reported in arterialized saphenous vein grafts (8). Furthermore, arterial remodeling is a dynamic phenomenon that takes place alongside atherosclerotic plaque development, with early, softer plaques causing positive remodeling and older, harder plaques associated with negative remodeling (5–7). It is fair to conclude that the process of vascular remodeling is now well ingrained into our concept of coronary anatomy and pathophysiology.

So why do we need yet another study on vascular remodeling? Although the evidence is rapidly mounting to support the concept of arterial remodeling, there remain some very important gaps of knowledge. All too many times, "well accepted principles" were not ultimately supported by definitive trials.

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What will it take to have definitive proof that arterial remodeling occurs? There are at least two major areas of deficiencies for which we need data: 1) current cross-sectional methods of assessing remodeling assume that there is no remodeling in the reference segment, with all the remodeling occurring in the lesion segment; and 2) there are virtually no longitudinal data (other than case reports or small series [9]) demonstrating a change in arterial size in response to a change in plaque over time.

**References segment disease.** While IVUS advanced our ability to assess remodeling, it also alerted us to the diffuse nature of plaque distribution. It is rare to have a completely normal segment within a coronary artery. On average, approximately 30% to 50% of the cross-sectional area of the *angiographically normal reference segment* will be filled with plaque (10). In fact, the original observations by Glagov were in non-stenotic segments of the left main coronary artery with diffuse disease. However, the "IVUS definition" of remodeling (an arterial area at the reference site different from the lesion site) assumes that the reference site is "normal" and non-remodeled. But can the assumption be valid or reasonable if the average reference segment is, on average, 50% obstructed by plaque and the reference may have also undergone remodeling? In this case, we would only be assessing relative remodeling of the lesion compared with that of the reference segment. The "negative remodeling" (lesion EEM $<$ reference EEM) may not faithfully describe the lesion if it is significantly influenced by positive remodeling of the reference segment.

The study by Hong et al. (11) in this issue of the *Journal* puts this vexing issue to rest. By capitalizing on a subset of Korean patients with very little diffuse atherosclerotic disease, these investigators identified focal lesions with minimal reference segment disease (mean of 14% plaque burden). By including patients without substantial reference segment disease, they avoided the potential confounding effects of reference segment remodeling. In their subgroup, 48% demonstrated negative remodeling and 26% demonstrated positive remodeling. The remaining 26% had "intermediate" remodeling (which may represent no remodeling). This study provides two important aspect to our understanding of remodeling: 1) it further supports the concept of remodeling as a real phenomenon and proves that remodeling is not just an "artifact" of reference segment disease; and 2) it provides support that there is a higher prevalence of negative remodeling than previously appreciated (especially among patients with minimal atherosclerotic disease in their non-lesion segments). If minimal diffuse disease is a marker of early disease formation, this study implies that negative remodeling may be an early manifestation of atherosclerotic pathogenesis for (at least) some lesions. This is opposite to conventional teaching in which the early, soft lesions are associated with positive remodeling and older, hard lesions with negative remodeling (5–7). Consequently, as in so many other important studies, Hong et al. (11) clarify one issue (i.e., remodeling is not a methodological artifact) and question another conventional concept (i.e., that arteries exhibit positive remodeling early in the process of plaque formation). Unfortunately, neither the study of Hong et al. (11) nor any other current IVUS study can definitively address which comes first, positive or negative remodeling. The fundamental problem with IVUS studies to date is that they represent a cross-sectional observation of several patients at one point in time and infer vascular changes by comparing the lesion to the reference segment.

**The future: longitudinal IVUS studies.** The time has come to finally put this issue to rest. Direct evidence of arterial remodeling will be available only when patients with very early atherosclerotic disease are followed over time with serial IVUS studies. Although this will not be easy, it is not impossible. Several large progression/regression studies using serial IVUS examinations two years apart are ongoing to test different pharmacologic treatment strategies. Within these studies, there should be several arterial segments with minimal disease that show progression. With careful alignment of the IVUS images, changes in arterial area (increase in EEM) proportional to increases in the plaque area will definitively prove the presence of positive remodeling. These studies should also be able to demonstrate whether early lesions more often have positive or negative remodeling. Is positive versus negative remodeling a patient-specific or lesion-specific characteristic? Does a lesion change from one type of remodeling to another? Does the type of remodeling in a stenotic lesion parallel the type of remodeling in the non-stenotic reference segment? These and many more important aspects of remodeling need to be addressed with longitudinal studies.

Most importantly, longitudinal studies may identify unique patient characteristics and treatment strategies that are associated with favorable, positive remodeling which maintains lumen dimensions and prevents luminal obstruction. Eventually, longer term studies will be necessary to answer important questions regarding the relationship between remodeling and patient outcomes. For example, are lesions with positive remodeling more likely to rupture and be associated with an acute coronary syndrome, or has that conclusion been the result of selection bias from retrospective studies?

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