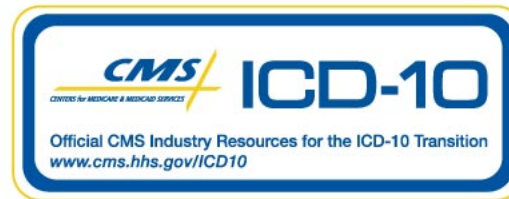


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EDITORIAL COMMENT

Imaging of De Novo Atherosclerotic Arterial Remodeling

Clinical Sense or Research Sensibility?*

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Atherosclerotic lesion progression and the formation of luminal thrombosis superimposed on a ruptured or eroded vulnerable plaque is well recognized as the pathological cause of the majority of cardiovascular events, such as stroke and myocardial infarction. The artery is not a rigid tube because it is capable of adapting to plaque growth by expansive remodeling (1). The increase in arterial diameter is a natural adaptation in response to lesion growth so that luminal blood flow remains preserved. However, it has been shown that arteries may also undergo constrictive remodeling, which accelerates luminal narrowing by plaque growth (2). Both types of geometrical remodeling may be observed in 1 individual in the same arterial segment. Arterial geometrical remodeling is a double edged sword because expansively remodeled plaques harbor inflammatory and protease activity beneath the surface of the lumen. Expansion of vessel diameter in response to progression of atherosclerotic disease is associated with the presence of an inflammatory lipid-rich plaque phenotype that is more likely to give rise to acute coronary syndromes, whereas constrictive remodeling is associated with a more fibrous stable plaque phenotype (2–4).

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Many researchers have focused on the clinical and biological relevance of the variation in remodeling responses and used in vivo intravascular ultrasound and post-mortem-obtained arterial specimens for this purpose.

In this issue of the *Journal*, Miao et al. (5) report the use of coronary wall magnetic resonance imaging (MRI) to study coronary vessel wall remodeling in asymptomatic patients. The investigators suggest that coronary wall MRI

is more likely applicable as a screening method for studying vessel wall characteristics compared with intravascular ultrasound because of its noninvasive nature. In 179 asymptomatic patients, they studied the coronary vessel size in relation to coronary wall thickness. This study confirms the earlier post-mortem observations by Glagov et al. (1); for example, correlating plaque area and vessel area measurements from multiple individuals showed that on average, expansive remodeling fully compensated the plaque growth, thereby preventing luminal narrowing. Even more, the increase in plaque area was associated with a concomitant increase in lumen area because of overcompensation. This study is of interest because the presence of expansive remodeling is shown in vivo in asymptomatic patients using a noninvasive imaging tool.

After 2 decades with numerous research studies that explored the phenomenon of de novo atherosclerotic remodeling, the question remains: what is the clinical relevance of in vivo visualization of the degree and mode of geometrical atherosclerotic remodeling? Does the direction of a remodeling response have a prognostic value, or can it serve as a surrogate measure of progression of disease or facilitate the testing of therapeutic efficacy of newly developed drugs?

The development and testing of drugs that aim to stabilize vulnerable plaques to prevent acute manifestations of atherosclerotic disease is a major challenge. Atherosclerotic lesion formation is slowly progressing, and large patient numbers are required for pharmacological hard end point studies to reach sufficient power. Currently there are no surrogate measures for plaque stabilization that are accepted as end points in pharmaceutical studies. Next to the use of coronary angiography, changes in carotid intima-media thickness using duplex ultrasound and plaque cross-sectional area assessed with intravascular ultrasound are the most appreciated surrogate end points in clinical trials of novel atherosclerotic disease therapies alongside ongoing clinical end point trials (6).

The ultrasound techniques have an advantage over the traditional method of coronary angiography for imaging atherosclerosis in that they allow direct visualization of atherosclerotic plaques in situ. The search for additional surrogate imaging markers for progression of atherosclerotic disease is ongoing and is explored in longitudinal studies (7). As mentioned earlier, the variation in arterial diameter, for example, geometrical remodeling, is a widely appreciated geometrical measure in ultrasound research. The association between variability in vessel size and histological features of the vulnerable plaque makes geometrical atherosclerotic remodeling a potential ultrasound measure that could serve as a surrogate for drug efficacy. Indeed, Schoenhagen et al. (8) showed in a subgroup of the REVERSAL (Reversal of Atherosclerosis With Aggressive Lipid-Lowering Therapy) trial that constrictive remodeling of the arterial wall occurred during plaque-stabilizing therapy with statin medi-

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cations. Moreover, in a study in 137 patients who presented with acute coronary syndromes, the presence of expansively remodeled lesions before stenting was predictive for the occurrence of cardiac events and lesion revascularization at 2 years (9). On the other hand, however, in the same aforementioned substudy of the REVERSAL trial it was also shown that the mode of arterial remodeling (expansive or constrictive) was not related to a change in atheroma volume comparing serial ultrasound data at baseline and follow-up (10), suggesting that the mode of geometrical remodeling cannot serve as an alternative surrogate measure for plaque progression over time. To summarize, hard evidence that the direction and extent of arterial remodeling has prognostic value for the occurrence of adverse cardiovascular events is lacking. Solid scientific arguments for screening of patients for the absence or presence of expansively remodeled plaques are yet to be provided.

Imaging studies that attempt to assess the degree and direction of atherosclerotic remodeling are hampered by a methodological limitation that is difficult to overcome. How can one accurately and reproducibly assess a degree of atherosclerotic remodeling? Pathological studies (1) and the MRI study by Miao et al. (5) correlated plaque and vessel areas by pooling data from single-vessel segments. This approach requires correction for many factors that could influence local vessel size, such as sex, age, length, level of exercise training, anatomical localization, and so on. This cross-sectional approach may suggest a positive correlation between plaque, lumen, and vessel size but will not provide a remodeling measure for a specific individual. Another approach has been widely applied by researchers who systematically examined multiple histological sections or ultrasound images in arterial segments. Subsequently, a site that appeared least affected by the atherosclerotic disease was used as a reference that allowed the calculation of a remodeling index for a lesion of interest. However, this is also a cross-sectional method suffering from the limitation that the reference site is likely to have undergone geometrical remodeling as well. The remodeling response can also be assessed by executing serial imaging studies. Indeed, it has been shown that cross-sectional and serial assessments of arterial remodeling are discordant (11). This was found to be caused by concomitant remodeling of the reference sites. However, thus far only limited patient numbers have been studied to assess arterial remodeling in a longitudinal study.

The current concepts describing the natural history of atherosclerosis and subsequent arterial remodeling are mainly based on cross-sectional pathological observations and studies in genetically modified animals. Longitudinal studies on the progression of atherosclerotic disease in humans are still in their infancy and mainly address the

advanced stages of the disease (7). Imaging studies that depict the grade and direction of de novo atherosclerotic remodeling may help to understand the natural progression of the disease. However, longitudinal studies will need to reveal that the extent and direction of atherosclerotic remodeling has prognostic relevance or that it may serve as a surrogate for disease progression. Until then, geometrical remodeling will remain in the clinical experimental research arena.

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Key Words: imaging ■ atherosclerosis ■ remodeling ■ biomarker.

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