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No Relationship Between Compensatory Arterial Remodeling of Focal Stenotic Atherosclerotic Lesions and Tortuosity of the Arterial Segment Involved

To the Editor:

Arterial remodeling (change in vessel size) is an important yet poorly understood component of coronary atherosclerotic disease: it is a stronger predictor of stenosis than plaque burden and has also been linked to plaque rupture and acute coronary syndromes.¹ Extracellular matrix (ECM) protein turnover is necessary for flow-dependent physiological remodeling and postangioplasty remodeling, and recent studies have shown a correlation between de novo atherosclerotic remodeling patterns and local expression of matrix metalloproteinases (MMPs).² However, heightened local MMP activity and ECM turnover with atherosclerotic remodeling may have other effects on the vessel. Breakdown or deficiency of elastin not only is associated with radial vessel enlargement but also leads to axial vessel enlargement and tortuosity.³ It therefore seems intuitive that tortuosity and remodeling might be interrelated: if tortuosity develops before atherosclerotic plaque build-up, then the already weakened vessel wall may have a lower threshold for compensatory enlargement; conversely, compensatory enlargement may weaken the wall and promote tortuosity. To examine this hypothesis, we assessed whether tortuosity is associated with enhanced compensatory enlargement at the site of focal de novo atherosclerotic lesions.

We retrospectively examined our combined intravascular ultrasound (IVUS) databases to identify de novo coronary lesions (excluding ostial, bifurcation, and calcified lesions and those patients who had undergone previous coronary artery bypass grafting). From the angiographic plane in which the lesion-containing segment was maximally elongated, the tortuosity ratio (TR) was defined as the length of the segment in diastole along the midline of the lumen divided by the direct length between the ends of the vessel segment (measured by quantitative angiography with the guiding catheter as a reference, where the vessel segment is defined as that between significant [>1.0 -mm diameter] side branches). Offline IVUS measurements of vessel area (VA: area within the external elastic lamina) and plaque area (PA: VA minus lumen area) were used to calculate normalized vessel area (NVA: $VA_{\text{lesion}}/VA_{\text{reference}}$) and the remodeling compensation index (RCI: $[VA_{\text{lesion}} - VA_{\text{reference}}]/[PA_{\text{lesion}} - PA_{\text{reference}}]$), where the reference site is the site proximal to the lesion within the same segment with the least PA (mostly <10 mm proximal). Simple linear regression and multiple linear regression were used to try to ascertain any relationship between TR and either NVA or RI, with coronary risk factors (smoking, hypertension, hypercholesterolemia, family history, and diabetes), age, sex, and vessel segment as independent covariates in the multivariate model.

In 86 patients, there was no relationship between TR and NVA or RCI by either simple linear ($R=0.09$, $P=0.47$; $R=0.01$, $P=0.96$, respectively) or multiple linear ($P=0.18$, $P=0.68$, respectively) regression. When the analysis was confined to the proximal left anterior descending coronary artery ($n=44$), where there is minimal natural curvature of the vessel, there was also no relationship ($P=0.77$, 0.41 , 0.90 , and 0.99 , respectively).

Tortuosity is frequently associated with generalized vessel enlargement, which in turn is frequently seen in normal segments of otherwise diseased vessels where compensatory enlargement has also taken place.⁴ However, we found no relationship between tortuosity and focal compensatory enlargement, possibly for a number of reasons. The most likely reason is that generalized vessel enlargement, both axial (tortuosity) and radial, has completely different mechanisms from the localized compensatory enlargement that occurs as a response to atherosclerosis. Generalized enlargement is frequently seen as an active response to impaired flow-mediated dilatation⁵ or as an aging response.⁴ Localized enlargement may be more of a passive response to atheroinflammation-induced MMP induction.¹ Alternatively, localized compensatory enlargement may only be associated with very localized tortuosity. Because the latter is very difficult to measure, it would be almost impossible to confirm or refute this possibility. Last, it may be that compensatory enlargement has a limit, as first suggested by Glagov et al,⁶ and that generalized enlargement thus limits additional localized enlargement. However, tortuosity would then be inversely related to localized remodeling, not unrelated. Our findings, though negative, add to the limited observational data characterizing de novo atherosclerotic remodeling, which are important starting points when conducting interventional studies in the newly identified animal models of atherosclerotic remodeling, such as in genetically manipulated mice, and Watanabe rabbits.

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