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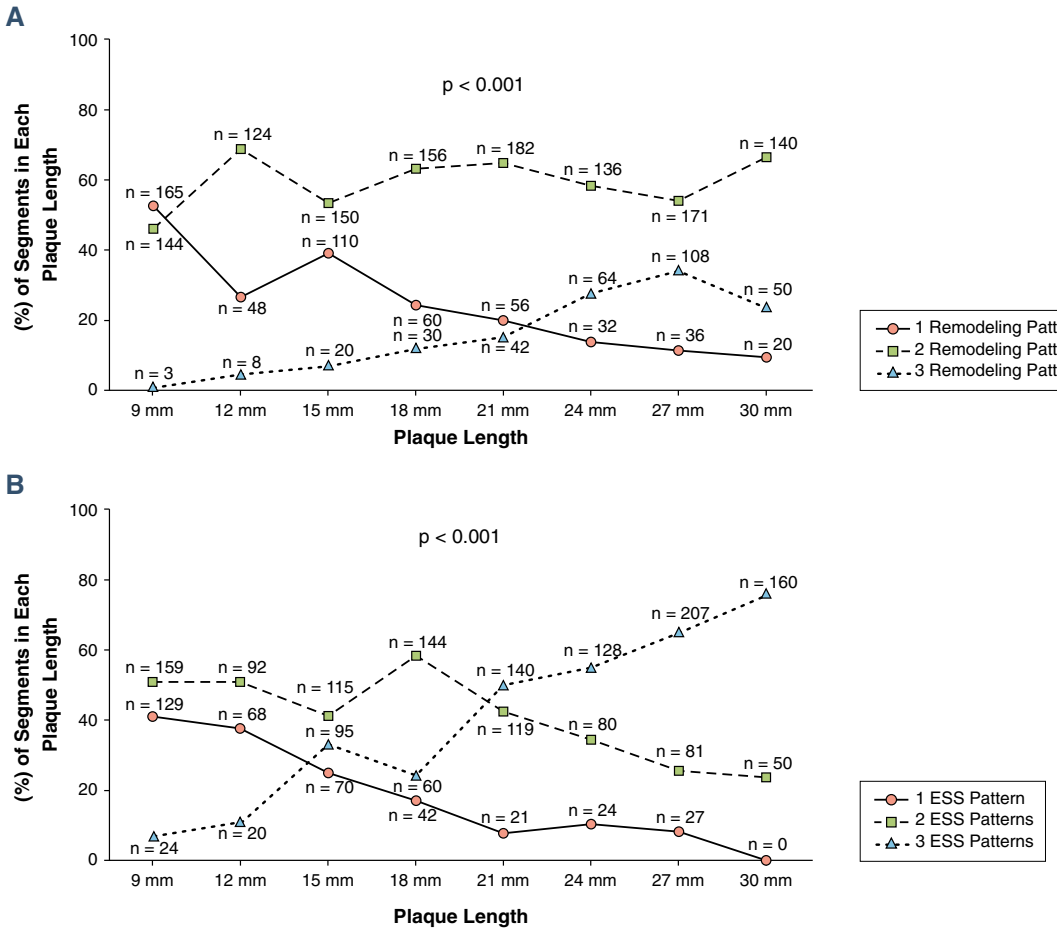
LETTERS TO THE EDITOR

Arterial Remodeling and Endothelial Shear Stress Exhibit Significant Longitudinal Heterogeneity Along the Length of Coronary Plaques

Atherosclerosis is determined by both systemic risk factors and local vascular mechanisms. The arterial remodeling in response to plaque development plays a key role in atherosclerosis. Compensatory expansive remodeling is an adaptive mechanism that maintains lumen patency as a plaque develops. In contrast, excessive expansive remodeling, signifying an enlargement in vascular and lumen volume as a result of local plaque buildup, is a consistent attribute of high-risk plaques. Local hemodynamic factors, in particular low endothelial shear stress (ESS), is an intensely proinflammatory and proatherogenic stimulus and largely accounts for the spatially diverse distribution of atherosclerotic plaques. However, plaque, remodeling and ESS have hitherto been investigated only in the cross-sectional arterial axis and their distribution in the longitudinal axis of individual plaques has not been characterized.

We performed a detailed and comprehensive description of the longitudinal spatial heterogeneity

FIGURE 1 Heterogeneity of Remodeling and Endothelial Shear Stress Patterns Per Plaque Length



(A) Heterogeneity of remodeling patterns per plaque length. **(B)** Heterogeneity of endothelial shear stress patterns per plaque length. ESS = endothelial shear stress.

of plaque, arterial remodeling and ESS in human coronary plaques. Patients enrolled in the PREDICTION (Prediction of Progression of Coronary Artery Disease and Clinical Outcome Using Vascular Profiling of Shear Stress and Wall Morphology) study (n = 219) underwent coronary angiography and intravascular ultrasound for 3-dimensional reconstruction and blood flow simulation in all major coronary arteries at the time of an acute coronary syndrome (1). A total of 371 plaques (maximum thickness ≥0.5 mm, mean length 16.62 ± 0.35 mm [range 9 to 30 mm]) were identified in 313 arteries and categorized in 3-mm subsegments. Plaque length was highly variable: the most frequently encountered plaque length was 9 mm (28.03%), but the majority of plaques were longer, ranging from 12 to 30 mm in various proportions.

Compensatory remodeling was the most frequent remodeling type (1,622 of 2,055 subsegments, 78.9%). Excessive expansive remodeling occurred in 205 subsegments (10.0%) and constrictive remodeling in 228 subsegments (11.1%). A single remodeling pattern was seen in 117 plaques (31.5%) whereas 211 (56.9%) manifested 2 distinct remodeling patterns in different locations and 43 (11.6%) demonstrated all 3 remodeling patterns along the plaque length ($p < 0.001$). The frequency of uniform remodeling progressively decreased as the plaques became longer, whereas a mixed remodeling profile with coexistence of all 3 remodeling patterns was more frequent as the plaque length increased (**Figure 1A**).

The distribution of ESS was also highly variable along each plaque. Only 90 plaques (24.3%) exhibited a uniform ESS profile, whereas 164 (44.2%) manifested 2 distinct ESS patterns in different locations within the plaque and 117 (31.5%) demonstrated low, moderate, and high ESS patterns simultaneously along the plaque length. The frequency of uniform ESS progressively decreased, and the presence of mixed ESS profiles was more frequent, as the lesions became longer (**Figure 1B**).

Our analysis underscores the longitudinal variation of plaque morphology, remodeling, and ESS, which are evident in the majority of plaques, especially longer plaques. Intravascular ultrasound studies commonly focus on the single site of minimum luminal dimension along a lesion (2). This strategy inevitably underestimates the longitudinal variability of plaque constituents, vascular morphologies and local flow conditions, which determine the natural history of each plaque. Longitudinal variability may account for the challenges encountered by clinical studies attempting to correlate plaque features with subsequent clinical events (3,4) because most plaques exhibit a greater degree of heterogeneity along their length and, therefore, at every single point in time, parts of the same plaque may exhibit different stages and trajectories of progression. This divergent evolution profile along a plaque does not allow an accurate risk stratification on the basis of the characteristics of a single specific location. The presence and potential implications of plaque morphology and remodeling heterogeneity have been previously noted (5), but that earlier study did not assess local ESS patterns along the length of each plaque. The present analysis, by incorporating hemodynamic and vascular assessments in a large population, may set the paradigm for a more accurate characterization of human atherosclerosis. The detailed assessment of arterial remodeling and ESS along the longitudinal aspect of lesions may enhance the early identification of plaques at highest risk for adverse outcomes.

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Noninvasive Prediction of Atherosclerotic Progression: The PROSPECT-MSCT Study

Intravascular imaging-based natural history studies of atherosclerosis have provided insight into atherosclerotic evolution and demonstrated that local hemodynamic factors, plaque burden, and the composition of the atheroma regulate plaque growth and determine vulnerable plaque formation (1,2). However, intravascular imaging is time consuming, is associated with a risk of complications, and does not allow complete assessment of plaque pathophysiology. Recent reports suggest that multislice computed tomography (MSCT) provides useful prognostic information and permits reliable quantification of luminal dimensions and plaque burden, characterization of the composition of the plaque, coronary reconstruction blood flow simulation, and estimation of the local endothelial shear stress (ESS) (3). However, the potential of MSCT in identifying lesions that are prone to progress is undetermined.

The present analysis processed data from the patients enrolled in the PROSPECT-MSCT (Providing Regional Observations to Study Predictors of Events in the Coronary Tree-MSCT) study in order to investigate the value of MSCT-derived variables in predicting plaque evolution (4). PROSPECT-MSCT recruited 32 patients with an acute coronary syndrome, who were enrolled in the PROSPECT study, and underwent MSCT imaging at baseline (after percutaneous coronary intervention of the culprit lesions responsible for the acute coronary syndrome),

TABLE 1 Univariate and Multivariate Analysis of the Variables Associated With Atherosclerotic Disease Progression

	Univariate Analysis			Multivariate Model	
	Associated Factor	**β (95% CI)**	**p Value**	**β (95% CI)**	**p Value**
Increase in lumen area (per 1 mm^2)	Presence of low endothelial shear stress at baseline	−1.06 −(−1.34 to −0.78)	<0.001	−0.47 (−0.78 to −0.16)	<0.001
	Baseline lumen area (per 1-mm^2 increase)	−0.28 (−0.33 to −0.23)	<0.001	−0.22 (−0.28 to −0.16)	<0.001
	Baseline outer vessel wall area (per 1-mm^2 increase)	−0.13 (−0.16 to −0.09)	<0.001	–	–
	Baseline plaque area (per 1-mm^2 increase)	0.08 (0.01 to 0.15)	0.029	–	–
	Baseline plaque burden (per 10% increase)	1.08 (0.88 to 1.28)	<0.001	–	–
	Presence of expanding remodeling at baseline	−1.04 (−1.38 to −0.70)	<0.001	−0.21 (−0.58 to 0.17)	0.277
Increase in plaque area (per 1 mm^2)	Baseline lumen area (per 1-mm^2 increase)	−0.04 (−0.9 to 0.01)	0.083	–	–
	Baseline outer vessel wall area (per 1-mm^2 increase)	−0.14 (−0.17 to −0.10)	<0.001	–	–
	Baseline plaque area (per 1mm^2 increase)	−0.42 (−0.48 to −0.37)	<0.001	−0.40 (−0.46 to 0.33)	<0.001
	Baseline plaque burden (per 10% increase)	−0.66 (−0.84 to 0.48)	<0.001	−0.23 (−0.41 to 0.05)	0.014
	Baseline % fibrofatty tissue (per 10% increase)	0.30 (0.05 to 0.55)	0.017	−0.07 (−0.29 to 0.16)	0.569
	Baseline % calcific tissue (per 10% increase)	−0.21 (−0.44 to 0.03)	0.081	–	–
Increase in plaque burden (per 10%)	Presence of low endothelial shear stress at baseline	0.28 (0.18 to 0.37)	<0.001	0.11 (0.02 to −0.21)	0.018
	Baseline lumen area (per 1-mm^2 increase)	0.05 (0.03 to 0.06)	<0.001	–	–
	Baseline plaque area (per 1-mm^2 increase)	−0.12 (−0.14 to 0.10)	<0.001	−0.10 (−0.12 to −0.07)	<0.001
	Baseline plaque burden (per 10% increase)	−0.46 (−0.53 to −0.40)	<0.001	−0.40 (−0.48 to −0.32)	<0.001
	Baseline % necrotic tissue (per 10% increase)	0.05 (0.01 to 0.09)	0.044	−0.03 (−0.08 to 0.01)	0.154
	Baseline % calcific tissue (per 10% increase)	−0.10 (−0.19 to −0.01)	0.035	0.22 (0.13 to 0.31)	<0.001
	Presence of expanding remodeling at baseline	0.20 (0.09 to 0.31)	<0.001	−0.04 (−0.15 to 0.07)	0.506
Increase in necrotic core (per 1 mm^2)	Presence of low wall shear stress at baseline	0.13 (−0.02 to 0.27)	0.097	0.01 (−0.14 to 0.17)	0.872
	Baseline plaque area (per 1-mm^2 increase)	−0.05 (−0.08 to −0.01)	0.017	−0.08 (−0.12 to −0.04)	<0.001
	Baseline plaque burden (per 10% increase)	−0.17 (−0.27 to −0.07)	0.001	−0.14 (0.25 to 0.03)	0.016
	Baseline % necrotic tissue (per 10% increase)	−0.25 (−0.31 to −0.18)	<0.001	–	–
	Baseline % fibrofatty tissue (per 10% increase)	0.16 (0.02 to 0.31)	0.028	0.17 (0.03 to 0.31)	0.016
	Baseline % fibrous tissue (per 10% increase)	0.22 (0.16 to 0.28)	<0.001	0.29 (0.23 to 0.36)	<0.001

CI = confidence interval.