Association of Remodeling With Endothelial Shear Stress, Plaque Elasticity, and Volume in Coronary Arteries: A Pilot Coronary Computed Tomography Angiography Study

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Abstract

We sought to noninvasively assess the relationship between arterial remodeling, endothelial shear stress (ESS), and wall stiffness in coronary arteries. We studied 28 coronary arteries from 22 patients undergoing coronary computed tomography angiography (CCTA). The ESS was calculated in 2-mm long segments using computational fluid dynamics. Local remodeling, plaque dimensions, and local wall stiffness were assessed in each segment. The ESS was lower in the regions of excessive expansive remodeling versus compensatory expansive versus inadequate expansive versus constrictive remodeling. Areas of decreased wall stiffness more frequently exhibited excessive expansive remodeling. Plaque volume was higher in segments showing excessive expansive and inadequate remodeling than segments with constrictive remodeling. In conclusion, CCTA enables the noninvasive assessment of coronary hemodynamics and arterial/plaque morphology. Excessive expansive remodeling is associated with high-risk plaque features, such as low ESS, decreased plaque stiffness, and increased plaque volume. This methodology may be useful in the risk assessment of individual coronary lesions.

Keywords

coronary computed tomography angiography, arterial remodeling, endothelial shear stress, coronary stiffness, plaque volume

Introduction

Despite the systematic effect of the established risk factors for atherosclerosis in the entire vasculature, plaque preferentially develops in certain parts of the coronaries that is bifurcations, branching points, and the inner aspect of curvatures. The effect of hemodynamics, endothelial shear stress (ESS) in particular, largely accounts for this asymmetrical presence of atherosclerosis in the coronary tree.[1] The ESS is the tangential component of the frictional force exerted in the endothelial layer by the flowing blood. Basic research, animal studies, and very lately the PREDICTION clinical study in human have demonstrated the causative relationship of low ESS with atherosclerosis and high-risk plaque formation.[2-4]

Atherosclerosis causes alterations in the structural scaffolding of the coronary arterial wall.[5] Degradation of elastin and collagen fibers by enzymes induced during the atherosclerotic process causes internal elastic lamina fragmentation, which in turn facilitates migration of vascular smooth muscle cells and macrophages from the media to the intima and ultimately lesion expansion. In developed plaques, collagen content augments the biomechanical strength of the fibrous cap and enhances its integrity. Thus, collagen degradation predisposes to instability, and the local decrease in arterial stiffness as a result of collagen and elastin breakdown is likely associated with high-risk plaques.[6] Also, such changes in the extracellular matrix in conjunction with local blood flow alterations determine vascular remodeling. Positive (expansive) remodeling denotes an increase in vascular volume in response to plaque growth, while negative (constrictive) signifies a decrease in vascular volume. Expansive remodeling is further subdivided

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into 3 categories: excessive expansive (lumen dilatation), compensatory expansive (lumen preservation), and inadequate (lumen encroachment).[7]

An accurate assessment of ESS is carried out with computational fluid dynamics, in anatomically correct, 3-dimensional (3D) reconstructions of the coronary arteries. Fusion of coronary angiography and intravascular ultrasound is the most common methodology for such reconstructions, but it is still associated with the risks of invasive procedures. Coronary computed tomography angiography (CCTA) has recently emerged as an noninvasive alternative for coronary imaging and enables an accurate 3D assessment of both coronary lumen and wall.[8,9] The evolution of computed tomography scanning equipment together with the advent of modern scanning protocols (eg. tube current modulation and prospective electrocardiographic triggering) have led to considerable reduction in the total radiation dose as well as in the volume of contrast media, thereby diminishing safety concerns.[10-12] The CCTA therefore has the potential to investigate the atherosclerosis severity, coronary hemodynamics, remodeling, and elasticity.

The objectives of this study were to noninvasively assess remodeling and to associate it with ESS, wall stiffness, and plaque volume.

Patients and Methods

Study Patients

We investigated 28 coronary arteries from 22 patients (19 men, mean age 62 ± 12 years) undergoing CCTA for the investigation of suspected coronary artery disease or with known coronary disease but unable to undergo invasive coronary angiography. Patients with renal failure, irregular heart rate, contraindications to receiving β-blockers, or history of allergic reaction to contrast media were excluded from the study. Patient characteristics are shown in Table 1.

All study participants gave written informed consent, and the institutional medical ethics committee approved the study.

CCTA Protocol

A 128-slice CCTA was performed with SOMATOM definition AS (Siemens, Munich, Germany). Prior to examination, the arterial pressure was measured using an arm sphygmomanometer. A bolus intravenous dose of iodine contrast was administered through a brachial vein. The examination took place in hold inspiration with simultaneous electrocardiographic monitoring. For best image quality, the patients with heart rates >75 beats/min received a β-blocker (propranolol 20-40 mg) orally 15 to 30 minutes prior to examination.[9] Nitrates were not used during the study.

3D Coronary Reconstruction

The major coronary arteries were reconstructed in both diastole and systole on the basis of the electrocardiogram with the use of MIMICS, Materialise Software (Leuven, Belgium). The coronary lumen was reconstructed in both phases while the wall only

Table 1. Patient Characteristics.

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Medical history, n	
Myocardial infarction	3 (13.64%)
Arterial disease	5 (22.73%)
Risk factors, n	
Smoking	10 (45.45%)
Diabetes mellitus	6 (27.27%)
Hypercholesterolemia (>240 mg/dL)	13 (59.09%)
Arterial hypertension	14 (63.64%)
Positive family history	2 (9.09%)
Exercise, n	13 (59.09%)
Drug treatment, n	17 (77.27%)
Statins	11 (50%)
ω3-Fatty acids	2 (9.09%)
β-Blockers	8 (36.36%)
Calcium channel blockers	4 (18.18%)
Angiotensin-converting enzyme inhibitors	5 (22.73%)
Diuretics	9 (40.91%)
Angiotensin receptor blockers	7 (31.82%)
Aspirin	8 (36.36%)
Clopidogrel	4 (18.18%)

in diastole, since the image quality was not optimal in systole as a result of the radiation dose-reduction protocol (Figure 1).

Segments of Interest

Each reconstructed artery was divided into 2-mm long segments using Rhinoceros, Robert McNeel & Associates, Seattle, Washington. The study segments were matched between diastole and systole with the use of fiducial anatomical landmarks as bifurcations, side branch take-off, and plaque location. These segments were then categorized as diseased or nondiseased according to the visual presence of atheroma.

Grid Generation and Computational Fluid Dynamics

In each of the coronary reconstructed models, a computational grid was generated with the use of Gambit, Fluent Inc Products, Lebanon. A finite element unstructured mesh with tetrahedral elements was employed for the lumen volume. Subsequently, the arterial models were imported in a computational solver (Fluent, Fluent Inc Products), where ESS was calculated in each of the nodes of the computational mesh, by solving the incompressible transport equations governing the conservation of mass and momentum (Figure 2).[13] We modeled blood as a non-Newtonian fluid with power-law index = 0.7, minimum viscosity limit = 0.0001 kg/m/s, maximum viscosity limit = 0.1 kg/m/s, and density 1058 kg/m^3. Steady laminar flow was assumed, and at the inlet, a velocity of 0.17 m/s was specified according to the literature.[14,15] At the flow outlet, zero pressure conditions were defined, and the no-slip condition was applied at the wall that was considered rigid. The ESS was computed as the product of blood viscosity and the gradient of blood velocity at the arterial wall. Mean ESS values were calculated for each of the arterial segments for both diastole and systole. Segments were classified in tertiles of low, medium, and high ESS. The local wall pressure was also assessed in each segment.
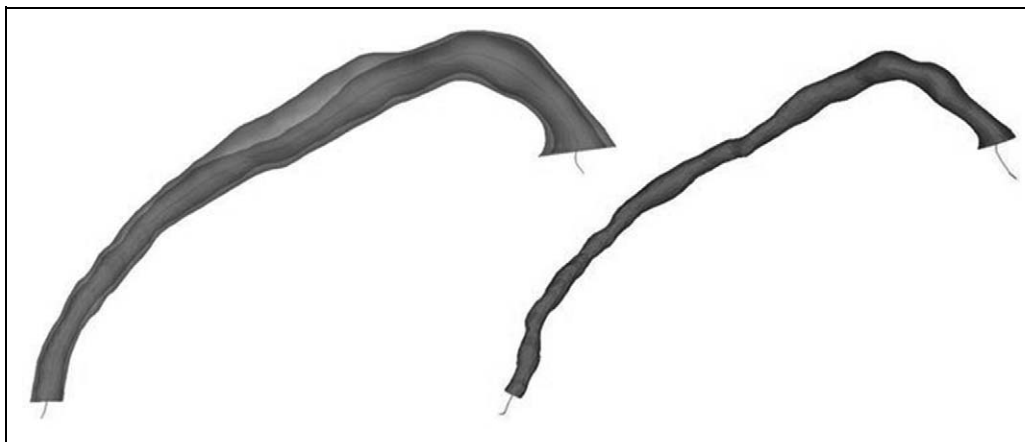
Figure 1. Three-dimensional coronary reconstruction. The coronary lumen (in both cardiac phases) and wall (in diastole) were 3-dimensionally reconstructed using coronary computed tomography angiography data. Diastole on the left and systole on the right.
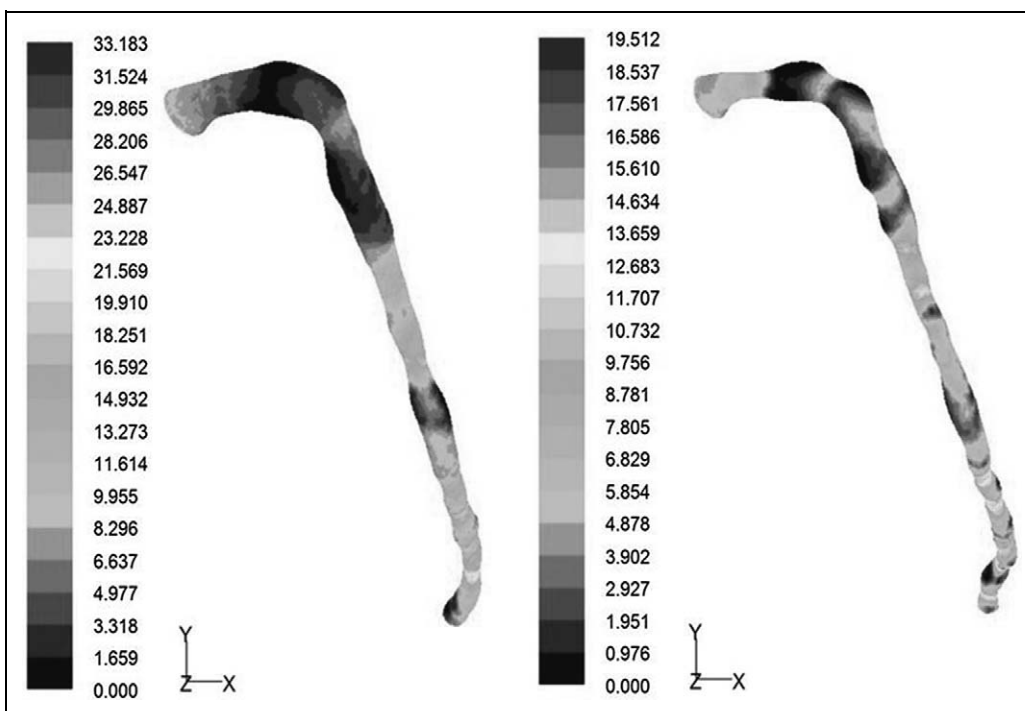
Figure 2. Computational fluid dynamics. Endothelial shear stress in a 3-dimensional reconstruction of the left main-left anterior descending artery in diastole (left) and in systole (right).

Assessment of Luminal Stenosis and Wall Enlargement

In each study segment, we calculated the proximal and distal luminal and plaque cross-sectional area as well as the luminal and plaque cross-sectional area in the middle of each segment. In each segment with plaque, we calculated the percentage of luminal stenosis using the following equation:

$$\% \, \text{Stenosis} = \frac{E_{\text{reference}} - E_{\text{segment}}}{E_{\text{reference}}} \times 100,$$

where $E_{\text{reference}}$ is the mean luminal area of the plaque-free proximal and distal segments and E_{segment} is the mean luminal

area of the segment. By convention, the negative values denote lumen enlargement in the respective segment when compared to the reference segments.

Using $E_{\text{reference}}$ as the mean vessel area of the plaque-free proximal and distal segments and E_{segment} as the mean vessel area of the segment, we calculated the enlargement or constriction of the vessel.

Assessment of Wall Stiffness

Wall stiffness was calculated in each segment with the following formula:
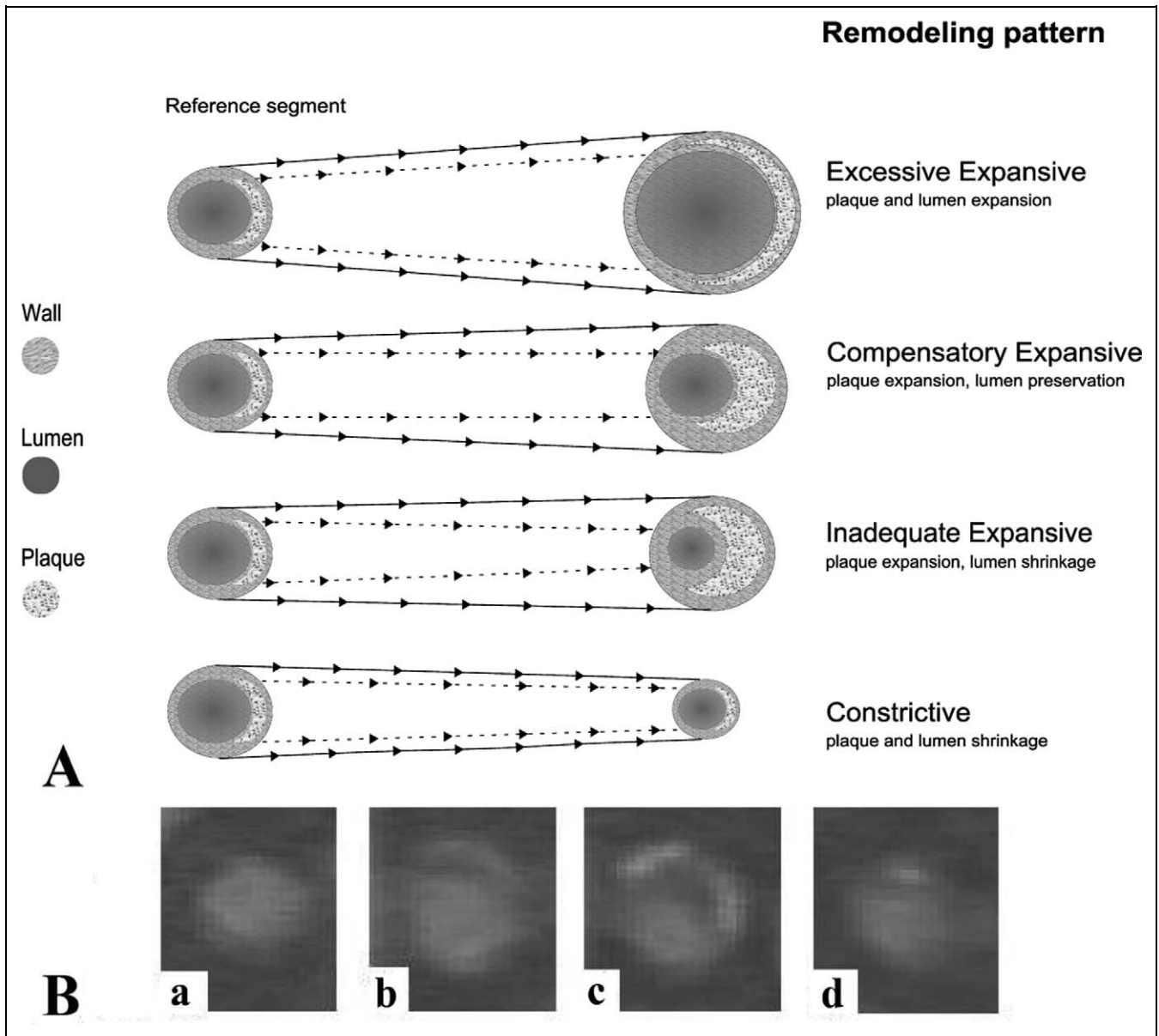
Figure 3. Arterial remodeling patterns. A, Arterial cross-sections depicting different patterns of remodeling. B. Cross-sections of a 33.3-mm long plaque in a left anterior descending artery: (a) normal segment before the plaque, (b) proximal atherosclerotic segment with excessive expansive remodeling, (c) mid atherosclerotic segment with inadequate expansive remodeling, and (d) distal atherosclerotic segment with constrictive remodeling.

$$\text{Wall stiffness} = \frac{\Delta P}{\Delta V / V}$$

where ΔP is the arterial pressure variation between diastole and systole, V is the initial luminal volume, and ΔV is the luminal volume change between diastole and systole.[16] Segments were classified in tertiles of low, medium, and high stiffness.

Assessment of Arterial Remodeling

Local remodeling was assessed on the basis of luminal and plaque dimension compared to reference segments as described

previously ("Assessment of luminal stenosis and wall enlargement" section). Segments with plaque expansion and luminal expansion were classified as featuring excessive expansive remodeling, segments with plaque expansion and lumen preservation as having compensatory expansive remodeling, segments with plaque expansion and lumen constriction as showing inadequate expansive remodeling, and segments with both plaque and lumen shrinkage as exhibiting constrictive remodeling (Figure 3).

Statistical Analyses

Categorical variables are summarized as absolute counts and percentages, while continuous variables as mean $\pm$ standard
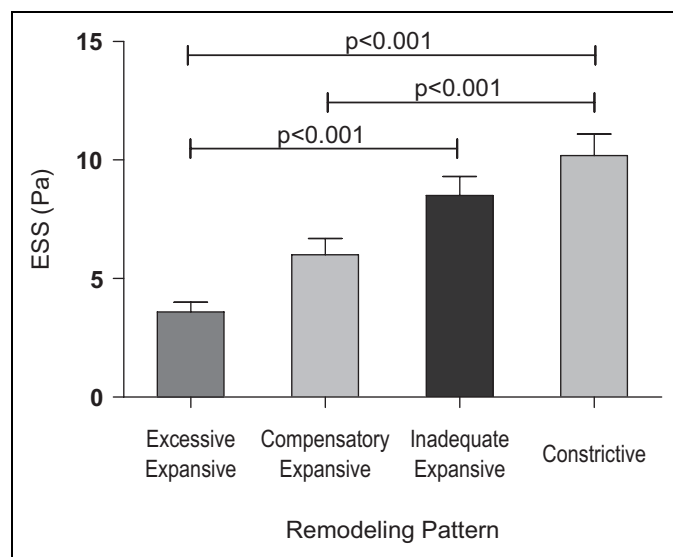
Figure 4. The endothelial shear stress (ESS) in different remodeling patterns. The ESS was lower in segments with excessive expansive remodeling (n = 86) compared to segments with compensatory expansive (n = 30), inadequate expansive (n = 85), and constrictive remodeling (n = 71). Also, ESS was lower in segments with compensatory expansive remodeling than in segments with constrictive remodeling.

error of the mean, standard deviation (SD), 95% confidence interval (CI) of the mean, median and interquartile range (IQR). The clustering of arterial 2-mm segments within patients introduces a systematic error, which was assessed with the following methods; to investigate the association of continuous variables with categorical variables, mixed-effects analysis of variance with the patient and artery designated as random effects was used. The statistical significance for multiple comparisons was adjusted with the use of the Scheffé method; to investigate the association of binary variables, logistic regression with a robust variance estimator (Huber-White Sandwich) was implemented. All statistical tests were 2-tailed, and statistical significance was defined as an α level of or below .05.

Results

We reconstructed n = 28 arteries (left main-left anterior descending n = 14, left circumflex n = 5, and right coronary artery n = 9) of total 3.63 m in length (1.87 m in diastole and 1.76 m in systole). The mean length of reconstruction was 65.1 $\pm$ 5.6, SD 29.5, 95% CI of the mean 53.7 to 76.6, median 56.0, and IQR 47. A total of 1824 segments were identified (912 in each cardiac phase), and 32% had visual atheromatous plaque and 68% were normal. A total of 87 discrete plaques were noted.

Remodeling and ESS

Specifically, regions with excessive expansive remodeling were more likely to have low ESS than regions with other remodeling patterns (odds ratio 4.8, 95% CI 1.9-12.1, and $P <$ .001). Furthermore, using ESS as a continuous variable

yielded similar results, because ESS values were lower in segments featuring excessive expansive remodeling (3.6 $\pm$ 0.4 Pa, SD 3.6, 95% CI of the mean 2.8-4.4, median 2.6, and IQR 2.4) compared to segments with compensatory expansive remodeling (6.0 $\pm$ 0.7 Pa, SD 3.9, 95% CI of the mean 4.5-7.5, median 5.4, IQR 4.8, and $P =$ .055), inadequate expansive remodeling (8.5 $\pm$ 0.8 Pa, SD 6.8, 95% CI of the mean 7.0-10.0, median 6.8, IQR 7.4, and $P <$ .001), and constrictive remodeling (10.2 $\pm$ 0.9 Pa, SD 7.2, 95% CI of the mean 8.4-12.0, median 7.6, IQR 10.3, and $P <$ .001). Also, ESS was lower in segments with compensatory expansive remodeling compared to those with constrictive remodeling ($P <$ .001; Figure 4). These results suggest that excessive expansive remodeling was associated with low ESS.

Remodeling and Stiffness

Segments with excessive expansive remodeling were more likely to present low regional stiffness (low vs mid/upper stiffness tertile, odds ratio 2.54, 95% CI 1.1-5.8, and $P <$ .05). These results suggest that excessive expansive remodeling was associated with low coronary stiffness. On the other hand, compensatory, inadequate, and constrictive remodeling was not associated with either low or high stiffness.

Remodeling and Atheroma Volume

Plaque volume was significantly higher in segments with excessive expansive remodeling (32.9 $\pm$ 2.7 mm^3, SD 25.2, 95% CI of the mean 27.5-38.2, median 28.3, and IQR 16.0) and inadequate remodeling (32.2 $\pm$ 2.8 mm^3, SD 25.7, 95% CI of the mean 26.7-37.8, median 24.5, and IQR 15.2) compared to those with constrictive remodeling (19.6 $\pm$ 0.75 mm^3, SD 6.4, 95% CI of the mean 18.1-21.1, median 19.8, IQR 7.1, and $P <$ .001). Also, segments with compensatory expansive remodeling (25.8 $\pm$ 1.9 mm^3, SD 10.4, 95% CI of the mean 22.0-29.7, median 28.3, and IQR 11.8) obtained higher plaque volume than constrictive remodeling ($P <$ .001).

Multivariate Analysis

In multivariate analysis, low ESS, low stiffness, and high plaque volume were independent determinants for the development of excessive expansive remodeling. Specifically, regions of low ESS showed an odds ratio of 3.6, 95% CI of 1.5 to 8.7, and $P <$ .01 versus the remaining regions for the development of excessive expansive remodeling, and regions of low stiffness had an odds ratio of 2.3, 95% CI 1.1 to 4.9, and $P <$ .05. Finally, increased plaque volume was associated with the presence of excessive expansive remodeling, odds ratio of 1.04 per mm^3 of volume increase, 95% CI of 1.02 to 1.07, and $P <$ .01.

Discussion

We conducted a pilot human study using CCTA. We found that regions with excessive expansive remodeling had increased elasticity, low ESS, and increased atheroma volume, all of which are high-risk features. On the other hand, we found that

regions with constrictive remodeling had low elasticity, high ESS, and low atheroma volume, features observed in stable plaques.

Remodeling and ESS

We demonstrated that plaques with excessive expansive remodeling manifest low-ESS values. On the contrary, high ESS is encountered in areas with luminal stenosis, which is either with inadequate expansive or with constrictive remodeling. According to Glagov's description, during plaque growth, the lumen is preserved up to the point that the plaque occupies 40% of the vascular cross-sectional area.[17] This is thought to be a compensatory mechanism aiming to preserve undisturbed blood flow through the coronaries and cardiac perfusion. Further plaque growth may trigger multiple response mechanisms, and lumen encroachment is the most usual scenario; however, in a smaller fraction of cases, further luminal enlargement takes place in the form of excessive expansive remodeling. Finally, in a proportion of cases, atherosclerosis causes vascular constriction encompassing both luminal and plaque shrinkage.[7,18] Areas with excessive expansive coronary remodeling, despite not showing luminal compromise, may indeed accommodate plaques with high risk of rupture. Low ESS in these areas may act as an ongoing pathobiologic stimulus triggering not only plaque growth but also vascular inflammation, extracellular matrix breakdown, and platelet activation, thus setting the stage for the destabilization of plaque.[19]

Remodeling and High-Risk Plaques

Plaques with increased elasticity are encountered more frequently in regions with excessive expansive remodeling and feature increased plaque volume and low ESS. These results suggest that atherosclerotic regions with excessive expansive remodeling encompass high-risk plaque characteristics. Increased plaque volume is related to the presence of a large lipid core with intense inflammation.[20] The in vivo effects of low ESS in plaque progression and risk profile have been assessed in animal studies; mouse carotid regions exposed to low-ESS accommodated vulnerable plaques.[21] Furthermore in swine models of atherosclerosis, the magnitude of low ESS showed a temporal association and dose-dependent relationship with plaque inflammation and development of thin-cap fibroatheromas.[3,22] Increased elasticity is likely pathophysiologically associated with high-risk plaques; metalloproteinases and elastases within the vascular wall during atherosclerosis ultimately lead to intense extracellular matrix degradation and increased elasticity.[23-25] Low ESS in expansively remodeled arteries is associated with reduced stiffness.[26,27] Furthermore, low ESS is associated with upregulation of metalloproteinases and cathepsins.[3,20] During the natural history of atherosclerosis, each lesion may switch to a different remodeling pattern over time numerous times. A recent animal intravascular ultrasound study demonstrated that regions exposed to low ESS culminated in high-risk expansive remodeling. In contrast,

coronary segments with compensatory remodeling showed higher baseline ESS values than those with expansive remodeling.[4]

In Vivo Noninvasive Assessment of ESS and Wall Stiffness

This study noninvasively assesses plaque dimensions and the local coronary hemodynamic milieu in a direct manner. Also, the above methodology enables the direct calculation of coronary wall stiffness in all parts of the coronary arteries instead of using indirect measures of vascular stiffness based on the peripheral circulation. Finally, the use of CCTA has the advantage of avoiding the anatomic deformations and flow disturbances introduced by the insertion of the intravascular ultrasound catheter within the coronary lumen. This methodology provides the conceptual framework for the preventive use of 3D coronary reconstruction with CCTA for the risk stratification of coronary lesions. Atheroma volume, ESS, and stiffness are known to be mutually related, and this study confirmed this interrelation. These factors however were shown to independently influence remodeling in multivariate analysis. In prospective analyses, this methodology could be used to quantify the effects of aggressive risk factor management in plaque constituents and morphology and in the long-term outcomes of patients with coronary disease.

Study Limitations

Blood pressure measurements were performed immediately prior to CCTA using an arm-band sphygmomanometer and not continuously during the examination, assuming that blood pressure remains constant for short term. The study calculations were performed in 2-mm long segments, thereby not investigating more subtle variations in the study parameters. The cross-sectional nature of our study does not permit the demonstration of causal relationships between the associated variables. Systole reconstruction may have been influenced by the reduced dose during CCTA performance. The diastolic reconstructed data were used to generate the results presented.

Conclusions

This study is unique in that it employs a noninvasive assessment of coronary remodeling, ESS, plaque stiffness, and plaque volume and their association with in vivo human settings. This adds a new perspective to current knowledge with regard to ESS and plaque growth. This hypothesis-generating study confirms the association of excessive expansive remodeling with low ESS, reduced stiffness, and high plaque volume that is high-risk plaque features. Further prospective, multiple-timepoint studies are the next logical step to demonstrate the etiological contribution of excessive expansive remodeling in the generation of rupture-prone plaques causing acute clinical events.

Declaration of Conflicting Interests

Funding

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