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Clinical Investigations

Prospective Comparison of Coronary Artery Remodeling between Acute Coronary Syndrome and Stable Angina in Single-Vessel Disease: Correlation between C-Reactive Protein and Extent of Arterial Remodeling

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Summary

Background: Retrospective intravascular ultrasound (IVUS) studies showed that positive remodeling of coronary artery was associated with unstable clinical presentation. However, no prospective IVUS study has been performed to demonstrate such relationship. The relationship between C-reactive protein (CRP) and coronary artery remodeling is unknown.

Hypothesis: Positive remodeling might be related with acute coronary syndrome in the prospective IVUS study. C-reactive protein levels might be associated with coronary artery remodeling.

Methods: Preintervention IVUS images were prospectively obtained in 93 patients with single-vessel disease (30 for acute coronary syndrome and 63 for stable angina). Serum sample for CRP measurement was collected 24 h prior to coronary intervention. The remodeling index was defined as a ratio of (lesion/average reference) external elastic membrane area. Positive remodeling was defined as a remodeling index > 1.05 and negative remodeling as a remodeling index < 0.95.

Results: The remodeling index was 0.99 ± 0.13 in acute coronary syndrome versus 0.95 ± 0.12 in stable angina ($p = 0.048$). Positive remodeling was associated with acute coronary syndrome (43 vs. 19%), whereas negative remodeling was more frequent in stable angina (49 vs. 33%) ($p = 0.047$). C-reactive protein levels were significantly higher in acute coronary syndrome than in stable angina (1.4 ± 2.0 vs. 0.5 ± 0.6 mg/dl, respectively, $p = 0.002$). However, there was no significant correlation between CRP levels and remodeling index ($r = 0.078$, $p = 0.475$).

Conclusions: Positive remodeling may be related with acute coronary syndrome in the prospective IVUS analysis. C-reactive protein levels may not predict the extent of arterial remodeling.

Key words: coronary artery disease, intravascular ultrasound

Introduction

Arterial remodeling of the coronary artery was originally described in a necropsy study by Glagov *et al.*[1] and later confirmed in vivo with intravascular ultrasound (IVUS).[2] Compensatory enlargement or positive remodeling of the coronary artery might delay the progression of lumen narrowing induced by expanding atheromatous plaque. Arterial remodeling, not plaque size, has been identified as a major determinant of lumen size.[3–6]

The rupture of atheromatous plaque exposes subintimal tissue to coronary blood flow and results initially in thrombus formation and finally in coronary artery occlusion.[7] The plaque rupture is associated with plaque vulnerability and inflammation. The results of several studies, taken together, suggest a prominent role of inflammation in acute coronary syndrome.[8, 9] The histologic analysis demonstrated the presence of inflammatory cell in atheromatous plaque obtained at autopsy in patients with acute coronary syndrome.[10, 11] Therefore, the biologic markers of inflammation, such as C-reactive protein (CRP), have been proposed as potential indicators of unstable coronary lesions. Several clinical studies have demonstrated that CRP is a potent predictor of mortality in acute coronary syndrome.[12, 13] Recently, it has been suggested that compensatory enlargement or positive remodeling may be associated with an increased risk of plaque rupture, the underlying cause of acute coronary syndrome and sudden cardiac

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death.[14] However, the relationship between the degree of inflammatory activity (i.e., CRP level) and the extent of coronary arterial remodeling has not been sufficiently evaluated.

Previous IVUS studies showed that positive remodeling of the coronary artery was associated with unstable clinical presentation. However, most of the previous IVUS studies evaluating the relationship between clinical presentation and coronary artery remodeling were retrospectively performed in the patients from their IVUS database,[15–17] and those studies included the patients with multivessel disease. Therefore, despite the fact that the culprit lesion was identified by coronary anatomy and localization of ST-T segment change on the electrocardiogram, it was sometimes difficult to identify the culprit lesion clearly. To clarify the relationship between clinical presentation and coronary artery remodeling, the IVUS analysis should be prospectively performed in patients with single-vessel disease and single-culprit lesion.

The objective of the current study was prospectively (1) to evaluate the relationship between clinical presentation and coronary artery remodeling, and (2) to evaluate the relationship between CRP levels and the extent of coronary artery remodeling in patients with single-vessel disease and single-culprit lesion.

Materials and Methods

Study Population

Preintervention IVUS images of 93 de novo lesions of native coronary artery (mean lesion length 12.2 ± 2.4 mm) were obtained in 93 patients with single-vessel disease and single-culprit lesion. All patients had objective evidence of myocardial ischemia and ≥ 50% angiographic diameter stenosis by visual estimate. The exclusion criteria were as follows: (1) ostial lesion, (2) bifurcation lesion, (3) multivessel disease, (4) chronic total occlusion, (5) diffuse lesion (lesion length ≥ 20 mm), (6) lesion at left main trunk or bypass graft, (7) restenotic lesion, (8) severely calcific lesions, (9) multiple lesions in a single native artery, and (10) history of old myocardial infarction (MI). The acute coronary syndrome included the patients with acute MI (Q-wave and non-Q-wave MI, elevated level of creatine kinase [CK]-MB isoenzyme and/or ST-segment elevation within 24 h of chest pain) and unstable angina with resting chest pain (Class IIIB or IIIC by Braunwald classification[18]) and ST-segment depression. Preintervention IVUS image was obtained within 7 days in acute MI and 3 days in unstable angina after onset of the event. Stable angina was defined as a clinically constant pattern of severity being treated in an outpatient clinic for > 2 months. Patients were studied after giving written informed consent as part of ongoing protocols approved by our Institutional Review Board.

Serum samples in the fasting state were collected 24 h before coronary intervention. C-reactive protein was analyzed by turbidimetric assay on a Cobas Integra (Roche Diagnostics, Indianapolis, Ind., USA). Normal value of CRP level using this method was ≤ 0.6 mg/dl.

Intravascular Ultrasound Imaging Protocol

The preintervention IVUS study was performed after intracoronary administration of 0.2 mg nitroglycerin. The ultrasound catheter was advanced approximately 10 mm beyond the target lesion, and an imaging run was performed from beyond the target lesion to the aorto-ostial junction. Studies were performed with a commercially available system (Boston Scientific Corporation/Cardiovascular Imaging System, Inc., Natick, Mass., USA) which used a 30 MHz single-element beveled transducer mounted on the end of a flexible shaft and rotated at 1,800 rpm within a 3.2 F short monorail imaging sheath. With this system, the transducer was withdrawn automatically at 0.5 mm/s to perform the imaging sequence. Ultrasound studies were recorded on 1/2" high-resolution s-VHS tape for off-line analysis.

Quantitative Intravascular Ultrasound Measurements

Validation of cross-sectional area (CSA) measurements of external elastic membrane (EEM), lumen, and plaque + media (P + M) by IVUS has been reported previously.[19, 20] The EEM CSA (that represents total arterial CSA) was measured by tracing the leading edge of the adventitia. The P + M CSA (that represents atherosclerotic plaque) was calculated as EEM CSA minus lumen CSA. The plaque burden was measured as 100 × (P + M CSA/EEM CSA). The target lesion and both proximal and distal reference segments were assessed quantitatively. The preintervention lesion site was the image slice with the smallest lumen CSA; among image slices with the same minimum lumen CSA, the one with the largest plaque burden (and, therefore, the largest P + M CSA) was measured. The proximal and distal reference segments were the most normal-looking segments within 5 mm proximal and distal to the lesion. At each image slice, EEM and lumen CSA were measured with a commercially available program for computerized planimetry.

The remodeling index was defined as (lesion/average reference segment) preintervention EEM CSA. The average reference EEM CSA was calculated as (proximal reference EEM CSA + distal reference EEM CSA)/2. Positive remodeling was defined as a remodeling index > 1.05, negative remodeling as a remodeling index < 0.95, and intermediate remodeling as remodeling index between 0.95 and 1.05.[15]

Statistical Analysis

Statistical analysis was performed with SPSS software program (Statistical Package for Social Sciences, SPSS, Inc., Chicago, Ill., USA). Categorical data are presented as frequencies. Continuous data are presented as mean ± 1 standard deviation (SD). Comparison was performed with chi-square or Fisher's exact test and unpaired *t*-test. The linear regression analysis was performed to evaluate the relationship between CRP levels and the extent of coronary artery remodeling. A p-value < 0.05 was considered statistically significant.

TABLE I Baseline characteristics in 93 patients

	Acute coronary syndrome	Stable angina	p Value
Number of patients	30	63	
Age (years)	56 ± 8	57 ± 9	0.607
Males (%)	22 (73)	45 (71)	0.956
Hypertension (%)	9 (30)	23 (37)	0.701
Diabetes mellitus (%)	2 (7)	6 (10)	0.491
Hypercholesterolemia (> 240 mg/dl) (%)	6 (20)	13 (21)	0.838
Cigarette smoking (%)	15 (50)	31 (49)	0.881
Coronary artery lesions			0.896
Left anterior descending (%)	21 (70)	47 (75)	
Left circumflex (%)	4 (13)	7 (11)	
Right coronary (%)	5 (17)	9 (14)	

TABLE II Intravascular ultrasound analysis in 93 patients

	Acute coronary syndrome	Stable angina	p Value
Number of lesions	30	63	
Proximal reference segment			
EEM CSA (mm^2)	14.9 ± 4.0	15.0 ± 4.6	0.986
Lumen CSA (mm^2)	8.8 ± 2.6	8.8 ± 2.9	0.980
P+M CSA (mm^2)	6.1 ± 1.8	6.1 ± 2.1	0.997
Plaque burden (%)	41 ± 6	41 ± 6	0.936
Culprit segment			
EEM CSA (mm^2)	14.6 ± 4.6	13.4 ± 4.6	0.254
Lumen CSA (mm^2)	1.8 ± 0.4	1.8 ± 0.4	0.707
P+M CSA (mm^2)	12.8 ± 4.5	11.6 ± 4.4	0.260
Plaque burden (%)	86 ± 6	85 ± 5	0.422
Remodeling index	0.99 ± 0.13	0.95 ± 0.12	0.048
Distal reference segment			
EEM CSA (mm^2)	14.1 ± 4.5	13.3 ± 4.3	0.462
Lumen CSA (mm^2)	8.2 ± 2.6	8.0 ± 2.8	0.698
P+M CSA (mm^2)	6.9 ± 2.1	5.4 ± 2.0	0.280
Plaque burden (%)	42 ± 6	40 ± 7	0.398

Abbreviations: CSA = cross-sectional area, EEM = external elastic membrane, P+M = plaque+ media.

Results

Baseline clinical and angiographic characteristics of 93 patients are presented in Table I. There were no significant differences in baseline characteristics between 30 patients with acute coronary syndrome and 63 patients with stable angina. The IVUS findings between the two groups are shown in Table II. The remodeling index was 0.99 ± 0.13 in acute coronary syndrome versus 0.95 ± 0.12 in stable angina (p = 0.048). Positive, intermediate, and negative remodeling were observed in 13 (43%), 7 (23%), and 10 lesions (33%), respectively, in patients with acute coronary syndrome and in 12 (19%), 20 (32%), and 31 lesions (49%), respectively, in patients with stable angina (p = 0.047). The CRP levels were significantly higher in acute coronary syndrome than in stable angina (1.4 ± 2.0 vs. 0.5 ± 0.6 mg/dl, respectively, p = 0.002). However, there was no significant difference of remodeling index between lesions with elevated (> 0.6 mg/dl) and normal CRP levels (0.96 ± 0.13 vs. 0.96 ± 0.12, respectively, p = 0.837). The CRP level was 0.8 ± 1.5 mg/dl in negative, 0.7 ± 1.3 mg/dl in intermediate, and 0.7 ± 0.8 mg/dl in positive remodeling (p = 0.830). There was no significant correlation between CRP levels and remodeling index (r = 0.078, p = 0.475).

Discussion

In a recent IVUS study of 131 patients by Schoenhagen *et al.*, positive remodeling was more frequent in unstable than in stable lesions (51.8 vs. 19.6%), whereas negative remodeling was more frequent in stable lesions (56.5 vs. 31.8%) (p = 0.001).[15] Nakamura *et al.*[16] and Smits *et al.*[17] reported the similar results that positive remodeling was more frequently observed in acute coronary syndrome than in stable angina. Those previous IVUS studies were retrospectively performed and included patients with multivessel disease. Therefore, the angiographic and electrocardiographic findings should have been used to determine the selection of culprit lesions. However, it would be difficult to determine the culprit lesions when there were no specific changes in the electrocardiogram and there was a similar degree of diameter stenosis or similar lesion morphology by angiography in patients with multivessel disease. Another limitation of the retrospective study was the heterogeneous nature of unstable angina: because of some uncertainty in the location of plaque rupture, observer bias may be difficult to avoid in those kinds of retrospective studies.[21] To overcome the limitations, the current study was prospectively performed in single-vessel disease and single-culprit lesion. Therefore, the possibility of mismatching between clinical presentation and culprit lesion should not exist in this study. The findings of the current prospective study confirmed those of the previous retrospective studies:[15–17] positive remodeling or compensatory enlargement might be associated with acute coronary syndrome.

Histopathologic study showed a linear increase in atheromatous lipid core and inflammatory infiltrates with increasing cross-sectional narrowing in patients who died with unstable angina.[22] This implies that positive remodeling may have more vulnerable properties and may be associated with inflammation. A postmortem study with femoral artery revealed that the lesions with positive remodeling had significantly more markers of plaque vulnerability (more matrix metalloproteinase-secreting macrophage and T-lymphocyte) than the lesions with negative remodeling.[14] Those findings constitute the concept of the remodeling paradox that positive remodeling prevents luminal narrowing on one hand, but may be associated with vulnerable plaques on the other hand.[14]

The acute-phase reactant CRP is a very sensitive, although nonspecific, marker of inflammation. Circulating levels of CRP may constitute an independent risk factor for cardiovascular disease.[23] These levels have been considered to reflect

the severity and progression of atherosclerotic process in the vessel.[24] The macrophages tend to be more prevalent in the plaques of segments with positive remodeling than in those with negative remodeling.[25] Immunohistologic staining for matrix metalloproteinase-2 and matrix metalloproteinase-9 were more prevalent in the plaques of segments with positive remodeling than in those with negative remodeling.[25] These findings mean that inflammation and matrix metalloproteinase may play a role in both inward plaque vulnerability and outward positive remodeling.[25] Therefore, the role of CRP as a marker predicting the extent of arterial remodeling was evaluated in this study; however, CRP levels might not predict the extent of coronary artery remodeling. The different levels of inflammatory process (tissue vs. system level) might in part explain the negative results between CRP levels and the extent of coronary artery remodeling. The CRP levels as a system level indicator of inflammation might not predict the inflammatory process of the tissue level (i.e., the extent of macrophage or T-lymphocyte infiltration in the atheromatous plaque).

Limitations

This study has several limitations. First, the number of patients was relatively small to suggest clinical implications. Second, the lesions with severe calcifications were excluded in this study because the calcium interferes with the exact evaluation of EEM. Therefore, the findings of this study could not be applied to severe calcific lesions.

Conclusions

The prospective IVUS analysis of single-vessel disease confirmed that positive remodeling might be associated with acute coronary syndrome. C-reactive protein levels might not predict the extent of coronary artery remodeling.

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