〔千葉医学 77：321～327, 2001〕

〔Original Paper〕

Correlation of the patterns of coronary artery remodeling with coronary flow velocity

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(Received January 11, 2001, Accepted January 26, 2001)

SUMMARY

The objective of this study was to determine whether the patterns of coronary artery remodeling are related to coronary flow velocity. The coronary flow velocity was measured with a Doppler guidewire, and intravascular ultrasound (IVUS) was performed in 26 patients with angina pectoris. We classified the lesions into the following three remodeling groups by external elastic membrane-cross-sectional area (EEM-CSA) : compensatory enlargement, coronary shrinkage, and no remodeling. There were differences in average peak velocity (APV), coronary flow reserve (CFR), diastolic / systolic velocity ratio (DSVR) and time velocity integral in diastole (TVI) between these groups and the ranking from highest to lowest was compensatory enlargement, no remodeling, coronary shrinkage (49.8±14.1 vs. 43.5±17.0 vs. 31.0±8.4cm/s, P=0.06 ; 2.32±0.88 vs. 1.82±0.47 vs. 1.80±0.60, P=0.25 ; 2.92±2.5 vs. 1.90±0.99 vs. 1.49±0.66, P=0.18 ; 37.0±16.3 vs. 24.1±10.4 vs. 18.8±7.4cm, P=0.02). Coronary remodeling patterns seemed to be related to CFR, APV, DSVR and TVI. Coronary flow velocity seemed to be one of factors involved in coronary remodeling mechanism.

Key words : Doppler guidewire, intravascular ultrasound, compensatory enlargement, coronary shrinkage

I . Introduction

Coronary angiography has been used as a gold standard for evaluating the morphology of the coronary disease. However, the pathologic studies indicated that angiography underestimates the extent and severity of coronary atherosclerosis[1]. Intravascular ultrasound (IVUS) allows detailed, high quality cross-sectional imaging of the coronary artery in vivo[2-4]. Recent IVUS studies have demonstrated that coronary arteries

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長橋達郎, 高田博之, 吉崎 彰, 櫻井和弘, 鈴木建則, 増田善昭[1)] : 冠動脈のリモデリングパターンと冠血流因子との関係についての検討.
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2001年1月11日受付, 2001年1月26日受理.

undergo bidirectional serial changes ranging from compensatory enlargement to coronary shrinkage[5-8]. According to Glagov et al., early compensatory enlargement of diseased coronary arteries delays luminal compromise until atherosclerotic plaque occupies 40% of the internal elastic lamina[9].

Before the interventional procedures, we perform IVUS study and make a decision of that strategy. Each of the coronary remodeling patterns (compensatory enlargement, no remodeling or coronary shrinkage) has been seen at the site of atherosclerotic target lesions with IVUS.

The previous studies demonstrated that risk factors for coronary artery disease (hypertension, hypercholesterolemia, diabetes mellitus and smoking) were associated with coronary artery remodeling[10-14]. On the other side, it has been demonstrated that the coronary risk factors are associated with functional abnormalities in coronary flow reserve (CFR)[14-16]. And then in a recent study the association between coronary remodeling and endothelial-dependent CFR was reported[17]. However, coronary artery remodeling in association with each of coronary flow velocity parameters including CFR has not been explored.

The objective of this study was to investigate coronary remodeling observed with the progress of coronary atherosclerosis, by using IVUS and Doppler guidewire, focusing on the relationship between coronary remodeling patterns and coronary flow velocity patterns.

Ⅱ. Materials and Methods

Patient selection

During the period between March, 1998 and April, 2000, a total of 210 patients underwent elective coronary angioplasty at our hospital. Twenty-six patients of them suffering from stable angina with "de novo" lesions were selected as the subjects of the present study. These patients neither had history of myocardial infarction, hypertensive heart disease nor hypertrophic cardiomyopathy. And, the following lesions were excluded: vessels responsible for infarct, the lesions formed in the branched parts, calcified lesions with an angle of more than 90 degrees, complete obstructive lesions and tandem lesions. Before the intervention, coronary flow factors were measured by using IVUS and a Doppler guidewire.

IVUS measurement

Before the intervention, IVUS was conducted by using 30-MHz mechanical transducer (UltraCross® 2.9 Fr, Boston Scientific). The tip of IVUS catheter was placed at the site at least 10㎜ distal to the lesion and the observation was conducted at a speed of 0.5 ㎜ / sec. by using the automatic pullback system. The images obtained in the observation were recorded on a 0.5 inch high-resolution super VHS videotape and the measurement was conducted under the off-line condition (TapeMeasure®, Indec).

The portion of coronary artery which had the minimum lumen cross-sectional area (CSA) was regarded as the target lesion. Either of the portions less than 10㎜ apart from the lesion on both sides was used as a reference. The reference was to satisfy the following two conditions: 1) severity of stenosis per unit of vascular area $<50\%$, 2) portion without the intervention of side branches. The proximal and distal reference portions were respectively measured. The lumen-CSA, external elastic membrane (EEM)-CSA and plaque+media-CSA were measured in the three portions respectively. Plaque thickness was defined as the distance between EEM and lumen. The severity

of stenosis per unit area (%) was obtained by dividing plaque+media-CSA by EEM-CSA.

Definition of coronary remodeling

The lesions whose EEM-CSA were larger than 105% × proximal reference were classified as compensatory enlargement. Those whose EEM-CSA were smaller than 95%×distal reference were classified as coronary shrinkage. Those whose EEM-CSA were similar to the area of proximal or distal reference within the range of 5% were classified as no remodeling.

Coronary flow velocity measurement

Coronary flow velocity was obtained by using a 0.014 in. Doppler angioplasty guidewire (FloWire®, Cardiometrics). The intracoronary administration of 2.5㎎ isosorbide dinitrate was conducted so that the coronary artery might be sufficiently dilated. The coronary flow velocity data (average peak velocity (APV), diastolic peak velocity integral (TVI), diastolic / systolic velocity ratio (DSVR), coronary flow reserve (CFR)), ECG and the coronary entrance pressure waveform were simultaneously displayed on the video monitor (FloMap®, Cardiometrics) and continuously recorded on a 0.5 in. super VHS videotape. Coronary flow reserve was obtained as the ratio of the maximum hyperemic average peak velocity to the baseline average peak velocity. On the distal site 2㎝ apart from the lesion, once a stable baseline Doppler signal was obtained, hyperemia was induced by administering adenosine triphosphate (ATP) to the right coronary artery in a dose of 30 μg and to the left coronary artery in a dose of 50 μg[18].

Angiography measurement

The pretreatment cinefilms were reviewed in the angiographic laboratory under the condition that the results of IVUS were not notified. Automated edge detection algorithm was used for quantitative angiographic analysis (CARDIO500®, KONTRON ELEKTRONIK, GmbH, Munich, Germany).

Statistical analysis

StatView version 5.0 was used for the statistic analysis of the results obtained. The data were expressed as mean±standard deviation. The categorical variables were evaluated by using chi-square test or factorial analysis of variance (ANOVA). A p value of less than 0.05 was considered significant.

Ⅲ. Results

Patient characteristics

Patient characteristics were given in Table 1. A total of 26 patients including three females was studied. No remodeling included three patients who received treatment for diabetes mellitus. Compensatory enlargement and coronary shrinkage included no diabetic patients.

Table 1. Patient characteristics

	Compensatory Enlargement (n=5)	No Remodeling (n=13)	Coronary Shrinkage (n=8)
Age (yr)	56±10	61±12	65±9
Height (㎝)	166±10	163±61	161±5
Weight (㎏)	64±13	56± 7	56±7
Men	5	12	6
Diabetes mellitus	0	3	0
Hypertension	1	4	2
Hypercholesterolemia	3	4	2
Smoking	3	3	3

Lesion characteristics

Lesion characteristics were given in Table 2. According to ACC / AHA classification, the lesions of coronary shrinkage detected in the present study were classified as type B. No lesions were classified as type A or type C.

Table 2. Lesion characteristics including angiographic and IVUS findings

	Compensatory Enlargement (n=5)	No Remodeling (n=13)	Coronary Shrinkage (n=8)
Location			
LAD	4	8	3
LCx	0	2	2
RCA	1	3	3
ACC / AHA Classification			
A	0	1	0
B1	2	6	3
B2	1	5	5
C	1	1	0
Lesion Length (mm)	7.7±6.1	8.7±3.4	7.5±2.9
EEM-CSA (mm²)	16.2±5.2	12.8±3.0	11.1±4.0*
Lumen-CSA (mm²)	1.8±0.27	1.9±0.9	1.4±0.33§
P+M-CSA (mm²)	14.4±4.9	10.9±2.8	9.7±3.9¶
Plaque burden (%)	88.2±2.2	85.0±5.6	86.4±4.5
reference EEM-CSA (mm²)	14.3±3.3	13.0±3.1	13.9±4.0

*P=0.07, §P=0.26, ¶P=0.08
Plaque burden=P+M-CSA/EEM-CSA×100,
EEM=external elastic membrane, P+M=plaque+media, CSA=cross sectional area, reference EEM-CSA=(proximal EEM-CSA+distal EEM-CSA)/2

QCA was used to make a comparison of the length of lesion and no significant differences were recognized among compensatory enlargement, no remodeling and coronary shrinkage (7.7±6.1 vs. 8.7±3.4 vs. 7.5±2.9 mm, P=NS). According to QCU based on the results of IVUS, the affected vascular area and plaque area were calculated in each group. These areas decreased in the order of compensatory enlargement, no remodeling and coronary shrinkage respectively (16.2±5.2 vs. 12.8±3.0 vs. 11.1±4.0 mm², P=0.07; 14.4±4.9 vs. 10.9±2.8 vs. 9.7±3.9 mm², P=0.08). The severity of stenosis per unit of area was expressed by the ratio of plaque area to vascular cross sectional area. The percentages calculated in compensatory enlargement, no remodeling and coronary shrinkage were 88.3±2.2%, 85.0±5.6% and 86.4±4.5% respectively (P=0.26). No statistically significant differences were recognized among three groups.

Relationship with coronary flow factors

The relationship with coronary flow factors at maximum hyperemic phase was given in Table 3. There were significant differences in TVI among compensatory enlargement, no remodeling and coronary shrinkage (37.0±16.3 vs. 24.1±10.4 vs. 18.8±7.4 cm, P=0.02). Regarding APV, CFR and DSVR, there were decreasing tendencies in the order of compensatory enlargement, no remodeling and coronary shrinkage respectively (49.8±14.1 vs. 43.5±17.0 vs. 31.0±8.4 cm/s, P=0.06; 2.32±0.88 vs. 1.82±0.47 vs. 1.80±0.60, P=0.25; 2.92±2.5 vs. 1.90±0.99 vs. 1.49±0.66, P=0.18).

Table 3. Coronary flow velocity parameters with hyperemia

	Compensatory Enlargement (n=5)	No Remodeling (n=13)	Coronary Shrinkage (n=8)
APV (cm/s)	49.8±14.1	43.5±17.0	31.0±8.4*
CFR	2.32±0.88	1.82±0.47	1.80±0.60#
DSVR	2.92±2.5	1.90±0.99	1.49±0.66*
TVI (cm)	37.0±16.3	24.1±10.4	18.8±7.4†
TPV (ms)	164.6±27.8	149.8±85.4	140.3±41.5
VHT (ms)	319.2±75.9	308.3±150.3	321.0±119.0
DDR (cm/s²)	76.2±23.3	81.4±55.3	50.6±23.8

*P=0.06, #P=0.25, *P=0.18, †P=0.02
APV=average peak velocity, CFR=coronary flow reserve, DSVR=diastoric / systoric velocity ratio, TVI=time-velocity integral in diastole, TPV=time of peak velocity, VHT=diastoric deceleration half time, DDR=diastoric deceleration rate

IV. Discussion

The present study revealed the relationship between the remodeling pattern and the coronary flow pattern.

Several reports mention the relationship between coronary flow and remodeling. These reports, which were based on the concept that remodeling was a homeostatic response to changes in flow, regarded shear stress and endothelial response as the main factors involved in remodeling mechanism[19].

Krams et al. reported that the inner curves of tortuous segments showed low shear but high wall thickness. They discovered the inverse relationship between wall thickness

and shear stress[20]. Furthermore, Ward et al., referring to a prior in vitro model study, demonstrated that on upstream side of lesions where increases in endotherial shear stress occur, remodeling compensates more for atherosclerotic plaque than it does on the downstream side, and translesional deterioration in remodeling is strongly correlated with estimated shear differences[21]. In addition, Schwarzacher et al. reported that vessel remodeling in transplant vasculopathy was significant greater and hyperemic flow was higher in eccentric lesions than in concentric lesions[22].

In the present study, three coronary remodeling patterns were used to carry out a comparative study. The target lesions had nearly the same reference size, plaque burden and length. Regarding APV, which indicates coronary perfusion velocity, and TVI and DSVR, which indicate the diastolic perfusion volume, a decreasing tendency in both these indexes was seen in the following order : the compensatory enlargement group, the no remodeling group and the coronary shrinkage group. A recent study has revealed that local shear stress should be the accessory parameter used to assess, whether flow-dependent remodeling was adequate[23]. Hayashi et al. illustrated that mean wall shear stress could be estimated using a modification of Hagen-Poiseuille equation : $\tau = 4\eta Q/\pi r^3 = 4\eta APV/r$ (τ : shear stress, η : blood viscosity, r : coronary radius of the lumen)[24]. In the present study, there were no significant differences in lumen-CSA at the target lesion. Thus, on the assumption that blood viscosity was approximately the same, this finding demonstrated a relationship between high flow/high shear stress and compensatory enlargement.

According to Lerman et al., endothelial dysfunction occurs earlier than the progress of stenotic lesion in the course of coronary arteriosclerosis, which results in coronary remodeling. They reported the association between vascular remodeling and endothelial-dependent coronary blood flow reserve[17]. In the present study, the coronary flow reserve obtained by the ATP reaction was not different significantly among three groups. Thereby, it is necessary that the coronary flow reserve is investigated in a larger number of patients in an attempt to reveal the relation between the coronary remodeling and the endothelial-dependent coronary flow reserve.

According to recent reports, coronary arteries tend to show the remodeling pattern of compensatory enlargement due to nitric oxide and gelatinase matrix metalloprotease (MMPs) produced as a result of endothelial response to shear stress or endothelial dysfunction[25,26]. In the present study, the remodeling pattern was related to the coronary flow velocity pattern regardless of the severity of stenosis. This relationship appeared to be mediated by the endothelium-derived vasorelaxing factor involved in the coronary flow.

Study limitations

This study has several limitations.

Firstly, it was a single-center study with a relatively small number of patients in an attempt to overcome specific difficulties in the evaluation of the relation between coronary flow velocity patterns and coronary remodeling patterns.

Secondly, the technical limitations of Doppler flow velocimetric measurements have been described[27].

Thirdly, direct correlation of focal shear stress with remodeling is difficult, because the shear stress at the focal endotherial surface is difficult to measure in vivo. The

degree of shear stress was thus hypothesized based on coronary flow velocity patterns obtained using a Doppler guidewire located on the distal site of the target lesion[24].

Finally, although diabetes mellitus is said to affect both coronary remodeling and coronary flow velocity, only the no remodeling group included patients with diabetes mellitus[13,28].

Conclusion

Coronary flow velocity appeared to be one of several factors involved in coronary remodeling mechanism.

V. Acknowledgment

We acknowledge the technical staff of our cardiac catheterization laboratory, Asami Kobayashi, Megumi Nagashima, Chieko Higashi and Ken Harigae for their skilled assistance.

要　旨

【目的】冠動脈のリモデリングパターンと冠動脈の機能的因子である冠血流反応性との関係を検討すること。

【方法】冠狭心症26例を対象とし，Doppler guidewire にて冠血流波形を記録し，ATP を用いて冠予備能を測定した。その後 IVUS にて病変および対照部の全血管面積，内腔面積，プラーク面積を計測した。内腔面積の最小部を病変部（L）とし，その遠位部（D）および近位部（P）10㎜以内で最も正常に近い部位を対照部として，全血管面積が，L＞105％×P を compensatory enlargement（E 群），L＜95％×D を coronary shrinkage（S 群），±5％以内で L＝P／L＝D を no remodeling（N 群）とした。群間で IVUS 上の狭窄度に差を認めなかった。

【結果】冠平均冠血流速度（APV），冠予備能（CFR），拡張期収縮期血流速比（DSVR），時間流速積分値（TVI）は各々，E 群，N 群，S 群の順で低くなる傾向にあった。

【結論】冠リモデリングパターンは冠血流因子のうち CFR，APV，DSVR，TVI と関係していた。冠血流反応性は，冠動脈リモデリング現象のメカニズムに関与している因子のひとつと考えられた。

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