Original articles

Normal distribution of an intravascular ultrasound index of vessel remodeling

Francesco Prati, Filippo Crea*, Antonella Labellarte**, Luigi Sommariva, Paola Marino, Eugenio Caradonna, Alessandro Manzoli, Alessandro Pappalardo, Alessandro Boccanelli

*Catheterization Laboratory, San Giovanni Hospital, *Institute of Cardiology, Catholic University, **European Imaging Laboratory, European Hospital, Rome, Italy*

Key words:
Atherosclerosis; Intravascular ultrasound; Remodeling.

Background. **As a consequence of plaque accumulation, coronary arteries may undergo both compensatory enlargement and paradoxical constriction. The aim of this study was to address the distribution of the different remodeling patterns in patients with obstructive coronary atherosclerosis.**

Methods. **Eighty-seven non-branching segments of native coronary arteries with *de novo*, focal, non-ostial lesions were imaged at intravascular ultrasound (IVUS). Images were acquired with a motorized pull-back at a speed of 0.5 mm/s. The cross-sectional area (CSA) circumscribed by the external elastic membrane (EEM), the plaque + media complex and the lumen area were measured at its narrowest site (CSA with the minimal lumen area) and in the reference segment (average of proximal and distal reference cross-sections, defined as the most normal looking sites). The IVUS index of vessel remodeling (VRI) was calculated using the following formula: (narrowest site EEM CSA - reference EEM CSA)/reference EEM CSA*100. The index was tested for normality using the Kolmogorov-Smirnov goodness-of-fit test.**

Results. **The frequency distribution of VRI was found to have a normal unimodal distribution (p = 0.60). VRI ranged from -60 to +164, with a mean of 9.3 ± 28.0 and a median of 3.6. Frequency distribution of VRI slightly skewed towards right (skewness index 1.69). None of the analyzed clinical and morphological variables predicted the presence of compensatory enlargement as opposed to paradoxical constriction.**

Conclusions. **The frequency distribution of the vascular remodeling of *de novo* coronary lesions is unimodal. Therefore, compensatory enlargement and paradoxical constriction represent the extremes of a continuous spectrum.**

(Ital Heart J 2002; 3 (12): 710-714)

Received September 23, 2002; accepted October 10, 2002.

Address:
Dr. Francesco Prati
Via N. Piccolomini, 34
00165 Roma
E-mail: f.prati@libero.it

Introduction

As a consequence of atherosclerotic plaque growth the arterial wall frequently undergoes a process of compensatory enlargement which can prevent a reduction in lumen dimensions[1-4]. On the other hand, the arterial wall may react to an atherosclerotic plaque with the opposite mechanism of paradoxical constriction which contributes to lumen narrowing[5-8].

The clinical and morphological predictors of compensatory enlargement as opposed to paradoxical constriction are still poorly known. In an attempt to shed some light on the mechanisms of coronary artery remodeling, we imaged *de novo*, focal, non-ostial coronary artery stenoses by means of intravascular ultrasound (IVUS) at the end of routine coronary angiography in a consecutive series of patients with obstructive coronary artery disease.

Methods

Study population. Eighty-seven consecutive patients (78 males, 9 females, mean age 59 ± 9 years) with obstructive coronary stenoses (> 50% reduction in the internal lumen diameter) but without a recent myocardial infarction (< 2 weeks) were enrolled. Eighty-seven *de novo*, focal, non-ostial lesions in non-branching segments were analyzed. IVUS was used to measure the target lesions and hence to guide catheter-based interventions in 31 patients (36%) and to better define the lesion severity in another 31 (36%). In the remaining 25 observations (28%) IVUS was obtained prior to randomization of patients enrolled in a placebo-controlled trial on the effect of pravastatin on plaque modification. The protocol was accepted by the institutional review board and written informed consent was obtained prior to the procedure.

Intravascular ultrasound image acquisition and analysis. *Image acquisition.* IVUS images were obtained using 30 MHz mechanical ultrasound imaging catheters (Cardiovascular Imaging Systems, Inc., Sunnyvale, CA, USA). At the end of routine coronary angiography, patients were administered 7000 IU of heparin delivered in the arterial sheath and 200 μg of intracoronary nitroglycerin to prevent possible vasospasm. The imaging probe was positioned distal to the target lesions and withdrawn at a constant speed of 0.5 mm/s, using a motorized pullback device. Ultrasound studies were recorded on high-resolution S-VHS tapes for off-line analysis. Images were evaluated off-line by a core IVUS laboratory.

Definitions of the quantitative ultrasonographic parameters. The area circumscribed by the external elastic membrane (EEM), the plaque + media complex and the lumen area were measured at the narrowest lesion site [cross-sectional area (CSA) with the minimal lumen area] and at the reference segment. The reference segment was defined as the average of the most normal looking cross-sections in a non-branching segment proximal and distal to the target lesion. The vessel remodeling index (VRI) was calculated according to the following formula: (narrowest site EEM CSA - reference EEM CSA)/reference EEM CSA*100. Compensatory enlargement was defined as vessel remodeling with a VRI > 0; paradoxical constriction was defined as vessel remodeling with a VRI < 0.

Plaque eccentricity was calculated as the ratio of the maximum to the minimum plaque thickness > 3[9].

IVUS measurements were obtained using a program for computerized planimetry (Tape Measure, Indec Systems, Mount View, CA, USA).

Qualitative intravascular ultrasound assessment. The composition of target lesions was assessed at the site of the minimal lumen area. The following classification was adopted:

• fibrous plaques: lesions with a predominant dense fibrous composition that produces bright, heterogeneous echoes having an echo-reflectivity equal or superior to that of the adventitia;

• calcific plaques: lesions having a total calcific arc (highly echogenic segments having a density greater than that of the adventitia and causing acoustic shadowing) > 90°;

• soft plaques: highly cellular fibromuscular lesions or lesions with extensive lipid infiltration which have a low echo-reflectivity (lower than that of the adventitia);

• mixed plaques: presence of multiple plaque components not matching the 80% criterion of prevalence.

Statistical analysis. The demographic, clinical and morphological variables were analyzed using standard statistical methods. Data were expressed as percentages for nominal variables and as the mean ± SD for continuous variables.

Continuous variables were compared by means of the two tailed Student's t-test or the Fisher exact test. Nominal variables were compared using the Fisher exact test. A p value of < 0.05 was considered statistically significant. The IVUS VRI was tested for normality using the Kolmogorov-Smirnov goodness-of-fit test. Statistical evaluations were performed using the Statview 4.57 software program (Abacus Concepts, Inc., Berkeley, CA, USA).

A two-way ANOVA analysis was performed to relate vessel remodeling with anatomical and morphological variables.

Results

The demographic and clinical features are summarized in table I. Of note, 66 patients had stable angina (76%) and 21 patients had unstable angina (18 patients were in Braunwald class IIB and 3 patients in Braunwald class IIIB). The location and the morphological and quantitative features of the target lesions are summarized in table II.

Table I. Demographic and clinical features of the enrolled patients.

No. patients	87
Age (years)	58 ± 5
Males	78 (90%)
High cholesterol	57 (66%)
Smokers	38 (44%)
Hypertension	47 (54%)
Diabetes	13 (15%)
Stable angina	66 (76%)
Unstable angina	21 (24%)
Previous myocardial infarction	41 (47%)

Table II. Location and intravascular ultrasound characteristics of the target lesion.

Vessel location	
Left main	1 (1%)
LAD	48 (55%)
LCx	14 (16%)
RCA	24 (28%)
Lesion location	
Proximal	42 (48%)
Mid	38 (44%)
Distal	7 (8%)
Plaque features	
Soft	22 (25%)
Fibrous	31 (36%)
Mixed	19 (22%)
Calcific	15 (17%)
Eccentric	31 (36%)
Concentric	56 (64%)
Plaque dimensions	
Lumen area (mm^2)	4.2 ± 2.3
EEM area (mm^2)	14.5 ± 4.9
Plaque area (mm^2)	10.3 ± 4.1

EEM = external elastic membrane; LAD = left anterior descending artery; LCx = left circumflex artery; RCA = right coronary artery.

The minimal lumen area, the EEM area and the plaque area were 4.2 ± 2.3 mm^2, 14.5 ± 4.9 mm^2 and 10.3 ± 4.1 mm^2 respectively. The average of the proximal and distal reference lumen areas and the EEM area were 9.2 ± 3.1 mm^2 and 13.3 ± 4.4 mm^2 respectively. The percent reduction in the minimal lumen area relative to the average of the proximal and distal reference lumen areas was 54.3%. The frequency distribution of VRI was found to have a normal unimodal distribution (p = 0.60). VRI ranged from -60 to +164, with a mean of 9.3 ± 28.0 and a median of 3.6. The frequency distribution of VRI skewed slightly towards the right (skewness index 1.69) (Figs. 1 and 2). None of the analyzed clinical and morphological variables predicted the presence of compensatory enlargement as opposed to paradoxical constriction (Tables III and IV).

Discussion

Following Glagov's demonstration of left main stem compensatory enlargement in response to atherosclerotic plaque formation, a number of *post-mortem* and IVUS studies have confirmed this observation in other epicardial coronary artery segments[1-4]. On the other hand, more recent IVUS studies have convincingly proven that vascular remodeling can also result in paradoxical constriction, thus contributing to further lumen narrowing[5-9]. The reasons why plaque growth elicits compensatory enlargement or, rather, paradoxical constriction are still largely unknown.

Our study shows that vessel remodeling follows an unimodal normal frequency distribution, thus suggesting that compensatory enlargement and paradoxical

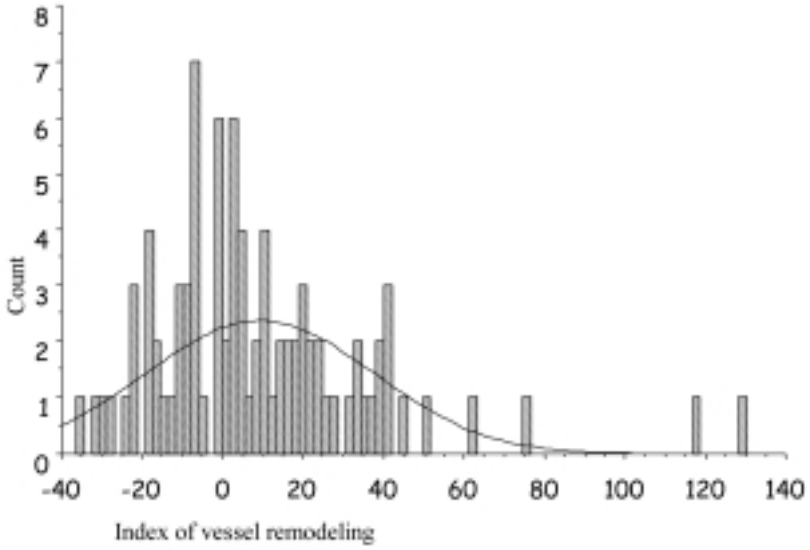

Figure 1. *Histograms of the measurements of the intravascular ultrasound index of vessel remodeling obtained in 87 lesions. Given the mean value and SD of the study group, the curve superimposed on the histogram represents the theoretical Gaussian distribution curve.*

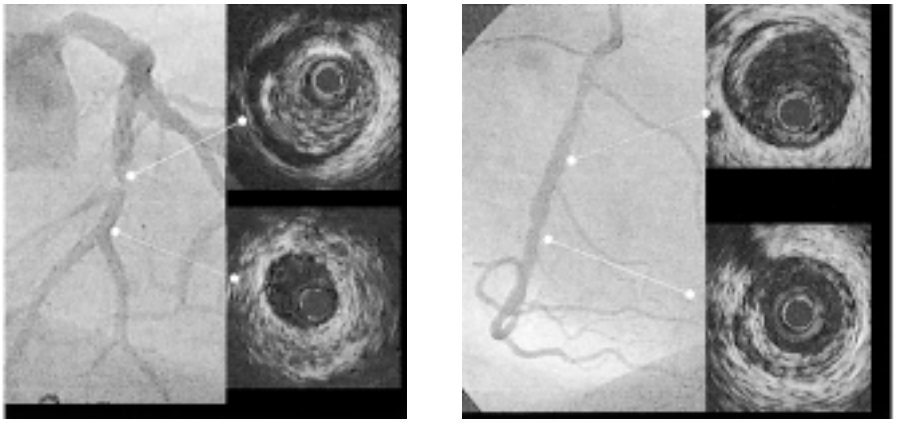

Figure 2. Left panel: *example of compensatory enlargement in response to an atherosclerotic fibrous plaque. The area delimited by the external elastic membrane is larger at the lesion site* (upper line) *than at the distal reference site* (lower line). Right panel: *example of paradoxical constriction in response to an atherosclerotic fibrous plaque. The area delimited by the external elastic membrane is smaller at the lesion site* (lower line) *than at the proximal reference site* (upper line).

Table III. Correlation between demographic and clinical variables and intravascular ultrasound index of vessel remodeling.

	CE	PC	p
Age (years)	57 ± 10	59 ± 9	0.48
Males	44 (56%)	34 (44%)	0.96
Unstable angina	10 (48%)	11 (52%)	0.35
Stable angina	40 (60%)	26 (40%)	0.24
Previous MI	22 (54%)	19 (46%)	0.63
Hypertension	24 (51%)	23 (49%)	0.96
Hypercholesterolemia	31 (54%)	26 (46%)	0.61
Diabetes	6 (46%)	7 (54%)	0.79
Smoking	22 (58%)	16 (42%)	0.80

CE = compensatory enlargement; MI = myocardial infarction; PC = paradoxical constriction.

Table IV. Correlation between anatomical and morphological variables and intravascular ultrasound index of vessel remodeling.

	CE	PC	p
No. diseased vessels			0.42
Single-vessel disease	32 (59%)	22 (41%)	
Two-vessel disease	17 (63%)	10 (37%)	
Three-vessel disease	3 (50%)	3 (50%)	
Vessel			0.44
LAD	29 (60%)	19 (40%)	
LCx	6 (42%)	8 (58%)	
RCA	4 (58%)	10 (42%)	
Location			0.75
Proximal	22 (52%)	20 (48%)	
Mid	23 (60%)	15 (40%)	
Distal	4 (57%)	3 (43%)	
Plaque distribution			0.09
Concentric	26 (46%)	30 (54%)	
Eccentric	18 (58%)	13 (42%)	
Plaque composition			0.80
Soft	12 (55%)	10 (45%)	
Fibrous	16 (52%)	15 (48%)	
Calcific	10 (67%)	5 (33%)	
Mixed	11 (58%)	8 (42%)	

Abbreviations as in tables II and III.

constriction represent the extremes of a continuous spectrum.

In accordance with this observation, we failed to find any differences between the demographic and clinical variables of patients exhibiting compensatory enlargement and those of patients exhibiting paradoxical constriction. Besides, even the morphological and quantitative variables of the target stenosis were similar in the two groups.

Previous IVUS studies reported a higher frequency of compensatory enlargement in the presence of "soft plaques" and, conversely, a higher frequency of paradoxical constriction in the presence of calcific plaques[7,10,11]. In a series of 87 coronary lesions, Tauth et al.[10] found that a fibrocalcific composition was present in 96% of cases exhibiting constrictive remodeling and in 12% of cases exhibiting adaptive remodeling. Similarly, Sabatè et al.[11] imaged 80 coronary artery lesions at IVUS and found that hard lesions were present in 32% of the lesions with adequate remodeling vs 50% of the lesions with non-adequate remodeling ($p < 0.05$). Finally, Mintz et al.[7] analyzed 603 coronary artery atherosclerotic plaques and found that the length of superficial calcium was slightly but significantly less in lesions with adequate remodeling than in lesions with non-adequate remodeling (92 ± 97 vs 102 ± 108°). These findings might suggest that fibrocalcific lesions limit the adaptive remodeling which occurs as a consequence of plaque growth.

At variance with these previous studies we failed to find any differences in the plaque composition of patients exhibiting compensatory enlargement and that of patients exhibiting paradoxical constriction[7,10,11]. The discrepancy between our and previous findings might be due to differences between the analyzed patient populations.

Study limitations. The relatively limited number of analyzed lesions may justify the discrepancy between our study and previous reports, revealing that the presence of calcification and of unstable angina influences VRI[7-11].

In the present study the remodeling index was calculated at the narrowest CSA. The adoption of a longitudinal IVUS view of the analyzed segments would have improved the analysis of vessel remodeling, since it favors the assessment of the EEM vessel contour in the presence of calcium and it reduces the variability of vessel measurements.

Consistently with a previous observation[7] lesions were divided into two groups (lesions with compensatory enlargement and lesions with paradoxical constriction), without taking into account plaques with intermediate vessel remodeling. The definition of intermediate vessel remodeling would have been instrumental in order to avoid those cases in which the definition of a given pattern of vessel remodeling is unclear.

The location of plaque (myocardial vs pericardial), that has been recently found to influence vessel remodeling, was not analyzed as a morphological characteristic of the atherosclerotic plaque[12,13]. In fact, the assessment of the plaque location (myocardial vs pericardial) needs a more accurate IVUS analysis based on a three-dimensional reconstruction.

It has to be noted that, although the VRI follows a unimodal frequency distribution, the latter is slightly skewed towards the right. This suggests that a higher number of observations might result in a bimodal distribution.

Conclusions. Vascular remodeling in *de novo* coronary lesions follows a unimodal normal frequency distribution. This observation lends support to the hypothesis that compensatory enlargement and paradoxical constriction represent the extremes of a continuous spec-

trum which is not influenced by detectable demographic and clinical variables or by the composition or hemodynamic severity of the atherosclerotic plaque.

Acknowledgments

This study was supported by a grant from "Centro per la Lotta Contro l'Infarto", Rome, Italy. IVUS analyses were performed at the European Imaging Laboratory, Rome, Italy.

References

1. Glagov S, Weisenberg E, Zarins CK, Stankunavicius R, Kolettis GJ. Compensatory enlargement of human atherosclerotic coronary arteries. N Engl J Med 1987; 316: 1371-5.
2. McPherson DD, Sirna SJ, Hiraztka LF, et al. Coronary arterial remodeling studied by high frequency epicardial echocardiography: an early compensatory mechanism in patients with obstructive coronary atherosclerosis. J Am Coll Cardiol 1991; 17: 79-86.
3. Gerber TC, Erbel R, Gorge G, Ge J, Rupprecht HJ, Meyer J. Extent of atherosclerosis and remodeling of the left main coronary artery determined by intravascular ultrasound. Am J Cardiol 1994; 73: 666-71.
4. Losordo DW, Rosenfield K, Kaufman J, Pieczek A, Isner JM. Focal compensatory enlargement of human arteries in response to progressive atherosclerosis. In vivo documentation using intravascular ultrasound. Circulation 1994; 89: 2570-7.
5. Pasterkamp G, Wensing PJW, Post MJ, Hillen B, Mali WPTM, Borst C. Paradoxical arterial wall shrinkage may contribute to luminal narrowing of human atherosclerotic femoral arteries. Circulation 1995; 91: 1444-9.
6. Nishioka T, Luo H, Eigler NL, Berglund H, Kim CJ, Siegel RJ. Contribution of inadequate compensatory enlargement to development of human coronary artery stenosis: an in vivo intravascular ultrasound study. J Am Coll Cardiol 1996; 27: 1571-6.
7. Mintz GS, Kent KM, Pichard AD, Satler LF, Popma JJ, Leon MB. Contribution of inadequate arterial remodeling to the development of focal coronary artery stenoses. An intravascular ultrasound study. Circulation 1997; 95: 1791-8.
8. Smits PC, Bos L, Quarles van Ufford MA, Eefting FD, Pasterkamp G, Borst C. Shrinkage of human coronary arteries is an important determinant of de novo atherosclerotic luminal stenosis: an in vivo intravascular ultrasound study. Heart 1998; 79: 143-7.
9. Mintz GS, Popma JJ, Pichard AD, et al. Limitations of angiography in the assessment of plaque distribution in coronary artery disease. A systematic study of target lesion eccentricity in 1446 lesions. Circulation 1996; 93: 924-31.
10. Tauth J, Pinnow E, Sullebarger JT, et al. Predictors of coronary arterial remodeling patterns in patients with myocardial ischemia. Am J Cardiol 1997; 80: 1352-5.
11. Sabatè M, Kay IP, Feyter PJ, et al. Remodeling of atherosclerotic coronary arteries varies in relation to location and composition of plaque. Am J Cardiol 1999; 84: 135-40.
12. Ward MR, Jeremias A, Hibi K, et al. The influence of plaque orientation (pericardial or myocardial) on coronary arterial remodeling. Atherosclerosis 2001; 154: 179-83.
13. Prati F, Arbustini E, Labellarte A, et al. Eccentric atherosclerotic plaques with positive remodeling have a pericardial distribution: a permissive role of epicardial fat? A three-dimensional intravascular ultrasound study of left anterior descending artery lesions. Eur Heart J, in press.