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Contribution of Inadequate Compensatory Enlargement to Development of Human Coronary Artery Stenosis: An In Vivo Intravascular Ultrasound Study

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Objectives. **This intravascular ultrasound study sought to examine to what extent native coronary artery stenosis is accompanied by vessel wall thickening or inadequate compensatory enlargement (relative vessel constriction), or both.**

Background. **In human femoral arteries, inadequate compensatory enlargement is reported to be a paradoxic mechanism for the development of severe arterial lumen narrowing. However, it is unclear in human coronary arteries whether inadequate compensatory enlargement contributes to the development of critical arterial stenosis.**

Methods. **Thirty-five primary coronary artery lesions from 30 patients (19 men, 11 women; mean [±SD] age 65 ± 13 years) were imaged by intravascular ultrasound. The vessel cross-sectional area and lumen area were measured, and the wall area (vessel cross-sectional area minus lumen area) was calculated at the lesion site and at the proximal and distal reference sites. We defined compensatory enlargement to be present when the vessel cross-sectional area at the lesion site was larger than that at the proximal reference site, inadequate compensatory enlargement when the vessel cross-sectional area at the lesion site was smaller than that at the distal reference site and intermediate remodeling when the vessel cross-sectional area at the lesion site was intermediate between the two reference sites.**

Results. **Compensatory enlargement was observed in 19 (54%) of 35 lesions, inadequate compensatory enlargement in 9 (26%) of 35 and intermediate remodeling in 7 (20%) of 35. In the inadequate compensatory enlargement group, reduction of the vessel cross-sectional area contributed to 39% of lumen reduction.**

Conclusions. **Compensatory enlargement commonly (54%) occurs at stenotic coronary lesions. However inadequate compensatory enlargement results in a substantial amount (39%) of the lumen area reduction in 26% of primary coronary artery lesions.**

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Compensatory arterial enlargement in response to plaque formation was first described in coronary arteries (1) and peripheral arteries (2) of monkeys and subsequently detected in human left main coronary arteries using postmortem histologic examination (3). Histopathologic studies (3,4), intraoperative high-frequency epicardial coronary ultrasound imaging (5), as well as intracoronary ultrasound imaging (6,7) have shown that human coronary arteries enlarge in parallel with the formation of atherosclerotic plaque and that the lumen area is preserved until the progressive accumulation of plaque exceeds the compensatory mechanisms of the vessel. Similar findings have also been identified in human carotid (8) and superficial femoral arteries (9). These studies (1–9) indicate that compensatory enlargement is a common phenomenon in the atherosclerotic process. However, the previous reports (3,4,6,7) on compensatory enlargement in human coronary arteries are based on the pooled data collected from different subjects, and no comparison of plaque and lumen areas was made in the same vessel. In a combined intravascular ultrasound and pathology study of human atherosclerotic femoral arteries, Pasterkamp et al. (10) reported that arterial wall constriction (shrinkage) or inadequate compensatory enlargement may be a different mechanism associated with the development of severe arterial lumen narrowing in addition to plaque proliferation.

Accordingly, the aim of this intravascular ultrasound study, comparing the lumen area, the vessel wall area and the vessel cross-sectional area within the same vessel, is to examine to what extent de novo native coronary artery stenosis is accompanied by vessel wall thickening and/or inadequate compensatory enlargement (relative vessel constriction).

Methods

Patients, vessels and coronary lesions studied. Forty-eight consecutive patients (35 men, 13 women; mean [±SD] age

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67 ± 12 years, range 40 to 88) who had not undergone previous catheter intervention were studied with a single intravascular ultrasound system. Informed consent was obtained from each patient before the intravascular ultrasound procedure. The following vessels were excluded from the quantitative intravascular ultrasound image analysis: one vessel in which we failed to introduce the imaging catheter into the coronary artery, five vessels in which intravascular ultrasound images were suboptimal for quantitative measurements because of heavy intimal calcification or a technical problem with the intravascular ultrasound system and five vessels in which the percent diameter stenosis at the lesion site was <70% compared with the reference site by angiography. In total, images of 42 primary lesions from 42 coronary arteries of 37 patients (25 men, 12 women; mean age 66 ± 12 years, range 40 to 88) were included and analyzed in this study. All 37 patients were considered to be clinically manifesting myocardial ischemia and all 42 lesions underwent subsequent coronary catheter interventions.

Intravascular ultrasound system and imaging procedure. The intravascular ultrasound imaging system consisted of an imaging catheter (Sonicath, Boston Scientific Corporation) and a Sonos Intravascular System imaging console (Hewlett-Packard). The imaging catheter has a 30-MHz single piezoelectric crystal transducer mechanically rotating at 1800 rpm within a 3.5F monorail over-the-wire catheter sheath.

After the completion of angiography, the imaging catheter was introduced into the target artery through an 8F to 9F coronary guiding catheter over a 0.014- or 0.018-in. (0.36 or 0.46 mm) guide wire. To prevent possible vasospasm, reported in up to 3% of intravascular ultrasound studies (11,12), and to obtain maximal vasodilation, 100 to 200 μg of nitroglycerin was administered directly into the coronary artery before or during the intravascular ultrasound catheter imaging. After the imaging catheter had been advanced across the lesion to the distal portion of the vessel under fluoroscopic guidance, intravascular ultrasound imaging was performed during the slow pullback (1 mm/s) of the imaging catheter. X-ray fluoroscopy was used to confirm the coaxiality of the imaging catheter at a region of interest in the coronary artery. Intravascular ultrasound images were recorded on a 0.5-in. Super-VHS videotape for subsequent review and quantitative analysis.

Image analysis. Intravascular ultrasound images were analyzed off line with a Sonos Intravascular System. In each coronary artery, a 1- to 2-cm vessel segment of interest was identified in which the most severe stenosis was included and no apparent side branches were observed by angiography and intravascular ultrasound imaging. Three sites were selected for quantitative intravascular ultrasound analysis in this vessel segment using digital angiographic images as a road map. The three sites selected for analysis included the lesion site, which had >70% diameter stenosis by angiography and the smallest lumen area by intravascular ultrasound, and the proximal and distal reference sites that had minimal narrowing by angiography and the largest lumen area and <50% area stenosis determined by intravascular ultrasound in the proximal and distal portion of the vessel segment adjacent to the lesion site. Of 42 lesions in 37 patients analyzed, 7 lesions were excluded because the proximal or distal reference site, or both, could not be identified as a result of the ostial location of the lesion or diffuse intimal hyperplasia in the whole length of the vessel segment defined. In total, images of 35 primary lesions in 35 coronary arteries (15 left anterior descending, 6 left circumflex, 14 right coronary arteries) of 30 patients (19 men, 11 women; mean age: 65 ± 13 years, range 40 to 86) were finally enrolled in the study. No patient was included in whom the imaging catheter occluded the stenotic lumen during the imaging procedure.

For these three sites in each coronary artery, the vessel lumen area (mm^2) was measured by tracing the lumen–intimal border using a planimeter. Contrast medium was injected to enhance the ultrasound definition of the lumen in cases in which the lumen–intimal border was ambiguous. The external elastic lamina of the vessel was defined as the outer border of the sonolucent zone, which has been reported to represent media (13,14), and the area within the external elastic lamina was measured as the vessel cross-sectional area (mm^2) by planimetry. The vessel wall area (mm^2) was defined and calculated by subtracting the lumen area from the vessel cross-sectional area. The percent area stenosis at each site was calculated as (Wall area/Vessel cross-sectional area) × 100. Because the lumen area reduction at the lesion site could theoretically result from the wall area increase or the vessel cross-sectional area reduction compared with the reference sites, the following indexes were defined. The *lumen area reduction* at the lesion site was calculated as (Average of lumen areas at the proximal and distal reference sites − Lumen area at the lesion site). Similarly, the *wall area increase* was calculated as (Wall area at the lesion site − Average of wall areas at the proximal and distal reference sites), and the *vessel cross-sectional area reduction* was calculated as (Average of the vessel cross-sectional areas at the proximal and distal reference sites − Vessel cross-sectional area at lesion site). Contribution of the wall area increase and the vessel cross-sectional area reduction to the lumen area reduction was calculated as (Wall area increase/Lumen area reduction) × 100 and (Vessel cross-sectional area reduction/Lumen area reduction) × 100, respectively.

Compensatory enlargement was considered present when the vessel cross-sectional area at the lesion site was larger than that at the proximal reference site, and *inadequate compensatory enlargement* was considered present when the vessel cross-sectional area at the lesion site was smaller than that at the distal reference site. When the vessel cross-sectional area at the lesion site was intermediate between the proximal and distal reference sites, it was defined as *intermediate remodeling*.

Statistical analysis. Results are expressed as mean value ± SD. Measured and calculated areas at three different sites were compared using repeated measures analysis of variance (ANOVA), and comparison of data among the three different groups was performed using ordinary one-way ANOVA with Student-Newmann-Keuls test as the post hoc test in both

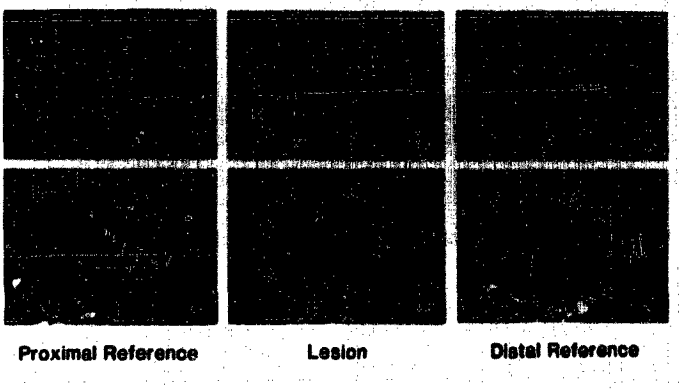

Figure 1. Intravascular ultrasound images of two coronary arteries. Compensatory enlargement was observed in one artery (**top panels**) but was inadequate in the other (**bottom panels**). **White dotted lines** show the lumen–intimal borders; **white dotted lines with white arrowheads** indicate the external elastic lamina. **Top panels**, Vessel cross-sectional area at the lesion site was larger than the proximal and distal reference sites (28.5 vs. 15.9 and 13.1 mm^2). **Bottom panels**, Vessel cross-sectional area at the lesion site was smaller than the proximal and distal reference sites (18.2 vs. 27.7 and 24.2 mm^2).

comparisons. A p value of less than 0.05 was considered statistically significant.

Results

The intravascular ultrasound studies of human in vivo coronary arteries were completed without any vascular complications. No angiographic change was observed before or after the intravascular ultrasound imaging procedure.

Compensatory enlargement in primary coronary artery lesions. Figure 1 shows intravascular ultrasound images of two coronary arteries: one (top panels) in which compensatory enlargement was observed and the other (lower panels) in which compensatory enlargement was inadequate. In 54% of coronary arteries (Fig. 1, top panels), the vessel cross-sectional area at the lesion site was larger than those at the proximal and distal reference sites. In 26% of coronary arteries (Fig. 1, bottom panels), the vessel cross-sectional area at the lesion site was smaller than the proximal and distal reference sites. The size of the vessel cross-sectional area at the lesion site was intermediate between the proximal and distal reference sites in 20% of lesions. There was no relation between the frequency or pattern of coronary artery remodeling and the location of the lesion sites, namely, in which coronary artery branch or in which portion of each coronary artery (proximal, middle or distal) the lesion site is located.

The measured and calculated data on coronary arteries are summarized in Table 1 and Figure 2. As expected, the lumen area was significantly ($p < 0.01$) smaller, and the wall area was significantly ($p < 0.01$) larger at the lesion site than the proximal and distal reference sites in all three groups. The vessel cross-sectional area at the lesion site in the compensatory enlargement group was significantly ($p < 0.01$) larger and the vessel cross-sectional area at the lesion site in the inadequate compensatory enlargement group was significantly ($p < 0.01$) smaller than those at the proximal and distal reference sites, as apparent from the definition of these groups.

At the proximal and distal reference sites, there was no significant difference in the vessel cross-sectional area, lumen area or wall area among the three groups. The average percent area stenosis of the three groups at the proximal and distal reference sites was 34 ± 12%. If we assume an exactly circular

Table 1. Summary of Intravascular Ultrasound Measurements and Calculated Data (mean ± SD)

Area and Site	Compensatory Enlargement Group (n = 19)	Intermediate Remodeling Group (n = 7)	Inadequate Compensatory Enlargement Group (n = 9)
Lumen area (mm^2)			
Proximal	9.6 ± 4.0	9.7 ± 3.0	11.3 ± 3.4
Lesion site	2.7 ± 1.0*	2.6 ± 0.5*	2.9 ± 0.9*
Distal ref.	8.3 ± 2.2	9.3 ± 2.7	10.5 ± 2.3
Vessel wall area (mm^2)			
Proximal ref.	5.8 ± 3.1	7.8 ± 4.0	6.2 ± 3.0
Lesion site	16.5 ± 5.9*†	12.4 ± 5.9*	10.8 ± 3.2*
Distal ref.	4.5 ± 3.2	4.1 ± 3.6	5.7 ± 2.3
Vessel CSA (mm^2)			
Proximal ref.	15.3 ± 5.8	17.5 ± 6.1	17.4 ± 4.8
Lesion site	19.2 ± 6.3*†	15.0 ± 5.9‡	13.7 ± 3.7*
Distal ref.	12.9 ± 4.5	13.4 ± 5.7	16.2 ± 4.3

*$p < 0.01$ versus proximal and distal reference (ref) sites. †$p < 0.01$ versus proximal reference site. ‡$p < 0.05$ versus inadequate compensatory enlargement group. CSA = cross-sectional area.

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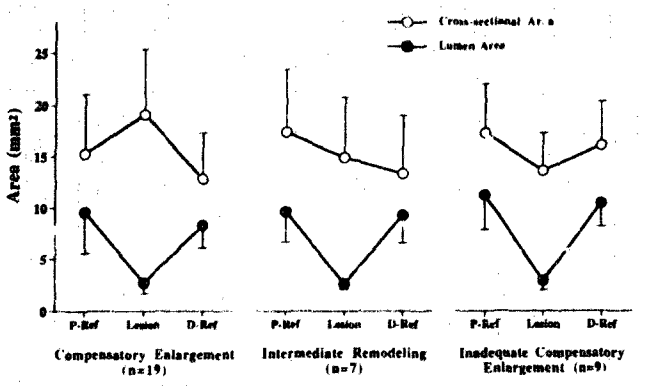

Figure 2. Line graphs showing serial changes in vessel cross-sectional area and lumen area from the proximal to distal reference site in three groups with compensatory enlargement, intermediate remodeling and inadequate compensatory enlargement. The lumen area at the lesion site was significantly ($p < 0.01$) smaller than that at the proximal and distal reference sites and almost identical among the three groups. The vessel cross-sectional area at the lesion site was significantly ($p < 0.01$) larger in the compensatory enlargement group and was significantly ($p < 0.01$) smaller in the inadequate compensatory enlargement group than that at the proximal and distal reference sites. D-Ref = distal reference; P-Ref = proximal reference. **Error bars** show standard deviation for each measurement.

vessel with the external elastic lamina diameter of 3 mm, a 34% area stenosis is compatible with <20% diameter stenosis, which represents the thickness of uniform concentric plaque <0.3 mm.

At the lesion site, there was no significant difference in the lumen area among the three groups. However, the vessel cross-sectional area was significantly larger in the compensatory enlargement group than the inadequate compensatory enlargement group (19.2 ± 6.3 vs. 13.7 ± 3.7 mm^2, $p < 0.05$). Similarly, at the lesion site, the wall area had a significantly greater value in the compensatory enlargement group than the inadequate compensatory enlargement group (16.5 ± 5.9 vs. 10.8 ± 3.2 mm^2, $p < 0.05$). The average percent area stenosis of the three groups at the lesion sites was 82 ± 6%.

Figure 3 demonstrates the contribution of the vessel cross-sectional area reduction and the wall area increase to the lumen area reduction at the lesion site compared with the average of lumen areas at the proximal and distal reference sites. In the inadequate compensatory enlargement group, the vessel cross-sectional area reduction contributed to 39% of the lumen area reduction at the lesion site, whereas the wall area increase also caused 61% of the lumen area reduction at the lesion site. In the intermediate remodeling group, the contribution of the vessel cross-sectional area reduction to the lumen area reduction was 7%, and the rest of the lumen area reduction (93%) resulted from the wall area increase. In contrast, in the compensatory enlargement group, the wall area increase (182%) markedly exceeded the lumen area reduction and was partially (82%) compensated by the vessel cross-sectional area increase.

Discussion

This in vivo intracoronary ultrasound study in human coronary arteries demonstrates that compensatory enlargement occurred in 54% (19 of 35) of lesions; however, apparent compensatory enlargement was not found in 46% (16 of 35) of lesions. Specifically, inadequate compensatory enlargement occurred in 26% (9 of 35), and intermediate remodeling in 20% (7 of 35) of primary coronary artery lesions. At the lesion sites where inadequate compensatory enlargement was observed, 39% of the lumen area reduction resulted from the vessel cross-sectional area reduction, and a 61% reduction in the lumen area occurred through an increase in the vessel wall

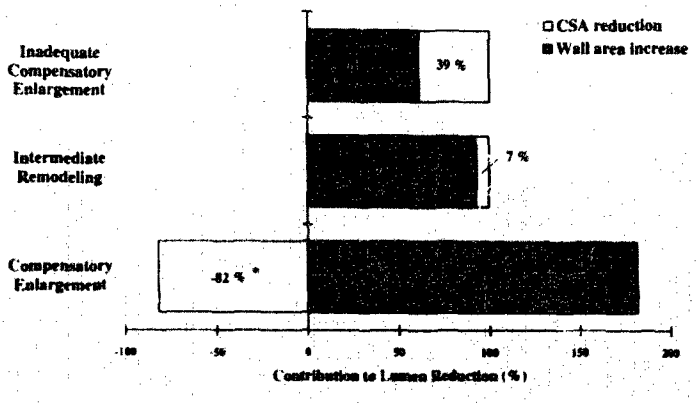

Figure 3. Bar graph showing the contribution of vessel cross-sectional area (CSA) reduction and vessel wall area increase to the lumen area reduction at the lesion site compared with average lumen areas at both reference sites. In the inadequate compensatory enlargement group and intermediate remodeling group, vessel cross-sectional area reduction contributed to 39% and 7% of the lumen area reduction at the lesion site, whereas vessel wall area increase also caused 61% and 93% of the lumen area reduction, respectively. In contrast, in the compensatory enlargement group, vessel wall area increase (182%) markedly exceeded the lumen area reduction and was partially (82%) compensated by the vessel cross-sectional area increase. *Negative value of the vessel cross-sectional area reduction represents an increase in the vessel cross-sectional area.

area (plaque burden). As shown in Figures 2 and 3, these findings are in marked contrast to vessels with compensatory enlargement, where the wall area increase accounts for 100% of the lumen area reduction (182% to 80%).

Compensatory enlargement in coronary arteries. Compensatory enlargement of human coronary arteries in response to the development of intimal plaque has been reported by many investigators (3–7). Our findings revealing inadequate compensatory enlargement in 26% of the stenotic native coronary arteries are different from the previous reports (3–7), which only demonstrated the presence of compensatory enlargement in coronary arteries. As previously described by Losordo et al. (9), many of the conclusions of pathologic and intravascular ultrasound studies (3,4,6,7) are based on the significant correlation between the plaque area and the vessel area (within the external or internal elastic lamina) pooled from measurements of different vessels of different individuals, and with no comparisons made within the same vessel. If the vessels from different individuals with a substantial range of sizes are analyzed together, interpretation of the data becomes complicated because the larger vessels tend to have more plaque than the smaller vessels. Using a 12-MHz epicardial ultrasound imaging transducer to study atherosclerotic human coronary arteries, McPherson et al. (5) have shown that on average, total arterial area increases from the proximal reference site to the lesion site of the coronary artery, findings consistent with the concept of compensatory coronary artery enlargement. However, in their study of 25 coronary arteries with stenotic lesions, the total arterial area in 20% (5 of 25) of the vessels was smaller at the lesion site than at the proximal reference site. Thus, these findings are not inconsistent with our results, although no distal reference site was defined in their study (5).

It is possible to argue that inadequate compensatory enlargement was observed when the coronary artery was imaged by intravascular ultrasound before it achieved full compensatory enlargement. However, even in this situation, most of the vessel cross-sectional area at the lesion site should be larger than that at the distal reference site, because originally the vessel must have tapered from the proximal to the distal segment. According to our definition of inadequate compensatory enlargement, the vessel cross-sectional area at the lesion site is smaller than that at the distal reference site. This means that the degree of compensatory enlargement at the lesion site (which has more plaque burden than the distal reference site) is definitely less than that at the distal reference site (a site with less pronounced disease). It is unlikely that the lesion site where compensatory enlargement is so restricted in spite of severe lumen narrowing at the time of imaging will subsequently develop a substantial degree of vessel enlargement.

Mechanisms. The mechanisms of compensatory arterial enlargement are believed to be twofold (15): 1) the local increase in wall shear stress caused by plaque development may stimulate endothelium-dependent arterial dilatation, and/or 2) the development of plaque may lead to degradation of the media and adventitia, resulting in passive bulging of the plaque. The mechanism of inadequate compensatory enlargement found in one-fourth of the stenotic coronary arteries we studied is unknown. However, potential explanations could relate to local impairment of endothelial vasomotor function and/or locally preserved media and adventitial structure during atherogenesis at the lesion site, causing restricted compensatory enlargement of the vessel (10). Moreover, an inflammatory process or change in the adventitial or vessel wall tissue composition might be also responsible for the local impairment of vessel enlargement.

Study limitations and clinical implications. Our findings are based on the observation of 35 primary coronary lesions that excluded ostial lesions as well as coronary arteries with severe calcification. Therefore, our findings might not be applicable to heavily calcified, restenotic and ostial lesions.

We used an intracoronary injection of 100 to 200 μg of nitroglycerin to prevent vasospasm, and no angiographic change was actually observed before and after the intravascular ultrasound imaging procedure. However, this procedure does not guarantee that the local vasospastic activity is eliminated.

Although there was no case in which the imaging catheter completely occluded the stenotic lumen, the presence of the imaging catheter decreased the lumen by ~1.2 mm^2 and might have caused a reduction in filling pressure and distending pressure within the imaged arterial segment.

The clinical implications of our findings are 1) natural history of the coronary lesions with the same degree of lumen narrowing might be different according to the degree of vessel remodeling; and 2) interventional procedures on the coronary lesions with different degrees of vessel remodeling may result in different acute and long-term outcome.

Conclusions. This in vivo intravascular ultrasound study of de novo human coronary arteries demonstrates that compensatory enlargement commonly occurred in 54% (19 of 35) of lesions, inadequate compensatory enlargement in 26% (9 of 35) lesions, and intermediate remodeling in 20% (7 of 35) lesions. The inadequate compensatory enlargement (relative vessel constriction) at the lesion site appears to be a potentially important contributing factor along with the plaque proliferation in approximately one-fourth of the stenotic lesions in native human coronary arteries. These findings may also have relevance for the natural history of coronary lesions as well as the acute and long-term outcomes of catheter-based coronary interventions, including the restenosis process.

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