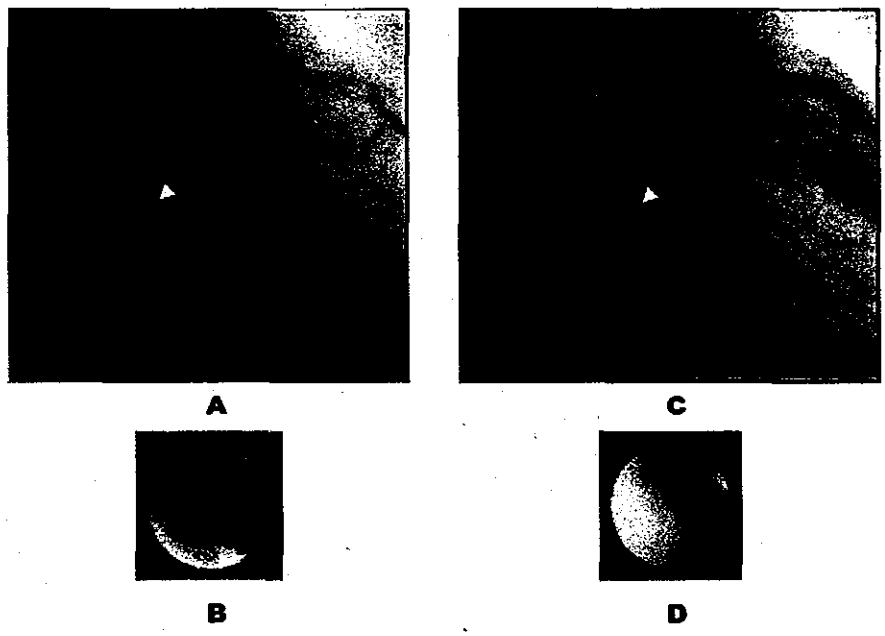

Figure 2. Healing of nonculprit plaque in acute coronary syndrome (ACS). **(A)** Coronary angiogram of the left circumflex artery (LCx) in a patient with ACS. **(B)** A pinkish-white thrombus on the yellow plaque was observed in the mid-portion of the LCx at baseline **(white arrowhead in A)**. **(C)** A 12-month follow-up coronary angiogram in the same patient. **(D)** The thrombus disappeared and a smooth white intima was found **(white arrowhead in C)**. In the quantitative coronary angiogram measurements, %DS at the angioscopic image site **(white arrowhead in A and C)** increased from 34.5% at baseline to 43.1% at follow-up.

Lesion characteristics at follow-up. Follow-up angioscopy was performed 13 ± 9 months after the baseline studies to document the changes in the nonculprit ruptured plaques that had been previously identified. At follow-up, 35 thrombi still remained on the same plaques at baseline (Table 3). The frequency of red thrombi decreased to 17%, and pinkish-white thrombi became predominant. Fifteen ruptured plaques in 11 patients healed completely (Fig. 2), and the overall healing rate of the plaque was 30%. The frequency of yellow plaques in the healed plaques was 47%. The healing rate of the plaque increased according to the follow-up period (23% [9 of 39] at ≤12 months vs. 55% [6 of 11] at >12 months, p = 0.044) (Fig. 3).

On QCA analysis, the %DS of the healed plaques at follow-up was greater than that at baseline (22.7 ± 11.6% vs. 12.3 ± 5.8%; p = 0.0004), whereas that of nonhealed plaque was not significantly different between that at follow-up and baseline (19.1 ± 12.0% vs. 18.0 ± 10.6%; p = 0.6).

Clinical characteristics at follow-up. In 29 patients, all plaques in the same patient could be categorized as either healed or not. One patient who had both two healed plaques and one residual ruptured plaque was excluded from the following analysis. The clinical characteristics at follow-up in patients with healed plaques (n = 10) and in those without healed plaques (n = 19) are summarized in Table 4. The frequency of statin use in patients with healed plaques was higher than that in those without healed plaques (p = 0.009). In patients with healed plaques, the serum CRP level did not change significantly from 0.24 ± 0.34 mg/dl at baseline to 0.07 ± 0.03 mg/dl at follow-up (p = 0.16). The serum CRP level in patients with healed plaque was lower than that in those without healed plaques (0.07 ± 0.03 mg/dl vs. 0.15 ± 0.11 mg/dl; p = 0.007).

The results of univariate logistic regression analyses indicated that the serum CRP level at follow-up and statin use were predictors for plaque healing in nonculprit lesions (Table 5). Multivariate logistic regression analysis was performed, in which the serum CRP level at follow-up and statin use were the independent variables. Two clinical variables were not statistically significant (serum CRP level at follow-up: p = 0.12, odds ratio 1.21, 95% confidence interval 0.99 to 1.62; statin use: p = 0.19, odds ratio 0.27, 95% confidence interval 0.04 to 1.83).

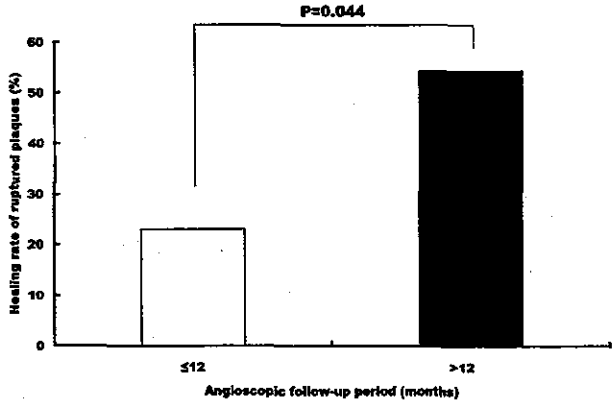

Figure 3. Relationship between the angioscopic follow-up period and healing rate of the nonculprit ruptured plaques. The healing rate of ruptured plaques of ≤12 months and >12 months were 23% and 55%, respectively. The healing rate increased according to the angioscopic follow-up period.

Table 4. Patient Characteristics at Follow-Up

	Patients With Healed Plaques (n = 10)	Patients Without Healed Plaques (n = 19)	p Value
Serum LDL-C level (mg/dl)	109 ± 28	128 ± 31	0.13
Changes in serum LDL-C level (mg/dl)	−51 ± 50	−24 ± 37	0.15
Serum CRP level (mg/dl)	0.07 ± 0.03	0.15 ± 0.11	0.007
Medication			
Antiplatelet	10 (100%)	19 (100%)	>0.99
Warfarin	0	1 (5%)	0.46
Angiotensin-converting enzyme inhibitor	5 (50%)	6 (32%)	0.33
Angiotensin receptor blocker	3 (30%)	5 (26%)	0.83
Beta-blocker	2 (20%)	6 (32%)	0.51
Statin	7 (70%)	4 (21%)	0.009

Data are presented as the mean value ± SD or number (%) of patients. The Fisher exact test was used for categorical data. Abbreviations as in Table 1.

Clinical events. All patients underwent successful PCI for culprit lesions at baseline. The clinical follow-up period was 38 ± 16 months. Five patients underwent repeat PCI for restenosis at three to six months after baseline. A new onset of effort angina (SAP) occurred in one patient 25 months after baseline. In this patient, a healed plaque confirmed by angioscopy showed progression on an angiogram, and PCI was performed. All patients were free from bypass surgery, ACS, and death during the clinical follow-up period.

DISCUSSION

Multiple coronary plaque ruptures, including culprit plaque and other plaques, can occur in patients with various ischemic heart disease (6–10). At the present time, ruptured plaque in the culprit lesion is commonly treated by PCI. This follow-up study clarified the changes in ruptured plaques in nonculprit lesions.

Change of thrombus color and plaque healing. A previous IVUS study reported the frequencies of thrombus in nonculprit ruptured plaques in ACS and in non-ACS to be 32% and 8%, respectively (8). In this angioscopic study, 48 (96%) of 50 ruptured plaques were associated with superimposed thrombi. Coronary angioscopy might be superior to IVUS regarding its ability to differentiate plaque from thrombus. Moreover, angioscopy can show the thrombus color, which allows us to estimate the age and components of the thrombus. In this study, the predominant thrombus color changed from red at baseline to pinkish-white at follow-up. A red thrombus on angioscopy is considered to be a fresh one and is mainly composed of red blood cells and fibrin. In the process of thrombus organization, a red thrombus changes into a pinkish-white one with platelets and fibrin formation (3,16). Our observations on the changes in thrombus color might show the process of thrombus organization.

Table 5. Predictors for the Healing of Nonculprit Ruptured Plaques

	p Value	Odds Ratio	95% CI
Serum LDL-C level at follow-up	0.057	1.03	0.99–1.06
Changes in serum LDL-C level	0.151	1.01	1.00–1.04
Serum CRP level at follow-up	0.004	1.28	1.06–1.68
Statin use	0.010	0.11	0.02–0.60

CI = confidence interval; other abbreviations as in Table 1.

In our study, the angioscopic follow-up period varied. However, the frequency of disappearance of thrombus and healed plaque increased gradually according to the follow-up period. The frequency of yellow plaques in the healed plaques was lower than that at baseline. In several cases, the plaque color changed from yellow to white during the healing process. Similar to the healing of culprit plaques after PCI, a white neointima on angioscopy may cover the nonculprit ruptured plaques and also play a role in the repair process (17). Surprisingly, several thrombi were still found on the ruptured plaque after 12 months of follow-up. These results may suggest that ruptured plaques heal very slowly. A previous pathologic study demonstrated that repetitive ruptures occur in the healed plaques (10). Perhaps part of the thrombi form after recurrent ruptures, and repetitive ruptures could not be excluded in our study.

Change in angiographic stenosis. The %DS of the healed plaques increased significantly from baseline to follow-up. A postmortem study in patients with sudden cardiac death reported that the area within the internal elastic lamina is less in healed plaque after a subclinical rupture than in acute ruptured plaque (10). Furthermore, a cellular proliferation of smooth muscle cells is higher at healed plaque than at ruptured plaque (10). These facts suggest that plaque healing results in an increased plaque burden and negative remodeling.

Our past combination study using angioscopy and IVUS revealed that nondisrupted white plaque and negative remodeling are often found in the culprit lesions of SAP (18). Probably, in several cases of SAP, stenosis of the coronary lumens developed, and clinical symptoms have appeared in the process of plaque healing after previous ruptures. The precise mechanism of angiographic progression was not clarified in this angioscopic study, although progression of

the healed plaques might have resulted from negative remodeling and cell infiltration into the plaques.

Serum CRP level. The serum CRP level predicts the risk of MI or stroke better than total and low-density lipoprotein cholesterol levels (12). A previous angiographic study revealed the presence of multiple complex stenosis in ACS patients, and such stenosis was found to correlate with elevated CRP levels (19). In our study, the serum CRP level in patients with healed plaques did not significantly decrease from baseline to follow-up. The serum CRP level in patients with healed plaques was lower than that in those without healed plaques, thus suggesting that the serum CRP level should reflect the disease activity of the plaque ruptures.

Pharmacologic intervention with statin therapy has been shown to reduce the serum CRP level. We previously reported that statin therapy reduces the serum CRP level and angioscopic complexity of the plaques (the existence of the thrombus and the irregularity of the plaque) in nonculprit lesions (20). Our present data show that frequency of administration of a statin in patients with healed plaques was significantly higher than that in those without healed plaques. Moreover, the serum CRP level in patients with healed plaques was lower than that in those without healed plaques. Our results from univariate logistic regression analyses indicated that both statin therapy and serum CRP level at follow-up are considered predictors of healing in nonculprit ruptured plaques. However, a multivariate logistic regression analysis showed that neither statin therapy nor serum CRP level at follow-up is an independent predictor of plaque healing. These results should be explained so that these two factors correlate to each other.

Clinical events. In this study, no patients had any ACS events during the 38-month follow-up without PCI for nonculprit ruptured plaques. A previous angiographic study in ACS patients with complex coronary lesions demonstrated a poor clinical prognosis, particularly in terms of recurrent ACS episodes (21). On the other hand, an IVUS study of multiple coronary ruptures revealed no recurrence of ACS during 10-month clinical follow-up (6). In the same study, the stenosis of ruptured plaques in nonculprit lesions was less severe than that in culprit lesions (39% vs. 70%, respectively). In our study, the %DS was only 16.3% in ruptured plaques of baseline and 19.1% in nonhealed plaques of follow-up. A quantitative cross-sectional analysis by IVUS revealed that ruptured plaques at nonculprit lesions have larger lumens than do culprit lesions (6,8). Such evidence indicates that a plaque rupture itself does not always result in acute ischemic events. Our follow-up study suggests that even though there are residual ruptured plaques and thrombi, the associated lesions do not lead to the development of ACS in cases with large coronary lumens.

However, an important question remains. Angiographic studies have shown that preexisting stenoses of the culprit lesions were previously mild to moderate (22,23). It is impossible to explain that the degree of stenosis on the angiogram can help determine whether the patient develops ACS or the plaque ruptures remain asymptomatic. When patients have a systemic or local increased potential of thrombogenicity, ruptured plaques in lesions with mild to moderate stenosis may lead to ACS (24). Several IVUS studies have demonstrated that culprit lesions of ACS have a greater plaque burden than do ruptured plaques in nonculprit lesions (6–8). In the event of a plaque rupture, a large plaque is considered to contribute to accelerated local thrombogenicity and the development of thrombosis because of the exposure of a large amount of its contents, such as tissue factor and collagen (25). Conversely, at the nonculprit plaques in smaller sized plaques, even though thrombi still remain, growth of the thrombi may be limited. Therefore, both the degree of stenosis and plaque size, which are unable to be validated by an angiogram, may thus be determinant factors in the clinical course of ruptured plaques.

Atherosclerosis is a progressive disease. Repetitive coronary plaque ruptures on the healed plaques can occur, and then the degree of luminal narrowing should progress (10). A significant degree of stenosis thus appears to be associated with the cause acute thrombotic events (26). Further follow-up studies are needed to examine the development of severe stenosis and acute coronary events.

Study limitations. The number of analyzed plaques and patients represent a limitation of this study. Coronary angioscopy was not performed in all segments of coronary arteries in all patients. Some selection bias is therefore inevitable, beginning with the selection of patients to undergo cardiac catheterization and angioscopy. The follow-up angioscopic examination, which was performed at a single time point, also has some limitations.

Conclusions. This follow-up study documented that plaque ruptures in nonculprit lesions tend to heal slowly with a progression of luminal stenosis, and the serum CRP level might reflect the disease activity of the plaque ruptures.

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Reprint requests and correspondence: Dr. Kyoichi Mizuno, Department of Internal Medicine, Chiba-Hokusoh Hospital, Nippon Medical School, 1715 Kamakari, Imba, Chiba, Japan 270-1694. E-mail: mizunok@nms.ac.jp.

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Effects of Statins on Circulating Oxidized Low-density Lipoprotein in Patients With Hypercholesterolemia

Shigenobu INAMI,[1] MD, Kentaro OKAMATSU,[1] MD, Masamichi TAKANO,[1] MD, Gen TAKAGI,[1] MD, Shunta SAKAI,[1] MD, Junko SANO,[1] MD, *and* Kyoichi MIZUNO,[1] MD

SUMMARY

Recently, it has been reported that circulating oxidized low-density lipoprotein (Ox-LDL) might be a pivotal indicator for coronary artery disease and the severity of acute coronary syndromes. The purpose of this study was to investigate the effects of statins on Ox-LDL in patients with hypercholesterolemia.

Sixteen patients with hypercholesterolemia were randomly assigned to 2 groups, one received 10 mg of pravastatin (n = 8) and the other received 20 mg of fluvastatin (n = 8). The plasma level of Ox-LDL was measured using a newly developed sandwich enzyme-linked immunosorbent assay (ELISA) method.

There were no differences between the two groups in Ox-LDL, total cholesterol (TC), or LDL cholesterol (LDL-C) at the baseline. The reduction in Ox-LDL in the fluvastatin group was significantly higher than that in the pravastatin group (47.5% versus 25.2%, P = 0.033). The reductions in TC and LDL-C did not differ between the two groups. Conclusion: The present study has shown for the first time that the level of circulating Ox-LDL was significantly decreased by treatment with statins. In addition, the lowering effect of statins on the circulating Ox-LDL was independent of their lipid-lowering effect. Fluvastatin was more effective than pravastatin with regard to decreasing the circulating Ox-LDL. (Jpn Heart J 2004; 45: 969-975)

Key words: Statin, Pleiotropic effect, Oxidized low-density lipoprotein

STATINS have been demonstrated to reduce the risk of coronary heart disease (CHD) via their potent effect on lowering the plasma level of low-density lipoprotein-cholesterol (LDL-C) in several large-scale trials.[1,2] On the other hand, it has also been reported that not only the increased levels but also the oxidative modification of LDL-C contributes to the development of atherosclerosis and CHD.[3-5] Therefore, treatment to oxidatively modify LDL-C should be considered in addition to lowering its plasma levels to prevent CHD.

From the [1]Department of Internal Medicine, Chiba Hokusoh Hospital, Nippon Medical School, Chiba, Japan.

Address for correspondence: Kyoichi Mizuno, MD, Department of Internal Medicine, Chiba Hokusoh Hospital, Nippon Medical School, 1715, Kamakari, Imba-mura, Imba-gun, Chiba 270-1694, Japan.

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Recently, it has become possible to measure circulating oxidized LDL (Ox-LDL). It was demonstrated that an elevated level of plasma Ox-LDL was associated with the existence of CHD[6] and the severity of acute coronary syndromes (ACS).[7] In addition, Hulthe, *et al* demonstrated that the circulating Ox-LDL was associated with the development of subclinical atherosclerosis and inflammatory processes.[8] Therefore, it would appear to be important to control the plasma level of Ox-LDL in patients with subclinical atherosclerosis as well as stable, unstable ischemic syndromes.

We were unable to find in the literature any reports concerning the effects of statins on circulating Ox-LDL. Several statins can be used clinically. We were particularly interested in fluvastatin, which reportedly has radical scavenging activity and is effective in the oxidative modification of LDL-C,[9-11] and pravastatin which is used worldwide. The purpose of this study was to investigate the effects of fluvastatin and pravastatin on circulating Ox-LDL. The plasma level of Ox-LDL was measured by a sandwich enzyme-linked immunosorbent assay (ELISA) method, which is a sensitive assay using a monoclonal antibody (DLH3)[12,13] recently developed by Itabe and Kohno.

METHODS

This study is a prospective, randomized trial to investigate the effects of fluvastatin and pravastatin on the plasma levels of Ox-LDL. At our outpatient clinic, we examined 16 patients with hypercholesterolemia (men: $n = 5$, women: $n = 11$), who were randomly divided into 2 groups; a fluvastatin group ($n = 8$) and a pravastatin group ($n = 8$). Informed consent was obtained from each subject, and our study protocol was approved by our institutional review boards. All subjects were asked about their medical history and life-style including smoking status, consumption of red wine and other beverages, antioxidant vitamin use, and dietary intake of selected foods. Fluvastatin or pravastatin was administered for 12 weeks orally to the groups without any life-style modification. Standard doses for both drugs (fluvastatin, 20 mg per day and pravastatin 10 mg per day) were used. At the start and end of the study, venous blood samples were withdrawn after a 12 hour-fasting period, with no alcohol intake during the previous 24 hours and no smoking in the morning on that day. The blood samples were collected in EDTA-containing tubes and centrifuged at 3000 g for 15 minutes at room temperature within 20 minutes. The plasma was collected in antioxidant-containing tubes and stored at 0°C. The plasma levels of total cholesterol (TC), triglycerides (TG), LDL-C, high-density lipoprotein-cholesterol (HDL-C), lipoprotein(a) (Lp(a)), and Ox-LDL were also measured.

Laboratory assays: The plasma TC, TG, LDL-C, and HDL-C levels were measured using established methods with commercial kits. The plasma Ox-LDL assays were performed by Kyowa Medics Corporation according to the assay described by Kohno, *et al.*[13] The method includes sandwich-type ELISA using anti-oxidized phosphatidylcholine monoclonal antibody (DLH3) and anti-human apolipoprotein-B antibody.

Statistical analysis: The data are presented as the mean ± SD. Whether the data were normally distributed or not was examined using the Kolnogrove-Siminov test. If the data were normally distributed, the unpaired *t*-test was used to compare between the two groups, otherwise the Mann-Whitney U-test was used. Discontinuous parameters were compared by χ^2 analysis. The correlation between the baseline plasma levels of LDL-C and Ox-LDL was assessed with the Pearson correlation and scatter plots. A P value < 0.05 was considered to be statistically significant.

RESULTS

Baseline characteristics: The baseline characteristics for each group are summarized in Table I. The plasma Ox-LDL and lipid levels were similar in the 2 groups at baseline. There were no significant differences in the frequency of coronary risk factors between the 2 groups. None of our subjects was taking antioxidant supplements and none were habitual consumers of red wine. Before intervention, the plasma level of Ox-LDL in our cohort did not correlate with that of LDL.

Table I. Baseline Characteristics of Patients

		Pravastatin (n = 8)	Fluvastatin (n = 8)	P value
Age		62.4 ± 8.7	61.3 ± 14.9	0.147
Gender (male)	n (%)	2 (25.0)	3 (37.5)	0.589
Hypertension	n (%)	3 (37.5)	4 (50.0)	0.610
Diabetes mellius	n (%)	2 (25.0)	1 (12.5)	0.520
Obesity	n (%)	4 (50.0)	4 (50.0)	1.000
Smoking	n (%)	2 (25.0)	2 (25.0)	1.000
Ox-LDL	U/dl	12.0 ± 5.5	17.8 ± 9.5	0.157
TC	mg/dL	240.9 ± 21.3	261.4 ± 29.5	0.133
LDL-C	mg/dL	166.5 ± 24.6	178.0 ± 15.2	0.283
TG	mg/dL	123.8 ± 61.1	131.6 ± 42.5	0.771
HDL-C	mg/dL	52.3 ± 20.5	54.7 ± 12.5	0.781
Lp (a)	mg/dL	25.6 ± 15.2	25.3 ± 14.7	0.968

Values presented are mean ± SD or number (%).
Ox-LDL = oxidized low-density lipoprotein; TC = total cholesterol ; LDL-C = low-density lipoprotein cholesterol; TG = triglycerides; HDL-C = high-density lipoprotein cholesterol; Lp (a) = Lipoprotein (a).

Changes in plasma levels of TC, TG, LDL-C, HDL -C, and Lp(a): In both the fluvastatin and pravastatin groups, the plasma levels of TC and LDL-C decreased significantly after treatment (Table II). Pravastatin and fluvastatin resulted in 12.7% and 14.1% reductions in the plasma levels of TC and 21.5% and 15.1% reductions in LDL-C, respectively. The percent reduction in TC and LDL-C did not differ significantly between the two groups ($P = 0.66$, $P = 0.19$, respectively).

Table II. Change in Plasma Levels of Lipids

		Pravastatin		Fluvastatin	
		Before	After	Before	After
TC	mg/dL	240.9 ± 21.3	210.1 ± 19.2*	261.4 ± 29.5	223.3 ± 33.0*
LDL-C	mg/dL	166.5 ± 24.6	130.7 ± 21.2*	178.0 ± 15.2	151.0 ± 27.3*
TG	mg/dL	123.8 ± 61.1	110.3 ± 47.4	131.6 ± 42.5	102.6 ± 37.9
HDL-C	mg/dL	52.3 ± 20.5	55.1 ± 22.6	54.7 ± 12.5	57.8 ± 12.2
Lp (a)	mg/dL	25.6 ± 15.2	26.3 ± 17.9	25.3 ± 14.7	24.4 ± 22.1
Ox-LDL	U/dL	12.0 ± 5.5	9.5 ± 6.1*	17.8 ± 9.5	8.7 ± 4.4*
Ox-LDL/LDL-C (U/dL)/(mg/dL)		0.071 ± 0.026	0.071 ± 0.038	0.101 ± 0.054	0.058 ± 0.024*

Values presented are mean ± SD.
TC = total cholesterol; LDL-C = low-density lipoprotein cholesterol; TG = triglycerides; HDL-C = high-density lipoprotein cholesterol; Lp (a) = lipoprotein (a); Ox-LDL = oxidized low-density lipoprotein.
*: versus before treatment $P < 0.05$.

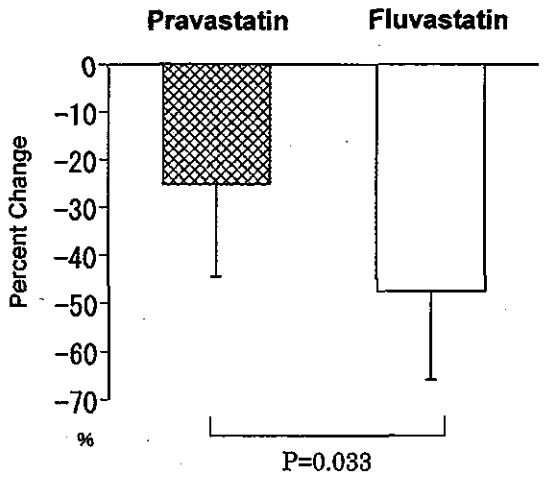

Figure 1. The percent reduction in plasma levels of oxidized low-density lipoprotein.
The percent reduction in the plasma levels of oxidized low-density lipoprotein was significantly higher in the fluvastatin group than in the pravastatin group (47.5% versus 25.2%, $P = 0.033$).

Although the plasma levels of TG decreased and the plasma HDL-C levels increased after treatment in both groups, both changes were not significant.

Changes in the plasma levels of Ox-LDL: The plasma levels of Ox-LDL in the pravastatin and fluvastatin groups decreased significantly after intervention (P = 0.003, P = 0.010, respectively) (Table II). The percent reduction in the plasma levels of Ox-LDL was significantly higher in the fluvastatin group than in the pravastatin group (47.5% versus 25.2%, P = 0.033) (Figure 1). Furthermore, the Ox-LDL/LDL-C ratio in the plasma decreased significantly in the fluvastatin group (P = 0.026) (Table II).

DISCUSSION

As an atherogenic factor, Ox-LDL has been reported to have various actions resulting in the chemotaxis of monocytes, the up-regulation of endothelial adhesion molecules, stimulation of growth factor and chemokine expression, and proliferative effects on smooth muscle cells and monocytes.[14,15] In addition, the cytotoxicity of Ox-LDL from cultured endothelial cells has been clearly demonstrated to be atherogenic. In a pathophysiological study, Ox-LDL was shown to accumulate in atherosclerotic lesions.[16] Although the origin and physiological significance of the circulating Ox-LDL have not been fully clarified, it is believed to originate from atherosclerotic lesions. It is also possible that LDL-C is modified to Ox-LDL during circulation by free-radicals or other molecules. Toshima, *et al* reported that Ox-LDL was significantly elevated in patients with CHD.[6] Ehara, *et al* also showed the clinical relevance of circulating Ox-LDL to the severity of ACS.[7] Furthermore, circulating Ox-LDL was found to be correlated with inflammatory cytokines and clinically silent ultrasound-assessed atherosclerotic changes in the carotid and femoral arteries.[8] Accordingly, it is believed circulating Ox-LDL may be a potential key marker for atherosclerosis and CHD.

The present study proves for the first time that statins can significantly decrease circulating Ox-LDL. It also has demonstrated that the lowering action of fluvastatin on Ox-LDL was stronger than that of pravastatin, while the reductions in LDL-C were not significantly different between the two statins. Fluvastatin has been reported to show radical scavenging activity based on its structure and to reduce the susceptibility of LDL to lipid peroxidation.[10] The results of the present study suggest that fluvastatin could decrease circulating Ox-LDL by not only a lipid-lowering effect, but also by a direct action on the oxidative modification of LDL. Recently, Serruys, *et al* in the LIPS trial have demonstrated that fluvastatin significantly reduced the risk of cardiac events following percutaneous coronary intervention.[17] In this trial, the mean baseline LDL-C was 132 mg/dL, which was the lowest range of those reported in previous major long-term secondary preven-

tion statin trials.[18-20] Furthermore, in the CARE and LIPID trials, the benefits of pravastatin were diminished in patients with baseline LDL-C values less than 130 mg/dL.[19,21] In contrast, LIPS showed that the benefit of fluvastatin is equal regardless of the baseline cholesterol values, indicating that fluvastatin has beneficial effects other than its lipid-lowering effect in cardiac events. Recent reports have demonstrated that in addition to their lipid-lowering effects, statins have many pleiotropic effects, such as inhibiting oxidative stress, improving endothelial function, decreasing vascular inflammation, and enhancing plaque stability. Since the chemical structures of statins are distinct from each other, the potencies of their pleiotropic effects are also considered to be different. In addition to its antioxidant activity, fluvastatin may have more potent pleiotropic effects than pravastatin.

Conclusion: The present report documents a novel observation that statin therapy results in a significant reduction in circulating Ox-LDL. Furthermore, fluvastatin is more effective than pravastatin in lowering the level of circulating Ox-LDL. In order to elucidate whether treatment for circulating Ox-LDL will have an impact on the development of CHD and ACS, and whether fluvastatin with its direct antioxidant activity will have a beneficial effect on the prevention of the cardiac events, further investigations should be conducted.

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Catheterization and Cardiovascular Interventions 62:175–180 (2004)

Variability in Quantitative Measurement of the Same Segment With Two Different Intravascular Ultrasound Systems: In Vivo and In Vitro Studies

Yuxin Li, MD, Junko Honye, MD, Satoshi Saito*, MD, Tadateru Takayama, MD, Shin-Ichiro Yokoyama, MD, Tadahiro Saruya, MD, Motoko Kotani, MD, Kazuo Harasawa, MD, Hideyuki Ando, MD, Masayoshi Endo, MD, and Katsuo Kanmatsuse, MD

We evaluated two different intravascular ultrasound (IVUS) systems, Atlantis and Intrafocus, to verify their accuracy and reproducibility. In an in vivo study on 20 consecutive patients with coronary artery diseases, the minimum lumen diameter (MLD), vessel diameter, lumen area (LA), vessel area, plaque area, and area stenosis rate (% AS) were respectively measured. In an in vitro study, MLD and LA were measured in four metal tubes with different diameters. All of the measured values except for % AS by Atlantis were significantly larger than the values obtained with Intrafocus. Nonuniform rotational distortion (NURD) was estimated as 34% in Atlantis and 1% in Intrafocus. The measurements by Atlantis were larger than the true values while the measurements by Intrafocus were less than the true values in all four metal tubes. These findings suggest that we should clearly avoid the use of different IVUS systems in the same study. *Catheter Cardiovasc Interv 2004;62:175–180.* © 2004 Wiley-Liss, Inc.

Key words: intravascular ultrasound; quantitative measurement; variability of different systems; in vivo

INTRODUCTION

Intravascular ultrasound (IVUS) has been applied for guidance in percutaneous coronary intervention (PCI). The morphometric measurements of IVUS are clinically important for estimating the residual lumen, vessel, and plaque size in order to determine the device size and endpoint during PCI [1]. Currently, several kinds of IVUS systems are commercially available, and validation studies among these systems are required. Some previous investigations have demonstrated significant differences in image representation among different IVUS systems when diagnosing the tissue components of complex atherosclerotic plaque [2,3]. However, most of the previous studies were performed only in vitro. The purpose of the present investigation was to compare two different mechanical IVUS systems both in vivo and in vitro in terms of quantitative measurements of the lumen, plaque, and vessel sizes.

MATERIALS AND METHODS

Ultrasound Imaging Systems

Two commercially available intravascualr ultrasound systems and catheters were employed: a mechanical rotating 40 MHz transducer (Atlantis, 2.6 Fr; Boston Scientific) and a mechanical rotating 35 MHz transducer (Intrafocus, 2.4 Fr; Terumo).

Twenty consecutive patients with native coronary artery disease were enrolled in this study. All patients gave written informed consent for the study. The patients underwent IVUS before and after PCI by both IVUS systems. The IVUS images were optimized under visual inspection by manipulating the system settings provided with each device. Both IVUS catheters were automatically pulled back at 0.5 mm/sec with the same autopullback device. The IVUS images were continuously recorded on SVHS videotapes.

IVUS Imaging Analysis

The IVUS images recorded on the SVHS tapes were analyzed with an IVUS 3D imaging system (NetraIVUS software package for Windows NT, SciImage). In the

Division of Cardiology, Second Department of Medicine, Nihon University School of Medicine, Tokyo, Japan

*Correspondence to: Dr. Satoshi Saito, Division of Cardiology, Second Department of Medicine, Nihon University School of Medicine, 30-1 Oyaguchi-Kami-machi, Itabashi-ku, Tokyo, 173-8610, Japan. E-mail: satoshis@med.nihon-u.ac.jp

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coronary arteries with significant stenosis (quantitative coronary angiography ≥ 75%), images of the smallest stenotic segments, proximal edges, distal edges, proximal reference segments, and distal reference segments were selected for measurement. In other coronary arteries without significant stenosis, 5 to 10 arbitrary segments were also selected for measurement. In total, 280 pairs of IVUS images from the two systems were selected and stored for further analysis. Two-dimensional longitudinal reconstruction images and short-axis cross-sectional images were used to identify the same location of the images. The images were interpreted and measured by two independent well-trained observers at different times. The two observers were not involved in acquiring the images and had no influence on the system settings.

Quantitative Analysis

Images with a significantly reduced quality and plaque with a calcium arc > 90° were excluded. Thus, 247 images were measured. Cross-grids recorded on the IVUS images were used for calibration. The interface between the plaque and lumen and the outer border of the external elastic membrane were traced manually. On the basis of the manual tracing, the computer software determined the following measurement parameters: minimum lumen diameter (MLD), maximum lumen diameter, minimum vessel diameter (MVD), maximum vessel diameter, lumen area (LA), and vessel area (VA). From these direct measurements, the following parameters were estimated: plaque area (PA), calculated as the area within VA minus LA; and plaque area stenosis rate (% AS), calculated as PA/VA × 100%.

Other Analyses

The plaque characteristics and image quality were also analyzed between the two systems. Plaque calcium was defined as an area of high echo intensity, with acoustic shadowing. The plaque calcium was divided into four semiquantitative types according to the radial degrees of calcium: no calcium, less than 90°, from 90° to 180°, and greater than 180°. We also compared the incidence of nonuniform rotational distortion (NURD) between the two systems, which is an important factor that influences image quality in mechanical IVUS systems.

In Vitro Study

Four phantom metal cylindrical tubes with different diameters were observed using the two IVUS systems. Images were obtained in a saline-filled tank maintained at 37°C. Each ultrasound catheter from the two systems was inserted sequentially into the distal edge of the tube and slowly pulled back manually to the proximal edge. All procedures were performed by the same operator for both systems. In each tube, 10 arbitrary segments were selected for analysis by two independent observers. The measurement parameters consisted of the MLD and LA. After completion of all IVUS measurements, the four tubes were measured with a laser camera for their MLD and LA, and the results obtained were regarded as the actual values. In the procedures for pulling back the catheter manually, the transducer positions were randomly placed in the center or off-center of the tubes. Since angle-related variance in image quality also occurs with an eccentric catheter position [4], we contrasted the distortion index (maximum lumen diameter/MLD) between the central and off-central transducer positions in the two systems.

Statistical Analysis

Measured values are expressed as mean ± standard deviation. The least significant difference (LSD) posthoc test was used to compare the values between the two systems on analysis of variance. Chi-square analysis was employed to compare other values such as the degree of calcification and NURD between the two systems. The interobserver variability was analyzed by linear regression. In these analyses, $P < 0.05$ was considered as statistically significant.

RESULTS

In Vivo Study

The mean age of the 20 patients was 63 ± 8 years (range, 51–78 years). The number of male patients was 17. In total, 280 segments of IVUS images from 47 coronary arteries (RCA, 18; LAD, 20; LCx, 9) were selected for analysis.

Both mechanical rotation systems showed good sensitivities for identifying the lumen boundary and a high identity of representation of the plaque characteristics such as the plaque calcium, low echogenic plaque, high echogenic plaque, lipid pool, plaque rupture, and thrombus.

Quantitative Variability

Excluding images with a significantly reduced quality and a calcium arc > 90°, 247 pairs of images were measured. The average values and standard deviations of MLD, MVD, LA, VA, PA, and % AS from the two systems are summarized in Table I. The measured values of MLD, MVD, LA, VA, and PA by Atlantis were statistically larger than the values obtained with Intrafocus ($P < 0.05$; Fig. 1). The values of % AS from the two systems were similar with no statistical difference.

Calcium and NURD Variability

Excluding the images with a significantly reduced quality, 268 pairs of images were measured. Table II

TABLE I. Comparison of Average Measured Values In Vivo*

	MLD (mm)	MVD (mm)	LA (mm^2)	VA (mm^2)	PA (mm^2)	% AS (%)
Atlantis	3.0 ± 0.7[a]	4.5 ± 0.6[a]	9.6 ± 4.1[a]	18.9 ± 5.0[a]	9.3 ± 3.2[a]	49.8 ± 14.6
Intrafocus	2.8 ± 0.6	4.1 ± 0.6	8.0 ± 3.3	15.8 ± 4.1	7.8 ± 2.8	49.7 ± 14.5

*n = 247 for both systems.
[a]$P < 0.05$.

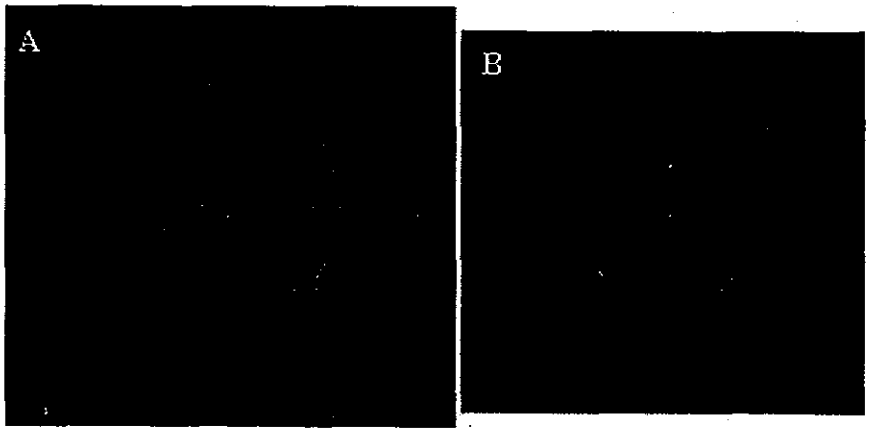

Fig. 1. Images of a coronary artery at the same cross-section obtained with two intravascular ultrasound systems. A: Atlantis. B: Intrafocus. There were no significant differences in representing the plaque characteristics. The measured values from the two systems were as follows. Atlantis: MLD, 2.6 mm; LA, 7.4 mm^2; VD, 5.2 mm; VA, 23.5 mm^2. Intrafocus: MLD, 2.5 mm; LA, 6.3 mm^2; VD, 4.8 mm; VA, 20.7 mm^2. All parameters from Atlantis were larger than those from Intrafocus.

TABLE II. Incidence of Plaque Calcium*

	0°	0–90°	90–180°	> 180°
Atlantis	190	57	16	5
Intrafocus	199	52	13	4

*n = 268 for both systems.

TABLE III. Comparison Among Four Tubes: MLD (mm)*

	Tube 1	Tube 2	Tube 3	Tube 4
Actual value	3.94	4.96	6.92	8.93
Atlantis	3.96 ± 0.23	4.94 ± 0.16	6.80 ± 0.34	8.68 ± 0.34
Intrafocus	3.47 ± 0.05[a]	4.38 ± 0.06[a]	6.24 ± 0.13[a]	8.31 ± 0.14[a]

*n = 10 for every tube with both systems.
[a]$P < 0.05$ vs. actual value.

shows the incidence of the four types of plaque calcium. Atlantis tended to indicate a higher incidence of plaque calcium than Intrafocus, but there was no statistical difference between the two systems ($P = 0.61$).

Among the total of 280 pairs of images, 12 images from Atlantis (4%) could not be analyzed because of a significantly reduced quality with severe NURD. Adding another 83 images from Atlantis with different degrees of NURD that did not significantly influence the image quality, 95 images from Atlantis (34%) were confirmed with NURD by the two observers. NURD was frequently evident at tortuous lesions with calcium and/or near a branch. On the other hand, only two images from Intrafocus (1%) showed NURD. Atlantis thus demonstrated a significantly higher incidence of NURD than Intrafocus ($P < 0.05$).

In Vitro Study

Table III shows the average MLD values of the four metal tubes obtained with the two systems and the actual values. There was no statistical difference between the values from Atlantis and the actual values, while the values from Intrafocus were significantly less than the actual values ($P < 0.05$).

Table IV shows average LA values among the metal tubes obtained with the two systems and the actual values. The values from Atlantis were larger than the actual values, while the values from Intrafocus were less than the actual values in all four of the metal tubes ($P < 0.05$).

Table V shows the average values of the distortion index (maximum lumen diameter/MLD) between the central and off-central transducer positions in the two

TABLE IV. Comparison Among Four Tubes: LA (mm^2)*

	Tube 1	Tube 2	Tube 3	Tube 4
Actual value	12.2	19.3	37.6	62.6
Atlantis	14.3 ± 0.9[a]	22.4 ± 1.8[a]	43.1 ± 4.4[a]	68.0 ± 4.3[a]
Intrafocus	10.8 ± 0.3[a]	16.8 ± 0.4[a]	34.5 ± 0.6[a]	59.5 ± 2.1[a]

*n = 10 for every tube with both systems.
[a]$P < 0.05$.

TABLE V. Comparison of Distortion Index*

	Central position	Off-central position
Atlantis	1.07 ± 0.03	1.18 ± 0.09[a,b]
Intrafocus	1.07 ± 0.02	1.10 ± 0.03[a]

*n = 18 for both systems.
[a]$P < 0.05$ vs. central.
[b]$P < 0.05$ vs. Intrafocus off-central.

systems. The data were almost equal between the two systems when the transducers were located at the central position within the tubes. Both systems revealed statistically larger distortion indexes when the transducers were placed in off-central positions ($P < 0.05$). Furthermore, the distortion index from Atlantis was significantly larger than that from Intrafocus ($P < 0.05$; Fig. 2).

Interobserver Variability

Among all the in vivo and in vitro measured values, there were no statistical differences between the two observers. Table VI shows the correlation coefficients for the relationship between the two independent observers for the in vivo and in vitro measurements. The two observers provided a close correlation for all values ($P < 0.05$), especially the in vitro values.

DISCUSSION

IVUS produces unique cross-sectional images of arterial walls that yield accurate morphometric measurements of coronary arteries [5–8]. Some articles have demonstrated considerable variability for IVUS with different systems; this involves imaging preparation (e.g., saline versus blood, room versus body temperature), catheter position, etc. [2,3,8,9]. Most previous investigations were performed in vitro. Our study is the first prospective study to compare different IVUS systems directly in the same arteries in vivo. The major finding was that significant variability exists in the quantitative analysis that can influence the determination of the device sizes and endpoint, although high correlation coefficients were noted between the different systems. Atlantis tended to overestimate the measurements, while Intrafocus underestimated the measurements.

Although both systems were accurate for representing morphologic features, Intrafocus has a greater ability to avoid NURD, especially in the case of tortuous lesions. To identify calcified plaque by IVUS is important for guiding interventional strategies and for predicting clinical outcome after the interventions. The present data demonstrated that both systems have a similar capability for identifying calcium within the plaque [10,11].

Reasons for Variability Between Two Systems

Ultrasound image quality is determined not only by ring down artifacts, but also by multiple other factors, including the frequency, resolution, distance from the catheter to tissue, catheter size, dynamic range, gain setting, quality of image processing software, rotational speed, noise isolation, and ultrasound beam contours [3,12–14]. In our study, although extensive efforts were made to optimize all of the images obtained from each of the two systems, there were significant differences in system frequency, catheter design, catheter size, transducer size, composition, and electronic processing of the ultrasound backscatter to produce the images [2,15,16]. Measurements on IVUS images obtained in clinical settings are not always optimal because of limited image resolution, eccentric catheter placement, shadowing by calcium within the plaque, catheter artifacts, NURD, and significant movements of the catheter within the vessel. The angle and position of the IVUS catheter are also important factors in image quality and in making quantitative measurements. In our in vitro study, when the transducers were placed in the off-center position, the ultrasound beams were not parallel to the long axis of the tubes so that only elliptical images were obtained. Calcium deposits cause acoustic shadowing and obscure underlying structures behind the calcium. Systolic-to-diastolic differences and beat-to-beat variability should be considered when selecting frames for analysis. The systolic vascular dimensions were significantly greater than the diastolic dimensions [4,13]. The differences between both systems could account for the differences in interpretation and measurements. For example, the speed of ultrasound is 1,562 m/sec in Atlantis and 1,530 m/sec in Intrafocus. Such differences may have contributed to the results. It is important to understand the limitations of each system. We should be careful to determine the size of the device and/or endpoint of coronary intervention and be cautious in interpreting studies performed with the different machines.

Interobserver Variability

The present study revealed a high correlation coefficient between the two observers in both systems. This is similar to previous articles that reported a low interobserver variability [1,17–20]. In our study, the high correlation between the two observers may have been due to

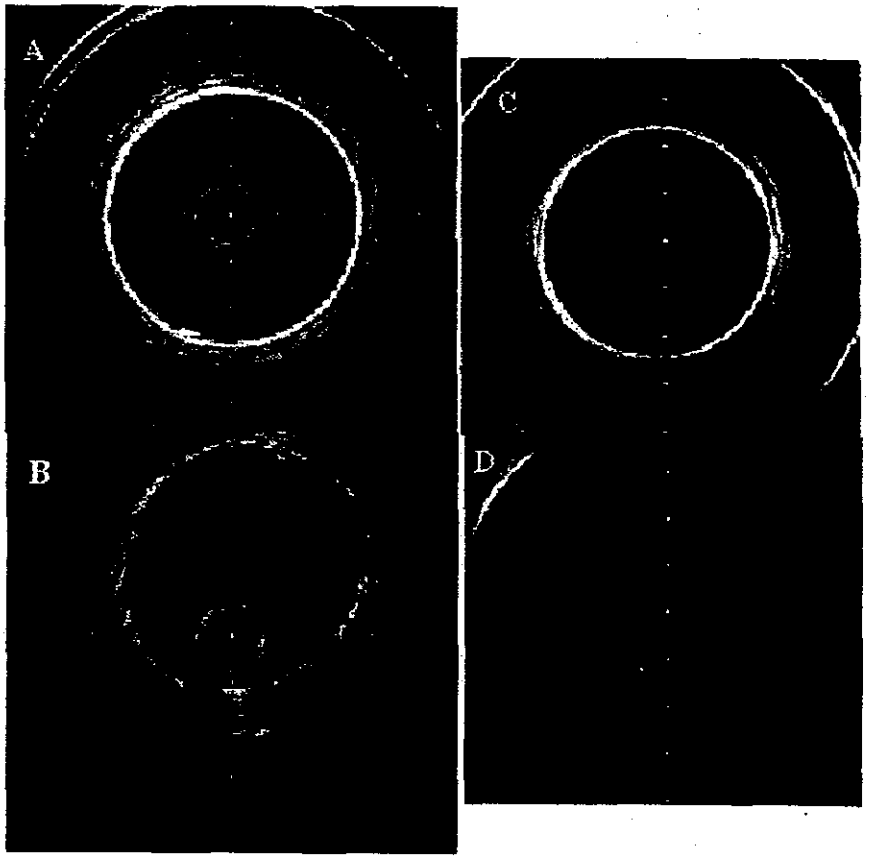

Fig. 2. Images of tube 2 obtained with two IVUS systems. A and B: Atlantis. C and D: Intrafocus. In the two top images, both transducers were placed in the center of the tube. In the two bottom images, both transducers were placed in the off-center position of the tube. The sizes of the tube and measured values were as follows: real diameter, 4.98 mm; real LA, 19.3 mm^2. A: MLD, 5.2 mm; LD max, 5.4 mm; LA, 22.2 mm^2; distortion index, 1.04. B: MLD, 4.7 mm; LD max, 5.5 mm; LA, 20.3 mm^2; distortion index, 1.17. C: MLD, 4.5 mm; LD max, 4.8 mm; LA, 17.4 mm^2; distortion index, 1.07. D: MLD, 4.3 mm; LD max, 4.8 mm; LA, 16.7 mm^2; distortion index, 1.12. Measured values were larger than the actual values by Atlantis and less than the actual values by Intrafocus. When the transducers were placed in the off-center position, the cross-section images were represented as ellipses.

TABLE VI. Correlation Coefficients for the Relationship Between Two Independent Observers*

	In vivo					In vitro	
	MLD	MVD	LA	VA	PA	MLD	LA
Atlantis	0.97	0.96	0.98	0.98	0.93	0.99	0.99
Intrafocus	0.95	0.97	0.98	0.97	0.93	0.99	0.99

*n = 247 for in vivo; n = 40 for in vitro.

the high resolution of plaque and training levels of each observer.

Clinical Implications

Since the transducer of Atlantis is pulled back within the sheath, this can ensure stability of long-axis movement. On the other hand, a high incidence of NURD is the most important factor influencing the quality of IVUS images that leads to errors in the measurements. Intrafocus has excellent characteristics for reducing the incidence of NURD. Since the transducer of Intrafocus is pulled back with the catheter itself, long-axis measurement is not precise. We should clearly avoid the use of different IVUS systems in the same study.

There were significant variabilities in quantitative measurement between the two different IVUS systems. These variabilities should be considered when interpreting IVUS results obtained with different systems, especially in purely quantitative studies. We must remember that Intrafocus tends to underestimate measured values when determining the device sizes and endpoint during interventional therapies. On the other hand, the high

frequency of NURD in Atlantis has an important influence on the accuracy of measurement. Each operator should be aware of these variabilities.

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Catheterization and Cardiovascular Interventions 63:314–316 (2004)

Intravascular Ultrasound Evaluation of Ruptured Plaque in the Left Main Coronary Artery Misinterpreted as an Aneurysm by Angiography

Yuxin Li, MD, Junko Honye, MD, Tadateru Takayama, MD, and Satoshi Saito,* MD

We report a patient who demonstrated a left main coronary aneurysm by angiography. Intravascular ultrasound (IVUS) revealed that it was in fact an ulceration, which indicated ruptured plaque. This case provides evidence that IVUS can permit a more powerful definition of ruptured plaque than angiography. On IVUS, ulceration exhibits significantly different characteristics from aneurysm. *Catheter Cardiovasc Interv 2004;63:314–316.*

Key words: intravascular ultrasound; ulceration; coronary aneurysm

INTRODUCTION

Although angiography has continued for > 40 years as the predominant method for delineating and diagnosing the coronary anatomy, many studies have challenged the accuracy and reproducibility of this technique [1–3]. Intravascular ultrasound (IVUS) has evolved as a valuable adjunct to angiography due to its visualization of the full circumference of the vessel wall [1,4,5]. We report here a patient with angiographically left main coronary aneurysm that turned out to be an ulcerative lesion on IVUS.

CASE REPORT

A 50-year-old male who was admitted to hospital because of palpitations and dyspnea was diagnosed as congestive heart failure. An electrocardiogram (ECG) on admission demonstrated atrial flutter and fibrillation. His coronary risk factors were smoking (30 cigarettes a day for 15 years) and hyperlipidemia. His family history for cardiac disease was negative. A transthoracic echocardiogram revealed moderate mitral valve regurgitation.

At the time of undergoing electrophysiologic studies, this patient received coronary angiography to determine if he had coronary heart disease. The coronary angiography disclosed a 99% stenosis at the ostial right coronary artery, a 90% stenosis at the second diagonal branch, and a 90% stenosis at the posterior descending artery of the left circumflex artery. In addition, despite some haziness, the coronary angiography indicated a big coronary aneurysm at the left main trunk (Fig. 1). We successfully treated the calcified lesion at the ostial right coronary artery with stent implantation following rotational atherectomy. To determine the etiology of the aneurysm at the left main coronary artery, we decided to perform IVUS, which demonstrated that the angiographic aneurysm was in fact an ulcerative lesion with a thin fibrous cap flapping into the lumen (Fig. 2) and the vessel wall was preserved. The lumen diameter was enlarged to 12.0 mm at the ulcerative segment, 8.2 mm at the proximal segment, and 8.0 mm at the distal segment. These findings indicated that this lesion was an unrecognized ruptured plaque. There were no CK or troponin elevation after the procedure. Since there was no significant stenosis in the left main coronary artery, we decided to follow up this patient medically.

DISCUSSION

A coronary aneurysm is usually diagnosed angiographically as an area of localized coronary dilation whose diameter is 1.5 to 2 times larger than the diameter of the adjacent normal segment [6]. Since coronary angiography demonstrates the contrast-filled lumen contours, it is unable to distinguish true or false aneurysm or other local dilated lesions such as plaque rupture with ulcerative formation [4–6,7–9]. In recent years, IVUS

Division of Cardiology, Second Department of Medicine, Nihon University School of Medicine, Tokyo, Japan

*Correspondence to: Dr. Satoshi Saito, Division of Cardiology, Second Department of Medicine, Nihon University School of Medicine, 30-1 Oyaguchi-Kami-machi, Itabashi-ku, Tokyo, 173-8610, Japan. E-mail: satoshis@med.nihon-u.ac.jp

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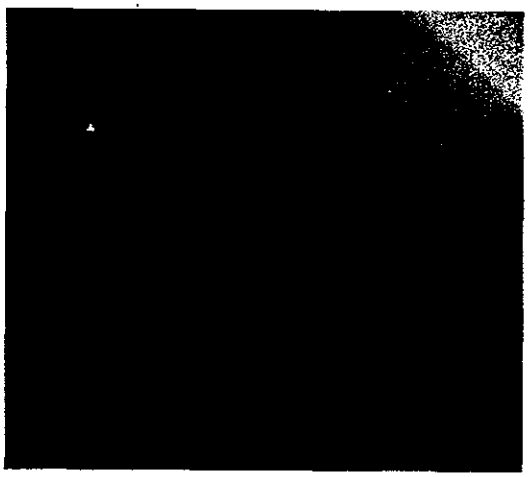

Fig. 1. Coronary angiogram (RAO 30°) indicating a coronary aneurysm (arrow) at the proximal segment of the left main coronary artery.

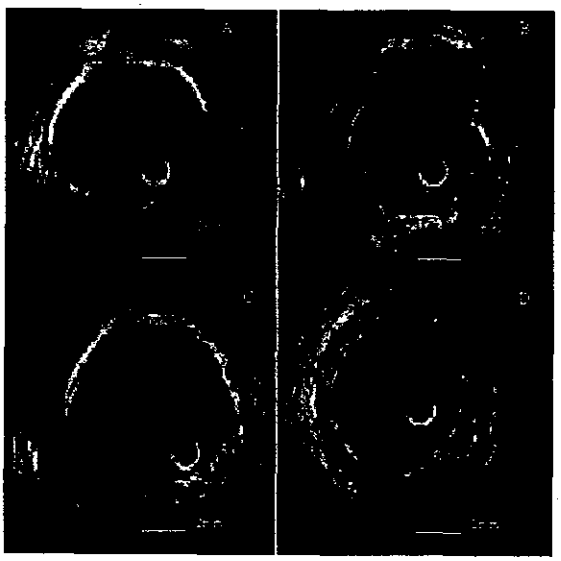

Fig. 2. IVUS images showing an ulcerative lesion in the left main coronary artery. A: Proximal segment. B: Proximal edge of lesion. C: Lesion segment. D: Distal segment. Fibrous and calcified plaque occupied most of the vessel with an ulceration occurring between 6:00 and 9:00 (B and C). Rupture of the fibrous cap was evident overlying the ulceration flapping into the lumen at the proximal edge of the lesion (B). The distal segment revealed mixed plaque (D).

has evolved as a valuable adjunct to angiography, offering detailed high-resolution images of both the lumen and vessel wall [4,6,10,11]. Miskolczi et al. [12] reported that IVUS could permit a more powerful definition of small ulceration than other available diagnostic methods. In the present case, the angiographic aneurysm was so big that it appeared reasonable to infer that it was an aneurysm. IVUS provided overriding evidence to distinguish a ruptured plaque from coronary aneurysm.

It is important to differentiate ulcerative lesions from aneurysms because their clinical significance is totally different. Aneurysms are thought to involve degenerated media, which offer inadequate support [6,7,13]. Although atherosclerosis plays an important role in the formation of coronary aneurysms, no significant differences in plaque area and plaque composition are found between the aneurysmal segment and adjacent proximal and distal vessel segments. IVUS demonstrates that coronary aneurysms often have a large dilated thin-wall segment opposite the eccentric plaque and the medial boundary can be seen surrounding the dilated lumen [6]. Ulceration, in contrast, is found to involve spontaneous plaque rupture with an emptied plaque cavity. In our case, IVUS images showed typical plaque rupture with ulceration formation: a ruptured plaque contained a cavity that communicated with the lumen with an overlying residual fibrous cap fragment. The rupture appeared to have occurred at the shoulder of the fibrous cap. Plaque rupture is usually encountered in the course of acute coronary syndrome. Since the lesions in patients with acute coronary syndrome are often compensatorily dilated, they sometimes resemble aneurysmal formation on angiography [14].

Pathological examinations reveal that ulcerated plaque represents a disruption of the fibrous cap that leads to exposure of the thrombogenic lipid core into the flowing blood. Histologically, this is identified as an irregular plaque surface with a break in or loss of the fibrous cap usually associated with a surface thrombus directly overlying the lipid-rich necrotic core of the lesion [15]. Yamagishi et al. [16] demonstrated a heterogeneous distribution of regional wall distensibility in noncircumferential lesions, with the regional distensibility index at the lesion portion being significantly lower than that at the normal portion. This may result in a mechanical mismatch between the lesion and normal portions, which could be related to the occurrence of the plaque rupture that is frequently found to take place at the edge of the plaque where the fibrous cap is often thinnest [16]. In the present case, the rupture of the fibrous cap occurred at the boundary of the lesion and proximal segment.

Although plaque rupture is now considered to be a major cause of acute coronary syndrome, there is some evidence to support the hypothesis that spontaneous plaque rupture occurs sporadically and does not necessarily lead to occlusion [7,9,17]. In the present case, since the patient was admitted because of heart failure and arrhythmia, angina symptom might be masked. Both ECG and myocardial scintigraphy failed to show any

signs of myocardial ischemia in the region of the left coronary artery. We think it as a silent plaque rupture.

Besides IVUS, other noninvasive diagnostic modalities can be recommended to diagnose ruptured plaque. Recently, multislice CT has been developed rapidly as an accurate method for assessing coronary artery anatomy. Plaque composition could be clearly differentiated and classified by determining tissue density within the lesion. These noninvasive modalities can be used to assess atherosclerotic plaques responsible for early silent disease and may become important tools for early detection and prevention [18].

The present case provides evidence that IVUS can permit a more powerful definition of ulceration than angiography, and the ulceration exhibits significantly different characteristics from an aneurysm on IVUS.

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