Remodeling of In-Stent Neointima, Which Became Thinner and Transparent Over 3 Years
Serial Angiographic and Angioscopic Follow-up

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Background—Recently, it has been reported that the luminal diameter shows phasic changes after stenting: the progression of luminal narrowing followed by its regression. To elucidate the mechanisms involved in the phasic changes in luminal diameter after stenting, we examined the changes in neointimal thickness and the appearance of neointima by a series of angiographic and angioscopic observations for 3 years after stent implantation.

Methods and Results—In 12 patients who received a Wiktor coronary stent, serial angiographic and angioscopic examinations were performed immediately, 2 to 4 weeks, 3 months, 6 months, and 3 years after the stenting without repetition of angioplasty. Neointimal thickness was determined by angiography as the difference between stent and luminal diameters. The angioscopic appearance of neointima over the stent was classified as transparent or nontransparent according to the visibility of the majority of the stent. Neointimal thickness increased significantly at 3 months (0.75 ± 0.32 mm) without further changes at 6 months (0.74 ± 0.32 mm). Thereafter, however, it decreased significantly over 3 years (0.51 ± 0.26 mm). The angioscopic appearance was classified as transparent in 8 patients (100%) immediately after stenting, 6 patients (100%) at 2 to 4 weeks, 2 patients (17%) at 3 months, 2 patients (20%) at 6 months, and 7 patients (58%) at 3 years.

Conclusions—The neointima became thick and nontransparent until 6 months and then became thin and transparent by 3 years. We conclude that neointimal remodeling exists after stenting and plays a major role in the alteration of coronary luminal diameter after stenting. (Circulation. 1998;97:2003-2006.)

Key Words: stents ■ angiography ■ remodeling ■ restenosis ■ imaging

Two randomized trials revealed that coronary stenting reduces the incidence of restenosis after angioplasty. A recent study on the 3-year follow-up after stent implantation reported an increase in luminal diameter in the later phase, although the mechanisms involved in this phenomenon were not clarified. We hypothesized that a thinning of in-stent neointima occurs and increases the luminal diameter in the long-term follow-ups. In the present study, to elucidate the process of neointimal maturation and the mechanism of luminal diameter increase in the long-term follow-up, we observed the neointimal thickness and the appearance of neointima using a series of angiographic and angioscopic examinations for 3 years after the implantation of coronary stents.

Methods

Study Patients
Between April 1992 and June 1993, Wiktor stents (Medtronic) were implanted prospectively and consecutively in 30 patients, 40 to 80 years old (mean, 61 years), 27 male and 3 female, with effort angina.

We previously reported the results of 3-month follow-up of 21 of these patients. The inclusion criteria were (1) coronary artery disease with >75% stenosis, (2) angiographic demonstration of severe elastic recoil or coronary dissection immediately after angioplasty that was thought to cause acute or subacute closure or restenosis after previous angioplasty, and (3) informed consent given for the use of the device and follow-up examinations. The exclusion criteria were (1) left main coronary artery disease, (2) lesions of coronary artery bypass grafts, (3) contraindications to aggressive anticoagulant or antiplatelet therapy, (4) a long coronary dissection that required >2 stents, (5) chronic total occlusion, (6) acute myocardial infarction, and (7) poor cardiac function as defined by left ventricular global ejection fraction <30%. The patients who died or underwent repeated angioplasty before the 3-year follow-up were excluded from analysis in the present study. This study protocol was approved by the Osaka Police Hospital Ethical Committee.

Study Protocol
Serial angiographic and angioscopic examinations were scheduled immediately, 2 to 4 weeks, 3 months, 6 months, and 3 years after stent implantation. The angioscopic observations were made while the blood was cleared away from view by the injection of 3% dextran-40. The images from the angioscope (VFS-1300 or MC-...
800E, Nihon Kohden) were recorded by an S-VHS videotape. We used conventional anticoagulant and antiplatelet therapy throughout the study. Intravenous heparin (200 U/kg body wt), oral aspirin (300 to 330 mg/d), dipyridamole (75 mg/d), and warfarin were administered.

Angiographic and Angioscopic Evaluations
The minimal luminal diameter of the lesion and the stent diameter were measured by hand calipers on pictures in the same view for each patient by 2 cardiologists. Because, with the radiopacity of the Wiktor stent, its diameter and luminal diameter can be measured simultaneously on an angiogram, the neointimal thickness was calculated as the difference between them.6,7 The angioscopic images were reviewed by two specialists. The neointima over the stent was judged to be transparent or nontransparent according to the visibility of the majority of stent. Both transparent neointima and uncovered stent were classified as transparent in this study. The existence of thrombus over the neointima was also evaluated. The two observers independently evaluated 100 pictures, and 10 days later, they reevaluated the same 100 pictures to check the intraobserver and interobserver variabilities. The intraobserver variability was 2% and 3% for each specialist, respectively, and interobserver variability was 5%.

Statistical Analysis
The data from the angiographic measurements are shown as mean±SD. The changes and the differences of these data were analyzed with a one-way ANOVA and Scheffe’s multiple comparison test. A value of P<0.05 was regarded as statistically significant.

Results
Patient Characteristics
Thirty patients were enrolled in this study, but 1 patient died, 2 received angioplasty for acute stent occlusion on the day of stenting, and 6 received angioplasty for the in-stent restenosis within 6 months. No patient required angioplasty after 6 months. In 1 patient, angioscopic examination could not be performed because of the significant stenosis in the left main coronary artery at 3-year follow-up. The catheterization was not performed at 3 years in 8 patients: 2 because of noncardiac diseases and 6 because they refused the examination. The remaining 12 patients (mean age, 59 years; 11 male and 1 female) were analyzed in this study.

Angiographic and Angioscopic Follow-up
Angiographic data (Figure 1) revealed phasic changes in minimal luminal diameter and in neointimal thickness. Minimal luminal diameter decreased at 3 to 6 months but increased at 3 years after the stenting: This time course is associated with the changes in neointimal thickness. No significant change in stent diameter was observed, suggesting that the stent prevented recoil for 3 years.

![Figure 1](http://circ.ahajournals.org/)

**Figure 1.** Serial changes in minimal luminal diameter, stent diameter, and neointimal thickness. Data are mean±SD. *P<0.05 vs immediately after stenting, †P<0.05 vs 6 months after stenting.

Angioscopic images of a representative case are shown in Figure 2. The neointima (Table) was classified as transparent in 8 patients (100%) immediately after stenting, in 6 (100%) at 2 to 4 weeks, 2 (17%) at 3 months, 2 (20%) at 6 months, and 3 years after the stenting. The catheterization was not performed at 3 years in 8 patients: 2 because of noncardiac diseases and 6 because they refused the examination. The remaining 12 patients (mean age, 59 years; 11 male and 1 female) were analyzed in this study.

![Figure 2](http://circ.ahajournals.org/)

**Figure 2.** Representative case of neointimal maturation observed by angioscopy in a 58-year-old man with effort angina. In this case, stent was implanted because a large dissection was recognized after balloon angioplasty in right coronary artery. (a) Proximal end of stent wire immediately after implantation. Uncovered stent wire was observed. This image was classified as transparent. (b) Proximal end of stent wire 2 weeks after implantation. Uncovered stent wire was observed. This image was classified as transparent. (c) Proximal end of stent wire 3 months after implantation. Stent wire, covered by white neointima, was not visible. This image was classified as nontransparent. (d) Proximal end of stent wire 6 months after implantation. Although stent was partially visible, this image was classified as nontransparent. (e) Proximal end of stent wire 3 years after implantation. Stent wire covered by transparent neointima became visible again. This image was classified as transparent.
and 7 (58%) at 3 years. In 2 patients, the neointima was consistently classified as transparent at 3 months, 6 months, and 3 years. In 5 patients, although the neointima was classified as nontransparent at 3 or 6 months, it became transparent at 3 years. Even in 4 patients who were classified as nontransparent at 3 years, the neointima became partially transparent compared with that at 3 or 6 months. The thrombus (Table) was occasionally observed on the stent or neointima in the earlier period after stenting, but no thrombus was observed over the neointima at 3 years in any patient.

### Discussion

The minimal luminal diameter decreased significantly at 3 to 6 months and then increased significantly at 3 years. The decrease in in-stent luminal diameter by 6 months is due to neointimal thickening, as we have previously reported, although the vascular constriction (vascular remodeling) is thought to be a major mechanism of restenosis after balloon angioplasty without stenting. The main mechanisms of in-stent restenosis and in-stent lumen diameter increase may be attributable to the thickening and subsequent thinning of neointima, respectively. The present study is the first to reveal that the increase in the luminal diameter at 3 years is attributable to the thinning of the neointima.

Gradual luminal narrowing after stenting has been thought to be due to intimal hyperplasia in the animal experiments. Schatz et al reported in a dog model that the in-stent neointima became thick and nontransparent in the early phase, with cellular proliferation and matrix production, but became thinner and sclerotic in the later phase, with cell number decrease. The neointimal remodeling defined as the paroxysmal process of hyperplasia (thickening) and cell number decrease (thinning) is detected in animal models of coronary artery injury and is a common observation in the healing process after injury.

The present study revealed that the neointima first became nontransparent with thickening and then became thinner and transparent over 3 years. Thrombus was observed more often in the earlier follow-ups and disappeared completely at 3 years. The finding of thrombus over the neointima in the early follow-up may reflect incomplete anticoagulant activity of the neointima. Thus, the disappearance of thrombus over the neointima may be an indicator of functional neointimal maturation. The neointimal maturation appeared to occur after 3 to 6 months in human coronary arteries. The present results revealed that neointimal remodeling also exists in human coronary arteries after stent implantation. The mechanism of neointimal thinning may be associated with the decrease in cellular components. Isner et al reported that apoptosis is a feature of human vascular pathology in restenotic lesions and suggested that apoptosis may modulate the cellularity of lesions with extensive proliferative activity. Apoptosis in neointima may be involved in the mechanisms of cell number decrease and of neointimal thinning. Although the transparency of neointima may be determined in part by its thickness, it may reflect the histological composition of the neointima.

Our results may support the concept that the amount of luminal narrowing detected at 6 months is not always the final outcome of angioplasty with stents and that it can improve thereafter. Although we often observe lesions with restenosis at 6 months, we may be able to follow them up without reintervention if they do not cause severe myocardial ischemia. Although our findings were based on observations in a relatively small number of patients, it does occur that the neointima regresses naturally, at least in a selected group of patients. Further investigations are necessary to determine in which group of patients this phenomenon commonly occurs. These findings may stimulate research to determine the mechanisms involved in this intimal thinning, with a possible value in limiting stent restenosis.

### References


### Table: Angioscopic Data

| Patient | Immediate | 2–4 wk | 3 mo | 6 mo | 3 y | Immediate | 2–4 wk | 3 mo | 6 mo | 3 y |
|---------|-----------|--------|------|------|----|-----------|--------|------|------|----|---|
| 1       | TP        | TP     | Non-TP | Non-TP | Non-TP | – | + | – | + | – |
| 2       | TP        | TP     | TP    | TP    | TP | – | + | – | – | – |
| 3       | Not seen  | Not done | Non-TP | Non-TP | TP | Not seen | Not done | + | + | – |
| 4       | TP        | TP     | Non-TP | Non-TP | TP | – | + | – | – | – |
| 5       | TP        | TP     | Non-TP | Non-TP | Non-TP | – | + | – | – | – |
| 6       | TP        | Not done | Non-TP | Non-TP | Non-TP | – | Not done | – | – | – |
| 7       | TP        | TP     | Non-TP | Non-TP | TP | – | – | + | + | – |
| 8       | TP        | TP     | Non-TP | Not done | Non-TP | – | + | + | Not done | – |
| 9       | Not seen  | Not done | TP    | TP    | TP | Not seen | Not done | – | – | – |
| 10      | TP        | Not seen | Non-TP | Non-TP | TP | – | Not seen | + | + | – |
| 11      | Not seen  | Not done | Non-TP | Not done | TP | Not seen | Not done | – | Not done | – |
| 12      | Not seen  | Not done | Non-TP | Non-TP | Non-TP | Not done | Not done | + | + | – |

TP indicates transparent type; Non-TP, nontransparent type; and Not seen, angioscopy was performed, but no clear image was acquired.


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