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Long-Term (Three-Year) Outcomes After Stenting of Unprotected Left Main Coronary Artery Stenosis in Patients With Normal Left Ventricular Function

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The purpose of this study was to analyze long-term follow-up information from patients treated with stenting for unprotected left main coronary artery (LMCA) stenosis. Stenting of unprotected LMCA stenosis is often performed in selected patients, but the long-term safety of this therapy is not yet established. Between January 1995 and September 2000, 270 consecutive patients with unprotected LMCA stenosis and normal left ventricular function who underwent treatment at 4 clinical centers were included in this study. Data were forwarded to the coordinating center using a standard case report form. The procedural success rate was 98.9%. There were no deaths, 3 stent thromboses, and 3 Q-wave myocardial infarctions during the hospitalization. Angiographic follow-up was performed in 237 patients (follow-up rate 87.8%), and the restenosis rate was 21.1%. The reference size was an independent predictor of binary restenosis (odds ratio 0.543, 95% confidence interval 0.308 to 0.957, p = 0.03). During the follow-up period (32.3 ± 18.5 months), there were 20 deaths (8 cardiac, 12 noncardiac) and 5 nonfatal myocardial infarctions. Target and new lesion revascularizations were required in 45 (16.7%) and 31 (11.5%) patients, respectively. The cumulative probabilities free from major adverse cardiac events were 81.9 ± 2.4%, 78.4 ± 2.6%, and 77.7 ± 2.7%, respectively, at 1, 2, and 3 years. Combined coronary artery disease and postprocedural minimal luminal diameter were the significant predictors of major adverse cardiac events. Thus, the long-term prognosis of patients after stenting of unprotected LMCA stenosis was favorable in selected patients with normal left ventricular function. ©2003 by Excerpta Medica, Inc.

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Recent progress in techniques and devices makes it possible to expand the use of stents to the treatment of unprotected left main coronary artery (LMCA) stenosis. Several studies have shown that stenting of unprotected LMCA stenosis may be a promising alternative to bypass surgery in selected patients.[1–5] Initially, one of the concerns with this therapy was the potential for stent thrombosis, but this does not appear to be the case, because an increasing number of studies have documented safety and early efficacy.[1–5] However, data are lacking as to the impact of stenting on long-term outcomes in this particular group of patients. Resolution of this issue will further define the role of stenting for treatment of unprotected LMCA stenosis, and provide a rationale for generalization of this therapy. It is known that the time course of restenosis is relatively self-limited after stenting, generally occurring 6 to 12 months after the procedure.[6,7] Clinical events occurring >6 months after stenting in non-LMCA stenosis are usually related to new lesions, and the progression of disease becomes a more likely cause of events at longer follow-up.[8–10] In this study, we tested the hypothesis that: (1) the long-term outcomes after stenting of unprotected LMCA stenosis are favorable, and (2) late coronary events are primarily due to new lesions.

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METHODS

Study population: The Asian Pacific Multicenter Registry for Stenting of Unprotected LMCA Stenosis includes 3 clinical centers and a coordinating center. In September 2001, the coordinating center was founded, and data collection for the Asian Pacific Multicenter registry was begun. The participating hospitals were selected on the basis of recognized experience with percutaneous intervention of unprotected LMCA stenoses. To be eligible for the registry, patients had to present with symptomatic LMCA disease or documented myocardial ischemia and angiographic evidence of ≥50% diameter stenosis of the LMCA suitable for stent placement. Exclusion criteria consisted of contraindications to antiplatelet or anticoagulation therapy and left ventricular dysfunction (ejection fraction <40%). Between January 1995 and September 2000, 270 consecutive patients who underwent stent placement to an unprotected LMCA stenosis were enrolled in the registry.

Data collection and follow-up: Data were reported on a standard case report form, and forwarded to the coordinating center. Baseline clinical and procedural data were collected for all patients. Angiographic analysis was performed using a quantitative angiographic analysis system at each center, and quantitative angiographic data were obtained before predilation, after the stenting procedure, and at follow-up. Clinical information about death, myocardial infarction, repeated revascularization, bypass surgery, and stroke was obtained during clinic visits or telephone interviews. All the patients were followed up for >12 months.

Definitions: Procedural success was defined as a ≤30% residual diameter by quantitative coronary angiography with no major procedural or in-hospital complications (death, Q-wave myocardial infarction, or emergency bypass surgery). A major adverse cardiac event (MACE) was defined as the occurrence of cardiac death, nonfatal myocardial infarction, or target lesion revascularization during follow-up. Deaths were classified as either cardiac or noncardiac. Deaths that could not be classified were considered cardiac. Myocardial infarction was diagnosed when cardiac enzymes (creatine kinase-MB) were elevated more than threefold times normal, with chest pain lasting ≥30 minutes, or with the appearance of new electrocardiographic changes.

Statistical analysis: Data are expressed as mean ± SD for continuous variables, and as frequencies for categorical variables. Survival and MACE-free survival distribution was estimated according to the Kaplan-Meier method. Logistic regression analysis was performed on all variables to identify the predictors of cardiac death, target lesion revascularization, or MACE. Statistical significance was defined as $p < 0.05$.

TABLE 1 Baseline Characteristics (n = 270)

Characteristics	
Age (yrs)	61.3 ± 13.1
Men (%)	182 (67.4%)
Systemic hypertension	100 (37.0%)
Diabetes mellitus	69 (25.6%)
Total cholesterol >200 mg/dl	102 (37.8%)
Current smoker	57 (21.1%)
Prior myocardial infarction	73 (27.0%)
Unstable angina pectoris	133 (49.3%)
Left ventricular ejection fraction (%)	62.7 ± 10.2
Extent of coronary artery disease	
Left main only	187 (69.3%)
Left main and other coronary artery	83 (30.7%)
Lesion locations	
Ostium	113 (41.9%)
Body	57 (21.1%)
Distal	100 (37.0%)
Debulking atherectomy before stenting	52 (19.3%)
Type of stents (n)	
Slotted tube	254 (94.1%)
Coiled design	14 (5.1%)
Hybrid design	2 (0.8%)

TABLE 2 Quantitative Angiographic Data (n = 270)

Characteristics	
Reference artery diameter (mm)	3.9 ± 0.6
Lesion length (mm)	11.2 ± 6.1
MLD (mm)	
Before	1.2 ± 0.5
After	3.7 ± 0.7
Follow-up	2.6 ± 1.0
DS (%)	
Before	71.5 ± 12.9
After	-3.6 ± 12.0
Follow-up	29.6 ± 25.4
Acute gain (mm)	2.97 ± 0.71
Late loss (mm)	1.30 ± 0.98
Loss index	0.45 ± 0.40
Balloon/artery ratio	1.05 ± 0.18
Maximum inflation pressure (atm)	14.6 ± 3.0
Angiographic restenosis rate	21.1%
Ostium	20.4%
Body	18.4%
Distal location	23.3%

DS = diameter stenosis; MLD = minimal lumen diameter.

RESULTS

Baseline characteristics: Clinical characteristics and angiographic data are listed in Tables 1 and 2. One hundred thirteen lesions (41.9%) were located in the ostium of the LMCA, 57 lesions (21.1%) in the body, and 100 lesions (37.0%) in the distal portion. Eighty-three patients (30.7%) had combined coronary artery disease not in the LMCA. The procedural success rate was 98.9%, and 79 patients (29.3%) had therapy for other coronary lesions. There were no in-hospital deaths, but 3 stent thromboses (1.1%), and 3 Q-wave myocardial infarctions (1.1%) occurred. During admission, there were 3 emergency bypass surgeries and 1 repeat coronary intervention. In the remaining patients, the in-hospital clinical outcome was uneventful.

Angiographic follow-up: Angiographic follow-up was performed in 237 patients (follow-up rate 87.8%), and the restenosis rate (≥50% diameter stenosis) was 21.1%. In univariate and multivariate analyses, the reference size was the only independent predictor of binary restenosis (odds ratio [OR] 0.543, 95% confidence interval [CI] 0.308 to 0.957, p = 0.03). Restenosis occurred at the proximal and distal margin of the stents (n = 11) or within the stents (n = 39): focal in-stent restenosis in 19 lesions (49%) and diffuse in-stent restenosis in 20 lesions (51%).

Long-term outcome: The medication profile during the follow-up period is outlined in Table 3. In all, 20 patients (7.4%) died during the follow-up period of 32.3 ± 18.5 months (Table 4); 8 of these 20 patients (40%) died of cardiac causes. Noncardiac deaths were due to carcinoma (n = 5), pneumonia (n = 3), stroke (n = 2), sepsis (n = 1), and acute renal failure(n = 1). Age, diabetes mellitus, other combined coronary arterial disease, and postprocedural minimal luminal diameter were validated as univariate determinants of

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TABLE 3 Use of Antianginal Medications (n = 270)	
Aspirin	262 (97.3%)
β blocker	99 (36.7%)
Calcium antagonist	185 (68.5%)
Nitrate	150 (55.6%)
ACE inhibitor	29 (10.7%)
Lipid-lowering agent	50 (18.5%)

ACE = angiotensin-converting enzyme.

TABLE 4 Major Adverse Cardiac Events (MACE) During Follow-up (n = 270)	
Cardiac events	
Death	20 (7.4%)
Cardiac	8
Noncardiac	12
Nonfatal myocardial infarction	5 (1.9%)
Repeat revascularization	
Target lesion revascularization	45 (16.7%)
New lesion revascularization	31 (11.5%)
MACE*	59 (21.9%)

*Death, myocardial infarction, and target lesion revascularization.

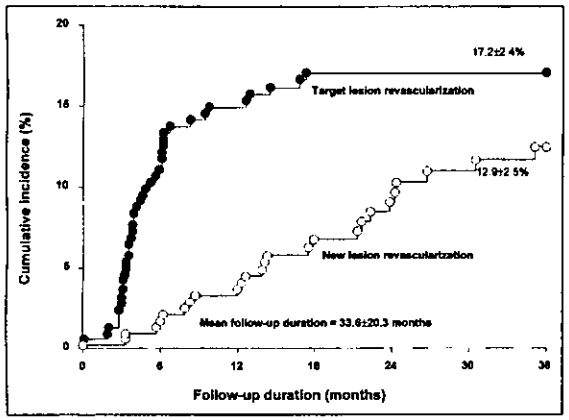

FIGURE 1. Kaplan-Meier analysis of the incidence of repeat revascularization.

survival during follow-up. In multivariate analysis, however, age (OR 1.109, 95% CI 1.054 to 1.116, p <0.001) and other combined coronary arterial disease (OR 2.982, 95% CI 1.143 to 7.779, p = 0.026) were significant predictors of survival.

There were 5 nonfatal myocardial infarctions (1.9%), and 45 repeat revascularizations of the LMCA restenosis (16.7%): repeat interventions (26 patients) and bypass surgery (20 patients). Thirty-one patients (11.5%) required percutaneous interventions of a nontarget vessel during follow-up. Most target lesion revascularization events occurred within 6 months and reached a plateau thereafter, whereas nontarget lesion revascularization increased beyond 6 months after stenting (Figure 1). The survival rate was 95.4 ± 1.3%, 93.6 ± 1.6%, and 92.1 ± 1.9% at 1, 2, and 3 years, respectively (Figure 2). The cumulative probability of MACE-free survival was 81.9 ± 2.4%, 78.4 ± 2.6%, and 77.7 ± 2.7% at 1, 2, and 3 years, respectively, with few late target lesion revascularizations after 9 months. Table 5 lists the univariate and multivariate determinants of a MACE during follow-up. In multivariate analysis, other combined coronary arterial disease (OR 1.812, 95% CI 1.060 to 3.080, p = 0.028) and postprocedural minimal luminal diameter (OR 0.493, 95% CI 0.337 to 0.723, p <0.001) were the significant predictors of a MACE.

DISCUSSION

This study demonstrates that: (1) the overall long-term survival after stenting of unprotected LMCA stenosis was good; (2) target lesion revascularization remained a significant problem; (3) combined coronary arterial disease and postprocedural minimal luminal diameter were the important predictors of a MACE; and (4) late coronary events were primarily due to new lesions. These results indicate that the clinical course after stenting of unprotected LMCA stenosis is similar to that of non-LMCA intervention, and provides a rationale for this strategy.

Procedural safety: An increased risk of early death was initially reported in patients who underwent balloon angioplasty for unprotected LMCA stenosis, primarily due to a high incidence of acute closure.[11–13] However, the outcomes associated with percutaneous coronary intervention have improved dramatically with the introduction of stents and glycoprotein IIb/IIIa inhibitors. Coronary stents eliminate the risk of acute recoil, and make LMCA disease an attractive area for angioplasty because of its larger caliber and short lesion length. Furthermore, the incidence of stent thrombosis is now approximately 1% with use of high-pressure balloon dilation and potent antiplatelet agents.[14] Traditionally, early mortality after bypass surgery in patients with LMCA involvement is about 2% to 3%.[15] In the present study, 30-day mortality after stenting of unprotected LMCA stenosis did not occur, supporting consideration of this therapy as an alternative to bypass surgery in selected patients. However, extra caution may be warranted for patients with impaired left ventricular function and unstable symptoms for whom bypass surgery should be considered the standard treatment.[16]

In-stent restenosis: Restenosis remains a significant problem after stenting of unprotected LMCA stenosis. In this study, the angiographic restenosis rate was 21.1%, and seemed to be rather high despite the larger

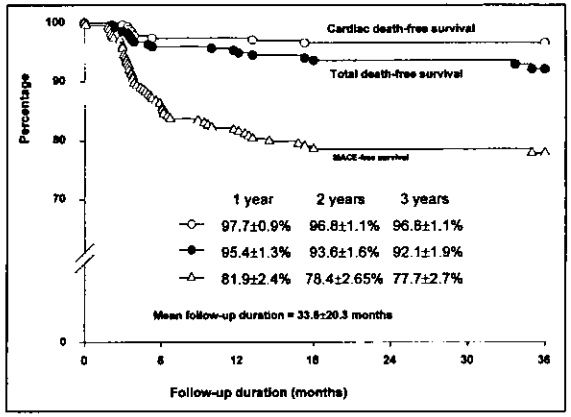

FIGURE 2. Cumulative probability of survival free from cardiac death, total death, and MACEs.

TABLE 5 Correlates of Major Adverse Cardiac Events			
Variables	OR	95% CI	p Value
Univariate predictor			
Age	1.028	1.007–1.049	0.007
Diabetes mellitus	1.533	0.886–2.654	0.127
Reference size	0.491	0.317–0.760	0.001
Combined CAD	1.828	1.090–3.065	0.022
Post-MLD	0.494	0.338–0.720	<0.001
Multivariate predictor			
Combined CAD	1.812	1.066–3.080	<0.001
Post-MLD	0.493	0.337–0.723	0.028

CAD = coronary artery disease; Post-MLD = postprocedural minimal luminal diameter.

final lumen dimension. Recently, drug-eluting stents have been reported to be promising in preventing in-stent restenosis.[17,18] In the future, this therapy may be used to reduce the incidence of restenosis for patients with unprotected LMCA stenosis. In general, bypass surgery is recommended for treatment of in-stent restenosis, and in-stent restenosis in this group does not interfere with subsequent bypass procedures. However, a substantial number of patients (57% of those with target lesion revascularizations) underwent repeat intervention because of the patients' preference.

Long-term outcomes: The long-term efficacy of this technique in the treatment of non-LMCA stenosis has become clearly established. Several studies have shown that the medium-term prognosis of patients after unprotected LMCA stenting is good in low-risk groups. However, most studies may have been limited by small sample sizes and medium-term follow-up. In the present study, the cumulative MACE-free survival rates were 81.9 ± 2.4%, 78.4 ± 2.6%, and 77.7 ± 2.7% at 1, 2, and 3 years, respectively (Figure 2). Target lesion revascularization was usually required within 6 months after stenting, and thereafter repeat revascularization was primarily due to new lesions (Figure 1). After 6 months, cardiac deaths or target lesion revascularizations were rare, indicating that long-term outcomes may be excellent after stenting of unprotected LMCA stenoses in selected patients. This result is consistent with previously published data showing that stented lesions are clinically stable 6 months after revascularization.[6,7] It is well established that bypass surgery is the standard treatment modality for treatment of LMCA disease, which lessens symptoms and significantly prolongs survival compared with patients treated medically. Until now, no data were available for comparison of the risks and benefits of elective stenting and bypass surgery, which requires further studies. As shown in non-LMCA disease, elderly patients who have multivessel diseases may be at particular risk of higher mortality rates after the index procedure. This may be explained by more extensive coronary artery disease, with possibly less complete revascularization in this group of patients. However, it remains uncertain as to whether bypass surgery should be recommended for these patients.

Study limitations: First, our findings may not be generalized to the entire range of unprotected LMCA stenoses because selected patients were included in this study. Second, angiographic data were not analyzed by a core laboratory. Third, the data could be biased due to selection of interventional cardiologists with prior recognized experience with LMCA stenting.

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Functional variation in *LGALS2* confers risk of myocardial infarction and regulates lymphotoxin-α secretion *in vitro*

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Myocardial infarction (MI) has become one of the leading causes of death in the world. Its pathogenesis includes chronic formation of plaque inside the vessel wall of the coronary artery and acute rupture of the artery, implicating a number of inflammation-mediating molecules, such as the cytokine lymphotoxin-α (LTA)[1]. Functional variations in *LTA* are associated with susceptibility to MI[2]. Here we show that LTA protein binds to galectin-2, a member of the galactose-binding lectin family[3]. Our case–control association study in a Japanese population showed that a single nucleotide polymorphism in *LGALS2* encoding galectin-2 is significantly associated with susceptibility to MI. This genetic substitution affects the transcriptional level of galectin-2 *in vitro*, potentially leading to altered secretion of LTA, which would then affect the degree of inflammation; however, its relevance to other populations remains to be clarified. Smooth muscle cells and macrophages in the human atherosclerotic lesions expressed both galectin-2 and LTA. Our findings thus suggest a link between the LTA cascade and the pathogenesis of MI.

To understand better the role of LTA in the pathogenesis of this disease, we searched for proteins that interact with LTA. Using the *Escherichia coli* two-hybrid system and the phage display method, we identified galectin-2 as a binding partner of LTA. We purified the two recombinant proteins using a bacterial expression system, and confirmed direct binding of galectin-2 to LTA using an *in vitro* binding assay (Fig. 1a). We further examined their interaction in mammalian cells using constructs designed to express Flag-tagged LTA or S-tagged galectin-2 and western blot analysis; co-immunoprecipitation of galectin-2 and LTA confirmed their interaction (Fig. 1b). Using antibodies specific to each protein, we also investigated subcellular localization of native galectin-2 and LTA in U937 cells, and found that these proteins co-localized in the cytoplasm (Fig. 1c).

We then examined whether any genetic variation in *LGALS2* was associated with susceptibility to MI. Re-sequencing the *LGALS2* genomic region using DNA from 32 MI samples revealed 17 additional single nucleotide polymorphisms (SNPs) (Fig. 2a). Next, we compared the genotype frequencies of approximately 600 individuals with MI, and 600 controls at these SNP loci, and found that one SNP (3279C → T) in intron-1 of *LGALS2* was significantly associated with MI (designated SNP9 in Supplementary Table 1). This association was confirmed by increasing the number of samples to 2,302 for patients with MI and 2,038 for controls, and by including another set of samples (Table 1 and Supplementary Table 2).

We also analysed linkage disequilibrium using a subset of markers with minor allele frequency of >0.20, and investigated haplotype structure within the *LGALS2* region (Supplementary Table 3). This allowed us to identify a haplotype block containing three SNPs (SNP9, SNP10 and SNP11); no particular haplotype showed a higher statistical significance for association with MI than the single SNP alone (Supplementary Table 4). Because the minor allele frequency of the associated SNP was lower in the patients' group (Table 1), we concluded from these genetic studies that the minor variant protects against the risk of MI, although our study included only Japanese subjects and so its relevance to other populations remains to be clarified.

To investigate the biological significance of this genetic variation in intron-1 of *LGALS2*, we constructed reporter plasmids with a genomic fragment containing the SNP downstream of a luciferase gene and the SV40 enhancer sequence, and examined the effect of the intron-1 SNP on gene expression. The clone containing the 3279T allele showed nearly 50% less transcriptional activity than those containing the 3279C allele or the vector alone (Fig. 2b, c). These observations indicated that the nucleotide substitution could potentially reduce the level of the galectin-2 transcript.

We then hypothesized that the amount of intracellular galectin-2 might regulate the extracellular secretion level of LTA, thereby influencing the degree of inflammation. To test this hypothesis, we examined the effect of the level of galectin-2 on the secreted level of LTA in the medium by repressing galectin-2 expression using a small interference (si)RNA technique, and by over-expressing

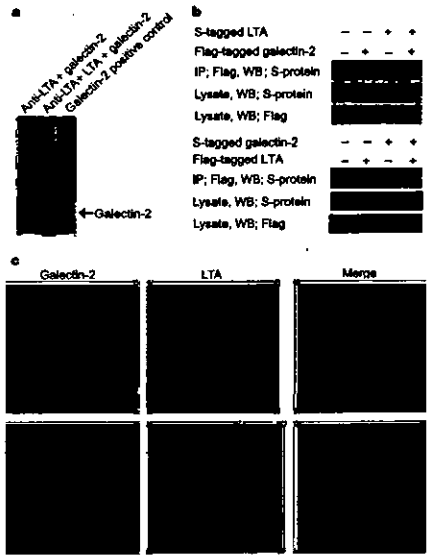

Figure 1 LTA binds to galectin-2. a, *In vitro* binding assay. b, Co-immunoprecipitation of tagged LTA and galectin-2 in COS7 cells. c, Co-localization of endogenous LTA with galectin-2 in U937 cells (top row) with enlarged images of representative cells in the upper panels (bottom row). IP, immunoprecipitation; WB, western blot.

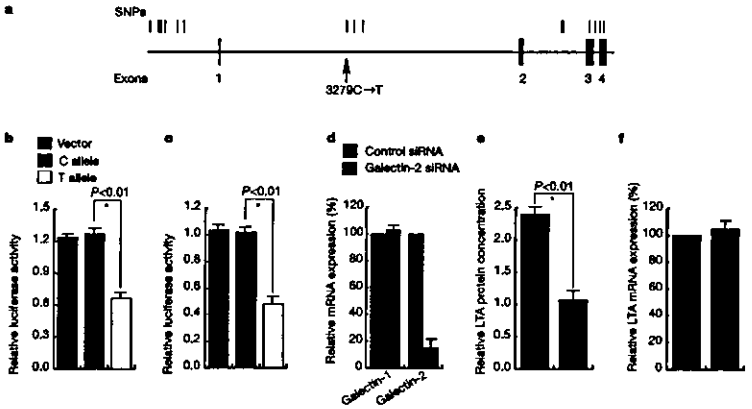

Figure 2 Association of a SNP in *LGALS2* with myocardial infarction and its functionality. a, Map of SNPs in *LGALS2* locus. b, c, Transcriptional regulatory activity of intron-1 SNP of *LGALS2* in HeLa (b) and HepG2 (c) cells. d–f, Inhibition of galectin-2 expression. Levels of galectin-1 or galectin-2 mRNA (d), supernatant LTA protein (e), and LTA mRNA (f) after 48 h transfection with siRNA vectors. *Student's *t*-test. Each experiment was repeated three times and each sample was studied in triplicate.

galectin-2. One siRNA for galectin-2 repressed galectin-2 messenger RNA to nearly one-fifth of its original level (Fig. 2d) and resulted in inhibition of LTA secretion into the medium (Fig. 2e). Over-expression of galectin-2 enhanced LTA secretion (Supplementary Fig. 1a). As shown in Fig. 2f, the LTA mRNA level was unchanged by knockdown or over-expression of galectin-2 (see also Supplementary Fig. 1b).

To further investigate the regulatory mechanism of LTA secretion by galectin-2, we searched for intracellular molecules that associate with galectin-2, using a tandem affinity purification (TAP) system[4]. We identified two unique bands that could be observed only when the galectin-2-TAP tag was expressed (Fig. 3a). On the basis of a MALDI/TOF (matrix-assisted laser desorption/ionization–time of flight) mass spectrometry analysis, these two bands were shown to correspond to α- and β-tubulins—important components of microtubules. Using HeLa cells transfected with a plasmid to express Flag-tagged galectin-2, we confirmed co-immunoprecipitation of endogenous tubulins and galactin-2 (Fig. 3b and data not shown). Interestingly, the tubulins were also co-immunoprecipitated with LTA (Fig. 3b and data not shown). Images from serial confocal sections of double-immunostained U937 cells revealed that galectin-2 and α-tubulin co-localized as reticular filamentous networks developed in the cytoplasm (Fig. 3c). Recently, microtubule cytoskeleton networks have been implicated in the subcellular transport of some proteins, including glucose transporter isoform (GLUT4) or thiamine transporter (THTR1)[5,6]. It is likely that LTA is another molecule that uses the microtubule cytoskeleton network for translocation. It is also conceivable that galectin-2 has a role in intracellular trafficking, although the precise role of galectin-2 in this trafficking machinery complex has yet to be elucidated.

To examine whether these proteins are expressed in the lesion of MI—that is, in atherosclerotic lesions of the coronary artery—and if so, to investigate in which part of the lesion they are expressed, we performed immunohistochemical staining of human coronary atherectomy specimens with anti-LTA or anti-galectin-2 antibody. As shown in Fig. 4a, b, immunoreactivities for both LTA and galectin-2 were detected in intimal cells in atherosclerotic plaques, some of which were spindle-shaped or contained vacuolated, round cytoplasms. Immunostaining of adjacent sections with anti-smooth muscle cell (SMC) α-actin or anti-CD68 showed that the majority of these cells were either SMCs or SMC-derived foam cells, with

Table 1 Association between MI and intron-1 SNP in *LGALS2*

Genotype	Number of patients with MI	Number of patients with MI (%)	Number of controls	Number of controls (%)
LGALS2 intron-1 3279C → T				
CC	1,077	46.8	856	42.0
CT	1,014	44.0	903	44.3
TT	211	9.2	279	13.7
Total	2,302	100.0	2,038	100.0
	χ^2	*P* value	Odds ratio	95% CI
Genotype frequency	26.2	0.0000034		
Allele frequency	21.1	0.0000045	1.23	1.13–1.35
CC versus others	10.0	0.0016	1.21	1.08–1.37
TT versus others	22.1	0.0000026	1.57	1.30–1.90

Nucleotide numbering is according to the mutation nomenclature[16]. CI, confidence interval.

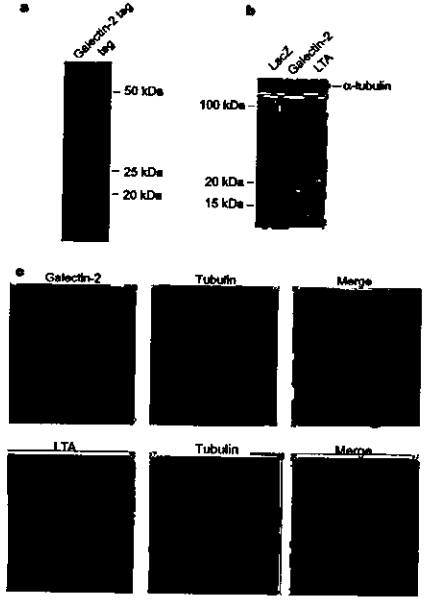

Figure 3 Galectin-2 interacts with microtubules. **a**, Isolation of TAP-tagged galectin-2 and interacting proteins. Arrowheads indicate α- and β-tubulins, revealed by MALDI/TOF mass spectrometry analyses. **b**, Co-immunoprecipitation of endogenous α-tubulin with Flag-tagged galectin-2 or LTA. Immunoprecipitations were done using anti-Flag M2 agarose, and immunoprecipitates were detected using anti-α-tubulin antibody (upper panel) or anti-Flag antibody (lower panel). Flag-tagged LacZ encoding β-galactosidase was used as a negative control. **c**, Co-localization of endogenous α-tubulin with endogenous galectin-2 or LTA in U937 cells.

occasional macrophages being observed (Fig. 4c, d and Supplementary Fig. 2). Co-expression of LTA and galectin-2 was also observed in the majority of polymorphic SMCs by double-labelled immunohistochemistry (Fig. 4e). In contrast, expression of either protein was not detectable in atrophic SMCs of fibrous plaques with scanty cellularity or in normal medial SMCs (Fig. 4f for LTA; data not shown for galectin-2).

These results showed that LTA and galectin-2 were co-expressed in SMCs and macrophages in the intima of human atherosclerotic plaques, but were absent in quiescent or normal medial SMCs. We also confirmed their co-expression by counting immunohistochemically double-labelled cells (Supplementary Table 5). A recent report also indicated that LTA was expressed in atherosclerotic lesions in mice and that loss of LTA reduced the size of the lesions[7]. Together, these results indicate that LTA, as one of the mediators of inflammation, along with galectin-2, as a regulator of LTA secretion, might have roles in the pathogenesis of MI, although the functional correlation of galectin-2 and LTA with the development, progression or rupture of atherosclerotic plaques has yet to be clarified.

We have identified galectin-2 as another risk factor for MI. We believe that the results of this study provide an anchoring point for better understanding of the pathogenesis of MI. □

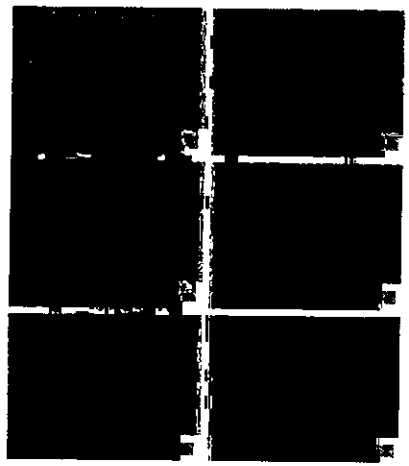

Figure 4 Expression and co-localization of galectin-2 and LTA in the coronary atherectomy specimen. Single-labelled immunohistochemistry of serial sections of primary atherosclerotic lesions from human coronary arteries obtained by directional coronary atherectomy, stained with anti-human LTA (**a**), anti-human galectin-2 (**b**), monoclonal anti-SMC α-actin (**c**), and monoclonal anti-CD68 (**d**). Magnification, ×100. **e**, Double-labelled immunohistochemical staining with anti-LTA (brown) and galectin-2 (blue) antibodies. Magnification, ×119. **f**, Single-labelled immunohistochemical staining with anti-human LTA for atrophic SMCs of fibrous plaques with scanty cellularity and normal medial SMCs. Magnification, ×100.

Methods

DNA samples

The study included 2,638 Japanese patients with MI, referred to as the Osaka Acute Coronary Insufficiency Study (OACIS) group. The diagnosis of definite MI has been described previously[8]. The control subjects consisted of 2,499 general populations recruited through several medical institutes in Japan. All subjects were Japanese and gave written informed consent to participation in the study; or if they were under 20 years old, their parents gave consent according to the process approved by the Ethical Committee at the SNP Research Center, The Institute of Physical and Chemical Research (RIKEN), Yokohama.

SNP analysis

Design for polymerase chain reaction (PCR) primers, PCR experiments, DNA extraction, DNA sequencing, SNP discovery, genotyping of SNPs and statistical analysis has been described previously[8–10].

E. coli two-hybrid and phage display screening

We constructed a two-hybrid complementary DNA (cDNA) library using mRNA isolated from Jurkat cells (RIKEN Cell Bank; RCB0806) and BacterioMatch two-hybrid system library construction kit (Clontech), and screened the library using pBT-human LTA as the 'bait'. For the phage display system, we constructed a phage display cDNA library using mRNA isolated from Jurkat cells and T7 select cDNA cloning system (Novagen). We screened the library using the immobilized LTA as the 'bait'.

Tandem affinity purification

The tandem affinity purification procedure was carried out essentially as described in ref. 4, with some modifications. We constructed a fusion cassette encoding a His tag, a TEV cleavage site, and an S tag as a TAP tag sequence in pCMV–Myc vector (Sigma). This TAP vector expresses amino-terminal Myc-tagged target protein with carboxy-terminal TAP tags in mammalian cells under the control of cytomegalovirus promoter. The TAP vector was transiently transfected into HeLa cells (Health Science Research Resources Bank (HSRRB); JCRB9004). Target protein bands were analysed by MALDI/TOF mass spectrometry at APRO Life Science.

In vitro binding assay and co-immunoprecipitation experiment

We prepared purified S-tagged recombinant LTA and T7-tagged galectin-2 derived from *E. coli* using the pET system (Novagen), and combined them. The co-immunoprecipitation experiments were performed using a monoclonal antibody against LTA (R&D Systems) coupled to HiTrapTM NHS-activated Sepharose HP (Amersham). We visualized the immune complex using T7 tag antibody (Stratagene) and horseradish peroxidase (HRP) conjugated with anti-mouse IgG antibody. For co-immunoprecipitation in mammalian cells, we transfected expression plasmids of Flag or S-tagged LTA, galectin-2 and LacZ (as a negative control) into COS7 cells (HSRRB; JCRB9127) or HeLa cells using Fugene. Immunoprecipitations were done in lysis buffer (20 mM Tris pH 7.5, with 150 mM NaCl, 0.1 % Nonident P-40). Twenty-four hours after transfection, cells were lysed, and immunoprecipitations were performed using anti-Flag tag M2 agarose (Sigma). We visualized the immune complex using HRP-conjugated S-protein (Novagen), anti-Flag M2 peroxidase conjugate (Sigma) or mouse monoclonal antibody against human α-tubulin (Molecular Probes) and HRP-conjugated anti-mouse IgG antibody.

Confocal microscopy

Polyclonal anti-human galectin-2 antisera were raised in rabbits using recombinant protein synthesized in *E. coli*. The antisera showed no cross-reactivity to structurally related molecules galectin-1 and galectin-3, analysed by western blot. Polyclonal anti-galectin-2 antisera and either goat anti-human LTA IgG (R&D Systems) or mouse anti-human α-tubulin monoclonal IgM antibodies were used with Alexa secondary antibodies (Molecular Probes). U937 cells (HSRRB; JCRB9021) were stimulated for 30 min with phorbol myristate acetate (PMA) (20 ng ml^{-1}) and fixed. They were subsequently incubated with the corresponding primary antibodies in phosphate-buffered saline containing 3% bovine serum albumin, and the corresponding Alexa secondary antibodies.

siRNA and over-expression experiments

The target sequences for galectin-2 (5′-AATCCACCATTGTCTGCAACT-3′) were cloned into pSilencer 2.0-U6 siRNA vector (Ambion). For the over-expression experiment, the galectin-2 was cloned into pFlag-CMV5a vector. After transfection, Jurkat cells were stimulated with PMA (20 ng ml^{-1}) for 24 h, and cells and supernatants were collected separately. LTA concentration was measured using an LTA-specific ELISA system (R&D Systems), and normalized by comparison with total protein concentration. The mRNA quantification procedure has been described previously[3].

Luciferase assay

A DNA fragment, corresponding to nucleotides 3,188 to 3,404 of intron-1 of *LGALS2*, was cloned into pGL3–enhancer vector (Promega) in the downstream of SV40 enhancer in the 5′ to 3′ orientation. After 24 h transfection, luciferase activity was measured using the Dual-Luciferase Reporter Assay System (Promega).

Immunohistochemistry

Tissue samples were obtained from 16 patients with MI by elective directional coronary atherectomy. Immunohistochemical protocols were carried out as described previously[1,11] using goat anti-human LTA IgG (R&D Systems) and rabbit polyclonal anti-human galectin-2 antibody. Staining of adjacent sections was carried out using human-cell-type-specific monoclonal antibodies against SMC 2-actin and CD68 (DAKO). For double-labelled immunohistochemistry, sections were incubated with anti-LTA antibody, then with biotinylated swine anti-goat IgG, and then with avidin–biotin–peroxidase conjugate, followed by visualization with 3,3′-diaminobenzidine tetrahydrochloride (Vector Labs). The section was subsequently incubated with rabbit polyclonal anti-human galectin-2 antibody, followed by incubation with alkaline phosphatase–conjugated swine anti-rabbit IgG and visualized with the 5-bromo-4-chloro-3-indoxyl phosphate and nitro-blue tetrazolium chloride (BCIP/NBT) substrate system.

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Differential modulation of endotoxin responsiveness by human caspase-12 polymorphisms

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Caspases mediate essential key proteolytic events in inflammatory cascades and the apoptotic cell death pathway. Human caspases functionally segregate into two distinct subfamilies: those involved in cytokine maturation (caspase-1, -4 and -5) and those involved in cellular apoptosis (caspase-2, -3, -6, -7, -8, -9 and -10)[1,2]. Although caspase-12 is phylogenetically related to the cytokine maturation caspases, in mice it has been proposed as a mediator of apoptosis induced by endoplasmic reticulum stress including amyloid-β cytotoxicity, suggesting that it might contribute to the pathogenesis of Alzheimer's disease[3]. Here we show that a single nucleotide polymorphism in caspase-12 in humans results in the synthesis of either a truncated protein (Csp12-S) or a full-length caspase proenzyme (Csp12-L). The read-through single nucleotide polymorphism encoding Csp12-L is confined to populations of African descent and confers hypo-responsiveness to lipopolysaccharide-stimulated cytokine production in *ex vivo* whole blood, but has no significant effect on apoptotic sensitivity. In a preliminary study, we find that the frequency of the Csp12-L

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Pathological analyses of long-term intracoronary Palmaz–Schatz stenting Is its efficacy permanent?

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Abstract

Background: Angiographic regression of luminal narrowing occurs 6 months to 3 years poststenting. However, after 4 years lesions progressed gradually and late restenosis was observed in 28% of 179 Palmaz–Schatz-stented lesions during the past 10 years. Elucidating its pathogenesis is pivotal to developing preventive strategies. **Methods and Results:** Histopathological and immunohistochemical studies were performed in 19 stented coronary arteries obtained from 19 patients autopsied after noncardiac death 2–7 years poststenting. The quality/severity of chronic inflammatory cells (T lymphocytes, macrophages and multinucleated giant cells) infiltration around the stent struts that is observed even in the absence of restenosis depended on the time elapsed from stenting: a) 2 years postprocedure, in spite of angiographic regression during the first year and pathologically expressed as maturation of the neointimal scar, there was chronic inflammatory response evidence: neovascularization and lymphocyte infiltration; b) ≧ 3 years: the neointimal smooth muscle cells were sparse with abundant proliferation of collagen fibers. Presence of slight helper/inducer T lymphocytes and mild macrophage infiltration around the stent struts was evident immunohistochemically; c) ≧ 4 years: prominent infiltration by lipid-laden macrophages with strong collagen-degrading matrix metalloproteinase immunoreactivity was observed around the struts. In two of these arteries, the surface contacting the stent was focally disrupted and covered by nonocclusive mural thrombi. **Conclusions:** Stainless steel stents evoke a remarkable foreign-body inflammatory reaction to the metal. These persistent peri-strut chronic inflammatory cells may accelerate new indolent atherosclerotic changes and consequent plaque vulnerability. © 2004 Elsevier Inc. All rights reserved.

Keywords: Stents; Inflammation; Atherosclerosis; Pathology

1. Introduction

Intracoronary stenting is effective in reducing clinical and angiographic restenosis after balloon coronary angioplasty [1,2] and has become the mainstay of cardiological interventional treatment of ischemic heart disease.

Stenting of single-vessel coronary disease with the Palmaz–Schatz stent has been reported to provide clinical stability and favorable outcome without particular long-term stent-related complications for as long as 9 [3] or even 10 years [4], and hence assumed to be patent, free of alterations.

However, to date there are no unequivocal pathologic data supporting such assumption, and definitive evidence is as yet nonexistent. Late migration of the stent, metal fatigue, endarteritis and late restenosis have been proposed but not proven as potential late clinical complications of coronary stent implantation [5].

Previously, we had reported that angiographic regression of the stented lumen narrowing occurred between 6 months and 3 years after Palmaz–Schatz stenting [6]. However, after 4 years or more lesions progressed gradually to relevant late restenosis (28% of 179 Palmaz–Schatz stented lesions), in 11 or slightly more than one fifth being extremely severe or resulting in total occlusion within the past 10 years [7]. This prompted us to look deeper into the phenomena. Coronary artery specimens from necropsied patients expiring from noncardiac death 2 to 7 years after stenting were subjected to detailed histopathological and immunohistochemical studies.

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Table 1
Dominant histology after Palmaz–Schatz stenting

Poststenting (years)	SMCs	ECs	Neovascularization	T cells	Mϕ	Foamy cells	MMPs
2–3	+	+	+	+	±	±	±
3–4	±	+	+	±	+	+	+
>4	± to −	+	+	±	+	++	++

Abbreviations: ECs = endothelial cells; MMPs = matrix metalloproteinases; Mϕ: macrophages; SMCs = smooth muscle cells; T cells = T lymphocytes. +, positive; ++, strongly positive; ±, weakly positive; −, negative.

2. Methods

2.1. Study patients

Nineteen hearts obtained from patients (11 men and 8 women, mean age 77±10 years) who had been stented for stable angina and died from noncardiac reasons were studied. Hyperlipidemia was present in 4 who were controlled by diet only, none received statin postangioplasty, hypertension in 5, diabetes mellitus in 4, and no risk factors in the remaining 6. None had autoimmune diseases involving systemic vasculitis, such as polyarteritis nodosa or Takayasu's disease. All 19 native coronary artery lesions had been implanted with only one type of stent, the Palmaz–Schatz stent: 1 in the left main, 9 in the left anterior descending, 3 in the left circumflex, and 6 in the right coronary. All were given at least aspirin or aspirin and ticlopidine if tolerated. None had shown restenosis at 6 months and 1-year serial follow-up angiography. The interval between coronary stenting and death was distributed as follows: 2–3 years, 9 lesions; 3–4 years, 4 lesions; 4–5 years, 3 lesions; >5 years, 3 lesions. Four patients died of pneumonia; 4 of renal failure; 3 of cerebral infarction and/or hemorrhage; 3 of cancer (2 stomachs and 1 lung); 1 each of liver cirrhosis, ischemic colitis, acute pulmonary embolism; and 2 of sudden death (rupture of abdominal aneurysm and status asthmaticus). No patient had evidence of systemic inflammatory state, that is, generalized sepsis prior to death.

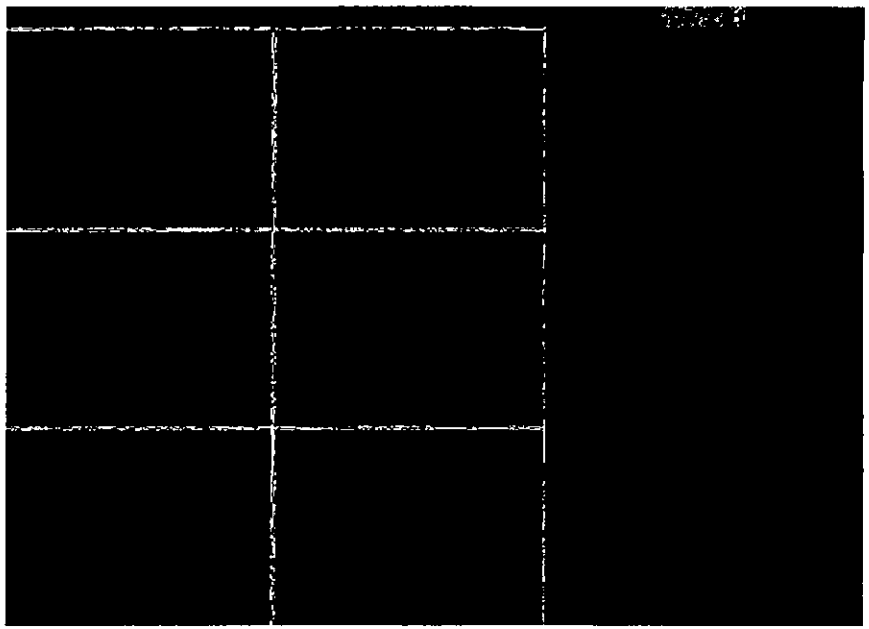

Fig. 1. Note the angiographic regressive changes of the LAD stented segment (arrows) over 2 years; the right lower corner figures denote MLD of the stented portion. Abbreviations: LAD, left anterior descending coronary artery; MLD, minimal luminal diameter. Right panels: macroscopic appearance of the specimen harvested 2 years 5 months after stenting showed only minimal neointimal formation.

2.2. Procedures

All hearts were fixed in 10% buffered formalin. The stent containing coronary segments, identified by comparing the angiograms with the heart specimens, were dissected using a scalpel blade, and cut longitudinally with fine wire cutters. The vessels were transversely sectioned serially at intervals of 2 mm. The metal stent wires were removed by careful pulling under a dissecting microscope with a pair of watchmaker's forceps. Each 2-mm coronary slab was routinely processed and embedded in paraffin. Ten serial 5-μm-thick slices from each slab were mounted; 3 slices were stained, one each with hematoxylin and eosin, Masson's trichrome and Weigert's elastic van Gieson's stain, respectively, and the remaining 7 were used for immunohistochemical staining.

Standard immunohistochemical staining with antibodies against matrix metalloproteinases (MMPs) (Novocastra Laboratories, Newcastle, UK), von Willebrand factor (vWF) (Dako Japan, Kyoto, Japan), thrombomodulin (TM) (Dako), and cluster of differentiation CD3, CD4, CD20 and CD68 (Dako) were performed. Details of the staining procedures have been previously reported [8].

3. Results

The time-dependent pathologic features were semiquantitatively assessed and summarized in Table 1. Grossly, all specimens showed only evidence of mild nonsignificant stenosis. But importantly, the microscopic inflammation severity was generally time dependent irrespective of the age, gender of patients, presence or absence of hypertension, hyperlipidemia or diabetes, and were unrelated to the underlying nature of the plaque (fibrous or atheromatous plaque).

In arteries that had been stented for 2–3 years, angiopraphically characterized by lesion regression, typically the luminal surface of the stent was covered completely by the regenerated mature endothelium composed of ordered, spindle-shaped, smooth muscle cells, the intercellular spaces containing dense collagenous tissue. In addition, apparent chronic inflammatory cell infiltration (mostly T lymphocytes, occasional macrophages and multinucleated giant cells) and neovascularization was recognizable around the struts (Figs. 1, 2 and 3).

In the neointima of arteries that had been stented for more than 3 years the smooth muscle cells were atrophic and sparse, with abundant proliferation of collagen fibers. Immunohistochemically, there was persistent infiltration with helper/inducer T lymphocytes in similar degree to but more foamy macrophages around the stent struts than the specimens at 2 years poststenting (Figs. 4 and 5). Accumulation of these reactive inflammatory cells was limited to the area in contact with the stent and not found in vessel segments proximal or distal to the stent, including junctional areas.

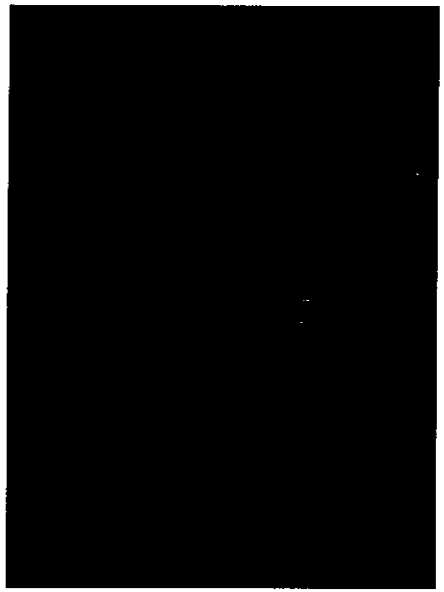

Fig. 2. Micrographs: (a) Hematoxylin–eosin stain; note the spindle-shaped smooth muscle cells ordered along the luminal surface; arrows indicate neovascularization and lymphocyte infiltration, and arrowhead points multinucleated giant cell. (b) Masson's trichrome stain: abundant collagen fibers in the intercellular space; the luminal surface of the neointima is lined by endothelial cells (arrowheads).

In arteries that had been stented for more than 4 years, prominent infiltration by lipid-laden macrophages around the struts was typical (Fig. 6). There was collagen-degrading MMP immunoreactivity within and around these foamy macrophages (Fig. 7). In two of these arteries, the luminal surface where the Palmaz–Schatz stent had been in contact was focally disrupted and covered by nonocclusive mural thrombi (Fig. 8).

No B lymphocytes with immunoreactivity to CD20 were observed in any sample regardless of the time elapsed between stenting and the histopathological study.

4. Discussion

The long-term clinical outcome after Palmaz–Schatz stenting is reportedly favorable without any particular stent-related complications [3,4]. However, the possibility of late deterioration has been entertained, and accelerated atherosclerosis, metal corrosion and endothelial dysfunction have been postulated to explain it [5], but to the best of our knowledge not documented.

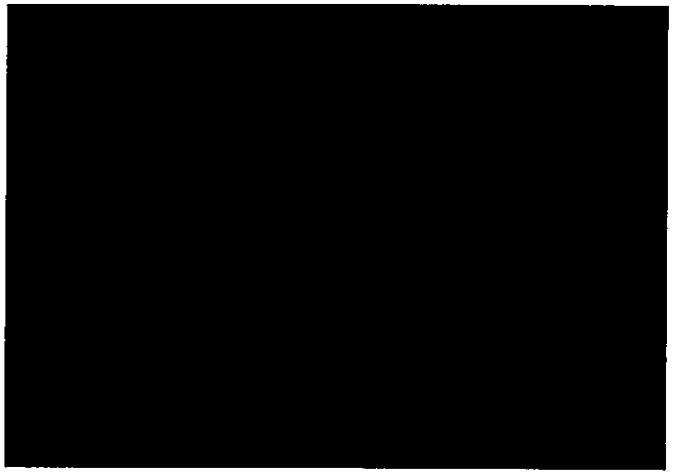

Fig. 3. The regenerated endothelial cells of the neointima (arrowheads) express vWF (a) and TM (b) just like those of normal vasa vasorum (arrows).

In our recent study, angiographic luminal changes after coronary stenting was demonstrated to be triphasic, consisting of an early restenosis phase (up to 6 months) and an

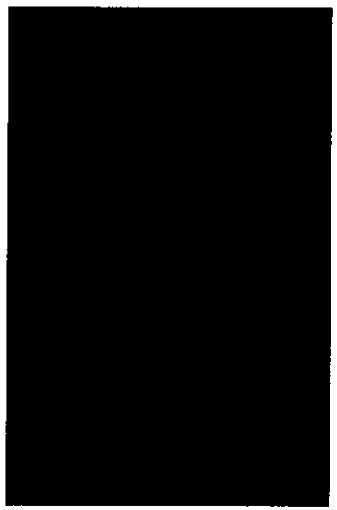

Fig. 4. Immunoreactivity to (a) CD3 and (b) CD4 of helper/inducer T lymphocyte infiltration persisted around the struts.

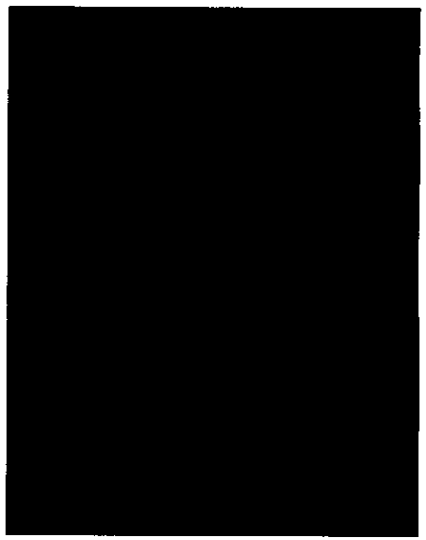

Fig. 5. Histological sections of a coronary segment stented for more than 3 years. (a) Hematoxylin–eosin stain: the smooth muscle cells in the neointima are sparse. (b) Masson's trichrome stain: dense collagenous fibers are evident, but now a remarkable infiltration of lipid-laden macrophage is visible around the stent struts (arrowheads).

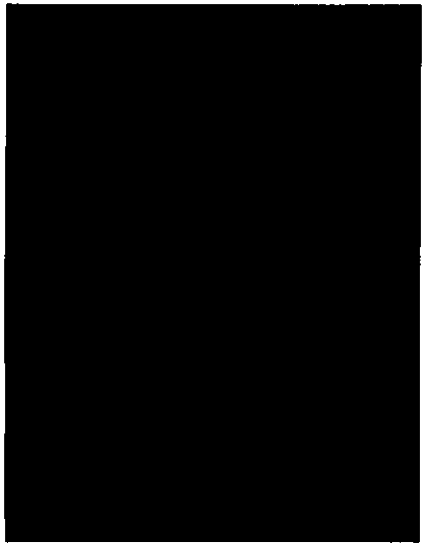

Fig. 6. Segment of the right coronary artery stented for 7 years. Light microscopy clearly revealed heavy infiltration of foamy cells around the stent struts (arrowheads). (a) Hematoxylin–eosin stain. (b) Masson's trichrome stain.

intermediate-term regression phase (6 months to 3 years), followed by a late renarrowing phase (beyond 4 years) [7].

Maturation of fibrotic scar characterized by reduction of myxomatous proteoglycans and redifferentiation and disappearance of smooth muscle cells seems to be the mechanism of such regression between 6 months to 3 years following coronary stenting as well as balloon coronary angioplasty [9,10].

Although this study is limited to the Palmaz–Schatz stent we have observed similar changes following implantation of the ACS Multilink stent and the NIR stainless steel stents within 3 years of implantation and referred here anecdotally because we do not have specimens of >3 years implantation. Limited as it might be, our study revealed unmistakable evidence of chronic immunocompetent T-cell infiltration around the struts persistently beyond 2 years after coronary stenting.

In spite of the general belief that the highly corrosion-resistant stainless steel is inert, metallosis followed by metallic sensitivity has been found in human beings several months after implantation of stainless steel prosthesis [11]. There are no reasons to believe coronary stent struts to be exempt. Early restenosis that might have been triggered by an immune-type reaction was reported by Kōster et al. [12], and the chronic inflammatory reaction characterized by infiltration of macrophages and T lymphocytes reported by others [13,14] could also be explained by this metallosis.

Furthermore, it has also been reported that the foreign body reaction consisting mainly of macrophages and foreign-body giant cells can persist at the tissue–implant interface for the lifetime of the implant [15]. The observed heavy infiltration of macrophages around the struts of stents implanted for more than 4 to 5 years gives support to the notion of such a persistent foreign-body reaction. Neovascularization around the stent struts, as a result of granulation tissue generation, may sustain the influx of the inflammatory cells [16].

Foamy cells, especially those deriving from macrophages, expressed collagen-degrading MMPs [17] (MMP-3 or stromelysin-1, and MMP-9 or gelatinase B) diffusing into the cell surroundings that may predispose plaques to disruption [18]. We surmise the MMPs degrade the collagen fibers rendering unstable the hereto stable neointima. Furthermore, recent pathological studies have shown that subclinical episodes of plaque disruption followed by healing are a stimulus for sudden plaque growth, a major causative factor of chronic stenosis [19]. Chronic immunological stimulation incites T lymphocytes to elaborate interferon-γ that could activate macrophage functions, including synthesis of MMPs [20] followed by plaque vulnerability.

Thus, after completion of the vascular repair following a successful stenting without restenosis at 6 months, the stable

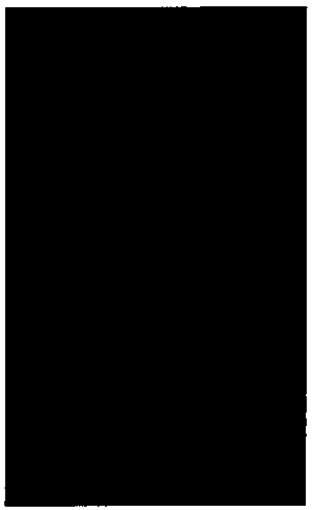

Fig. 7. These foamy cells (arrowheads) clearly showed immunoreactivity to CD68 (a), MMP-3 (b) and MMP-9 (c). Positive staining for these MMPs was also observed in the extracellular space.

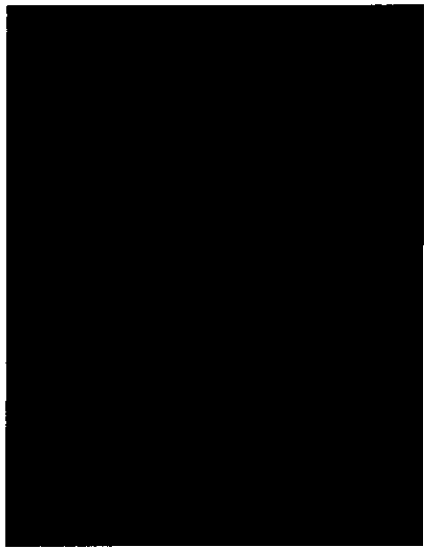

Fig. 8. Histological sections of the Fig. 6 case. Note intimal disruption and adherent thrombus: (a) hematoxylin–eosin stain; a multinucleated giant cell is also visible in contact with the stent strut (arrowhead); (b) Masson's trichrome stain: collagen fiber disruption is evident (arrows).

neointimal layer is composed of hypocellular fibrous tissue for 2–3 years [9]. However, 4 to 5 years after stenting the peri-strut persistent chronic inflammatory cells may cause accelerated new and indolent atherosclerotic changes leading to plaque vulnerability [21]. We assume these findings are related to the metal per se more than the design morphology or type of the stent. Thus, we firmly believe that even if free of restenosis within 1 year of stenting, patients need a careful long-term follow-up, for metallosis is a potential problem.

The clinically beneficial effects of hydroxymethylglutaryl coenzyme A (HMG-CoA) reductase inhibitor (statin) in reducing the incidence of ischemic events by stabilization of the atherosclerotic plaque [22] might be mediated through the reduction of activation and proliferation of macrophages [23], and consequent inhibition of MMPs secretion [24]. Thus, administration of this type of drug might be anticipated to perhaps prevent late lesion progression after coronary stenting especially with stainless stents.

5. Study limitations

This study is limited to autopsied samples after implantation of Palmaz–Schatz coronary stents in a very small number of patients, which preclude detailed correlation to known or unknown factors that might predispose to a specific pathology. Whether the findings could be extended to other stents is not addressed. The study is not a serial one in the same patient, and the described sequence of neointima maturation might actually be just a coincidence of patients dying at various time intervals after stenting, rather than actually representing the maturation process itself. The implied natural history of neointima transition correlating with the angiographic appearance at equivalent poststenting times might be speculative. Nevertheless, the present study is the first to report histological findings of native human coronary arteries stented for >3 years, and it is a plea for careful late follow-up of not only angiographic but detailed pathological studies as well after coronary stenting.

6. Summary

Prominent infiltration of T lymphocytes and macrophages with matrix metalloproteinases activity around the struts occurred in 19 coronary arteries 2–7 years poststenting even in the absence of restenosis. Focal disruption covered by mural thrombi was observed in 2. Chronic inflammation, compatible with persistent stent-metal-evoked foreign body reaction may cause indolent atherosclerotic changes, in some vulnerable enough to cause obstruction.

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Long-Term Clinical and Angiographic Follow-Up After Coronary Stent Placement in Native Coronary Arteries

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Background—Although coronary stents have been proved effective in reducing clinical cardiac events for up to 3 to 5 years, longer term clinical and angiographic outcomes have not yet been fully clarified.

Methods and Results—To evaluate longer term (7 to 11 years) outcome, clinical and angiographic follow-up information was analyzed in 405 patients with successful stenting in native coronary arteries. Primary or secondary stabilization, which was defined as freedom from death, coronary artery bypass grafting, and target lesion–percutaneous coronary intervention (TL-PCI) during the 14 months after the initial procedure or after the last TL-PCI, was achieved in 373 patients (92%) overall. Only 7 patients (1.7%) underwent TL-PCI more than twice. After the initial 14-month period, freedom from TL-PCI reached a plateau at 84.9% to 80.7% over 1 to 8 years. However, quantitative angiographic analysis in 179 lesions revealed a triphasic luminal response characterized by an early restenosis phase until 6 months, an intermediate-term regression phase from 6 months to 3 years, and a late renarrowing phase beyond 4 years. Minimal luminal diameter in 131 patients with complete serial data were 2.62±0.4 mm immediately after stenting, 2.0±0.49 mm at 6 months, 2.19±0.49 mm at 3 years, and 1.85±0.56 mm beyond 4 years ($P<0.0001$).

Conclusions—The efficacy and safety of coronary stenting seemed to be clinically sustained at 7 to 11 years of follow-up. However, late luminal renarrowing beyond 4 years was common, which demonstrates the need for further follow-up. (*Circulation*. 2002;105:2986-2991.)

Key Words: stents ■ restenosis ■ angioplasty

Coronary stenting has been shown to reduce clinical and angiographic restenosis after balloon coronary angioplasty in 2 randomized trials.[1,2] Adjunctive use of potent antiplatelet agents such as ticlopidine or clopidogrel markedly decreased the incidence of stent thrombosis and bleeding complications[3] and thereby promoted the widespread use of coronary stents. Despite these favorable observations, there remained concerns about the long-term outcome after the permanent placement of metallic prosthetic devices inside the coronary artery. Medium-term follow-up studies at 3 to 5 years revealed a paucity of late clinical stent-related problems[4-8] and even angiographic regression of the stented lesions.[8,9] Recently, Choussat et al[10] reported clinical stability of the stented target site at 8 to 10 years after coronary stenting. However, there is still no long-term angiographic data supporting sustained patency of the stented target site and absence of local complications specific for permanent implantation of metallic prosthesis. Furthermore, although diffuse in-stent restenosis has been known to be refractory to repeated percutaneous coronary intervention (PCI),[11] long-term outcome of those patients undergoing repeated PCI has not yet been fully clarified. To address these issues, we analyzed clinical and angiographic outcome at 7 to 11 years after Palmaz-Schatz stent placement in native coronary arteries.

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Methods

Study Patients

From June 1990 through December 1993, 422 consecutive patients (443 lesions) underwent placement of the Palmaz-Schatz stent in native coronary arteries. This study population included all the 143 patients whose 3-year follow-up result was reported previously.[8] All stents were placed with a commercially available stent delivery system (Johnson & Johnson) by standard techniques.[12] In 411 patients (97%), stents were successfully deployed to the target sites. In-hospital major complications included death in 6 patients (1.4%), stent thrombosis in 9 patients (2.1%), Q-wave myocardial infarction (MI) in 9 patients (2.1%), and urgent coronary artery bypass grafting (CABG) in 3 patients (0.7%). Anticoagulant therapy after stent placement included aspirin, dipyridamole, dextran, heparin, and warfarin and has been described in detail elsewhere.[13] A total of 405 patients (424 lesions) undergoing successful stent placement who were discharged alive constituted the study population for long-term follow-up. All the patients gave informed consent for the procedure and the follow-up treatment, which was approved by the institutional review board.

Clinical Follow-Up

Clinical follow-up data were obtained by either a review of the hospital records or telephone contacts with the patients or their referring physicians. When a patient reported a clinical event, it was confirmed by contacts with the referring physician whenever possible. The referring physicians were requested to send all the follow-up angiograms.

With regard to the follow-up events, only the out-of-hospital events were analyzed on per-patient basis. The major clinical events studied were death, MI, CABG, and PCI for stented target lesions (TLs) and non-TLs. Death was regarded as cardiac except for those of proven noncardiac origin. MI was defined as an increase in serum creatinine kinase activity to more than twice the normal value, in association with new pathological Q waves. TL-PCI was defined as that involving not only inside the stent but also the stent edges within the injured segment of the initial procedure. Discrimination of TL-PCI from non-TL-PCI was assessed by a consensus of 2 experienced angiographers, who analyzed the initial and follow-up angiograms side by side. Primary stabilization of the stented lesion was defined as survival without TL-PCI or CABG at 14 months after the initial procedure. When patients underwent early TL-PCI, secondary stabilization was defined as survival without further TL-PCI or CABG at 14 months after the last TL-PCI. The specific time point of 14 months was chosen because many patients in this study underwent the angiographic study at 1 year, which tended to be a driving force of TL-PCI. Late TL-PCI was defined as that performed after achievement of primary or secondary stabilization.

Angiographic Follow-Up

In the initial series of patients of this study population, follow-up angiography was to be performed 6 months, 1 year, and 3 years after the procedure according to the study protocol.[8] In the later series of patients, only the follow-up angiography at 6 months was dictated by the protocol. The 6-month follow-up studies were defined as those performed between 4 and 14 months after the procedure. When the patients underwent TL-PCI, follow-up angiography at 6 months after the TL-PCI was recommended. The early follow-up studies were defined as either 6-month studies in patients with primary stabilization or those studies at 6 months after the last TL-PCI in patients with secondary stabilization. The 3-year follow-up studies were defined as those performed between 27 and 48 months. The late follow-up studies beyond 4 years were not dictated by the protocol but were performed according to the decision of the attending physicians. If a patient underwent multiple angiographic studies beyond 4 years, the late follow-up study was defined as either the latest one in patients without late TL-PCI or that at the time of late TL-PCI.

Quantitative angiographic analysis was performed with the Cardiovascular Angiography Analysis System II.[14] Detailed methods and reproducibility of quantitative angiographic analysis in our laboratory were described previously.[8] Restenosis was defined as stenosis ≥50% at follow-up.

Statistical Analysis

Values were expressed as mean±SD except for rates of event-free survival, which were expressed as mean±SEE. Paired numerical data obtained by serial angiography were compared by the paired t test, and other continuous variables were compared with the unpaired t test. Categorical variables were compared with the χ^2 test. Rates of event-free survival were studied with Kaplan-Meier analysis and displayed as survival curves. Comparison between curves was performed by the log-rank method. Multivariate predictors of late death were analyzed by Cox proportional hazards regression. Adjusted hazard ratios, 95% confidence intervals, and probability values were reported. Probability values <0.05 were considered statistically significant.

TABLE 1. Patient, Lesion, and Procedural Characteristics

Patient characteristics	
Number of patients	405
Age, y (range)	64±9 (34–89)
Male sex, n (%)	320 (79)
Extent of coronary artery disease, n (%)	
Single vessel disease	179 (44)
Multivessel disease	200 (49)
Prior coronary artery bypass grafting	26 (6)
Prior MI, n (%)	221 (55)
Left ventricular dysfunction, n (%)	47 (12)
Class 3 or 4 angina, n (%)	192 (47)
Hypertension, n (%)	180 (44)
Hypercholesterolemia, n (%)	130 (32)
Diabetes mellitus, n (%)	117 (29)
Chronic renal failure, n (%)	51 (13)
Smokers, n (%)	105 (26)
Use of statins, n (%)	69 (17)
Use of angiotensin-converting enzyme inhibitors, n (%)	34 (8)
Lesion characteristics	
Number of lesions	424
Lesion location, n (%)	
Left anterior descending coronary artery	181 (43)
Right coronary artery	183 (43)
Left circumflex coronary artery	46 (11)
Left main coronary artery	14 (3)
Restenotic lesion, n (%)	177 (42)
MLD before procedure, mm	0.98±0.38
Reference diameter before procedure, mm	3.16±0.55
Lesion length, mm	10.4±5.6
Procedural characteristics	
Final balloon size, mm	3.53±0.4
Final balloon pressure, atm	9.9±2.5
Indication for coronary stenting, n (%)	
Planned	331 (78)
Unplanned	93 (23)
Abrupt closure	31 (7)
Suboptimal result	62 (15)
Multiple stents, n (%)	27 (7)
Multivessel coronary intervention, n (%)	93 (23)

Values are mean±SD or n (%).

Results

Patient, Lesion, and Procedural Characteristics

The patient, lesion, and procedural characteristics of the 405 study patients are shown in Table 1. Focal lesions in large arteries were preferentially selected for stent placement, as evidenced by the large reference diameter with a short lesion length. Multiple overlapping stents were used very infrequently. Therefore, the study population reflected classic characteristics of coronary stenting.

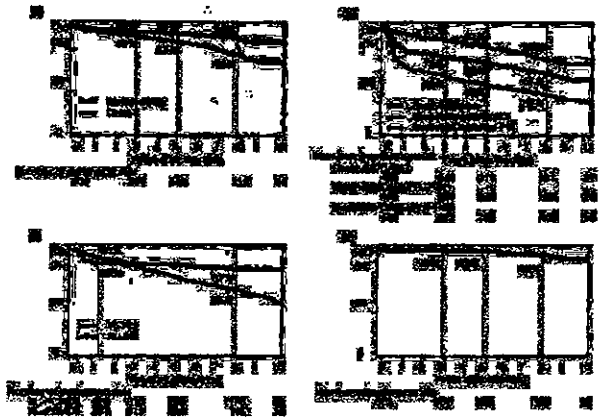

Figure 1. Kaplan-Meier curves showing rates of (a) survival, (b) event-free survival, (c) freedom from repeated PCI for either TLs or new lesions (NL), and (d) freedom from late TL-PCI.

Outcome of Clinical Follow-Up

Clinical follow-up information was obtained in 400 patients (99%) at 3 years and 396 patients (98%) at 7 years. The follow-up interval of the 298 survivors was 8.4±1.4 years (range, 1–11 years).

Primary stabilization was achieved in 317 patients (78%); 19 patients who died and 8 and 61 patients who required CABG and TL-PCI within 14 months, respectively, were excluded. Among the 61 patients undergoing TL-PCI, 3 patients died, 1 patient received CABG, and 1 patient was lost to follow-up within 14 months. Therefore, secondary stabilization was achieved in 56 patients (92%). Primary or secondary stabilization was achieved in 373 patients (92%) overall. The number of TL-PCI procedures to achieve secondary stabilization was only 1 in 41 patients (73%), 2 in 8 patients (14%), 3 in 5 patients (8.9%), 5 in 1 patient (1.8%), and 6 in 1 patient (1.8%). Therefore, only 7 (1.7%) of 405 study patients underwent TL-PCI more than twice.

The cumulative survival rates were 76.1±2.2% at 8 years (Figure 1a). Among 107 patients who died during follow-up, the causes of death were cardiac in 41%, noncardiac but vascular in 20%, and noncardiovascular in 39% (Table 2). By multivariate analysis of various factors that may have affected late mortality, age, chronic renal failure as defined by serum creatinine level ≥1.3 mg/dL, left ventricular dysfunction as defined by ejection fraction <0.4, and diabetes mellitus were found to be independent predictors of late death (Table 3).

At 8 years, 90.5±1.6% of patients were free from Q-wave MI. Among 35 documented episodes of Q-wave MI, only 3 (8.6%) were related to problems at the stented lesions. Major event-free survival rates (death/MI/CABG and death/MI/CABG/TL-PCI) were 67.2±2.4% and 57.2±2.5% at 8 years, respectively (Figure 1b). After the initial 14-month period, freedom from TL-PCI reached a plateau at 84.9±1.8% to 80.7±2.0% over 1 to 8 years (Figure 1c). Although sporadic episodes of late TL-PCI did occur beyond 5 years, late revascularization procedures were predominantly targeted to progressive disease at nontarget sites. (Figures 1c and 1d). Because of the frequent need for PCI for new lesions, only 36.7±2.4% of patients were completely free from any events at 8 years (Figure 1b).

Outcome of Angiographic Follow-Up

The 6-month follow-up studies were performed in 394 patients (95%; 412 lesions) at 193±54 days after the procedure. Angiographic restenosis was found in 82 lesions (20%). Among 56 patients with secondary stabilization, the minimal luminal diameter (MLD) immediately after the final TL-PCI was significantly smaller than that after initial stent placement (2.13±0.49 mm versus 2.47±0.44 mm; P=0.004). Angiography at 6 months after the final TL-PCI was performed in 51 patients at 13.6±7.2 months after the initial procedure. MLD at the early study was significantly smaller in patients with secondary stabilization compared with those with primary stabilization (1.63±0.42 mm versus 2.04±0.5 mm; P=0.0001). Ten patients (20%) fulfilled the criteria of angiographic restenosis but did not undergo further revascularization procedures.

TABLE 2. Causes of Death

Cardiac death, n (%)	44 (41)
Sudden death	21
Congestive heart failure	8
Acute MI	5
Postoperative death (CABG)	2
Unknown	8
Noncardiac vascular death, n (%)	21 (20)
Stroke	8
Aortic aneurysm	6
Chronic renal failure	5
Pulmonary embolism	1
Systemic embolism	1
Noncardiovascular death, n (%)	42 (39)

TABLE 3. Univariate and Multivariate Predictors of Late Death

	Univariate Analysis		Multivariate Analysis	
Variables	Hazard Ratio (95% CI)	P	Hazard Ratio (95% CI)	P
Age	1.07 (1.04–1.1)	<0.0001	1.06 (1.04–1.09)	<0.0001
Female sex	0.8 (0.47–1.34)	0.389		
History of CABG	0.65 (0.25–1.66)	0.365		
Multivessel disease	0.8 (0.51–1.25)	0.327		
History of MI	0.76 (0.49–1.18)	0.217		
Smokers	1.02 (0.64–1.62)	0.948		
Diabetes mellitus	1.9 (1.24–2.9)	0.003	1.65 (1.1–2.46)	0.015
Chronic renal failure	2.29 (1.44–3.64)	0.0005	2.26 (1.45–3.54)	0.0003
Hypertension	0.97 (0.65–1.46)	0.893		
Hypercholesterolemia	1.07 (0.6–1.92)	0.823		
Left ventricular dysfunction	2.67 (1.55–4.59)	0.0004	2.17 (1.37–3.45)	0.001
Class 3 or 4 angina	0.9 (0.6–1.36)	0.617		
Use of ACE inhibitors	1.08 (0.55–2.13)	0.819		
Use of statins	0.52 (0.23–1.14)	0.101		

ACE indicates angiotensin-converting enzyme; CI, confidence interval.

The late follow-up studies beyond 4 years were performed in 182 patients (51%) out of 355 survivors at 4 years, with a mean interval of 6.6±1.6 years. Symptomatic status at the time of the late studies included acute MI in 15 patients (9%), congestive heart failure in 5 patients (3%), class 3 or 4 angina in 35 patients (19%), and class 1 or 2 angina in 49 patients (27%). Seventy-eight patients (43%) were asymptomatic but underwent the late angiographic studies according to the decision of the attending physicians. Compared with the patients without late studies, patients with late studies were younger (62±8.6 versus 64.8±9.4 years; P=0.004) and were followed longer (8.4±1.1 versus 8.0±1.4 years; P=0.001). Other baseline characteristics and outcome at the early angiographic studies were not different between the 2 groups (data not shown). Cine films were available for quantitative analysis in 173 patients (179 lesions). MLD decreased significantly from 1.98±0.51 mm at the early study to 1.83±0.58 mm at the late study (P<0.0001; Figure 2a). This late decrease in MLD was similarly seen in both groups of patients with primary and secondary stabilization (Figures 2b and 2c). In 131 lesions with the 3-year study, MLD increased significantly from 2.0±0.49 mm at the early study to 2.19±0.49 mm at the 3-year study (P<0.0001), but it decreased significantly to 1.85±0.56 mm at the late study (P<0.0001; Figure 2d). Among the 78 asymptomatic patients at the time of the late follow-up study, complete sequential angiographic study was performed in 54 patients (57 lesions). The triphasic luminal response was also seen in these patients

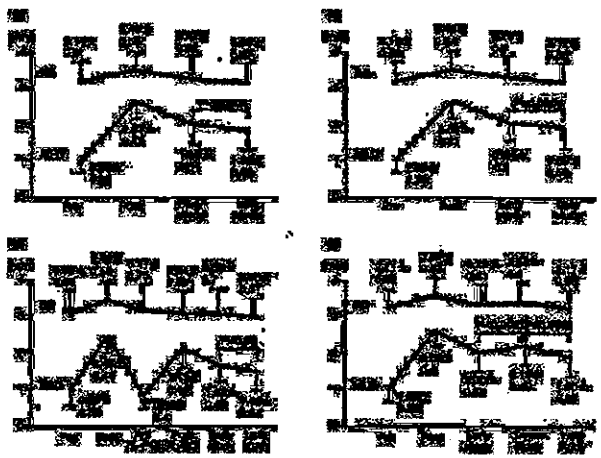

Figure 2. Serial changes in MLD and reference diameter (RD) at the stented sites for (a) all lesions (n=179), (b) lesions with primary stabilization (n=153), (c) lesions with secondary stabilization (n=26), and (d) lesions studied at 3 years (n=131).

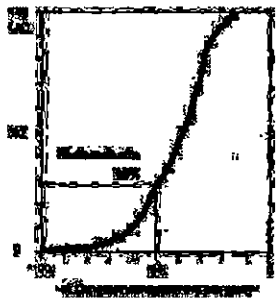

Figure 3. Cumulative distribution function curve of percent diameter stenosis at the late follow-up study.

who were asymptomatic at the time of the late follow-up study (1.95±0.5 mm at the early study, 2.14±0.42 mm at the 3-year study, and 1.87±0.49 mm at the late study; $P<0.0001$). Angiographic restenosis was observed in 50 lesions (28%) at the late study. However, late TL-PCI was performed only in 20 lesions because many of the lesions with angiographic restenosis were in the range of 50% to 60% diameter stenosis.(Figure 3). Treatment strategies after the late angiographic studies were PCI for new lesions in 73 patients (41%), PCI for late in-stent restenosis in 14 patients (8%), PCI for both late in-stent restenosis and new lesions in 6 patients (3%), CABG in 9 patients (4%), and medical management in 80 patients (44%).

In the previous report of 3-year follow-up after coronary stenting,[8] we described a patient with formation of aneurysm at the stent site. The patient died from a cerebral infarction unrelated to the aneurysm 5 years after the initial procedure. No other potentially deleterious vascular effects were noted on late angiographic follow-up.

Discussion

Early in-stent restenosis remains a major limitation of coronary stenting. Diffuse in-stent restenosis has been known to be refractory to repeated PCI.[11] However, the extent of refractoriness could only be assessed by long-term follow-up study. In the present study, primary or secondary stabilization was achieved in >90% of patients. Furthermore, only 1.7% of all study patients underwent early TL-PCI more than twice. Therefore, although in-stent restenosis is still a vexing problem of coronary stenting, it was truly refractory in a minority of patients in this study. Diffuse in-stent restenosis was reported to be associated with a smaller reference artery diameter, longer lesion length, female sex, longer stent length, and use of coil stents.[15] Favorable outcome in terms of infrequent refractory restenosis in our study may be related to our selection of short lesions in big arteries.

Long-term outcome of clinical follow-up in the present study confirmed the observation of Choussat et al,[10] who reported the rate of revascularization of stented sites was <10% beyond 1 year for up to 10 years, and late revascularization was performed predominantly to treat progressive disease at nontarget sites. Therefore, the clinical benefits of coronary stenting in terms of reduction in the rate of TL revascularization seemed to be sustained at 7 to 11 years of follow-up. The paucity of clinical events related to the treated sites was similar to the event rates reported after balloon coronary angioplasty.[16] It was also reassuring that long-term angiographic follow-up of a large patient series did not disclose any deleterious vascular effects other than formation of an aneurysm in a patient.

Despite the favorable long-term clinical outcome, a significant decrease in MLD was observed from 6 months to late follow-up by quantitative coronary angiography. In the previous studies, MLD was shown to improve from 6 months to 3 to 4 years after coronary stenting or balloon coronary angioplasty,[8,9,17] which was confirmed in this study. Fibrotic scar formation associated with maturation of smooth muscle cells and reduction in matrix proteoglycans was suggested as one of the possible mechanisms of late angiographic regression, protecting the TLs from atherosclerotic progression or plaque rupture after both balloon coronary angioplasty and coronary stenting.[18] However, the long-term luminal response after coronary stenting was clearly demonstrated to be triphasic in this study. The early restenosis phase (until 6 months) and the intermediate-term regression phase (from 6 months to 3 years) were followed by a late renarrowing phase beyond 4 years. It is not clear whether the late renarrowing phase is specific for coronary stenting. However, complete sequential angiographic follow-up of 48 lesions undergoing balloon coronary angioplasty revealed no change in MLD from 6 months (2.13±0.6 mm) to 10 years (2.18±0.61 mm).[16] Pathological analysis of the stented human coronary arteries demonstrated heavy infiltration of lipid-laden macrophages around the struts beyond 5 years after coronary stenting, which indicated chronic inflammatory reactions. In contrast, it was not until >7 years after balloon coronary angioplasty that a slight infiltration of lipid-laden macrophages was observed in the subendothelial spaces.[19] This chronic inflammation might induce late atherosclerotic progression of the treated lesions. These pathological findings are consistent with our angiographic observation of late luminal renarrowing beyond 4 years.

A potential problem with this study is the fact that late angiographic follow-up studies were not dictated by the protocol but were driven by clinical indications. Analysis of the late luminal response might be biased by the predominance of symptomatic patients in the angiographic follow-up group. However, nearly half of those patients with late angiographic studies were asymptomatic. The triphasic luminal response was also seen in these asymptomatic patients. Furthermore, treatment strategies after late angiographic studies were more often PCI for new lesions, which were regarded as the culprit lesions for symptom, rather than PCI for late in-stent restenosis. Therefore, it seems unlikely that the indication of late angiographic follow-up studies heavily biased the observed serial changes in luminal diameter.

It should be noted that there was some discrepancy between the late angiographic restenosis rate and the frequency of TL-PCI. Because many of the lesions with late angiographic restenosis were in the range of 50% to 60% diameter stenosis, attending physicians tended to decide not to perform PCI. Also, the lesions with late in-stent restenosis were rarely associated with acute MI. If late in-stent restenosis is a self-limited process, late luminal renarrowing of this degree would be clinically acceptable. Therefore, the real clinical impact of late in-stent restenosis could only be clarified by follow-up for a more extended period of time. Progressive luminal renarrowing late after coronary stent placement, as shown in the present study, warrants the need for further follow-up.

Acknowledgments

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Successful endovascular repair of an aneurysm of the ductus diverticulum with a branched stent graft: Case report and review of literature

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Aneurysm of the ductus diverticulum rarely has been reported in adults, and the reported aneurysms were treated with conventional open surgery or were diagnosed at autopsy. We report a successful endovascular repair of an aneurysm of the ductus diverticulum with the Inoue branched stent graft. In a 78-year-old woman, an abnormal shadow was noted at the aortopulmonary window on a chest x-ray film. A computed tomography scan demonstrated a 3.8-cm saccular aneurysm, which protruded inferiorly from the distal end of the aortic arch. The aneurysm was considered an aneurysm of the ductus diverticulum, and surgery was required. However, the patient was considered at high risk for respiratory dysfunction with conventional open surgery. Endovascular repair with an Inoue single-branched stent graft was performed with the patient under local anesthesia, successfully and without complication or endoleak. To our knowledge, this is the first report of endovascular treatment of an aneurysm of the ductus diverticulum. (J Vasc Surg 2004;40:1228-33.)

Aneurysm of the ductus diverticulum is rare in adults, and most reported cases were repaired with surgery.[1-11] Transluminal endovascular stent-graft placement in patients with thoracic aortic aneurysm is emerging as an attractive alternative to conventional open surgery.[12,13] However, its application is limited to descending thoracic aortic aneurysms distal to the aortic arch. Endovascular repair of aneurysms of the thoracic aortic arch is challenging. One option is to perform a surgical bypass from either the proximal ascending aorta or the femoral arteries[14,15]; another is to use a stent graft with side branches to the innominate, left carotid, and left subclavian arteries.[16-19] Except for the Inoue branched stent graft, reports of endovascular techniques of repair of complex aneurysms with branched stent grafts have been limited to animal studies and incidental case reports.[16-18] In March 2003 we began performing endovascular repair of aortic aneurysms in various locations with the Inoue stent graft, after approval of our ethics committee. We performed a successful endovascular repair of the aneurysm of the ductus diverticulum with a single-branched Inoue stent graft. To our knowledge, this is the first report of endovascular treatment of an aneurysm of the ductus diverticulum.

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Competition of interest: none.

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CASE REPORT

A chest roentgenogram in a 78-year-old woman indicated a subtle abnormal prominence. Computed tomography (CT) scans revealed a saccular aneurysm originating from the aortic arch in the aortopulmonary window. The aneurysm diameter was 3.8 cm (Fig 1, *A*). A 3-dimensional (3-D) CT scan showed that the aneurysm was located in a minor curvature of the distal aortic arch at the bifurcation of the left subclavian artery. The aneurysm end was in the direction of the top of the left pulmonary artery (Fig 1, *B*). On the basis of findings on the 3-D CT scan, a diagnosis of aneurysm of the ductus diverticulum was made. An aortogram demonstrated a saccular aneurysm at the distal aortic arch, and a coronary angiogram revealed no stenosis of the coronary arteries. The patient had a history of tuberculosis and chronic obstructive lung disease. Pulmonary function tests demonstrated severe pulmonary dysfunction: forced vital capacity, 1.45 L; forced expiratory volume in 1 second, 0.83 L; FVC·FEV_1 ratio, 57.0%. Thoracotomy was considered high risk, and the patient was referred to Kyoto University Hospital for endovascular stent grafting. After obtaining informed consent from the patient and approval from our institutional review board, we performed endovascular repair with a single-branched Inoue stent graft.

The endovascular Inoue stent-grafting system and its implantation techniques have been described in detail.[19-21] The Inoue stent graft was custom made for the patient, with a computer-assisted stent-graft design system.[22] A 3-D model was constructed from helical CT images of the aneurysm. The stent graft was designed and positioned endoluminally on the computer. The diameter of the aorta in the proximal position of the stent graft was 32 mm, 26 mm in the distal position of the stent graft, and 9 mm in the left subclavian artery. The diameter of the designed stent graft was 34 mm in the proximal neck, 28 mm in the distal neck, and 10 mm in the branch. The diameter of the aortic section of the graft was oversized by 2 mm, and by 1 mm in the branched section, to achieve effective sealing. The length of the graft at the center was 85 mm.

With the patient under local anesthesia, the right femoral artery was surgically isolated and a transverse arteriotomy was performed. A 7F sheath was inserted percutaneously in the left brachial artery. A 22F introducer sheath was inserted through the right femoral artery, and was advanced to the descending thoracic aorta under fluoroscopic guidance. After administration of 10,000 U of heparin, the folded branched stent graft was introduced into

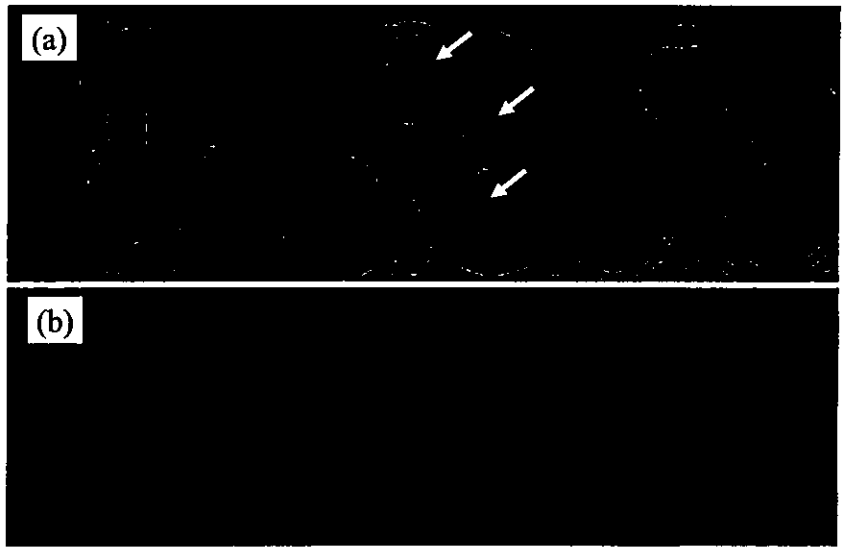

Fig 1. **a**, Enhanced 2-dimensional computed tomography scan demonstrates 3 circles located in a hook shape beneath aortic arch (*arrows*), or the "triple star sign." Maximum diameter of the aneurysm is 3.8 cm. Atherosclerotic changes in adjacent aorta were not found. Diameter of descending aorta is 2.6 cm. **b**, Three-dimensional reconstructions of computed tomography scan show the aneurysm projecting to the left pulmonary artery from the minor curvature of the aortic arch. Aneurysm had thrombus, and compressed the left pulmonary artery.

Table 1. Confirmed cases of aneurysm of the ductus diverticulum reported in literature

Author (year)	*Language*	*Number of patients*	*Course*
Mitchell et al (1983)[1]	English	21	Six patients: underwent successful repair Another patients: died before or after surgery
Kitahara et al (1986)[2]	English	1	Successfully repaired
Tsujimoto et al (1987)[3]	English	1	Refused surgery, died of rupture
Baisden et al (1989)[4]	English	1	Successfully repaired
Ueno et al (1990)[5]	English	3	Successfully repaired in all patients
Baker et al (1993)[6]	English	1	Successfully repaired
Okada et al (1993)[23]	Japanese	1	Successfully repaired
Hattori et al (1994)[24]	Japanese	1	Successfully repaired
Shichijo (1994)[25]	Japanese	1	Successfully repaired
Taneja et al (1997)[7]	English	2	Successfully repaired in all patients
Ferrera et al (1997)[8]	English	1	Successfully repaired
Shimazaki et al (1998)[9]	English	1	Successfully repaired
Kido et al (1998)[10]	English	1	Successfully repaired
Jinnno et al (2002)[26]	Japanese	1	Successfully repaired
Sugimoto et al (2003)[11]	English	2	Successfully repaired in all patients

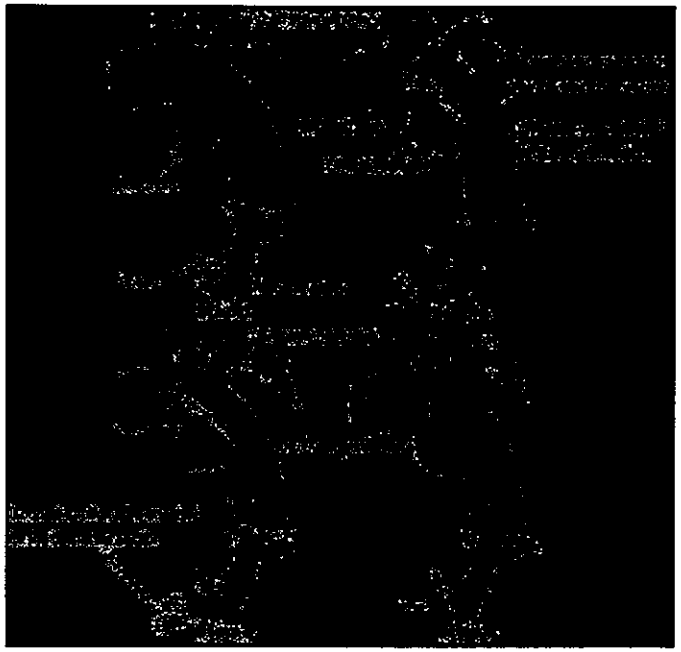

Fig 2. Technique of single-branched stent-graft placement. Step 1, 22F introducer sheath is inserted in the descending thoracic aorta through the right femoral artery. Step 2, Folded stent graft is advanced to the descending thoracic aorta with a carrying wire. Step 3, 10F guiding catheter is inserted through the introducer sheath, along with the traction wire attached to the branched section. Free end of traction wire is inserted in the 10F guiding catheter and caught by the gooseneck wire. Step 4, Stent graft is unfolded and dilated with balloon inflation. Finally, carrying wire and traction wire are detached.

the sheath, advanced to the ascending aorta, and released from the sheath. Then the folded graft was advanced to the distal aortic arch. A 7F catheter with gooseneck wire was inserted through the 7F sheath in the left brachial artery. The free end of the traction wire attached to the tip of the branched graft section was caught by the gooseneck wire and pulled back into the left subclavian artery. With manipulation of the carrying wire and traction wire, the aortic and branched graft sections were properly positioned. After unfolding the branched graft, the aortic section and the branched section of the graft were dilated with a compliant balloon. The balloon was custom-made, and inserted through the 22F sheath. We did not use hypotension to place the graft or for balloon inflation. Implantation technique is shown in Fig 2. Aortograms confirmed that the graft was placed at the proper position and that the aneurysm was completely excluded. Fig 3 depicts aortograms obtained before and after endovascular repair. Finally, all delivery systems were removed and the arteriotomy was closed. An intimal injury of the right external iliac artery occurred during introduction of the 22F sheath, which was repaired successfully with implantation of a Palmaz stent. No other complications occurred during the procedure. Total procedure time was 190 minutes, and volume of contrast media used was 143 mL. The postoperative course was uneventful. A CT scan obtained 10 days after the procedure demonstrated complete exclusion of the aneurysm, and no endoleak was detected (Fig 4). The patient was discharged 12 days after the stent grafting, without any disorders. She remained in the hospital for more than a week for social reasons, but could have been discharged as early as postoperative day 2.

DISCUSSION

Aneurysm of the ductus diverticulum is rarely reported in adults, and preoperative diagnosis is difficult.[1-4] With the advent of more sophisticated diagnostic methods, preoperative recognition of these aneurysms is more frequent. We found 39 reports of aneurysm of the ductus diverticulum in the literature (Table).[1-11,23-26] The aortic end of the ductus diverticulum is patent, whereas the pulmonary end is usually closed. The aneurysm forms as a result of incomplete closure of the ductus arteriosus in its aortic site, from pressure overload, such as hypertension and atherosclerotic changes of aging. The 3-D CT scan, in which 3 circles are located in a hook shape beneath the aortic arch, is called the "triple star sign," and this finding was reported to be a typical sign of this disease.[5] Sugimoto et al[11] reported that a 2D CT scan is useful for differentiation of aneurysm of the ductus diverticulum from common atherosclerotic aneurysm. Compared with atherosclerotic aneurysm in the distal aortic arch, aneurysm of the ductus diverticulum is located in the minor curvature of the distal aortic arch, at the bifurcation of the left subclavian artery, and the direction of the aneurysm end is toward the top of the left subclavian artery. The diagnosis of aneurysm of the ductus diverticulum was made with contrast-enhanced 2-D and 3-D CT scans in our patient.

There is little information about the size of aneurysms of the ductus diverticulum that ruptured. We found 39 cases in 15 reports. Only 2 articles reported patients who died before surgery. Tsujimoto et al[3] reported a patient who refused surgery, and that patient died of rupture of the aneurysm. The maximum diameter of the aneurysm was 11.8 cm. Mitchell et al[1] reported their experience with successful repair of 5 aneurysms of the ductus diverticulum. They reviewed the literature, and found 16 cases. Ten of these patients died of rupture of the aneurysm or a related complication before surgery. The minimum diameter of the ruptured aneurysm was 4 × 3 cm. They concluded that aneurysm of the ductus diverticulum is frequently fatal, even when small compared with saccular atherosclerotic aneurysms. They recommend surgical intervention for aneurysms of the ductus diverticulum greater than 3 cm in greatest diameter. However, this report was published 20 years ago. Most recent reports are case reports or case series of successful surgical repair.[2,4-11,23-26] Therefore the natural history of this rare aneurysm is still unknown. The aneurysm diameter was 3.8 cm in our patient, and thoracotomy was considered too high risk because of the patient's severe pulmonary dysfunction and advanced age. Transluminal endovascular stent grafting was considered suitable in this patient. Although the safety and efficacy of stent-graft placement in thoracic aortic aneurysms has been reported, placement of these stent grafts was limited to sites

Fig 3. A, Preprocedural angiogram shows the aneurysm. B, Folded stent graft is advanced. C, Aortic section of graft is dilated. D, Branched section of graft is dilated. E, No endoleak is seen on final angiogram.

Fig 4. Two-dimensional *(top)* and 3-dimensional *(bottom)* computed tomography scans demonstrate complete exclusion of aneurysm.

that did not include the origin of the major aortic arterial branches.[12,13] Aneurysm of the ductus diverticulum is located at the aortic arch, and a single-branched stent graft was required. The major complication of the branched Inoue stent graft in thoracic aortic aneurysms is cerebral infarction.[19] Unlike true atherosclerotic aneurysms, there was little arteriosclerosis in the aortic wall in this patient, and the risk for cerebral infarction was estimated to be low. We estimated that the risk for rupture outweighed the risk of stent grafting in this patient.

Implantation of a single-branched Inoue stent graft to treat aneurysm of the ductus devirticulum was successful, without complications or endoleak. However, because the procedure was performed only 2 months before the writing of this report, only early success can be confirmed. Inasmuch as true success of endovascular stent-graft repair is determined with long-term results, careful long-term evaluation is needed.

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CORRECTION

In: "Flow-induced neointimal regression in baboon polytetrafluoroethylene grafts is associated with decreased cell proliferation and increased apoptosis" (Berceli SA, Davies MG, Kenagy RD, and Clowes AW. J Vasc Surg 2002;36:1248-55).

On page 1251, in the "Results" portion of the "Materials and Methods" section, Fig 1, *C* is incorrect. The black and white bars representing high and low flow were reversed. The following is the correct figure:

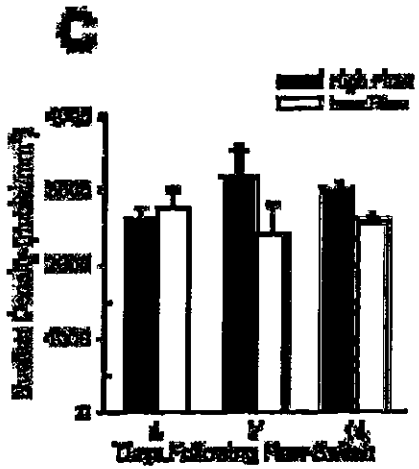

Fig 1. Neointimal SMC proliferation (BrdU labeling index; **A**), apoptosis (TUNEL labeling index; **B**), and nuclear density (**C**) in normal-flow and high-flow grafts after fistula placement. Values are mean ± standard error of mean.

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Late Restenosis of the Balloon-Dilated Site
—— Serial Angiographic Observations Beyond 7 Years ——

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Background The present retrospective study was performed to assess the long-term (>7 years) fate of stabilized balloon-dilated sites.

Methods and Results Between February and April 1986, 171 patients underwent successful percutaneous balloon angioplasty. Early restenosis (<1 year) occurred in 53%, but repeat balloon angioplasty stabilized the balloon-dilated site. The early period was defined as 6 months, late years as 3–5 years and long-term years as 7–12 years. Angiographic evaluation at both early year or late year periods (mean=4.7 years) and long-term (mean=10.4 years) periods following stabilization was available in 71 patients (94 lesions) with mean age of 61.7±8.5 years. Of the 71 patients 69.6% were male. Restenosis occurring after 1 year was defined as late restenosis. The mean diameter stenosis changed from 6 months (50.3±12.4%) to late-period (44.2±13.2%; $p<0.05$) and long-term period (50.3±16.1%; $p<0.001$); but the reference vessel diameter did not change significantly. Late restenosis occurred in 28% (3–5 years) and 33% (7–12 years) of 94 lesions, and 13.8% of lesion required repeat target lesion revascularization. During this period, 5.3% of patients (5 lesions) underwent revascularization for new proximal or distal lesions.

Conclusions Decrease of luminal diameter during the early 6 months, was followed by regression after stabilization of the balloon-dilated site up to 5 years, but luminal re-narrowing occurs again over 7 years after balloon angioplasty. (*Circ J* 2005; **69**: 380–385)

Key Words: Angioplasty; Coronary disease; Follow-up studies; Restenosis

Percutaneous coronary balloon angioplasty (PTBA) has become a popular alternative to bypass surgery as a less invasive revascularization therapy for chronic coronary artery disease (CAD) since the 1980s. However, published documents have been reported where a high percentage of patients with occuring restenosis within 6 months of angioplasty and this has limited its use[1–10] Early clinical investigations reported that restenosis rarely occurs beyond 6 to 12 months after balloon angioplasty. Experimental studies in a number of species have shown that the initial myointimal thickening response composed of proliferation of smooth muscle cells and extracellular matrix to injury reaches a maximum within a few months; in the absence of further injury, luminal enlargement ensues reported as 'late regression'![1] Further angiographic investigations have reported preservation of balloon-dilated site for a decade if the patient is stable after 6 months after balloon angioplasty![2] In contrast, our pathological findings suggest that atherosclerosis progresses again after 7 years from balloon angioplasty.

In the present study, we report re-progression after late regression occurring more than 7 years after balloon angioplasty.

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Methods

Patient Population

Between February and April 1986, 203 consecutive patients underwent clinically uneventful coronary balloon angioplasty for de novo native coronary artery lesions at Kokura Memorial Hospital, Kitakyushu, Japan. According to angiographic criteria (>20% increase of minimal luminal diameter by visual estimation) and clinical criteria (improvement of symptom status without major complications), the procedure was considered successful in 171 patients (84.2%). Angiographic follow-up studies at 6 months (0.6 years=early), 3–5 years (4.7 years=late) and beyond 7 years (7–12 years; 10.4 years=long-term) in 71 (41.5%) patients with 94 lesions (group A), 23 of whom were followed up to 15 years, were available for retrospective analysis. Lesions with restenosis that were amenable to conservative treatment or restenosis treated by repeat angioplasty within 1 year after balloon angioplasty were eligible for enrollment in the study. Lesions with no need for bypass surgery, repeat-balloon angioplasty or death for 1 year were defined as 'stabilized'.

Follow-up Angiography

Coronary angiography at the early, late and long-term periods after PTBA was performed regardless of symptoms in these 71 patients. Quantitative angiographic analysis was performed with the Cardiovascular Angiography Analysis System II. Minimal lesion lumen diameter and lesion length was measured; percentage diameter stenosis as well as the interpolated reference diameter was calculated. Care was taken by the operator to select the same reference points for the post-intervention and follow-up studies. The minimal lumen diameter was determined by computer at the same ballooned site taking the most severe narrowing, even if it was far from the initial narrowest point providing it was within the balloon-dilated site. The measurements of 2 angiographic views were averaged. Isosorbide dinitrate (5 mg) was injected intracoronally before each angiography. The diameter of 5F to 8F catheter tips free of contrast medium filmed at the center of the image were caliper measured and used for calibration in each study. Early restenosis was defined as more than 50% diameter stenosis observed at the 6-month angiography; late restenosis (LR) was defined as restenosis occurring beyond 1 year after angioplasty.

Statistical Analysis

Continuous variables are expressed as mean±1SD and compared with paired t-test for matched observations, or unpaired t-test if non-matched. Categorical variables were compared by the chi-square or Fisher's exact test. All tests of significance were two-tailed, and p-values of less than 0.05 were considered to be statistical significant. A change of stenosis diameter by >0.5 mm was defined as significant between late and long-term periods.

Table 1 Derivation of the Study Patients (Serial Late Angiographic Follow-up)

First time balloon angioplasty in 1986 (n=203)	
Unsuccessful	*19*
CABG	*7*
Death	*6*
Successful (n=171)	
Angiographic follow-up beyond 7 years (study group) (n=71)	
Angiographic follow up <7 years	*74*
CABG <7 years	*12*
Death <7 years	*13*
TLR after stabilization <7 years	*1*
Total (n=71)	*100*

CABG, coronary artery bypass graft; TLR, target lesion revascularization.

Table 3 Symptomatic Status at Late and Long-Term Angiographic Follow-up Period

	Late (n=71)	*%*	*Long-term (n=71)*	*%*
Asymptomatic	*43*	*60.6*	*29*	*41.4*
Symptomatic	*28*	*39.4*	*41*	*58.6*
CCS 3/4	*12*	*16.9*	*19*	*27.1*
Acute MI	*1*	*1.4*	*3*	*4.3*
Vasospasm	*2*	*2.8*	*0*	*0.0*
New leison related	*25*	*35.2*	*24*	*34.3*
Balloon-dilated lesion related	*1*	*1.4*	*9*	*12.9*
Unclear	*0*	*0.0*	*8*	*11.4*

CCS, angina classification of Canadian Cardiovascular Society; MI, myocardial infarction.

Results

Patient Characteristics

Seventy-one of 171 patients (group A) had follow-up angiography beyond 7 years, 23 of whom were followed beyond 12 years (Table 1), but in 74 patients (group B) angiography beyond 7 years was not available. Table 2 describes and compares the baseline characteristics of both groups.

There were no significant differences between the 2 groups. Follow-up angiography of group A patients showed: (i) early period at a mean of 7.2 months (range: 1.5 to 11.6 months); (ii) late or 3–5 years at 4.7 years (range: 2.9 to 6.3 years) after stabilization; and (iii) long-

Table 2 Baseline Characteristics of Group A Study Group Patients and Group B Patients Without Late Angiographic Follow-up

	Group A	*%*	*Group B*	*%*	*p value*
Patients	*71*		*74*		
Lesions	*94*		*105*		
Old MI	*40*	*56.3*	*33*	*44.6*	*0.14*
CCS 3/4	*27*	*38.0*	*33*	*44.6*	*0.25*
Multivessel disease	*32*	*45.1*	*38*	*51.4*	*0.39*
Acute MI	*12*	*16.9*	*8*	*10.8*	*0.47*
Target vessel					
LAD	*37*	*39.4*	*45*	*42.9*	
LCX	*32*	*34.0*	*30*	*28.6*	
RCA	*25*	*26.6*	*29*	*27.6*	
LMT	*0*	*0.0*	*1*	*1.0*	
Poor LVEF	*2*	*2.8*	*2*	*2.7*	*0.99*
Age	*61.7±8.5*		*62.9±8.9*		*0.36*
Male	*49*	*69.0*	*51*	*68.9*	*0.99*
Hypertension	*30*	*42.3*	*25*	*33.8*	*0.30*
Hyperlipidemia	*17*	*23.9*	*21*	*28.4*	*0.58*
Diabetes mellitus	*15*	*21.1*	*15*	*20.3*	*0.86*
Smoking	*28*	*39.4*	*30*	*40.5*	*0.89*
Total cholesterol	*189±59*		*192.1±42*		*0.73*
Triglycerides	*143.2±83*		*137.1±60*		*0.61*
High-density cholesterol	*41.1±18*		*42.1±16*		*0.35*
HbA1c	*5.96±1.8*		*5.97±1.6*		*0.98*
Creatinine	*1.38±1.6*		*1.20±0.2*		*0.56*
TLR <1 year	*18*	*25.4*	*16*	*21.6*	*0.49*

MI, myocardial infarction; CCS, angina classification of Canadian cardiovascular society; LAD, left anterior descending coronary artery; LCX, left circumflex coronary artery; RCA, right coronary artery; LMT, left main trunk; HbA1c, Hemoglobin A1c.

Table 4 Quantitative Coronary Angiographic Analysis at Various Follow-up Periods

	Pre (n=94)	Immediate (n=94)	Early 6 months (n=94)	Late 3–5 years (n=94)	Long-term 7–12 years (n=94)	Long-term 12–15 years (n=23)
Minimal lumen diameter, mm	0.75±0.32	1.49±0.39	1.38±0.43	1.54±0.45	1.41±0.54	1.24±0.54
p-value	<0.0001	0.0671	<0.0001	0.0007	0.0862	
Reference diameter, mm	2.74±0.56	2.72±0.57	2.77±0.59	2.76±0.51	2.79±0.58	2.48±0.51
p-value	0.1254	0.9734	0.9815	0.4192	0.2345	
Diameter stenosis, %	70.9±11.4	48.9±11.3	50.7±12.1	44.2±13.2	51.6±16.9	48.7±18.9
p-value	<0.0001	0.3839	<0.0001	0.0005	0.573	
Lesion length, mm	13.1±8.3	10.7±4.9	12.1±6.4	10.9±4.6	11.4±6.3	11.7±7.2
p-value	0.0016	0.1453	0.0295	0.526	0.2553	
%Diameter stenosis >50	100%	33%	52%	28%	33%	48%

Statistical analysism paired t-test used.

Table 5 Need of Repeat Percutaneous Coronary Intervention (PCI) Beyond 7 Years Post-Stabilization

	n=94	%
LR at long-term	31	33.0
LR (%DS >70)	11	11.7
Total occlusion at long-term	7	7.4
AMI	3	3.2
Silent occlusion	2	2.1
Proximal total occlusion	2	2.1
PCI of new lesion in non-dilated vessel	25	26.6
PCI of same vessel	18	19.1
PCI of LR	13	13.8
PCI of new proximal or distal lesion	5	5.3
Proximal	3	3.2
Distal	2	2.1

LR, late restenosis; %DS, percentage diameter stenosis.

term or beyond 7 years between 6.9 to 11.8 years after stabilization, or 12 to 14.6 years for the subgroup of 23 patients.

There were fewer symptomatic patients at the late follow-up period than at the long-term follow-up. The incidence of unstable angina and acute myocardial infarction was slightly more frequent at the long-term follow-up period. While the incidence of new lesion-related ischemia was the same for both late and long-term follow-up periods, balloon-dilated site-related ischemia was greater at the long-term period (Table 3). One patient required repeat angioplasty for LR by the late-follow-up period, and was therefore excluded from the long-term follow-up. Repeat percutaneous coronary interventions (PCI) were required for disease progression in 22 (31%) patients with 25 (27%) new lesions, and 13 (18%) patients with 13 (14%) late restenotic lesions.

Angiographic Results

The mean minimal lumen diameter attained at the initial balloon angioplasty decreased, although not significantly during the first 6 months, and subsequently increased up to the late follow-up period, but then decreased significantly to the long-term follow-up period. The derived parameters changed accordingly. In contrast the reference diameter remained practically unchanged (Table 4).

While the incidence of lesions with percentage diameter stenosis >50 decreased from the early to the late follow-up period, it increased significantly to the long-term period. This resulted in an LR rate of 26 lesions (28%) for the late period, and 31 lesions (33%) for the long-term follow-up, the stenosis being severe (percentage diameter stenosis >70) in 11 lesions (12%). Seven lesions resulted in total occlusion (Table 5).

Regression and Progression After Stabilization

There was significant lesion regression in 23 of 94 lesions (24.5%), while in 6 (6.4%) there was significant progression occurred up to the late follow-up period; thus regression being dominant during the first 5 years (Fig 1).

In contrast lesion-progression dominated at the long-term follow-up period and was observed in 22 patients (23.4%; Fig 2).

Discussion

Many clinical investigations have reported that restenosis in balloon-dilated sites mainly occurred during the first 6 months after successful angioplasty, and rarely beyond that time, for the phenomenon of regression occurs thereafter up to 5 years[1,13–16] In a previous clinical study the stenotic diameter did not change significantly between 6 months and 10 years after angioplasty[12] The results from the present study confirmed the phenomenon of late regression up to 5 years after balloon angioplasty, but also late progression at 10 years. Interestingly lesions with more than 40% of diameter stenosis at the late follow-up time did not progress by the long-term period, but those with less than 40% progressed significantly with no further enlargement of vessel diameter, in contrast to the reported regression after 5 years of balloon angioplasty[1]

Our early restenosis rate of 52%, somewhat higher than published data[17–20] may be due to the relatively small mean luminal diameter of the dilated reference arteries (2.74± 0.56, n=94). However, there was no significant differences about patient characteristics between with and without late angiographic follow-up. Disease progression in CAD is an insidious phenomenon, but often responsible for the late recurrence of cardiac symptoms and events. Angioplasty per-se may trigger the appearance of a new lesion(s) proximal to the balloon-dilated site[21–23] Five (5.3%) of our study lesions needed repeat PCI. Three (60%) lesions were proximal, but 2 (40%) occurred in the same vessel, distal and unrelated to the dilated lesion several years after balloon angioplasty. Therefore, this indicates that this phenomenon may or may not be secondary to the endothelial injury by the guidewire or balloon catheter, but rather suggests disease progression.

A rigorous and quantitatively evaluated serial angiographic study at 1, 3, 6 and 12 months after angioplasty showed that most of the reduction in mean minimum luminal diameter occurred between 1 and 3 months after angioplasty, and that there was no change from 6 to 12 months! Lesion regression between 6 months and 3 years[3] or between 1 and 2 years[24] have been reported, but the actual consensus is that late lesion regression occurs between 7 months and 4.5 years after angioplasty![1]

Early restenosis is caused by the combination of neointimal thickening, consisting of smooth muscle cells and extracellular matrix, and arterial remodeling leading to vessel shrinkage. Experimental, pathological and intracoronary ultrasound studies suggest that the role of this constriction or shrinkage of the arterial in restenosis is greater than had previously been appreciated[25–30] In animals, the myointimal thickening in response to balloon injury reaches a maximum before 6 months and then regresses![13–16] This regression has been confirmed in pathological studies in humans dying at various time intervals after intracoronary metallic stent implantation; evidence of neointimal proliferation decreases with time and was difficult to find in patients who had died more than 2 years after angioplasty[31] Although the role of remodeling is not known, regression of the intimal hyperplasia after PTBA might be also the major contributor to late regression.

Other pathological studies reported that endothelial cells regenerate as the result of the healing process maturation following balloon angioplasty, during which the initially proliferated and migrated smooth muscle cells are replaced by collagen fibers or extracellular matrix[31] This process leads to luminal enlargement and result in late lesion regression, which might explain the low incidence of symptoms ascribable to the balloon-dilated site. In fact repeat angioplasty to the balloon-dilated site was required in only

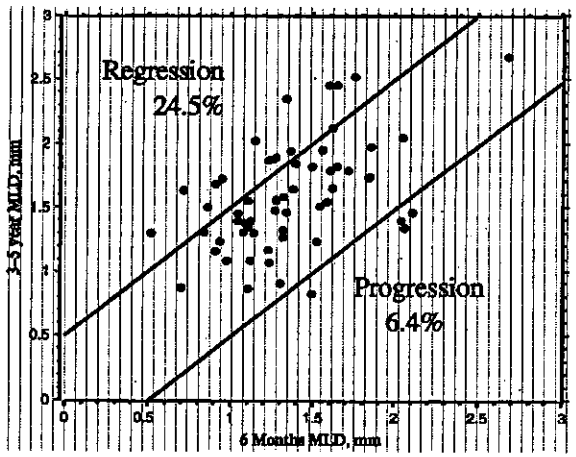

Fig 1. Lesion progression during the early (6 months) period post-balloon angioplasty, is substituted by regression up to the late (3–5 years) period.

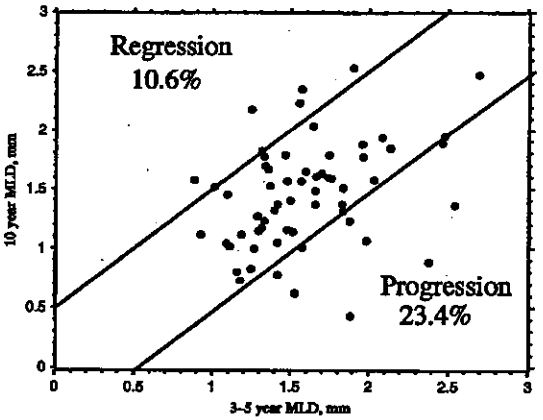

Fig 2. Progression of coronary stenosis is the prevailing feature by the long-term follow-up period (7–12 years) over the regression dominant late period (3–5 years).

1 patient up to the late (3–5 years follow-up) period in the current study.

However, while CAD progression-related ischemia did not increase from late to long-term follow-up (35.2% vs 34.3%), balloon-dilated site-related ischemia increased from 1.4% to 12.9%.

In an another pathological study of 7 years or more after balloon angioplasty demonstrated infiltration of lipid-laden macrophages mainly in the shoulder regions of the subendothelial space. After more than 10 years, thin fibrous caps heavily infiltrated by foam-cells were observed around the circumference of the lumen at balloon-dilated sites. These changes are suggestive of re-atherosclerotic process, which might be the pathogenetic mechanism of late progression or restenosis that may result in plaque vulnerability and even cause acute coronary syndromes[32] In a few lesions (n=23) analyzed at 13.3 years (range: 11.7–14.6 years) after balloon angioplasty this tendency of late progression continued further.

Inward remodeling in addition to atherosclerotic changes might have contributed to late progression in 23.4% of lesions. In a small number of lesions (10.6%), outward remodeling might have accounted for the luminal enlargement[33–36] Long-term studies using intravascular ultrasound[37,38] are needed to further elucidate the mechanism of arterial remodeling.

Study Limitations

The major limitation is the retrospective nature of the study and the potential bias by enrolling only 71 of 171 patients with successful angioplasty and serial angiographic investigation. However, there were no significant background differences between patients followed with or without angiography. Because of the retrospective nature there was a wide dispersion in the follow-up interval between late and long-term angiography.

Conclusions

The current study confirmed the lesion regression occurring up to 5 years after balloon angioplasty, but lesion progression occurred over 7 years after successful balloon angioplasty. Lesion progression is more likely to occur and be of greater magnitude in lesions with relatively little severity at 5 years. Pathologically late progression represents atherosclerotic changes and might become symptomatic beyond 7 years after the late regression phase of balloon angioplasty, but clinical events are more often caused by new non-dilated lesions at 10 or more years of observation.

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Cardiac Functional Analysis with Multi–Detector Row CT and Segmental Reconstruction Algorithm: Comparison with Echocardiography, SPECT, and MR Imaging[1]

Evaluation of global left ventricular (LV) function, especially ejection fraction (EF), and mass is important in the treatment of various cardiac diseases. To date, cardiac functional assessment has been performed with various noninvasive modalities, such as echocardiography (1,2), nuclear medicine (3), single–detector row helical computed tomography (CT) (4), electron beam CT (5–8), and magnetic resonance (MR) imaging (9–19). Cardiac MR imaging provides excellent temporal and spatial resolution, allows image acquisition

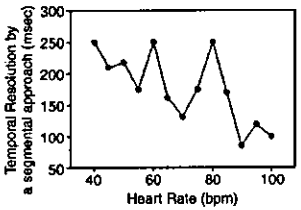

Figure 1. Graph shows temporal resolution of the multi–detector row CT system with segmental approach (rotation time, 500 msec; helical pitch, 2.0) at various heart rates. *bpm* = Beats per minute.

TABLE 1
Patient Characteristics and Final Diagnoses

Characteristics and Diagnoses	Multi–Detector Row CT and MR Imaging	Echocardiography	SPECT
Age (y)*	67 ± 10	67 ± 10	68 ± 10
Sex			
Male	28	22	17
Female	22	19	10
Heart rate (beats per minute)*	71 ± 13	71 ± 13	74 ± 13
Angina pectoris	12	9	12
Myocardial infarction	12	10	11
Valve disease	20	17	1
Other diagnoses	6	5	3
Total diagnoses	50	41	27

Note.—Unless otherwise indicated, data are numbers of patients.
* Data are mean ± standard deviation.

in any desired plane, and has a high degree of accuracy and reproducibility concerning quantitative measurements. In addition, MR imaging can be used to measure LV volume, without assumptions about LV cavity geometry. Thus, MR imaging is currently considered the reference standard in assessment of cardiac function (1,3,9–12,18,19).

In the past few years, multi–detector row CT has been increasingly used for noninvasive coronary artery imaging (20–31). In the evaluation of cardiac function, multi–detector row CT with a temporal resolution of 125–250 msec has been shown to be promising by comparing with biplanar cineventriculography (32) or MR imaging (33). However, it was indicated that reconstructed images obtained in patients with a high heart rate were of low quality because of motion artifacts; thus, manual tracing of endocardial contours had limited accuracy (32,33). A segmental reconstruction algorithm that uses data from several heartbeats has been introduced to further improve temporal resolution (34). The basic principle of segmental reconstruction is that data needed to reconstruct one image are collected retrospectively from several heartbeats by dividing into several segments. Each segment obtained in one cardiac cycle represents a shorter time period. Thus, a segmental reconstruction algorithm is considered to be effective in shortening the temporal resolution and reducing motion artifacts in patients with a high heart rate. Thus, the aim of this study was to evaluate the accuracy of cardiac functional analysis with multi–detector row CT and a segmental reconstruction algorithm over a range of heart rates.

MATERIALS AND METHODS

Phantom Studies

To evaluate artifacts of reconstruction images obtained with two retrospective electrocardiographically (ECG)-gated reconstruction methods, phantom (AZ-631N; Anzai Medical, Tokyo, Japan) studies were performed with various heart rates (every 5% of cardiac cycle, from 40 to 100 beats per minute). Method 1 involved a half reconstruction algorithm, and method 2 involved a segmental reconstruction algorithm that used data from several heartbeats. CT examinations were performed by using a multi–detector row CT scanner with eight detector rows (Aquilion Multi V1.10 JR 002 system; Toshiba, Otawara, Japan). In the scanning protocol, a collimation of 8 × 1 mm, a helical pitch of 2.0, and a rotation time of 500 msec were used. The temporal resolution with a half approach was 250 msec, while the temporal resolution with a segmental approach was further improved, depending on heart rate (Fig 1). Each helical CT scan was obtained with a tube voltage of 135 kV and a tube current of 200 mA. Image reconstruction was performed with a 1-mm increment by using both algorithms for each of these heart rates (35,36). Twenty sets of reconstructions at every 5% of the cardiac cycle, ranging from 0% to 95%, were performed in each study. One short-axis image and two long-axis cine images were reoriented from these sets of reconstruction data by using cardiac MPR software (Toshiba). The optimal end-diastolic and end-systolic phases were visually determined with these cine images.

Artifacts were evaluated on the reconstructed end-diastolic and end-systolic images of the different heart rates by two observers, each with 2 years of experience (S.K. and H.T.). The blurring artifact was scored visually with a five-point scale (0, no artifact; 1, slight artifact; 2, mild artifact; 3, moderate artifact; and 4, severe artifact). The stair-step artifact was scored with a three-point scale (0, no artifact; 1, mild artifact; and 2, severe artifact).

Human Studies

Patients referred for coronary multi–detector row CT from August 2002 to July 2003 for clinical reasons were included in this retrospective study. Among these 50 patients, MR imaging was used to assess cardiac function within 10 days before or after multi–detector row CT, during which time the condition of patients was stable. The study group consisted of 28 men (age range, 47–83 years; mean age, 67 years) and 22 women (age range, 46–84 years; mean age, 67 years). A test for the proportion with normal distribution with a 5% significance level was used to analyze the proportion of men and women, a two-sample *t* test with a 5% significance level was used to analyze the age difference between men and women, and an F test with a 5% significance level was used to analyze equality of variance between the age of men and women. No statistically significant difference was observed regarding age or sex. Mean heart rate during acquisition of CT scans ranged from 49 to 106 beats per minute (mean ± standard deviation, 71 beats per minute ± 13). A total of 20 patients had aortic and/or mitral valve disease, 12 had myocardial infarction, 12 had angina pectoris, two had infectious endocarditis, two had sarcoidosis, one had pericarditis, and one had dilated cardiomyopathy. During the same period, conventional two-dimensional echocardiography was performed in 41 patients, and ECG-gated single photon emission computed tomography (SPECT) was performed in 27. Patient characteristics and final diagnoses are shown in Table 1. Our