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Spontaneous Regression of Restenosis: An Angiographic Study

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Objectives. **This study was designed to examine the possibility that spontaneous regression in stenosis severity occurs over time in patients with restenosis after percutaneous transluminal coronary angioplasty.**

Background. **The underlying mechanisms of restenosis are intimal hyperplasia and smooth muscle cell proliferation in response to vascular injury. We hypothesized that the initial hyperplastic response is followed by dynamic remodeling and eventual spontaneous regression, leading to stabilization or a reduction in stenosis severity.**

Methods. **A total of 136 patients participated in a trial to evaluate the efficacy of fish oil versus placebo in preventing restenosis after angioplasty. One hundred thirteen patients completed this study with angiographic follow-up, of whom 56 had restenosis. Of these, 19 were asymptomatic and did not undergo repeat revascularization; 15 consented in a separate study to undergo repeat angiography, which was performed 6 to 25 months later to assess the possibility of regression.**

Results. **There was a significant mean (±SD) decrease in lesion severity from 66.9 ± 8.7% to 47.5 ± 9.0% ($p < 0.0001$) and a significant mean increase in minimal lumen diameter from 0.91 ± 0.31 mm to 1.44 ± 0.35 mm ($p < 0.0001$). No patient showed progression of stenosis, but regression of restenosis, defined as a decrease in minimal lumen diameter ≥0.2 mm, was noted in 12 of the patients.**

Conclusions. **Although all 15 study patients were asymptomatic, similar changes may occur in symptomatic patients. A trial of medical therapy may be appropriate in asymptomatic or mildly symptomatic patients before further interventions. This strategy would avoid unnecessary invasive procedures, prevent a "restenosis cycle" and result in significant cost savings.**

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Despite dramatic improvements in equipment design and the primary success rate of coronary angioplasty, the long-term efficacy of the procedure remains limited because of the perplexing problem of restenosis (1,2). Although significant advances have been made in understanding various mechanisms of the restenosis process (3–6), attempts to lower the incidence of restenosis by using aggressive pharmacotherapy and newer devices have met with very limited success. Restenosis remains the major drawback of all transcatheter interventions, resulting in repeat procedures, increased morbidity and rising costs (7).

In recent published reports the process of restenosis is regarded as a unique vascular expression of the systemic wound-healing response (6) and is initiated by injury to the vessel wall, resulting in the release of thrombogenic, vasoactive and mitogenic factors (7). The major events to follow are platelet aggregation, thrombus formation, inflammatory cell infiltration, smooth muscle cell migration and proliferation with proteoglycan deposition. Passive contraction of the dilated segments causing elastic recoil may also be evident in the early hours after angioplasty (8). This process results in a variable degree of lumen renarrowing in almost all patients after angioplasty (9). According to the definitions used in various angiographic trials, 25% to 55% of these segments are identified as restenotic (10).

Despite a plethora of data on 6-month angiography, the standard measure of restenosis, little is known about the natural history of restenosis beyond this time frame. We propose that in the absence of further vascular injury, the initial hyperplastic response is followed by a dynamic remodeling of the vessel wall, leading to significant spontaneous angiographic regression of restenosis. Two distinct mechanisms may account for the increase in the lumen diameter. Restenosis is regarded in recent reports (6,11,12) as a unique vascular expression of systemic wound healing. Similar to the contraction of scar tissue during the final phase of systemic wound healing, the hyperplastic neointimal mass at the restenosis site may shrink, and this neointimal thinning in the chronic phase would result in spontaneous regression of restenosis. Another independent mechanism playing a role during this chronic phase is arterial dilation as a compensatory response to intimal hyperplasia, as demonstrated by intravascular ultrasound in a subgroup of patients after transcatheter interven-

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tions (13). These factors would result in significant spontaneous angiographic regression of restenosis.

Methods

Patients. Between October 6, 1990 and May 7, 1993, 136 patients were enrolled at the Kaiser Permanente Medical Center in Los Angeles in the multicenter double-blind placebo-controlled Fish Oil Restenosis Trial (FORT) (14) to evaluate the efficacy of fish oil in preventing restenosis after angioplasty. Of these, 113 completed the study and underwent exit angiography to evaluate possible restenosis. By the study definition of restenosis—≥30% increase in narrowing or a loss of 50% of the gain achieved at the time of successful angioplasty, and a stenosis ≥50% on exit angiography (15)—56 patients were found to have restenosis during the 6 months of follow-up. Thirty-seven of the patients with restenosis had recurrent ischemic symptoms and were treated by repeat revascularization. Nineteen patients with restenosis were asymptomatic and did not undergo further intervention. Fifteen of these patients prospectively consented to participate in a separate angiographic study designed to assess the late natural history of restenosis and the hypothesis of spontaneous regression. The study protocol was reviewed and approved by the institutional review board. The time interval between exit from the parent trial and repeat late angiography in this study was 6 to 25 months (mean [±SD] 13 ± 6 months). All study patients were evaluated and followed up clinically.

Angiography. All angiographic procedures were performed by experienced operators under optimally standardized conditions to minimize measurement variability using the same procedure room, catheter equipment, matched angiographic projections and the administration of intracoronary nitroglycerin before each angiographic study.

Quantitative coronary angiography was performed by the core angiographic laboratory used in the FORT study (Baylor College of Medicine) using the computer-based Cardiovascular Angiographic Analysis System (CAAS) (16,17). This system, which utilizes automated edge detection and corrects for pincushion distortion, has been extensively validated (16,17). The intraobserver variability using this system is 0.2 mm (18). The values for the reference diameter (normal-appearing segment proximal to the stenotic segment), minimal lumen diameter (MLD) and percent diameter stenosis ([1 − MLD/Reference diameter] × 100) were measured before and immediately after angioplasty and at 6-month and late follow-up angiography.

Definition of regression and progression. *Regression* was defined as an increase in minimal lumen diameter ≥0.2 mm on late angiography compared with that at 6-month angiography. Conversely, *progression* was defined as a decrease ≤0.2 mm in minimal lumen diameter between these two time frames. A lesion was considered *stabilized* if it showed neither regression nor progression.

Statistical analysis. Results are expressed as mean value ± SD. Comparative analysis between 6-month and late follow-up angiography was based on the paired *t* test. The relation of changes in stenosis severity and minimal lumen diameter with potential risk factors, including those in Table 1, length of follow-up time and reference diameter were examined using analysis of covariance methods. A probability value <0.05 was regarded as significant.

Table 1. Demographic and Clinical Characteristics of 15 Study Patients

Mean age (yr)	63.7
Range	48–75
Male/female	11/4
Cardiac risk factors	
Hypertension	9
Diabetes mellitus	2
Smoking	5
Hypercholesterolemia	9
Family history	5
Angina	None
Fish oil/placebo in parent trial	9/6
Vessel undergoing angioplasty	
LAD	5
Cx	5
RCA	5

Data presented are number of patients, unless otherwise indicated. Cx (LAD, RCA) = circumflex (left anterior descending, right) coronary artery.

Results

Fifteen of 19 patients with asymptomatic restenosis from the parent trial consented to repeat angiography at least 6 months after exiting from the study (mean 13 ± 6 months, range 6 to 25). Four patients declined repeat angiography. The demographics and clinical characteristics of the patients are presented in Table 1.

Angiography. The quantitative coronary angiographic measurements of minimal lumen diameter and percent diameter stenosis and the interval changes in these measurements are shown in Table 2. All patients manifested an improvement in minimal lumen diameter and a reduction in percent diameter stenosis from 6-month to late follow-up angiography. In 12 patients the magnitude of improvement exceeded the intraobserver variability of the angiographic technique (0.2 mm) and therefore constituted significant regression of the stenosis. No patient exhibited progression of restenosis. Overall the mean (±SD) percent diameter stenosis for the 15 patients at exit from the parent study was 66.9 ± 8.7%. The final follow-up percent stenosis was 47.5 ± 9.0%. This result represents a significant ($p < 0.0001$) absolute mean decrease of 19.3 ± 12.5%. The mean minimal lumen diameter at exit from the parent study was 0.91 ± 0.31 mm. The final follow-up minimal lumen diameter was 1.44 ± 0.35 mm. The absolute mean increase in minimal lumen diameter was 0.53 ± 0.36 mm, which represents a significant mean increase in lumen diame-

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Table 2. Quantitative Coronary Angiographic Measurements at 6 Months After Angioplasty and at Late Follow-Up, Demonstrating Interval Change Representing Degree of Regression in Each Patient

Pt No.	Minimal Lumen Diameter (mm)			Percent Diameter Stenosis		
	6 mo	Late	Interval Change	6 mo	Late	Interval Change
1	1.59	1.70	0.11	53	50	− 3
2	0.71	1.47	0.76	73	43	−30
3	1.36	1.64	0.28	53	44	− 9
4	0.83	1.73	0.90	70	37	−33
5	1.21	1.64	0.43	55	39	−16
6	0.99	1.67	0.68	67	45	−22
7	0.57	0.92	0.35	74	58	−16
8	1.19	1.60	0.41	56	42	−14
9	0.69	1.99	1.30	77	36	−41
10	0.58	1.66	1.08	79	40	−39
11	0.86	1.09	0.23	66	56	−10
12	0.54	1.26	0.72	76	45	−31
13	1.08	1.43	0.35	62	49	−13
14	0.59	0.70	0.11	70	64	− 6
15	0.86	1.05	0.19	72	65	− 7

Pt = patient.

ter ($p < 0.0001$). The mean values of the reference diameter and diameter before and after angioplasty and at 6-month and late angiography are shown in Figure 1. The reference diameter remained remarkably constant at each time frame. The individual measurements of minimal lumen diameter and percent diameter stenosis are graphically displayed in Figures 2 and 3, respectively. The angiographic sequence in one patient (Patient 4) is shown in Figure 4.

There were no adverse clinical events during the follow-up period. There was no relation of regression to the particular vessel in which the angioplasty was performed. The results of the covariate analysis are presented in Table 3. The model includes all potential predictors that measurably explained (partial correlation) the variation in the regression in stenosis

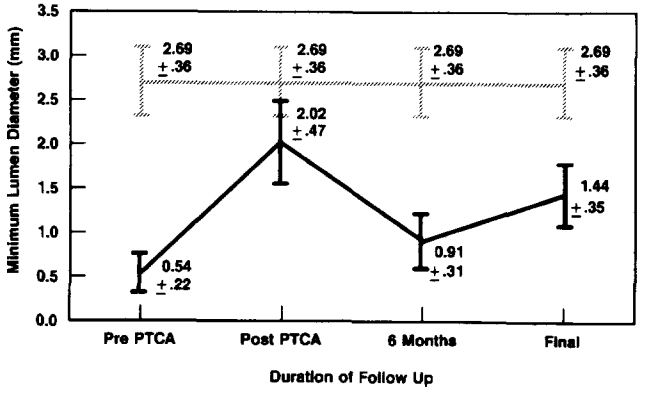


Figure 1. Serial changes in mean absolute diameter of the reference segments **(hatched line)** and stenotic segments **(solid line)** before (Pre PTCA) and immediately after angioplasty (Post PTCA) and at 6-month and late (Final) follow-up angiography.

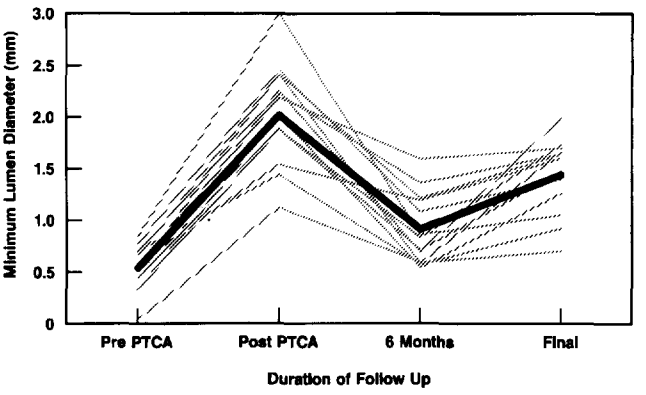


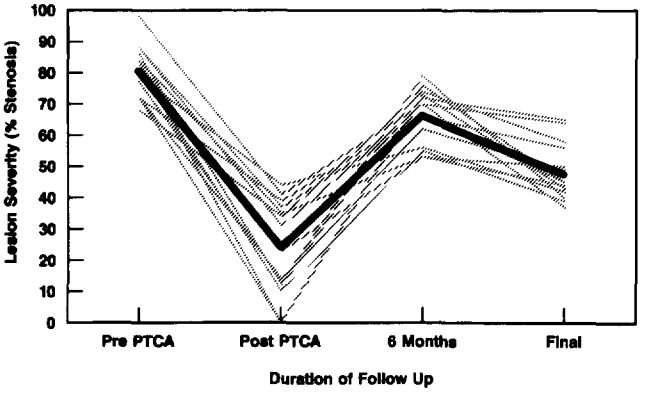
Figure 2. Serial changes in individual measurements of absolute diameter of the stenotic segments for each patient **(hatched lines)** and mean absolute diameter of the stenotic segments for the study group **(solid line)** before (Pre PTCA) and immediately after angioplasty (Post PTCA) and at 6-month and late (Final) follow-up angiography.

severity. None of the factors reached statistical significance. Of special interest was the time span between exit from the parent study and the performance of final angiography (days), which was not related to the regression in stenosis severity ($p = 0.7443$). The multiple correlation coefficient that measures the variation explained by all the factors considered was also not significant ($R = 0.679$, $p = 0.844$).

Discussion

Previous studies. Restenosis remains an enigmatic problem, occurring in 25% to 55% of patients (9,10,18–22) despite application of newer interventional techniques and use of a wide variety of pharmacologic agents (14,23–30). This variability in restenosis rates appears to be related to the criteria and angiographic techniques used in each study (18,20,21,31–34). Angiographic studies have shown that almost all lesions dete-

Figure 3. Serial changes in percent diameter stenosis for each patient **(hatched lines)** and mean percent diameter stenosis for the study group **(solid line)** before (Pre PTCA) and immediately after angioplasty (Post PTCA) and at 6-month and late (Final) follow-up angiography.



riorate to a certain degree by 120 days after angioplasty (9) and that restenosis peaks at 4 months, with little further loss of lumen diameter up to 1 year after angioplasty (9,19). A reduction in overall lesion severity at 3 years compared with that 6 months after angioplasty in all patients undergoing the procedure has been shown (35); however, the natural history of restenotic lesions has not been described.

Present study. The present study describes a previously unrecognized phenomenon of spontaneous regression of restenotic lesions. All 15 patients showed improvement in the measured variables of minimal lumen diameter and percent stenosis, and 12 manifested distinct regression as defined.

Table 3. Potential Predictors of Regression in Stenosis Severity (covariate analysis)

Factor	Coefficient	SE	p Value
Constant	0.9939	1.5501	0.5497
Days	−0.0004	0.0012	0.7443
Age	−0.0032	0.0234	0.8952
Male gender	−0.1158	0.3371	0.7452
Hypertension	−0.0346	0.3110	0.9156
Diabetes	−0.0762	0.6548	0.9118
Smoking	0.4663	0.4944	0.3889
Cholesterol	−0.2833	0.6501	0.6811
Family history	0.4330	0.5532	0.4693
Treatment (fish oil)	−0.1804	0.5405	0.7522

There was a relative increase in minimal lumen diameter of 58% (0.91 to 1.44 mm, $p < 0.0001$) (Fig. 2) and relative reduction in lesion severity of 28.9% (66.9% to 47.5%, $p < 0.0001$) (Fig. 3).

Pathogenesis of restenosis. The pathogenesis of restenosis is not completely understood. The process is multifactorial,

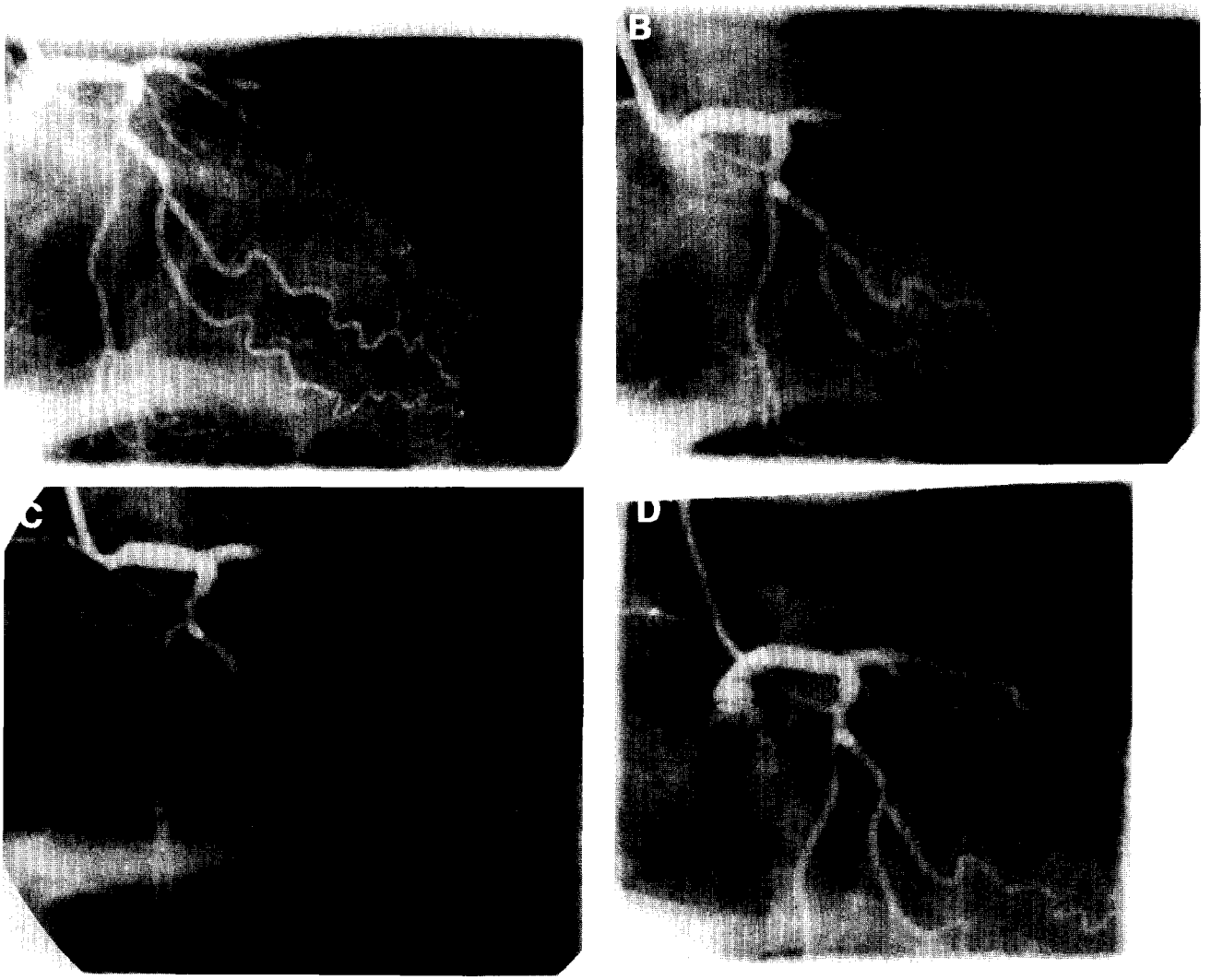


Figure 4. Right anterior oblique projection of the left anterior descending coronary artery in Patient 4. **A,** Preangioplasty angiogram showing a minimal lumen diameter of 0.33 mm and 88% diameter stenosis. **B,** Angiogram immediately after angioplasty showing a minimal lumen diameter of 1.88 mm and 31% diameter stenosis. **C,** Six-month follow-up angiogram demonstrating restenosis, with a minimal lumen diameter of 0.83 mm and 70% diameter stenosis. **D,** Final follow-up angiogram showing regression of restenosis, with a minimal lumen diameter of 1.73 mm and 37% diameter stenosis.

involving mural thrombus formation (18,36–40) and elastic recoil (41–45) early after the procedure. Later events are believed to be a vascular expression of similar events seen in wound healing (6,46). Balloon angioplasty leads to intimal denuding and medial stretch injury (47–51), which is followed by platelet aggregation at the site (6,52). The distorted endothelium and platelets release vasoactive substances and growth factors (53–57). In response to these stimuli, smooth muscle cells migrate from the media and surrounding tissue to the intima and proliferate, with formation of a connective tissue matrix (56,58–62). This process occurs to a certain extent in all patients (9) and leads to restenosis in some.

Mechanism of regression. The mechanism of regression seen in our patients remains speculative. Smooth muscle cells have two phenotypes (56,58,63,64). The *contractile phenotype* predominates in the normal vessel wall and is unresponsive to growth factors. The *synthetic phenotype* is closely related to the fibroblast. This phenotype is responsive to growth factors and is secretory, producing extracellular matrix, proteoglycan and collagen. After arterial injury, the synthetic phenotype smooth muscle cells migrate and proliferate in response to growth factors. By 2 weeks the synthetic smooth muscle cells are replaced by the contractile phenotype (6,64,65). Intimal hyperplasia reaches a peak at 4 to 12 weeks (66–69). As proliferation of smooth muscle cells diminishes, proteoglycan synthesis continues, and the relative volume of the intimal hyperplasia mass occupied by smooth muscle cells decreases (6,67). By 180 days the relative percent of contractile phenotype smooth muscle cells has returned to baseline levels (64). At this point there is a decreasing stimulus for proliferation, and regression may occur through a process similar to the final phase of wound healing. The underlying mechanism during this period in wound healing is contraction of the extracellular matrix and collagen fibers (11). A compensatory arterial dilation in response to restenosis has also been demonstrated by intravascular ultrasound (13). The exact relation of this observation to the regression observed in the present study is unclear, and the mechanism of this phenomenon needs to be studied.

Clinical implications. Although angiographic restenosis occurs frequently, 24% to 48% (20,70) of patients remain asymptomatic and have an excellent prognosis (70). All 15 patients in the present study remained asymptomatic and without adverse cardiac events. This result, coupled with the observed spontaneous regression, suggests that searching for ischemia in asymptomatic patients by elaborate, expensive and invasive tests may not be necessary. Because the incidence of acute myocardial infarction in patients with restenosis is low (71,72), repeat interventions could be reserved for more symptomatic patients. It is conceivable that mildly symptomatic patients treated medically may become asymptomatic through this process of spontaneous regression. This avoids the cycle of repeat interventions and their consequences. A prospective trial in mildly symptomatic patients may be needed to assess the full clinical implications of the present study.

Conclusions. Significant spontaneous regression or stabilization of restenotic lesions was noted in all 15 patients. There were no adverse clinical events in this group. Although no predictors of spontaneous regression of restenosis were found, this result may be related to the small number of patients in the present study. Similar to the process of restenosis, a variable degree of regression appears to involve the entire study population and therefore may be expected in patients with symptomatic restenosis as well. A trial of medical therapy in mildly symptomatic patients with restenosis may be appropriate before further interventions. This strategy will lead to avoidance of unnecessary interventions and prevent the "restenosis cycle," resulting in significant cost savings.

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