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Directional Atherectomy for Treatment of Restenosis Within Coronary Stents: Clinical, Angiographic and Histologic Results

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Objectives. The safety and long-term results of directional coronary atherectomy in stented coronary arteries were determined. In addition, tissue studies were performed to characterize the development of restenosis.

Methods. Directional coronary atherectomy was performed in restenosed stents in nine patients (10 procedures) 82 to 1,179 days after stenting. The tissue was assessed for histologic features of restenosis, smooth muscle cell phenotype, markers of cell proliferation and cell density. A control (no stenting) group consisted of 13 patients treated with directional coronary atherectomy for restenosis 14 to 597 days after coronary angioplasty, directional coronary atherectomy or laser intervention.

Results. Directional coronary atherectomy procedures within the stent were technically successful with results similar to those of the initial stenting procedure (2.31 ± 0.38 vs. 2.44 ± 0.35 mm). Of five patients with angiographic follow-up, three had restenosis requiring reintervention (surgery in two and repeat atherectomy followed by laser angioplasty in one).

Intimal hyperplasia was identified in 80% of specimens after stenting and in 77% after coronary angioplasty or atherectomy. In three patients with stenting, 70% to 76% of the intimal cells showed morphologic features of a contractile phenotype by electron microscopy 47 to 185 days after coronary intervention. Evidence of ongoing proliferation (proliferating cell nuclear antigen antibody studies) was absent in all specimens studied. Although wide individual variability was present in the maximal cell density of the intimal hyperplasia, there was a trend toward a reduction in cell density over time.

Conclusions. Although atherectomy is feasible for the treatment of restenosis in stented coronary arteries and initial results are excellent, recurrence of restenosis is common. Intimal hyperplasia is a nonspecific response to injury regardless of the device used and accounts for about 80% of cases of restenosis. Smooth muscle cell proliferation and phenotypic modulation toward a contractile phenotype are early events and largely completed by the time of clinical presentation of restenosis. Restenotic lesions may be predominantly cellular, matrix or a combination at a particular time after a coronary procedure.

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Restenosis remains the major limitation of percutaneous transluminal coronary angioplasty, occurring in 20% to 40% of patients within the 1st 6 months after angioplasty (1). The implantation of stents in coronary arteries or saphenous vein bypass grafts as an adjunct or alternative to coronary angioplasty was initially proposed to prevent late restenosis (2). However, restenosis has now been documented in a significant number of patients in the 1st 6 months after stenting (3,4). The optimal method to prevent restenosis or to treat its occurrence (or recurrences) after coronary angioplasty or coronary stenting is unknown. No pharmacologic treatment has been consistently successful in reducing restenosis rates after angioplasty (5). Although restenosis occurs with the use of mechanical interventions other than coronary angioplasty, no randomized trials have yet been reported to determine if more favorable restenosis rates result from their use. Directional atherectomy is one of these alternative mechanical interventions for nonoperative coronary vascularization. In selected patients excellent postprocedural results have been documented (6). Furthermore, because the tissue can be removed, it offers a unique opportunity to study the histologic features of the restenosis tissue.

In the past 2 years we have collected data from 10 procedures performed for restenosis within a stented coronary segment treated with directional atherectomy. The

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Table 1. Clinical Characteristics of Study Group

Pt No.	Age (yr)/Gender	Previous MI	Previous CABG	Smoker	Hypercholesterolemia	DM	Hypertension
1	56/M	1986	1982	–	–	–	+
2	58/M	—	—	–	+	–	–
3	41/M	—	—	–	–	–	+
4a	55/M	Inferior, 1977	1977/1983	–	+	+	–
5	64/M	—	1986/1987	+	+	+	+
6	67/F	Posterior	1986	–	+	–	–
7	67/M	—	1989				
4b	55/M	Inferior, 1977	1977/1983	–	+	+	–
8	44/M	Inferior, 1989	—	–	+	–	–
9	76/M	Inferior, 1974	1974	–	+	–	–

CABG = coronary artery bypass surgery; DM = diabetes mellitus; F = female; M = male; MI = myocardial infarction; Pt = Patient; – = not present; + = present.

purpose of this study was twofold: 1) to determine the feasibility, safety and late results of directional atherectomy for treatment of restenosis within coronary stents; and 2) to assess the tissue removed from the restenotic lesion that caused the narrowing within these stents. Although restenosis after coronary angioplasty has been characterized by proliferating smooth muscle cells associated with extracellular matrix formation, we were particularly interested to assess whether differences existed in restenosis after stenting. In addition, because the temporal changes in the histologic pattern after coronary angioplasty have been studied in only a limited number of patients (7), we wanted to study the proliferation rates and cell density of restenotic tissue removed at specific intervals of time to better characterize the development of restenosis. For the pathologic studies, we compared tissue retrieved by coronary atherectomy in nine patients with restenosis in stented arteries with tissue obtained from 13 patients with restenosis after coronary angioplasty or previous atherectomy without adjunct stenting.

Methods

The stent study groups consisted of nine patients who underwent 10 separate atherectomy procedures within the stent. Five of the patients were treated in Rotterdam, two in Belgium, one in the U.S. and one in Toulouse, France. The clinical characteristics are presented in Table 1. Five of the procedures were performed in stents placed in bypass grafts and the other four stents were implanted in native vessels (Table 2). Six of the stented vessels contained the Wallstent (Schneider), which is a self-expandable, stainless steel woven mesh stent (3,4). Two patients had an implanted Palmaz-Schatz stent (Johnson and Johnson), which is a balloon-expandable stainless steel tubular stent (8). One patient had received a Wiktor stent (Medtronic), a tantalum balloon-expandable stent with a helical coil design (9). In five patients stenting was performed for a primary lesion; in the remaining four patients stenting was originally performed for restenosis after coronary angioplasty. Two of these patients (Patients 4 and 9) had multiple restenoses, and one of these (Patient 4) underwent a second atherectomy procedure within the stent for a recurrence of restenosis after the initial atherectomy. All patients with coronary stents were treated with heparin initially and then maintained on therapy with aspirin and vitamin K antagonist (warfarin or acenocoumarol) for a mean of 230 days (range 42 to 1,179). Atherectomy was performed within the narrowed stent 82 to 1,179 days after stenting. Three of the patients had separate coronary angioplasty procedures for stent-related problems

Table 2. Characteristics of Vessel and Lesion

Pt No.	Stent Vessel	Reason for Stenting (lesion type)	Stent Type	Stent Diameter (mm)	Time to Atherectomy (days)*	Present Status (NYHA class)
1	CABG	Primary	Wallstent	3.5	47 (144)	Surgery for restenosis
2	LAD	Restenosis	Palmaz-Schatz	3	82	Surgery for restenosis
3	LAD	Primary	Palmaz-Schatz	3.5	89	Class I
4a	CABG	Restenosis	Wallstent	3.5	96 (462)	Laser angioplasty
5	LCx	Primary	Wallstent	3.5	130	Dead (renal failure)
6	CABG	Primary	Wallstent	4	135	Class I
7	CABG	Primary	Wallstent	4	143	Class II
4b	CABG	Restenosis	Wallstent	3.5	156 (366)	Atherectomy
8	RCA	Restenosis	Wiktor	3.5	183	Class I
9	CABG	Restenosis	Wallstent	5	609 (1,179)	Class II

*Figures in parentheses represent the number of days after the stent procedure when additional procedures were required. CABG = coronary artery bypass graft; LAD = left anterior descending artery; LCx = left circumflex coronary artery; NYHA = New York Heart Association; Pt = Patient; RCA = right coronary artery.

before the atherectomy. Patient 1 initially underwent coronary angioplasty for restenosis 97 days after stenting and then required atherectomy 47 days later for a second restenosis within the stent. Patient 4 underwent balloon angioplasty for restenosis 210 days after stent implantation and then atherectomy 156 days later (366 days after stenting). Because of restenosis, a second atherectomy procedure was performed 96 days after the first atherectomy (462 days after stenting). Patient 8 had a symptomatic acute occlusion 5 days after stenting. After recanalization with intracoronary streptokinase and coronary angioplasty, he had an uneventful recovery until angina recurred 5 months later because of restenosis within the stent. Patient 9 received a second stent for a different lesion in the bypass graft 570 days after the first stent. A lesion subsequently developed in the initial stent and was treated by atherectomy 1,179 days after the first stent implantation (602 days after the second stent implantation). After atherectomy, two patients (Patients 1 and 9) remained on Coumadin therapy and all patients took aspirin for at least 3 months after atherectomy.

For the histologic evaluation of the tissue, we selected a control group that consisted of all patients in the Thorax-center experience who underwent an atherectomy procedure for restenosis after coronary angioplasty, atherectomy or laser treatment (n = 13) (see Table 5). This group consisted of 11 men and 2 women, from 40 to 71 years old. The interval between the most recent intervention and atherectomy for restenosis ranged from 14 to 597 days.

Angiographic analysis. All cineangiograms were analyzed with use of the computer-assisted cardiovascular angiography analysis system (CAAS), which has previously been discussed in detail (10). In brief, any area 6.9 × 6.9 mm in a selected cine frame (overall dimensions 18 × 24 mm) encompassing the desired arterial segment can be digitized by a high resolution CCD camera with a resolution of 512 × 512 pixels and eight bits of gray level. Contours of the desired segment are determined automatically on the basis of weighted sum of the first and second derivative functions applied to the digitized brightness information along scan lines perpendicular to the local centerline directions of the vessel segment of interest. A computer-derived estimation of the original dimension at the site of the narrowing is used to define the interpolated reference diameter. This technique is based on a computer-derived estimation of the original diameter values over the analyzed region (assuming that no narrowing was present) according to the diameter function. The absolute diameter of the stenosis and the reference diameter are measured by the computer, which uses the diameter of the guiding catheter as a calibration factor after correction for pincushion distortion.

Tissue analysis. After extraction of the tissue with the Simpson Coronary Atherocath, the specimens were carefully removed from the housing chamber of the catheter, washed with 0.9% saline solution and cut into pieces approximately 1 × 1 to 2 mm. Representative pieces were fixed in 10% buffered formalin for light microscopic studies. The specimens were processed according to standard procedures, and then paraffin sections were stained with hematoxylin-azophloxine and with van Gieson. Three to five slides were prepared at various levels through the paraffin block. The tissue was specifically assessed for the presence of intimal hyperplasia and atherosclerotic plaques according to the definitions of Johnson et al. (11). Intimal hyperplasia was defined as highly cellular tissue consisting of randomly arranged stellate and spindle cells in an abundant, collagen-containing extracellular matrix. Atherosclerotic plaques consisted of dense fibrous tissue with abundant collagen, scattered fibroblasts and occasional mononuclear cells including lymphocytes and macrophage/foam cells.

Immunohistochemical studies. In deparaffinized sections immunostaining was performed with monoclonal antibodies directed against alpha-smooth muscle cell actin (Sigma) with the use of an indirect conjugated peroxidase procedure. Proliferating cells were identified immunocytochemically by

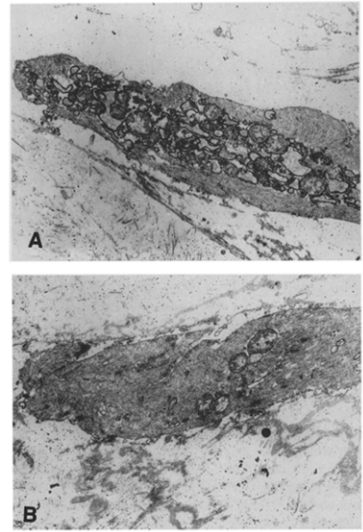

Figure 1. Transmission electron micrograph showing (A) a smooth muscle cell with the synthetic phenotype. There are abundant cytoplasmic organelles including endoplasmic reticulum, Golgi apparatus and ribosomes. Only a few myofilaments are present and are located in the periphery of the cell. B, Contractile smooth muscle cell cytoplasm consists mostly of myofilaments and a few mitochondria.

Table 3. Angiographic Results

Pt No	Reference Diameter (mm)	Before Stenting MLD (mm)	Before Stenting DS (%)	After Stenting MLD (mm)	After Stenting DS (%)	Stent Follow-Up Days* After Stenting	Stent Follow-Up MLD (mm)	Stent Follow-Up DS (%)	After Atherectomy MLD (mm)	After Atherectomy DS (%)	Atherectomy Follow-Up Days After Atherectomy	Atherectomy Follow-Up MLD (mm)	Atherectomy Follow-Up DS (%)
1	2.37	1.07	56	1.95	22	49 (144)	0.91	62	2.58	8	131	0.63	74
2	2.84	1.15	59	2.67	5	82	1.19	56	2.26	24	14	1.89	39
3	3.14	1.84	49	2.84	14	89	1.34	58	2.18	32	44	1.34	58
4a	3.1					96	0.90	58	2.33	47		—	
5	3.1	1.1	60	2.1	19	130	1.30	59	2.37	25		—	
6	2.9	0.6	72	2.0	38	135	0.63	78	1.77	32	186	2.46	22
7	2.25	0.75	78	2.55	30	143	0.70	69	2.1	29		—	
4b	3.1	1.2	61	2.8	15	156 (366)	1.03	66	2.81	21	96	0.9	58
8	3.33	0.96	71	2.36	28	183	1.11	62	2.34	29	75	2.37	20
9	2.75	1.40	64	2.71	21	609	0.81	71	2.4	22		—	
Mean	2.89	1.12	63	2.44	21		0.99	64	2.31	27		1.79	39
±SD	0.35	0.36	9	0.35	10		0.24	7	0.28	10		0.67	19

*Figures in parentheses represent the number of days after the stent procedure when additional procedures were required. DS = diameter stenosis; MLD = minimal lumen diameter; Pt = patient; — = not done.

using a monoclonal mouse antihuman proliferating cell nuclear antigen antibody (PCNA) (DAKO-PCNA, PC10). This antigen is a deoxyribonucleic acid (DNA) polymerase auxiliary protein and is expressed during G1, S (DNA synthesis) and G2 phases of the cell cycle (12–14) but not in the quiescent G_0 phase. Small intestinal mucosa served as positive control for PCNA staining.

Electron microscopy. Representative pieces were fixed in a solution of glutaraldehyde-formaldehyde (4CF-1G). Postfixation was done with osmium oxide$_4$. The specimens were then embedded in Epon and ultrathin sections were stained with uranyl acetate and lead citrate. All specimens contained smooth muscle cells in an abundant extracellular matrix. Cells were assessed as either contractile or synthetic type smooth muscle cells based on the following morphologic features (15): 1) The synthetic cells were characterized by extensive cytoplasmic organelles, including endoplasmic reticulum, Golgi apparatus and ribosomes, and by peripheral location of myofilaments (Fig. 1A); 2) the cytoplasm of the contractile cells consisted mostly of myofilaments and a few mitochondria (Fig. 1B); and 3) cells were counted in multiple fields (at least 150 cells in total) and classified according to these criteria into two phenotypes.

Cell density of intimal hyperplasia. In hematoxylin- and azophloxine-stained sections, areas of intimal hyperplasia were identified, and cell number was assessed in several fields by a computerized morphometry system (IBAS, Kontron). The maximal value recorded was used to determine cell density, which was expressed as cell number/mm^2 intimal tissue. Specimens without intimal hyperplasia were excluded from this measurement because this part of the study was specifically designed to look for temporal changes in cellularity occurring in areas of intimal hyperplasia formed in response to the coronary procedure.

Results

Clinical findings. All atherectomy procedures were technically successful (residual stenosis <50% with retrieval of tissue), and there were no procedural complications other than a transient ischemic attack that occurred during coronary angioplasty of a separate lesion in one patient. The only technical problem occurred with the Wiktor stent; after the procedure the configuration of the stent was disrupted, although no complications ensued. Tiny fragments of the tantalum wire were observed in the atherectomy material. All patients had immediate alleviation of their symptoms. At late follow-up study (4 to 15 months), Patient 2 had died after bypass surgery for restenosis after atherectomy and Patient 5 had died because of end-stage renal failure. Two other patients required additional interventions for recurrence of symptoms due to restenosis after atherectomy. Patient 1 underwent bypass surgery 6 months after the atherectomy, and Patient 4 was treated with excimer laser therapy. Five of the patients remained in New York Heart Association functional class I or II.

Quantitative angiography (Table 3). Immediately after placement of the stent there was an overall significant increase in the minimal lumen diameter and a significant decrease in the percent of the diameter with stenosis (changing from a mean value ± SD of 1.12 ± 0.36 to 2.44 ± 0.35 mm and from 63 ± 9% to 21 ± 10%, respectively; $p < 0.001$). However, at follow-up study before the atherectomy, all of the lesions had deteriorated, and the respective overall values were 0.99 ± 0.24 mm and 64 ± 7%. The immediate result after atherectomy was similar to the immediate results of stenting (2.31 ± 0.28 mm, 27 ± 10%). Late follow-up study after atherectomy was performed in only five lesions, with significant deterioration (loss ≥0.72 mm) occurring in three lesions. Figure 2 shows an example of the angiographic

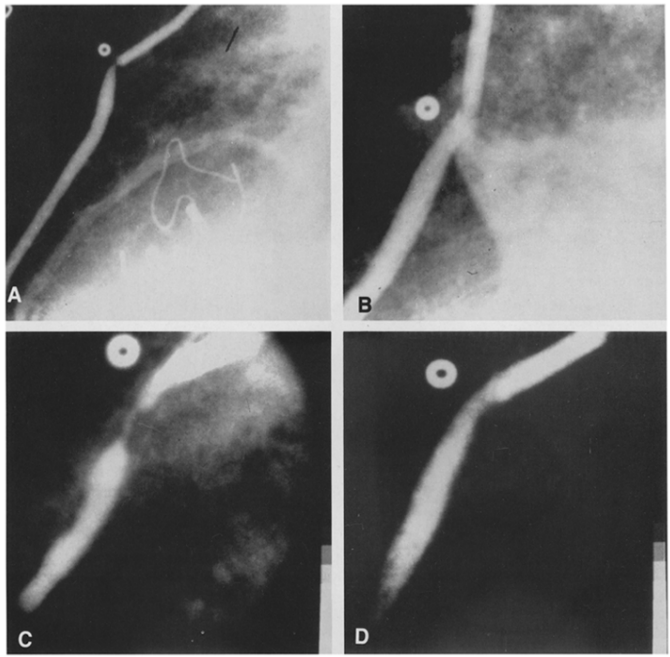

Figure 2. Stenosis in a proximal bypass graft. **A,** Before stenting. **B,** Immediate result after stenting. **C,** Restenosis in the stent distal to the original site of stenosis. **D,** Immediate result after atherectomy within the stent.

Table 4. Histologic Results in Study Group

Pt No.	Duration After Procedure (days)*	Intimal Hyperplasia	Media	Adventitia	Actin	PCNA
1	47 (144)	–	–	–	++	–
2	82	+	+	–	NA	NA
3	89	+	–	–	++	–
4a	96 (462)	+	–	–	++	–
5	130	+	+	–	NA	NA
6	135	+	–	–	++	–
7	143	+	–	–	++	NA
4b	156 (366)	–	–	–	++	–
8	183	+	–	–	++	–
9	609 (1,179)	+	–	–	++	–

*Duration after procedure refers to the most recent procedure; numbers in parentheses represent the number of days after the stent procedure when additional procedures were required. NA = not assessed; PCNA = proliferating cell nuclear antigen; Pt = patient; – = not present; + = present; ++ = strongly positive.

appearance of the lesion before and immediately after stenting and at follow-up study before and after atherectomy.

Histology. *After stenting (Table 4).* The characteristic feature in tissue obtained in eight of the lesions was intimal hyperplasia, defined as a proliferative cellular response associated with a matrix of loose connective tissue. The area of intimal hyperplasia was typically sharply demarcated from the underlying sclerotic plaque. However, the cellularity, amount of collagen and extracellular matrix of the intimal hyperplasia varied among patients (Fig. 3 and 4). In eight of the lesions the main cell type within the lesions was identified as smooth muscle cells as assessed by the presence

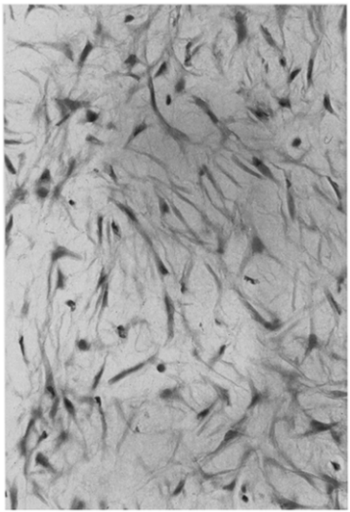

Figure 3. Hematoxylin-azophloxine-stained section of tissue removed from a stent 89 days after stenting. The section has the typical appearance of intimal hyperplasia (highly cellular tissue consisting of randomly arranged stellate and spindle cells in a loose extracellular matrix). Original magnification ×25, reduced by 35%.

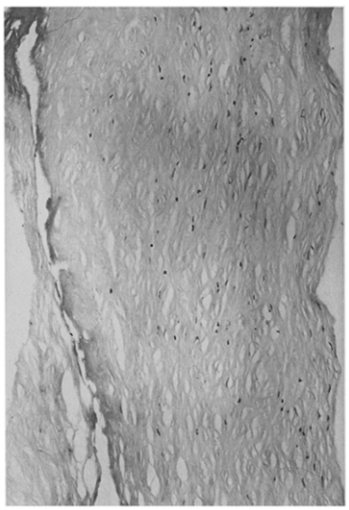

Figure 4. Hematoxylin-azophloxine-stained section of tissue removed from a stent 156 days after stenting. No intimal hyperplasia was present. The tissue consisted of a few cells embedded in an abundant collagen-containing extracellular matrix. Original magnification ×10, reduced by 35%.

of smooth muscle cell specific alpha actin. Results of specific staining for endothelial cells and macrophages were negative in two specimens tested although lymphocytes were identified in tissue from Patient 3. No giant cells, indicative of a foreign body reaction, were identified in any tissue specimen. Prominent capillary ingrowth was evident in three specimens. In two specimens the internal elastic lamina and adjacent media were identified (Fig. 5). No evidence of adventitia was recovered. Ultrastructural studies in three patients with stenting (Patients 1, 6 and 8) showed that the majority (70% to 76%) of intimal cells were contractile in morphology. No differences could be appreciated at the different time intervals. No differences were found in histologic or immunochemistry features between types of lesions (primary vs. de novo), vessels (native artery vs. bypass graft) or stents.

After angioplasty or atherectomy (Table 5). In the control coronary angioplasty or atherectomy group, the histologic appearance of the tissue was indistinguishable from the stent tissue. Intimal hyperplasia was evident in 10 of the 13 specimens, and various stages of cellularity were evident. Media was obtained in three specimens (22%). No evidence of adventitia was recovered.

Proliferation studies (Tables 4 and 5). In all specimens studied, no cells could be identified that reacted with the antibody to PCNA.

Cell density. The maximal cell density of the intimal hyperplasia in the patients with stenting and the control group is shown in Figure 6. Although wide individual variability was present, there was a trend toward a reduction in cell density of the intimal hyperplasia over time.

Discussion

Restenosis persists as an important limitation to all forms of nonoperative coronary revascularization despite increasingly more complex forms of interventions, such as stenting, atherectomy and laser-assisted therapy. It remains to be established whether any mechanical method can effectively treat (and prevent recurrent) restenosis after coronary balloon angioplasty or stenting. This study demonstrates in a limited number of patients the feasibility and safety of

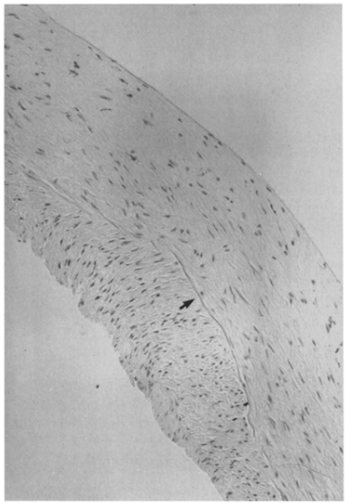

Figure 5. Hematoxylin-azophloxine-stained section of tissue removed from a stent 82 days after stenting. The presence of the media is indicated by the internal elastic lamina (**arrow**) and the typical architecture of the smooth muscle cells in the media. Original magnification ×10, reduced by 35%.

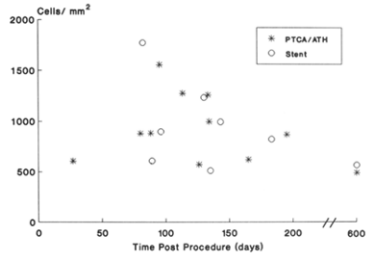

Figure 6. Maximal cell density (cell number/mm²) in restenotic lesions after stenting and coronary angioplasty (PTCA) or atherectomy (ATH). The x-axis represents the number of days after the procedure. Only restenotic lesions with intimal hyperplasia were evaluated. There is a trend toward decreasing cellularity over time in these lesions, although considerable individual variability is evident.

performing directional atherectomy for stent restenosis. In fact, atherectomy may be a safer procedure in stented than in nonstented vessels because the wires appear to limit the depth of the cutter into the vascular wall and thus reduce the possibility of perforation. However, it is still possible to remove media (as in Patients 3 and 6) either between the stent wires or if the stent wire has penetrated the internal elastic lamina.

Angiographic findings. The angiographic restenosis and the requirement of reintervention after 4 of the 10 procedures suggest that directional atherectomy is not particularly effective in preventing recurrence of restenosis in stented coronary arteries. The high rate (42%) of angiographic restenosis in our control group (5 of 12 patients) also supports other studies that indicate that atherectomy is not superior to conventional coronary angioplasty in preventing the recurrence of restenosis in nonstented restenosed lesions (and, in particular, saphenous vein bypass grafts) (16). The

Table 5. Histologic Results of Restenosis After Coronary Angioplasty (PTCA) or Atherectomy in the Control Group

Pt No.	Age (yr)/ Gender	Vessel	Procedure	Duration After Procedure (days)*	Intimal Hyperplasia	Media	Adventitia	PCNA
1	66/F	LAD	PTCA	14	–	+	–	–
2	51/M	LAD	Atherectomy	24 (58)	+	–	–	–
3	66/M	RCA	PTCA	56	–	–	–	·
4	67/M	LAD	PTCA	80	+	–	..	–
5	60/M	LCx	PTCA	88	+	–	–	NA
6	75/M	LAD	PTCA	95	–	–	–	NA
7	56/M	LAD	PTCA	113	+	+	–	NA
8	52/M	LAD	PTCA	126 (201)	+	–	–	NA
9	40/M	LAD	Atherectomy	133	+	–	–	–
10	71/F	LAD	PTCA	134	+	+	–	NA
11	49/M	LAD	Laser	165	+	–	–	NA
12	64/M	LAD	Atherectomy	195	+	–	–	NA
13	58/M	RCA	PTCA	397	+	–	–	NA

*Duration after procedure refers to the most recent procedure; numbers in parentheses represent the number of days after the initial coronary intervention when additional procedures were required. Abbreviations and symbols as in Tables 1, 2 and 4.

recurrence of angiographic restenosis after atherectomy in three of four patients with symptomatic restenosis of a stented vessel within 3 months of the stenting procedure also emphasizes the relation between recurrence of restenosis and a short interval between initial procedure and presentation of restenosis seen in several angioplasty studies (17,18). Similarly, a recent (<4 months) coronary angioplasty predicted recurrent restenosis treated with directional atherectomy in a study in which the restenosis rate was 44% (19).

Histologic findings. Histologic evaluation of the tissue retrieved from restenotic lesions (after stenting, coronary angioplasty, atherectomy or laser treatment) confirms the findings of previous studies: 1) intimal hyperplasia is the characteristic feature in 75% to 80% of restenotic tissue specimens from arteries treated with atherectomy, and the remaining 20% to 25% of specimens contain only atherosclerotic plaque material without the features of intimal hyperplasia (11); and 2) smooth muscle cells are the predominant cell type found in restenotic lesions (20–22). It is unclear whether the absence of intimal hyperplasia in such lesions is due to a sampling error by the atherectomy catheter or another mechanism of restenosis, such as elastic recoil or inadequate initial dilation. If larger studies confirm this observation, it indicates that restenosis interventional trials (pharmacologic or mechanical) with the intention of preventing smooth muscle cell proliferation and the formation of intimal hyperplasia can potentially affect only approximately 75% of patients at risk for restenosis. Future study designs may consider this in determining sample size for restenosis trials. In addition, our study also illustrates that intimal hyperplasia predominates in restenotic tissue regardless of the initiating procedure, with no unique features attributable to stenting in general or to a particular type of stent. This observation underscores the fact that intimal hyperplasia is a nonspecific response to vascular injury regardless of the method of damage (23,24).

The temporal sequence of events in the formation of intimal hyperplasia after coronary intervention remains largely unknown. Our results suggest the following:

Smooth muscle cell proliferation is an early event and barely detectable 2 months after the procedure. To date there are no data on the cell proliferation rates in humans after balloon angioplasty, although the use of cyclin to label proliferating cells in human de novo atherosclerotic plaques has previously shown a labeling index ranging from <1% to >4% (25,26). Our results, showing no proliferative activity in the smooth muscle cells 82 days to 700 days after stenting, suggest that smooth muscle cell proliferation is an early and limited process after vascular injury in humans. This is similar to the results after vascular balloon denudation in animals in which smooth muscle cell proliferation is first observed 48 h after vascular injury, and peak proliferation occurs at about 1 week, followed by a rapid decline and reaching baseline values by a month after the vessel injury (27). Owing to the limited period of smooth muscle cell proliferation early after coronary angioplasty, pharmacologic agents designed to reduce proliferation may only be required in the 1st 2 months after the procedure rather than the 6 months usually prescribed.

The vast majority of smooth muscle cells modulate toward the contractile phenotype early after the procedure. Therefore, only a relatively small percentage of the smooth muscle cells (that is, those with the synthetic phenotype) appear to be responsible for the synthesis of extracellular matrix proteins because in vitro studies have shown that the production of proteoglycans and collagen is 5-fold and 26 to 45-fold higher, respectively, in the synthetic phenotype (28,29). In our study synthetic type smooth muscle cells only comprised 24% to 30% of the overall smooth muscle cells in the three patients with stented arteries who underwent atherectomy 47 to 183 days after coronary intervention. In contrast, Nobuyoshi et al. (7) identified "synthetic" type smooth muscle cells as the predominant cell type in the 1st 6 months; thereafter, the "contractile" type smooth muscle cell was dominant. This earlier predominance of contractile smooth muscle cells in our study may be due to differences in methods of assessment (electron microscopy vs. less reliable light microscopic features in the series of Nobuyoshi et al.) or possibly related to differences in procedures (stenting vs. coronary angioplasty alone). In a balloon injury model in rats, Kocher et al. (30) observed a phenotypic change (toward a contractile type) similar to that in our study in lesions 75 days after injury, based on the ratio of smooth muscle to nonmuscle actins that had returned to levels of normal medial (contractile) smooth muscle cells.

Lesion cellularity decreases as a function of time but with a wide interindividual variability. As a consequence, lesions may be predominantly cellular, matrix or a combination at a particular time after a coronary procedure. Restenosis has been regarded as a process that is largely completed by 6 months after a procedure. Although cellular proliferation and matrix synthesis are recognized as the components of the restenotic lesion, the remodeling of the vessel wall after vessel injury is not understood and the relative contribution (and possibly the preeminent role) of the matrix components (proteoglycans and collagen) has not been appreciated. An inverse relation appears to exist between the cellularity of the intimal hyperplastic lesions and the number of days after a procedure, although there is great individual variability.

A temporal relation between the cellularity of the intimal hyperplastic lesions appears to exist, although wide individual variability is present. Because cellular proliferation appears to be an early event, the cellularity of the lesion is primarily related to the amount of synthesized matrix. The wide range of cell density at a particular time interval may be related to either inherent biologic variability or possible sampling error. The total amount of matrix present at a particular time is related to the synthesis and resorption of the particular component. The turnover of proteoglycans is unknown, although the limited data show low collagen and elastin turnover in experimental models of hypertension (31). The individual variability in cell density emphasizes the

differential importance of matrix deposition in individual lesions. Determining the composition and extent of the matrix synthesis during remodeling of the vessel after atherectomy, stenting or coronary angioplasty is an important step in understanding the process of restenosis. It should lead to new and synergistic pharmacologic approaches beyond control of smooth muscle cell proliferation, which appears to be an early process and difficult to limit.

Study limitations. This study is primarily limited by the relatively small amount of tissue extracted by the atherectomy catheter, which causes a potential sampling bias error. In particular, the device may not have removed the region of intimal hyperplasia containing the highest cell density or high cell proliferation or possibly even may have completely missed areas of intimal hyperplasia in specimens that showed only old atheroma. Therefore, the findings from this study with respect to the remodeling of the lesion over time should be confirmed in more extensive studies.

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