ANGIOGRAPHIC ASSESSMENT OF RESTENOSIS AFTER PTCA

ANGIOGRAFISCHE BEOORDELING VAN RE-STENOSE NA PERCUTANE TRANSLUMINAL CORONAIRE ANGIOPLASTIEK

Proefschrift

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To my parents for their tolerance, encouragement, wisdom and company.

To Karen for her selfless support,

and to my two best friends James and Lawrence.

Introduction and Overview

The work presented in the following chapters covers a period from 1985 to 1992. Progress in our understanding the clinical problem of restenosis following coronary angioplasty has been slow and has been due not only to our failure to accurately determine the pathophysiology of restenosis but also to our inability to understand the limitations of our measurement systems in documenting and assessing the process.

The original restenosis study, conducted at the Thoraxcenter, in which all patients were to have follow-up angiography at a predetermined time was begun in an era when assessment was entirely on a categorical basis, the value of angiographic follow-up questionable and the use of quantitative angiography largely unknown amongst clinical cardiologists. The initiative to start the study by the Cardiac Catherisation laboratory and the impetus by Patrick Serruys to carry it through reflects an insight into the problem that was well ahead of its time.

Chapters 2 and 3 detail our understanding of the early results and represent the first attempts to move away from the established criteria for assessing restenosis and to make the distinction between restenosis as it applies to the individual patient and the assessment of restenosis as it applies to populations undergoing coronary angioplasty. Chapter 2 is the first publication to delineate the timing of restenosis which prior to this was described as occurring within six months, and Chapter 3 is the first to describe the Gaussian distribution of the restenosis population, a concept whose importance has only this year been widely recognised.

Chapter 4 represents another major landmark in our understanding of clinical restenosis. This was published simultaneously with complementary animal studies and had the effect of reversing the considerable resistance to the concept built up over the previous 2 years. The distribution of the restenosis parameters, first addressed in Chapter 2, are further developed This controversial paper makes the distinction between a sub-optimal angioplasty results and late restenosis. It describes new risk factors for restenosis and questions the relevance of virtually all previous publications dealing with risk factors related to restenosis.

The final chapter in this section summarises the developments at the end of the first decade of angioplasty and makes recommendations for more appropriate methodology in future studies, which are particularly relevant to the assessment of new devices.

Part II deals with the application of quantitative angiography as applied to the assessment of new devices in general and to stent implantation in particular. The assessment of the clinical utility of these devices have been controversial, with disagreement between published reports. The failure of investigators to report the benefits and limitations in a clear and scientifically precise manners has lead investigators to undertake many unnecessary studies subjecting patients inappropriate and inconvenient investigations. Chapter 9 in particular conveys a different and more appropriate evaluation of the benefits and complications of intracoronary stent implantation. The adoption of concepts developed in Part I, particularly the distinction between the dilating effect and the restenosis process, have allowed more appropriate evaluation. There is now a much greater acceptance among interventional cardiologists of the methods covered in Part 1, and it seems likely that this will lead to a more uniform and cohesive understanding of the benefits and limitations. However, the exact way in which the results should be documented remains controversial. The proposal put forward by the author is dealt with in Chapter 14, and is the only one that adequately takes into account the "paradox" of restenosis.

Part I

Populations and Characteristics of coronary angiographic variables in patients following angioplasty

Chapter 1

Incidence of restenosis after successful coronary angioplasty: a time-related phenomenon. A quantitative angiographic study in 342 consecutive patients at 1, 2, 3, and 4 months. Circulation 1988; 77:361-371.

Incidence of restenosis after successful coronary angioplasty: a time-related phenomenon

A quantitative angiographic study in 342 consecutive patients at 1, 2, 3, and 4 months

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ABSTRACT Data from experimental, clinical, and pathologic studies have suggested that the process of restenosis begins very early after coronary angioplasty. The present study was performed to determine prospectively the incidence of restenosis with use of the four National Heart, Lung, and Blood Institute and the 50% or greater diameter stenosis criteria, as well as a criterion based on a decrease of 0.72 mm or more in minimal luminal diameter. Patients were recatheterized at 30, 60, 90, or 120 days after successful percutaneous transluminal coronary angioplasty (PTCA). After PTCA all patients received 10 mg nifedipine three to six times a day and aspirin once a day until repeat angiography. Of 400 consecutive patients in whom PTCA was successful (<50% diameter stenosis), 342 underwent quantitative angiographic follow-up (86%) by use of an automated edge-detection technique. A wide variation in the incidence of restenosis was found dependent on the criterion applied. The incidence of restenosis proved to be progressive to at least the third month for all except NHLBI criterion II. At 4 months a further increase in the incidence of restenosis was observed when defined as a decrease of 0.72 mm or more in minimal luminal diameter, whereas the criteria based on percentage diameter stenosis showed a variable response. The lack of overlap between the different restenosis criteria applied affirms the arbitrary nature of angiographic definitions currently in use. Restenosis should be assessed by repeat angiography, and preferably ascertained according to the change in absolute quantitative measurements of the luminal diameter.
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PREVIOUS STUDIES with exercise thallium-201 scintigraphy and exercise-gated radionuclide ventriculography performed in asymptomatic patients after successful percutaneous transluminal coronary angioplasty (PTCA) have suggested that the process of restenosis begins early after the procedure.[1–3] Data from experimental, clinical, and pathologic studies have indicated that restenosis may occur within 60 days via two mechanisms: first, platelet deposition at the site of endothelial denudation early after angioplasty (minutes to days) can induce spasm and the formation of a mural thrombus, which may subsequently undergo organization and cause restenosis[4–7]; second, release of platelet-derived growth factor may induce an excessive intimal fibroproliferative response consisting mostly of proliferating smooth muscle cells which may contribute to late (7 to 150 days) restenosis.[5, 8–15]

It is generally considered that evidence of restenosis usually presents itself within 6 months after angioplasty, and is extremely infrequent after 12 months. However, several angiographic studies have demonstrated that most patients with symptomatic restenosis manifest anginal symptoms by the third month after angioplasty.[16–21] The timing and incidence of "silent" restenosis (e.g., recurrent stenosis without symptoms) in the first 3 months after PTCA remains unknown.

The present study was performed to determine the incidence and time to restenosis with the use of six different angiographic criteria in a consecutive series of patients. For this purpose the study population was subdivided into four groups of patients allocated to be recatheterized at 30, 60, 90, and 120 days after suc-

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cessful PTCA, respectively. This approach permits a critical assessment of the values and limitations of the currently used restenosis criteria and raises several methodologic issues, including those related to how we define and quantify restenosis: should we express our quantitative measurements in absolute values or in relative percentages?

Materials and methods

Study population. The initial cohort of patients consisted of 400 patients who had undergone successful coronary angioplasty, defined as: (1) less than 50% diameter stenosis on visual inspection of the postangioplasty coronary angiogram obtained in multiple views, (2) no in-hospital complications, namely recurrence of angina, coronary bypass grafting, repeat PTCA, acute myocardial infarction, or death.

Patients with stable and unstable angina pectoris, as defined previously,[22, 23] were included. Patients with acute myocardial infarction were excluded.

The recruitment period for the study was subdivided into four equal time intervals of 5 months each. Patients with a successful PTCA enrolled during the first time interval were allocated to undergo follow-up angiography at 30 days, the second at 60 days, the third at 90 days, and the fourth at 120 days.

Of the 400 patients who met the inclusion criteria, 342 patients had repeat angiograms suitable for quantitative analysis. The reasons for failure to complete the study are detailed in figure 1.

Recatheterization was considered to be contraindicated for the following reasons: disabling concomitant disease (e.g., renal failure, lung cancer), severe peripheral vascular disease, or more than four prior angiographic investigations.

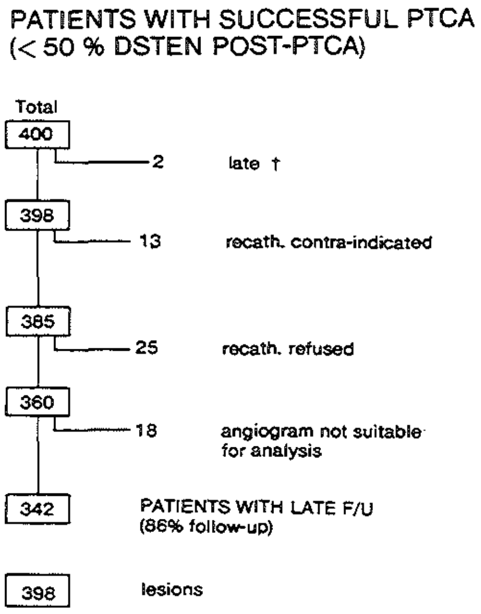

FIGURE 1. Total number of patients who met the inclusion criteria, and the reasons for failure to complete the study. Dsten = diameter stenosis; F/U = follow-up; Recath. = recatheterization.

Of the total study population of 342 patients (398 lesions), 93 patients were scheduled for recatheterization at 30 days (110 lesions), 79 patients at 60 days (89 lesions), 82 patients at 90 days (93 lesions), and 88 patients at 120 days (106 lesions) after PTCA.

The baseline clinical characteristics of patients in the four groups were comparable for the variables listed in tables 1 and 2. The mean time from PTCA to follow-up angiography in the four study groups were 40 days, 61 days, 102 days, and 120 days, respectively. Patients who were reinvestigated before their preset time because of evidence of recurrent ischemia were retained in their initially assigned follow-up group for the purpose of analysis.

Prior myocardial infarction was defined according to the Minnesota code,[24] and in the case of conduction abnormality the presence of regional akinesia or dyskinesia on the left ventriculogram was used as the criterion. In table 2 the vessels dilated, the number of patients with tandem lesions, and the number of patients with more than one lesion dilated is listed for each follow-up group.

Methods

Coronary angioplasty was performed with a steerable, movable guidewire system via the femoral route. Details regarding the procedure used in our laboratory have previously been reported.[22, 23] At the beginning of the angioplasty procedure all patients received 10,000 IU of intravenous heparin, 500 mg of intravenous aspirin, and a continuous infusion of Rheomacrodex (low molecular weight dextran) was started. After dilatation 10 mg nifedipine was given orally every 2 hr for the first 12 hr after PTCA, and thereafter three to six times a day together with 500 mg aspirin orally once a day for at least 6 months. β-blockers were withdrawn unless hypertension was present.

Quantitative coronary angiography. The quantitative analysis of the stenotic coronary segments was carried out with the computer-assisted Cardiovascular Angiography Analysis System (CAAS), which has been described in detail elsewhere.[25, 26] To analyze a coronary arterial segment in a selected frame of 35 mm cinefilm, an optically magnified portion of the image encompassing that segment was converted into video format by means of a cine-video converter. The contours of the vessel were detected automatically on the basis of the weighted sum of first and second derivative functions applied to the digitized brightness information. Calibration of the diameter data of the vessels in absolute values (mm) was achieved by use of the contrast catheter as a scaling device. To this end, the contours of a user-defined portion of the optimally magnified catheter (optimal magnification factor 2 $\sqrt{2}$) were detected automatically and corrected for pincushion distortion caused by the image intensifiers. From the contours, the vessel diameter functions, in absolute millimeters, were determined by computing the shortest distances between the two contour positions.

A representative analysis, with the detected contours and the diameter functions superimposed on the original video image, is shown in figure 2. Multiple matched views, orthogonal if possible, were analyzed for each dilated lesion and the results were averaged.

To standardize the method of acquisition and analysis of the PTCA and follow-up angiograms, the following four measures were undertaken.[26] First, the x-ray system was repositioned to correspond as much as possible to the projections and settings used during the previous angiographies. For this purpose, the angular settings of the x-ray gantry and the various height levels were readjusted according to the values previously documented with the on-line registration system.

TABLE 1

Clinical characteristics of the 342 patients with successful PTCA entered into the study

	Follow-up period				
	30 days	60 days	90 days	120 days	Overall
No. of patients	93	79	82	88	342
No. of lesions	110	89	93	106	398
Mean No. of lesions dilated/patient	1.18	1.13	1.13	1.20	1.16
Age (yr; mean ± SD)	57 ± 9 (range, 35–75)	57 ± 9 (range, 31–75)	56 ± 9 (range, 32–74)	57 ± 9 (range, 31–74)	57 ± 9 (range, 31–75)
Sex ratio (M/F)	5.6 (79/14)	5.1 (66/13)	3.3 (63/19)	3.9 (70/18)	4.3 (278/64)
Time from PTCA to F/U (days)	40 ± 7 (range, 18–62)	61 ± 12 (range, 11–80)	102 ± 18 (range, 33–164)	120 ± 32 (range, 4–226)	80 ± 38 (range, 4–226)
Extent of CAD					
1 vessel	62 (67%)	56 (71%)	52 (63%)	62 (70%)	232 (68%)
2 vessels	24 (26%)	13 (16%)	21 (26%)	16 (18%)	74 (22%)
3 vessels	7 (8%)	10 (13%)	9 (11%)	10 (11%)	36 (11%)
Previous coronary bypass grafting (n)	9 (10%)	7 (9%)	6 (7%)	8 (9%)	30 (9%)
Previous myocardial infarction (n)	40 (43%)	39 (49%)	32 (39%)	30 (34%)	138 (40%)
Previous coronary angioplasty (n)	10 (11%)	2 (3%)	11 (13%)	12 (14%)	35 (10%)

CAD = coronary artery disease; F/U = follow-up angiography.

Second, for all studies cineframes to be analyzed were selected at end-diastole to minimize any possible foreshortening and blurring effect.

Third, the user-determined beginning and end points of the major coronary segments were identified according to the definitions of the American Heart Association.[27]

Finally, Polaroid photographs were taken of the video image with the detected contours superimposed to ensure that the analyses were performed on the same coronary segment in the consecutive angiograms. "Interpolated" percent diameter stenosis measurements were used. This is a method that expresses the severity of a coronary obstruction without dependency on a user-defined reference region. The principle of this technique is the computer estimation of the original vessel diameter at the site of the obstruction, assuming there is no coronary artery disease present.[25] The interpolated percent diameter stenosis measurement was obtained by comparison of the minimal luminal diameter value at the obstruction site with the corresponding value of the reference diameter in this position.

The accuracy of this quantification method has previously been validated with Plexiglas phantoms filled with contrast medium (Perspex models).[28]

Definitions of restenosis. To allow comparison of our results with those of other published studies and to evaluate the differences between various criteria, the following six previously proposed definitions of restenosis were applied: (1) an increase in diameter stenosis of at least 30% by the time of follow-up angiography (National Heart, Lung, and Blood Institute [NHLBI] I), (2) an immediate post-PTCA diameter stenosis of less than 50% increasing to greater than or equal to 70% at follow-up (NHLBI II), (3) an increase in stenosis severity to within 10% or less of the predilatation diameter stenosis at the

TABLE 2

Vessel dilated, number of patients with tandem lesions, and number of patients with more than one lesion dilated in each of the four study groups

	Follow-up period									
	30 days		60 days		90 days		120 days		Overall	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Vessel dilated										
LAD	61	(56)	61	(69)	55	(59)	62	(58)	239	(60)
LCX	18	(16)	16	(18)	19	(20)	16	(15)	69	(17)
RCA	26	(24)	11	(12)	16	(17)	23	(22)	76	(19)
Bypass	4	(4)	0	(0)	2	(2)	4	(4)	10	(3)
LMCA	1	(1)	1	(1)	1	(1)	1	(1)	4	(1)
No. of patients with tandem lesion	6	(6)	2	(3)	2	(2)	5	(6)	15	(4)
No. of patients with more than one lesion dilated	15	(16)	10	(13)	10	(12)	18	(20)	53	(15)

Bypass = aortocoronary bypass graft; LAD = left anterior descending coronary artery; LCX = left circumflex coronary artery; LMCA = left main coronary artery; RCA = right coronary artery.

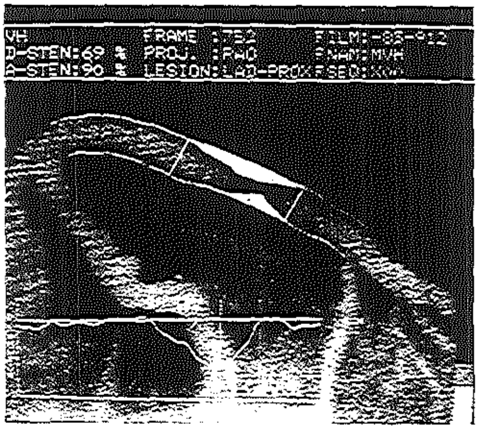

FIGURE 2. A single-frame angiogram of a left coronary artery with superimposition of the automated contours at the coronary artery segment of interest. Beneath this is shown the diameter function of the detected contours of the left anterior descending coronary artery. The minimal luminal diameter (vertical line) is 1.29 mm, corresponding to a diameter stenosis of 69% and an area stenosis of 90%.

time of follow-up angiography (NHLBI III), (4) a loss of at least 50% of the gain in luminal diameter achieved at PTCA (NHLBI IV), (5) an increase of the diameter stenosis from less than 50% after angioplasty to greater than or equal to 50% at follow-up, and (6) a decrease in minimal luminal diameter of greater than or equal to 0.72 mm with respect to the post-PTCA situation. This last definition is based on the variability of minimal luminal diameter measurements in millimeters (0.36 mm). This variability is 1 SD of the difference of the means of two observations on the same lesion, which if used would result in a 17.5% false-positive restenosis rate, while the use of 2 SDs as a criterion ($2 \times 0.36 = 0.72$ mm) results in a false-positive rate of 2.5%.[25]

Statistical analysis. To test for differences in mean values and proportions between the four follow-up groups with respect to the baseline characteristics (tables 1 and 2), univariate analysis of variance was performed for the continuous variables, and multiway chi-square analysis was used for the discrete variables. For the quantitative variables listed in tables 3A and 3B, univariate analysis of variance was performed (BMDP statistical software, University of California Press, Berkeley 1985). Analysis of variance for a linear trend was done on the change in minimal luminal diameter from after PTCA to follow-up (Glim statistical package). All statistical tests were two tailed. A probability value below .05 was regarded as indicating statistical significance.

Results

The results of quantitative angiography in the 342 patients who completed angiographic follow-up are detailed in tables 3A and 3B, together with the p value computed by analysis of variance for the individual variables used to compare the follow-up groups. Before and after PTCA all the quantitative angiographic variables for the four groups were comparable, except for a smaller reference diameter in the 4 month group before angioplasty, and a slightly lower percentage diameter stenosis immediately after PTCA in the 4 month group. After PTCA there was, as expected, a significant improvement in minimal luminal diameter and diameter stenosis for each of the four follow-up groups ($p<.0001$). However, analysis of variance performed on the obstruction-related variables at follow-up showed a significant difference in the four groups: there was no significant change at 1 and 2 months, but a significant increase in the severity of the stenosis in the 3 month group ($p<.001$ for each obstruction-related variable), and a further but smaller increase that did not reach statistical significance in the 4 month group.

Table 4 and figure 3 illustrate the incidence of restenosis according to the NHLBI criteria and the two cri-

TABLE 3A

Results of quantitative coronary angiography, expressed as mean±1 SD, for the 93 patients (110 lesions) recatheterized at 30 days, the 79 patients (89 lesions) recatheterized at 60 days, the 82 patients (93 lesions) recatheterized at 90 days, and the 88 patients (106 lesions) recatheterized at 120 days after PTCA

Variable	30 day group	60 day group	90 day group	120 day group	p value^
Minimal luminal diam. (mm)					
Pre	1.16±0.41	1.16±0.37	1.20±0.40	1.13±0.41	.70
Post	2.06±0.46	2.00±0.42	2.14±0.42	2.10±0.40	.25
FU	2.11±0.56	1.93±0.64	1.77±0.58	1.69±0.55	<.00001
Diameter stenosis (%)					
Pre	58.2±12.5	59.5±11.8	59.3±11.8	57.7±15.2	.73
Post	28.5±12.0	31.0±12.0	28.1±11.0	26.3±9.9	.04
FU	26.9±14.7	33.5±19.8	37.1±18.4	35.4±16.7	<.0001
Reference diameter (mm)					
Pre	2.81±0.66	2.86±0.62	2.96±0.58	2.69±0.68	.03
Post	2.92±0.63	2.92±0.50	3.02±0.56	2.86±0.49	.31
FU	2.90±0.60	2.92±0.54	2.86±0.55	2.62±0.51	.003

Pre = before PTCA; Post = immediately after PTCA; FU = follow-up.

^By analysis of variance.

TABLE 3B

Absolute change in listed variables from pre- to post-PTCA, and from post-PTCA to the respective time of the follow-up angiography

Variable	30 day group	60 day group	90 day group	120 day group	p value^
Minimal luminal diam. (mm)					
Pre to post	+0.89	+0.86	+0.94	+0.97	.33
Post to FU	+0.04	−0.06	−0.37	−0.42	<.00001
Diameter stenosis (%)					
Pre to post	−29.8	−28.5	−31.2	−31.5	.53
Post to FU	−1.6	+2.5	+9.0	+9.1	<.00001
Reference diameter (mm)					
Pre to post	+0.12	+0.06	+0.07	+0.19	.03
Post to FU	−0.02	−0.01	−0.17	−0.26	<.00001

Abbreviations are as in table 3A.
^By analysis of variance.

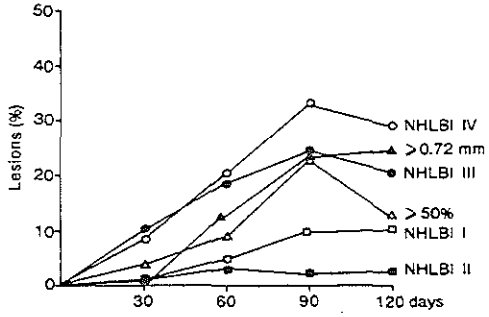

FIGURE 3. Percentages of lesions that fulfilled the various restenosis criteria at 30, 60, 90, and 120 days.

teria used at our institution. Table 4 also lists the percentage of patients experiencing recurrent angina at the time of repeat angiography. From these data two conclusions can be drawn: first, there is a wide variation in the incidence of restenosis according to the criterion applied, and second, the incidence of restenosis is progressive to at least the third month for all the criteria except NHLBI II. At 4 months a further increase is observed in the percent restenosis defined as a decrease of 0.72 mm or more in minimal luminal diameter, whereas use of the criteria based on diameter stenosis shows a variable response.

The relationship between the different criteria for restenosis was also analyzed and the results are illustrated in figure 4, which shows the total number of lesions meeting each criteria and also the overlap among individual criteria. Comparison of the four NHLBI criteria showed that all lesions that fulfilled criteria I and II met criteria III and IV. Few patients met all four criteria (n = 9), but when NHLBI criteria III and IV were compared with the two criteria used at our institution, additional lesions were defined as having undergone restenosis. Finally, a large number of lesions (119 of 398) fulfilled at least one of the six criteria with 29 lesions fulfilling all six of them. Although the percentages of lesions fulfilling the four criteria for restenosis were similar, it must be emphasized that each of the four criteria identified unique lesions that were not identified by the other three.

Figure 5 shows the individual minimal luminal diameters (mm) of all lesions immediately after PTCA compared with the follow-up value at 1, 2, 3, and 4 months. Lesions that had at least a 0.36 mm change are represented by closed circles. Lesions in which there was regression, defined as an increase, and progression, defined as a decrease in minimal luminal diameter of at least 0.72 mm (2 × 0.36 mm), are represented by the closed circles that fall outside of the dashed lines in figure 5. There was a wide scatter in the change in minimal luminal diameter of the individual lesions within each group, and also a clear trend with time. Lesion regression was observed mainly in the first 2 months (6.4% and 5.6%, respectively), while an increasing trend in the number of lesions undergoing progression was demonstrated up to 120 days. These trends could be fitted with the following linear model based on linear trend analysis ($p<.0001$):

$$\Delta\text{MLD post-fu (mm)} = 0.21 - 0.17 \times \text{time (months)}$$

TABLE 4

Lesion-related incidence of restenosis for each of the four follow-up groups according to six previously proposed angiographic definitions of restenosis

	Recurrent angina	Criterion: NHLBI I	NHLBI II	NHLBI III	NHLBI IV	≥50% DS	≥0.72 mm
1 month (%)	15	0.9	0.9	10.0	9.1	3.6	0.9
2 month (%)	19	4.5	3.4	19.1	20.2	9.0	12.4
3 month (%)	28	9.7	2.2	24.7	33.3	23.7	22.6
4 month (%)	32	10.4	2.8	21.7	30.2	13.2	25.5
Cumulative (%)	23	6.3	2.3	18.6	22.9	12.1	17.7

DS = diameter stenosis.

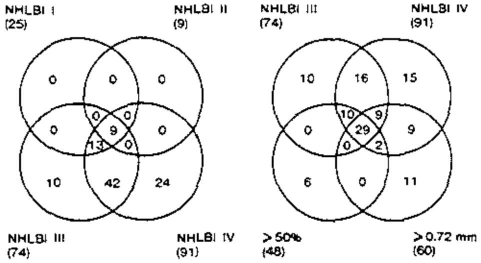

FIGURE 4. The relationships between the different restenosis criteria. On the *left* relationships between all four NHLBI criteria, and on the *right* that between NHLBI criteria III and IV and the two alternative criteria are given. The total number of lesions fulfilling the various restenosis criteria are shown in brackets, and the breakdown of these numbers according to overlap are shown within the circles. The center (overlapped by all four circles) represents the number of lesions fulfilling all four criteria. Three additional lesions were identified as having restenosis according to NHLBI criteria I and IV (left-sided Venn diagram). Similarly, one additional lesion complied with the NHLBI IV and the 50% or greater criteria in the right Venn diagram.

where ΔMLD post-fu = change in minimal luminal diameter from after angioplasty to follow-up.

Discussion

With the high success and low complication rate, restenosis remains the "Achilles' heel" of PTCA.[29] The rate of restenosis reported in a profusion of studies varies from 12% to 48% (table 5): however, critical evaluation and valid comparison of the available data in the literature is extremely difficult for a number of reasons.

First of all, the diagnosis of recurrent stenosis should be based on reproducible quantitative angiographic measurements. Visual estimation of stenosis severity alone yields unacceptable variation in the assessment of changes of coronary artery lesions.[39–43] To obtain objective and reproducible values a computer-assisted technique using either automated edge detection or videodensitometry should be applied.[44–56]

Second, the rate of restenosis varies considerably according to the definition used.[17] Essentially, angiographic definitions of restenosis are either based on the increase in narrowing with respect to the immediate post-PTCA angiographic appearance, or are defined as a loss of the gain achieved by successful PTCA. Since many angiographic definitions of restenosis are now used (table 5), comparative evaluation of these definitions is crucial for interpretation of the data in the literature, and for the assessment of the values and limitations of the currently used criteria for restenosis.

Third, to prevent over- or underestimation, the detection of restenosis requires strict adherence to a protocol that involves routine follow-up angiography at a predetermined time in all patients.

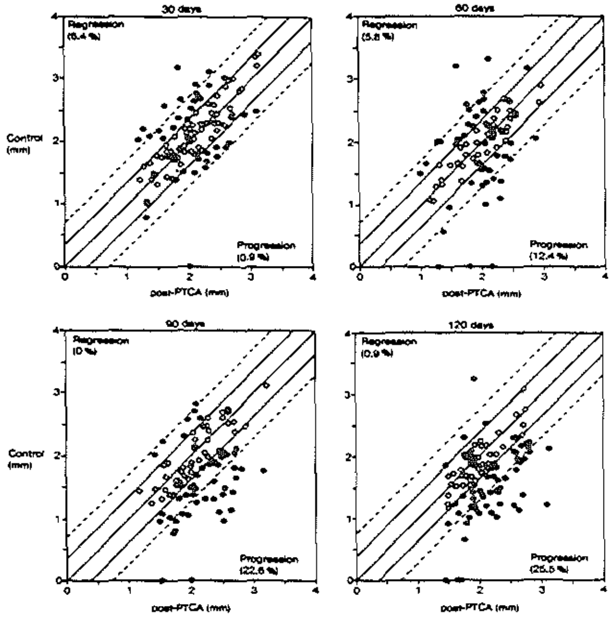

FIGURE 5. Individual minimal luminal diameter (mm) after PTCA compared with that at control angiography for the four groups. The two solid lines on either side of the identity line correspond to the long-term variability (0.36 mm) of repeated measurements for this variable.[25] This variability is 1 SD of the difference in the means of duplicate angiographic measurements. Here 2 SDs were used (2 × 0.36 = 0.72 mm; dashed lines) as a criterion for lesion progression or regression. Based on this criterion the percentages of lesions showing progression or regression (● outside dashed lines) are shown within the relevant brackets.

TABLE 5

Reported restenosis rates, together with the angiographic definition(s) applied, the number of patients studied, and the time interval between PTCA and follow-up angiography

Study	Year	Patients	FU angiography (%)	Interval PTCA–FU (months)	Restenosis criterion	% restenosis
M. Nobuyoshi[30]	1987	137	100	Next day	≥50% loss of gain	5.1
				1	≥50% loss of gain	12.0
				3	≥50% loss of gain	36.4
M. Kaltenbach[18]	1985	356	94	5.6	Ds <20% below pre-PTCA Ds	12
T. Corcos[31]	1985	92	100	8.2	≥70% Ds at FU	18.5
J. Meyer[32]	1983	70	90	6	>85% area stenosis^A^	20
R. Uebis[33]	1986	100	89	5.9	≥50% loss of gain	24.8
P. de Feyter[22]	1985	56^B^	82	2.3	<50% to >50% Ds at FU	28
P.P. Leimgruber[20]	1986	1758	57	7	>50% Ds at FU	30.3
M.A. Thornton[34]	1984	248	72	6–9	≥50% loss of gain	31
M.E. Bertrand[35]	1986	3198	Not reported	7	≥50% loss of gain	32
D.R. Holmes[17]	1984	665	84	6.2	≥30% Ds increase or ≥50% loss of gain	33.6
S. Levine[36]	1985	100	92	6	≥50% loss of gain	40
E. Fleck[37]	1984	51	100	6	>1 mm^2 stenosis area	42
A.R. Zaidi[38]	1985	184	100	Not reported	Not reported	48

The percent restenosis varies considerably. Likewise, the definition(s) used, rate and timing of repeat catheterization, and method of assessment of the arteriograms are far from uniform, making a critical comparison extremely difficult. The authors cited were selected primarily for the purpose of pointing out the variability in rates and definitions, rather than in an attempt to cover all literature on restenosis to date.

Ds = diameter stenosis; FU = follow-up.

^A^Percent stenosis of cross-sectional area.

^B^Patients with unstable angina.

The current literature suggests that evidence of restenosis usually becomes apparent within 5 months of the angioplasty procedure,[17, 20, 21] and the vast majority of restenosis in the series of Kaltenbach et al.,[18] occurred within 3 months. However, some of these studies exhibit a methodologic bias in that the time to and indication for repeat angiography was dictated predominantly by the recurrence of symptoms. In two of the larger studies,[17, 20] the prevalence of ischemic symptoms in patients angiographically reevaluated within 5 months exceeded 80%, whereas the observed restenosis rates were "as low as" 32.8% and 31.6%, respectively (≥50% loss of gain criterion). The selection of symptomatic patients might be expected to either artificially increase the angiographic restenosis rate, or to decrease the rate by not identifying asymptomatic patients with angiographic recurrence.

In the present study only 23% of the total study population of 342 was symptomatic at the time of reinvestigation, while the overall incidence of restenosis within the first 4 months was 22.9% (NHLBI criterion IV; table 4). It therefore appears that the difference in the restenosis rate of 9% to 10% (22.9% vs 32.8% or 31.6%)[17, 20] might be related to the substantial dissimilarity in the percentage of patients with recurrent angina at the time of repeat angiography. This point emphasizes the importance of routine angiographic reevaluation, irrespective of ischemic symptoms, in establishing the "true" incidence of restenosis and consequently in identifying the determinants of this process.

As previously alluded to, direct comparison of our observed rates of restenosis with those of Holmes and Leimgruber and their colleagues[17, 20] is hampered by major differences in study design and follow-up strategy. For instance, Leimgruber et al.[20] reported the follow-up of 998 patients originating from an initial cohort of 1758 patients with single-vessel disease in whom PTCA was successful (57% angiographic follow-up). The observed restenosis rate of 31.6% (≥50% loss of gain criterion) at a mean follow-up time of 7 ± 5 months pertains to a time window ranging from less than 2 to 42 months. This is in contrast to the 22.9% overall restenosis rate at a mean follow-up time of 80 ± 38 days (range 4 to 226 days) in this study (86% angiographic follow-up).

The PTCA Registry of the NHLBI reported on 557 patients who underwent angiographic reinvestigation from a group of 665 with successful PTCA (84% angiographic follow-up). Their definition of success, a greater than 20% reduction in luminal diameter narrowing, is in contrast to our definition of less than 50% diameter stenosis immediately after PTCA. In this particular report time to follow-up ranged from less than 1 month to approximately 12 months, with only 42% of the patients being reinvestigated within the first 6 months.[17] Moreover, although the number of patients in our study may appear to be relatively small (n = 342) in comparison with the total study population in the reports of Holmes et al.[17] (n = 557) and Leimgruber et al.[20] (n = 998), it should be pointed out that the number of patients reinvestigated within the first 4 months in these two studies did not exceed 125 and 200, respectively.

In view of the above, the question of whether the incidence of restenosis peaks within the first 3 to 5 months can be answered more precisely by an approach that minimizes multiple biases as much as possible. Based on the criteria of the NHLBI, our data show that the incidence of restenosis appears to reach a plateau at 4 months, while restenosis according to the absolute criterion (≥0.72 mm) is still increasing at 4 months.

An interesting observation of this study was that the percent restenosis fell rather unexpectedly from 23.7% to 13.2% between 90 and 120 days, when defined as a 50% or greater diameter narrowing at follow-up. However, this apparent reduction was paralleled by a disproportionate decrease in the reference diameter compared with the change in minimal luminal diameter (figure 6 and table 3B). Consequently, use of the individual diameter stenosis values, derived from the ratio of the reference diameter over the minimal luminal diameter, results in an erroneous lowering of the restenosis rate by the 50% or greater criterion. Additionally, this reduction is discordant with the observation that the mean minimal luminal diameter is still diminishing between 90 and 120 days after angioplasty. Although no definite explanation can be given for the fact that the mean reference diameter progressively decreases with time, it could be hypothesized that this is in some way related to the local remodeling process within the arterial vessel wall after the uncontrolled barotrauma at the site of the obstruction.

The absence of standardization with respect to definition of restenosis, method of angiogram assessment, and timing and indication for angiographic control may lead investigators to prematurely draw important — and possibly erroneous — conclusions about factors responsible for a low or high rate of restenosis, such as technique of angioplasty, drug regimen after angioplasty, or modification of risk factors.[56]

In addition to this, it is becoming clear that the

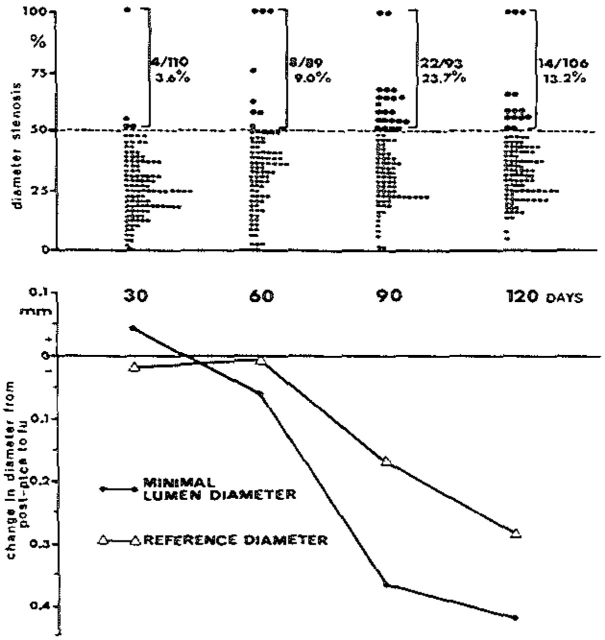

FIGURE 6. The mean changes in minimal luminal and reference diameters from after PTCA to follow-up at 30, 60, 90, or 120 days are graphically displayed by the solid lines in the *bottom* panel. The decrease in reference diameter is most apparent at 120 days after PTCA, and is disproportionate to the decrease in minimal luminal diameter. The effect of this phenomenon on the individual percentage diameter stenosis values, derived from the ratio of the reference over to the minimal luminal diameter, is shown in the *top* panel. The number of lesions with a 50% or greater diameter stenosis diminished from 90 to 120 days. As a result, the incidence of restenosis according to this criterion falls from 23.7% at 90 days to 13.2% at 120 days.

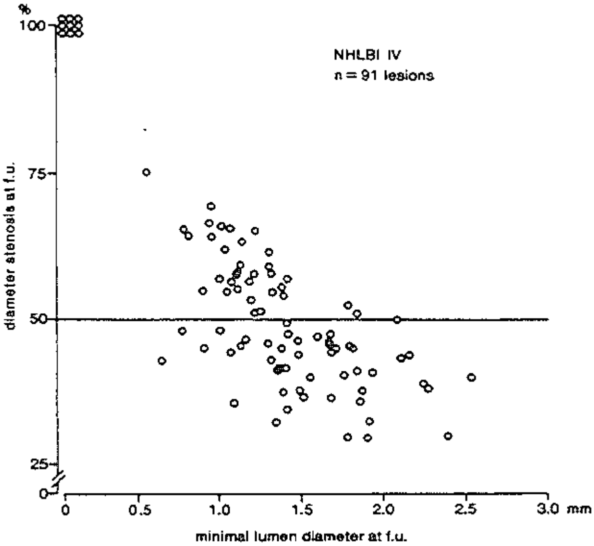

FIGURE 7. Relationship between percent diameter stenosis and the minimal luminal diameter at follow-up for lesions that fulfill NHLBI criterion IV. A total of 48 of the 91 lesions have a diameter stenosis of less than 50%. f.u. = follow-up.

definitions of restenosis in current use, which are based on relative percentages with more or less arbitrary cutoff points, do not adequately describe the progression to a physiologically significant obstruction. For instance, as can be seen from the individual lesion data plotted in figure 7, lesions that fulfill a criterion for restenosis based on changes in the relative percent diameter stenosis (NHLBI criterion IV) may represent relatively mild obstructions (percent diameter stenosis between 30 and 40 with absolute minimal luminal diameters ranging from 2 to 3 mm), amounting to what is a very satisfactory long-term result. Therefore, to avoid the arbitrariness of these floating-scale criteria the use of measurements in absolute terms (mm, mm^2) is advocated.

The most often reported visually assessed percent diameter stenosis overestimates lesion severity by 15% to 25%, as demonstrated by Bove et al.[57] Our quantitative measurements, showing a mean diameter stenosis before PTCA of 58% to 60% (table 3A) corresponding to an area stenosis of 80 to 81%, support this finding. Thus, since values obtained before PTCA or at follow-up are generally below 70% diameter stenosis, we suggest that the more than 70% criterion (NHLBI criterion II) for restenosis not be used when quantitative measurements are employed.

To circumvent the previously mentioned multiple biases and to define the true incidence of restenosis in the first 4 months, we tried to standardize as much as possible our methods and protocol of investigation. The problem of defining restenosis is not trivial. Applying the stringent criteria of the NHLBI PTCA Registry to visual estimates of severity of stenosis has major limitations, due to the large intra- and interobserver variabilities in interpretation, especially for stenoses of between 20% and 80%.[41] Therefore, in this study stenoses were analyzed by computerized edge detection.[25] Although this method may not be optimal for those lesions with an irregular angiographic vessel wall outline[54, 56] immediately after angioplasty, it provides an objective and reproducible quantitative measurement that avoids unintentional bias in reading the angiogram. The overall accuracy (average difference) and precision (pooled standard deviation of the differences) of this contour detection technique for the percentage diameter stenosis measurements are 2.00% and 2.68%, respectively, and for the minimal luminal diameter, -30 and +90 μm, respectively. The mean differences and standard deviations of the differences in the minimal luminal diameter and interpolated reference diameter, as well as in the interpolated percentage diameter stenosis, have previously been published for the short (5 min), medium (60 min) and long term (90 days). The variability in minimal luminal diameter for these three types of studies ranged from 0.22 mm for the medium-term study to 0.36 mm for the least well controlled long-term study. In the long-term study group, the lack of significant variation in the mean difference in the minimal luminal diameters suggests that no detectable progression or regression of atherosclerotic lesions occurred over the period of 90 days. Therefore, a change greater than the long-term measurement variability of repeated coronary cineangiography and quantitative analysis (0.72 mm for the minimal luminal diameter; i.e., 2 SDs of difference of duplicate measurements) was considered significant and indicative of restenosis. This change in absolute values corresponds to a change of $2 \times 6.5\% = 13.0\%$ in percentage diameter stenosis.[25]

It is important to realize that the process of restenosis may be viewed either as a purely angiographic progression in focal narrowing without implication of any functional or clinical consequence, or as a functional deterioration assessed by means of a criterion able to identify a physiologically significant obstruction to blood flow. It is unclear what percent diameter narrowing — which is the traditional method for grading a coronary stenosis — will consistently lead to myocardial ischemia during exercise. However, a number of patients who meet the criteria for restenosis will have no symptoms and an adequate luminal diameter. It is therefore not surprising to see that the arbitrary nature of angiographic definitions of restenosis have further obscured the relationship between angiographic and functional result.

In conclusion, we believe that restenosis, when envisaged as a progressive encroachment on the lumen by the disease process in the vessel wall, should be assessed by repeat angiography and preferably ascertained according to the change in absolute quantitative measurements of the luminal diameter. By doing so, the comparison of various studies and different treatment groups will be more scientifically valid, and more importantly will provide a sound basis for the identification of the determinants of lesion recurrence.

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Chapter 2

Change in diameter of coronary artery segments adjacent to stenosis after percutaneous transluminal coronary angioplasty: failure of percent diameter stenosis measurement to reflect morphologic changes induced by balloon dilation. Journal of the American College of Cardiology 1988; 12:315-323.

Change in Diameter of Coronary Artery Segments Adjacent to Stenosis After Percutaneous Transluminal Coronary Angioplasty: Failure of Percent Diameter Stenosis Measurement to Reflect Morphologic Changes Induced by Balloon Dilation

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To determine the changes in stenotic and nonstenotic segments of a dilated coronary artery, detailed quantitative angiographic measurements were performed in 342 patients (398 lesions) immediately after angioplasty and at a predetermined follow-up time of 30, 60, 90 or 120 days after the dilation. Measurements of the stenotic segments were expressed as minimal luminal diameter, and the adjacent nonstenotic segments were expressed as interpolated reference diameter (both in millimeters). A follow-up rate of 86% was achieved.

In the patients followed up at 30 and 60 days, there was no significant change in either the mean minimal luminal diameter or the mean reference diameter. However, at 90 and 120 days, there was significant deterioration in both the mean minimal luminal diameter (−0.37 and −0.42 mm, respectively) and the mean reference diameter (−0.17 and −0.26 mm, respectively), all of the changes being highly significant (p < 0.00001). The reference diameter is involved in the dilation process and may be subject to the same restenosis process that takes place in initially stenotic segments. Percent diameter stenosis measurements, which are conventionally used to express the change in the severity of a stenosis after angioplasty, will tend to underestimate the change when there is a simultaneous reduction in the reference diameter.

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The incidence of restenosis after coronary angioplasty has become an important index for defining the long-term success rate of the procedure. The relatively high incidence rate (range 12 to 48% [1–5]) of restenosis, as defined by a number of arbitrary criteria, is regarded as the predominant limiting factor to the long-term success rate of angioplasty.

The usual definition of restenosis (2) is based on changes in percent diameter stenosis. This value is used to reflect the changes in minimal luminal diameter in relation to the so-called normal diameter of the vessel in the immediate vicinity of the obstruction. It assumes that this "normal" or reference diameter of the vessel proximal or distal to the obstruction does not change as a result of angioplasty or during the immediate follow-up period when restenosis of the dilated lesion is a well recognized phenomenon. With this criterion for restenosis, which depends on changes that occur in two independent variables (namely, minimal luminal diameter and "normal" luminal diameter), it is not possible to independently examine the absolute changes in either variable, each of which may be important in its own right. In addition, the selection of an arbitrary reference diameter may introduce a further source of error because the selection procedure is not always well standardized and, in practice, is difficult to reproduce reliably during sequential analysis.

Animal experiments (6) have suggested that balloon dilation of a normal coronary artery is capable of inducing the same fibrocellular response seen after dilation of atheroscle-

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Table 1. Clinical Characteristics of 342 Patients With Successful Coronary Angioplasty

	Follow-Up Period				
	30 Days	60 Days	90 Days	120 Days	Overall
No. of patients	93	79	82	88	342
No. of lesions	110	89	93	106	398
Mean no. of lesions dilated per patient	1.18	1.13	1.13	1.20	1.16
Age (yr)					
Mean ± SD	57 ± 9	57 ± 9	56 ± 9	57 ± 9	57 ± 9
Range	35 to 75	31 to 75	32 to 74	31 to 74	31 to 75
Gender ratio (M/F)	5.6 (79/14)	5.1 (66/13)	3.3 (63/19)	3.9 (70/18)	4.3 (278/64)
Time from PTCA to F/U (days)					
Mean ± SD	40 ± 7	61 ± 12	102 ± 18	120 ± 32	80 ± 38
Range	18 to 62	11 to 80	33 to 164	4 to 226	4 to 226
Extent of CAD (no. [%])					
One vessel disease	62 (67)	56 (71)	52 (63)	62 (70)	232 (68)
Two vessel disease	25 (27)	20 (25)	21 (26)	16 (18)	74 (22)
Three vessel disease	5 (5)	4 (5)	5 (6)	10 (11)	36 (11)
Previous coronary bypass grafting (no. [%])	9 (10)	7 (9)	6 (7)	8 (9)	30 (9)
Previous myocardial infarction (no. [%])	40 (43)	39 (49)	32 (39)	30 (34)	138 (40)
Previous coronary angioplasty (no. [%])	10 (11)	2 (3)	11 (13)	12 (14)	35 (10)

CAD = coronary artery disease; F = female; F/U = follow-up angiography; M = male; PTCA = percutaneous transluminal coronary angioplasty.

rotic vessels. However, no data exist to show whether this is important in the clinical setting, where the dilating process frequently involves relatively normal coronary artery segments. To determine the changes in stenotic and nonstenotic segments in the period immediately after angioplasty and to assess their importance in relation to the change in diameter stenosis occurring in the same period, we used a computer-generated angiographic measurement system in a detailed follow-up study of patients who had undergone successful angioplasty.

Methods

Study patients. Four hundred consecutive patients who underwent successful coronary angioplasty and agreed to have a follow-up angiogram were entered into an ongoing study on restenosis. Successful coronary angioplasty was defined as: 1) <50% diameter stenosis on visual inspection of the postangioplasty coronary angiogram performed in multiple views; and 2) no in-hospital complications (namely, recurrence of angina, coronary bypass grafting, repeat coronary angioplasty, acute myocardial infarction or death). Patients with stable and unstable angina pectoris, as defined previously (7), were included. Patients with acute myocardial infarction receiving a thrombolytic agent who subsequently had immediate coronary angioplasty were excluded.

Allocation of patients at the time of angioplasty to one of four predetermined times for follow-up angiography was made sequentially according to the study period in which the dilation was performed; patients undergoing angioplasty in the first study period were reinvestigated at 30 days, the second group at 60 days, the third group at 90 days and the fourth group at 120 days. Of the 400 patients who met the inclusion criteria, 342 had repeat angiograms suitable for quantitative analysis. Reasons for failure to complete the study were late death (2 patients), recatheterization contraindicated or refused (38 patients) and angiograms unsuitable for quantitative analysis (18 patients).

Of the total study group of 342 patients (398 lesions), 93 patients underwent repeat catheterization at 30 days (110 lesions), 79 at 60 days (89 lesions), 82 at 90 days (93 lesions) and 88 (106 lesions) at 120 days after angioplasty.

The baseline clinical characteristics in the four groups were comparable for the variables shown in Table 1. The mean time from angioplasty to follow-up angiography in the four study groups was 40, 61, 102 and 120 days, respectively.

When clinically indicated (early recurrence of symptoms), patients were reinvestigated before their preset time, but analysis was performed according to that for their original allocation group. This was done to allow a valid statistical comparison of the changes occurring among the individual groups. We assume that changes seen at the early investigation would be present if a further investigation was performed at the original preassigned time. Most patients restudied early had a further intervention (coronary angioplasty or bypass surgery) and, thus, a further investigation was not appropriate. This method was chosen to avoid biasing the early groups with patients who underwent early investigation because of symptoms and who were thus more likely to show a deterioration in the dilated lesion. Table 2 shows the type of vessel, the number of patients with tandem

Table 2. Type of Vessel Dilated and Number of Patients in the Four Study Groups With Tandem Lesions and More Than One Lesion Dilated

	Follow-Up Period				
	30 Days	60 Days	90 Days	120 Days	Overall
Vessel dilated (no. [%])					
LAD	61 (56)	61 (69)	55 (59)	62 (58)	239 (60)
LCx	18 (16)	16 (18)	19 (20)	16 (15)	69 (17)
RCA	26 (24)	11 (12)	16 (17)	23 (22)	76 (19)
Bypass graft	4 (4)	0 (0)	2 (2)	4 (4)	10 (3)
LMCA	1 (1)	1 (1)	1 (1)	1 (1)	4 (1)
No. of patients with tandem lesion (no. [%])	6 (6)	2 (3)	2 (2)	5 (6)	15 (4)
No. of patients with (no. [%]) >1 lesion dilated	15 (16)	10 (13)	10 (12)	18 (20)	53 (15)

LAD = left anterior descending artery; LCx = left circumflex artery; LMCA = left main coronary artery; RCA = right coronary artery.

lesions and the number of patients with more than one lesion dilated for each study group.

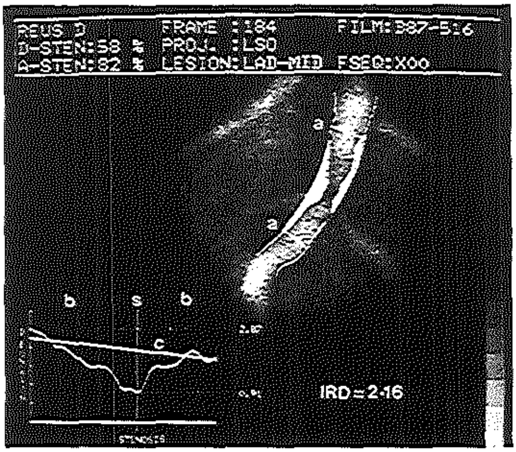
Angioplasty protocol. Coronary angioplasty was performed with a steerable movable guidewire system by means of the femoral route. Details regarding the procedure used in our laboratory have been described previously (7). At the beginning of the procedure, all patients received infusions of heparin, 10,000 IU and aspirin, 500 mg, and a continuous infusion of Rheomacrodex (low molecular weight dextran) was started. After dilation, 10 mg of nifedipine was given orally every 2 h for the first 12 h, and then three to six times a day together with 500 mg/day of aspirin orally until repeat angiography. Beta-adrenergic blocking agents were withdrawn unless indicated for hypertension.

Quantitative coronary angiography. The quantitative analysis of the stenotic coronary artery segments was carried out with the computer-assisted Cardiovascular Angiography Analysis System (CAAS), which has been described in detail (8,9). In summary, to analyze a coronary artery segment in a selected frame of 35 mm cinefilm, an optically magnified portion of the image encompassing that segment is converted into video format by means of a cine-video converter. The region of interest is defined and the contours of the vessel are detected automatically on the basis of the weighted sum of first and second derivative functions applied to the digitized brightness information. Calibration of the diameter data of the vessels in absolute values (in millimeters) is achieved by using the contrast catheter as a scaling device (10). To this end, the contours of a user-defined portion of the optimally magnified catheter (optimal magnification factor $2\sqrt{2}$) are detected automatically and corrected for pincushion distortion caused by the image intensifiers. From the contours, the vessel diameter functions are determined by computing the shortest distances between the two contour positions. All aspects of this process apart from the selection of angiographic frames for analysis are independent of the user and were performed without knowledge of previous results.

A representative analysis, with the detected contours and the diameter functions superimposed on the original video image, is shown in Figure 1. The reference diameter is difficult to define and is usually selected visually as the nearest coronary artery segment that appears normal. To standardize this measurement and minimize potential errors, we used an "interpolated" reference diameter measurement. This method has the advantage of eliminating the arbitrary choice of a reference diameter, which will vary among individual observers, and also provides a smoothing effect for the segments adjacent to the stenosis so that extreme irregularities in the vessel have little influence on the reference diameter. The principle behind this technique has been described previously (11–13), as have the precision and overall accuracy of the system (13). The method of obtaining angiograms and the precautions taken to reduce error were recently reported (14).

A change ≥0.72 mm was taken to represent a significant change. This is based on twice the variability (0.36 mm) of the minimal luminal diameter measurement (in millimeters) when coronary angiography is repeated over an interval of 90 days (8).

Statistical methods. To test for differences in mean values and proportions among the four follow-up groups with respect to the baseline characteristics (Tables 1 and 2), univariate analysis of variance was performed for the continuous variables, and multiway chi-square analysis for the discrete variables. For the quantitative variables listed in Table 3, univariate analysis of variance was performed (BMDP statistical software, University of California Press, Berkeley, CA, 1985). All statistical tests were two-tailed. A



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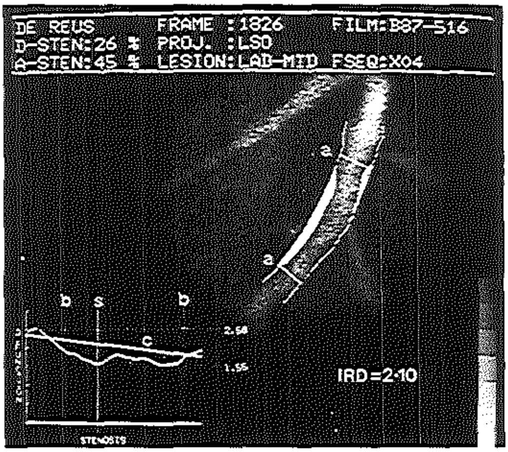

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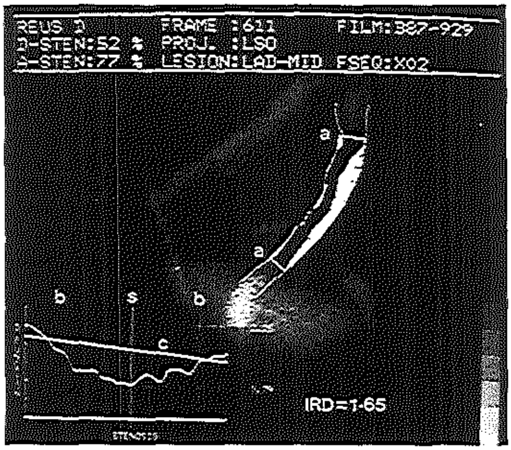


C

Figure 1. A series of single frame angiograms of the same left anterior descending coronary lesion, before dilation (**A**), after dilation (**B**) and at 60 days follow-up study (**C**). The interpolated reference diameters (IRD) are shown to the **right** of the diameter function curve, and the corresponding percent diameter stenosis (D-STEN) and percent area stenosis (A-STEN) at the **top left of each frame**. The arterial boundary of the segments of interest is defined by the automated edge detection process, and the length of the lesion is defined automatically by curvature analysis as shown by the **lines** (a,a) proximal and distal to the stenosis and the **vertical lines** (b,b) on the diameter function plot. The interpolated reference contour line (c) is computed from the contours proximal and distal to the lesion, and the reference diameter value is taken at the point coincident with the point of maximal narrowing, shown by the **line** (s). The postangiographic analysis (**B**) shows a satisfactory result. The follow-up analysis (**C**) shows that a significant restenosis has taken place, and the lesion is longer as defined by the computer. However, the adjacent contours outside the boundaries have also become narrower, resulting in a reduction in the reference diameter. This results in an erroneously low percent diameter stenosis of 52%, rather than 70% if the measurement had been based on the reference diameter immediately after angioplasty. The choice of a single reference diameter in such a dynamic setting would be inappropriate and result in misleading errors.

probability (p) value <0.05 was regarded as indicating statistical significance.

Results

Changes in mean minimal luminal diameter and reference diameter. The mean results of quantitative angiography for the 342 patients who completed the study, divided into four follow-up groups, are shown in Table 3 along with the changes that occurred between angioplasty and follow-up study. The changes in mean minimal luminal diameter and mean reference diameter that occurred between postangioplasty and follow-up study are shown in Figure 2. In the groups who underwent follow-up angiography at 30 and 60 days, there were small nonsignificant changes in both minimal luminal diameter and reference diameter, with a small improvement in minimal luminal diameter and a reduction in reference diameter at 30 days and a reduction in both values at 60 days. However, at 90 and 120 days, both minimal luminal diameter and reference diameter show a highly significant ($p < 0.00001$) deterioration, with the values at 120 days being greater than those at 90 days.

Distribution of individual changes in luminal diameter. The individual changes in reference diameter and minimal luminal diameter are represented in Figures 3 and 4, respectively. The progressive shift of the distribution of the minimal

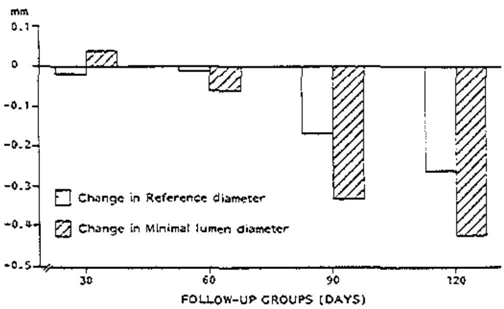
Table 3. Quantitative Coronary Angiographic Findings Postcoronary Angioplasty and at Follow-Up in the Four Study Groups

	Follow-up Period				
	30 Days	60 Days	90 Days	120 Days	p Value
Minimal luminal diameter (mm)					
Post	2.06 ± 0.46	2.00 ± 0.42	2.14 ± 0.42	2.10 ± 0.40	0.17
Follow-up	2.11 ± 0.56	1.93 ± 0.64	1.77 ± 0.58	1.68 ± 0.55	<0.0004
Post to follow-up	+0.04	−0.06	−0.37	−0.42	<0.00001
Reference diameter (mm)					
Post	2.92 ± 0.63	2.91 ± 0.50	3.02 ± 0.56	2.86 ± 0.49	0.34
Follow-up	2.90 ± 0.60	2.92 ± 0.54	2.86 ± 0.55	2.62 ± 0.51	0.84
Post to follow-up	−0.02	−0.01	−0.17	−0.26	<0.00001
Diameter stenosis (%)					
Post	28.5 ± 12.0	31.0 ± 12.0	28.1 ± 11.0	26.3 ± 9.5	0.20
Follow-up	26.9 ± 14.7	33.5 ± 19.8	37.1 ± 18.4	35.4 ± 16.7	<0.0002
Post to follow-up	−1.6	+2.5	+9.0	+9.1	<0.00001

Variables are expressed as mean ± SD. The Post to follow-up values are the mean of the individual differences; the p values are derived from the analysis of variance comparing the four groups.

luminal diameter with time to follow-up is evident and shows that it is not just a limited number of lesions that "restenose," but rather almost all lesions deteriorate to some extent by 120 days after angioplasty. The degree of change is normally distributed about the mean value (−0.42 mm at 120 days), and the number of lesions that undergo "restenosis" will depend on the criterion chosen. Figure 4 shows the percent of lesions that undergo change (either progression or regression) if 0.72 mm is used as the criterion for change. For patients who were reinvestigated at 30 days, the percent of individual lesions that achieved the 0.72 mm criterion for regression was 6%, with 1% showing progression. At 60 days, a similar percent showed regression, but the number showing progression had increased to 12%. The rate of progression then increased to 23 and 26%, respectively, in the subsequent two follow-up groups, with virtually no lesions showing regression. The pattern of change for

Figure 2. Change in reference diameter and minimal luminal diameter for the four follow-up groups. At 90 and 120 days, both these changes are significant ($p < 0.00001$) and are different from the changes at 30 and 60 days ($p < 0.00001$).



the reference diameter was very similar to that of minimal luminal diameter, although the degree of change was less (Fig. 3 and 4).

Discussion

Change in minimal luminal diameter: mechanism and timing. *Early changes.* The design of this study allows some insight into the course of a dilated coronary lesion after angioplasty. Many of the previously published studies reported mean results for patients with a wide range of follow-up times, so that little information on the behavior of the lesion with time is available. The published data are further distorted by preferential recatheterization of symptomatic patients, who can be expected to show a higher incidence of restenosis. To determine a significant change within individuals, we have taken 0.72 mm, two times the variability for duplicate measurements, as the criterion for change. The variability (0.36 mm) represents 1 SD of the mean difference between duplicate measurements on the same lesion and would result, if used as a criterion for change, in a 16% false positive rate, whereas the use of 2 SD (0.72 mm) as a criterion results in a false positive rate of only 2.5%. When this value is used as the criterion for change, it can be seen that, in patients reinvestigated at 30 and 60 days, the immediate response is variable, with more lesions initially showing regression than progression (Fig. 4). A 30% rate of lesion regression after angioplasty was previously described (14), but only in a small group of patients, with use of different criteria and without specific reference to the time after angioplasty in the selected subgroups. Spontaneous lesion regression may occur as part of the atherosclerotic process (15–18) in undilated coronary artery lesions, but the rapid improvement of 6% of the dilated lesions in our study suggests that some lesions may undergo a remodeling proc-

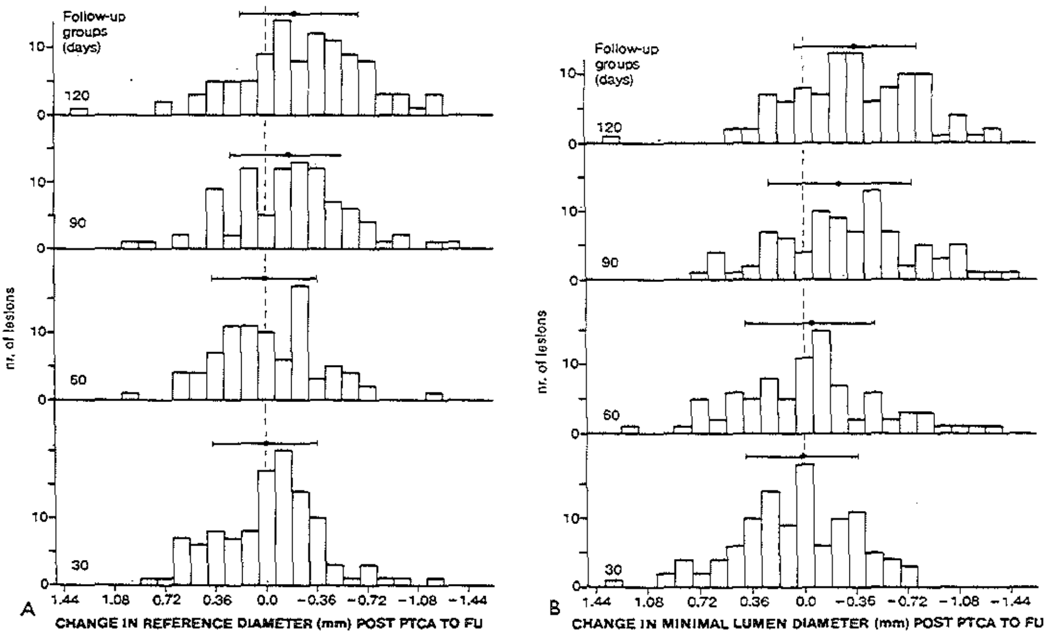


Figure 3. Histograms for the four follow-up groups. A. Distribution in the change of reference diameter with time. The **vertical interrupted line** represents no change. The mean value for each follow-up group ± 1 SD is also shown. B. Distribution in the change of minimal luminal diameter for the four follow-up groups. FU = follow-up study; nr = number; POST PCTA = postangioplasty.

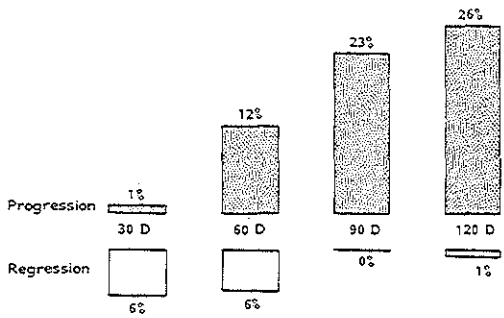
ess early after dilation that is different from the normal atherosclerotic process.

Late changes. At 90 and 120 days, there were virtually no lesions showing regression, indicating that, even after initial improvement, significant progression of stenosis may occur. The more well established trend of lesion progression starts to become evident between 30 and 60 days, but it is not confirmed statistically until 90 days, with some further deterioration at 120 days.

In the pig model, Steele et al. (6) found evidence of smooth muscle proliferation as early as 7 to 14 days after dilation. This same process was identified in at least seven postmortem hearts (19–22) that were examined over a time period (17 to 150 days after dilation) similar to that used in our study. It seems likely that the process also begins early in human patients, but because of the limitations in recognizing small changes even with an accurate system of analysis, we do not see highly significant deterioration until 90 days. Our data suggest that the restenosis process takes place to some extent in virtually all lesions dilated.

Change in reference diameter: response of nonstenotic segments to intraarterial balloon injury. Animal studies (6,23,24) have shown that, after angioplasty of normal carotid arteries, there is initially significant platelet deposition, particularly if a deep intimal tear has occurred, and subsequent proliferation of smooth muscle cells. During angioplasty, the relatively normal coronary artery segments adjacent to the stenosis are inevitably involved in the angioplasty process because the balloon is usually longer than the

Figure 4. Percent of patients within each of the individual follow-up groups who fulfilled the 0.72 mm criterion for change. D = days to follow-up study.



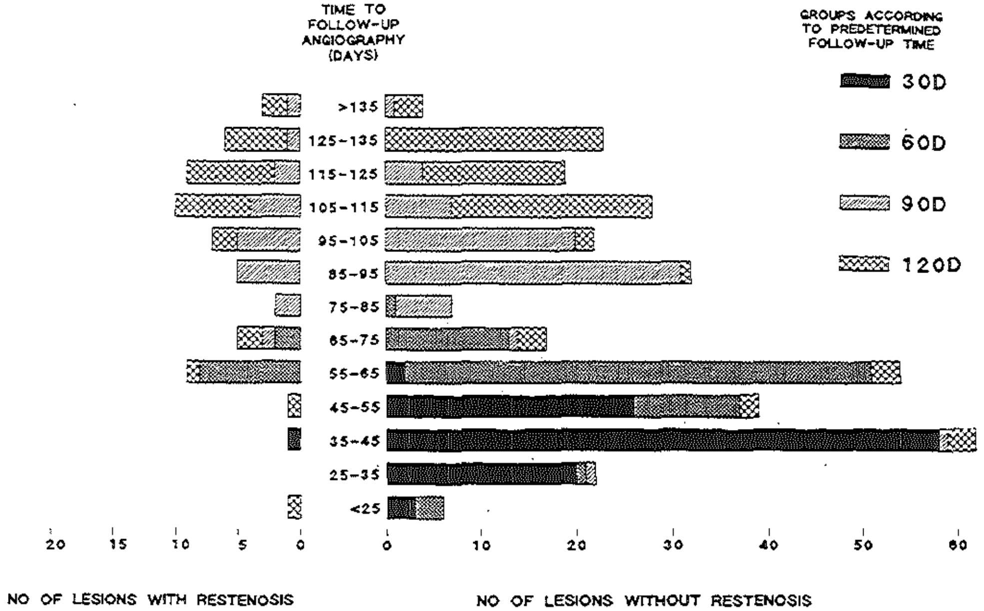


Figure 5. Actual time to follow-up according to predetermined follow-up groups, comparing lesions with restenosis (≧0.72 mm) (left) with those without (right). See text for details.

stenosis and positioning of the balloon across the stenosis cannot always be done precisely. The diameter of these adjacent segments (considered to be relatively normal coronary arteries) is conventionally used as the reference diameter because the use of segments at a distance from the stenosis, which are not involved in the dilation process, will no longer reflect the "normal" diameter at the site of the stenosis. In the previously mentioned postmortem studies (19–22), the authors made the distinction between dilated and nondilated segments, but did not differentiate between those having changes within stenotic segments and those who did not. More recently, Waller et al. (21) observed fibrocellular proliferation in the left main stem coronary artery, which was not targeted for angioplasty, but was involved in the dilation process because of the proximity of a left anterior descending coronary artery stenosis. The proliferation was limited to the segments dilated by the balloon whether or not they were stenotic. Other case reports (26–28) also implicated intraarterial trauma as the cause for a new stenosis in segments not targeted for angioplasty.

Rationale for choosing variables to be measured. Conventionally, the severity of a coronary artery stenosis is expressed as percent diameter stenosis (that is, the diameter of the stenotic lumen as a percent of the normal lumen of the vessel). The so-called normal lumen has to be selected individually from a segment of the coronary artery immediately adjacent to the stenosis, that appears to the angiographer to be normal. This approach has several limitations (29,30). The first is that we now know that it is not possible with cineangiography to identify reliably the normal diameter of a coronary artery because of the general compensatory dilation associated with coronary artery disease (31). Also, the presence of diffuse atherosclerotic narrowing may give rise to a normal regular appearance (32), leading to an underestimation of the diameter of the normal arterial segment. Second, because of the normal variation in diameter of diseased coronary arteries composed of stenotic and ectatic segments, the selected normal segment is subject to considerable individual variation; this problem is compounded when sequential analyses are performed on the same lesion. Third, between two analyses the selected normal segment may undergo a significant change that will not be recognized unless the segment is measured quantitatively. The use of the interpolated reference diameter minimizes these potential errors because it is not arbitrarily selected by the angiographer and it is based not on how an artery behaves at one point alone, but reflects the change in the segments adjacent to the stenosis both proximally and distally.

Factors contributing to variability of measurement. Despite these considerations, serial analysis of a dilated lesion still presents significant methodologic problems. Figure 1 shows single frame angiograms analyzed before dilation, after dilation and at 60 day follow-up. The vessel concerned is the left anterior descending coronary artery. Before dilation, there is a discrete stenosis at the origin of a diagonal branch. Angioplasty achieves a satisfactory result, but there is a long restenosis at follow-up. The length of the lesion is defined automatically on the basis of the derivative of the diameter function curvature analysis and demarcated by the lines on either side of the lesion on the angiogram and by the vertical lines on the plot. The interpolated contour is then superimposed on the plot on the basis of the contours to either side of the lesion, and the reference diameter for the lesion is taken as the value coincident with the site of maximal narrowing. In such analyses, the reference contour is computed from the same segments of the coronary artery, but excluding the length of the stenosis, which is automatically defined by the computer. In this way, any real change in these contours will be reflected in the change in reference diameter.

Like the change in the minimal luminal diameter, the change in interpolated reference diameter (Fig. 3) constitutes a normal distribution about the mean value for each of the follow-up groups, with a trend to deterioration with time. The greatest deterioration is seen between 60 and 90 days, but the trend is still evident between 90 and 120 days. The possibility that this change in reference diameter is artifactual has been addressed; there are reasons why this is unlikely. The first is that the change follows the same trend as that of the minimal luminal diameter, suggesting the underlying causative mechanism is the same. Second, if there was a factor (such as the degree of pharmocologic vasodilation) causing the change, it would be expected that a similar change would be seen in all the follow-up groups and not just in the latter two.

The incidence of restenosis and the timing will be influenced by the selection of patients for reinvestigation, and the selection of symptomatic patients has certainly been relevant to other studies (1,2). It is inevitable that not all patients will be restudied at their originally allocated time, usually because recurrent symptoms dictate early investigation. Figure 5 shows the actual time from angioplasty to follow-up study, comparing those lesions that underwent restenosis with those that did not. Most patients were restudied at or near their preset time. Analysis of the data according to actual time to follow-up study rather than allocated time to follow-up study does not materially alter the results.

Restenosis: implications for follow-up studies. All of the larger follow-up studies after coronary angioplasty have expressed the results in terms of the changes in percent diameter stenosis. Thus, there is little information available on the change in minimal luminal diameter independent of the change in reference diameter. Any change in the reference diameter, as one of the variables on which percent diameter stenosis measurement is based, will influence the rate of restenosis. A reduction in reference diameter will tend to underestimate any coincident reduction in the vessel luminal diameter expressed as a percent of this diameter. As a consequence, a restenosis rate based entirely on the change in percent diameter stenosis will tend to underestimate the incidence of restenosis after angioplasty.

Conclusions. The use of a computer-assisted system for the measurement of coronary artery lesions has enabled the accurate determination of the changes that occur in these lesions after balloon dilation. Early after the procedure, there is a variable response, some lesions showing improvement and thus deterioration of the minimal luminal diameter. Between 60 and 90 days, there is a significant deterioration that is maintained at 120 days. The reference diameter obtained from the adjacent "normal" segment, also shows a similar late deterioration, presumably because this segment is involved in the dilation process. This change in reference diameter will lead to an underestimation of changes in the dilated lesion if, as is the convention, the percent diameter stenosis is used as the sole measurement.

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Chapter 3

Early regression and late progression in coronary artery lesions in the first three months following angioplasty. New Developments in quantitative coronary angiography Nijhoff 1988; 167-180.

11. Early regression and late progression in coronary artery lesions in the first 3 months following coronary angioplasty

KEVIN J. BEATT, H. E. LUIJTEN, J. H. C. REIBER and P. W. SERRUYS

SUMMARY. In order to determine the changes in stenotic lesions following coronary angioplasty, detailed quantitative angiographic measurements were performed in 254 patients (292 lesions) immediately post-angioplasty and then at one of three predetermined follow-up times, at 30, 60 or 90 days. The absolute changes in mm of the minimal lumen diameter were compared for the three groups, and a relatively high follow-up rate of 88% was achieved. In the groups of patients followed-up at 30 and 60 days, the response was variable with 6% of the lesions showing a significant improvement in both groups and 1% and 12% respectively, showing a deterioration. At 90 days no lesions were seen to improve with 23% deteriorating.

Early following angioplasty lesions exhibit a variable response with more improving than deteriorating. At 60 days the restenosis process is evident, with the number of lesions deteriorating almost doubling between 60 days and 90 days.

Introduction

The incidence of restenosis following PTCA has become an important index for defining the longterm success rate of the procedure. However, despite a number of studies, some involving relatively large numbers of patients, the incidence of restenosis in the overall PTCA population remains poorly defined. This is due to a number of factors, which alone or in combination may lead to distortion of the data. The first of these is the failure to use a reproducible quantitative angiographic measurement system for defining the vessel diameter. Visual estimation of stenosis severity alone yields unacceptable errors in the assessment of changes in the coronary lesion [1—4], and an automated edge detection system will further enhance the accuracy of a quantitative system [5].

Secondly, the rate of restenosis varies considerably according to the definition used. Restenosis rates are conventionally based on the change in percentage diameter stenosis; the criteria used are arbitrary and may not reflect the true changes occurring in the vessel.

Thirdly, follow-up studies addressing restenosis should be performed prospectively, with all or as many patients as possible undergoing repeat angiography at preset follow-up times. Reinvestigation determined predominantly by the recurrence of symptoms, will bias the results so that they do not reflect the outcome of the PTCA population as a whole.

In order to better define the true incidence of restenosis, and to determine the change of lesion characteristics with time, we performed an angiographic study in patients who had undergone a successful PTCA. Patients were reinvestigated at 30, 60 and 90 days (following the dilatation procedure) and measurements were performed using a computer based quantitative angiographic system (CAAS).

Study population

Initially 290 patients were entered into the study having undergone successful coronary angioplasty, defined as: (1) less than 50 percent diameter stenosis on visual inspection of the post-angioplasty coronary angiogram performed in multiple views; (2) no in-hospital complications, namely recurrence of angina, coronary bypass grafting, repeat percutaneous transluminal coronary angioplasty (PTCA), acute myocardial infarction, or death.

Both patients with stable and unstable angina pectoris, as defined previously [6], were included. Patients with acute myocardial infarction receiving a thrombolytic agent who subsequently had immediate coronary angioplasty were excluded.

Allocation of patients to one of three predetermined times for follow-up angiography was made sequentially according to the study period in which the dilatation was performed; those falling in the first study period being reinvestigated at 30 days, the second at 60 days, the third at 90 days. Of the 290 patients who met the inclusion criteria, 254 patients had repeat angiography suitable for quantitative analysis. The reasons for failure to complete the study are detailed in Fig. 1.

Recatheterization was considered to be contra-indicated for the following reasons: severe concomitant disease (e.g. renal failure, lung cancer), peripheral vascular disease, or multiple (> 4) prior angiographic investigations.

Of the total study group of 254 patients (292 lesions), 93 patients were recatheterized at 30 days (110 lesions), 79 patients at 60 days (89 lesions) and 82 patients at 90 days (93 lesions).

The baseline clinical characteristics in the three groups were comparable for the variables shown in Table I. The mean time from PTCA to follow-up angiography in the three study groups was 40 days, 58 days and 102 days, respectively.

Where clinically indicated (early recurrence of symptoms), patients were re-investigated before their preset time, but in order not to adversely bias the earlier groups and so allow valid statistical comparison of the individual groups, analysis was performed according to their original allocation group.

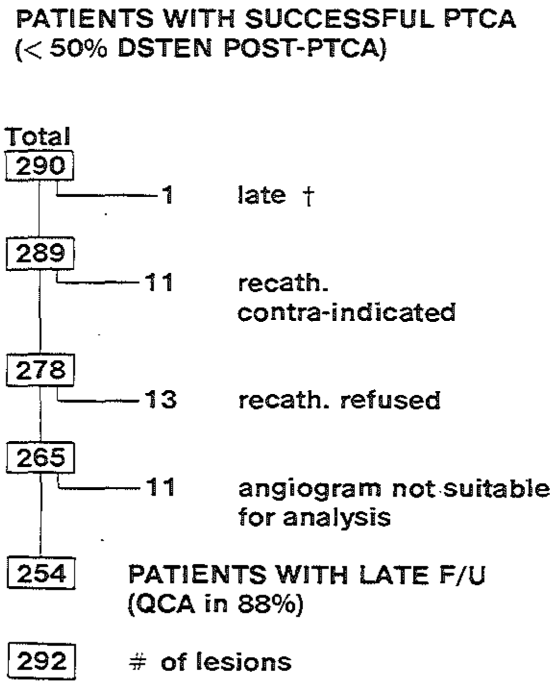

Figure 1. Flow chart of the total number of patients who met the inclusion criteria, and the reasons for failure to complete the study. F/U = follow-up; QCA = quantitative coronary angiography; Recath. = recatheterization.

Prior myocardial infarction was defined according to the Minnesota code, [7] and in the case of an electrocardiographic conduction abnormality making interpretation difficult, the presence of regional akinesia or dyskinesia on the left ventriculogram was used as the criterion for a previous infarction. In Table II are shown for each study group the type of vessel dilated, the number of patients with tandem lesions, and the number of patients with more than one lesion dilated.

Methods

Coronary angioplasty was performed with a steerable, movable guide-wire system via the femoral route. Details regarding the procedure used in our laboratory have previously been described [6]. At the beginning of the angioplasty procedure all patients received 10,000 I.U. of heparin i.v., 500 mg of acetylsalicylic acid i.v., and a continuous infusion of Rheomacrodex® (low molecular weight dextran) was started. After dilatation 10 mg of nifedipine

Table I. Clinical characteristics of 290 patients with successful percutaneous transluminal coronary angioplasty entered into the study.

Characteristics	Follow-up period			
	30 Days No. (%)	60 Days No. (%)	90 Days No. (%)	overall No. (%)
No. of patients	93	79	82	254
No. of lesions	110	89	93	292
Mean no. of lesions dilated/pt.	1.18	1.13	1.13	1.15
Age (mean ± s.d.)	57±9 (range, 35—75)	57±9 (range, 31—75)	56±9 (range, 32—74)	57±9 (range, 31—75)
Sex ratio (M/F)	5.6 (79/14)	5.1 (66/13)	3.3 (63/19)	4.5 (208/46)
Time from PTCA to F/U (days)	40±7 (range, 18—62)	61±12 (range, 11—80)	102±18 (range, 33—164)	80±38 (range, 11—164)
Extent of C.A.D.				
(No. of vessels) 1	63 (68)	55 (70)	59 (72)	177 (70)
2	25 (27)	20 (25)	18 (22)	63 (25)
3	5 (5)	4 (5)	5 (6)	14 (6)
Previous coronary bypass grafting	8 (9)	4 (5)	3 (4)	15 (6)
Previous myocardial infarction	25 (27)	24 (30)	20 (24)	69 (27)
Previous coronary angioplasty	10 (11)	2 (3)	11 (13)	23 (9)

C.A.D. = coronary artery disease; F = female sex; F/U = follow-up angiography; M = male sex; s.d. = standard deviation.

was given orally every two hours for the first twelve hours after PTCA, and then three to six times a day together with 500 mg of acetylsalicylic acid orally once a day until repeat angiography. Beta-blockers were withdrawn unless hypertension was present.

Quantitative coronary angiography

The quantitative analysis of the stenotic coronary segments was carried out with the computer-assisted Cardiovascular Angiography Analysis System (CAAS), which has been described in detail [8, 9]. In summary, to analyze a coronary arterial segment in a selected frame of 35 mm cinefilm, an optically magnified (magnification factor 2) portion of the image encompassing that segment is converted into video format by means of a cine-video converter. The contours of the vessel are detected automatically on the basis of the weighted sum of first- and second-derivative functions applied to the digitized brightness information. Calibration of the diameter data of the vessels in absolute values (mm) is achieved by using the contrast catheter as a scaling device. To this end, the contours of a user-defined portion of the optically magnified catheter (optical magnification factor $2\sqrt{2}$) are detected automatically. Both the arterial segment and catheter contours are corrected for pincushion distortion caused by the image intensifier. From the arterial contours, the vessel diameter function, in millimeters, is determined by computing the shortest distances between the two contour sides. A representative analysis, with the detected contours and the diameter function superimposed on the digitized video image, is shown in Fig. 2.

The reference diameter or the normal diameter of the coronary artery at the site of obstruction is difficult to standardize and is usually defined visually using the nearest coronary artery segment that appears normal. A number of errors may be produced in this way: firstly, there is a large individual variation in the choice of the segment used, and secondly, because of the variation in the vessel diameter, typical of atherosclerotic vessels, adjacent segments will not always represent the normal diameter of the vessel at the site of the obstruction. To avoid these potential errors we have used an 'interpolated' reference diameter measurement. The principle behind this technique is the computer estimation of the original diameter within the obstructed region assuming that no local coronary disease is present. This is calculated from the computed reference diameters of the proximal and distal segments, and after the vessel has been reconstructed the interpolated reference diameter is taken as the value coincident with the site of maximal narrowing [10—11]. The precision of the contour detection process has previously been validated using plexiglass phantoms filled with contrast medium [12]. We have found that using our measurement system, the overall accuracy (average difference between true and measured values) and the precision (pooled standard deviation of the differences) of the obstruction diameter is minus 30 and plus 90 microns, respectively [8].

In order to standardize the method of analysis of the PTCA and follow-up angiograms, the following four measures were undertaken: first, multiple matched views, orthogonal if possible, were analyzed for each patient and the results averaged; second, the X-ray system was repositioned in the settings corresponding as much as possible to the projections used during the previous angiographies. For this purpose, the angular settings of the X-ray gantry and the various height levels were readjusted according to the values previously documented with the on-line registration system. Third, for all studies cineframes to be analyzed were selected at end-diastole to minimize any possible foreshortening effect. Fourth, the user-determined

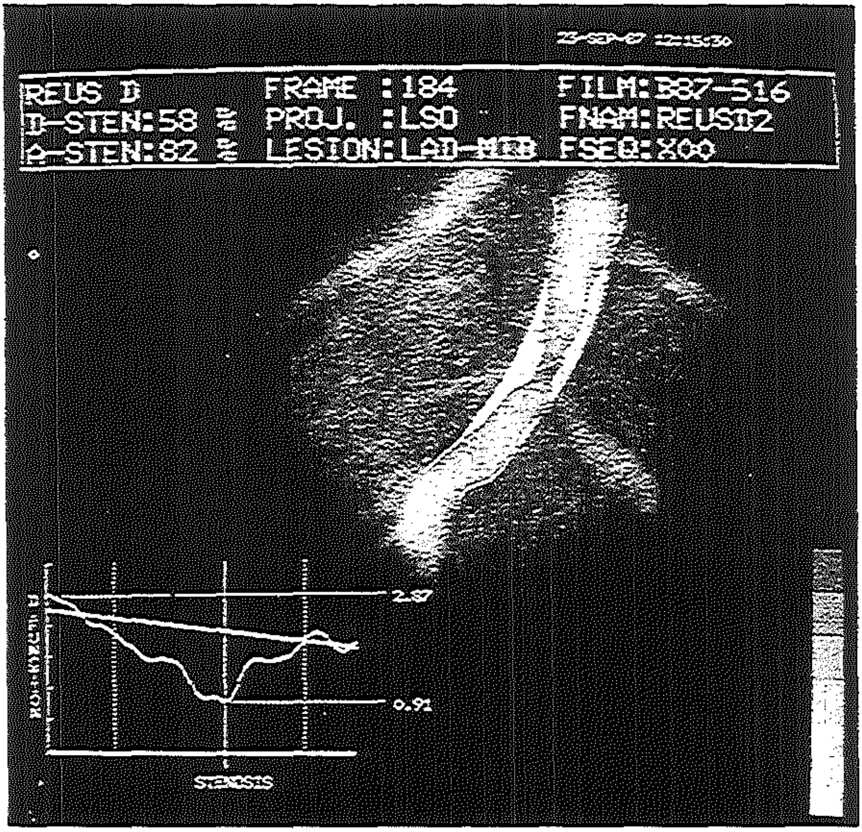

Figure 2. A single frame angiogram of a left coronary artery with superimposition of the automated contours at the coronary artery segment of interest. Beneath this is shown the diameter function of the detected contours of the left anterior descending coronary artery. The minimal lumen diameter (0.91 mm) and the interpolated diameter function line (i) from which the reference diameter is derived, are shown on the diameter function plot.

beginning and end-points of the major coronary segments between side branches, where possible, were identified according to the definitions of the American Heart Association. Finally, Polaroid pictures were taken of the video image with the detected contours superimposed, to ensure that the analyses were performed on the same coronary segment in the consecutive angiograms.

Absolute measurements of the reference diameter and minimal obstruction diameter were recorded in millimeters. A change of greater than 0.72 mm was taken to represent a significant change. This is based on twice the variability of the obstruction diameter (0.36 mm) when coronary angiography is repeated over an interval of 90 days [8].

Statistical analysis

To compare the three follow-up groups with respect to baseline characteristics (Tables I and II), univariate analysis of variance was performed for the continuous variables, and chi-square analysis for discrete variables. Univariate analysis (BMDP statistical software, University of California Press, Berkeley, California 1985) was performed on the quantitative angiographic data.

Table II. Type of vessel dilated, number of patients with tandem lesions, and number of patients with more than one lesion dilated for each of the four study groups.

	30 Days No. (%)	60 Days No. (%)	90 Days No. (%)	overall No. (%)
Vessel dilated				
LAD	61 (56)	61 (69)	55 (59)	177 (61)
LCX	18 (16)	16 (18)	19 (20)	53 (18)
RCA	26 (24)	11 (12)	16 (17)	53 (18)
Bypass	4 (4)	0 (0)	2 (2)	6 (2)
LMCA	1 (1)	1 (1)	1 (1)	3 (1)
No. of patients with tandem lesion	6 (6)	2 (3)	2 (2)	10 (4)
No. of patients with more than 1 lesion dilated	15 (16)	10 (13)	10 (12)	35 (14)

Bypass = aortocoronary bypass graft; LAD = left anterior descending artery; LCX = left circumflex artery; LMCA = left main coronary artery; RCA = right coronary artery.

Results

In the three follow-up groups 254 patients completed angiographic follow-up. As a result of PTCA there was an expected significant improvement in the minimal lumen diameter and diameter stenosis in each of the 3 groups ($p < 0.0001$). The changes in the mean minimal lumen diameter and the mean reference diameter occurring between post-PTCA and follow-up are shown in Fig. 3. In the groups that had follow-up angiography performed at 30 and 60 days, there were small nonsignificant changes in both these values. However, at 90 days there was a highly significant decrease in not only the minimal lumen diameter, but also in the reference diameter.

The changes in the individual minimal lumen diameters (mm) of all the lesions divided into the 3 follow-up groups are represented in Fig. 4. Individual lesions that have undergone a change greater or equal to 0.36 mm are distinguished by a closed circle. Regression is defined as an increase, and

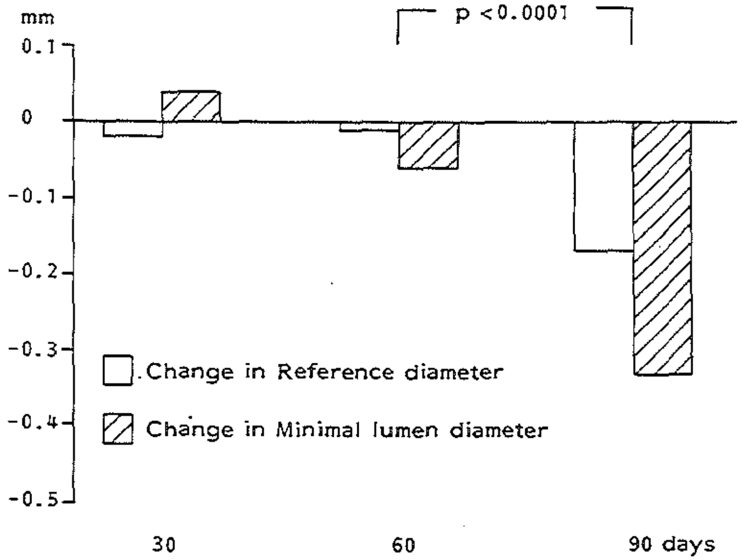

Figure 3. Change in reference diameter and minimal lumen diameter for the three follow-up groups. For the 90 days group both these changes are significantly greater than in the two previous follow-up groups ($p < 0.0001$).

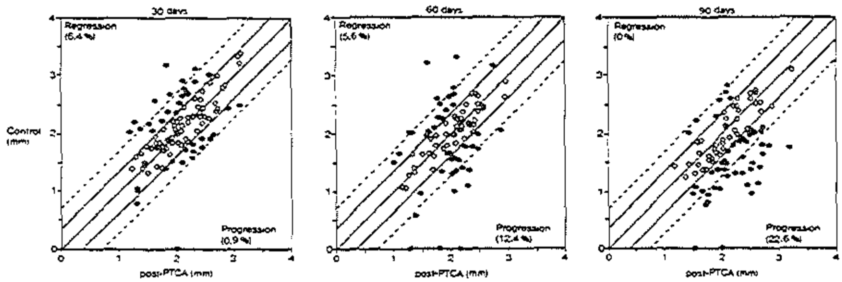

Figure 4. Individual minimal lumen diameter (mm) post-PTCA compared with that at control angiography for the three groups. The two solid lines on either side of the identity line correspond to the long-term variability (0.36 mm) of repeated measurements for this parameter. This variability is one standard deviation of the differences of the duplicate angiographic measurements. Here two standard deviations were used ($2 \times 0.36 = 0.72$ mm; dashed lines) as a criterion for lesion progression or regression. Based on this criterion the percentage of lesions showing progression or regression (outside of dashed lines) are shown within the relevant brackets.

progression as a decrease of at least 0.72 mm (twice the variability) and these values fall outside the dotted lines. It can be seen that the mean change for each group does not reflect the number of individual lesions undergoing a significant change. In the group followed up at 30 days there were a greater number of lesions undergoing regression than progression. At 60 days the percentage of patients showing progression was twice that of regression and at 90 days this percentage had doubled with virtually no lesions exhibiting regression.

Figure 5 illustrates the incidence of restenosis according to a number of commonly used criteria, and to the criterion for a change of greater than 0.72 mm. There is a wide variation in the incidence according to the criteria used, although the incidence of restenosis increases progressively up to at least 90 days, irrespective of the criteria chosen.

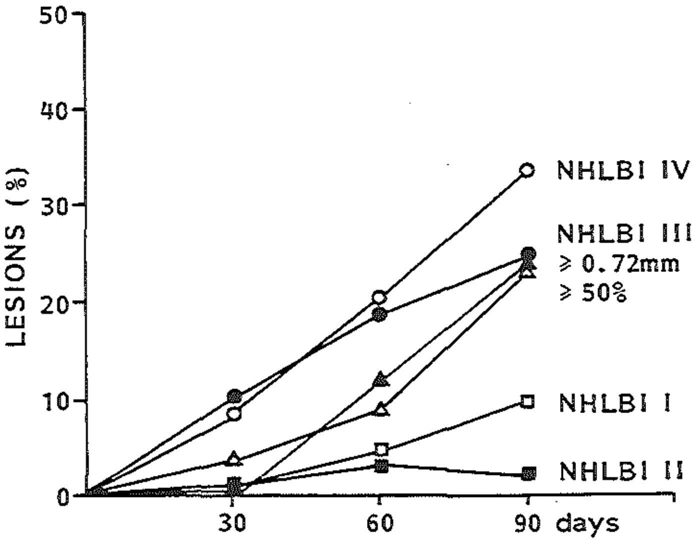

Figure 5. Shown are the percentages of lesions that fulfil three of the restenosis criteria: NHLBI IV, defined by a loss of greater than 50% of the gain achieved at PTCA; ≥0.72 mm, defined by a change of ≥0.72 mm between post-PTCA and follow-up; and thirdly, ≥50% stenosis at follow-up. Using these three criteria the incidence of restenosis increases up to at least 90 days.

Discussion

Method of assessment

Percutaneous transluminal coronary angioplasty has developed into a well accepted method of revascularization. Although the immediate benefits of the procedure are well established and often striking, the longterm outcome is less well defined; undoubtedly, the feature that most limits the usefulness of this procedure is the incidence in restenosis of the dilated lesion in the months following the procedure [14—17]. Various methods of assessing the results of angioplasty have been addressed by Serruys and others [10, 18]. The absolute measurement of a coronary stenosis based on a series of single frame angiograms remains the most direct method of assessing the degree of coronary artery obstruction. Accurate measurement of any change in the coronary artery stenosis must be based on reproducible quantitative measurements. The use of computer assisted automatic edge detection of the lesion contours is also important, particularly in the situation post-angioplasty when the contours of the dilated lesions tend to be irregular and are subject to a greater inter- and intra-observer variability [5]. Using an automatic edge detection measurement system in combination with a strict protocol, both for the timing of repeat follow-up measurements and for the angiographic projections studied, will allow a high degree of accuracy to be obtained. The variability of the mean minimal lumen diameter for repeat short (5 min.), medium (60 min.), and long term (90 days) observations was found to be 0.34 mm, 0.22 mm and 0.36 mm, respectively. We have taken the long term variability, the value for the least well controlled group, as the basis of our criteria for lesions that undergo a significant change. The variability represents one standard deviation of the differences between the paired measurements from the first and second angiograms, and would result in a 16% false positive rate, while the use of two standard deviations as a criterion (0.72 mm) results in a false positive rate of 2.5%. It provides an index of restenosis based on the absolute change in the lesion rather than a change relative to the reference diameter; by using this value we are able to obtain a better insight into the changes in coronary anatomy that occur following PTCA.

Early remodeling of dilated lesion

The data of patients followed up at 30 days suggest that the early response following PTCA is extremely variable with more patients exhibiting a regression of the stenosis than those exhibiting progression. This is well shown in Fig. 4. The lack of uniformity in response following PTCA has been documented in the past [16, 17], but no factor has been identified that can predict with any reliability or consistency the lesions that will show either progression or regression.

Lesion regression rates of 30% have previously been described following angioplasty, but in a small group of patients, using different criteria and without specific reference to time following angioplasty of the selected subgroups. Spontaneous lesion regression may occur as part of the atherosclerotic process [19—22] in undilated coronary artery lesions; however, we cannot exclude further changes following our last observation point at 90 days. It may be that the irregular nature of the lesion post-angioplasty does not allow accurate baseline measurement, particularly if a dissection has occurred, but our system using automatic detection of the vessel contours will minimize the variability of this measurement. Distortion of the baseline value will mean that any consequent measurement based on this will be inaccurate.

An alternative explanation for the early variable response is that of platelet deposition or dissolution. Thrombus may be present at the site of the stenosis prior to dilatation, or alternatively deposition may occur early after dilatation as has been demonstrated in animal models [23]. Therefore, behavior of platelets at the site of dilatation following angioplasty may account for the early variable response seen.

Late progression

In the group of patients followed up at 60 days the variability in response is again exhibited, but at 90 days there is a distinct change in the pattern. There are fewer patients exhibiting a regression in the minimal lumen diameter, with many more patients showing a deterioration. This general trend towards deterioration is responsible for the relatively large change in the mean minimal lumen diameter and the highly statistical difference between this group and the 2 groups followed up earlier at 30 and 60 days ($p < 0.0001$).

This progression of the minimal lumen diameter reflects the well known deterioration in percent diameter stenosis in studies where the mean follow-up time post-angioplasty was greater than two months [14—17]. Animal studies have shown that following angioplasty of normal arteries there is initially significant platelet deposition, particularly if an intimal tear has occurred, and subsequently proliferation of smooth muscle cells. In the pig model [23] it has been shown that intimal proliferation occurs between 7 and 14 days and this same process has been identified in at least 7 postmortem hearts that were examinated over a similar time period to that involved in our study (17—150 days) [24—28]. These reports comment on this difference between the dilated segments and nondilated segments, but do not differentiate between changes within stenotic segments and those without. More recently, Wallar *et al.* [29] has reported fribrocellular proliferation in the left main stem coronary artery which was not targeted for angioplasty, but may have been traumatized by either the balloon dilatation or guiding catheters. However, the former seemed the more likely as there was evidence of the restenosis process along the entire segment occupied by the dilating balloon. The histological evidence suggests that the restenosis process found in animals is the same as that responsible for the deterioration in the minimal lumen diameter and the reference diameter shown in our study. Kaltenbach *et al.* [13] in one of the few studies with a high percentage follow-up rate showed, that almost all patients who develop restenosis do so within the first three months. We are able to show that a restenosis process takes place predominantly between two and three months, but at this time we are unable to comment on the possibility of the process continuing beyond this period.

There is very little data concerning the change in the reference diameter following angioplasty, which is perhaps surprising as animal studies would suggest that coronary artery segments involved in the dilatation procedure would also expect to be involved in the intimal proliferation process [23]. The fact that, in our study, the acceleration of deterioration in the reference diameter occurs at the same time as that in the minimal lumen diameter suggests that the underlying process is the same. The change has an important effect on the percentage diameter stenosis measurement and will tend to underestimate the restenosis process. It further reinforces the importance of using an accurate measurement system in this type of study.

Conclusion

The use of an accurate computer-assisted system for the measurement of coronary artery lesions has enabled a more accurate determination of the changes that occur in coronary artery lesions following dilatation. Early following the procedure there is a variable response with both improvement and deterioration of the minimal lumen diameter, whereas by 90 days the response is more uniform with a significant deterioration being evident. The change in reference diameter follows a similar pattern to that of the mean minimal' lumen diameter, presumably because it is also involved in the dilatation process, and will lead to an underestimation of changes that occur if percentage diameter stenosis is used as the sole measurement.

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Chapter 4

Restenosis following coronary angioplasty. The paradox of initial improvement in lesion geometry and poor long term result. Journal of the American College of Cardiology 1992

CLINICAL STUDIES

Restenosis After Coronary Angioplasty: The Paradox of Increased Lumen Diameter and Restenosis

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Restenosis after coronary angioplasty is the single complication that most limits this revascularization procedure in clinical practice. The process is largely unpredictable and the lesion-related factors predisposing to restenosis are poorly understood, with little consensus in published reports. In this study using detailed quantitative angiographic measurements to assess 490 lesions, the simple lesion characteristics associated with restenosis were defined and the relation to the restenosis process documented. Restenosis was defined as an absolute deterioration in the minimal lumen diameter by ≥0.72 mm, a criterion based on the 95% confidence intervals for repeat angiographic measurements. This was chosen in an attempt to separate spurious changes due to a poor angiographic result and the variability of angiographic measurements from significant changes due to the restenosis process.

The principal determinants of restenosis were found to be a large improvement in the minimal lumen diameter at the time of dilation (1.13 mm for the restenosis group compared with 0.86 mm for the no restenosis group [$p < 0.0001$]) and an optimal postangioplasty result (minimal lumen diameter 2.28 mm in the restenosis group compared with 2.05 mm [$p < 0.001$] in the no restenosis group, corresponding to a 25% and a 30% diameter stenosis, respectively [$p < 0.0001$]).

These observations reported for the first time suggest that the distinction needs to be made between a "clinical restenosis" of ≥50% diameter stenosis and the "restenosis process" as measured by the absolute changes occurring during and after angioplasty. They lend support to the hypothesis that the degree of mechanical stretch produced by the dilating balloon on the vessel wall may be important in stimulating the restenosis process. This is in contradiction to deductions obtained if restenosis is based on "clinical restenosis," which suggests that restenosis is associated primarily with a poor angioplasty result. More important, it indicates that there is potential for misinterpreting the results of restenosis studies if the observations are based solely on conventional restenosis criteria without knowledge of the absolute changes occurring during and after the angioplasty procedure.

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Restenosis after angioplasty is conventionally determined by the angiographic restenosis rate. Although this is known to be an inaccurate reflection of "clinical restenosis" (1–6), it is the most objective and reproducible form of assessment and consequently it remains the index by which the long-term success of angioplasty (7–9) as well as other nonsurgical revascularization procedures is judged.

This index, however, is significantly influenced not only by the definition of restenosis employed, but also by a host of other factors such as incomplete dilation, method of angiographic analysis, low follow-up rates and biased patient study groups. The failure to adopt a standard method of assessment has led to varying reports concerning the factors that influence the restenosis process.

The current lack of information means that the optimal angioplasty result necessary to achieve good long-term success is not known. Overdilation is associated with an increased incidence of acute dissection (10) and may stimulate the restenosis process by the extent of deep arterial injury, which in turn is associated with increased platelet activation (11). Alternatively, as suggested in the animal model (12), the injury due to stretching itself, independent of platelet accumulation, may be an important stimulant for restenosis. Conversely, underdilation may leave a significant residual stenosis, resulting in increased turbulence (5,13), increased platelet activation and subsequent restenosis by the same common pathway. More recently, the important association of residual stenosis, a positive stress test and their relation to "restenosis" have been reported (14).

In this study, simple lesion variables (minimal lumen diameter, reference diameter and percent diameter stenosis)

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Table 1. Clinical Characteristics of 424 Patients

No. of lesions	490
Lesions/patient	1.16
Patient age (mean) (yr)	57 ± 9 (range 31 to 79)
Male/female ratio	346/78
Time from angioplasty to follow-up (days)	94 ± 43 (range 3 to 226)
Vessels with CAD (no. of patients)	
1	288 (68%)
2	97 (23%)
3	39 (9%)
Previous CABG (no. of patients)	31 (7%)
Previous angioplasty (no. of patients)	176 (42%)
Previous MI (no. of patients)	44 (10%)
Dilated vessel (no. of patients)	
LAD	239 (57%)
LCx	80 (17%)
RCA	97 (20%)
Bypass graft	10 (2%)
No. of patients with more than one lesion dilated	63 (15%)

CABG = coronary artery bypass graft; LAD = left anterior descending coronary artery; LCx = left circumflex coronary artery; MI = myocardial infarction; RCA = right coronary artery.

were measured and the changes in each of these during and after the procedure assessed. The influence of the simple lesion morphology and changes occurring at angioplasty on the restenosis process have been determined and the distinction made between this process and "clinical restenosis" as assessed by more conventional restenosis criteria.

Methods

Study patients (Table 1). Five hundred consecutive patients who underwent successful angioplasty and agreed to have a follow-up angiogram were studied (7). Successful coronary angioplasty was defined as 1) <50% diameter stenosis on visual inspection of the postangioplasty coronary angiogram performed in multiple views; and 2) no in-hospital complications (namely, recurrence of angina, coronary bypass grafting, repeat percutaneous transluminal coronary angioplasty, acute myocardial infarction or death).

Patients with stable and unstable angina pectoris, as defined previously (15), were included. Patients with acute myocardial infarction receiving a thrombolytic agent who subsequently had immediate coronary angioplasty were excluded.

Patients were allocated at a predetermined time for follow-up angiography at the time of angioplasty. Of the 500 patients who met the inclusion criteria, 424 patients (with 490 lesions) had repeat angiograms suitable for quantitative analysis, with a mean time to follow-up angiography of 94 ± 43 days. The reasons for failure to complete the study were late death (2 patients), recatheterization contraindicated or refused (52 patients) and angiograms unsuitable for quantitative analysis (22 patients).

When clinically indicated (early recurrence of symptoms), patients were reinvestigated before the original preset time. Table 1 shows the baseline characteristics of the patients included in the study. Data concerning patients followed-up within 4 months of angioplasty have previously been published (7).

Coronary angioplasty. This was performed with a steerable, movable guide wire system by means of the femoral route. At the beginning of the angioplasty procedure, all patients received 10,000 IU of heparin and 500 mg of aspirin intravenously. After dilation, 10 mg of nifedipine was given orally every 2 h for the 1st 12 h and then 20 mg three times a day together with 500 mg of aspirin orally once a day until repeat angiography.

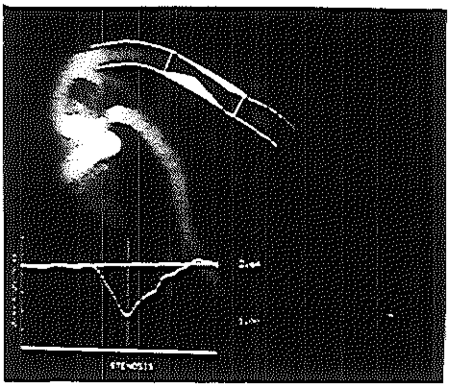
Quantitative coronary angiography. The quantitative analysis of the stenotic coronary segments was carried out with the computer-assisted Cardiovascular Angiography Analysis System (CAAS), which has been described in detail (16,17). Calibration of the diameter of the vessels in absolute values (mm) was achieved by using the guiding/diagnostic catheter as a scaling device (16).

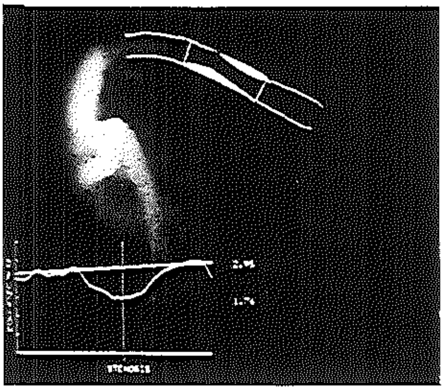
A representative series of analyses, with the detected contours and the diameter functions superimposed on the original video image, are shown in Figure 1. To standardize the measurements and minimize potential errors, the "interpolated" reference diameter measurement was used whenever possible. This method has the advantage of eliminating the arbitrary choice of a reference diameter that will vary among individual observers and provides a smoothing effect for the segments adjacent to the stenosis so that extreme irregularities in the vessel will not artificially bias the reference diameter measurement. It also reduces the effect of the change in reference diameter at follow-up angiography that occurs as part of the restenosis process (18). The principle behind this technique has previously been described (19–21), as have the precision and overall accuracy of the system, the method of obtaining angiograms and precautions taken to reduce error (7).

Restenosis criteria. The restenosis group was defined as those patients with a deterioration in the minimal lumen diameter from postangioplasty to follow-up of ≥0.72 mm, a criterion based on the 95% confidence limits for determining a significant change using a quantitative angiographic system (CAAS) (7,16). The relevance of using this criterion and its comparison with the conventional cutoff criterion of ≥50% diameter stenosis at follow-up are addressed in the Discussion.

Data analysis. All angiographic and procedural variables were entered into a relational data base and statistical analysis was performed with use of BMDP statistical software (University of California, Berkeley, California, 1985). The tertile with the highest incidence of restenosis was identified for each variable, and the relative risk of restenosis in this group was compared with that in the remainder of the study group. An odds ratio for restenosis ≥2 with 95% confidence limits ≥1 was considered to have clinical relevance in this study group.

The variables selected for analysis in this study were all continuous with gaussian distributions. The determination





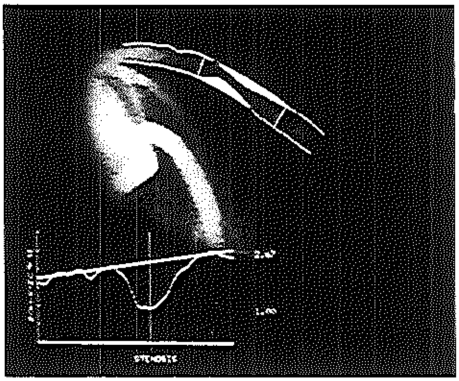


Figure 1. Single frame angiograms of a proximal left anterior descending artery stenosis before dilation (**top left**), after dilation (**top right**) and at follow-up angiography (**bottom**). Quantitative coronary analysis was performed using the Cardiovascular Angiography Analysis System. The arterial boundaries detected by the system are shown on the angiogram, and the diameter function curve derived from these contours is **below**. The example is chosen to illustrate a successfully dilated proximal left anterior artery lesion that undergoes a severe restenosis at 4 months.

of risk of restenosis for continuous variables is dependent on the arbitrary subdivision of data comparing the subgroup with the highest risk with the remainder of the study group. The risk may be artificially influenced by selecting small subgroups that vary from the population by chance and do not reflect the true nature of the population they are drawn from. To define the groups, the data were classified into three groups according to convenient cutoff points, so that each group contained one-third of the overall study patients and the group with the highest restenosis rate was identified. The two remaining groups were then combined to form the group considered to be at "normal risk" and the odds ratio of restenosis determined by comparing the third of the patients in the high risk group with this reference group (the remaining two-thirds of the study patients). (The identification of subgroups for postangioplasty percent diameter stenosis is illustrated in Fig. 2.) This method of subdivision has the advantage of being consistent for all variables and thus avoids any bias in selection of subgroups that might be undertaken to emphasize a particular point. The 95% confi-

Figure 2. Frequency histograms grouped by percent diameter stenosis after angioplasty showing how the group defined by the ≥0.72-mm criterion is divided to determine a relevant odds ratio. The **top line** shows the number of lesions in each third of the group with restenosis (NO WITH REST). The **vertical arrows** with the values beneath show the points of subdivision. POST-PTCA = after coronary angioplasty.

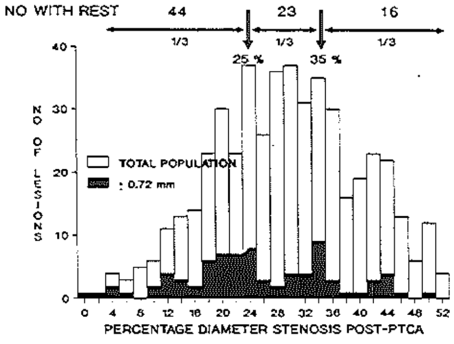


Table 2. Angiographic Variables of Restenosis Subgrouped According to Two Criteria

	≥50% Diameter Stenosis*			≥0.72 mm†		
	Restenosis	No Restenosis	p Value	Restenosis	No Restenosis	p Value
Minimal lumen diameter before angioplasty	1.18	1.21	NS	1.15	1.18	NS
Minimal lumen diameter after angioplasty	2.02	2.10	NS	2.28	2.05	<0.001
Minimal lumen diameter at follow-up	1.06	1.99	<0.0001	1.16	2.01	<0.0001
% diameter stenosis before angioplasty	62.6	57.7	<0.01	58.8	58.3	NS
% diameter stenosis after angioplasty	32.7	28.3	<0.005	24.8	29.7	<0.005
% diameter stenosis at follow-up	64	29.1	<0.0001	54.3	29.7	<0.0001
Normal vessel diameter before angioplasty	2.95	2.8	NS	2.86	2.85	NS
Normal vessel diameter after angioplasty	3.05	2.94	NS	3.06	2.93	NS
Normal vessel diameter at follow-up	2.92	2.81	NS	2.60	2.93	<0.001
Change in minimal lumen diameter at angioplasty (mm)	0.93	0.91	NS	1.13	0.86	<0.0001
Change in % diameter stenosis at angioplasty	30	29.4	NS	34	28.6	<0.01
Change in minimal lumen diameter at follow-up (mm)	0.97	0.10	<0.0001	1.12	0.04	<0.0001
Change in % diameter stenosis at follow-up	31.2	0.77	<0.0001	29.7	0.07	<0.0001

*Criterion of ≥50% diameter stenosis at follow-up angiography. †Deterioration in minimal lumen diameter by ≥0.72 mm after angioplasty to follow-up.

dence intervals then provide an index of the degree of certainty for the result obtained.

Results

Pre- and postangioplasty coronary stenosis measurements. For the total study group, the mean minimal lumen diameter was 1.18 mm before angioplasty, 2.09 mm after angioplasty and 1.85 mm at follow-up. The corresponding mean reference diameters were 2.85, 2.96 and 2.83 mm, giving rise to a percent diameter stenosis of 58.4% before angioplasty, 28.9% after angioplasty and 33.9% at follow-up.

The mean values for the angiographic variables subgrouped according to the ≥0.72-mm criterion and the ≥50% diameter stenosis criterion are shown in Table 2, emphasizing the differences between the two criteria. The grouping of the data for statistical analysis, showing the numbers in each group and the odds ratio for restenosis, are shown in Tables 3 to 5, again comparing the values obtained using the ≥0.72-mm criterion with the ≥50% diameter stenosis criterion.

Preangioplasty variables predictive of restenosis (Table 3). None of the preangioplasty variables were found to be associated with restenosis. A severe >65% diameter stenosis before angioplasty was the most relevant factor, with an odds ratio of 1.63 and confidence intervals from 0.85 to 3.31.

Table 3. Angiographic Variables Before Angioplasty

Grouped by ≥0.72-mm Change Criterion				Grouped by ≥50% Diameter Stenosis			
Minimal Lumen Diameter Before Angioplasty							
	≤1 mm	>1 mm	Total		≤1 mm	>1 mm	Total
No restenosis	129 (85)	278 (82)	407 (83)	No restenosis	128 (85)	295 (87)	423 (86)
Restenosis	22 (15)	61 (18)	83 (17)	Restenosis	23 (15)	44 (13)	67 (13)
Total	151	339	490	Total	151	339	490
Odds ratio = 1.29 (0.76–2.19)				Odds ratio = 1.21 (0.70–2.08)			
% Diameter Stenosis Before Angioplasty							
	≤65%	>65%	Total		≤65%	>65%	Total
No restenosis	312 (85)	94 (78)	407 (83)	No restenosis	328 (89)	95 (79)	423 (86)
Restenosis	57 (16)	26 (22)	83 (17)	Restenosis	42 (11)	25 (21)	67 (14)
Total	370	120	490	Total	370	120	490
Odds ratio = 1.63 (0.85–3.13)				Odds ratio = 1.42 (0.82–2.54)			
Normal Diameter Before Angioplasty							
	≤3.2 mm	>3.2 mm	Total		≤3.2 mm	>3.2 mm	Total
No restenosis	289 (84)	107 (82)	396 (83)	No restenosis	301 (87)	111 (85)	412 (87)
Restenosis	57 (16)	23 (18)	80 (17)	Restenosis	45 (13)	19 (15)	64 (13)
Total	346	130	476	Total	346	130	476
Odds ratio = 1.09 (0.64–1.86)				Odds ratio = 1.15 (0.64–2.04)			

Table 4. Angiographic Variables After Angioplasty

Grouped by ≥0.72-mm Change Criterion				Grouped by ≥50% Diameter Stenosis Criterion			
Minimal Lumen Diameter After Angioplasty							
	≤2.3 mm	>2.3 mm	Total		<2.3 mm	>2.3 mm	Total
No restenosis	304 (86)	103 (72)	107 (83)	No restenosis	285 (71)	77 (89)	362 (74)
Restenosis	42 (14)	41 (28)	83 (17)	Restenosis	119 (29)	9 (11)	128 (26)
Total	346	144	490	Total	404	86	490
Odds ratio = 2.88 (1.77–4.68)				Odds ratio = 0.28 (0.13–0.60)			
% Diameter Stenosis After Angioplasty							
	≤25%	>25%	Total		≤25%	>25%	Total
No restenosis	139 (75)	288 (89)	407 (83)	No restenosis	168 (81)	254 (80)	422 (86)
Restenosis	47 (25)	36 (11)	83 (17)	Restenosis	17 (9)	50 (20)	67 (14)
Total	186	324	490	Total	185	304	490
Odds ratio = 2.60 (1.40–4.82)				Odds ratio = 0.51 (0.28–0.95)			
Normal Diameter After Angioplasty							
	≤3.2 mm	>3.2 mm	Total		≤3.2 mm	>3.2 mm	Total
No restenosis	295 (86)	112 (76)	407 (83)	No restenosis	301 (88)	122 (83)	423 (86)
Restenosis	47 (14)	36 (24)	83 (17)	Restenosis	41 (12)	26 (18)	67 (14)
Total	342	148	490	Total	342	148	490
Odds ratio = 2.04 (1.25–3.31)				Odds ratio = 1.58 (0.92–2.69)			

Postangioplasty variables predictive of restenosis (Table 4). The restenosis group had a significantly better postangioplasty result as judged by minimal lumen diameter (2.28 mm) and percent diameter stenosis (24.8%) compared with the no restenosis group (2.05 mm and 29.7%: $p < 0.001$ and $p < 0.0001$, respectively). A postangioplasty minimal lumen diameter >2.3 mm was significantly associated with restenosis (odds ratio = 2.88) as was a postangioplasty percent diameter stenosis ≤25% (odds ratio = 2.60). A vessel ≥3.2 mm in diameter was less clearly predisposed to restenosis according to the ≥0.72-mm criterion with an odds ratio of 2.04.

Changes at angioplasty (Table 5). The factor most associated with restenosis was a large change in the minimal lumen diameter at angioplasty: 1.13 mm for the restenosis group and 0.86 mm for the no restenosis group ($p < 0.0001$), which corresponds to a change in percent diameter stenosis of 34% and 28.6%, respectively. The risk associated with a large improvement in the stenosis in terms of descending order of magnitude were: minimal lumen diameter ≥1.14 mm, minimal lumen diameter adjusted for vessel size ≥0.35 mm and percent diameter stenosis ≥35%, giving odds ratios of 3.30, 2.98 and 2.20, respectively. There was also a trend for a large change in reference diameter >0.36 mm to be associated with an increased risk of restenosis (≥0.72-mm criterion) with an odds ratio of 1.83.

Discussion

Criteria for postangioplasty restenosis. Soon after the introduction of coronary angioplasty as a revascularization procedure, it became clear that restenosis after the procedure was a significant limitation (22,23) and with the improvement in acute results over the years, this limitation has assumed increasing significance. Despite intensive investigation, there is as yet no known intervention that is able to reduce the incidence of restenosis. The reported risk factors associated with restenosis are unsatisfactorily documented, with little agreement among the various studies. These differences are primarily due to the failure of investigators to adopt a suitable standardized methodology with a uniformly accepted definition of restenosis that is relevant to the restenosis process. It has frequently been pointed out that different restenosis criteria give rise to similar restenosis rates (5,24). Although this is true, these similar restenosis rates do not define the same groups of patients (with sometimes as little as 50% overlap) and therefore risk factors may well be very different for different restenosis criteria (7). Figure 3 illustrates the distribution of the two restenosis groups in relation to the total number of lesions studied. Of the 104 lesions fulfilling at least one of the two criteria (21% of the total group of 490 lesions) <50% fulfilled both criteria, and 24% and 33%, respectively, fulfilled the ≥50% diameter stenosis and the ≥0.72-mm criteria.

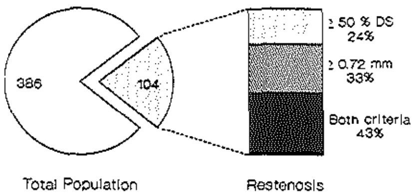
Risk factors for restenosis. There are as yet no prospective studies using quantitative coronary angiography that report on the risk factors for restenosis in large numbers of patients. However, a small number of factors relating to the restenosis process have been identified and confirmed in more than one study. These include dilation of a proximal left anterior descending coronary artery stenosis (5,25), a totally occluded vessel before angioplasty (26) and the presence of collateral vessels supplying the distal part of the

Table 5. Angiographic Variables: Change at Angioplasty

Grouped by ≥0.72-mm Change Criterion				Grouped by ≥50% Diameter Stenosis Criterion			
Change in Minimal Lumen Diameter at Angioplasty							
	≤1.14	>1.14	Total		≤1.14	>1.14	Total
No restenosis	314 (88)	93 (69)	407 (83)	No restenosis	308 (85)	115 (86)	423 (86)
Restenosis	42 (12)	41 (31)	83 (17)	Restenosis	48 (15)	19 (14)	67 (14)
Total	366	134	490	Total	356	134	490
Odds ratio = 3.30 (2.02–5.37)				Odds ratio = 1.06 (0.60–1.88)			
Adjusted Change in Minimal Lumen Diameter at Angioplasty							
	≤0.35	>0.35	Total		≤0.35	>0.35	Total
No restenosis	260 (89)	147 (74)	407 (83)	No restenosis	115 (89)	243 (86)	358 (86)
Restenosis	31 (11)	52 (26)	83 (17)	Restenosis	23 (14)	44 (14)	67 (14)
Total	291	199	490	Total	178	284	490
Odds ratio = 2.98 (1.82–4.84)				Odds ratio = 0.40 (0.22–0.76)			
Change in Diameter Stenosis at Angioplasty							
	≤35%	>35	Total		≤35%	>35%	Total
No restenosis	290 (75)	117 (75)	407 (83)	No restenosis	288 (75)	135 (87)	423 (86)
Restenosis	44 (25)	39 (25)	83 (17)	Restenosis	46 (25)	21 (13)	67 (14)
Total	234	156	490	Total	334	156	490
Odds ratio = 2.20 (1.36–3.56)				Odds ratio = 0.98 (0.67–1.70)			
Differences in Reference Diameter at Angioplasty							
	≤0.36	>0.36	Total		≤0.36	>0.36	Total
No restenosis	320 (85)	75 (76)	395 (83)	No restenosis	327 (87)	84 (84)	411 (86)
Restenosis	56 (15)	24 (24)	80 (17)	Restenosis	49 (13)	15 (15)	64 (14)
Total	376	99	475	Total	376	99	475
Odds ratio = 1.83 (1.07–3.14)				Odds ratio = 1.19 (0.64–2.23)			

dilated coronary artery (27,28). The most frequently identified risk factor for restenosis has been incomplete dilation or a variable directly related to a poor angioplasty result, such as a residual pressure gradient (5,9). In our study, a restenosis criterion that is dependent solely on the changes occurring after angioplasty was chosen to avoid having the results influenced by factors other than the restenosis process. The distinction between the restenosis process and a suboptimal result has been made by comparing the ≥0.72-mm criterion with that of ≥50% diameter stenosis. The analysis has been limited to the simple pre- and postangioplasty morphology (minimal lumen diameter, reference diameter and percent diameter stenosis) and the changes occurring during the procedure. Analysis of data in this form represents a significant change from the convention and gives rise to conclusions that are at odds with some of those previously published.

Figure 3. Of the 490 lesions analyzed, 386 were free of restenosis and 104 lesions (21%) had restenosis by either of the two criteria for restenosis. The column (**right**) illustrates how each criterion is associated with a substantial proportion of lesions that are exclusive to that criterion, with <50% of the lesions (43%) fulfilling both criteria. A similar lack of correlation exists with other conventionally used restenosis criteria. DS = diameter stenosis.



Predilation variables. Of the predilation variables analyzed, only the severity of the initial lesion has previously been reported (9) to be associated with restenosis although many studies have failed to find this association. Other predilation variables not analyzed in this study, such as eccentricity, bend point location and proximal left anterior descending artery stenosis, presence of collateral vessels and a totally occluded artery, have also been implicated (5,24,29).

The initial stenosis severity (Fig. 4) was not found to be associated with an increased risk as assessed with either of the two criteria: odds ratios = 1.29 and 1.21 when using the ≥0.72-mm criterion and the ≥50% diameter stenosis criterion, respectively. Likewise, if the severity of the initial stenosis is expressed as a percent of the normal diameter, a severe initial stenosis >65% was not significantly associated with an increased risk and this observation is in broad agreement with most published reports.

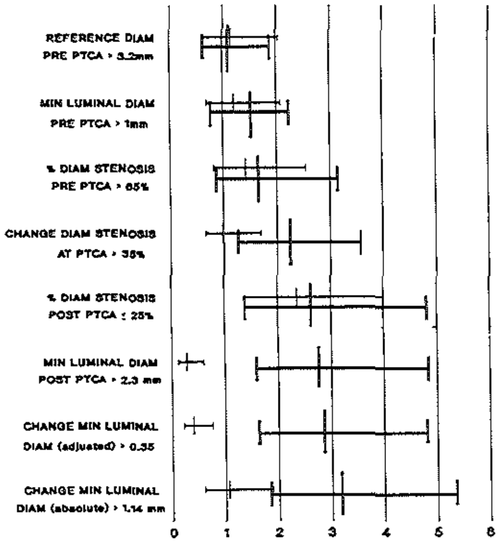


Figure 4. Odds ratios and 95% confidence intervals for restenosis in the third of the study group at highest risk are shown for the ≥0.72-mm criterion (**bold lines**) and for comparison the corresponding group according to the ≥50% diameter stenosis (fine lines). The cutoff point defining the relevant group at highest risk is indicated. CHANGE MIN LUMINAL DIAM (adjusted) = change in minimal lumen diameter divided by normal diameter of vessel; DIAM = diameter; MIN = minimal; other abbreviations as in Figure 2.

Postdilation variables. A poor postangioplasty result (or incomplete dilation) and factors associated with incomplete dilation such as a residual pressure gradient are most frequently reported to be associated with restenosis. The data from this study show that the associated risk is highly dependent on the restenosis criterion employed: essentially a good result (<25% diameter stenosis) is associated with restenosis if the ≥0.72-mm criterion is used and, conversely, a suboptimal result (>35% diameter stenosis) is a risk factor if ≥50% diameter stenosis is used (Fig. 4).

It is, perhaps, not surprising that incomplete dilation should be identified as a risk factor if the criterion for restenosis is a ≥50% diameter stenosis. However, the question remains as to whether a more severe residual stenosis actually induces the restenosis process or whether it reflects the use of a restenosis criterion that preselects lesions with less than optimal results. The answer to this question is crucial because some theories addressing the cause of restenosis incorporate this concept but, more important, if this question is not critically addressed, studies that are designed to determine the effect of therapeutic interventions on restenosis may be falsely interpreted.

Our study suggests that the latter of these two possibilities is the more likely and the frequency histogram (Fig. 5) illustrates why the discrepancy occurs, showing the distribution of the two restenosis groups. The lesions with restenosis (≥50% diameter stenosis criterion) tend to lie near the 50% threshold immediately after the procedure. It seems that if a "cut-off" criterion is used to define restenosis, it will preselect those lesions that lie close to the cut-off value and this appears to be the most relevant factor for the ≥50% diameter stenosis criterion. The reason for this is twofold. First, it should be remembered that the variability of the measurement using a quantitative measuring system is in the region of 6.5% (95% confidence limits ± 13%) (16), which suggests that if a ≥50% criterion is used, a significant number of lesions will be defined as restenosis due to methodologic limitations of the measurement system, when in reality no change has taken place between angioplasty and follow-up. The potential for this type of error will be magnified many times if visual estimates for stenosis severity are used. Lesions with a better postangioplasty result will fall outside this error of measurement and therefore will not be falsely defined as restenosis due to methodologic limitations. Second, after angioplasty, most lesions deteriorate to some extent (30), with the patients showing a normal distribution around a mean deterioration of −0.22 mm; thus, if a deterioration in the lumen diameter is an integral part of the healing process, any "cut-off" criterion that lies in the direction of population shift can be expected to choose preferentially those lesions near to the "cut-off" point. Conversely, the lesions that meet the ≥0.72-mm criterion tend to be distributed at the opposite end of the histogram and as a group have a much better result than those selected by the ≥50% diameter stenosis criterion. The mean postangioplasty percent diameter stenosis in this study was 25% for

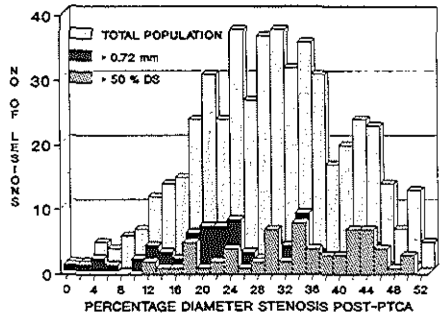


Figure 5. Frequency histogram of 490 lesions after successful angioplasty (POST-PTCA) grouped according to the postangioplasty percent diameter stenosis (DS). The distribution for the total study group is "normal" about a mean value of 29%. The lesions fulfilling each of the two criteria are also shown and the discrepancy between their distributions is clearly demonstrated: The group defined by the ≥0.72-mm criterion is distributed around a mean value of 25% and the group defined by the ≥50% diameter stenosis criterion is distributed around a mean value of 32%.

those lesions fulfilling the ≥0.72-mm criterion and 32% for the ≥50% diameter stenosis criterion.

Variables of change at angioplasty. The factors found to be associated with an increased risk according to the ≥0.72-mm criterion in ascending order were change in reference diameter, change in diameter stenosis, change in minimal lumen diameter and change in minimal lumen diameter adjusted for vessel size by dividing by the normal diameter of the vessel (Fig. 4). It is clear that the more the lesion is improved at the time of the angioplasty procedure, the greater the subsequent deterioration in the months after the procedure. As one might expect, lesions that are improved less than the norm tended to have a greater residual stenosis after angioplasty. These lesions, although likely to meet the ≥50% diameter stenosis criterion because they lie close to it after angioplasty, undergo less deterioration than lesions that have a better result. The distinction should therefore be made between the postangioplasty result and the change in lumen diameter at angioplasty. Although the postangioplasty result is highly relevant to the long-term outcome, it is the change occurring at angioplasty that is the strongest predictor of subsequent deterioration between angioplasty and follow-up. This observation, which previously has not been generally recognized, is not entirely without rationale (10–14).

Substantial improvements in lumen diameter during angioplasty (from a severe stenosis to an optimal result) imply dispersion of large amounts of plaque into the vessel wall or alternatively a deeper dissection into the arterial wall to achieve the same effect. In either case, the degree of improvement is likely to correlate with the degree of trauma to the vessel wall. If the restenosis process is influenced by the degree of trauma, then the greater and deeper the trauma, the more the restenosis process will be stimulated. These results suggest that those lesions that are likely to experience the largest deterioration after dilation are those severe initial lesions that have the optimal postangioplasty result. The frequency histogram (Fig. 6) of change in minimal lumen diameter for the total study group and for those with restenosis according to the two criteria illustrates the discrepancy and relevance of the two criteria.

Implications for clinical practice. There seems to be a consensus among clinicians that the better the result at angioplasty, the less chance there is of restenosis. This premise is not supported by hard experimental evidence, although clearly if the lesion is not effectively dilated, the long-term result cannot be expected to be good. The data from this study suggest that there may well be a compromise result somewhere between a 20% and 30% postangioplasty diameter stenosis that has a good chance of a satisfactory long-term result and may avoid the increased risk of acute dissection and occlusion (9) incurred by using an oversized balloon to achieve an optimal result.

Perhaps more important, the postangioplasty result has implications for clinical restenosis studies, particularly when assessing the affect of pharmacologic interventions. If the

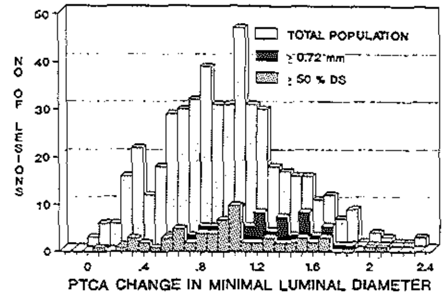


Figure 6. Frequency histogram similar to that in Figure 5 grouped according to change in minimal lumen diameter at angioplasty (PTCA). Again, the distribution is "normal," but with a skew to the right. According to the ≥0.72-mm criterion, the lesions in the third of the group with the largest improvement in the minimal lumen diameter at angioplasty (n = 44) have the highest risk of restenosis. DS = diameter stenosis.

criterion of a ≥50% diameter stenosis is used as the sole definition of restenosis, the preselection of poor postangioplasty results by this criterion may be of such influence that any effect produced by pharmacologic intervention may not be realized by statistical hypothesis testing. More subtly, as the lesions that fulfill the ≥50% diameter stenosis criterion undergo less change between angioplasty and follow-up, it will become statistically difficult to show the effect of a truly beneficial agent because of inadequate statistical power—a verdict of "no benefit" being returned when in fact a benefit exists. It is interesting to note that almost universally the conclusions from these studies have been that no agent has a beneficial effect on restenosis.

The use of restenosis criteria alone for assessing the long-term results of coronary angioplasty has the potential for producing misleading results. A distinction should be made between the postangioplasty result and the restenosis process as measured by the change in minimal lumen diameter or minimal lumen area after the procedure.

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Chapter 5

Angioplasty for stable versus unstable angina pectoris: are unstable patients more likely to get restenosis? Int J Cardiac Imaging, 1988; 3: 87-97.

Angioplasty for stable versus unstable angina pectoris: Are unstable patients more likely to get restenosis?

A quantitative angiographic study in 339 consecutive patients

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Key words: recurrent stenosis, quantitative coronary angiography

Summary

Current evidence with regard to the possible association between clinical expression of coronary disease prior to the time of angioplasty, and the subsequent risk of restenosis following successful dilatation, remains inconclusive.

To prospectively compare the incidence of restenosis in stable versus unstable angina pectoris patients, follow-up angiography was performed in 85 percent of patients from a consecutive series with a successful PTCA, irrespective of presence or absence of recurrent ischemic symptoms. Furthermore, changes in lesion severity were assessed quantitatively by an automated edge-detection technique rather than visual analysis. Employing such a study-design and follow-up protocol, it was found that the incidence of restenosis in patients with stable coronary artery disease was similar to that of patients with unstable rest angina, irrespective of the type of angiographic definition used.

Introduction

Increasing operator experience and technical innovations have made percutaneous transluminal coronary angioplasty (PTCA) a safe and successful treatment modality for patients with symptoms of either stable or unstable angina pectoris [1–7]. However, the long-term outcome of PTCA is still significantly curtailed by the so far unpredictable progression to recurrent stenosis in 12 to 48 percent of patients [4, 5, 8–15].

Although the exact pathophysiological mechanisms involved in recurrent stenosis remain unsolved, its development is most likely the result of the little understood, but apparent, interplay of growth factors and chemoattractants from each of the four cell types involved in atherosclerosis; namely, endothelium, platelets, smooth muscle cells, and macrophages [16].

Furthermore, current evidence with regard to the possible association between clinical expression of coronary disease prior to the time of angioplasty, and the subsequent risk of restenosis following successful dilatation, remains inconclusive. Whereas some previous reports have indicated that angioplasty for unstable angina is associated with an increased risk of lesion recurrence as compared with stable angina [10, 17], this has not been corroborated by others [4, 5, 7, 9, 12, 18, 19].

In view of these discrepant results, and given the distinctly different coronary morphology observed by angioscopy in patients with stable exercise-induced angina versus those with unstable rest angina [20, 21], elucidation of the question whether the

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incidence of restenosis differs in these two ischemic coronary syndromes merits further attention.

Since the incidence of restenosis appears to be influenced by the rate of follow-up angiography, and by the method of assessment of the coronary angiograms, a protocol was implemented in this study that involved repeat quantitative coronary angiography, irrespective of the presence or absence of recurrent ischemic symptoms.

Study population

During the period from January 1984 to September 1985, PTCA was attempted in 282 patients with stable angina and in 177 patients with unstable angina. Stable angina pectoris was defined as chest discomfort related to effort or emotion; these patients underwent elective coronary angioplasty. Unstable angina pectoris was defined as prolonged chest pain at rest with documented reversible ST-segment or T-wave changes, without subsequent myocardial necrosis as evidenced by a rise in creatine phosphokinase to at least twice the normal level or by pathological Q-wave development ($Q > 0.04$ s). The ischemia-related coronary lesion was dilated in unstable angina patients in whom multivessel disease was present. The offending lesion was identified on the basis of recorded electrocardiographic changes and coronary anatomy. Electrocardiographic changes in leads V1 to V5 were associated with lesions of the left anterior descending artery, changes in I, aVL, and V6, with the marginal branch of the circumflex artery or the diagonal branch of the left anterior descending artery, and changes in inferior leads with either the right coronary artery or the circumflex artery.

Two-hundred forty-two consecutive patients with stable angina pectoris, which represents a 85.8% primary success rate, and 155 patients with unstable angina pectoris, which represents a 87.6% primary success rate ($p = NS$), underwent successful coronary angioplasty, defined by: 1) clinical relief of ischemic symptoms; 2) less than 50 percent diameter stenosis on visual inspection of the post-angioplasty coronary angiogram performed in multiple views; 3) no in-hospital complications, such as recurrence of angina, coronary bypass grafting, repeat PTCA, acute myocardial infarction, or death.

After obtaining informed consent all patients with a successful PTCA were requested to undergo follow-up angiography. Of the 242 patients with stable angina and the 155 patients with unstable angina who underwent a successful dilatation, 206 stable patients (85.1% follow-up) and 133 unstable patients (85.8% follow-up) had repeat angiography suitable for quantitative analysis. Coronary angiograms that were technically inadequate because of suboptimal visualization of the dilated segment, most commonly due to vessel overlap, and/or incomplete opacification were not included in the analysis. The reasons for failure to complete the study for the stable and unstable groups combined are detailed in Fig. 1. Recatheterization was considered contra-indicated in the event of disabling concomitant disease (e.g. renal failure, lung cancer), severe peripheral vascular diseases, or more than four prior angiographic investigations.

The clinical characteristics of the study population with subdivision into patients with a history of stable and unstable angina pectoris prior to the time of PTCA, are detailed in Table 1. The extent of coronary artery disease was defined as the number of vessels with a $\geqslant 50\%$ diameter narrowing, and prior myocardial infarction was diagnosed according to the Minnesota code [22].

Methods

Angioplasty procedure and medication

Coronary angioplasty was performed with a steerable, movable guide-wire system via the femoral route. At the beginning of the procedure all patients received 10.000 I.U. of heparin i.v., 250 mg of acetylsalicylic acid i.v., and a continuous infusion of low molecular weight dextran (Rheomacrodex®) was started. To prevent coronary spasm, intracoronary nifedipine or isosorbide dinitrate was given. ECG and blood pressure were continuously monitored. Initial balloon inflation pressure was 2.0 atmospheres, with subsequent inflations ranging up to 12.0 atmospheres. Inflation was

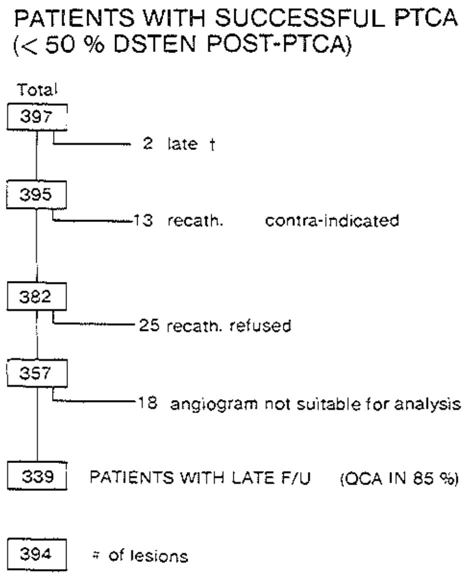


Fig. 1. Flow chart of the total number of patients who met the inclusion criteria, and the reasons for failure to complete the study. DSTEN = diameter stenosis; F/U = follow-up; QCA = quantitative coronary angiography; Recath. = recatheterization.

maintained according to ECG changes, degree of blood pressure drop or induced pain. Balloon dilatations were repeated until the severity of the obstruction was at least below 50% luminal diameter narrowing, as judged from repeat coronary angiograms obtained in multiple views immediately after the dilatation. Following the procedure all patients were monitored for at least 24 hours, by means of electrocardiography, and serial cardiac enzyme levels when necessary. Following coronary angioplasty 10 mg of nifedipine was given orally every two hours for the first twelve hours, and thereafter three to six times a day together with 500 mg of acetylsalicylic acid orally once a day for a period of six months. Beta blockers were withdrawn unless hypertension was present.

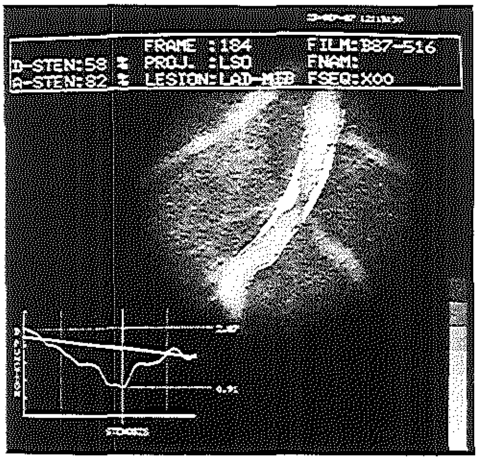
Quantitative coronary angiography

The quantitative analysis of the stenotic coronary segments was carried out with the computer-assisted Cardiovascular Angiography Analysis System (CAAS), which has been described in detail elsewhere [23, 24]. To analyze a coronary arterial segment in a selected frame of a 35 mm cinefilm, an optically magnified portion of the image encompassing that segment is converted into video format by means of a cine-video converter. The region of interest is defined and the contours of the vessel are detected automatically on the basis of the weighted sum of first and second derivative functions applied

Table 1. Clinical characteristics of the 206 stable and the 133 unstable angina pectoris patients with successful PTCA entered into the study.

Characteristics	Stable AP no (%)	Unstable AP no (%)
No. of patients	206	133
No. of lesions	239	155
Mean no. of lesions dilated per patient	1.16	1.17
Age (mean ± s.d.)	56 ± 9	58 ± 9*
(range)	(31–75)	(31–75)
Male sex	171 (83)	104 (73)
Time from PTCA	81 ± 38	79 ± 37
to FU (days)	(11–194)	(4–226)
Extent of CAD		
1	140 (68)	89 (67)
2	44 (21)	30 (23)
3	22 (11)	14 (11)
Previous coronary bypass grafting	22 (11)	8 (6)
Previous coronary angioplasty	24 (12)	11 (8)
Previous myocardial infarction	82 (40)	56 (42)
Vessel dilated		
LAD	138 (58)	97 (63)
LCX	43 (18)	26 (17)
RCA	48 (20)	28 (18)
Bypass	7 (3)	3 (2)
LMCA	3 (1)	1 (1)

Bypass = aortocoronary bypass graft; CAD = coronary artery disease; FU = follow-up angiography; LAD = left anterior descending coronary artery; LCX = left circumflex coronary artery; LMCA = left main coronary artery; RCA = right coronary artery; s.d. = standard deviation.
* p = 0.047 for difference with stable angina patients.



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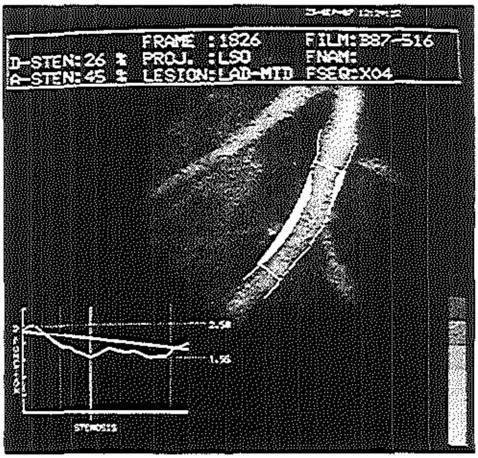

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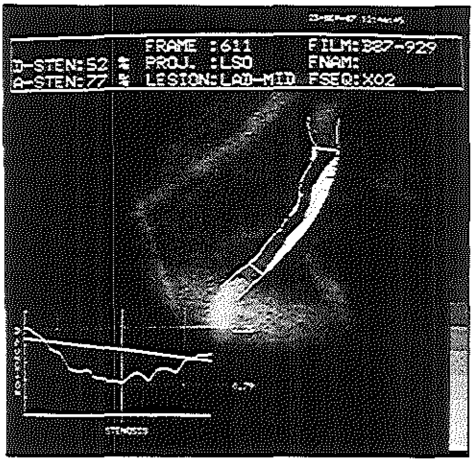

C.

Fig. 2. Series of single frame angiograms, with superimposition of the automatically detected contours, of the same left anterior descending artery lesion pre-dilatation (A), post-dilatation (B) and at follow-up (C). The interpolated percentage diameter stenosis (D-sten) and percentage area stenosis (A-sten) values are shown at the top left of each frame. The post-PTCA analysis shows a satisfactory result. The follow-up analysis shows that a significant restenosis has taken place.

to the digitized brightness information. Calibration of the diameter data of the vessels in absolute values (mm) is achieved by using the contrast catheter as a scaling device [25]. To this end, the contours of a user-defined portion of the optimally magnified catheter (magnification factor $2\sqrt{2}$) are detected automatically and corrected for pincushion distortion caused by the image intensifiers. From the vessel contours the 'interpolated' reference diameter Dr and the minimal lumen diameter Do – both in absolute mm – are then determined at the site of the shortest distance between the two contours. The 'interpolated' percentage diameter stenosis is then calculated according to the well known formula:

$$\text{interpolated } \% - \text{D stenosis} = \left(1 - \frac{\text{Do}}{\text{Dr}}\right) * 100\%.$$

A representative analysis pre- and post-PTCA and at follow-up, with the detected contours and the diameter function curves superimposed on the original video images, is shown in Fig. 2.

In order to standardize the quantitation technique and to minimize potential errors, 'interpolated' reference diameter and percentage diameter stenosis measurements were used. This method has the advantage of eliminating the arbitrary choice of a reference diameter, which will vary between individual observers. The principle behind this technique is the computer estimation of the original diameter values of the segment within the obstructed region (reference diameter function), assuming that no coronary disease is present. The interpolated reference diameter is then taken as the value of the reference diameter function at the site of maximal narrowing [26–28].

The automatic contour detection technique applied in this study has previously been validated using plexiglass phantoms filled with contrast medium [28]. The overall accuracy (average difference) and the precision (pooled standard deviation of the differences) of minimal lumen diameter measurements are minus 30 and plus 90 microns, respectively.

In order to standardize the method of acquisition and analysis of the pre- and post-dilatation and the follow-up angiograms, the following five measures were undertaken [24]. Firstly, the X-ray system was repositioned to correspond as much as possible to the projections and settings used during the previous angiographies. For this purpose, the angular settings of the X-ray gantry and the various height levels were readjusted according to the values previously documented with an on-line registration system.

Secondly, all cineframes to be analyzed were selected at end-diastole, to minimize any possible blurring effect as a result of vessel motion during systole.

Thirdly, the user-determined beginning and endpoints of the major coronary segments between side branches were identified according to the definitions of the American Heart Association [29].

Fourthly, multiple matched views, orthogonal if possible, were analyzed for each dilated lesion and then the results were averaged.

Finally, Polaroid pictures were taken of the video image with the detected contours superimposed, to ensure that the analyses were performed on the same coronary segment in the serial angiograms.

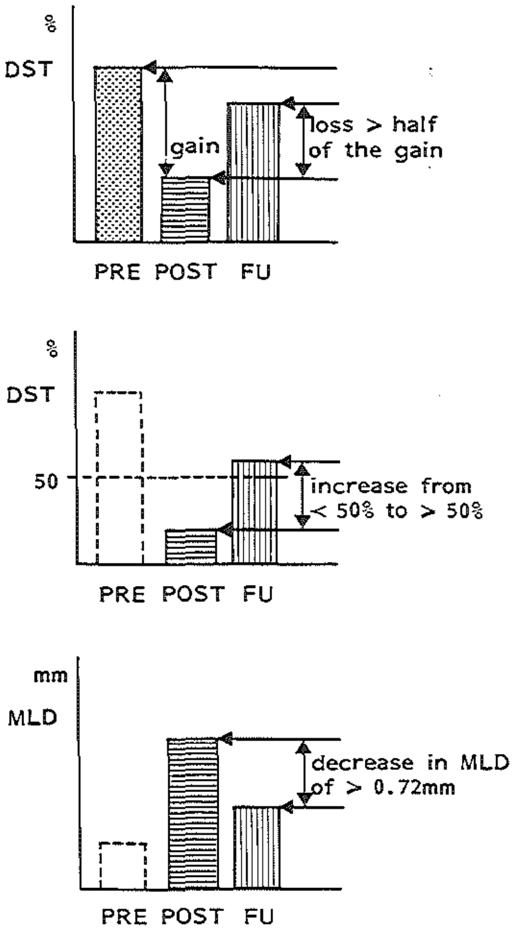

Fig. 3. Angiographic restenosis criteria employed (as explained in Methods section). DST = diameter stenosis (%); pre = pre-PTCA; post = post-PTCA; FU = follow-up; MLD = minimal lumen diameter (mm).

Definitions of restenosis

In order to allow comparison of our results with those of other published studies and to evaluate the various criteria, three previously proposed angiographic definitions of restenosis (Fig. 3) were applied: 1) a loss of at least 50% of the gain in luminal diameter achieved at PTCA (NHLBI IV) [9]; 2) an increase of the diameter stenosis from less than 50 percent post-PTCA to greater than or equal to 50% at follow-up, and finally; 3) a decrease in minimal lumen diameter of greater than or equal to 0.72 mm with respect to the post-PTCA situation. This last definition is based upon twice the variability (one standard deviation of the differences of duplicate measurements of the same lesion) of minimal lumen diameter measurements in mm (2 × 0.36 mm), when coronary angiography was repeated over a time interval of 90 days [23].

Statistical analysis

To test for differences between the stable and unstable angina patients with respect to their baseline clinical characteristics (listed in Table 1), the unpaired t-test was performed for the continuous variables, and the chi-square test for discrete variables. Univariate analysis of variance was also performed on the quantitative angiographic data obtained (Tables 2 and 3) (BMDP statistical software, University of California press, Berkeley, California, 1985).

Results are presented as mean ± one standard deviation, unless stated otherwise. All statistical tests were two-tailed. A probability (p) value below 0.05 was regarded as indicating statistical significance.

Results

The clinical characteristics of the 339 patients (206 with stable angina, and 133 with unstable angina) with a successful PTCA who completed angiographic follow-up are detailed in Table 1.

Comparison between the stable and unstable patient groups revealed a slightly higher overall mean age for unstable patients (56 ± 9 versus 58 ± 9, p = 0.047). Apart from this difference the stable

Table 2. Comparative results of quantitative coronary angiography, expressed as mean ± one standard deviation, for the 206 stable and 133 unstable angina pectoris patients. Variance analysis between the two groups was performed, for which the p-values are given.

Variable	Time	Stable AP (n = 239 lesions)	Unstable AP (n = 155 lesions)	p-value
reference	pre-PTCA	2.80 ± 0.64	2.85 ± 0.65	0.49
diameter	post-PTCA	2.93 ± 0.54	2.92 ± 0.56	0.96
(mm)	follow-up	2.81 ± 0.56	2.82 ± 0.58	0.91
minimal lumen	pre-PTCA	1.17 ± 0.41	1.14 ± 0.39	0.52
diameter	post-PTCA	2.09 ± 0.42	2.05 ± 0.44	0.32
(mm)	follow-up	1.86 ± 0.61	1.89 ± 0.59	0.66
diameter	pre-PTCA	58.3 ± 13.4	59.3 ± 12.3	0.44
stenosis	post-PTCA	28.0 ± 11.3	28.9 ± 11.3	0.44
(%)	follow-up	33.4 ± 18.1	32.4 ± 17.4	0.58

AP = angina pectoris.

Table 3. Absolute change in stenosis geometry as a result of PTCA (pre to post), and from post-PTCA to time of follow-up angiography (post to fu), comparing the stable and unstable angina patients. Differences are not statistically significant.

Variable	Time	Stable AP	Unstable AP
Reference	pre to post	+ 0.13	+ 0.08
diameter mm	post to fu	− 0.12	− 0.11
Minimal lumen	pre to post	+ 0.92	+ 0.91
diameter mm	post to fu	− 0.23	− 0.16
Diameter	pre to post	− 30.3	− 30.5
stenosis %	post to fu	+ 5.4	+ 3.5

AP = angina pectoris.

and unstable patients were comparable with regards to mean number of lesions dilated per patient, time to follow-up angiography (81 ± 38 days versus 79 ± 37 days, respectively), extent of coronary artery disease, prior coronary bypass grafting, prior coronary angioplasty, prior myocardial infarction and vessel dilated (Table 1).

The results of quantitative coronary angiography in the 206 patients (239 lesions) with stable angina and the 133 patients (155 lesions) with unstable angina who completed angiographic follow-up are detailed in Table 2. When collating the quantitative data for all the stable and unstable patients combined, the reference diameter and the severity of the dilated stenoses pre- and post-PTCA, and at follow-up, were not significantly different.

The changes in reference diameter, minimal lumen diameter, and the percentage diameter stenosis as a result of PTCA, and from post-PTCA to follow-up, are listed in Table 3. Following PTCA there was, as expected, a significant improvement in minimal lumen diameter and diameter stenosis for both groups of patients ($p < 0.0001$). Contrasting the changes in stenosis geometry in the stable and unstable patients occurring between post-PTCA and time of control angiography, reveals that both showed a comparable deterioration in lesion severity, as reflected by an increase in percentage diameter stenosis, and a decrease in minimal lumen diameter; similarly, a comparable decrease in reference diameter was observed (Fig. 4).

Table 4 delineates the incidence of restenosis in stable versus unstable angina patients according to three previously proposed angiographic criteria.

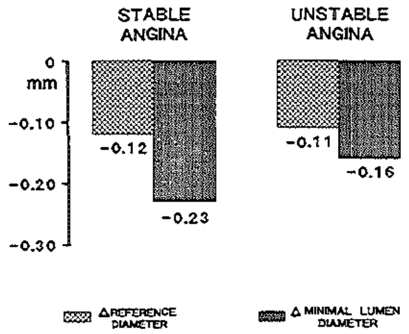

Fig. 4. Changes in reference diameter and minimal lumen diameter (mm) occurring between post-PTCA and time of follow-up angiography. Differences are not statistically significant.

Also listed in Table 4 are the percentages of patients experiencing recurrent ischemic symptoms at the time of repeat angiography (Fig. 5). The so-called 0.72 mm restenosis criterion identifies lesions with a decrease in minimal lumen diameter of at least 0.72 mm, corresponding to a change greater than or equal to two times the long-term variability of this type of measurement.

Looking at the patient restenosis rates (Table 4 and Fig. 4) several observations can be made. First of all, the percent restenosis varies considerably depending upon the angiographic definition chosen. Secondly, the incidence of restenosis in stable and unstable angina patients proved to be similar, irrespective of which restenosis definition is employed (Table 4).

Table 4. Patient restenosis rates (percent) in stable versus unstable angina patients according to three different angiographic definitions of restenosis. The percentage of patients with recurrent angina at the time of repeat angiography is shown in the bottom row. Differences are not statistically significant.

Restenosis definition	Stable AP (n = 206)		Unstable AP (n = 133)	
	n	%	n	%
NHLBI IV	55	26.7	33	24.8
≧50% DS	31	15.0	16	12.0
≧0.72 mm	37	18.0	24	18.1
Recurrent angina	46	22.3	33	24.8

AP = angina pectoris; DS = diameter stenosis.

Discussion

Baseline clinical characteristics and quantitative angiographic data pre- and post-PTCA

Existent differences in pathophysiology of effort angina and angina at rest, as evidenced by recent angioscopic findings that each of these clinical coronary syndromes appears to have its own specific underlying endothelial pathology [20–21], leads to the hypothesis that the early and 'late' vessel wall response to dilatation injury may be dissimilar in mechanism and/or magnitude.

To gain insight into the early and late changes in vessel caliber and hence determine the true incidence of restenosis, 85% of patients with a successful PTCA underwent repeat quantitative coronary angiography, irrespective of presence or absence of recurrent ischemic symptoms. In addition, in order to standardize the method of acquisition and analysis of the serial angiograms, several measures were undertaken to decrease the variability of repeated arterial measurements [24].

Employing such a study-design and follow-up protocol it was found that successful PTCA - defined as a less than 50% luminal narrowing in combination with clinical relief of ischemic symptoms – was associated with an increase in both the reference and minimal lumen diameter (Table 2). This suggests that the changes in reference diameter and minimal lumen diameter as a result of PTCA, both contributed to the luminal enlargement. The changes in lesion dimensions from post-PTCA to follow-up were also comparable for both groups of patients (Table 3 and Fig. 4). However, whereas the reference diameter at follow-up had decreased to that found pre-PTCA (Table 2), the minimal lumen diameter at follow-up was smaller than immediately post-PTCA, but still much improved relative to the mean values before angioplasty. In summary, the patients with stable angina were comparable to those with unstable angina with regard to the extent, location and quantitatively determined severity of coronary artery disease (Tables 1 and 2) before and after PTCA and at follow-up. Therefore, as suggested previously [30], this finding supports the notion that factors other than anatomic severity are important in the precipitation of these syndromes [30–32].

In fact, from histologic studies [33–35], postmortem coronary angiography [36], recent recognition of specific angiographic morphology [37, 38], and angioscopy in living man [20, 21], it has become evident that endothelial ulceration and thrombosis are important processes in unstable angina. Thus, unstable angina is related to endothelial ulceration, platelet aggregation and thrombus formation with or without spasm leading to partial occlusion or interrupted total occlusion [20, 21, 33, 35, 37–39]. In contradistinction, angioscopy of coronary lesions of patients with stable coronary artery disease has shown a noninterrupted smooth atheroma surface, without hemorrhage or ulceration [20, 21].

Incidence of restenosis

The major finding of this study is that although there was a wide variation in the incidence of restenosis according to the angiographic criterion applied (Table 4), the cumulative incidence of restenosis in patients with stable coronary artery disease was similar to that of patients with unstable rest angina, irrespective of the type of definition (Fig. 5). Likewise, the percentage of patients with recurrent angina at the time of reinvestigation, was also similar.

Although these data are consistent with those from some previous studies [4, 5, 7, 9, 12, 18, 19], they are not in agreement with two other reports which have indicated an increased risk of restenosis in patients suffering from unstable angina prior to the time of coronary angioplasty [10, 17]. However, comparison between the few published reports on angioplasty for stable and unstable angina must be done with caution for a number of reasons. Differences between studies in indication and timing of repeat angiography, follow-up rate, method of assessment of coronary angiograms, and most importantly, the bias introduced by studying a selected population, all potentially distort the data regarding incidence and time to restenosis.

Moreover, visual interpretation of serial coronary angiograms are marked by high intra- and

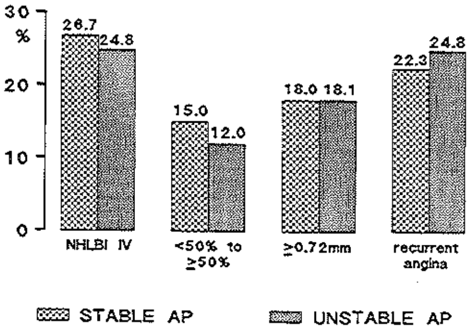

Fig. 5. Restenosis rates (%) post-PTCA in patients with stable versus unstable angina pectoris prior to the time of angioplasty, according to three previously proposed angiographic criteria. Also listed are the percentages of patients with recurrent ischemic symptoms at the time of recatheterization. Observed differences are not statistically significant. A) Loss of at least 50 percent of the gain in luminal diameter achieved at the time of PTCA (NHLBI IV); B) An increase of the diameter stenosis from less than 50 percent post-PTCA to greater than or equal to 50 percent at follow-up; C) A decrease in minimal lumen diameter of greater than or equal to 0.72 mm, corresponding to a change ≧ twice the variability of minimal lumen diameter measurements in mm.
AP = angina pectoris.

interobserver variabilities, and a poor reproducibility [40]. Hence, visual comparison of arteriograms from different patients, or at different times in the same patient, are of limited value for assessing severity or changes in severity of coronary artery stenoses.

Finally, the preferential reinvestigation of symptomatic patients in some studies on the one hand can be expected to result in an artificial increase of the angiographic restenosis rate, and on the other hand to a decrease of this rate by not identifying the 30% of asymptomatic patients with angiographic recurrence [41].

Data distortion caused by a variable combination of these methodological factors may increase the likelihood of type I (having statistically significant results when there is no relationship between variables studied) and Type II (to miss finding statistical significance for a trend that does exist in the data) errors [42], and can result in discrepancies amongst studies in patient, lesion and procedure related factors considered to be associated with an increased risk of restenosis.

To date two studies have noted a significantly higher restenosis rate following successful PTCA in patients with prior unstable angina [10, 17]. Dangoisse et al. [17] reported the follow-up of 103 consecutive patients recatheterized within six months. They observed a 50 percent restenosis rate (> 30% increase in diameter stenosis) in patients with unstable angina, relative to a rate of 25% in those without; a significant difference at $p < 0.025$. However, details regarding patient population, study design, follow-up strategy, definitions used and method of assessment of the angiograms are lacking in this abstract. In another report [10], concerning the multivariate analysis of clinical and angiographic data of 787 patients from an initial cohort of 1758 patients (45%) with single-vessel disease in whom PTCA had been successful, restenosis was observed in 26% of those with stable and 34% of those with unstable coronary disease ($p = 0.0534$). These results were obtained at a mean time to follow-up angiography of 7 ± 5 months, pertaining to a time frame ranging from less than two months to 42 months. However, if we just look at the patients recatheterized within four months for the sake of comparison, the observed restenosis rate was 53% and the prevalence of recurrent ischemic symptoms was 84% [10]. In contrast, in this study only 22.3% of all the stable and 24.8% of the unstable patients reported ischemic symptoms at the time of angiography, and the overall incidence of recurrent stenosis was less than half of that reported by Leimgruber et al. [10]. Thus, it appears that this major difference in observed restenosis rate within the first four months might be directly related to the substantial dissimilarity in the proportion of patients with recurrent angina. Furthermore, the patient population of our study, in which 32% had multivessel disease, may not be directly comparable to one consisting solely of patients with single-vessel coronary artery disease [10], as suggested by the apparently poorer prognosis of those with multivessel disease at long-term follow-up after coronary angioplasty [43].

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Chapter 6

Quantitative angiographic assessment of elastic recoil after percutaneous transluminal coronary angioplasty. American Journal of Cardiology 1990; 66:1039-1044.

Quantitative Angiographic Assessment of Elastic Recoil After Percutaneous Transluminal Coronary Angioplasty

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Little is known about the elastic behavior of the coronary vessel wall directly after percutaneous transluminal coronary angioplasty (PTCA). Minimal luminal cross-sectional areas of 151 successfully dilated lesions were studied in 136 patients during balloon inflation and directly after withdrawal of the balloon. To circumvent geometric assumptions about the shape of the stenosis after PTCA, a videodensitometric analysis technique was used for the assessment of vascular cross-sectional areas. Elastic recoil was defined as the difference between balloon cross-sectional area of the largest balloon used at the highest pressure and minimal luminal cross-sectional area after PTCA. Mean balloon cross-sectional area was 5.2 ± 1.6 mm² with a mean minimal cross-sectional area of 2.8 ± 1.4 mm² immediately after inflation. Oversizing of the balloon (balloon artery ratio >1) led to more recoil (0.8 ± 0.3 vs 0.6 ± 0.3 mm, p <0.001), suggestive of an elastic phenomenon. A difference in recoil of the 3 main coronary branches was observed: left anterior descending artery 2.7 ± 1.3 mm², circumflex artery 2.3 ± 1.2 mm² and right coronary artery 1.9 ± 1.5 mm² (p <0.025). The difference was still statistically significant if adjusted for reference area. Thus, nearly 50% of the theoretically achievable cross-sectional area (i.e., balloon cross-sectional area) is lost shortly after balloon deflation.

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Percutaneous transluminal coronary angioplasty (PTCA) is increasingly being used as an alternative to coronary artery bypass grafting in patients with acute and chronically obstructed vessels.[1,2] Despite many publications on the mechanism of this treatment modality, little is known about the elastic behavior of the vessel wall during and immediately after angioplasty. Castaneda-Zuniga et al[3] proposed an arterial paralysis model in which overstretching of the vessel wall beyond its limits of elasticity was associated with histopathologic features of smooth muscle cell lysis. According to Sanborn et al,[4] part of the angioplasty mechanism consists of stretching the vessel wall resulting in a fusiform dilatation or localized aneurysm formation. It is, however, a common clinical observation that in some lesions even the application of an oversized balloon leads to a poor angiographic result without a visible intimal tear or dissection. This phenomenon may be attributed to elastic recoil of the vessel wall after balloon angioplasty. Densitometrically assessed cross-sectional areas are independent of geometric assumptions on the shape of the stenosis and should theoretically be more reliable than geometrically derived cross-sectional areas, especially after the disruptive action of balloon angioplasty which is known to cause asymmetric enlargement of the lumen.[5] This study was undertaken to determine the contribution of elastic recoil to the immediate result of an angioplasty procedure, with the use of densitometric and contour detection analysis techniques.

METHODS

Contour detection: The quantitative analysis of the stenotic coronary segments was performed with the computer-assisted Cardiovascular Angiography Analysis System (CAAS), which has been described in detail elsewhere.[6,7] To analyze a coronary arterial segment a 35-mm cine frame was selected. Electronically, a region of interest (512 × 512 pixels) encompassing the arterial segment to be analyzed was digitized with a high-fidelity videocamera. Contours of the arterial segments were detected automatically on the basis of the weighted sum of first and second derivative functions applied to the digitized brightness profile. From these contours the vessel diameter functions are determined by computing the shortest distance between the left and right contour positions (the upper curve in Figure 1). Conversion of the diameter measurements of the vessels to absolute values was achieved by using the contrast catheter as a scaling device. To this end the contours of a user-defined portion of the optimally magnified catheter (optimal magnification factor $2\sqrt{2}$) are detected automatically and corrected for pincushion distortion caused by the image intensifiers. In arteries with a focal obstructive lesion and a clearly normal proximal or distal arterial segment, the choice of the reference region is straightforward and simple. However, in cases where the proximal or distal part of the arterial segment shows combinations of stenotic and ectatic areas, the choice may become difficult. To circumvent these problems, we implemented a method that is independent on a user defined reference region. This technique is denoted "interpolated reference diameter measurement."[8] The principle of this technique is the computer estimation of the original vessel diameter at the site of obstruction (Figure 1). The white areas in the figure are measures for the "atherosclerotic plaque" and are defined by the actual luminal contours and the reconstructed reference contours. The length of the obstruction site is determined from the diameter function on the basis of curvature analysis and expressed in millimeters. Using the reconstructed borders of the vessel wall, the computer can calculate a symmetry coefficient for the stenosis: a symmetrical lesion having a value of 1 and a severe eccentric lesion having a value of 0. Symmetry is defined as the coefficient of the left hand distance between the reconstructed and actual vessel contours and the right hand distance between reconstructed and actual contours at the site of obstruction. In this equation the largest distance between actual and reconstructed contours becomes the denominator. The curvature value at the obstruction site, as a measure for coronary bending, is computed as the average value of all the individual curvature values along the centerline of the coronary segment, with the curvature defined as the first derivative of the tangent as it moves along the centerline, which for a circle is equal to the reciprocal of the radius.

Densitometric procedure: Constitution of the relation between path length of the x-rays through the artery and the brightness value requires a detailed analysis of the complete x-ray/cine/video chain, including the film development process.[9] For the first part of the chain from the x-ray source to the output of the image intensifier, Lambert Beer's law is assumed to be valid for the x-ray absorption and certain models for the x-ray source and the image intensifier are applied. Sensitometric transfer functions were assessed from 21 calibrated density frames, which are processed photographically simultaneously with the coronary cine film. These 21 density frames are then exposed homogenously with a specially developed sensitometer having the same color temperature as the output screen of the image intensifier.

The contours of a selected arterial segment are detected as previously described. On each scanline perpen-

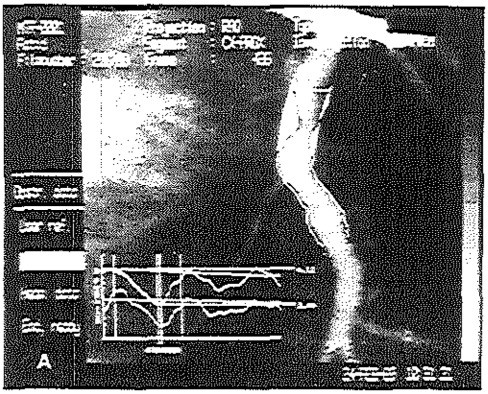
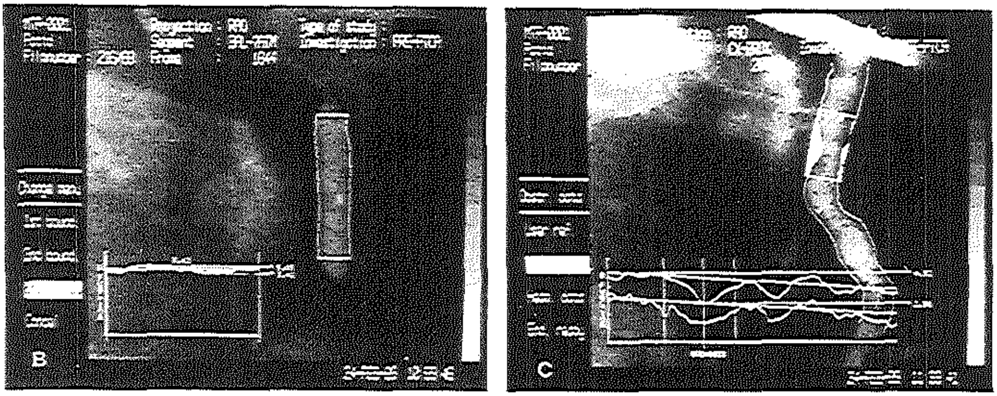


FIGURE 1. Single frame angiograms of a proximal, circumflex artery (CX-PROX). Contours and densitometric analysis of the severity of the obstruction (Obstr.). The white areas are a measure for the "atherosclerotic" plaque and are defined by the difference between the actual luminal contours and the "interpolated" reference contours. Superimposed on the videoimage are the diameter function curves *(upper curve)* and the densitometric area function curve *(lower curve)* together with the "interpolated reference" curves. *A*, predilatation (before percutaneous transluminal coronary angioplasty [PRE-PTCA]) minimal luminal cross-sectional area is 3.5 mm²; *B*, 3.5 mm balloon, filmed at highest inflation pressure; *C*, after dilatation (POST-PTCA), minimal luminal cross-sectional area is 6.0 mm².



dicular to the centerline a profile of brightness values is measured. This profile is transformed into an absorption profile by means of the computed transfer functions. The background contribution is estimated by an interpolative method and subtraction of this background yields the net cross-sectional absorption profile. Integration of this function results in a measure for the cross-sectional area at the particular scanline. By repeating this procedure for each scanline, the cross-sectional area function is obtained. The severity of the obstruction can thus be expressed in mm^2, by comparing the minimal area value at the obstruction with the reference value obtained after an interpolative approach, which is similar to that described earlier for diameter measurements.

Validation of this densitometric analysis technique was done by analyzing cine films of perspex models filled with a contrast agent and filmed at 4 kV levels. Accuracy was found to be 2.8% and precision 1.8%.[10] The densitometrically determined area stenosis, as found by other investigators, correlates well with percentage reduction of cross-sectional area measured histologically in postmortem hearts.[11,12]

Assessment of elastic recoil: One hundred fifty-one successfully dilated segments of 136 patients were analyzed. A successful PTCA was defined as a visually assessed diameter stenosis after PTCA of <50%. Single identical views before and after PTCA, and during complete expansion of the largest balloon at highest inflation pressure were chosen for densitometric analysis. Both polyvinyl chloride and polyethylene balloons were used for dilatation depending on the choice of the operator. Inflation pressure and duration of inflation were left to the discretion of the operator. Mean balloon cross-sectional areas were calculated from diameter values, assuming a circular cross section at maximal inflation pressure. The same x-ray setting in terms of kilovoltage and milliamperes was used during the 3 cine recordings. To have the segment to be analyzed as perpendicular to the incoming x-rays as possible, a view was chosen with the coronary artery appearing least foreshortened. The same amount of nitrates, either nitroglycerin, 0.1 to 0.3 mg, or isosorbide dinitrate, 1 to 3 mg, was given intracoronarily before the pre- and postangioplasty cine recordings. This was done to dilate the vessel maximally and thus to control the varying influence of vasomotor tone on luminal dimensions. Elastic recoil was then calculated as the difference between the minimal luminal cross-sectional area after PTCA and the mean balloon cross-sectional area (mm^2). A representative analysis, with the detected contours, the diameter function curve and the densitometric area function curve superimposed on the original video image, is shown in Figure 1 for a circumflex lesion.

RESULTS

At quantitative analysis 140 (92%) of the dilatations were successful using a <50% diameter stenosis after PTCA as the success criterion. If in addition a >20% improvement in diameter stenosis was required for a successful dilatation, 110 (72%) lesions were successfully dilated using quantitative measurements. The densitometric analysis of the 151 segments is listed in Table I. Mean age of the 136 patients was 56.8 ± 8 years. There was no significant change in "interpolated" reference area after PTCA: Before PTCA 6.0 ± 2.5 mm^2, after PTCA 6.2 ± 2.5 mm^2 (difference not significant). The minimal luminal cross-sectional area increased from 1.1 ± 0.9 to 2.8 ± 1.4 mm^2 ($p < 0.001$). The mean balloon cross-sectional area was 5.2 ± 1.6 mm^2. Elastic recoil was 2.4 ± 1.4 mm^2. Thus, nearly 50% of the theoretically achievable cross section (i.e., balloon cross-sectional area) was lost immediately after the last balloon deflation. A subset of 16 patients (18 lesions) were angiographically reexamined 24 hours after PTCA as part of a study looking at changes in coronary flow reserve in the first 24 hours after balloon dilatation. Minimal luminal cross-sectional area directly after PTCA in this group was 2.0 ± 0.8 mm^2 and 1.9 ± 0.5 at 24 hours (difference not significant).

Balloon oversizing and elastic recoil: For each stenotic lesion the balloon-artery ratio was calculated. A ratio >1 indicates oversizing of the balloon. The mean balloon-artery ratio in this study was 0.95 ± 0.18. This indicates a conservative balloon handling, considered to give optimal dilatation of the stenotic lesion with minimal residual stenosis and the smallest incidence of coro-

TABLE I Recoil in 151 Coronary Arterial Narrowings

	Before PTCA	After PTCA	p Value
Reference area (mm^2)	6.0 ± 2.5	6.2 ± 2.5	NS
MLCA (mm^2)	1.1 ± 0.9	2.8 ± 1.4	p <0.001
Balloon-CSA (mm^2)		5.2 ± 1.6	
Recoil (mm^2)		2.4 ± 1.4	p <0.001

CSA = cross-sectional area; MLCA = minimal luminal cross-sectional area; NS = difference not significant; PTCA = percutaneous transluminal coronary angioplasty; Recoil = balloon CSA − MLCA after PTCA.

TABLE II Effect of Balloon Oversizing on the Amount of Elastic Recoil

Balloon-Artery Ratio	≤1	>1	p Value
No. of lesions	87	64	
Reference-diameter (mm)	3.0 ± 0.5	2.3 ± 0.4	p <0.001
Balloon-diameter (mm)	2.5 ± 0.4	2.6 ± 0.4	NS
Recoil (mm)	0.6 ± 0.30	0.8 ± 0.3	p <0.001

Balloon-artery ratio = balloon diameter/reference diameter; NS = difference not significant.

TABLE III Clinical Characteristics and Recoil in 136 Patients

	Yes	No	p Value
Men (recoil)	112 (0.45 ± 0.31)	24 (0.42 ± 0.23)	NS
Smoking (recoil)	106 (0.46 ± 0.29)	30 (0.50 ± 0.23)	NS
Hypertension (recoil)	61 (0.40 ± 0.28)	75 (0.46 ± 0.29)	NS
Diabetes type 1 (recoil)	1	135	
Unstable angina (recoil)	23 (0.39 ± 0.27)	113 (0.44 ± 0.26)	NS

Recoil corrected for reference area.
NS = difference not significant.

TABLE IV Angiographic and Procedural Characteristics and Recoil of 151 Lesions

	Yes	No	p Value	Mean
Lesion length >5.2 mm and <7 mm (recoil)	50 (0.48 ± 0.25)	101 (0.43 ± 0.33)	NS	6.4 ± 2.4 mm
Calcified lesion (recoil)	22 (0.43 ± 0.29)	129 (0.45 ± 0.45)	NS	
Symmetry <0.37 (recoil)	51 (0.48 ± 0.33)	100 (0.41 ± 0.30)	p = 0.07	0.5 ± 0.3
Plaque area <4.5 mm² (recoil)	50 (0.53 ± 0.33)	101 (0.41 ± 0.27)	p <0.01	6.8 ± 3.9 mm²
Curvature <12.5 units (recoil)	51 (0.53 ± 0.34)	100 (0.43 ± 0.31)	p <0.01	17.7 ± 10.4
Max. infl. pres. <8 atm (recoil)	49 (0.46 ± 0.24)	102 (0.46 ± 0.35)	NS	9.6 ± 2.5 atm
Inflation duration <220 seconds (recoil)	50 (0.47 ± 0.30)	101 (0.44 ± 0.29)	NS	309 ± 170 seconds

Recoil corrected for reference area. See text for description of cutoff points.
Max. infl. pres. = maximal inflation pressure of the balloon; NS = difference not significant.

TABLE V Recoil in the Three Main Coronary Arteries

	LAD (n = 77)	LC (n = 34)	Right (n = 40)	ANOVA
Balloon CSA (mm²)	5.2 ± 1.7	5.5 ± 1.5	4.9 ± 1.4	NS
MLCA after PTCA (mm²)	2.5 ± 1.3	3.1 ± 1.2	3.0 ± 1.7	NS
Recoil (mm²)	2.7 ± 1.3	2.3 ± 1.2	1.9 ± 1.5	p <0.025
Recoil/reference area	0.5 ± 0.3	0.4 ± 0.2	0.3 ± 0.3	p <0.05

ANOVA = analysis of variance; CSA = cross-sectional area; LAD = left anterior descending artery; LC = left circumflex artery; MLCA = minimal luminal cross-sectional area; NS = difference not significant.

nary dissection.[13,14] Lesions with a ratio >1 (oversizing) were compared with lesions with a ratio ≤1. The comparative data are listed in Table II. No difference was found in balloon diameter between the groups. As expected, reference diameter was higher in the group with a ratio ≤1. Elastic recoil was more pronounced in the second group (0.84 ± 0.29 vs 0.64 ± 0.30 mm, p <0.001). Thus, oversizing of the balloon leads to more elastic recoil. These results agree with elastic phenomena: more stretch leads to more recoil (within limits of elasticity).

Clinical characteristics and recoil: Clinical characteristics and risk factors of the 136 patients are listed in Table III. No differences in elastic recoil were observed for gender, the presence or absence of risk factors and the presence or absence of unstable angina.

Quantitative angiographic lesion characteristics and recoil: Quantitative data on lesion morphology before angioplasty are listed in Table IV. To avoid arbitrary subdivision of data, cutoff criteria for lesion length, symmetry, plaque area and curvature value were derived by dividing the data in 3 groups so that each group contained about one-third of the population. The group with the highest amount of recoil was then compared with the 2 other groups. Lesions with a small plaque area and lesions with a shallow curvature showed significantly more recoil (Table IV).

Procedural related variables and recoil: Table IV lists the total inflation duration and maximal balloon inflation pressure in relation to elastic recoil. No differences in elastic recoil were observed.

Recoil in the three main coronary arteries: The amount of recoil was calculated in the left anterior descending artery (n = 77), the circumflex artery (n = 34) and in the right coronary artery (n = 40). Data are listed in Table V. The amount of recoil was significantly larger in the left anterior descending artery compared with the circumflex and right coronary arteries, 2.7, 2.3

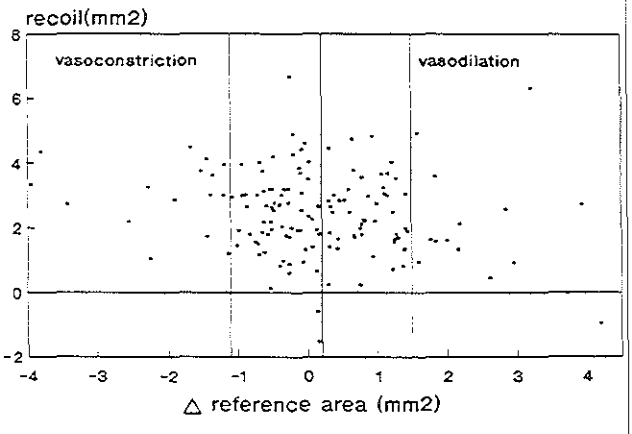


FIGURE 2. In this scatterplot the difference in interpolated reference area before and after percutaneous transluminal coronary angioplasty is plotted against the amount of recoil for each segment. The mean difference in reference area was 0.2 ± 1.3 mm² *(vertical lines in graph)*. The values are randomly distributed around the mean value of 0.2 mm², suggesting that spasm was effectively eliminated.

and 1.9 mm^2, respectively ($p < 0.025$). When normalized for reference area the difference was still statistically significant.

DISCUSSION

Vasoconstriction at the dilatation site is a common cause of early luminal narrowing. As has been shown elegantly by Fischell et al[15] this can be rapidly reversed by an intracoronary injection of nitrates. Because we gave intracoronary nitrates before the pre- and post-PTCA cine runs, it seems unlikely that the amount of recoil observed was caused by vasomotion. In Figure 2 the difference between the reference area before and after PTCA is plotted against the amount of recoil for each site. The values are randomly distributed around the mean value of 0.2 mm^2, suggesting the absence of vasoconstriction at the post-PTCA film.

Platelet deposition, and the formation of a nonocclusive mural thrombus despite full heparinization, is not an uncommon finding in postmortem hearts obtained from patients who die in the first hours after angioplasty.[16] This has also been confirmed by angioscopy 15 to 30 minutes after PTCA.[17] However, our post-PTCA angiograms were recorded within minutes of the last dilatation. Although we cannot rule out the possibility that mural thrombus formation is partly responsible for the observed phenomenon, we believe it cannot explain the 50% decrease in luminal area found. Subintimal hemorrhage is also a cause of severe early luminal narrowing or acute closure, a process which is usually impossible to reverse and nearly always results in a failed PTCA. In this study only successfully dilated lesions were analyzed.

The mean balloon cross-sectional area was derived over the total length of the balloon and compared with the minimal luminal cross-sectional area measured immediately after PTCA. In this study, recoil of the part of the dilated segment adjacent to this area was not specifically studied. We assumed a uniform expansion of the balloon at maximal inflation pressure. Theoretically, recoil should be assessed using the minimal luminal balloon cross-sectional area.

The 18 lesions restudied 24 hours after PTCA showed no difference in minimal luminal cross-sectional area with respect to the cross-sectional area directly after PTCA. This suggests that elastic recoil is an instantaneous phenomenon. This finding does not agree with the findings of Nobuyoshi et al,[18] who found a significant deterioration of minimal luminal diameter 1 day after PTCA. However, the small size of this subgroup may not be representative of the total population. A trend toward more recoil was observed in asymmetric lesions. In these lesions the balloon will preferrably stretch the nondiseased part of the vessel circumference with a subsequent larger elastic recoil.[19] The fact that a small plaque area and a low curvature value are attended with a significant higher amount of elastic recoil may be due to the fact that dissections have been found most often in areas containing thick atherosclerotic plaques and lesions with a high bending.[20,21] Gross disruption of the vessel wall may prevent the recoil phenomenon. Procedural variables had no influence on the amount of recoil. Longer inflations and higher inflation pressures are often used after an initially poor angioplasty result. Only a randomized trial can indicate to what extend procedural factors influence procedural outcome.

Jain et al[22] found, using an in vivo technique for obtaining balloon pressure-volume loops, a pattern consistent with stretching of the arterial wall in 56% of lesions. A pressure-volume loop consistent with stretching of the vessel was a far more common event than a cracking pattern (17%). Stretching within limits of elasticity implies its counterpart elastic recoil. More stretching should lead to more recoil. In our series, oversizing of the balloon (i.e., a balloon-artery ratio >1) was associated with more recoil, indicative of the elastic phenomenon. Dobrin described pressure radius curves of potassium cyanide–poisoned carotid arteries of mongrel dogs. At low pressures, the vessel exhibited large changes in radius with each step in pressure, whereas at high pressure it showed very slight changes in radius. The curve described an elastic hysteresis loop, with the ascending and descending limb close to each other at all pressures, suggesting no active muscle contraction involvement in the retraction process.[23]

The differences in elastic recoil observed in the 3 coronary arteries cannot be easily be explained. Differences in histologic structure or differences in plaque composition in the coronary arteries might be an explanation. To our knowledge these differences have not been reported.

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Chapter 7

Restenosis after coronary angioplasty: new standards for clinical studies. Beatt KJ, Serruys PW, Hugenholtz PG. Journal of the American College of Cardiology 1990; 15:491-498.

Restenosis After Coronary Angioplasty: New Standards for Clinical Studies

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With the high initial success rates for coronary angioplasty that are reported regularly, it has become increasingly difficult to demonstrate methods or techniques that are able to provide more beneficial early results than can be achieved by conventional angioplasty. On the other hand, the incidence of late restenosis has remained much the same over the 10 years that angioplasty has been part of clinical practice, and there is still no proved intervention that modifies the restenosis process. Therefore, the problem of restenosis has assumed increasing relevance in determining the clinical value of coronary angioplasty and, accordingly, studies that address the problem of restenosis need to become more exacting.

Although numerous articles have addressed the problem of restenosis in the clinical setting, many defining certain factors associated with restenosis and possible interventions to reduce the incidence of restenosis, there is surprisingly little consensus. Most of the discrepancies can be attributed to three factors: 1) the selection of patients, 2) the method of analysis, and 3) the definition of restenosis employed. This review shows how these three factors influence the outcome and conclusions of restenosis studies.

(J Am Coll Cardiol 1990;15:491–8)

Studies aimed at reducing the incidence of restenosis after coronary angioplasty have become an important field of investigation in interventional cardiology. In general, the early results of medical treatments and interventions are relatively simple to assess, but the long-term studies frequently prove more difficult to evaluate and, historically, often have been unreliable. Early or preliminary results often have been misleading and frequently contradict those of well controlled definitive studies. It appears that innovators and exponents of new treatments may allow their enthusiasm to compromise their objectivity. Therefore, it is important that any new technique or pharmacologic treatment is assessed objectively using a methodology with known reproducibility and in which the technical limitations are known and understood.

Over the past 2 to 3 years, there has been a rapid increase in new devices and techniques designed to augment or replace conventional balloon angioplasty. With the progressive improvement in the immediate success rate and complication rate of the conventional procedure, it has become more difficult to demonstrate the additional efficacy of new devices and interventions. Any improvement in the immediate results may be, as it was with coronary artery bypass surgery in the past, misleading and, therefore, the attention of investigators has rightly turned from the immediate results to the long-term outcome. Restenosis after coronary angioplasty, a recognized late complication in 25% to 35% of cases since the introduction of the procedure in 1977 (1), remains its main limitation.

Despite the established importance of this topic, there has been no consensus on how these studies should be performed, with widely differing methodologic approaches giving diverse and conflicting results. Although the long-term clinical outcome will remain important in any assessment, the most objective means of assessing restenosis following angioplasty is by carefully controlled coronary angiography at the time of the procedure and at a defined follow-up time. In the past the visual estimation of the angiographic films has been used, but a consensus is now beginning to emerge that

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Table 1. Studies Addressing the Incidence of Coronary Restenosis

First Author and Ref	Year	Patients: Total	Patients: % Follow-Up	Interval (mo) PTCA to Follow-Up	Restenosis Criterion	% Restenosis
Meyer (22)	1983	70	90	6	AS >85%	20
Thorton (5)	1984	248	72	6–9	NHLBI 4	31
Holmes (7)	1984	665	84	6.2	NHBLI 4	34
Kaltenbach (14)	1985	356	94	5.6	DS <20% of pre-PTCA	12
Levine (13)	1985	100	92	6	NHLBI 4	40
Corcos (8)	1985	92	100	8.2	>70% DS at follow-up	18.5
Leimgruber (6)	1986	1758	57	7	NHLBI 4	30
Bertrand (23)	1986	229	Not reported	7	NHLBI 4	32
Vandormael (3)	1987	129	62	7	≥20% reduction and ≥50% DS	33
Studies addressing the timing and incidence of restenosis						
Serruys (9)	1988	400	85	1	≥0.72 mm	0.9
				2	≥0.72 mm	12.4
				3	≥0.72 mm	22.6
				4	≥0.72 mm	25.5
Nobuyoshi (2)	1988	185	81	24 h	NHLBI 4	14.6
		229	100	1	NHLBI 4	12.7
		219	96	3	NHLBI 4	43.0
		149	65	6	NHLBI 4	49.4

AS = % area stenosis; DS = % diameter stenosis (mm); NHLBI 4 = criterion 4 of the National Heart, Lung, and Blood Institute (loss of ≥50% of gain); Ref = reference.

recognizes the limitations of this approach. The use of a quantitative angiographic measuring system for assessing both the immediate and the long-term results of therapeutic interventions such as angioplasty appears mandatory.

Methodologic Considerations

Currently there are many studies on coronary restenosis reported that are distinguished by their lack of consistency in their methodologic approach, their definition of restenosis and the reported factors influencing restenosis (Table 1). These studies are demanding in terms of time and financial resources and are also demanding on the patient because, at least for the time being, there is a need for repeat angiography even if the patient is asymptomatic. This is because of the reported incidence of silent restenosis, which may be as high as 33% if a sensitive enough index is used (2). Particularly with studies that look at the impact of a new intervention on restenosis, it is important that their design is capable of showing the effect of the intervention, if indeed one exists. Many of the studies published so far have failed to be sufficiently exacting to form a basis for their conclusions. In order to improve the situation, there are in principle three areas that need to be addressed:

1. Study population. If the results are intended to apply to the angioplasty population, then the study population must reflect this. This means a high angiographic follow-up rate with individual patient's time for restudy being predetermined at the time of angioplasty, and not influenced by the recurrence of symptoms or the anatomy of the lesion after angioplasty. This will avoid a selection bias of symptomatic patients or patients with borderline postangioplasty results.

It can be estimated that if a 30% reduction in the restenosis rate is to be realized at the 0.05 significance level, then in a double-blind randomized study 400 patients will be needed in each of the placebo and active treatment groups. For a 50% reduction in restenosis rate, 150 patients will be needed in each group.

2. A well validated system of analysis with known accuracy and variability should be employed. The use of a visual percent diameter stenosis measurement with its inherent variability precludes meaningful results, and edge tracing by hand or other techniques that can produce values not physiologically possible are also unacceptable.

3. The measured variables must be chosen so as to reflect the restenosis process and distinguish between the results of angioplasty and this process. The conventional assessment of percent diameter stenosis is not sufficiently discriminating to do this, because, when there is a concomitant decrease in the reference or normal diameter of the vessel, a smaller lumen may have a larger measured percent diameter stenosis.

Angiographic Definitions of Restenosis

Limitations of criteria to define restenosis. The definition of restenosis of choice has been the subject of much debate,

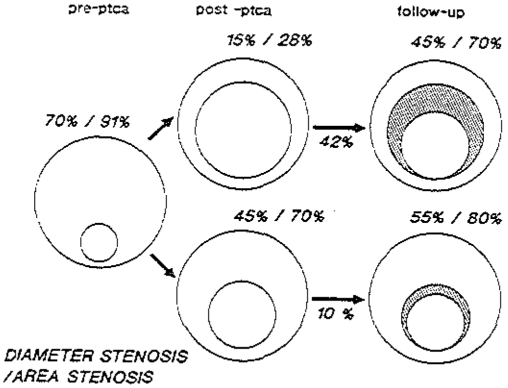


Figure 1. Shown in terms of cross-sectional area are two possible outcomes of an initially severe lesion after coronary angioplasty (PTCA). On the left, the lesion before angioplasty with a 70% diameter stenosis (area stenosis = 91%). **Middle**, a good result, represented by the upper profile leads to a 15% diameter stenosis (area stenosis = 28%). At follow-up (**right**), there has been a 42% change in the area of stenosis represented by the **shaded area** in the **top circle**. Although there is a considerable increase in the plaque cross-sectional area, the follow-up diameter stenosis is only 45% and, therefore, using the criterion of >50% diameter stenosis at follow-up, this is designated as not being a restenosis. In contrast, the lesion represented on the **bottom**, which is successfully dilated, but to a lesser degree (45% diameter stenosis after angioplasty), will be designated as restenosis if there is even a small deterioration in the plaque area (change in diameter stenosis of 10%) resulting in a follow-up diameter stenosis of 55% (percent diameter stenosis/percent area stenosis).

and there is currently no satisfactory definition that takes into account both the functional and the angiographic outcome of the patient after angioplasty. The confusion and controversy that surround the subject of restenosis are essentially due to four factors:

1) Many angiographic definitions try to combine the angiographic outcome with a clinical outcome. The known discrepancy between these two variables means that this objective will not be realized, particularly in multivessel disease (3).

2) A single "stenosis" measurement should not be confused with a measurement of "restenosis," which should represent the change in stenosis severity.

3) Criteria that are defined by a cut-off value at follow-up or that are biased by the improvement in lesion diameter obtained at angioplasty will preselect those lesions with a less satisfactory result postangioplasty. The definition of a ≥50% diameter stenosis at follow-up is used to illustrate this point in Figure 1.

4) Definitions based on percent diameter stenosis measurements may fail to identify lesions undergoing significant deterioration. These criteria are chosen to reflect the change in minimal luminal diameter in relation to the so-called normal diameter of the vessel in the immediate vicinity of the obstruction. It also assumes that this normal diameter (or the reference diameter) of the vessel, proximal or distal to the obstruction, does not change either as a result of angioplasty or during the immediate follow-up period when restenosis of the dilated lesion is a well recognized phenomenon. Quantitative angiographic studies have shown this premise to be false. This seriously questions the use of percent diameter stenosis as the only index of restenosis (2,4).

Figure 2 illustrates how the choice of reference diameter may influence the assessment of restenosis in what is a relatively simple segment to analyze. The choice of reference diameter, whether interpolated, proximal or distal, has little effect on the percent diameter stenosis in the examples before (Fig. 2A) or after (Fig. 2B) angioplasty because the reference diameter is similar in all cases. In contradistinction, the choice of reference diameter is highly relevant to the determination of the percent diameter stenosis at follow-up (Fig. 2C), largely because of the discrepancy between the reference diameter proximal to the stenosis and the one distal to it. The "moving baseline" created by the fact that the reference diameter may decrease means that lesions that should be regarded as restenosis may not be.

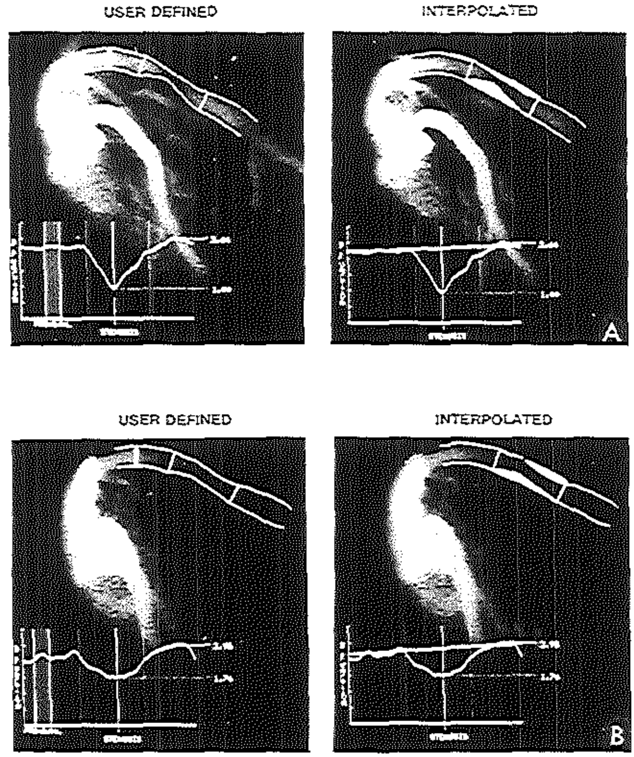
Criteria of restenosis in current use. What is the rationale for the restenosis criteria in current use? Most are entirely arbitrary, some are based on doubtful logic and some, although of some relevance for visual estimation of percent diameter stenosis, are unrealistic when applied to the more accurate values obtained from quantitative angiography.

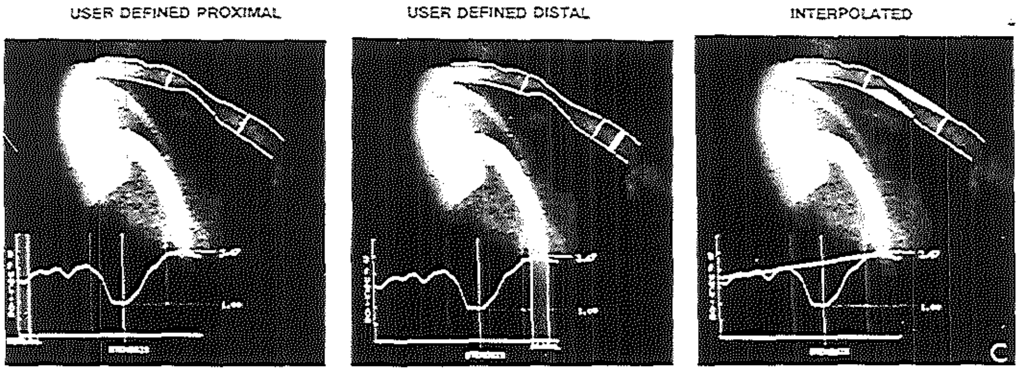
The definitions of restenosis used in major restenosis studies are:

1. Loss of at least 50% of the initial gain achieved at angioplasty (5).
2. A return to within 10% of the preangioplasty stenosis diameter (6).
3. An immediate postangioplasty stenosis diameter of <50% that increases to ≥50% at follow-up (6,7).
4. As for 3, but for a stenosis diameter ≥70% at follow-up (8).
5. Deterioration of 0.72 mm in minimal luminal diameter or greater from immediately postangioplasty to follow-up (9).
6. Deterioration of 0.5 mm in minimal luminal diameter or greater from immediately postangioplasty to follow-up (2).

Examining the commonly used definition of ≥50% stenosis diameter at follow-up. This is based historically on the physiologic concept of coronary flow reserve and is taken because it represents the approximate value in animals with normal coronary arteries at which a blunting of the hyperemic response occurs (10). Although this value may be of

Figure 2. Single frame angiograms of a proximal left anterior descending artery stenosis. A. predilation (PRE-PTCA), B. postdilation (POST-PTCA) and C at follow-up. Quantitative coronary analysis was performed using a coronary angiography analysis system. The arterial boundaries detected by the system are shown on the angiogram and below the diameter function curve derived from these contours. The example illustrates the importance of the choice of reference diameter, the fact that the dilated but nonstenotic coronary artery may be involved in the restenosis process, and the value of the interpolated reference diameter for calculating the appropriate diameter stenosis. A. Before angioplasty, the lesion is relatively easy to analyze. The segments proximal and distal to the stenosis are of similar caliber and the lesion is relatively discrete, so that its length can easily be defined on the diameter function curve. B. After angioplasty, there is a satisfactory result, the diameter stenosis decreasing from 59% to 36% (area stenosis from 83% to 59%). C. At follow-up, the result is very dependent on the method of analysis. The artery proximal to the stenosis has already been involved in the restenosis process; if this is chosen as a reference diameter (left), a 42% diameter stenosis is obtained (no "restenosis"). The distal portion is of a larger caliber than the proximal portion; if it is chosen as a reference diameter (middle), the result is a 62% diameter stenosis ("restenosis"). If the interpolated technique is used (right), the reference diameter is similar to the postangioplasty value, and a 58% diameter stenosis is obtained that accurately reflects what is happening between the post-angioplasty result and the follow-up. Even with this high quality angiogram of a well visualized segment with a discrete stenosis, there are problems in obtaining accurate and realistic results.





some relevance in determining a significant stenosis in human atherosclerotic vessels, it tells us nothing about the way the lesion has behaved since the angioplasty procedure. It is clear from Figure 1 that no criterion defining the restenosis as such can include the second example and not the first. Similar arguments concerning a bias in selection can be applied to the other commonly used definition of a loss >50% of the gain.

New restenosis criteria based on quantitative angiography. As a result of quantitative angiographic studies, a new concept for defining restenosis criteria based on the change in minimal luminal diameter has been introduced (9). The change in this value from postangioplasty to follow-up can be expected to give a good quantitative measurement of the degree of restenosis. The restenosis criterion or the cutoff point dividing the restenosis group from the nonrestenosis group is then derived by determining the variability of measurement (1 SD of the difference in means) of the same lesion taken from separate catheter sessions. Twice the variability (95% confidence intervals) defines with reasonable certainty those lesions that have undergone significant deterioration from those that have not. Reiber et al. (11) found this value to be 0.72 mm on the basis of angiograms taken 90 days apart, whereas Nobuyoshi et al. (2), using a different measurement system, have taken 0.5 mm on the basis of angiograms taken 7 to 10 days apart. It is important to realize that the variability will be considerably greater for angiograms taken from repeat catheterization sessions, as opposed to repeat angiograms from the same session (11), something that has not been appreciated by all investigators using this methodology (12).

Criteria based on the absolute change in minimal luminal diameter are nevertheless limited because they make no attempt to relate the extent of the restenosis process to the size of the vessel. What may be a significant increase in plaque area in a 1.5 mm diameter vessel may be of no hemodynamic consequence in a larger vessel of 3.5 mm. Studies need to be undertaken to assess the variability of measurement in different diameter vessels, and a "sliding scale" criterion created that adjusts for vessel size.

Incidence of Restenosis

Role of defined criteria of restenosis. In the same way as the method of analyzing an angiographic frame will influence the measurement of percent diameter stenosis, so it will influence the restenosis rate. However, the factor that most influences the rate is the definition of restenosis used. Figure 3 shows the number of lesions fulfilling three criteria of restenosis: although 43 of the lesions included by at least one criterion are included by all three, 32% of those included in one criterion ("a loss of greater than half the gain") are not included in either of the other two. Despite this discrepancy, the incidence of restenosis is not too dissimilar, ranging from 21% to 34% (Fig. 4). What should be clear is that a similar incidence of restenosis with different criteria may be defining different populations. This point has particular relevance when determining the risk factors for restenosis: if restenosis cannot be reliably determined, then it is unlikely that the associated risk factors will be identified. The most sensitive index of restenosis in common use is that of a loss of ≥50% of the gain, with reported incidence rates ranging from 16%

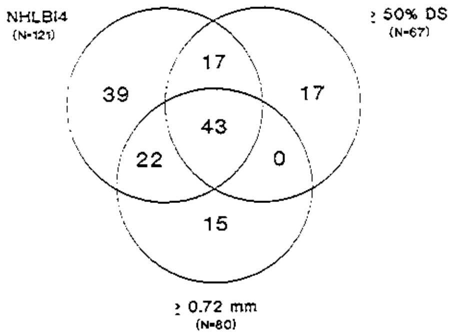
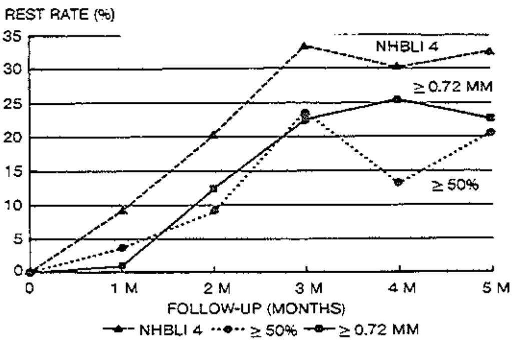


Figure 3. The number of lesions fulfilling three restenosis criteria, taken from a group of 490 lesions measured at follow-up within 6 months. The total number of lesions that fulfill each criterion are shown under the criteria, and those lesions fulfilling that criterion and none other are enclosed by only one circle. Lesions included by any two criteria are enclosed by two circles, and lesions that fulfill all three criteria (n = 43) are enclosed by all three circles. It can be seen that lesions that are designated as restenosis are highly dependent on the criteria for restenosis employed. NHLBI4 = criterion 4 of the National Heart, Lung, and Blood Institute: loss of >50% of the gain at angioplasty. ≥50% DS = ≥50% diameter stenosis at follow-up. ≥0.72 mm = ≥0.72 mm change from postangioplasty to follow-up.

to 52% (2,5,6,9,13). On the other hand, ≥50% diameter stenosis at follow-up will tend to give a lower incidence of restenosis because lesions that deteriorate significantly, but remain within the 0 to 49% range, are not designated as restenosis. Of the two studies with larger numbers that document the change in minimal luminal diameter, only one uses this value to derive a restenosis value of 26% at 4 months (9).

Figure 4. Incidence of restenosis (REST) according to three criteria in the first 150 days after angioplasty derived from the patient group with 490 successfully dilated lesions shown in Figure 3. Abbreviations in Figure 3.



Role of quantitative angiography. The use of quantitative angiography has given valuable insight into the problem of defining an incidence of restenosis. It has been demonstrated that the restenosis process takes place, to some extent, in most of the lesions dilated and, furthermore, it takes place not only in the stenotic portion, but also in the dilated but nonstenotic segments (4). This observation in itself demands the use of a measurement system that will define the change in the minimal luminal diameter independent of the change in the "reference diameter."

Timing of Restenosis

It has been clear for some time that restenosis most often takes place within the first 6 months after dilation (7,14). Further progression after this time is unusual, with lesion improvement or deterioration occurring in a small number of instances, a pattern more characteristic of coronary artery disease in general (15–17). Recently two reported studies (2,9) performing follow-up angiography at different preselected follow-up intervals gave remarkably similar results and showed more precisely how the lesion behaves after angioplasty. Early after angioplasty, within 30 min, "recoil" may take place, which in principle should be regarded as a separate problem from that of the restenosis (Fig. 5). This decrease in the luminal diameter may be exaggerated by a vasoconstrictive component if vasodilators are not administrated after the angioplasty procedure. The recoil, together with remodeling and possibly thrombus formation, results in "restenosis" in 11% to 16% of the lesions in the first 24 h (using the National Heart, Lung, and Blood Institute definition 4 of restenosis) (2). It then appears that healing and remodeling may lead to improvement in an appreciable number of lesions, so that at 30 days the restenosis rate lies between 6% and 13%. Between 1 and 3 months, most lesions that will develop restenosis do so, with the restenosis rate reaching 25% to 37% (Fig. 6). A small number may show further progression between 4 and 6 months. It seems likely that the restenosis process begins early and is progressive over the first 3 to 4 months.

The limitations of even the most accurate measurement systems mean that these early changes are not detected early, and it is not until substantial progression takes place at 3 months that the process is fully recognized. This early change has been shown in animals, with evidence of smooth muscle proliferation as early as 7 to 14 days after dilatation (18). This same process has been identified in at least 7 postmortem hearts (19–21) that were examined over a period of 17 to 150 days after angioplasty.

Videodensitometric Analysis

Although videodensitometric analysis has been advocated as the method of choice for studies addressing the problem of restenosis, it has not proved practical in large studies. The technique is promising, but the number of lesions that can be analyzed effectively by this technique is limited, and the use of the videodensitometric technique would mean that a significant number of patients undergoing routine angioplasty (>10%) would be excluded from restenosis studies. Future developments may mean that this method, which is potentially easier to perform and requires only one angiographic projection to obtain a three-dimensional representation, will become the method of choice for restenosis studies.

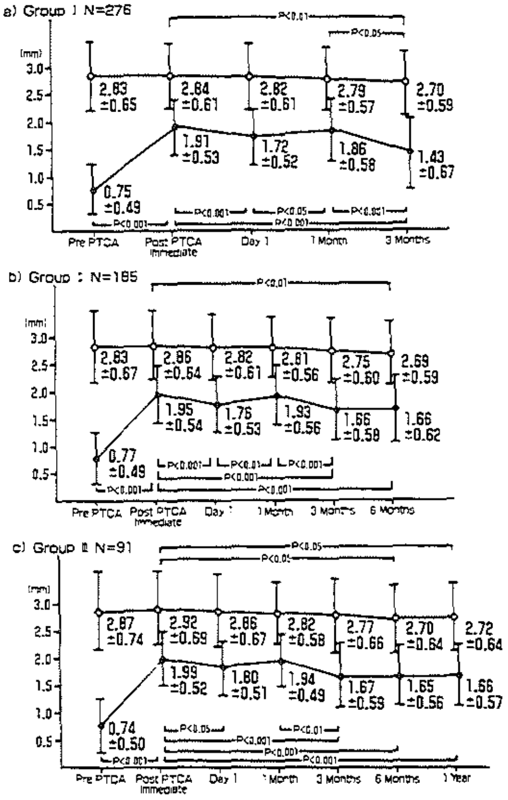


Figure 5. Serial changes in the absolute diameter of normal (open circles) and stenotic (closed circles) segments after coronary angioplasty (PTCA) for three follow-up groups. Group I = 3 month angiographic follow-up. Group II = 6 month angiographic follow-up. Group III = 1 year angiographic follow-up. The change in both the normal (O) and stenotic (●) segments with time are illustrated. Most of the deterioration in the stenotic segments occurs between 1 and 3 months, whereas there is a less pronounced steady deterioration in the nonstenotic segments up to 6 months. (Reprinted with permission from Nobuyoshi et al. [2]).

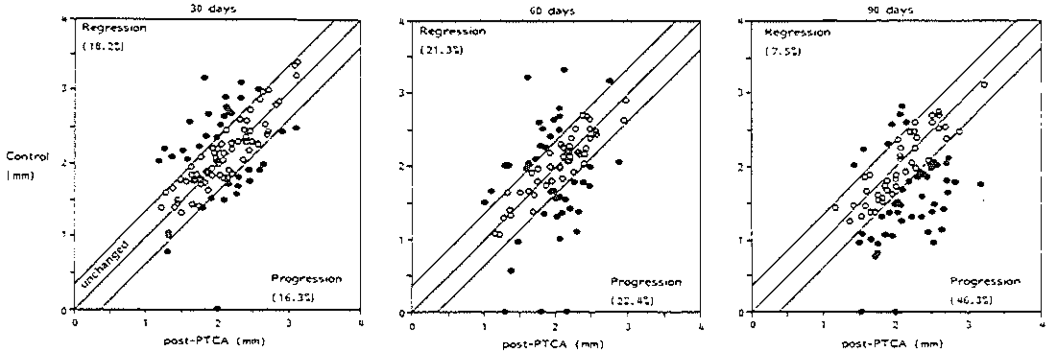


Figure 6. Individual minimal luminal diameter (mm) after coronary angioplasty (PTCA) compared with the control angiographic study for three different groups at 30, 60 and 90 days. The two **solid lines** on either side of the identity line correspond to the long-term variability (0.36 mm) of repeat measurement for this variable (5). This variability is 1 standard deviation of the difference in means of duplicate angiographic measurements. Therefore, 2 standard deviations ($2 \times 0.36 = 0.72$ mm) define the 95% confidence limits for lesion progression or regression. The lesions showing progression or regression is represented by **closed circles**, and the numbers are shown in the brackets in the left upper and right lower corners.

Risk Factors for Restenosis

Identifying the risk factors. There are no studies using quantitative coronary angiography that report on the risk factors in large numbers of patients. There are some factors relating to the restenosis process that have been identified and confirmed in more than one study. These include a proximal left anterior descending coronary artery stenosis, a totally occluded vessel before angioplasty, the presence of collateral vessels supplying the distal part of the dilated coronary artery and associated insulin-dependent diabetes. Factors that relate to the success of the angioplasty, such as a residual stenosis >30% or 40%, with current knowledge should not be considered as risk factors for "restenosis." For most of the other described risk factors, there are as many studies that do not as studies that do identify a particular factor. No procedure-related factor, that would allow the operator to modify the way angioplasty is performed has yet been identified, and no pharmacologic intervention has been able to show a reduced rate of restenosis. Quantitative angiography offers the possibility of objective measurement of lesion morphology, such as length of lesion and eccentricity, and when this more objective information becomes available, then perhaps it will be possible to identify lesion-related factors associated with restenosis.

Role of quantitative angiography in evaluating new procedures and interventions. To date, quantitative coronary angiography has been used in a limited number of studies addressing the problem of restenosis. It has already provided valuable insight into the restenosis problem and has identified some of the sources of confusion surrounding this topic. It seems likely that, with better measurement systems, particularly those that become on-line in the catheterization laboratory, it will be easier to perform these studies, and with more reliable data in smaller numbers of patients, the effect of various interventions to prevent restenosis will be assessed more accurately and more efficiently. Currently there is a wide variety of revascularization devices, procedures and pharmacologic interventions under investigation, and of crucial importance in their evaluation will be the restenosis rate associated with each of these strategies. It is already clear that a meaningful comparison among the various strategies and evaluation of their relative merits is not possible because of a lack of standardization of methodology and lack of objectivity. In the future, we should demand that quantitative analysis be employed in important studies addressing the long-term outcome of new coronary interventions, so that the present confusion is not perpetuated.

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Part II

New devices and their influence on Restenosis

Chapter 8

Stenting of coronary arteries. Are we sorcerer's apprentice? European Heart Journal 1989;10: 774-782.

Editorial

Stenting of coronary arteries. Are we the sorcerer's apprentice?

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Introduction

The original work of Andreas Gruentzig in 1977[1] provided the stimulus for the rapid technological growth of interventional cardiology. More recently there has been an explosion in the number of new devices designed to ablate coronary artery narrowings, recanalize occluded vessels, and prevent restenosis, so much so that it is currently difficult to evaluate the relative merits of each and to define their place in clinical practice. In many of these areas the cardiologist has been acting solely as technician, limiting his concern to the technical and procedural aspects, and sometimes overlooking the complex biological and physiological mechanisms of atherosclerosis in general, and more particularly of the restenosis process.

In achieving the perceived benefit of the therapeutic intervention with these devices the vessel wall is subjected to thermal and mechanical insults which may have hidden long-term consequences as novel as the restenosis process was when this new pathological mechanism was first described[2,3], and which has now been iatrogenically induced in tens of thousands of patients.

One of the most recent developments has been the use of the intravascular stent[4], although the original concept of intravascular stenting preceded the introduction of coronary artery interventional cardiology by many years. In 1969, Dotter developed a coilspring endovascular prosthesis in an attempt to improve the long-term patency of peripheral atherosclerotic vessels submitted to recanalization and dilatation. Even at that time he envisaged that 'prompt fibroblastic development and a rapid formation of a new, firmly anchored autogenous lining surface' would be a critical factor in the long-term patency of the device[5].

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Since the original description of Dotter's tubular coil spring[5], there have been many variants of the original concept deployed experimentally, including: thermal shaped memory alloy stents[6–8], self-expanding steel spirals[9–12], self-expandable stainless steel mesh stents[13–15], balloon expandable stainless steel mesh stents[16–19], balloon expandable interdigitating coils[20,21], synthetic polymeric stents and biodegradable stents[22]. These various devices differ greatly in their fundamental geometry (mesh, single wire), composition (metal, plastic) and mechanical behaviour (active or passive expansion). Besides these fundamental differences, there are a variety of subtle dissimilarities which may be important in themselves, such as thickness of filaments, alloy composition, electrostatic behaviour, biocompatible or therapeutic coatings[23]. The prolonged presence of these materials residing in the arterial wall may generate late unknown and unexpected consequences.

What is the rationale for stenting an atherosclerotic vessel during or after dilatation?

In the first place, the stent may optimize the dilatation process, by containing the irregular surface of the atherosclerotic plaque created by the disruptive action of the balloon. Two potential adverse effects, distal embolization of macroscopic debris originating from the plaque and a protruding obstructive flap may be contained by the stent acting as a scaffolding device. The balloon expandable stent in particular may be advantageous when the operator electively uses the device to dilate the lesion and implant the stent in a single manoeuvre. The self-expanding stent on the other hand, by exerting a continuous radial force, has the effect of increasing the diameter of the lumen until a balance is reached between the expanding force of the stent and the circumferential compliance of the vessel[4,24]. The physiopathological consequence of this is unknown, but recently this interaction has been documented to continue for at least 24 h and possibly longer, resulting in continued improvement in the vessel lumen over and above that obtained at implantation[25]. The recoil phenomenon which is poorly documented and probably underestimated as a cause of 'restenosis' will be equally prevented by both types of stent[26]. In addition, both types of stent have a smoothing effect which reduces the turbulent and laminar resistances and may be beneficial in preventing restenosis[14,15]. Much has been made of the ability of the stent to prevent restenosis, with various theoretical proposals as to how this can be achieved and why one particular design might be more effective than another[4,20]. An attractive concept which favours the rigid stent is that the limitation of vessel wall stress seems to be protective against atherogenesis[27]. The self-expanding stent, by stretching the wall, might have the effect of accelerating the restenosis process. However, whether the accelerated process is mostly related to pulsatile stress rather than stress per se remains to be demonstrated. Although there may be some experimental work in animals to support these claims, there is as yet no evidence to support them in the clinical situation and they must therefore be regarded as speculative. There may be ultimately little difference between compliant and uncompliant devices (considering the amount of radial forces at the site of the wires exerted on the vessel wall). The initial intuitive and simplistic concept, not supported by experimental evidence, that the stent may act as a barrier preventing the migration of cellular structures (monocytes, macrophages, smooth muscle cells) into the intima during the healing process, has not been realized and the other potential mechanisms of prevention of restenosis, by stenting the internal wall of the vessel, have not yet been fully elucidated or unequivocally demonstrated. An alternative mechanism is that chronic compression by the stent of vasa vasorum underlying an atherosclerotic plaque may result in ischaemia of this microscopic vascular network and thereby limit the subsequent progression of the atherosclerotic plaque[28].

The mechanism of restenosis prevention put forward by Palmaz *et al.*[18] is open to criticism on the basis that it is an interpretation too dynamic for what is in essence a series of post mortem 'snap shots' which are difficult to reconstruct in time (Fig. 1). This evidence, recently reiterated by Schatz, is extremely appealing and attractive, but remains an unsubstantiated interpretation[29]. The struts of the mesh prevent the protrusion of sizeable atherosclerotic plaques inside the lumen of the vessel and act as a 'macroscopic sieve', containing and pushing the atherosclerotic plaque away from the neo-intimal lining into the adventitia. In addition, a sclerotic thinning of the media is apparently induced, converting the muscular and dynamic medial layers of the vessel into a practically non-vasoactive and non-compliant 'pipe'. Whether this is true and applicable to the human clinical situation remains to be demonstrated.

There is a consensus among investigators in the field that stent implantation improves the immediate post-dilatation result, producing a smooth straight appearance of the dilated segment. This visual impression has been confirmed by quantitative analysis using both edge detection and video densitometric techniques[24]. Favourable results have also been reported in the 'bail-out' situation, when the stent has been implanted following dilatation where presence of intimal dissection had led to a poor and even critical haemodynamic result[30,31].

The thrombogenic nature of the stent remains a concern, although there may be important differences between different devices[29,32,33]. This concern is reflected in the anticoagulant regimens used in patients in whom the Medinvent stent was implanted (Table 1). This complex and aggressive protocol reflects the insecurity of the clinician and the knowledge that none of the anticoagulant agents on their own will reliably prevent thrombus formation. It is a paradox that similar devices, although with different metallic compositions, have been used for just the opposite effect — to create thrombotic occlusion in experimental animals[34–36].

At the tenth congress of the European Society of Cardiology, Richard Schatz reported the immediate results in 15 patients who had received a Palmaz stent. According to an FDA-approved protocol, the stents were implanted in vessels (mostly right coronary arteries) supplied by a collateral circulation. At that time he was convinced that all patients could be treated with heparin and dextran during the procedure and aspirin and dipyridamole alone after discharge. There were no instances of abrupt closure and no patient required warfarin. These initial results suggested that this balloon expandable stent was relatively non-thrombogenic, which eliminated the need for both routine administration of lytic agents during the procedure and warfarin thereafter. Unfortunately, the angiographic follow-up at 6 months of these first 15 patients

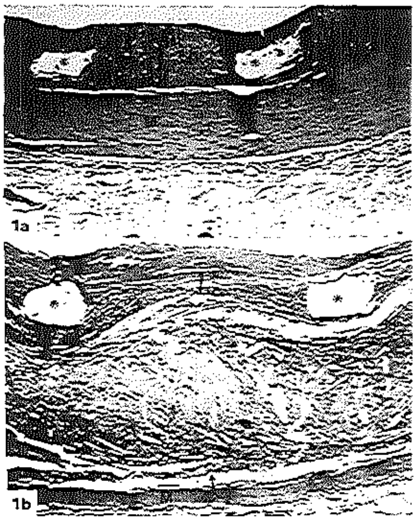

Figure 1 Microphotography of cross section of an atherosclerotic rabbit aorta (a) 1 week and (b) 6 months after stenting. Note the thin layer of thrombus (T) covering the stent struts (*) and the thick media (M) at 1 week. By 6 months, thrombus is replaced with acellular ground substance and endothelium. A large plaque is evident (arrows) but does not encroach the lumen (from Schatz[29], reprinted with the permission of *Circulation*).

disclosed four total occlusions and one restenosis. Since then, patients have been given coumadin.

Concern has also been expressed as to whether the composition of the stent is able to trigger an allergic response, particularly in individuals who may be hypersensitive to the individual metals that make up the device. Although there have been reports of transient inflammatory infiltrates in the adventitia following stent implantation, it is reassuring that there are no reports of foreign body cells in the immediate vicinity of the implanted device in the experimental animal model[13,18,37]. Human data to support this assumption are still lacking, however.

Stent-induced restenosis

DO WE KNOW WHAT HAPPENS AT PTCA AND UNDERSTAND THE PROCESS OF RESTENOSIS?

Data from normal and atherosclerotic arteries of experimental animals and human autopsied hearts have shown that following balloon dilatation the arterial intima or atherosclerotic plaque may split down to the internal elastic membrane[2,3,38]. Frequently also damage of the arterial media with overdistension and splitting occurs. Next to or partially as a result of locally turbulent blood flow, a complex interaction between the exposed subendothelial surface and blood elements occurs. This results in platelet deposition locally in the region

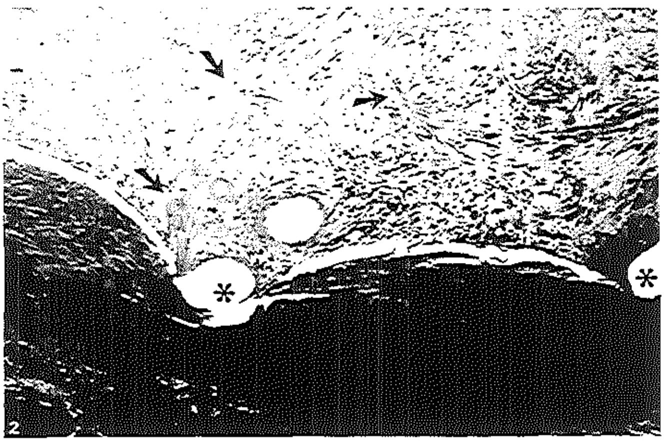

Figure 2 Histologic cross-section of a porcine left descending anterior coronary artery 1 month after stent placement (magnification × 120). The voids marked (*) originally contained the stent wires. In the neointima strands of elongated cells (arrows) are present in abundance.

Table 1 Intracoronary stent: Multicenter European Trial Drug Regimen

Day before implant procedure	— Salicylic acid 2 × 500 mg — Dipyridamole 4 × 75 mg — Sulphinpyrazone 4 × 200 mg — Ca-antagonist: nifedipine 3 × 20 mg day^{-1}
Day of implant procedure	— Salicylic acid 1 × 100 mg — Dipyridamole 4 × 75 mg (Patients above 90 kg: 3 × 150 mg) — Sulphinpyrazone 4 × 200 mg
Before PTCA	— Diltiazem 5 mg — Heparin 10 000 I.U. — Dextran 500 mg. (4 h)$^{-1}$
At implantation	— 100 000 I.U. Urokinase in 250 ml NaCl given intracoronary (i.c.) up to the end of the procedure. Start drip at guide-wire insertion given over 30–60 min and another 250 ml (100 000 I.U.) for each extra hour. — Heparin 5000 I.U. I.V.
(Post-implantation)	At start of transfer, patient to receive *heparin* at the rate of 24 000 I.U. (24 h)$^{-1}$ to control P.T.T. at minimum 70 s. (This corresponds to about 400 I.U. kg^{-1}. (24 h)$^{-1}$. For large patients, the maximum rate is 30 000 I.U. (24 h)$^{-1}$. If P.T.T. > 200 s (5 × control value) the infusion is slowed. If P.T.T. < 70 s infusion flow is increased. *No less than 24 000 I.U. heparin per 24 h is to be given.*
Post-implantation (day)	Start the oral anticoagulation with acenocoumarol to be started from the first day (i.e. six tablets of 1 mg each the first day, then four the day after and two the third day and then according to 'QUICK'.
Continuing anticoagulation	— Oral anticoagulation: acenocoumarol: Quick to be maintained in the range of: 17%–25% (T.P. Thromborel S, Behring). *N.B.* Heparin will be stopped when the therapeutic level of oral anticoagulants is reached. — Salicylic acid 1 × 100 mg day^{-1} — Dipyridamole 4 × 75 mg day^{-1} (Patients > 90 kg: 3 × 150 mg day^{-1}) — Sulphinpyrazone 4 × 200 mg day^{-1} — Ca-antagonist: nifedipine 3 × 20 mg day^{-1}
Long-term	This anticoagulation regimen is stopped after the 6-month coronary angiography control. Aspirin (100 mg 1 × day) should be given ad eternam.

of the internal elastic membrane, which may be massive in the case of medial tearing, and the release of a variety of mitogens which may contribute to neointimal cell invasion and proliferation[39]. The best recognized of these factors is platelet derived growth factor (PDGF) which is released predominantly by platelets, endothelial cells as well as intimal smooth muscle cells[40]. Recently the dimeric structure of this protein has been identified[41], the three isoforms of PDGF may stimulate effects unique to each isoform through interaction with different classes of PDGF receptor[42]. There is now evidence that intimal mesenchymal cells or modified smooth muscle cells (but not medial smooth muscle cells) may themselves release PDGF[40]. This may initiate the vicious circle responsible for the sustained proliferative process as it occurs in restenosis. However, neither the conditions under which this takes place nor the triggers responsible for this event are understood. In animal experiments, for example, two types of experimental arterial injury have been described: the first induced by passive trauma such as a catheter in situ or balloon denudation of the endothelial lining, and the second induced by a more disruptive stimulus, causing not only endothelial denudation, but also tearing of the media, which is the typical sequel of balloon dilatation[39,43,44]. Both are associated with the deposition of platelets on the vessel wall, with subsequent migration of smooth muscle cells from

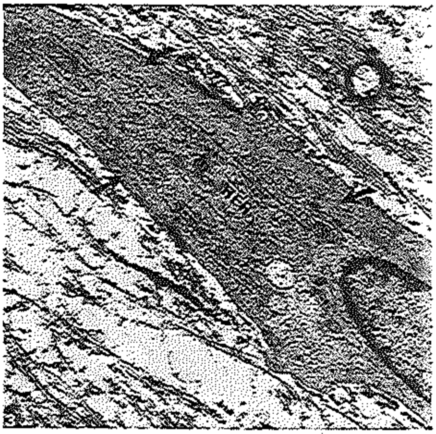

Figure 3 Transmission electron microscopy of the elongated cell-type of Fig. 2 (Magnification × 15 000). Abundant rough endoplasmic reticulum (RER) is present within these cells. Along the cell membrane bundles of myofilaments (arrows) are also prominent.

the media and their proliferation to form a neointima, and both can be prevented or inhibited by reducing the circulating platelets to very low levels. The first type, associated with repeated trauma, and presumably repeated thrombus formation, regresses following removal of the traumatizing stimulus. The second, more disruptive, type however results frequently in a lesion that is progressive in terms of smooth muscle cell proliferation and lipid accumulation. The reason that one type of lesion regresses while the other progresses is not clear. A possible explanation may come from studies on failure of synthetic arterial grafts. Once endothelial covering of synthetic grafts has progressed, smooth muscle cell proliferation appears to slow down, except in the region of anastomosis[45]. Thus a continued release of growth factors may occur even after complete endothelial covering either in areas of turbulent flow, which results in continuous endothelial damage and repair, or at sites where the barrier between neointima and media is minimal. Evidence for continued mediator release by endothelial cells under specific conditions has very recently been published[46]. The presence of a non-degradable stent in the arterial wall may form such a trigger for continued mediator release. Immediately after stent implantation its luminal surface becomes covered with a combined platelet-fibrin deposition[13]. Within 1 week of implantation into previously dilated normal porcine arteries (Fig. 2), there is complete endothelial covering of the stenting device[37] varying between 60 and 125 µm, which acts to isolate the thrombogenic stimulus from the vessel lumen. Within this layer are abundant myofibrillar cells and macrophages: the harbingers of the restenosis process. These cells can be seen to originate in the immediate vicinity of the individual stent filament adjacent to the internal elastic lamina, forming 'geysers' of elongated cells fanning out to fill the neointimal tissue in an evenly distributed fashion. In some animals this process results in complete obstruction of the stented coronary artery as early as 1 month after implantation. Electron microscopic examination (Fig. 3) of these fusiform elongated cells reveal oval nuclei with marginated chromatin, and abundant rough endoplasmatic reticulum. Bundles of contractile proteins can be demonstrated (small arrows) in a subplasmalemmal situation. These myofibroblasts or synthetic type smooth muscle cells are identical to those observed in the neointima after 1 week. It is therefore attractive to speculate that the same modified smooth muscle cells that migrate through the internal elastic membrane (IEM) and which are implicated in the restenosis process after PTCA,[46,47] can be operative in *an accelerated fashion* once a stenting device damages this natural barrier (IEM). Thus, the latter becomes more permeable to the migrating cells or providing a direct stimulus for cell migration. It has recently been suggested that restenosis following primary balloon angioplasty is an unfavourable lesion for interventions such as atherectomy and stenting[48–50]. From preliminary data presented by Simpson *et al.* at the 38th session of the American College of Cardiology, it appears that restenosis rate following atherectomy as a primary intervention is 23·5%, while the restenosis rates are 36·8%, 42·1% and 53·8% when atherectomy was performed as the secondary treatment following a first, second and third recurrence of stenosis[51]. A similar opinion has been expressed by the group of Sigwart *et al.*[48] Their preliminary data suggest that elective stenting for restenosis early after previous angioplasty carries an increased risk (41%) of restenosis within the stent. It could be that the active fibrocellular proliferation associated with the early phase of restenosis after balloon angioplasty is further stimulated by stent implantation.

In this respect, one of the questions posed by Spencer King III in his editorial is judicious and pertinent: is the treatment worse than the

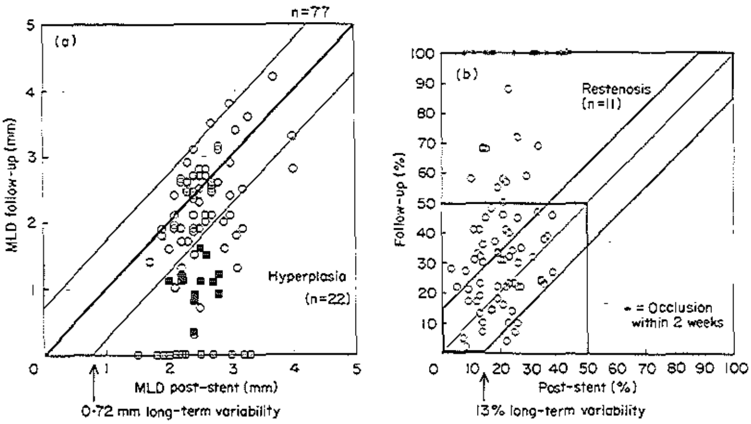

Figure 4 (a) Diagram demonstrating the change in the minimal luminal diameter following stent implantation. The individual minimal lumen diameter (MLD) immediately following stent implantation (horizontal axis) are compared with that at angiographic follow-up (vertical axis). The two lines to either side of the identity line represent the long-term variability for repeat measurement. All points (n = 22) that fall below the lower line are therefore considered to have undergone a significant deterioration (intimal hyperplasia >0·72 mm) and in addition the closed blocks also fulfil the criterion of ≥50% diameter stenosis. The open blocks represent early total occlusions (n = 13). (b) Similar diagram demonstrating the change in terms of percentage diameter stenosis. The circles falling both outside the limits of the long-term variability of quantitative angiographic measurement and have >50% diameter stenosis, represent true 'restenosis' unequivocal within the stent.

disease?[33] Perhaps a more appropriate question is whether we have to apply these more costly interventions, as the initial procedure, in order to achieve a reduction of the restenosis rate? Such is the dilemma we have to face. Certain authors have already drawn the conclusion that atherectomy, for example is a *favourable* primary approach for the treatment of selected *unfavourable* lesions[50].

The intracoronary stent like many other novel forms of treatment seems to be following the well-worn path of initially elated euphoria where enthusiasm holds sway over scientific evidence followed by critical scepticism with little optimism for the future. A period of criticial scientific evaluation is now needed, in which the lessons learned from the past are implemented. The initial experience has revealed three factors associated with complications: small vessels <3 mm, low blood flow with poor run off, and evidence of hypercoagulability or local thrombus formation. This has led most investigators to restrict the use of this stent to saphenous bypass grafts with large diameters and to the native circulation as 'bail-out' device. In Europe, according to the data from the Working group on endoluminal prostheses*, Medinvent stents have been implanted in 187 patients between March 1986 and June 1989 in both native coronary arteries and bypass grafts. Although stent implantation is capable of producing a superior haemodynamic result[19,25], the preliminary data suggest that the restenosis rate is between 15% and 30% according to the applied criteria (diameter stenosis ≥50%, ≥0·72 mm reduction in the minimal luminal diameter[52,53] [Fig. 4(a),(b)]. The Palmaz stent, currently used in three centres in Europe has been implanted in situations which are considered at low risk of acute problems, but at high risk of reocclusion (total occlusions, myocardium protected by collaterals). The intracoronary stent represents a 'double-edged sword': although the scaffolding properties of the device are attractive and of proven benefit it may provide an iatrogenic stimulus for erratic and uncontrolled cell proliferation. This potential has not been fully appreciated by the interventional cardiologist who may have opened a new

*Participating Centres and Collaborators: See appendix.

Pandora's box of complex biological interactions, but who may well be rescued by the cellular biologist in the future. The device is a logical vehicle for the topical release of agents that will ideally enhance endothelialization but suppress the keloid-type reaction of the traumatized vessel wall. Solution of this problem is not helped by the lack of joint effort on the part of the pharmaceutical industry and the industry producing the mechanical device. This is a source of frustration to investigators in the field, but hopefully will be overcome in the future. The initial hopes that stent implantation may prevent or diminish restenosis have not been fulfilled. In addition, early thrombotic occlusion in the native coronary circulation has led many temporarily to abandon this as an indication except for emergency 'bail-out' indications.

Are we sorcerer's apprentice?

A case report will illustrate our concern better than a long series of arguments. A male patient from Los Angeles, who had two major risk factors for CAD: diabetes and hypercholesterolaemia, sustained in 1977 an inferior myocardial infarction. Post infarction angina was treated by two saphenous vein grafts on an obtuse marginal and on a diagonal branch. Following recurrent angina he was reoperated upon and both internal mammary arteries were used to bypass the LAD and the RCA. Between 1984 and 1987 the vein graft on the left marginal artery was dilated on four occasions. In April 1987, his cardiologist referred the patient to Ulrich Sigwart in Lausanne for a stent implantation in both saphenous vein grafts. Seven months later, in November 1987, repeated dilatation was necessary within both stents. Five months later the patient again had restenosis; this time, a hot balloon angioplasty was considered but rejected by Richard Spears in Detroit (would the absorbed laser energy convert the stent into a 'hot roster'), and the first atherectomy inside the stent was performed by John Simpson in Palo Alto. In July 1988, the patient underwent a second atherectomy, which did not prevent restenosis. Disappointed by these results lasing with excimer laser (wavelength 308 nm) was successfully attempted in Los Angeles by Jim Forrester and his group[54]. Unfortunately for the patient, the stenotic lesion seemed to be more stubborn than the treating physicians and recurred once more. Tired of these multiple and varied interventions, the patient has decided for the time being to stay away from the sorcerer's apprentice and this long and thorny path has certainly brought down to earth the interventional cardiologist who has to face the unavoidable reality: in addition to a mechanical device a pharmacological approach will be necessary to achieve victory over restenosis.

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Appendix

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Chapter 9

Angiographic follow-up after placement of self-expanding coronary artery stent. New England Journal of Medicine. 1991; 324: 13-17.

ANGIOGRAPHIC FOLLOW-UP AFTER PLACEMENT OF A SELF-EXPANDING CORONARY-ARTERY STENT

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Abstract *Background.* The placement of stents in coronary arteries after coronary angioplasty has been investigated as a way of treating abrupt coronary-artery occlusion related to the angioplasty and of reducing the late intimal hyperplasia responsible for gradual restenosis of the dilated lesion.

Methods. From March 1986 to January 1988, we implanted 117 self-expanding, stainless-steel endovascular stents (Wallstent) in the native coronary arteries (94 stents) or saphenous-vein bypass grafts (23 stents) of 105 patients. Angiograms were obtained immediately before and after placement of the stent and at follow-up at least one month later (unless symptoms required angiography sooner). The mortality after one year was 7.6 percent (8 patients). Follow-up angiograms (after a mean [±SD] of 5.7±4.4 months) were obtained in 95 patients with 105 stents and were analyzed quantitatively by a computer-assisted system of cardiovascular angiographic analysis. The 10 patients without follow-up angiograms included 4 who died.

Results. Complete occlusion occurred in 27 stents in 25 patients (24 percent); 21 occlusions were documented within the first 14 days after implantation. Overall, immediately after placement of the stent there was a significant increase in the minimal luminal diameter and a significant decrease in the percentage of the diameter with stenosis (changing from a mean [±SD] of 1.88±0.43 to 2.48±0.51 mm and from 37±12 to 21±10 percent, respectively; $P<0.0001$). Later, however, there was a significant decrease in the minimal luminal diameter and a significant increase in the stenosis of the segment with the stent (1.68±1.78 mm and 48±34 percent at follow-up). Significant restenosis, as indicated by a reduction of 0.72 mm in the minimal luminal diameter or by an increase in the percentage of stenosis to ≥50 percent, occurred in 32 percent and 14 percent of patent stents, respectively.

Conclusions. Early occlusion remains an important limitation of this coronary-artery stent. Even when the early effects are beneficial, there are frequently late occlusions or restenosis. The place of this form of treatment for coronary artery disease remains to be determined. (N Engl J Med 1991; 324:13-7.)

TWO major limitations of coronary angioplasty are acute occlusion and late restenosis. The concept of implanting an endoluminal stent in the coronary arteries after balloon dilation to circumvent these problems was first suggested in 1964.[1] This procedure was successfully performed in patients in 1986.[2] In May 1988, the five European centers testing this device agreed to set up a core laboratory for quantitative angiographic analysis to assess the results objectively. The early follow-up results reported by the core laboratory showed that immediately after stent implantation, there was an additional increase in the minimal luminal diameter of the vessel and a decrease in the percentage of stenosis of the diameter.[3] However, after three months slight but diffuse narrowing was observed in the artery containing the stent.[4] In the present study, we have focused on the results of long-term angiographic follow-up of the initial 117 stent implantations.

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METHODS

Study Patients

One hundred five patients gave informed consent and were enrolled at participating study centers between March 1986 and January 1988. The study protocol was approved by the ethics committees of the individual hospitals. The clinical characteristics of the patients are shown in Table 1. Ninety-five patients received one stent, and 10 received more than one (Table 1). Seven of the 10 patients who received multiple stents required two overlapping ("telescoping") stents to cover long lesions adequately, and the other 3 required stents in multiple vessels or in different locations in the same vessel. The sites of stent placement are shown in Table 1. Seventy-one stents were implanted after redilation of a restenosis, 14 were placed as an emergency procedure during an angioplasty complicated by acute occlusion, 5 were placed after angioplasty for chronic occlusion, and 27 were placed as an adjunct procedure to primary percutaneous transluminal coronary angioplasty (PTCA). Some of the patients who received stents for bypass grafting or abrupt closure have been included in previous reports.[5,6]

In this trial, the endovascular prosthesis Wallstent (Medinvent, Lausanne, Switzerland) was used. The method of implantation and a description of this stent have been previously reported.[2] This stent is a self-expanding, stainless-steel, woven-mesh prosthesis that can be positioned in the coronary artery with an 8-French or 9-French guiding catheter, according to the standard over-the-wire technique. The device is constructed of 16 wire filaments, each 0.08 mm wide. It is constrained in an elongated configuration on a delivery catheter 1.57 mm in diameter; the distal end of the prosthesis is covered by a removable plastic sleeve. As the sleeve is withdrawn, the constrained device returns to its original, larger diameter and becomes anchored against the vessel wall. The diameter of the prosthesis ranges from 2.5 to 6 mm when the stent is unconstrained.

Table 1. Clinical Characteristics of the Study Patients.

No. of patients	105
Age (yr)*	57±9
Sex (M/F)	91/14
No. of stents	117
Site of stent implantation (no. of stents)	
Left anterior descending artery	62
Circumflex artery	6
Right coronary artery	26
Bypass graft	23
Indication for implantation (no. of stents)	
Restenosis	71
PTCA with acute occlusion	14
PTCA as adjunct procedure	27
Chronic occlusion	5
Time to angiographic follow-up (mo)*	
All patients	5.7±4.4
Patients with patent stents	7.2±3.6
No. of stents per patient (no. of patients)	
One	95
Two	8
Three	2

*Means ±SD.

We selected a diameter 0.50 mm larger than the reference diameter of the stenosed vessel.

Anticoagulation regimens evolved throughout the study period, and different protocols were used at the various centers. In the first 23 of the 32 patients treated in Toulouse, heparin was administered subcutaneously three times a day to maintain the activated cephalin–kaolin time (an index of coagulation status) at twice the control value, starting three to five days before the procedure and continuing for six weeks afterward. During the procedure, the 7th through the 32nd patients received an additional 10,000 units of heparin intravenously and 20,000 to 50,000 units of streptokinase by intracoronary infusion. Aspirin (100 mg) and dipyridamole (300 mg) were given daily by mouth, starting 24 hours before the procedure. The 24th through the 32nd patients treated in Toulouse received a vitamin K antagonist (warfarin or acenocoumarol) by mouth, started on the day of the procedure and continued for three to six months. The subcutaneous heparin injections were stopped after a therapeutic level of oral anticoagulant was reached (International Normalized Ratio, ≥2.3). In the other centers, aspirin (1 g orally) was started one day before the procedure. Heparin (10,000 to 15,000 units) and urokinase (100,000 units by intracoronary infusion) were administered during the procedure. Heparin was given intravenously, and then the vitamin K antagonist by mouth for three to six months as described above. Aspirin (initially 1 g daily and later 100 mg daily), dipyridamole (300 to 450 mg daily), and in some patients sulfinpyrazone (400 mg daily) were also administered. The first four patients treated in Rotterdam did not receive aspirin.

Quantitative Coronary Arteriography

All cineangiograms were analyzed at the core laboratory in Rotterdam by means of a computer-assisted cardiovascular-angiography analysis system, discussed in detail elsewhere.[7,8] The important steps will be briefly described. Selected areas of the cine frame encompassing the desired arterial segment were optically magnified, displayed in a video format, and then digitally converted. Vessel contour was determined automatically on the basis of the weighted sum of the first and second derivative functions applied to the digitized information on brightness. A computer-derived estimation of the original dimensions of the artery at the site of the obstruction was used to determine interpolated reference values for arterial diameter and area. The absolute diameter of the segment with stenosis as well as the reference diameter was measured by the computer, which used the diameter of the guiding catheter as a calibration factor, after correcting for pincushion distortion. The interpolated percentage of stenosis of the narrowed segment was then derived by assuming a circular model and comparing the observed value for stenosis with the reference value. The minimal luminal diameter of each segment immediately proximal and distal to the stent was also measured. The angiographic analysis was performed before and after angioplasty, immediately after stent implantation, and at long-term follow-up evaluation in all patients, with the use of the average of multiple matched views with orthogonal projections whenever possible.

Restenosis

Two different sets of criteria were applied to determine the rate of restenosis. We have found a reduction of 0.72 mm or more in the minimal luminal diameter to be a reliable indicator of angiographic progression of vessel narrowing.[7-9] This value takes into account the limitations of coronary angiographic measurements and represents twice the long-term variability of repeat measurements of a coronary-artery obstruction with the cardiovascular-angiography analysis system. The other criterion for restenosis was an increase in the percentage of stenosis from less than 50 percent after stent implantation to 50 percent or more at follow-up evaluation. This criterion was selected since common clinical practice has continued to express lesion severity as a percentage of stenosis.

Statistical Analysis

Values obtained by quantitative angiographic analysis are expressed as means ±SD. The means for each angiographic variable before PTCA, after PTCA, immediately after placement of the stent, and at follow-up were compared by analysis of variance. If significant differences were found, two-tailed t-tests were applied to paired data. A statistical probability of less than 0.05 was considered to indicate significance.

The results of angiographic and clinical follow-up were expressed in a life-table format according to the Kaplan–Meier method.[10] Stent occlusions, cardiac deaths (which were assumed to be due to occlusion, for statistical purposes), and restenosis as defined by the two criteria were considered angiographic end points. The following events were considered clinical end points: death, myocardial infarction, bypass surgery, and nonsurgical revascularization (PTCA or atherectomy). The life table was constructed according to the initial clinical event.

Results

The overall mortality after one year was 7.6 percent (eight deaths) (Table 2). The mean (±SD) period of angiographic follow-up was 5.7±4.4 months in all patients and 7.2±3.6 months in patients whose stents were patent at follow-up. Angiographic follow-up (Fig. 1) was performed in 95 patients (90 percent) with 105 stents (90 percent); 78 stents were patent, and 27 were occluded (Table 3). Angiographic follow-up could not be obtained in 10 patients for the following reasons: 4 patients died, 4 refused follow-up angiography, and 2 had follow-up angiograms that were technically inadequate for analysis (but did not show total occlusion). Twenty angiograms were obtained during the first month after stent implantation; all were obtained because clinical symptoms had occurred, and all showed occlusions. Angiograms obtained after the first month were part of the routine follow-up evaluation; all showed patent stents except in five patients with stent occlusions. Overall, the minimal luminal diameter increased from 1.21±0.56 mm to 1.88±0.43 mm after PTCA and then further, to 2.48±0.51 mm, immediately after stent implantation ($P<0.0001$) because of the intrinsic dilator function of the device (Table 4). At follow-up the diameter was found to have decreased to 1.68±1.20 mm. The percentage of stenosis changed similarly, with an initial decrease from 61±14 to 37±12 percent after angioplasty and an additional decrease to 21±10 percent immediately after stent placement (P<0.0001). However, at follow-up the percentage of stenosis had increased to 48±34 (P<0.0001). When only patent stents were included in the analysis of late follow-up, the minimal luminal diameter and the percentage of stenosis were 2.26±0.78 mm and 30±17 percent, respectively. A small, nonsignificant increase occurred in the reference diameter after stent placement (from 3.15±0.54 to 3.22±0.79 mm). During the study, no significant change was seen in the minimal luminal diameter of the proximal or distal segments adjacent to the stent.

The incidence of restenosis (Fig. 2) depended on the definition of stenosis (Fig. 3). When a change of ≥0.72 mm in minimal luminal diameter was used as a criterion, restenosis was observed within the patent stent in 17 patients (19 stents), in the proximal segment adjacent to the stent in 3 patients, in the segment immediately distal to the stent in 2 patients, and in both proximal and distal regions in 1 patient. Therefore, the total rate of restenosis was 32 percent among stents and 33 percent among patients. At follow-up the percentage of stenosis had increased to ≥50 percent within 10 stents (13 percent) in 9 patients (13 percent) and in the segment proximal to the stent in 1 stent in 1 patient, for a total rate of 14 percent. After one year of clinical follow-up, two of the patients with restenosis underwent repeat balloon angioplasty, one patient (two stents) underwent atherectomy, performed within the narrowed stent, and six patients underwent coronary bypass surgery. Death or myocardial infarction did not occur in any of these nine patients.

Table 2. Deaths after Stent Implantation.

Patient No.	Time after Implantation	Cause of Death
1	<24 hr	Stent occlusion after vessel closure during PTCA
2	48 hr	Sudden death
3	2 days	Stent occlusion after 24 hr, followed by emergency bypass procedure
4	8 days	Stent occlusion during implantation, myocardial infarction, shock
5	11 days	Sudden death
6	1½ mo	Sudden death
7	2½ mo	Surgery for new lesion of left main artery, after bypass procedure
8	6 mo	Chronic congestive heart failure

Discussion

The data from the six European centers at which the coronary-artery stent described above was used show a stent-occlusion rate of 24 percent. The anticoagulation regimens and methods for selecting patients differed among the centers, which may explain some of the variability in the occlusion rates between centers. The highest occlusion rate (39 percent) was observed at the Toulouse center, where the initial patients were treated with long-term subcutaneous heparin after placement of the stent, instead of a vitamin K antagonist. The clinical factors that contributed to the occlusions could be identified in 11 patients — i.e., disorders of the coronary artery that are associated with thrombosis (unstable angina, recent myocardial infarction, and chronic occlusion) in 5 patients, technical problems in stent placement in 3 patients, interruption of anticoagulation because of

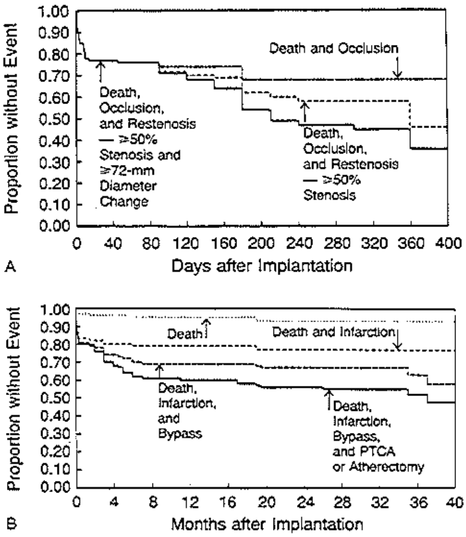


Figure 1. Angiographic and Clinical Follow-up in 95 Patients Who Received 105 Stents.

Occlusion of the stent, cardiac death, and restenosis as determined by either or both of the criteria used (≥50 percent stenosis of the vessel and a change of ≥72 mm in the minimal luminal diameter) were considered angiographic end points (Panel A). Death, myocardial infarction, bypass surgery, and PTCA or atherectomy were considered clinical end points (Panel B).

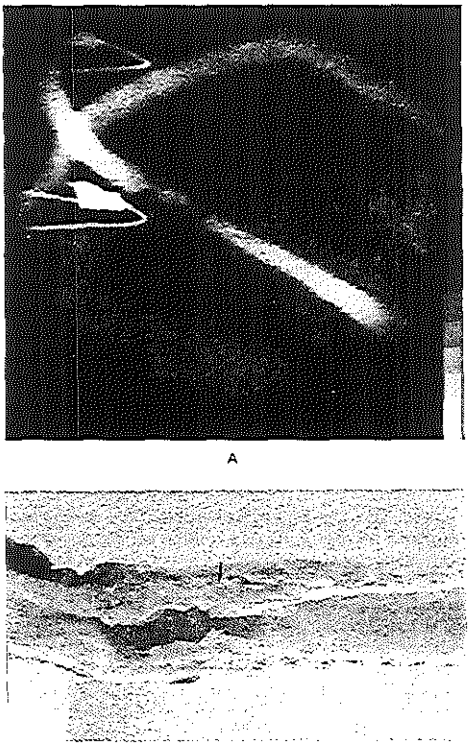
Table 3. Findings at Angiographic Follow-up.

Finding	No. of Stents (N = 117)	No. of Patients (N = 105)
	number (percent)	
Patent stent	78 (67)	70 (67)
Occluded stent	27 (23)	25 (24)
No follow-up angiography		
Death	6 (5)	4 (4)
Refusal	4 (3)	4 (4)
Inadequate study	2 (2)	2 (2)

Table 4. Findings at Quantitative Angiography.*

Variable	Before PTCA	After PTCA	After Stent Implantation	At Follow-up	
				Patent stents	All stents
Minimal luminal diameter (mm)	1.21±0.56	1.88±0.43	2.48±0.51	2.26±0.78	1.68±1.20
Stenosis (%)	61±14	37±12	21±10	30±17	48±34
	P<0.0001	P<0.0001	P<0.0001		
			P<0.002		

*Values (means ±SD) were compared by analysis of variance. If significant differences were found, two-tailed t-tests were applied to pairs of data. A probability of 0.05 was considered to indicate statistical significance.



A

B

Figure 2. Restenosis Six Months after Implantation of a Stent in a Bypass Graft.

In the follow-up angiogram (Panel A), the outline of the stent appears slighly radiopaque and hyperplasia has resulted in a complex narrowing within the vessel segment containing the stent.

In the gross specimen (Panel B) of the surgically retrieved bypass graft containing the segment shown in Panel A, the longitudinal cross section of the vessel shows the stent filaments (arrow) protruding from the wall. The striking similarity between the angiographic contours of the vessel and its actual appearance is evident.

bleeding problems in 2 patients, and hemodynamic compromise before placement of the stent in 1 patient with cardiogenic shock. In view of the early experience with stent occlusion, the investigators agreed to avoid placing stents in patients with acute coronary artery disorders and chronic occlusions or in patients with poor distal runoff (vessels with collateral flow, small vessels less than 3 mm in diameter, or vessels supplying akinetic or severely hypokinetic myocardium). In addition, four patients with six stents died before undergoing angiographic follow-up. Some of these deaths were sudden, suggesting possible stent occlusion. It was difficult to determine whether late occlusion (after 14 days) was superimposed on marked restenosis. Therefore, the rates of occlusion and restenosis may have been underestimated.

The patients in this study underwent two serial interventions, balloon dilation and then stent implantation. Quantitative coronary angiography showed that the initial effect of angioplasty in these patients was similar to that observed in previous angiographic studies,[8,11] and moreover, the result immediately after placement of the stent was markedly improved. However, the minimal luminal diameter in the entire study group at follow-up (including patients known to have occlusions) was 1.68 mm, which is comparable but not superior to values previously documented in late follow-up studies of coronary balloon angioplasty (1.69 to 1.82 mm).[8,11] The rate of restenosis in patent stents, when based on a change of ≥0.72 mm in the minimal luminal diameter, was 23 percent among segments within the stent and 8 percent among segments adjacent to the stent, for a total rate of 31 percent. When the alternative criterion, ≥50 percent stenosis of the luminal diameter, was used, the rate of restenosis was 13 percent among segments within the stent and 1 percent among segments adjacent to the stent. Two previous studies that used similar quantitative methods for late follow-up evaluation after coronary balloon angioplasty have been published. In one study,[8] the restenosis rate for angiograms obtained at four months was 25.5 percent when the criterion of a change of 0.72 mm was used, and 13.2 percent when the criterion of 50 percent stenosis was used. In the other

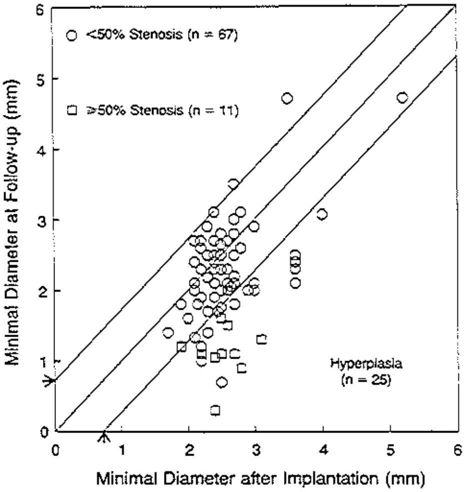


Figure 3. Change in the Minimal Luminal Diameter of 78 Patent Stents between Stent Implantation and Angiographic Follow-up.
The diameter of each segment immediately after implantation is plotted against the diameter at follow-up. The lines on each side of the identity line (diagonal) represent the limits of long-term variability of repeat measurements (a change of ≥0.72 mm [arrows]). The symbols below the right-hand line represent stents with involvement by severe hyperplasia.

study,[12] when the criterion of 50 percent stenosis was used, the restenosis rate was 37 percent for angiograms obtained four to seven months after angioplasty.

Studies in animals have confirmed that fibrointimal hyperplasia may develop in arterial segments containing stents. Within one week after stents (Wallstent) were implanted in normal porcine arteries, the prostheses became completely covered by endothelium and the vessel lumen had diffuse narrowing, varying in thickness from 60 to 125 μm.[13,14] By six months, the thickness of the neointima increased from 50 to 400 μm,[15] corresponding to a decrease of 0.1 to 0.8 mm in the vessel diameter.

Early thrombotic occlusion remains a serious clinical problem with this prosthesis despite anticoagulation. It remains to be determined whether increased experience of operators, changes in the anticoagulation regimen, or selection of patients will circumvent this limitation. New biologic coatings that may make the stent less thrombogenic are currently under investigation. Angiographically detectable narrowing, probably due to fibrointimal hyperplasia, occurs to a marked degree in patients whose stents are patent at late follow-up. Although six months is assumed to be the time frame for the development of restenosis after angioplasty, this may not be true of stent implantation. The clinical indications for the use of an endovascular prosthesis remain unclear. Controlled clinical trials are imperative to determine whether such devices can decrease the rate of restenosis among patients who have undergone PTCA and whether they can be of any benefit in particular clinical situations or subgroups of patients.

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Chapter 10

Stenting of venous bypass grafts: A new treatment modality for patients who are poor candidates for re intervention.

Stenting of venous bypass grafts: A new treatment modality for patients who are poor candidates for reintervention

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Patients first seen with medically refractory anginal symptoms after saphenous vein bypass surgery pose a difficult problem for cardiologists and cardiovascular surgeons. These patients are generally older, with more extensive, diffuse disease involving the native coronary arteries and venous bypass grafts. Repeat coronary artery bypass graft surgery (CABG) for recurrent ischemia is technically more difficult, is associated with a higher mortality and morbidity, and has inferior long-term clinical results when compared with a first bypass operation.[1-3] Conventional balloon angioplasty offers an alternative mode of revascularization in selected patients. The immediate results of this procedure have been shown to be favorable in patients with discrete lesions in venous bypass grafts but considerably less satisfactory in diffusely diseased, ulcerated, or thrombosed venous grafts.[4-6] Furthermore, it appears that the rate of restenosis is high, varying from 40% to 70% depending on the site of the lesions in the graft and the overall extent of disease in the conduit.[7-13]

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Stent implantation has been proposed as an alternative or adjunct to percutaneous transluminal coronary angioplasty (PTCA) for diseased venous bypass grafts. Results of early studies with small numbers of patients have shown that stents can be placed safely and successfully in bypass grafts with an encouraging low rate of restenosis.[14-21] Therefore we initiated this observational study to assess the acute and late results of stent implantation in stenosed coronary artery bypass grafts in symptomatic patients with diffuse, extensive native coronary artery and bypass graft disease who are poor candidates for conventional balloon angioplasty or reoperation.

METHODOLOGY

Study population (Tables I and II). Between January 1988 and March 1990, a total of 136 stents were implanted in 69 patients (12 women and 57 men) in the four participating hospitals in The Netherlands and Belgium. The study protocol was approved by the ethics committees of the individual hospitals and informed consent was obtained from all patients. A senior investigator (P. W. S.) was present for all stent implantations.

The decision to implant a stent was reached after discussion between cardiologists and surgeons (Table III). Forty-two patients were considered inoperable because of either a high risk/benefit ratio related to repeat surgery (n = 28), unfavorable coronary vessel anatomy such as diffusely diseased distal vessels (n = 4), poor left ventricular function (ejection fraction <35%) (n = 6), or concurrent noncardiac risk

Table I. Study population

No. of patients	69
No. of bypasses	74
No. of lesions	95
No. of stents	136
Ejection fraction (%)	53.9 (26-71)
Risk factors	
Hypercholesterolemia >7 mmol/L	26
Hypertension	15
Smokers	46
Diabetes mellitus	14

Table II. Specific lesion characteristics

No. of bypasses	74
Age of bypass graft (mo)	83 (1-166)
Mean diameter of graft (mm)	3.3 (1.6-7.0)
Mean minimal lumen diameter (mm)	1.4 (0-2.9)
Length of stenosis (mm)	16.5 (2-50)

factors (n = 4). Conventional coronary angioplasty was considered high risk in 39 patients because of the age of the grafts, the length of the stenosis, and/or unfavorable angiographic features (tandem lesions, eccentric lesions, lesions containing ulcers, aneurysms, calcifications, or dissections) (Figs. 1 to 4).

The mean age of the patients was 63 years (range 44 to 78), and the mean age of the implanted bypass grafts was 83 months (range 1 to 166). Forty-eight patients had at least one previous myocardial infarction, and eight had undergone more than one previous bypass procedure. Single-, double-, and triple-vessel disease was present in 3%, 23%, and 74% of the patients, respectively. Eleven patients were in New York Heart Association (NYHA) class II, 27 were in class III, and 29 were in class IV; in two patients the stents were implanted during evolving myocardial infarction. All patients had documented ECG evidence of ischemia.

The stent implantation data are presented in Table IV. A single stent was implanted in 30 patients, two stents in 24 patients, three stents in seven patients, four stents in five patients, five stents in one patient, and 6 stents in two patients. The stent was placed in single grafts in 25 patients and in sequential grafts in 44. In five patients the stent was implanted into totally occluded vessels (during an evolving myocardial infarction in two and in chronic occlusions in three.

Implanted device. In the first 26 patients we used the Medinvent Wallstent (Medinvent, Lausanne,

Table III. Reasons for preferring stent implantation (categories are not mutually exclusive)

Patients not suitable or high risk for repeat CABG	42
Reasons	
High risk/benefit profile	28
Unfavorable coronary vessel anatomy	4
Poor left ventricular function (ejection fraction <35%)	6
Concurrent noncardiac risk factors	4
Patients considered high risk for conventional PTCA	39
Reasons	
Long lesions (>15 mm)	32
Tandem lesions	23
Lesions containing ulcers	25
Dissections	17
Clot	18
Diffusely diseased bypass graft	34
Eccentric lesions	53

Table IV. Stent implantation data

No. of stents	136
Mean diameter of stent (mm)	4.3 (3.5-6.0)
Position	
Ostial	7
Shaft	127
Distal anastomosis	4
Procedure type	
Single stent-single lesion	30
Multiple stent-single lesion	90
Multiple stent-multiple lesion	16

Switzerland), and later we used the polymer-coated Medinvent Biogold stent. The stent consists of a stainless steel alloy with a self-expanding mesh design.[15] The unconstrained length varied between 15 and 27 mm, and its diameter in the fully expanded state was between 3.5 and 6.0 mm and was selected to be 0.50 mm larger than the reference diameter of the vessel.

After stent implantation the patients were monitored in the coronary care unit. The rigorous anticoagulation regimen has been described previously.[22] All patients received aspirin the day before the procedure and intravenous heparin (10,000 IU) at the beginning of the procedure. Before stent implantation 10,000 IU heparin and 500 mg dextran every 4 hours were given intravenously. Immediately after stent implantation 100,000 to 250,000 IU urokinase was infused into the coronary bypass graft via the guiding catheter. Intravenous heparin administration was continued at a minimum dosage of 24,000 IU/24 hours; the dosage was adjusted according to the activated partial thromboplastin time (80 to 120

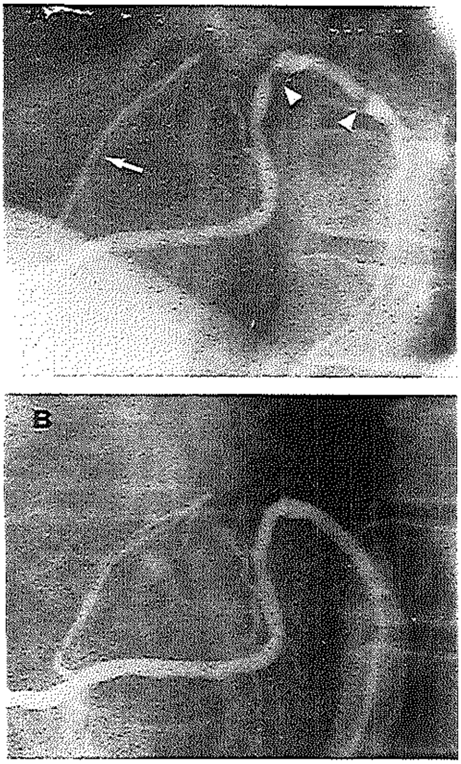

Fig. 1. Jump graft to left anterior descending artery *(arrow)*, then to first diagonal branch, and then to marginal branch. **A,** Two lesions in jump graft between diagonal and marginal branches *(arrowheads)*. **B,** Immediate result after stenting. Distal end of stent may have extended into native coronary artery.

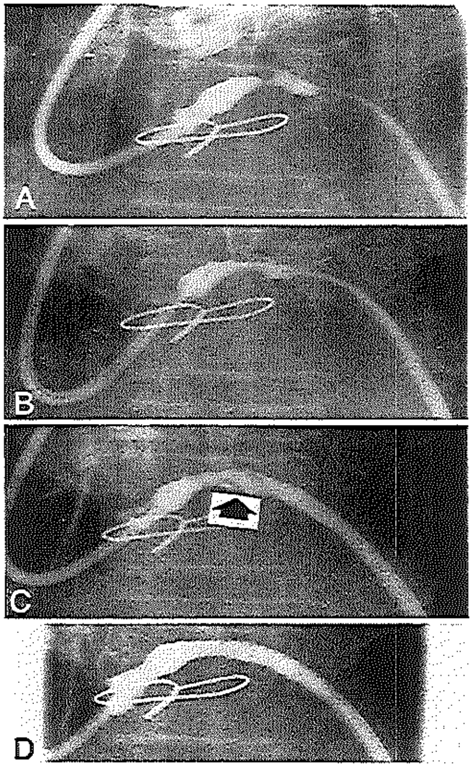

Fig. 2. *Top panel*, Two tandem lesions with aneurysm of bypass graft located proximal to first lesion. *Second panel*, Balloon angioplasty catheter in position across lesion. Balloon dilatation resulted in dissection. *Third panel*, After implantation of distal stent, intraluminal flap *(arrow)* is still evident in proximal lesion. *Lower panel*, After implantation of second stent in proximal lesion.

seconds). Oral acenocoumarol was started on the day of implantation. The heparin infusion was continued until the prothrombin time measured by thrombotest (Nycomed, Oslo, Norway) was lowered to 5% to 10% for 2 subsequent days and discontinued slowly thereafter. After stent implantation the patients were also given aspirin (300 mg/day), dipyridamole (300 to 450 mg/day), and nifedipine (30 to 60 mg/day), which in addition to the oral anticoagulant were maintained for 3 to 6 months after the procedure. The patients were followed at our outpatient clinic at 1 and 3 months and underwent repeat coronary angiography 6 months after the initial procedure or earlier if symptoms recurred.

Quantitative coronary angiography. The quantitative analysis of the stenotic coronary segments was carried out with the computer-assisted Cardiovascular Angiography Analysis System (CAAS), which has been described in detail.[23-28] The angiographic analysis was done before and after angioplasty, immedi-

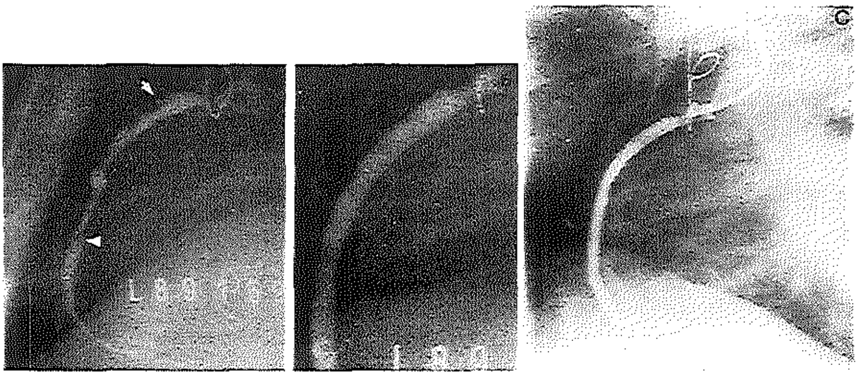

Fig. 3. A, Bypass graft to right coronary artery (7-inch image intensifier). Long segment bypass vessel is severely diseased with involvement of ostium and several complex features including ulceration in proximal aspect of graft *(arrow)* and intraluminal defect in midgraft *(arrowhead)*. **B,** After placement of three stents (5-inch image intensifier). **C,** Six-month follow-up angiogram showing late excellent result.

ately after stent implantation, and at follow-up in all patients with the average of multiple matched views with orthogonal projections wherever possible.

Restenosis. Two different sets of criteria were applied to determine the rate of restenosis. We have found a change in minimal luminal diameter of 0.72 mm or more to be a reliable indicator of angiographic progression of vessel narrowing.[23-25] This value takes into account the limitations of coronary angiographic measurements and represents two times the long-term variability for repeat measurements of a coronary obstruction by means of the CAAS. The other criterion for restenosis was an increase in the diameter of the stenosis (DS) from less than 50% after stent implantation to more than or equal to 50% at follow-up. This criterion was selected according to common clinical practice.[29]

OBSERVATIONS

Stent implantation procedure. All patients underwent successful stent implantation (DS <50% immediately after placement of the stent). In two patients the initial stent was not optimally positioned and did not cover the entire lesion, so that an additional procedure was required to implant another stent to achieve an optimal result. Although no immediate major complications occurred during the procedure, two patients required intracoronary thrombolytic therapy because of distal embolization without subsequent elevation of the creatine kinase level. Three other patients had increases in the creatine kinase level (<200 IU).

In-hospital complications. Acute thrombotic events in the stent occurred in seven patients (10%). One of these occlusions was related to cessation of anticoagulation treatment. This patient (considered inoperable) had a severe retroperitoneal hematoma 7 days after stent implantation, which necessitated discontinuation of the anticoagulation therapy. Thirty days after implantation the patient had an acute myocardial infarction, leading to cardiogenic shock and death. One patient, who had the stent implanted during an evolving myocardial infarction, had an acute thrombotic closure of the stented vessel 1 day after stent implantation. The resulting myocardial infarction was treated conservatively.

Two other patients, who had unstable angina pectoris and angiographic defects consistent with thrombi, had acute thrombotic occlusions and myocardial infarctions 7 and 12 days after stent implantation, respectively. One of these patients, who was treated conservatively, died suddenly 6 months after implantation, having remained stable with mild angina pectoris. The other patient underwent CABG after emergent reopening of the vessel during repeat PTCA. The last thrombotic occlusion occurred 1 day after implantation in one of the patients with stent implantation after recanalization of a chronically occluded graft. This patient was referred for repeat CABG.

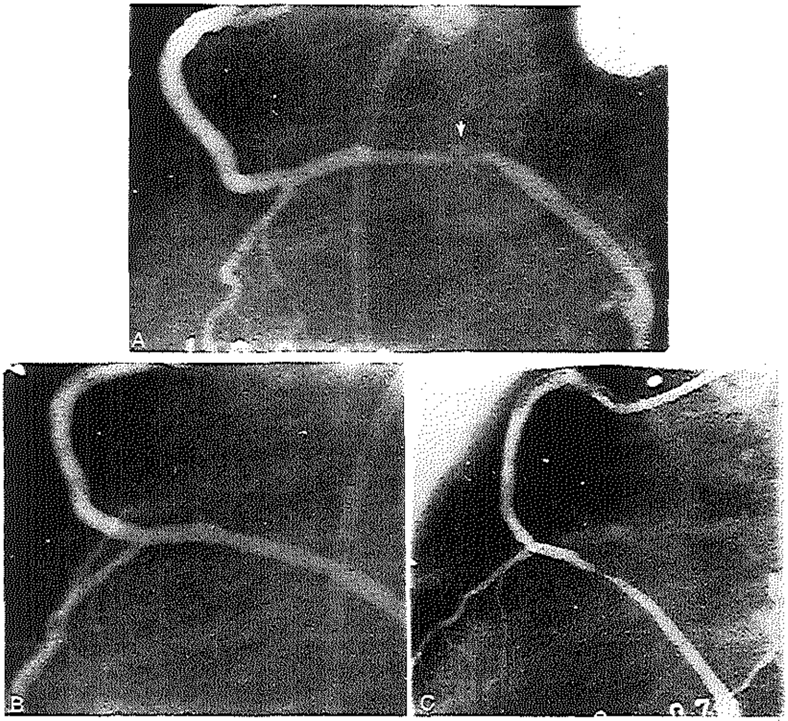

Fig. 4. **A,** Complex lesion with ulceration *(arrow)* in jump bypass graft before stenting. **B,** Immediate result after stenting. **C,** Six-month follow-up angiogram showing restenosis within stent. Outline of stent is faintly visible.

Two patients had unstable angina pectoris 3 and 10 days after stent implantation, which was related to an angiographically visible but nonocclusive thrombus. In one patient this thrombus was related to cessation of anticoagulation 6 days after the procedure as a result of Mallory-Weiss syndrome with persistent gastrointestinal bleeding.[30] Because of symptomatic recurrent ischemia, the patient was sent for surgery. The second patient, who had been treated for unstable angina pectoris, had resting angina pectoris 1 day after implantation of two stents. Angiography revealed a partially occlusive thrombus between the two stents and another stent was placed between the two previous stents. The following day resting angina pectoris recurred and the patient was treated surgically.

Bleeding complications occurred in 23 patients (33%). Two patients had fatal intracranial bleeding, one patient had a retroperitoneal hematoma, and two patients had gastric bleeding. An additional 18 patients had hematomas at puncture sites requiring blood transfusions, and seven of these patients required surgical repair of a false aneurysm. Bleeding complications were associated with a considerably longer hospital stay—18 days in comparison to 7 days when the postimplantation course was uneventful.

Discharge status. Stent implantation resulted in complete relief of angina pectoris (NYHA class I) in 45 patients (64%). Ten patients (14%) still had mild symptoms (NYHA class II) after stent implantation (NYHA class II), and five patients (7%) remained in NYHA class III. Four of these patients were considered inoperable and the fifth was referred for reoperation.

Long-term follow-up

Angiography. In 53 (90%) of the 59 patients with successful stenting and no major in-hospital complications, follow-up angiography was performed at 4.9 ± 3.4 months. Of the remaining six patients without angiographic follow-up, five refused to undergo control angiography, and in another patient the implantation film was technically inadequate for analysis, although no significant restenosis was seen at follow-up.

In the overall group the mean minimal luminal diameter increased significantly from 1.4 ± 0.82 to 2.7 ± 0.7 mm ($p < 0.001$) and the diameter stenosis decreased significantly from 58 ± 15% to 24 ± 9%. However, at late follow-up (including occlusions) there was a significant reduction in the mean minimal luminal diameter to 1.9 ± 1.1 mm ($p < 0.001$) and a significant increase in the diameter of the stenosis to 43 ± 30% ($p < 0.001$).

The incidence of restenosis depended on the definition. According to the criterion of a change in minimal luminal diameter of 0.72 mm, detectable angiographic narrowing occurred within the stent in 25 patients (47%). An increase in the diameter of the stenosis to 50% at follow-up was seen in 21 patients (40%) and immediately adjacent to the stent in four patients (7%). Stent occlusion was found in three of these patients.

Clinical follow-up. In the group of patients with angiographic restenosis (diameter stenosis >50% criterion) (n = 25), 19 patients had a recurrence of angina pectoris necessitating reintervention (repeat PTCA, n = 10; atherectomy, n = 2; repeat CABG, n = 7). Three of the patients who underwent surgery died during the postoperative period.

In the group without restenosis (n = 28), 15 patients had a recurrence of significant angina pectoris within 1 to 24 months after stent implantation. Ten patients underwent further intervention. In six a second stent was implanted in either the same or another bypass graft. Three patients underwent PTCA of one or more native vessels and one patient had repeat bypass surgery. The five remaining patients were treated medically. One patient without significant restenosis at the 6-month angiography died suddenly 500 days after stent implantation.

COMMENTS

The management of recurrent ischemia in patients who have had previous bypass surgery presents a serious and growing problem. Symptoms of myocardial ischemia recur or progress in approximately 5% of patients per year,[3,26,27] and after 5 years up to 25% of vein grafts are occluded and 25% may show stenoses greater than 70%.[28] Reoperation is technically more complicated to perform and is generally associated with a higher mortality and morbidity than a primary operation and achieves symptomatic relief in only 60% to 70% of patients as compared with the 80% to 90% success rate after primary operations. The perioperative myocardial infarction rate varies among surgical groups between 2.0% and 11.5%. The mortality rate after repeat bypass surgery ranges from 1.2% to 12.5%.[1-3] Conventional balloon angioplasty has reported angiographic success rates of 75% to 100% for bypass grafts,[7-13] with complications rates similar to angioplasty in native vessels. However, restenosis appears to occur more frequently with rates as high as 46% reported for proximal sites.[24,27]

The majority of our patients were considered high risk for surgery or repeat PTCA. Inasmuch as all of these patients had severe symptoms in spite of maximal medical therapy, it was decided to try to attempt stenting of the angina-related bypass graft, although in some cases it was clear that full relief could not be expected because of diffuse native vessel disease that prohibited additional intervention. Most of the procedures were done without surgical standby. Since the introduction of stenting of stenosed saphenous bypass grafts in our institution in 1988, a total of 69 patients have been treated successfully with this new intervention compared with only 84 patients who underwent conventional angioplasty for stenosed saphenous bypass grafts during the period 1980 to 1988. This new treatment modality has significantly expanded our therapeutic options in this particular patient group.

Our results show that stenting bypass grafts is technically feasible with excellent immediate results. Two advantages of the Wallstent for use in bypass grafts are (1) the length of the stent can be selected up to 25 mm for long lesions and (2) the self-expanding property appears to be an effective splint to tack back friable, protuberant atheromatous material and minimize embolization into the native coronary circulation. In 30 patients the stent was implanted directly without prior balloon dilatation for lesions that appeared high risk for embolization. No increase in creatine kinase levels was documented in this group of procedures.

Several important lessons emerge from this study.

First, the majority of stent occlusions occurred in patients with acute ischemic syndromes (myocardial infarction or unstable angina pectoris with angiographic evidence of thrombi). The combination of thrombi during evolving myocardial infarction and unstable angina and the implantation of intracoronary stents seems to be highly thrombogenic leading to further thrombus formation and acute occlusion of the stent. Therefore we now carefully select our patients and when the diagnostic angiogram suggests the presence of intravascular clots, the patients are treated with intravenous heparin (25,000 IU/24 hr) for 1 week before stent implantation. Although improved patient selection should decrease the occurrence of acute stent closure, it will remain an unpredictable event as evidenced by stent occlusion in one patient who was optimally anticoagulated and without the previously described risk factors. Furthermore, the timing of stent occlusion is also unpredictable (between 2 and 12 days), which complicates discharge planning decisions. Second, a meticulous anticoagulation schedule must be followed with frequent monitoring to minimize bleeding complications. As our experience evolved, bleeding and occlusion problems were encountered much less frequently and as a result, sulphinpyrazone was withdrawn because of a lack of evidence of its efficacy in the prevention of acute closure. Special care must also be given to insertion and removal of the femoral arterial sheath, since this accounted for the majority of bleeding complications. In particular, removal of the sheath >12 hours after implantation was associated with increased vascular complications. During the last 15 stent implantation procedures, no thrombolytic agents were administered leading to a considerable decrease in bleeding problems in the groin. Furthermore, oral coumadin was started the day before stent implantation leading to a quicker optimalization of the oral anticoagulation therapy, which made a shorter hospital stay possible.

The stent-related restenosis rate (47%) seems to be comparable to that in historical studies of conventional angioplasty in venous coronary bypass grafts.[4,5,30] However, these comparisons may not be valid since our population consisted of patients who were less than suitable candidates for conventional angioplasty. Earlier reports from Lausanne suggested a much lower restenosis rate (9%) in lesions implanted with the Medinvent stent in bypass grafts.[17,32] However, these differences may be the result of either differences in selection criteria, methods of angiographic assessment (quantitative vs visual estimation), or both.

Frequent reintervention in our study group was required because of restenosis or progression of disease in other lesions, a problem similar to that encountered with conventional angioplasty in bypass grafts. Three recent reports have been published on the late clinical follow-up of patients with conventional angioplasty in bypass grafts. The Thoraxcenter reported that only 41% of patients were alive and event free (myocardial infarction, repeat CABG, repeat PTCA) at a median follow-up period of 2.1 years.[4] A review of the overall Dutch experience also showed limited late beneficial results with 2-year and five-year event-free survival rates of 52% and 26%, respectively, in 454 bypass patients.[5] Webb et al.[31] have described a 71% freedom from death, infarction, and surgery at 5 years in bypass patients who underwent PTCA at their institution but did not include the 27% incidence of second angioplasty procedures also required in their patient group. It is clear that stenting and angioplasty are only short-term solutions and do not affect the underlying problems of progressive graft atherosclerosis and iatrogenically induced restenosis.

Conclusions. Patients with severe coronary artery disease and previous bypass surgery who have refractory symptoms as a result of progression of disease in the bypass graft comprise a difficult challenge to the physician. In patients who are poor surgical risks and unsuitable candidates for balloon angioplasty because of unfavorable anatomy, coronary stenting with the Wallstent can be performed successfully and offers an alternative therapy. However, stent implantation remains complicated by acute thrombotic occlusion and bleeding complications associated with the intense anticoagulation. The early benefits of stenting may be mitigated by the progression of disease in bypass grafts and iatrogenic induced restenosis. Stenting should be considered a palliative procedure in medically refractory patients with coronary bypass graft disease.

SUMMARY

During a 2-year period, 136 self-expanding Wallstents were implanted in saphenous vein bypass grafts in 69 patients with end-stage coronary artery disease. All patients had severe symptoms and the majority were poor candidates for either repeat surgery or conventional bypass coronary angioplasty because of unfavorable native anatomy, impaired left ventricular function, or a high-risk bypass lesion anatomy for coronary angioplasty. All procedures were technically successful without major complications and a need for emergency bypass surgery.

However, during the hospital stay acute thrombotic complications occurred in seven patients (10%) resulting in one death and acute myocardial infarction in five patients and necessitating emergency repeat PTCA in two patients and repeat CABG in four. Twenty-three patients had serious hemorrhagic complications directly related to the rigorous anticoagulation schedule. Two patients died of fatal cerebral bleeding. During follow-up, another five patients died accounting for a total mortality rate of 12%. At late angiographic follow-up (4.9 ± 3.4 months, n = 53), 25 patients (47%) had a restenosis (≥50% DS) within or immediately adjacent to the stent, necessitating reintervention in 19 patients (PTCA, n = 12; repeat CABG, n = 7). In the group without stent-related restenosis (n = 28), 15 patients had progression of disease in either the native or bypass vessels leading to recurrence of major anginal symptoms within 1 to 24 months. Ten of these patients required further intervention (stent, n = 6; PTCA, n = 3; repeat CABG, n = 1). Stenting in saphenous coronary bypass grafts can be performed safely with excellent immediate angiographic and clinical results. Early occlusion, late restenosis, and bleeding complications associated with the aggressive anticoagulant treatment remain significant limitations. Reintervention as a result of restenosis or progression of disease in other lesions is common. Stenting of diseased bypass grafts in symptomatic patients with end-stage coronary artery disease (who are at high risk for conventional angioplasty or surgical reintervention) may be useful as palliative therapy.

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Chapter 11

Comparative quantitative angiographic analysis of directional coronary atherectomy and balloon coronary angioplasty. American Journal of cardiology: 1991;68: 1556-1563

Comparative Quantitative Angiographic Analysis of Directional Coronary Atherectomy and Balloon Coronary Angioplasty

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An attempt to assess the "utility" of directional atherectomy was made using a new quantitative angiographic index. This index can be subdivided into an initial gain component and a restenosis component. The initial gain index is the ratio between the gain in diameter during intervention and the theoretically achievable gain (i.e., reference diameter). The restenosis index is the ratio between the decrease at follow-up and the initial gain during the procedure. The net result at long-term follow-up is characterized by the utility index, which is the ratio between the final gain in diameter at follow-up and what theoretically could have been achieved. For this purpose, 30 coronary artery lesions were selected from a consecutive series of successfully dilated primary angioplasty lesions and were matched with the initial 30 successfully treated primary atherectomy lesions. Matching by location of stenosis and reference diameter resulted in 2 comparable groups with identical preprocedural stenosis characteristics. Atherectomy resulted in an increase in minimal luminal diameter 2 times larger than angioplasty (1.53 vs 0.77 mm; p <0.0001). However, at follow-up there was a significant decrease in minimal luminal diameter and a significant increase in percent diameter stenosis in the groups with atherectomy and angioplasty (1.69 ± 0.58 vs 1.57 ± 0.58 mm, p = not significant [NS], and 37 ± 18 vs 47 ± 18%, p = NS, respectively). The decrease in minimal luminal gain was more pronounced in the group with atherectomy than in that with angioplasty (0.92 ± 0.69 vs 0.35 ± 0.51 mm; p = 0.0005). Consequently, directional atherectomy resulted in a significantly higher initial gain ratio than did balloon angioplasty (0.84 vs 0.41, p <0.00001). At follow-up, restenosis and utility ratios were comparable in both groups (0.56 vs 0.62, p = NS, and 0.29 vs 0.23, p = NS, respectively). In matched groups, directional atherectomy is a very effective device with a substantially better initial result than that with balloon angioplasty. However, it appears to be a potent stimulator of the restenosis process, because at follow-up this initial favorable result is lost, and the minimal luminal diameter is comparable to that after balloon angioplasty. Thus, the final utility of directional coronary atherectomy is not significantly different from that of conventional balloon angioplasty.

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Restenosis after conventional balloon angioplasty remains the major limitation of this procedure.[1–5] Despite extensive efforts to elucidate this phenomenon, our knowledge remains incomplete. In recent years studies have suggested that intimal hyperplasia is the major mechanism responsible for restenosis[6–9] and that lesion characteristics and regional flow dynamics influence this proliferative process.[10] Because improved operator experience and angioplasty techniques have not caused a reduction in restenosis rates, interventional cardiologists have designed new devices aimed at debulking instead of dilating atherosclerotic plaque. Directional atherectomy is a new technique with the potential advantage of creating smooth luminal surface. However, early experience with atherectomy indicates that restenosis rates are comparable with those after conventional balloon angioplasty, although a randomized study has not been initiated.[11–13] Recently it has been demonstrated that the immediate results of atherectomy are superior to those achieved by balloon angioplasty[14]; whether this initial advantage can be maintained during follow-up and may ultimately result in a reduction of the restenosis rate needs to be

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assessed. Therefore, the present study was performed to determine whether this initial favorable result obtained with atherectomy affects the incidence of restenosis.

METHODS

Patient group: From September 1989 through January 1991, 66 patients underwent 74 atherectomy procedures. For the purpose of this study, the initial 30 consecutive patients (23 men and 7 women, mean age ± standard deviation 60.2 ± 10.1) who underwent an angiographically successful procedure (postprocedural diameter stenosis <50%, with tissue retrieval) of a primary lesion in a native coronary artery were selected. At the time of atherectomy, 16 patients were in New York Heart Association functional class IV, 7 in III and 7 in II. Coronary angiography showed 1-vessel disease in 25 patients, 2-vessel disease in 4 and 3-vessel disease in 1. The site of obstruction was located in the left anterior descending coronary artery in 18 patients, the right coronary artery in 7 and the circumflex artery in 5.

Atherectomy procedure: After administration of local anesthesia, an 11Fr sheath was inserted in the femoral artery. All patients received 250 mg of acetylsalicylic acid and 10,000 U of heparin intravenously. Intracoronary injection of isosorbide dinitrate was performed to optimally vasodilate the vessel. After initial angiograms in multiple views were obtained, a special 11Fr guiding catheter was placed into the ostium of the coronary artery. Under fluoroscopy, the guidewire was advanced in the distal part of the artery. Then, the atherectomy device was directed over the guidewire and positioned across the stenosis. The support balloon was then inflated up to 0.5 atm, the cutter was retracted and balloon inflation pressure was increased to 2 to 3 atm. The driving motor was activated, and the rotating cutter was slowly advanced to cut and collect the protruding atherosclerotic lesion in the collecting chamber located at the tip of the catheter. After every pass, the balloon was deflated and either removed or repositioned. On average, 6.7 ± 2.9 passes in multiple directions were performed across a stenosis. Atherectomy was considered successful when the residual stenosis was <50% after tissue retrieval. After atherectomy, the arterial and venous sheaths were usually left in place for 6 hours. Patients were monitored for 24 hours, and electrocardiograms and cardiac enzyme levels were obtained twice daily. Nifedipine was administered every 2 hours for 24 hours after the procedure, and the patients were administered aspirin for 1 year.

Follow-up evaluation: After successful atherectomy or angioplasty (i.e., <50% postprocedural diameter stenosis on visual inspection), patients were examined at the outpatient clinic. The follow-up coronary angiogram was obtained within 2 weeks after an exercise test. Angiography was performed earlier if symptoms occurred within 6 months.

Quantitative coronary angiography: Quantitative analysis of the coronary segments was performed with the computer-based Coronary Angiography Analysis System (CAAS), previously described in detail.[4,5,15,16] In essence, boundaries of a selected coronary artery segment, were detected automatically from optically magnified and video-digitized regions of interest (512 × 512 pixels) of a cineframe. The absolute diameter of the stenosis in millimeters was determined using the guiding catheter as a scaling device. Each individual catheter was measured with a micrometer and used as a scaling device. Correction for pincushion distortion was performed. The computer-estimation of the original dimension of the artery at the site of the obstruction was used to define the interpolated reference diameter. The percentage diameter and area stenosis, as well as the cross-sectional area (mm^2), were then calculated.

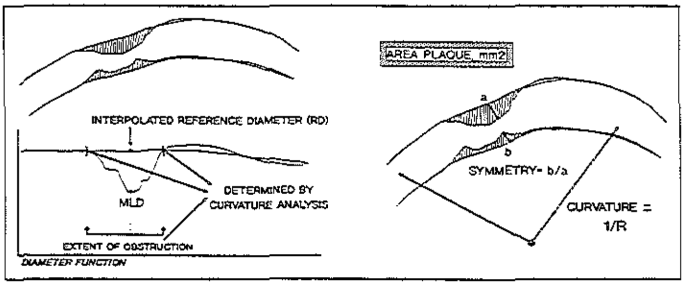

FIGURE 1. Graphic illustration of stenosis parameters obtained by quantitative coronary analysis. *Left*, y axis represents reference diameter, and vessel length is represented along x axis. Reference diameter and lesion length are determined by diameter at bounderies of lesion that are defined by curvature analysis. *Right*, curvature analysis is described. Curvature is defined by rate of change of angle through which tangent of curve turns, and which for a circle is equal to reciprocal of radius (R). MLD = minimal luminal diameter.

The length of the lesion (mm) was determined from the diameter function on the basis of curvature analysis (Figure 1). Symmetry was defined as the coefficient of the left-hand distance between the reconstructed interpolated reference diameter and actual vessel contours, and the right-hand distance between the reconstructed and actual contours at the site of the obstruction. Symmetry index ranged from 0 (totally eccentric stenosis) to 1 (symmetric). The degree of coronary bend was assessed by the curvature value at the obstruction site. This parameter was computed as the average value of all individual curvature values along the centerline of the coronary segment, with curvature defined as the first derivative of the tangent as it moves along the centerline, which for a circle is equal to the reciprocal of the radius. The area between the actual and reconstructed contours at the obstruction site was defined as the area plaque (expressed in mm^2). To standardize the method of analysis of the interventional and follow-up angiograms, the following measures were taken[16]: First, the x-ray system was exactly positioned, as was noted at the time of the intervention. Second, all study frames to be analyzed were selected at end-diastole to minimize foreshortening. Third, the investigator-determined beginning and end point of a segment of a major coronary artery were identified according to the definitions of the American Heart Association.[17] Finally, Polaroid photographs were taken of the video image with the detected contours superimposed to ensure that the analysis was performed on the same coronary segments in consecutive angiograms. Patients with balloon angioplasty were enrolled in ongoing restenosis trials, and therefore, according to the protocol, systematically received intracoronary nitroglycerin before and after angioplasty, and during follow-up catheterization, whereas patients with atherectomy were less frequently administered intracoronary nitroglycerin at recatheterization.

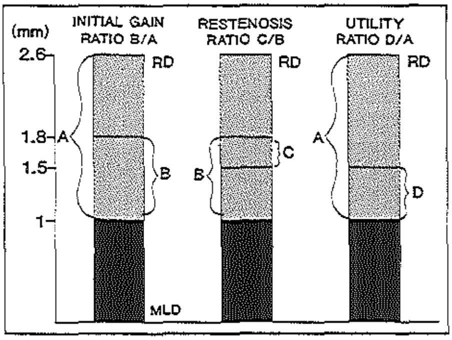

FIGURE 2. Graphic illustration of principle of initial gain, restenosis and utility indexes. Initial gain index is represented by the ratio B/A, restenosis index by C/B, and utility index by D/A. A = maximal achievable increase in minimal luminal diameter (MLD); B = gain in MLD during procedure; C = reduction during follow-up; D = long-term result; RD = reference diameter.

Restenosis: Two different criteria were used to define the restenosis rate. We have found a change in minimal lumen diameter $\geq$0.72 mm to be a reliable indicator of angiographic progression of vessel narrowing.[4,15,16] This value takes into account the limitations of coronary angiographic measurements and represents the long-term variability for repeat measurements of a coronary stenosis using CAAS. The second criterion for restenosis chosen was an increase in the diameter stenosis from <50% after intervention to $\geq$50% at follow-up. This criterion was selected because clinical practice continues to assess lesion severity by percent stenosis.

Assessment of initial gain, restenosis and utility ratio: To compare the relative efficacy of various interventional techniques, it is critical to relate the procedural outcome and changes during follow-up to the maximal achievable result. Therefore we propose the use of the aforementioned ratios in the evaluation of intracoronary interventions. Briefly, quantitative angiographic changes after intracoronary intervention may be divided in 3 stages (Figure 2). The first or "operational stage," is characterized by the interaction of the operational device with the lesion. In becoming operational, the diameter of the device may expand (directional atherectomy, balloon, stent) or maintain its original dimensions (laser, transluminal extraction catheter, rotational ablation). During this stage, the maximal effect of the device is achieved and determines to what extent the minimal luminal diameter may be increased. The initial gain index represents the ratio between the achieved luminal and maximal achievable luminal improvements (reference diameter minus minimal lumen diameter (MLD) before intervention), and is described by the following equation: initial gain index: change in MLD at intervention/reference diameter − MLD before intervention. The initial gain index ranges from 0 (no effect) to 1 (no residual stenosis). The second stage or "restenosis stage" begins during follow-up when biological processes determine the extent of intimal hyperplasia ultimately leading to a loss of luminal gain.

The restenosis index represents the ratio of decrease in luminal diameter improvement during follow-up and the achieved changes induced by intracoronary intervention, and is described by the following equation: restenosis index: MLD after intervention − MLD follow-up/change in MLD at intervention. The restenosis index ranges from 0 (initial benefit intact) to 1 (initial benefit completely lost).

The utility index represents the ratio of the net gain in lumen improvement at follow-up and the maximal achievable luminal improvement, and is described by the following equation: utility index: change in MLD at intervention − change in MLD at follow-up/reference diameter − MLD before intervention. The utility index ranges from 0 (no utility) to 1 (perfect result).

Matching process: The coronary artery tree was subdivided in 15 segments according to American Heart Association guidelines,[18] and the lesions were individually matched according to stenosis location and reference diameter. The principles of matching are threefold: the angiographic dimensions of matched lesions are assumed to be "identical," the observed difference between the 2 "identical" lesions must be within the range of CAAS reproducibility of 0.1 mm (1 standard deviation),[5] and finally, the reference diameters of the matched vessels are selected within a range of ± 0.3 mm (3 standard deviations; 99% confidence limits). To assess the immediate result of atherectomy and balloon angioplasty, 30 coronary artery lesions were selected by an independent technician (EMvS) from a consecutive series of successfully dilated balloon angioplasty lesions while complying with the selection criteria of matching. At the time of selection, the investigators were unaware of the 6-month angiographic outcome of these lesions. Matching was considered adequate if the mean difference of the reference diameter between the groups equaled 0 with standard deviation <0.3 mm.[19] Currently, the Thoraxcenter angiographic database contains quantitatively assessed stenosis data for 2,300 patients treated with either angioplasty (n = 1847), intracoronary stenting (n = 406), or directional or rotational atherectomy (n = 120).

Statistical analysis: All values are expressed as mean ± 1 standard deviation. Comparisons of the severity of minimal luminal diameter, area plaque, diameter stenosis, curvature value symmetry index and length between the groups were performed using analysis of variance and the unpaired Student's *t* test. Differences were considered statistically significant at $p < 0.05$.

TABLE I Matched Preprocedural Stenosis Characteristics of 30 Patients with Successful Coronary Atherectomy Compared with Successful Balloon Angioplasty

	Before Atherectomy	Before Angioplasty
Reference diameter (mm)	3.03 ± 0.57	3.07 ± 0.55
Minimal luminal diameter (mm)	1.08 ± 0.37	1.15 ± 0.36
Diameter stenosis (%)	64 ± 10	63 ± 8
Area plaque (mm²)	9.5 ± 6.4	8.4 ± 3.6
Curvature value	15.9 ± 7.0	22.2 ± 13.1*
Symmetry index	0.6 ± 0.2	0.5 ± 0.3
Length	6.8 ± 2.7	6.5 ± 2.6

*p <0.02.

TABLE II Quantitative Comparison of the Immediate and Long-Term Results of Atherectomy and Balloon Angioplasty (n = 30)

	Atherectomy	Angioplasty	Unpaired *t* Test
Reference diameter (mm)			
Pre	3.03 ± 0.57	3.07 ± 0.55	NS
Post	3.24 ± 0.32	3.09 ± 0.56	NS
Follow-up	2.81 ± 0.57	3.04 ± 0.65	NS
Minimal luminal diameter (mm)			
Pre	1.08 ± 0.37	1.15 ± 0.36	NS
Post	2.61 ± 0.33	1.92 ± 0.31	0.0000
Follow-up	1.69 ± 0.58	1.57 ± 0.58	NS
Difference in minimal luminal diameter (mm)			
Post to pre	1.53 ± 0.47	0.77 ± 0.30	0.0000
Post to follow-up	0.92 ± 0.69	0.35 ± 0.51	0.0005
Diameter stenosis (%)			
Pre	64 ± 10	63 ± 8	NS
Post	19 ± 9	37 ± 10	0.0000
Follow-up	37 ± 18	47 ± 18	0.04
Difference in diameter stenosis (%)			
Pre–post	45 ± 12	26 ± 12	0.0000
Follow-up–post	18 ± 17	10 ± 17	NS

NS = not significant; Post = after intervention; Pre = before intervention.

RESULTS

Preprocedural stenosis characteristics of the matched patients are listed in Table I. Matching for stenosis location and reference diameter resulted in groups of patient with comparable severity of lesions. Matching was considered adequate because the reference diameter was equal in both groups (3.03 ± 0.57 vs 3.07 ± 0.55 mm; p = not significant), whereas the mean difference for this parameter between the groups was 0.0 mm (standard deviation 0.2 mm). Preprocedural minimal luminal diameter in the groups with atherectomy and angioplasty were 1.08 ± 0.37 and 1.15 ± 0.36 mm, respectively. The other stenosis parameters (diameter stenosis, area plaque, symmetry index and length) did not differ significantly, with the sole exception of curvature value, which was lower in the group with atherectomy than in that with angioplasty (15.9 ± 7.0 vs 22.2 ± 13.1; $p < 0.02$).

The immediate efficacy of atherectomy and angioplasty as assessed by quantitative angiography is shown in Table II and Figure 3. As expected, both atherectomy and balloon angioplasty significantly improved minimal luminal diameter (1.08 ± 0.37 to 2.61 ± 0.33 mm [$p < 0.0001$], and 1.15 ± 0.36 to 1.92 ± 0.31 mm [$p < 0.001$], respectively), but the increase in minimal luminal diameter was superior in the group with atherectomy than in that with angioplasty (1.53 vs 0.77 mm; $p < 0.0001$). Accordingly, the initial gain ratio of atherectomy was also superior when compared with that of angioplasty (0.84 ± 0.36 vs 0.41 ± 0.18; $p < 0.00001$). Thus, percent diameter stenosis was reduced from 64 ± 10 to 19 ± 9% ($p < 0.0001$) in the group with atherec-

TABLE III Quantitative Assessment of Initial Gain, Restenosis and Utility Ratios After Atherectomy and Balloon Angioplasty (n = 30)

	Atherectomy	Angioplasty	Unpaired *t* Test
Initial gain ratio	0.84 ± 0.36	0.41 ± 0.18	0.0000
Restenosis ratio	0.56 ± 0.55	0.62 ± 1.10	NS
Utility ratio	0.29 ± 0.33	0.23 ± 0.28	NS

NS = not significant.

tomy, and from 63 ± 8 to 37 ± 10% ($p < 0.001$) in the that with angioplasty.

At follow-up, all patients with atherectomy and angioplasty included in this study underwent 6-month control catheterization. Angiographic follow-up in the groups with atherectomy and angioplasty were 95 and 92%, respectively. Angiographic analysis at follow-up (Table II and Figure 4) showed a decrease in minimal luminal diameter in both groups (2.61 ± 0.33 to 1.69 ± 0.58 mm with atherectomy, 1.92 ± 0.31 to 1.57 ± 0.58 mm with angioplasty). Thus, the loss in minimal luminal diameter was more pronounced in the group with atherectomy than in that with angioplasty (0.92 ± 0.69 vs 0.35 ± 0.51 mm; $p < 0.0005$). Accordingly, percent diameter stenosis increased from 19 ± 9 to 37 ± 18% in the group with atherectomy, and from 37 ± 10 to 47 ± 18% in that with angioplasty. The concomitant restenosis and utility ratios are listed in Table III. Percent restenosis (detectable hyperplasia by quantitative coronary analysis) according to the 0.72 mm decrease in minimal luminal diameter (2 times the standard deviation of the long-term variability of the mini-

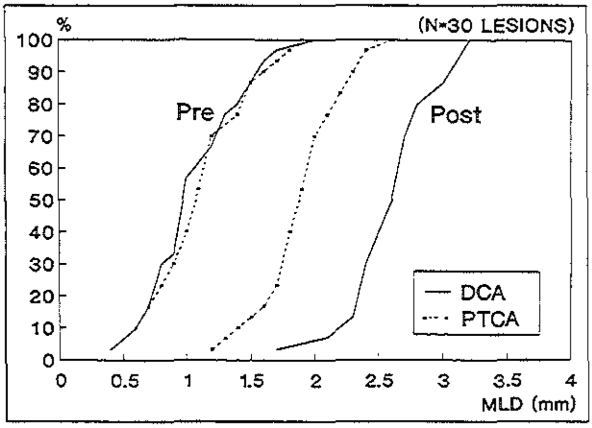

FIGURE 3. Cumulative frequency of immediate results of directional atherectomy (DCA) and balloon angioplasty (PTCA) in 30 matched lesions. Directional atherectomy resulted in an increase in minimal luminal diameter (MLD) from 1.08 to 2.61 mm, whereas angioplasty induced an increase from 1.15 to 1.92 mm. Post = after intervention; Pre = before intervention.

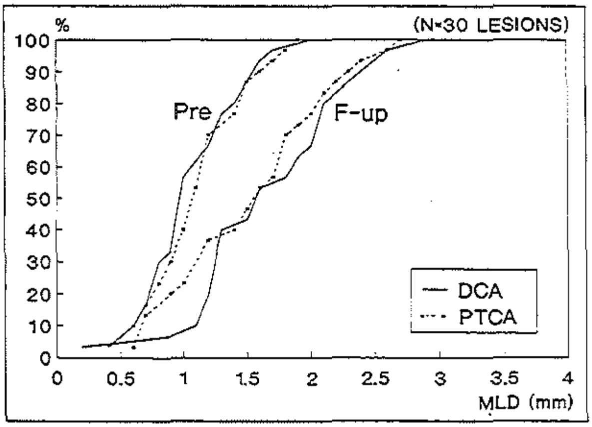

FIGURE 4. Cumulative frequency of long-term results of directional atherectomy and angioplasty in this matched population. At 6-month follow-up (F-up), initial favorable result of atherectomy is lost compared with that of balloon angioplasty. Other abbreviations as in Figure 3.

mal luminal diameter measurements using CAAS criterion) was 60% in the group with atherectomy versus 36% in that with angioplasty. When restenosis is defined by an increase in diameter stenosis ≥50% at follow-up, the restenosis percentages are 20 vs 16% (atherectomy vs angioplasty).

DISCUSSION

Coronary angioplasty is now an accepted form of treatment for patients with coronary artery disease. In the past, exponential growth in angioplasty has partly been the result of an increase patients returning with restenosis. Despite extensive efforts to improve catheter equipment we are still unable to effectively reduce the rate of restenosis. Because no fundamental design changes in balloon or balloon-derived catheter techniques are emerging, debulking techniques, such as directional atherectomy, have been introduced to improve the angioplastic process and to presumably reduce the rate of restenosis. The potential advantages of debulking atheromatous tissue over remodeling plaque with balloon angioplasty include: minimizing smooth muscle cell injury by wall stress; eliminating smooth muscle cells and thereby reducing their proliferative potential; improving regional blood flow and rheology by inducing fewer fissures or dissections; reducing radial stretch forces, as applied with a dilating balloon; and creating larger increases in minimal luminal diameter. Indeed, recent studies have reported a larger increment in luminal improvement after atherectomy than after conventional balloon angioplasty,[14] whereas other investigators observed a low incidence of postprocedural dissections.[11,12,14]

Study design: Whether atherectomy is superior to balloon angioplasty can only be assessed by a randomized study. This type of study would take several years, during which continuing refinements and improvements of catheter systems would take place, rendering the comparison unreliable and open to criticism. Therefore, we proposed a matching technique based on stenosis location and reference diameter to compare the results of various intracoronary interventional techniques. At present, this technique may be the best surrogate for a randomized trial when one tries to compare the short- and long-term results of atherectomy with those of conventional angioplasty. Using our matching program we selected comparable stenotic lesions with respect to baseline characteristics (minimal luminal diameter, diameter stenosis, length, area plaque and symmetry index) as assessed by quantitative angiography. This study group reflects the baseline stenosis characteristics in patients treated with atherectomy[20] or balloon angioplasty.[4,21]

Immediate results: This study confirms previous reports of improved luminal gain after atherectomy compared with that after conventional angioplasty.[14] Atherectomy resulted in a twofold increase in minimal luminal diameter (1.09 ± 0.37 to 2.61 ± 0.33 mm) compared with that with angioplasty (1.15 ± 0.36 to 1.92 ± 0.31 mm). Accordingly, percent diameter stenosis decreased more dramatically after atherectomy than after angioplasty. This improvement in luminal gain with atherectomy may be due to 3 mechanisms. First, introduction of the bulky device itself causes a lumen enlargement due to the "Dotter" effect. Second, the subsequent inflation of the support balloon may lead to further enlargement by stretching of the vessel wall. Finally, excision of the plaque determines the final result.

Restenosis: Recurrence of a stenosis after intracoronary intervention may be assessed by clinical symptoms, stress testing or coronary angiography. Because symptoms and functional achievement at exercise testing have low predictive values in regard to restenosis, diagnosis of restenosis should be based on reproducible quantitative angiographic measurements using a computer-assisted technique with either automated edge detection or videodensitometry. Furthermore, the definition of restenosis is a matter of ongoing debate. It has been shown by our investigative group,[4,22] as well as by others,[3] that the determination of the severity of stenosis using percent diameter stenosis does not reflect changes after angioplasty, because the adjacent part of the dilated vessel may also be involved in the restenosis process, or the reference diameter may be simultaneously reduced. Therefore, we selected minimal luminal diameter as a parameter for the morphologic changes after atherectomy or angioplasty. Minimal luminal diameter at follow-up was 1.69 mm for the group with atherectomy compared with 1.57 mm for that with balloon angioplasty (p = not significant). These findings are similar to previously documented late follow-up studies of coronary balloon angioplasty (1.69 to 1.82 mm)[4] and stenting (1.68 mm).[23] Using the ≥50% diameter stenosis criterion, the rates of restenosis after atherectomy and angioplasty were 20 and 16%, respectively. Previous studies on restenosis after primary coronary atherectomy reported an incidence of restenosis of 20%[11,12] using the ≥50% criterion. Thus, during follow-up, the initial greater gain in luminal diameter after atherectomy compared with that after balloon angioplasty is totally lost. At follow-up, the reduction in minimal luminal diameter was 0.92 mm after atherectomy compared with 0.35 mm after angioplasty (p = 0.0005). Although minimal luminal diameter changed more dramatically in the group with atherectomy than in that with angioplasty, both had equal restenosis (0.56 vs 0.62; p = not significant) and utility (0.29 vs 0.23; p = not significant) ratios, indicating that the relative changes are equal for both interventional techniques.

Animal and atherectomy studies[11-13,20] have demonstrated that fibrointimal hyperplasia may develop in coronary arteries previously treated by balloon angioplasty or atherectomy. Pathologic findings have raised a theory that deeper vascular injury is associated with a greater intimal proliferation. Injury beyond the subintimal level has been shown to be associated with more extensive intimal proliferation.[24] These data are supported by Webster et al[25] who found a greater smooth muscle proliferation after high-inflation pressure with the same balloon size when compared with that after low pressure. Furthermore, an initial follow-up study after atherectomy indicates that this process may be accelerated when deep vessel wall components such as media and adventitia are removed.[13] Additionally, atherectomy may lead to profound disrupture of the vessel wall architecture.[26] Finally, the introduction of the bulkier atherectomy device may potentially lead to a greater amount of vessel wall stretching compared with that with the smaller balloon catheter system. All these influences may account for the greater cellular proliferation of the lesion treated by atherectomy.

Study limitations: There are several limitations to this study. First, it is an uncontrolled, observational study limited to a subset of patients with successful coronary atherectomy or balloon angioplasty. This consecutive series of patients were studied by investigators unaware of the late angiographic results. Although matching for angiographic variables is a promising technique to assess the efficacy of intracoronary interventions, patient- and procedure-related variables are not included in the analysis. Second, lesion complexity was not incorporated in the analysis. This is usually defined qualitatively[27]; however, an objective and quantitative description of stenosis morphology has recently been introduced.[28] Further improvement in quantitative analysis may assess lesion morphology in a continuous scale fashion rather than assigning lesions to discrete categories. This type of analysis should be incorporated in future trials studying the efficacy of various interventional techniques. Third, this study is based on early experiences with atherectomy. Careful patient selection, future design changes and improved operator experience may further improve the immediate and long-term results. Thus, controlled clinical trials are needed in the future to determine the immediate angiographic results and long-term efficacy of these interventions, as well as the benefit, if any, to particular subgroups of patients. These studies should also address the presumed time frame for restenosis after any particular intervention.

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Chapter 12

Restenosis Index: a new concept for the evaluation of the restenosis process
(in preparation)

Comparative index for assessing the results of interventional devices in coronary angioplasty.

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Introduction

The limitations of balloon coronary angioplasty and the clinical, scientific and commercial pressures to provide more effective means of non-surgical revascularisation have led to the development and evaluation of an increasing number of new devices (1-11). In the past 3-4 years these devices have been introduced into clinical practice in the hope that they will be shown to improve the outcome of conventional balloon angioplasty, by achieving a better immediate result, reducing the acute complication rate, and perhaps most importantly by reducing the impact of restenosis on the long term outcome of patients undergoing the procedure. They have been designed to incorporate one of two principles pertinent to the long term success: debulcking to produce a sufficiently good result to more than compensate for the normal restenosis process, or alternatively by dilating the the stenosis in such a way that that the stimulus for restenosis will be minimised (12).

It has not always been possible to define clearly the utility of these devices and to place them accurately in the spectrum of angioplasty armamentarium. In the past our attempts at accurate evaluation were hampered by a lack of understanding of our measurement systems for assessing "restenosis". The realisation that the restenosis process has a Gaussian population distribution, has exposed many of our past efforts as being inaccurate and even misleading and has explained why some the early expectations have not been realised (13-14).

The most effective way to assess these devices would be to conduct well controlled clinical trials designed to compare each individual device, not only with balloon angioplasty but also to each new device as it becomes available. This is clearly not practical in the early evaluation stage and experience has shown that these trials take many years to organise and perform, by which time the device and related techniques have been further refined so that the results produced may no longer be regarded as revenant. In the absence of such accurate data a new index is proposed which will allow the comparison of the devices by the use of quantitative angiographic measurements. This index addresses the problem of the relationship between what is achieved at angioplasty and the restenosis process.

Rationale for indices

Resent studies have shown that the "restenosis process" is influenced by the angioplasty procedure and in particular there is increasing evidence that the magnitude of improvement in the minimal luminal diameter at the time of angioplasty is the factor that most influences the degree of restenosis. This so called "paradox of restenosis" means that by focusing on the ability to improve the immediate result the more important long term outcome may be compromised by a more aggressive restenosis response (15). This has particularly important implications in the assessment of new devices which have been promoted on their ability to improve the immediate results of the procedure; whether this benefit is maintained in the long term remains in some doubt, with the suggestion a more aggressive restenosis responsive with some of the devices (16-17).

It is unclear whether some of the new devices used clinically exert any potential additional benefit over balloon angioplasty, and clearly if we are to adopt more expensive and complicated techniques then it is important to have direct comparative information. In the absence of controlled clinical trials this comparative information is unlikely to become available in the near future. It is therefore useful to have some method of making comparisons and in particular to relate the outcome to the "gold standard of conventional balloon angioplasty."

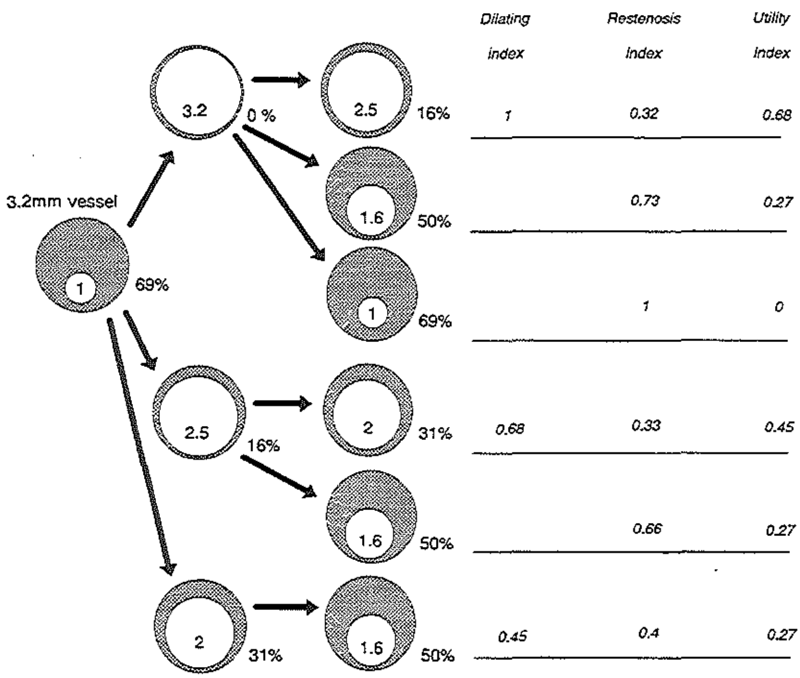


Fig 1

Shown are a number of possible outcomes of a vessel with a 69 % diameter stenosis (minimal luminal diameter = 1mm, vessel size = 3.2 mm) The outcomes from the initial dilatation are:

no residual stenosis, dilating index = 1

16% diameter stenosis, dilating Indices = 0.68

31% diameter stenosis, dilating index = 0.45

A selection of possible outcomes at follow-up ranging from 16% to 69%. The relevant restenosis indices and utility indices are shown. It can be seen that whatever the initial result a final residual stenosis of 50% gives a utility index of 0.27, whereas a return to a 69% stenosis gives a utility of 0.

Current Restenosis Criteria

In the past clinicians have tended to assess and document the acute results of angioplasty inaccurately with what can now be regarded as rather crude methodology. The most widely accepted definition of success has been a > 50% diameter stenosis with many reports offering no more discriminating documentation than this (degree of improvement, final post-PTCA stenosis). The long term result has in general been more carefully documented, but in general the concept of "restenosis" being an all or nothing process has favoured a "cut-off" point (> 50% diameter stenosis) so that often the distribution of change within the population is not documented. Detailed analysis ,using quantitative angiography, has shown that any potential benefit of some of the new devices is likely to be achieved at the time of the procedure and may be at the expense of stimulating the restenosis process (12).

It therefore seems logical to split the dilating effect and the restenosis process, so that the mechanism by which the device exerts its beneficial effect is fully realised. This can not be done without taking into account the fact that the severity of the initial stenosis and the acute gain influence the long term outcome and therefore the utility of the device.

Dilating Index:

This index is based on the assumption that if all the plaque is removed then the result is optimal. It is important to have some assessment of the how effective a particular device is at improving the luminal diameter of the artery. This is described by the following equation:

$$\text{Dilating index} = \frac{\text{Change MLD at PTCA}}{\text{(Vessel size - MLD pre PTCA)}}$$

Index range: 0 (no effect) -> 1 (perfect).

Restenosis Index:

This is designed to reflect the "restenosis process" and essentially assess the loss of the initial gain at long term follow-up. It is the ratio of the change in minimal luminal diameter from immediately post angioplasty to follow-up and the change in diameter at angioplasty. It is expressed by the following equation:

$$\text{Restenosis index} = \frac{\text{(MLD post PTCA - Change MLD at Follow-up)}}{\text{Change MLD at PTCA.}}$$

Index range: 0 (perfect) -> >1 (poor)

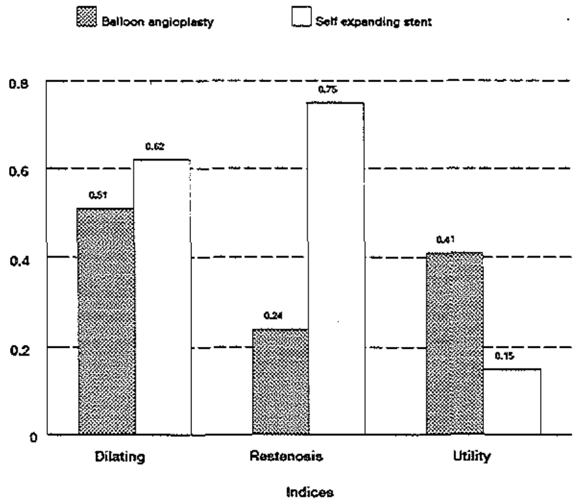
Utility Index:

The overall utility index is designed to give an assessment of the residual stenosis at follow-up in relation to the original stenosis prior to the procedure. It addresses the question of, "How effective is the device at improving the lumen of the vessel and maintaining this improvement at long term follow-up." It is expressed by the following equation:

$$\text{Utility Iindex} = \frac{(\text{Change MLD at PTCA - Change MLD at follow-up})}{(\text{vessel size - MLD pre PTCA})}$$

Index range: 0 (no utility) -> 1 (perfect)

[MLD = minimal luminal diameter, PTCA = coronary angioplasty.]



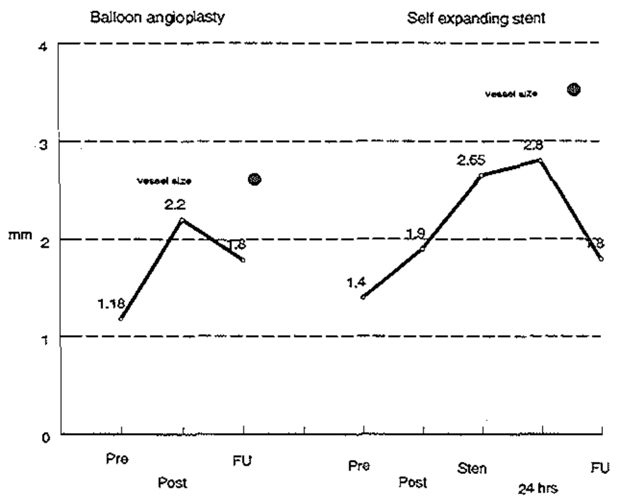


Fig 3

Shown are the changes in the minimal luminal diameters during and post angioplasty for the populations shown in Figure 2. The filled circles represent the mean reference diameter for the respective populations.

CONCLUSION

The uses of the three indices seem to reflect the changes occurring in the vessel lumen.

In the absence of more direct comparisons the proposed indices provide a means of comparing the short and long term benefits of new interventional techniques that are being introduced to improve on the results of conventional balloon angioplasty

Comparisons in this way should help to reduce the misinformation that seems to accompany the introduction of the new devices, and will allow the resources to be directed towards those areas which, at an early stage are shown to be the ones with the most promise.

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Summary

Percutaneous transluminal coronary angioplasty has made an important impact on the treatment of coronary artery disease. It has become an alternative to coronary bypass grafting as a revascularisation procedure for coronary artery disease, and for the past decade, each year there has been a greater degree of acceptance within the cardiological community as to the indications for the procedure and the benefits of it.

Our understanding of the acute complications has also improved, but progress in the field of restenosis, which can be regarded as the principal limitation of the procedure, has been disappointing. A reduction in the restenosis rate by as little as 25% would have enormous implications for the treatment of coronary artery disease. It would lead to an expansion in indications resulting in angioplasty becoming the main revascularisation procedure, while greater reductions in the restenosis rate would have important implications in the area of secondary prevention resulting in an even greater demand for the procedure.

The thesis deals entirely with the assessment of coronary anatomy by quantitative angiography, and while developing the technique for the assessment of restenosis it also points out the limitations of the technique. By not paying sufficient attention to fundamentals of clinical measurement, such as variability, precision and predictability, we have followed the same path that many other systems for assessing disease severity have trodden before us. The lessons learned in dealing with this relatively new clinical problem should be applied to other areas of clinical medicine.

The fundamentals of the restenosis process are not addressed. Rather the methods of assessing restenosis developed and some solutions to the uncertainties that have surrounded the topic in confusion have been put forward. The limitation in using a categorical approach for the assessment of restenosis is understood and developed is an alternate methodology for the assessment of the process. This methodology can be applied equally well to the new era of angioplasty as it has been to conventional balloon angioplasty. One of the major problems recognised at the beginning of these studies was the failure of the cardiological community to adopt a standardised methodology for the comparison of acute angioplasty results and the restenosis process. In this respect some progress has been made, and although there has been much controversy over the past five years, there is now broad agreement on both sides of the Atlantic that the arguments developed in this thesis are relevant to any assessment of the post-angioplasty patient, and are mandatory for any study critically addressing the problem of restenosis.

Current arguments regarding the best methods for assessing and comparing the newer generation of interventional devices are unresolved. It is expected that the Dilating, restenosis and Utility Indices with time will become as accepted as the other concepts derived from the these studies. These together with a more standard approach for reporting the early results so that potential problems have to be addressed rather than hidden will benefit our patients and the development of the field.

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