Angiographic Risk Factors of Luminal Narrowing After Coronary Balloon Angioplasty Using Balloon Measurements to Reflect Stretch and Elastic Recoil at the Dilatation Site

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Because many ongoing clinical restenosis prevention trials are using quantitative angiography to assess whether a drug is capable of reducing the amount of intimal hyperplasia, quantitative angiographic risk factors for angiographic luminal narrowing after balloon angioplasty were determined, including stretch and elastic recoil at the dilatation site. Quantitative analysis was performed on 666 lesions in 575 patients during angioplasty and at 6-month follow-up. Stretch was defined as balloon diameter minus minimal luminal diameter (MLD) before angioplasty/reference diameter, and recoil as balloon diameter minus MLD after angioplasty/reference diameter. Multivariate analysis was used to yield independent risk factors for luminal narrowing at follow-up. Predictors of absolute change in MLD were (1) relative gain at angioplasty (gain in millimeters normalized for reference diameter) and (2) lesion length. To allow risk stratification, logistic regression analysis was applied using the decrease in MLD as a binary outcome variable. A decrease in MLD at follow-up of ≥0.72 mm was considered significant. Variables retained in the model were: relative gain >0.3 mm (rate ratio 2.9), relative gain 0.2 to 0.3 (rate ratio 2.1), stenosis length ≥6.8 (rate ratio 1.7), and thrombus after angioplasty (rate ratio 2.6). Although stretch was significantly related to luminal narrowing at univariate analysis, it was not retained in the multivariate models.

A large gain in lumen diameter at angioplasty, dilation of long lesions, and angiographically determined thrombus after angioplasty were found to be accompanied by more severe luminal narrowing at follow-up.

(Am J Cardiol 1992;69:584–591)

Luminal narrowing after coronary balloon angioplasty still hampers the long-term vessel patency in a substantial percentage of patients. Several investigators have sought predictors of this untoward event.[1] A multitude of patient-, procedural- and lesion-related variables have been found to predict long-term outcome of an angioplasty procedure, but because these findings are based on different restenosis criteria and varying angiographic follow-up rates accurate comparison is difficult.[2]

Conventionally, restenosis is determined by follow-up angiography. Computer-assisted automated edge detection techniques enhance objectivity and reproducibility, and reduce the high inter- and intraobserver variability inherent to visual interpretation of the coronary cineangiogram.[3] Because many ongoing clinical restenosis prevention trials are using quantitative angiography to assess whether a pharmacologic agent is capable of reducing the amount of intimal hyperplasia (the underlying cause of restenosis), it is important to determine quantitative angiographic risk factors for angiographic luminal narrowing after balloon angioplasty. At the moment it is unknown which angiographic parameters are associated with an increased risk for luminal narrowing. Both over- and underdilating are reported to be associated with an increased risk for restenosis. Overdilation may trigger an excessive hyperplastic response, because of its relation with dissection and deep arterial injury with increased platelet activation.[4,5] Stretching of the vessel itself may also be an important stimulus for the fibroproliferative vessel reaction by being a determinant of medial smooth muscle injury[6] and by changing the phenotype of the medial smooth muscle cells from contractile to synthetic.[7] Elastic recoil after balloon deflation has (at least theoretically)[8,9] been linked to luminal narrowing at follow-up. Underdilation may leave a significant residual stenosis with a possible increased turbulence, platelet activation and restenosis.[10]

In this study, quantitative lesion measurements before and after angioplasty, and at follow up were obtained and correlated with loss in minimal luminal diameter (MLD) at follow-up. To examine the effect of degree of arterial stretching and elastic recoil on luminal narrowing at follow-up, balloon diameters were measured. Stretch was defined as the difference in mean balloon diameter and MLD before angioplasty,[6] and elastic recoil as the difference between mean

balloon diameter and MLD after angioplasty.[9] Both stretch and recoil were normalized for reference diameter to correct for the influence of vessel size and are therefore dimensionless.

METHODS

The study population consisted of 697 patients who were originally enrolled in 6 European centers for the CARPORT trial[11] (see Appendix). In this randomized, double-blind, placebo-controlled trial, a novel thromboxane A_2 receptor antagonist (GR32191) was investigated for its ability to prevent restenosis after primary coronary angioplasty. Follow-up of these patients was performed on a prospective basis, and all patients agreed to undergo repeat angiography at 6 months. Neither angiographic nor clinical benefit of the compound could be demonstrated,[11] so the placebo and active treatment groups could be pooled for the present study. All patients with both stable and unstable angina, and angiographically proven native coronary artery disease who were scheduled for primary angioplasty were considered for participation in the trial. Specific exclusion criteria are listed in Table I. A screening log was maintained at 2 centers to assess the relative frequencies of these exclusion criteria.

Unsuccessful angioplasty procedures occurred in 48 patients (6.9%). Successful angioplasty was defined as <50% residual stenosis by visual inspection of the angiogram after angioplasty, and no occurrence of in-hospital complications (death, acute myocardial infarction, repeat angioplasty, aortocoronary bypass grafting or recurrence of symptoms).

Five hundred seventy-five (88.6%) of the 649 patients with a successful angioplasty had a follow-up angiogram suitable for quantitative angiography. Reasons for not completing the study were late death (n = 2), contraindication for repeat catheterization (n = 18), and refusal (n = 46). Eight follow-up angiograms were unsuitable for quantitative analysis.

Angioplasty procedure and follow-up angiography: Coronary angioplasty was performed with a steerable, movable guidewire system by the femoral route. Standard available balloon catheters were used. Choice of balloon type and brand, as well as inflation duration and pressure, were left to the discretion of the angioplasty operator. At the beginning of the angioplasty procedure, all patients received 10,000 IU of intravenous heparin for the first 2 hours; afterward, they received 5,000 IU/hour for as long as the procedure continued. All patients received 10 mg of nifedipine every 2 hours for the first 12 hours after angioplasty. Thereafter they received 20 mg of slow-release nifedipine tablets 3 times during the second day after angioplasty.

Four coronary angiograms were obtained in each patient, 1 just before angioplasty, 1 during maximal inflation of the largest balloon used, 1 immediately after the procedure, and 1 at follow-up. Angiograms were recorded in such a way that they were suited for quantitative analysis by the Cardiovascular Angiography Analysis System (CAAS). All necessary details of the procedure were recorded, and drawings of the segments to be analyzed were made. For calibration purposes, catheter tips

Reason	No. (%)
Insufficient lead-in time*	235 (18)
Use of platelet inhibiting drugs or nonsteroid antiinflammatory drugs in 7 days preceding study	352 (27)
Refusal to participate or undergo 6-month recatheterization	364 (28)
Currently receiving oral anticoagulant drugs	119 (9)
Angioplasty for restenosis	105 (8)
Acute myocardial infarction in 2 weeks preceding angioplasty	52 (4)
Bypass graft dilatation	39 (3)
History of obstructive airway disease	26 (2)
History of peptic disease or upper GI bleeding	10 (1)
Previous participation in the trial	2 (0.2)
Other severe disease	6 (0.5)
Participation in other trial	6 (0.4)
History of intolerance to aspirin	1 (0.1)
Aged <21 years	1 (0.1)
Pregnant or likely to become pregnant during study	0 (0)
Total	1,318 (100)

*Urgent referrals outside working hours.
GI = gastrointestinal.

TABLE I Reasons for Exclusion of 1,318 of 1,614 Screened Patients in Two of Six Participating Centers

were cut off for later measurement with a microcaliper. To standardize the method of data acquisition and to ensure exact reproducibility of the angiographic studies, measures were obtained as described previously.[2,12] All angiograms were processed and analyzed at a central core laboratory (see Appendix).

The follow-up coronary angiogram was performed after 6 months. If symptoms recurred within 6 months, coronary angiography was performed earlier. If no definite restenosis was present and follow-up time was <4 months, the patient was asked to undergo another coronary arteriogram at 6 months.

Quantitative angiography (Figure 1): All cineangiograms were analyzed using the CAAS that has been described and validated previously.[13,14] A computer-derived reconstruction of the original arterial dimension at the site of obstruction (assuming there is no disease present) is used to define the interpolated reference diameter. The length of the obstruction is determined from the diameter function on the basis of curvature analysis and is expressed in millimeters. In addition, this technique allows for the calculation of an eccentricity index[9] of the lesion. The index ranges from 0 (severely eccentric) to 1 (perfectly symmetric). Because the algorithm can not measure total occlusions, a value of 0 mm was substituted for the MLD. In these cases, the reference diameter after angioplasty was substituted for that before. The mean change in MLD from angiography after angioplasty to follow-up and from before to after angioplasty was derived from matched angiographic projections. Balloon artery ratio was defined as the ratio of the mean balloon diameter measured in a nonforeshortened projection and the reference diameter of the dilated segment. Three parameters were calculated that reflect the changes occurring during angioplasty (Figure 2). These were (1) stretch (mean balloon diameter minus MLD before angioplasty/reference diameter), (2) elastic recoil (mean balloon diameter minus MLD after angioplasty/reference diameter) and (3) relative

TABLE II Baseline Characteristics	
Number of patients	575
Age (years)	56 ± 9
Men/women	464/111 (81%)/(19%)
Time to follow-up angiography (days)	172 ± 41
Number of narrowings dilated	666
Left anterior descending artery	321 (48%)
Left circumflex artery	154 (23%)
Right coronary artery	191 (29%)
Prior myocardial infarction	221 (38%)
Prior coronary bypass surgery	15 (3%)
Prior angioplasty at other site	10 (2%)

TABLE III Quantitative Angiographic Data of 666 Lesions	
	Mean ± SD (range)
Minimal luminal diameter (mm)	
Before angioplasty	1.04 ± 0.37 (0.00–2.83)
After angioplasty	1.76 ± 0.38 (0.85–3.04)
Follow-up	1.48 ± 0.59 (0–3.15)
Diameter stenosis (%)	
Before angioplasty	60 ± 13 (33–100)
After angioplasty	34 ± 9 (6–65)
Follow-up	45 ± 19 (4–100)
Difference in minimal luminal diameter	
Before and after angioplasty (mm)	0.75 ± 0.40
After angioplasty–follow-up (mm)	0.28 ± 0.52
Relative gain at angioplasty*	0.28 ± 0.16
Difference in % diameter stenosis	
Before and after angioplasty (%)	26 ± 14
After angioplasty–follow-up (%)	11 ± 19
*See Figure 2.	

gain achieved by angioplasty (MLD after minus MLD before angioplasty/reference diameter). All 3 parameters were normalized for interpolated reference diameter to correct for vessel size and are therefore dimensionless. Intracoronary thrombus was defined as an intraluminal filling defect visible in all projections or dye staining at the site of a total occlusion (interobserver concordance rate for the assessment of intracoronary thrombus in the core laboratory 89%).

Significant luminal narrowing: To predict significant luminal narrowing after angioplasty, we chose a cutoff point above which significant deterioration in MLD is likely. We have found a change in MLD of ≥0.72 mm to be a reliable indicator of angiographic progression of vessel narrowing.[2,14] This value takes into account the limitations of coronary angiographic measurements and represents twice the long-term variability for repeat measurements of a coronary obstruction using CAAS.[14] This variability reflects the long-term random variation in lesion measurements from coronary angiograms obtained at different catheterization sessions using CAAS. The use of 1 standard deviation would include 68.3% of the measurement variability, whereas the use of 2 stan-

dard deviations (2 × 0.36 = 0.72 mm) includes 95.5%. Therefore, a difference in MLD of more than twice the long-term measurement variability can be considered indicative of significant luminal narrowing. To compare the criterion of change in MLD with a more conventional criterion of restenosis, analyses were also performed with the ≥50% diameter stenosis criterion.

Data analysis: Data were analyzed using the BMDP statistical software package (University of California, Berkeley, California). In a univariate analysis (unpaired Student's t test), those continuous quantitative angiographic variables that were related to a significant loss in MLD were selected. These variables together with elastic recoil and balloon artery ratio (known from the literature to be related to restenosis) were entered in a stepwise multiple linear regression analysis to identify variables, with an independent contribution to the prediction of absolute decrease in MLD as a continuous variable (see Appendix).

To allow risk stratification, logistic regression analysis using indicator variables was subsequently applied, with the decrease in MLD (using a decrease of ≥0.72 mm as the cutoff value), and the 50% diameter stenosis
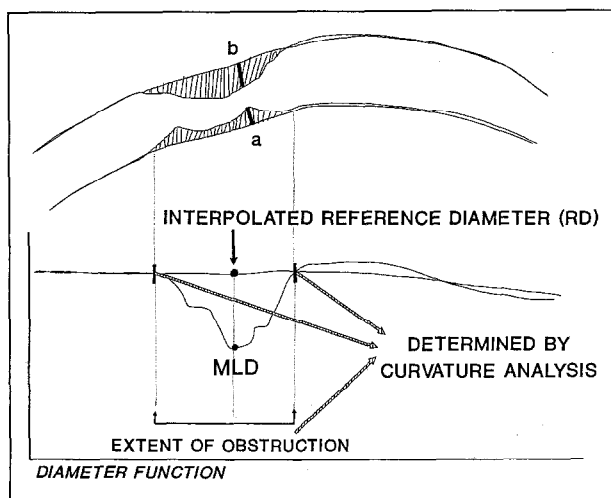

FIGURE 1. Graphic representation of quantitative angiographic measurements. *Upper panel* represents stenosed arterial segments. *Lower panel* is diameter function curve. Length of analyzed segment is depicted on *x axis*, and vessel diameter on *y axis*. Extent of obstruction = lesion length. Lesion length is determined with curvature analysis of descending and ascending limb of diameter function curve at site of minimal luminal diameter (MLD). Eccentricity is determined at site of MLD and calculated as a/b.
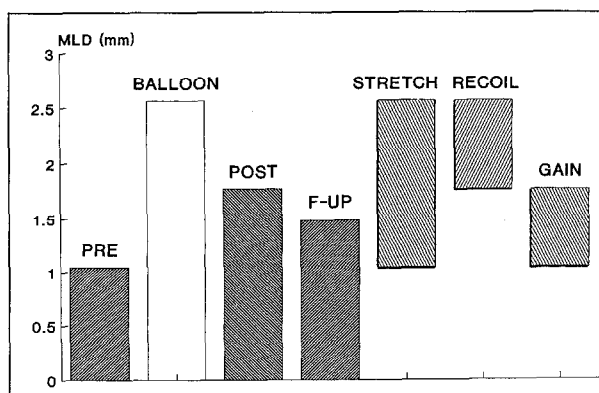

FIGURE 2. Graphic representation of terms used. Mean absolute values of variables are shown. Stretch, recoil and gain were normalized for vessel size (reference diameter) to correct for vessel size. BALLOON = balloon mean diameter; F-UP = follow-up MLD; MLD = minimal luminal diameter; POST = MLD after angioplasty; PRE = MLD before angioplasty.

criterion as binary outcome variables, because the logistic regression coefficients are easily related to adjusted-rate ratios for the different variables. Continuous variables were therefore grouped into 3 equally sized subgroups (tertiles). Three subgroups were selected to enable assessment of trends in the incidence of a ≥0.72 mm decrease and because more subgroups would weaken the strength of associations. The incidence of a ≥0.72 mm decrease was determined in each subgroup. If a trend for a higher incidence was present in each consecutive subgroup, then the one with the lowest incidence was chosen as the reference group. If no trend for an increasing incidence of a ≥0.72 mm decrease was present in each consecutive subgroup, the one with the highest incidence was compared with the 2 others combined (reference group).

Distortion of the relation between different determinants of a ≥0.72 mm decrease in MLD and the incidence of a decrease ≥0.72 mm (confounding) caused by unequal distributions of these determinants among the tertiles was eliminated by multivariate logistic regression analysis. Description of the multivariate logistic regression model and of the methodology to obtain adjusted-rate ratios and 95% confidence intervals (CIs) is given in the Appendix.

RESULTS

Baseline characteristics of the 575 patients with quantitative angiographic follow-up are summarized in Table II.

Overall quantitative angiographic findings before and after angioplasty, and at follow up are presented in Table III. Reference diameter was not different before and after angioplasty, and at follow up (2.64 ± 0.56, 2.71 ± 0.54 and 2.71 ± 0.56 mm, respectively), suggesting an accurate control of vasomotion during the 3 angiographic studies.

The incidence of significant luminal narrowing (≥ 0.72 mm) was 17.7% (117 of 666 lesions). The incidence of restenosis according to the 50% diameter stenosis criterion was 33% (220 of 666 lesions).

Univariate analysis: With univariate analysis (Table IV), the following quantitative angiographic variables were associated with a ≥0.72 decrease in MLD: MLD before and after angioplasty, increase in MLD obtained by angioplasty, length of obstruction, and stretch. Thirty-six lesions were totally occluded before angioplasty, and therefore, stenosis length and eccentricity coefficient could not be measured. For comparison with the traditional restenosis criterion of >50% diameter stenosis at follow-up, values were also broken down according to this criterion. The apparent difference in MLD after angioplasty for the 2 criteria, and the absence of a difference in relative gain in the ≤ and >50% diameter stenosis at follow-up groups are explained later.

More stretching was accompanied by more recoil. The amount of recoil in the tertile with the highest amount of stretch (≥0.65) was 0.42 compared with 0.25 in the other 2 tertiles combined (stretch <0.65) (p <0.0001; unpaired t test).

Multiple linear regression analysis: The variables significantly related to a ≥0.72 mm decrease in MLD

TABLE IV Univariate Analysis of Quantitative Parameters and Decrease in Minimal Luminal Diameter of ≥0.72 mm

	Decrease <0.72 mm (mean ± 1 SD)	Decrease ≥0.72 mm (mean ± 1 SD)	p Value	≤50% DS at F-up (mean ± 1 SD)	>50% DS at F-up (mean ± 1 SD)	p Value
MLD before PTCA (mm)*	1.06 ± 0.36 (n = 549)	0.94 ± 0.41 (n = 117)	0.0025	1.06 ± 0.40 (n = 446)	0.94 ± 0.37 (n = 220)	<0.001
Reference diameter before PTCA (mm)	2.64 ± 0.56 (n = 549)	2.65 ± 0.56 (n = 117)	NS	2.64 ± 0.54 (n = 446)	2.65 ± 0.60 (n = 220)	NS
Length of obstruction before PTCA (mm)*	6.08 ± 2.24 (n = 524)	6.94 ± 2.39 (n = 106)	<0.001	6.04 ± 2.20 (n = 424)	6.59 ± 2.41 (n = 206)	<0.01
Eccentricity	0.38 ± 0.25 (n = 524)	0.36 ± 0.23 (n = 106)	NS	0.37 ± 0.24 (n = 424)	0.38 ± 0.25 (n = 206)	NS
MLD after PTCA (mm)*	1.74 ± 0.36 (n = 549)	1.89 ± 0.37 (n = 117)	<0.0001	1.81 ± 0.36 (n = 446)	1.69 ± 0.37 (n = 220)	<0.001
MLD F-up (mm)	1.64 ± 0.44 (n = 549)	0.72 ± 0.59 (n = 117)	<0.0001	1.75 ± 0.40 (n = 446)	0.92 ± 0.52 (n = 220)	<0.0001
Balloon-artery ratio*	0.98 ± 0.19 (n = 490)	1.02 ± 0.24 (n = 105)	0.11	0.99 ± 0.18 (n = 396)	0.99 ± 0.23 (n = 199)	NS
Stretch*	0.58 ± 0.21 (n = 490)	0.66 ± 0.26 (n = 105)	<0.001	0.58 ± 0.21 (n = 396)	0.63 ± 0.25 (n = 199)	<0.05
Recoil*	0.31 ± 0.15 (n = 490)	0.30 ± 0.15 (n = 105)	0.29	0.30 ± 0.15 (n = 396)	0.33 ± 0.16 (n = 199)	<0.05
Gain at angioplasty*	0.27 ± 0.15 (n = 549)	0.37 ± 0.18 (n = 117)	<0.0001	0.29 ± 0.16 (n = 446)	0.29 ± 0.18 (n = 220)	NS
Decrease in MLD at F-up (mm)	0.10 ± 0.30 (n = 549)	1.17 ± 0.42 (n = 117)	<0.0001	0.07 ± 0.32 (n = 446)	0.77 ± 0.58 (n = 220)	<0.0001

*Subsequently entered in multiple linear regression analysis. DS = diameter stenosis; F-up = follow-up; Gain = (MLD after – before PTCA)/reference diameter; MLD = minimal luminal diameter; NS = not significant; PTCA = percutaneous transluminal coronary angioplasty; Recoil = (balloon diameter – MLD before PTCA)/reference diameter; Stretch = (balloon diameter – MLD before PTCA)/reference diameter.

in the univariate analysis, as well as elastic recoil and balloon artery ratio, were entered in the multiple linear regression analysis. Only relative gain in MLD at angioplasty, and the length of the stenosis were retained in the final model. The amount of stretch induced on the vessel wall, although significantly higher in the group of lesions with a ≥0.72 mm decrease in MLD with univariate analysis, was not retained in the stepwise multiple linear regression model.

Logistic regression analysis: The variables retained in the multiple linear regression analysis, and 6 variables known from the literature to be related to restenosis were entered in the logistic regression model. The latter variables were vessel dilated,[15] total occlusion before angioplasty,[16] angiographically determined thrombus before and after angioplasty, elastic recoil and balloon artery ratio. Thrombi before and after angioplasty were included, because it has been reported that thrombotic lesions are longer in length and that total occlusions frequently have a thrombotic component. Furthermore it is conceivable that thrombotic lesions have a larger relative gain and low elastic recoil. Angiographically, a thrombus was observed in 32 of 666 lesions before angioplasty (5%) and in 16 (1.6%) after. Type of trial medication (placebo or active treatment) was forced into the model to rule out any effect on the analysis results. Because dilation of totally occluded coronary arteries is associated with a higher restenosis rate,[16] and it could be argued that in these lesions in general a higher gain at angioplasty will be achieved, this determinant was also forced into the model to account for any confounding effect. Totally occluded lesions did not have length measurements; therefore, the indicator variable for lesion length was set to 0 in these cases.

A relative gain at angioplasty of ≥0.3 had an adjusted-rate ratio (RR) for developing a decrease in MLD ≥0.72 mm of 2.9. This means that the risk for developing a decrease of ≥0.72 mm with at least this relative gain is 2.9 times as high as it is for lesions with a relative gain <0.2. The 95% CIs were 1.9 to 4.5. Other variates retained were relative gain between 0.2 and 0.3 (RR 2.1, 95% CI 1.3 to 3.3), lesion length ≥6.8 mm (RR 1.7, 95% CI 1.2 to 2.3) and thrombus after angioplasty (RR 2.6, 95% CI 1.1 to 6.2). Total occlusion before angioplasty and use of active trial medication had no significant independent predictive contribution to a significant decrease in MLD (RR 1.5, 95% CI 0.8 to 3.0, and RR 1.1, 95% CI 0.7 to 1.5, respectively). Stretch, balloon artery ratio, elastic recoil, type of vessel, and thrombus before angioplasty were not retained in the final logistic regression model.

To assure that total occlusions did not unduly influence the results, analysis was repeated excluding these lesions. Adjusted-rate ratios were similar to those in the original analysis (relative gain 0.2 to 0.3: RR 2.2, 95% CI 1.4 to 3.4; relative gain >0.3: RR 3.2, 95% CI 2.0 to 5.1; lesion length ≥6.8 mm: RR 1.8, 95% CI 1.2 to 2.6).

The logistic regression analysis was also performed with the >50% diameter stenosis criterion as dependent variable. Type of trial medication was again forced into

the model. A lesion length of ≥6.8 mm (RR 1.3, 95% CI 1.1 to 1.4) and thrombus after angioplasty (RR 1.8, 95% CI 1.0 to 3.1) were retained in the final model. The use of GR32191 as trial medication had an adjusted-rate ratio of 0.98 (95% CI 0.9 to 1.1).

DISCUSSION

Luminal narrowing after coronary angioplasty is a complex process that is only partially understood. Histologic studies of coronary arteries after dilation obtained by either autopsy or atherectomy have provided direct and indirect evidence that strongly supports the concept of intimal hyperplasia or proliferation of smooth muscle cells of medial or intimal origin as the underlying cause of luminal narrowing after angioplasty.[5,17]

The 1 factor most strongly associated with luminal narrowing in this study was the relative gain in MLD achieved by angioplasty. This probably best reflects the combination of deep arterial injury and reversible stretch imposed on the diseased vessel wall. Deep arterial injury and smooth muscle cell stretch are known stimuli for smooth muscle cell proliferation. It is now believed that after balloon injury, denudation of endothelial cells is followed by platelet adhesion and aggregation with the release of growth factors (notably platelet-derived growth factor), and vaso- and platelet-active substances. Extensive damage to the endothelial lining of the vessel, which is always present after balloon dilatation, may upset the balance between the inhibiting effect of endothelial-derived heparin sulphates on medial smooth muscle cell growth, and the mitogenic and chemotactic effect of platelet-derived growth factor and of other growth factors on these cells.[18] Not only platelet exposure to the vascular layers, but also direct injury to the smooth muscle cells is reported to begin the proliferative response.[19] So, as suggested by Liu et al,[20] a major factor that determines the amount of intimal hyperplasia after balloon angioplasty seems to be the extent of permanent mechanical injury inflicted upon the vessel wall. Animal experiments with an atherosclerotic rabbit model have shown that the combination of balloon oversizing and long inflations caused most damage to the vessel wall and was associated with the greatest degree of intimal hyperplasia at follow-up.[21] Similarly Schwartz et al[22] described an aggressive proliferative response in a porcine model as a result of severe stent oversizing. This effect, which they attributed to penetration of the internal elastic membrane by the stent wires and subsequent deep arterial injury, was much less pronounced when the stent was matched more closely to the vessel diameter. This was recently also demonstrated in a clinical stent study.[23] Implantation of an oversized stent was combined with a more aggressive hyperplastic reaction than when the stent was more closely matched to the receiving artery.

Dilation of totally occluded coronary arteries is known to be associated with a higher restenosis rate.[16] However, total occlusions forced in the logistic regression model did not have a significant independent contribution to the prediction of a decrease in MLD of ≥0.72 mm, probably due to an unequal distribution of

thrombus after angioplasty over totally occluded and patent arteries; 6 of 36 (16.7%) total occlusions before angioplasty had a thrombus after versus 10 of 630 (1.5%) patent arteries. It could be argued that in total occlusions in general, a higher gain at angioplasty will be achieved, and that this may be the explanation for the relation found between gain and restenosis. In our population, 36 total occlusions were successfully dilated with a restenosis rate at follow-up of 33.3% (12 of 36; ≥0.72 mm criterion). However, if total occlusions before angioplasty are left out of the analysis, a high relative gain and lesion length were still associated with a significant adjusted risk for a decrease of ≥0.72 mm.

The fact that angiographically determined thrombus at the dilation site before angioplasty was not found to be a risk factor for a significant decrease in MLD tends to confirm our earlier report that showed no difference in significant luminal narrowing for patients with unstable angina.[24] Angiographically demonstrable intracoronary thrombus after angioplasty is the angiographic proof that massive platelet aggregation, thrombin activation and fibrin formation have occurred with the subsequent release of vasoactive substances[25] and growth factors involved in the fibroproliferative restenosis process. Furthermore, a recent postmortem study showed that part of early (<1 month) restenosis lesions consisted of mural thrombus.[5]

Longer lesions were found to be associated with a higher relative risk for restenosis at follow-up. In these lesions, more smooth muscle is possibly exposed to injury and platelet adhesion, which enhances the risk of restenosis. Several studies have indeed shown that long lesions and vessel areas containing thick atherosclerotic plaques are related to an increased incidence of dissections, and thus more extensive vessel wall injury.[26,27]

Several experimental studies have suggested that dilation of the vessel wall is a stimulus for smooth muscle cell proliferation and later intimal hyperplasia,[19,21] either by stretch or direct injury to smooth muscle cells. In the present study, univariate analysis (Table IV) showed that a significantly higher amount of stretch was induced on the vessel wall in the group with a ≥0.72 mm decrease in MLD. These findings correlate with the observations by Fischell et al[6] that showed a relation between the degree of arterial stretching and the severity of smooth muscle injury as determined by reduction of vasoconstrictor responsiveness and by histopathological examination, and, as emphasized previously, more smooth muscle injury has been shown to enhance intimal hyperplasia in a more controlled animal model.[21] However, after elimination of the unequal distribution of stretch over the various determinants of a significant decrease in MLD by multivariate analysis, stretch was not found to be an independent predictor of luminal narrowing.

Elastic recoil, as measured within minutes after the last dilatation,[9] was not found to be a determinant of restenosis. This finding is at variance with another report[8] that suggests that recoil may be a factor in luminal narrowing observed at follow-up. It may be that recoil is not an instantaneous phenomenon, but rather exerts its effect over a longer period of time, and thus could not be picked up by the angiogram after angioplasty that was obtained within minutes after the final balloon deflation.

Study limitations: To allow risk stratification for decrease in MLD with the use of multivariate analysis techniques, a cutoff point had to be chosen that accurately describes those lesions that underwent a significant deterioration at follow-up. The rationale for the 0.72 mm criterion as a marker for significant luminal narrowing is outlined previously. This criterion is not meant to be a restenosis criterion in this study, because that also implies some sort of functional measure of lesion severity at follow-up. The frequently used definition of 50% diameter stenosis at follow-up is historically based on the physiologic concept of coronary flow reserve introduced by Gould et al[28] in 1974 and is used because it represents the approximate value in animals with normal coronary arteries at which blunting of the hyperemic response occurs. Although this value may be of some relevance in determining a significant stenosis in human atherosclerotic vessels, it tells us nothing about the dynamic behavior of the restenosis process. If the 50% diameter stenosis at follow-up criterion is used, lesions with a suboptimal angioplasty result will preferentially be selected (i.e., have to undergo a small decrease in MLD to be termed restenosed). This is reflected by the lower MLD after angioplasty in the >50% diameter stenosis group (Table IV) compared with that of the >50% group. The mean percent diameter stenosis after angioplasty in the group with a relative gain <0.2 was 40%; in the group with a relative gain between 0.2 and 0.3 this was 34%, and in that with a gain ≥0.3 this was 28%. This means that lesions with a small relative gain generally tend to have a poorer result after angioplasty and are close to the 50% diameter stenosis cutoff point. Furthermore, because the long-term variability of diameter stenosis measurements using CAAS is 6.5%,[14] a significant number of lesions will be defined as restenosed, while in fact no change has occurred. The mean percent diameter stenosis after angioplasty was 31% for those lesions fulfilling the ≥0.72 mm criterion, and 37% for the >50% diameter stenosis criterion. Therefore, both criteria describe different populations at follow-up, and if one wants to examine risk factors for change in luminal diameter, the 50% diameter stenosis criterion is inappropriate.

The definition of stretch was essentially the same as that used by Fischell et al[6] in a series of in vitro experiments with isolated, perfused, nondiseased, whole vessel segments of rabbit aortas and dog carotid arteries. In our population of diseased arterial segments, stretch was calculated as the difference between mean balloon diameter and MLD before angioplasty divided by the relaxed reference diameter, because this reflects the maximal focal stretch induced on the vessel wall. This presumes that no compression or extrusion of the atherosclerotic plaque occurred during angioplasty.

The immediate luminal narrowing after balloon deflation that we attributed to elastic recoil could also be caused by spasm or nonocclusive mural thrombus for-

mation. It has been shown that the administration of intracoronary nitrates after angioplasty abolishes possible spasm.[19,29] Furthermore, the mean reference diameter after angioplasty was not different from that before. Our angiogram after angioplasty was obtained within minutes after the final balloon deflation, and although we cannot rule out the possibility of mural thrombus to occur in this short time period, we believe that it cannot explain the observed immediate 30% reduction in MLD.

APPENDIX

Linear regression analysis: Stepwise multiple linear regression analysis was performed (BMDP statistical package, program 2R) to assess the relation between the variables mentioned in Methods (independent variables $= X_i$) and the decrease in MLD from the angiogram before angioplasty to that at follow-up (dependent variable $= Y$): $Y = A + \Sigma_i B_i X_i$, where A is the intercept and B_i is the $_i$th regression coefficient. The standard 2R criteria of F >4 for inclusion, and F <3.9 for elimination were used.

Multivariate logistic regression analysis: Multiple logistic regression analysis was performed with the BMDP statistical package (program LR). The linear logistic model relates a probability (P) for the outcome event to the value of a baseline characteristic (X) using the linear logistic function: $P = 1/1 + e^{-(a+bX)}$. The relation between variables retained in the multiple linear regression model and restenosis according to the 0.72 mm criterion was expressed in a multivariate logistic regression model. Also, a set of variables reported to be predictors of restenosis was selected. All these variables were entered in a model, 1 at a time. The model to describe the risk for developing restenosis was fitted to the data of 595 lesion dilatations with balloon measurements. The standard LR criteria of p <0.1 for inclusion, and p >0.15 for elimination were used. Adjusted-rate ratios and 95% confidence intervals were obtained according to the method of Miettinen[30] by the following formulas, in which the incidence of restenosis was entered for all variates (X_i) other than the variates for which the adjusted-rate ratio was determined; 1 was entered for the variate under study (X_j) in the numerator and 0 in the denominator:

$$\text{Rate ratio} = \frac{[1 + \exp(-(\text{intercept} + \Sigma_i b_i X_i + b_j 1))]^{-1}}{[1 + \exp(-(\text{intercept} + \Sigma_i b_i X_i + b_j 0))]^{-1}}$$

95% confidence interval: rate ratio$^{(1 \pm 1.96/(bj/SE))}$.

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