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CLINICAL STUDIES

Lumen Narrowing After Percutaneous Transluminal Coronary Balloon Angioplasty Follows a Near Gaussian Distribution: A Quantitative Angiographic Study in 1,445 Successfully Dilated Lesions

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To determine whether significant angiographic narrowing and restenosis after successful coronary balloon angioplasty is a specific disease entity occurring in a subset of dilated lesions or whether it is the tail end of a gaussian distributed phenomenon, 1,445 successfully dilated lesions were studied before and after coronary angioplasty and at 6-month follow-up study. The original cohort consisted of 1,353 patients of whom 1,232 underwent repeat angiography with quantitative analysis (follow-up rate 91.2%). Quantitative angiography was carried out off-line in a central core laboratory with an automated edge detection technique. Analyses were performed by analysts not involved with patient care.

Distributions of minimal lumen diameter before angioplasty (1.03 ± 0.37 mm), after angioplasty (1.78 ± 0.36 mm) and at 6-month follow-up study (1.50 ± 0.57 mm) as well as the percent diameter stenosis at 6-month follow-up study (44 ± 19%) were assessed. The change in minimal lumen diameter from the postangioplasty angiogram to the follow-up angiogram was also determined (−0.28 ± 0.52 mm). Seventy lesions progressed toward total occlusion at follow-up. All observed distributions approximately followed a normal or gaussian distribution.

Therefore, restenosis can be viewed as the tail end of an approximately gaussian distributed phenomenon, with some lesions crossing a more or less arbitrary cutoff point, rather than as a separate disease entity occurring in some lesions but not in others.

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For more than a decade, investigators in the field of coronary balloon angioplasty have assumed a gaussian distribution of continuous (quantitative) angiographic variables used to describe the severity of the coronary lesion before and after angioplasty and at follow-up angiography. Therefore, they used parametric statistical tests for comparisons in their studies (1–7). In a recent study (8) it was reported that the percent diameter stenosis at follow-up angiography after coronary angioplasty follows a bimodal distribution. This finding seems to support the clinical observation that the restenosis process is a yes or no event occurring in some patients or lesions but not in others.

In this study we assessed the distributions of angiographic variables of lesion severity before and after angioplasty and at 6-month follow-up study in a large group of patients. Quantitative analysis was performed off-line in a central core laboratory with an objective, off-line, automated edge detection technique (9) by analysts not involved in the treatment of the patients.

Methods

Study patients. The original study cohort comprised 1,427 patients in whom primary coronary balloon angioplasty was attempted between December 1987 and June 1990 and who agreed to undergo a follow-up angiogram at 6 months. All patients signed informed consent and the study protocol was approved by the Institutional Review Board.

The procedure was successful in 1,353 patients (primary success rate 94.8%), defined as <50% residual stenosis of at least one lesion by visual inspection of the postangioplasty angiogram and no occurrence of in-hospital complications (death, acute myocardial infarction, coronary artery bypass grafting, repeat angioplasty or symptom recurrence). Patients with stable as well as unstable (10) angina were included. Patients with evolving myocardial infarction were excluded. In two cases the angioplasty angiogram could not be analyzed because of technical deficiencies. A total of 1,232 patients (91.2%) had a follow-up angiogram suitable for quantitative angiography and these form the study group. Reasons for not completing the study were late death (n = 8), contraindication for repeat catheterization (n = 24) and

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refusal (n = 76); 11 follow-up angiograms were unsuitable for quantitative analysis.

Angioplasty procedure and follow-up angiography. Coronary angioplasty was performed with a steerable, movable guide wire system by the femoral route. Standard available balloon catheters were used. The choice of balloon type and brand as well as inflation duration and inflation pressure was 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 1st 2 h, followed by 5,000 IU/h for as long as the procedure continued. All patients received 10 mg of nifedipine every 2 h for the 1st 12 h after angioplasty. Thereafter they received 20 mg of slow release nifedipine tablets three times during the 2nd day after angioplasty.

Three coronary angiograms were obtained in each patient, one just before and one immediately after angioplasty and one at follow-up. The angiograms were recorded in such a way that they were suitable for quantitative analysis by the computer-assisted Coronary Angiography Analysis System (CAAS). For calibration purposes the catheter tips 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 taken as described previously (3,11,12). All angiograms were processed and analyzed in a central core laboratory.

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

Quantitative angiography. All cineangiograms were analyzed with the computer-assisted CAAS technique, which has been described and validated earlier (9,13). In summary: any area of size 6.9 × 6.9 mm (512 × 512 pixels) in a selected cineframe (overall dimensions 18 × 24 mm) encompassing the desired arterial segment is digitized with a high resolution CCD camera. Vessel contours are determined automatically on the basis of the weighted sum of first and second derivative functions applied to the digitized brightness information along scanlines perpendicular to the local centerline directions of an arterial segment. A computer-derived reconstruction of the original arterial dimension at the site of obstruction (assuming no disease is present) is used to define the interpolated reference diameter. The absolute values of the diameter of the stenosis and the reference diameter are measured by the computer using the known contrast catheter diameter as a scaling device. The length of the obstruction is determined from the diameter function on the basis of curvature analysis and expressed in millimeters. All contour positions of the catheter and the arterial segment are corrected for pincushion distortion introduced by the image intensifiers. Because the algorithm is not able to measure total occlusions, a value of 0 mm was substituted for the minimal lumen diameter and a value of 100% for the percent diameter stenosis and percent area stenosis. In these cases the postangioplasty reference diameter was substituted for the reference diameter before angioplasty or at follow-up angiography. The mean change in minimal lumen diameter after angioplasty to follow-up angiography and before angioplasty to after angioplasty was derived from matched angiographic projections. The percent area stenosis was calculated by using the measured minimal lumen diameter and interpolated reference diameter assuming a circular cross section at the stenosis site.

Table 1. Baseline Patient (n = 1,232) and Lesion (n = 1,445) Characteristics

Male gender	1,002 (81%)
Age (years)	56 ± 9
Time to follow-up angiography (days)	165 ± 41
Dilated artery	
LAD	681
LCx	352
RCA	412
Extent of coronary artery disease	
1-Vessel	755 (61.3%)
2-Vessel	399 (32.4%)
3-Vessel	78 (6.3%)

Extent of coronary artery disease was visually assessed; >50% diameter stenosis was considered significant. LAD = left anterior descending coronary artery; LCx = left circumflex artery; RCA = right coronary artery.

Results

Baseline characteristics. Table 1 summarizes the baseline characteristics of the 1,232 patients with quantitative angiographic follow-up. These patients had 1,445 lesions successfully dilated (1.17 lesions/patient). Seventy-eight totally occluded lesions were successfully dilated. At follow-up, 70 lesions had progressed to total occlusion. Four hundred ninety-one patients (39.9%) had a history of myocardial infarction.

Quantitative angiographic findings and distributions (Table 2). The reference diameter was not significantly different before and after angioplasty and at follow-up, suggesting that vasomotion was accurately controlled during the three angiographic studies. Distribution plots of the minimal lumen diameter data are given in Figure 1, A to C. The distribution of the change in minimal lumen diameter from the postangioplasty angiogram to the follow-up angiogram (loss in minimal lumen diameter) is depicted as well (Fig. 1D). A positive change corresponds to a decrease in minimal lumen diameter. If the restenosis criterion of ≥0.72 mm loss in lumen diameter is applied (3), 244 lesions (16.9%) had restenosis at the follow-up study. All distributions are more or less bell-shaped and follow the theoretic normal or gaussian distribution given the mean and SD values of the minimal lumen diameters if the totally occluded lesions are not taken into account (curve superimposed on the distribu-

Table 2. Quantitative Angiographic Data of 1,445 Lesions

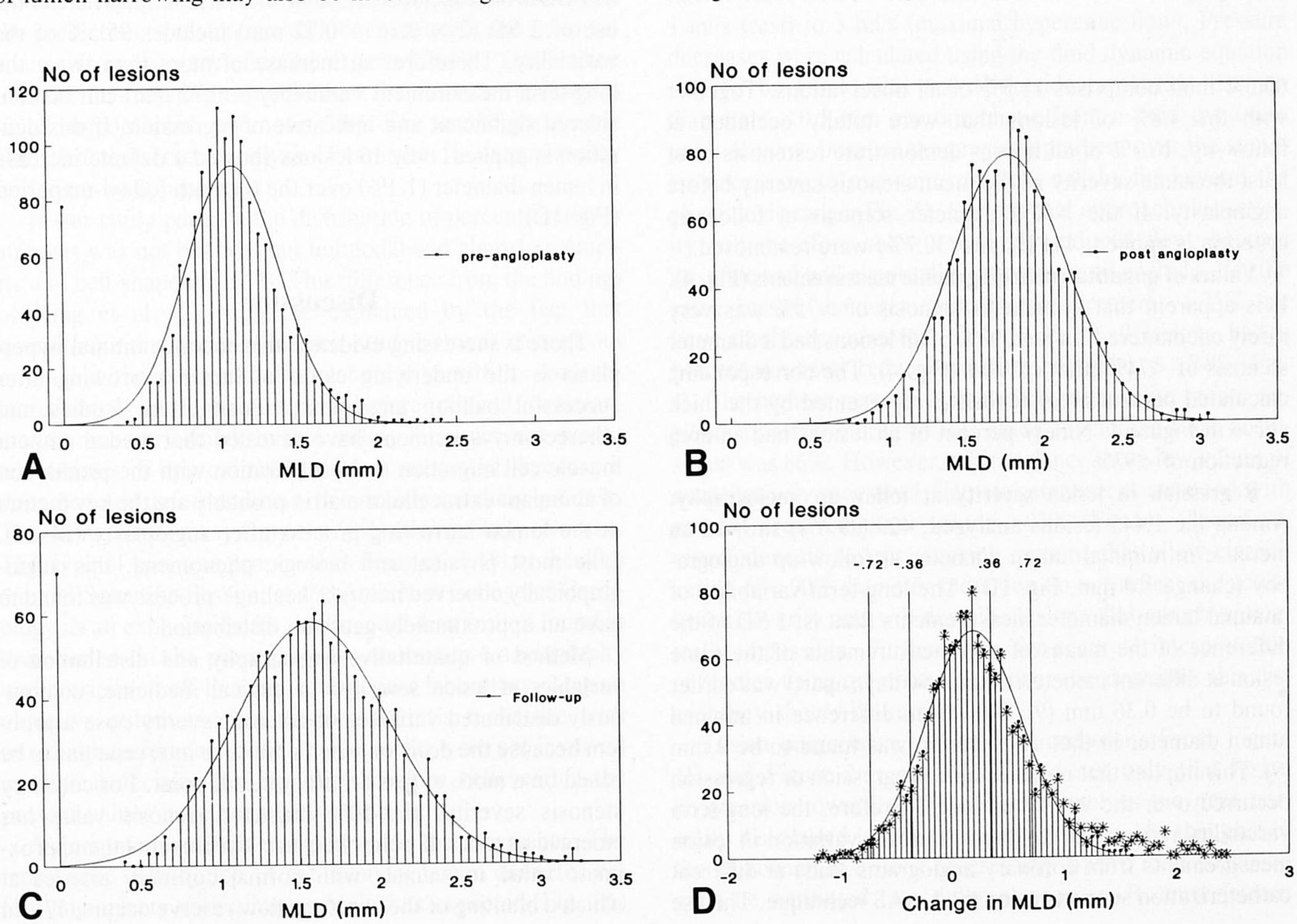
Minimal lumen diameter (mm)	
Before angioplasty	1.03 ± 0.37
After angioplasty	1.78 ± 0.36
Follow-up	1.50 ± 0.57
Reference diameter (mm)	
Before angioplasty	2.63 ± 0.54
After angioplasty	2.69 ± 0.52
Follow-up	2.70 ± 0.56
Change in minimal lumen diameter (mm)	
From before angioplasty to after angioplasty	0.75 ± 0.41
From after angioplasty to follow-up angiography	−0.28 ± 0.52
Diameter stenosis (%)	
Before angioplasty	60.5 ± 13.6
After angioplasty	33.6 ± 9.8
Follow-up angiography	44.2 ± 18.7

Values are mean values ± 1 SD.

tions). The distribution of the loss in minimal lumen diameter, excluding lesions that were totally occluded at follow-up (bars, Fig. 1D), is almost identical to the distribution including totally occluded lesions at follow-up (asterisks, Fig. 1D) with the latter lesions showing a greater loss in minimal lumen diameter. This finding suggests that lesions progressing to total occlusion are not necessarily lesions with a poor or marginal angioplasty result and that a different mechanism of lumen narrowing may also be involved. Figure 2 shows this more clearly. In this normal probability plot of change in minimal lumen diameter, slashes denote the expected gaussian distribution based on the rank of the observations and the squares denote the actual observed values. It appears that if the lesions that progress to total occlusion are excluded, the observed values closely follow the expected gaussian distribution.

The distribution of percent diameter stenosis at follow-up was found to be unimodal and almost symmetric and bell-shaped if lesions that progressed toward total occlusion were disregarded (Fig. 3). Disregarding these total occlusions, the mean percent diameter stenosis at follow-up was 41.3 ± 16.1%. The 60.5% mean diameter stenosis before angioplasty marks 1.2 SD to the right on the bell-shaped curve, and thus the area under the curve located to the right of the

Figure 1. Histograms of minimal lumen diameter (MLD) measurements of 1,445 lesions before (**A**) and after (**B**) angioplasty and at 6-month follow-up angiography (**C**). The **curves** superimposed on the histograms represent the theoretic gaussian distribution curves given the mean values and SD of the study group, excluding total occlusions. **D,** Histogram of change in minimal lumen diameter from the postangioplasty angiogram to the follow-up angiogram. The **asterisks** denote the distribution of the change in minimal lumen diameter, including those lesions that had progressed toward total occlusion. A positive change denotes a loss in minimal lumen diameter. The long-term variability cutoff points are shown in the histogram (see text for explanation).



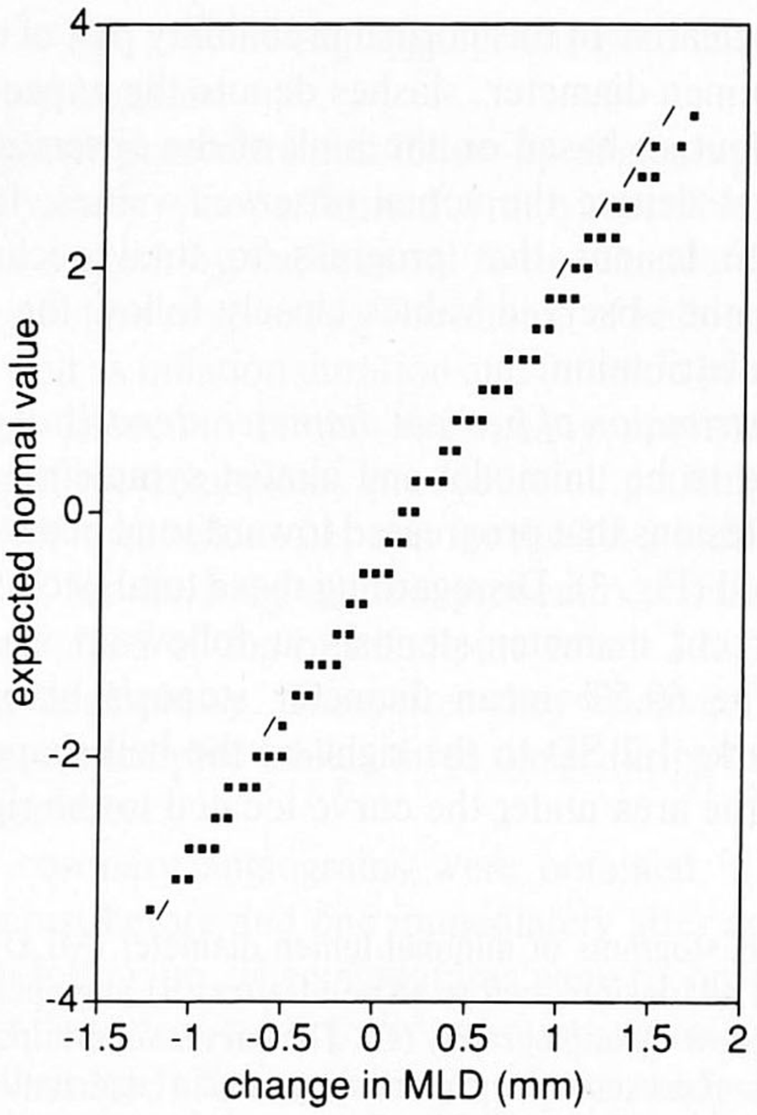


Figure 2. Normal probability plot of the change in minimal lumen diameter (MLD) from the postangioplasty angiogram to the follow-up angiogram, excluding lesions that had progressed toward total occlusion. The **slashes** depict the theoretic gaussian distribution; the **squares** are the values actually observed. A change >0 corresponds to a loss in minimal lumen diameter.

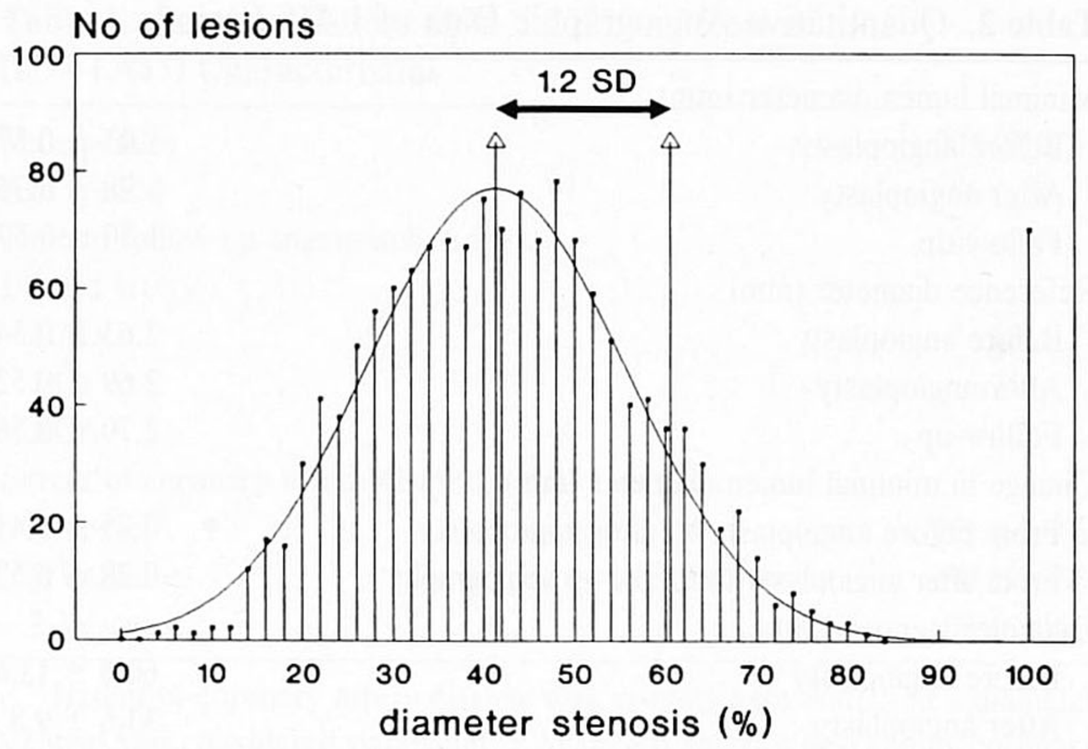


Figure 3. Histogram of percent diameter stenosis at follow-up angiography of 1,445 lesions. The **curve** superimposed on the histogram represents the theoretic gaussian distribution curves, given the mean values and SD of the study group, excluding total occlusions. Mean percent diameter stenosis excluding total occlusions is 41.3 ± 14.5%. Also shown is the mean 60.5% diameter stenosis before angioplasty. This limit marks 1.2 SD to the right of the 41.3% value, indicating that 11.5% of the observations under the curve are located to the right of the 60.5% limit. If the 4.8% of totally occluded lesions is added, 16.3% of all lesions demonstrate restenosis to at least the same severity as the mean stenosis severity before angioplasty.

60.5% limit comprises 11.5% of all observations. Together with the 4.8% of lesions that were totally occluded at follow-up, 16.3% of all lesions demonstrate restenosis to at least the same severity as the mean stenosis severity before angioplasty. If the >50% diameter stenosis at follow-up criterion is applied, 444 lesions (30.7%) were restenosed.

Values of quantitative angiographic measurements (Fig. 4). It is apparent that a diameter stenosis of >75% was very rarely encountered. In fact, 90% of all lesions had a diameter stenosis of <74% (thin curve in Fig. 4). The corresponding calculated percent area stenosis is represented by the thick curve in Figure 4. Ninety percent of all lesions had an area reduction of <93%.

Regression in lesion severity at follow-up angiography. Among the 1,445 lesions analyzed, 429 (29.6%) showed an increase in minimal lumen diameter at follow-up angiography (change <0 mm, Fig. 1D). The long-term variability of minimal lumen diameter measurements (that is, 1 SD of the difference of the means of two measurements of the same lesion at different catheterizations, 90 days apart) was earlier found to be 0.36 mm (9). The mean difference in minimal lumen diameter in that same period was found to be 0 mm (9). This implies that no detectable progression or regression occurred over the 90-day period. Therefore, the long-term variability reflects the long-term random variation in lesion measurements from coronary angiograms made at different catheterization sessions using the CAAS technique. The use of 1 SD would include 68.3% of the variability, whereas the use of 2 SD (2 × 0.36 = 0.72 mm) includes 95.5% of the variability. Therefore, an increase of more than twice the long-term measurement variability (≥0.72 mm) can be considered significant and indicative of regression. If this definition is applied, only 16 lesions showed a definite increase in lumen diameter (1.1%) over the 6-month follow-up period (Fig. 1D).

Discussion

There is increasing evidence that reactive intimal hyperplasia is the underlying cause of lumen narrowing after successful balloon angioplasty. Postmortem studies and atherectomy specimens have revealed that medial smooth muscle cell migration and proliferation with the production of abundant extracellular matrix probably are the key factors in the lumen narrowing process after angioplasty (14–16). Like most physical and biologic phenomena, this angiographically observed natural "healing" process was found to have an approximately gaussian distribution.

Method of quantitative angiography and distribution of variables of lesion severity. In clinical medicine, continuously distributed variables of disease severity pose a problem because the decision when or how to intervene has to be based on a more or less arbitrary cutoff point. For coronary stenosis severity, the 50% diameter stenosis value has emerged as a cutoff point, because it represents the approximate value in animals with normal coronary arteries at which a blunting of the coronary flow reserve occurs (17). In

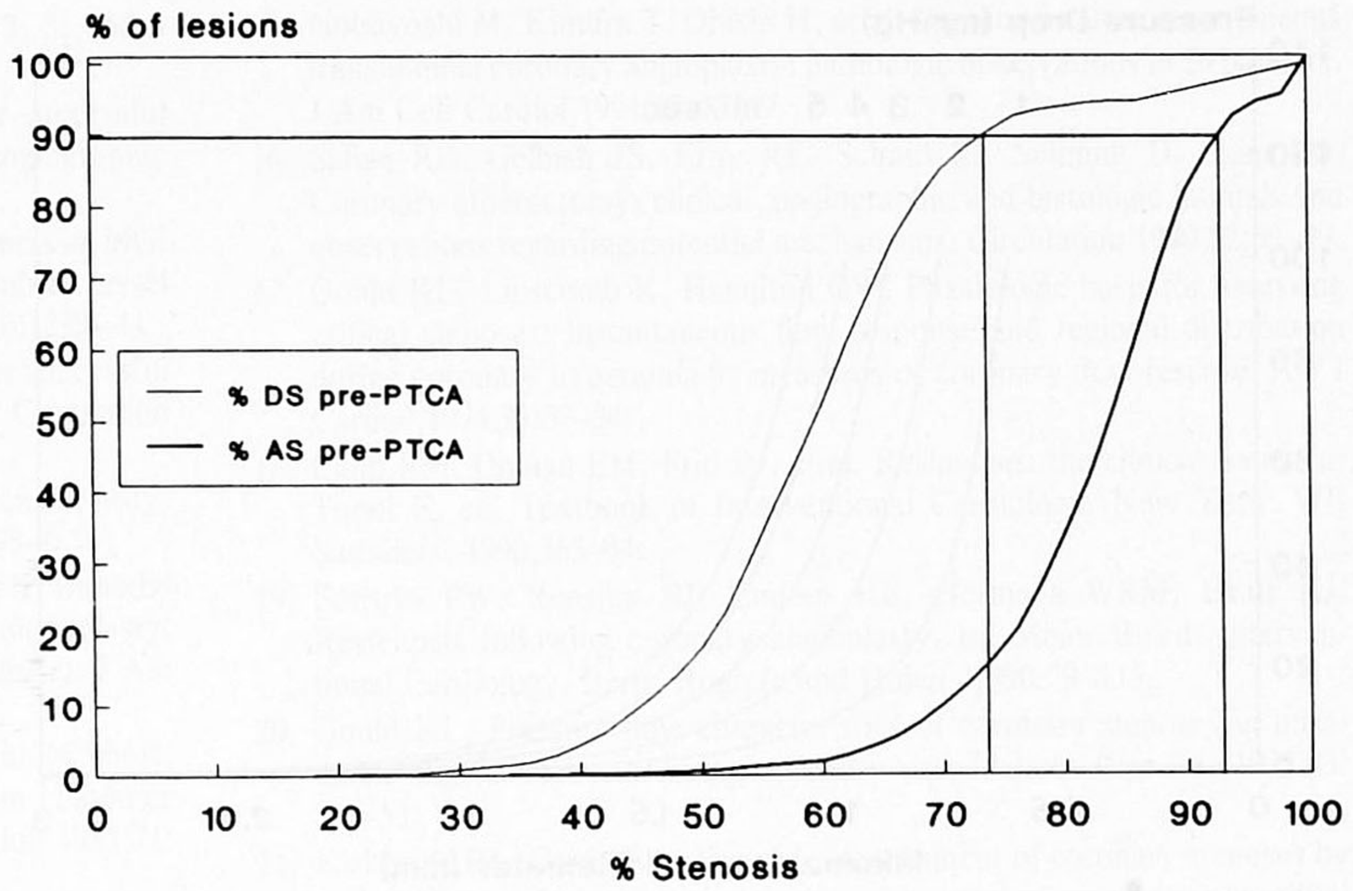


Figure 4. Cumulative distribution of percent diameter reduction (percent diameter stenosis [%DS], **thin curve**) and of percent area reduction (percent area stenosis [%AS], **thick curve**) for 1,445 lesions before angioplasty (pre-PTCA). Ninety percent of all lesions show a percent diameter stenosis of <74%, which corresponds to 93% area stenosis.

a recent study (8), it was reported that the percent diameter stenosis of lesions 4 months to 1 year after balloon angioplasty followed a bimodal distribution with the nadir between the two peaks at 50% diameter stenosis. This observation suggests that after balloon angioplasty, two types of lesion behavior can occur: a restenosing and a nonrestenosing reaction. If two different patient groups are present from the start, then it must be possible before angioplasty to isolate the patients who will develop restenosis; however, the prediction of restenosis with both invasive and noninvasive tools is not very effective at best (18,19). This finding also has far-reaching consequences for the statistical analysis of angiographic restenosis data. The use of parametric statistical tests (*t* test, analysis of variance, for example) may no longer be appropriate.

In our study patients the distribution of percent diameter stenosis was not bimodal but unimodal and almost symmetric and bell-shaped (Fig. 3). This difference from the findings of King et al. (8) might be explained by the fact that quantitative angiography in their study (8) was carried out on-line in the catheterization laboratory with a nonautomated analysis technique and before clinical decision-making was performed. In that setting (8), a percent diameter stenosis of approximately 50% is unwanted, because it does not add information to the decision-making process. Therefore, a bias away from the 50% value is likely to occur. This type of bias was proposed by King et al. (8) at the 40th Annual Scientific Session of the American College of Cardiology as an explanation for the bimodal distribution found in their series. In the present study, quantitative angiography was carried out off-line in a central core laboratory using an objective automated quantitative analysis technique with minimal interference of the analysts who were not involved in clinical decision-making. We therefore believe that the present values have been less biased.

Values of quantitative angiographic measurements. The leptokurtic distribution of the minimal lumen diameter before angioplasty with a higher peak than expected (Fig. 1A) can be explained by lesion selection. Values of approximately 1 mm correspond with diameter stenosis values in the range of 60% to 70%. These are generally the type of lesions selected for coronary balloon angioplasty.

Minimal lumen diameters <0.5 mm were not encountered. Figure 5 shows the theoretic pressure decrease over a stenosis with a length of 6.5 mm (mean stenosis length in this study) and an interpolated reference diameter of 2.6 mm (mean value in this study) at assumed flows ranging from 1 ml/s (rest) to 5 ml/s (maximal hyperemic flow). Pressure decreases were calculated using the fluid dynamic equation derived by Gould (20) and Kirkeeide et al. (21). Lumen diameters <0.5 mm are unrealistic from a fluid dynamics point of view, because the pressure gradient over the stenosis necessary to maintain rest flow will be far beyond the physiologic range (Fig. 5). Lesions that approach this severity will therefore show a severely reduced flow, become unstable and will eventually thrombose and occlude. For the same reason diameter stenosis measurements >75% are very rarely encountered. Only 10% of all lesions had a percent diameter reduction before angioplasty >74% (Fig. 4). The highest percent diameter stenosis value before angioplasty encountered in this study (excluding total occlusions) was 86%. However, at first glance these low values of quantitatively measured diameter stenosis correspond with percent area reduction values >93% (Fig. 4). Therefore, visual stenosis severity scoring systems that allow classification of >90% diameter reduction do not reflect the actual lesion severity and will describe lesions that are physiologically impossible. Furthermore, for accurate interpretation of studies using quantitative coronary angiography this discrepancy should be kept in mind.

Lesion progression toward total occlusion. From Figure 1D and Figure 2 it can be inferred not only that lesion progression toward total occlusion involves the near normally distributed lumen narrowing process, but that part of the narrowing in lesions progressing toward total occlusion must be attributed to a different process. Because lesions

JACC Vol. 19, No. 5
April 1992:939–45

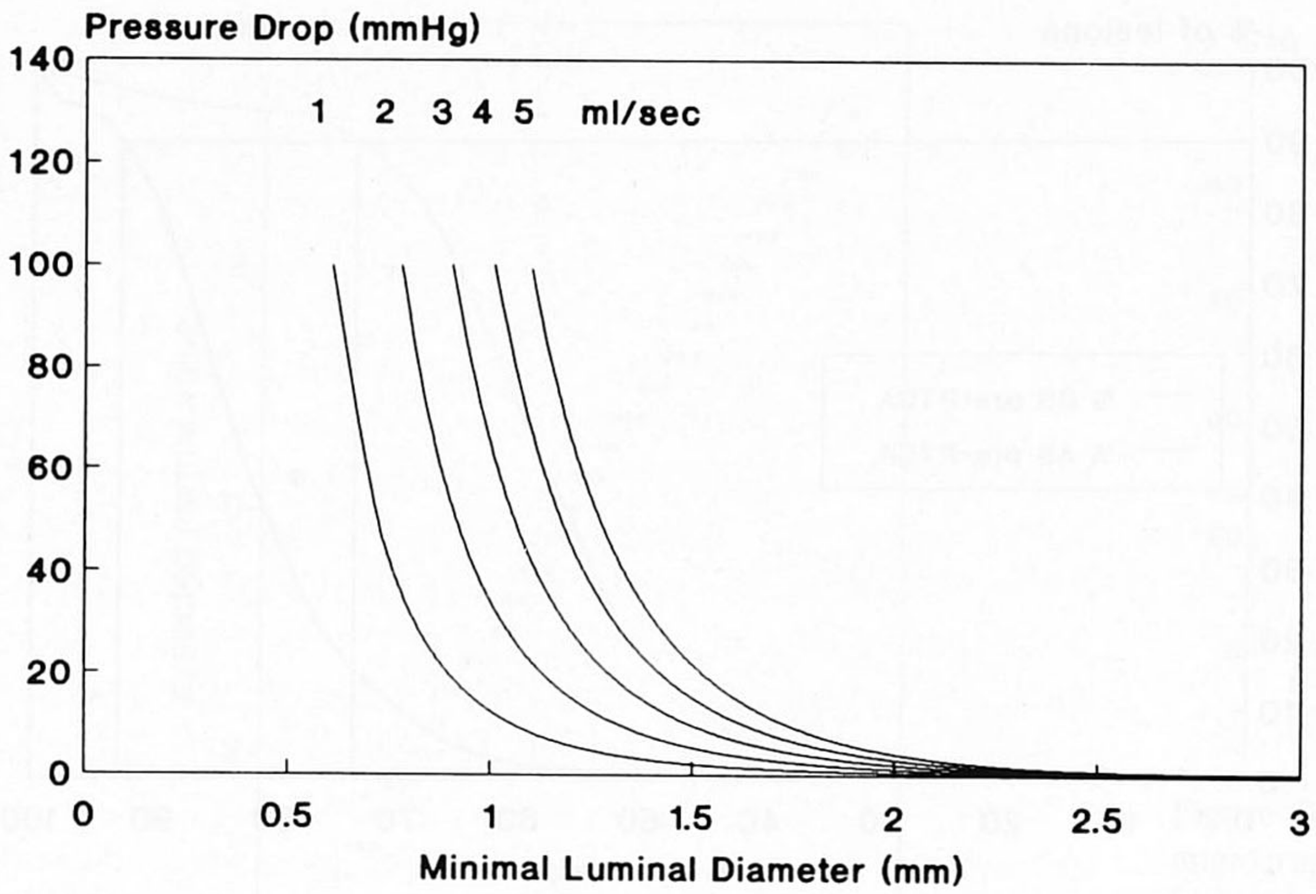


Figure 5. Theoretic pressure decreases calculated with the fluid dynamics equation derived by Gould (20) and Kirkeeide et al. (21) at assumed flows of 1, 2, 3, 4 and 5 ml/s, respectively. Reference diameter was assumed to be 2.6 mm and lesion length 6.5 mm.

with a minimal lumen diameter <0.5 mm are impossible because of the unphysiologic high pressure decreases necessary to maintain blood flow (Fig. 5), it is likely that the last step in lesion progression toward total occlusion is due to thrombosis. Delivery and activation of platelets is dependent on shear rate, which is a measure of the difference in blood velocity between the center and the periphery of the vessel. A tightening stenosis causes progressively higher shear rates to occur, which favors platelet activation and deposition (22,23). Animal experiments by Folts et al. (24) showed that platelet aggregation spontaneously occurs in partially obstructed coronary arteries. Another explanation might be that a "silent" thrombotic occlusion occurs early after angiographically successful angioplasty. In the absence of an important collateral circulation, one would expect a high incidence of myocardial infarction in patients with a total occlusion at follow-up angiography. Sixteen of the 70 totally occluded arteries at follow-up were also totally occluded before angioplasty and collateral flow was present before angioplasty. Of the 54 arteries patent before angioplasty, only 4 were related to an infarct during follow-up study (enzyme elevation to twice normal or presence of new Q waves, or both). Visible collateral circulation before angioplasty was present in 8 of these 54 lesions (Table 3). A slowly progressing lesion, on the other hand, could allow a gradual build-up of collateral circulation, enabling a total occlusion to develop later after angioplasty without myocardial necrosis.

Table 3. Total Occlusions at Follow-Up Angiography (n = 70)

No. of lesions totally occluded before angioplasty	16 (23%)
Presence of collateral circulation before angioplasty in the absence of total occlusion	8 of 54 (14.8%)
Myocardial infarction during follow-up	5 (7%)
Minimal lumen diameter (mm)	
Before angioplasty	0.73 ± 0.43*
After angioplasty	1.62 ± 0.36*

*Mean values ± 1 SD.

Lesion regression. A definite increase in minimal lumen diameter (regression) was observed in 16 patients only (1.1%) (Fig. 1D). This finding is in concordance with earlier reported data (3). True angiographic regression in the first months after angioplasty thus appears to be rare. However, Rosing et al. (25) described regression of the dilated lesion in 46 patients 3 years after successful angioplasty when values were compared with those of the 6-month angiogram. This finding can be attributed to a late resorption of the extracellular matrix in the neointima (15).

Conclusions. The process of lumen narrowing after coronary balloon angioplasty is approximately normally distributed, with few lesions showing regression, most showing no change and a considerable number showing progression. Restenosis can thus be viewed as the tail end of a near gaussian distribution, with some lesions crossing a more or less arbitrary angiographic cutoff point, rather than as a separate disease entity that occurs in some lesions but not in others. For comparison of the angiographic efficacy of pharmacologic agents and new interventional devices, we therefore recommend the use of changes in minimal lumen diameter rather than the rate of restenosis as the end-point.

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