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Therapeutic Dissection After Successful Coronary Balloon Angioplasty: No Influence on Restenosis or on Clinical Outcome in 693 Patients

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Objectives. The objective of this study was to examine the relation between an angiographically visible coronary dissection immediately after *successful* coronary balloon angioplasty and a subsequent restenosis and long-term clinical outcome.

Background. The study population comprised all 693 patients who participated in the MERCATOR trial (randomized, double-blind, placebo-controlled restenosis prevention trial of cilazapril, 5 mg two times a day).

Methods. Cineangiographic films were processed and analyzed at a central angiographic core laboratory, without knowledge of clinical data, with use of an automated interpolated edge detection technique. Dissection was judged according to the National Heart, Lung, and Blood Institute classification. Angiographic follow-up was obtained in 94% of patients with 778 lesions. Two approaches were used to assess the restenosis phenomenon: 1) *categoric*, using the traditional cutoff criterion of >50% diameter stenosis at follow-up, and 2) *continuous*, defined as absolute change in minimal lumen diameter (mm) between the postcoronary angioplasty and follow-up, adjusted for the vessel size (relative loss). Clinical outcome was ranked according to the most serious adverse clinical event per patient during the 6-month follow-up period, ranging from death, nonfatal myocardial infarction, coronary revascularization and recurrent angina requiring medical therapy to none of these.

Results. Dissection was present in 247 (32%) of the 778 dilated lesions. The restenosis rate was 29% in lesions with and 30% in lesions without dissection (relative risk 0.97; 95% confidence interval 0.77 to 1.23). The relative loss in both groups was 0.10 (mean difference 0; 95% confidence interval −0.03 to 0.03). Clinical outcome ranged from death in 4 patients (0.9%) without dissection and 1 patient (0.4%) with dissection; nonfatal myocardial infarction in 4 (0.9%) without and 8 (3.2%) with dissection; coronary revascularization in 73 (16.6%) without and 32 (12.7%) with dissection; recurrent angina requiring medical therapy in 88 (20%) without and 47 (18.7%) with dissection to no serious adverse event in 272 (61.7%) without and 114 (65.1%) with dissection.

Conclusions. These data indicate that a *successfully* dilated coronary lesion with an angiographically visible dissection is no more likely to develop restenosis, and is not associated with a worse clinical outcome, at 6-month follow-up than is a dilated lesion without visible dissection on the post-balloon angioplasty angiogram.

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Percutaneous transluminal coronary angioplasty is an accepted revascularization procedure for treatment of patients with stable or unstable angina pectoris with single or multivessel disease (1,2). Despite the therapeutic success of coronary angioplasty, the exact mechanism of dilation remains speculative and apparently involves multiple processes, including endothelial denudation, cracking and splitting or disruption of the intima and atherosclerotic plaque, dehiscence of the intima and plaque from the underlying media and stretching or tearing of the media with persistent aneurysmal dilation of the media and adventitia (3–7). Irrespective of the mechanism, coronary angioplasty results in an angiographically visible dissection in 20% to 45% of the dilated lesions (Table 1) (8–20). This dissection 1) might result in a complete or near complete total obstruction of the dilated vessel, leading to an acute ischemic syndrome requiring urgent treatment with a further coronary revascularization procedure (the so-called unwanted type of dissection [21,22]), or 2) might not compromise the lumen significantly, so that neither reduction in blood flow nor impairment of

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Table 1. Studies in Which the Relation Between Lesions With or Without Dissection and Restenosis Was Examined

First Author (reference no.)	Year	Patients	Angio Follow-Up (%)	Definition of Restenosis	Restenosis (%)	Dissection (% of lesions)	Restenosis With/Without	p Value
Holmes (8)	1984	665	84	NHLBI I→IV	34	NR	No difference	
Leimgruber (9)	1985	1650	60	>50% DS	30	25	35% vs. 39% gradient >15	NS
							19% vs. 28% gradient ≤15	<0.05
Guiteras Val (10)	1987	181	98	↑ ≥30% DS	28	45	56% severe diss vs. 25% mild diss vs. 21% no diss	<0.02
Vandormael (11)*	1987	209	62	>50% DS	82 (symp) 30 (no symp)	NR	No difference	
Matthews (12)	1988	216	30	Loss >50% of gain or lack of symptoms	21	30	18% vs. 23%	NS
Black (13)†	1988	384	39	>50% DS	31‡	34	29% vs. 32%	NS
de Feyter (14)§	1988	179	88	>50% DS	32	25	No difference	
Fleck (15)‖	1988	110	86	ΔMLCA >1 mm²	58	31	No difference	
Quigley (16)†	1989	114	88	>50% DS	32	20	35% vs. 31%	NS
Renkin (17)**	1990	278	47	>50% DS	—	33	No difference	
Rupprecht (18)	1990	676	70	>50% DS or loss >50% of gain	29	NR	24% vs. 30%	NS
Bourassa (19)	1991	307	80	>50% DS with minimal 10% DS ↑	36	41	33% vs. 36%	NS
Hirshfeld (20)	1991	694	73	>50% DS	40	39	40% vs. 39%	NS

*Multivessel dilation. †For restenosis; ‡Only the ones with follow-up angiography; §Unstable angina. ‖Excluded total occlusions; **Angiography + exercise thallium scintigraphy. Angio Follow-Up = percent of patients with angiographic follow-up; ΔMLCA = change in minimal lumen cross-sectional area; Diss = dissection; DS = diameter stenosis; NHLBI I→IV = change from National Heart, Lung, and Blood Institute category I to category IV; NR = not reported; NS = not significant; Symp = symptoms; ↑ = increase.

clinical performance occurs, and the patient leaves the hospital as scheduled (the so-called therapeutic type of dissection [9,12,23]).

It could be postulated that an angiographically visible dissection occurs predominantly in lesions where more injury is imparted to the vessel wall, triggering an excessive proliferative response. Nobuyoshi et al. (24) have demonstrated, using histopathologic examination, that deep arterial injury is associated with more extensive intimal proliferation. In addition, Schwartz et al. (25) showed in a porcine model that the severity of vessel injury was strongly correlated with neointimal thickness. In addition, the existence of an intimal tear could predispose to greater platelet deposition, mural thrombus and growth factor release with a consequently higher risk of restenosis. In contradistinction, early angiographic reports (Table 1, 8–20,23) suggested that the therapeutic type of dissection was associated with a trend toward lower restenosis rates. Thus, conflicting data have been reported. Most of these earlier studies had one or more methodologic problems, including 1) retrospective analysis of small patient groups, 2) incomplete angiographic follow-up influenced by the recurrence of symptoms without a predetermined time interval for restudy, 3) angiographic assessment by visual estimation of stenosis, which is known to have wide interobserver and intraobserver variability, 4) unknown or unreported interobserver and intraobserver variability for the assessment of dissection, 5) failure to assess data in blinded manner (26–29).

This study examined the relation of an angiographically visible dissection, restenosis and long-term clinical outcome with use of a validated automated edge detection technique on prospectively collected data. The study group comprised a large series of patients undergoing successful balloon angioplasty with a high angiographic follow-up rate.

Methods

Study patients. The study group consisted of all randomized patients enrolled in 26 centers for the MERCATOR trial, which was carried out according to the declaration of Helsinki (1963), revised in Venice (1983) (Appendix). The results of the trial demonstrated that cilazapril, 5 mg twice a day, had no effect on restenosis or clinical outcome in the 1st 6 months after angioplasty (30).

Subjects were eligible for study if they were symptomatic or asymptomatic men (or women without childbearing potential) with stable or unstable angina pectoris (defined as characteristic pain at rest requiring intravenous nitrates), were <75 years old, had proved angiographically significant narrowing in one or more major coronary arteries, and gave written informed consent before the coronary angioplasty procedure. Exclusion criteria were coronary angioplasty performed for revascularization in a patient with acute myocardial infarction, a history of sustained hypertension, maintenance therapy with diuretic agents, a Q wave myocardial infarction <4 weeks before study entry, previous or failed coronary angioplasty at the same site, and coronary angioplasty of a bypass graft. Patients were excluded from

Table 2. Flowchart of the MERCATOR Study

Total patients group	735
No coronary angioplasty performed	4
Unsuccessful coronary angioplasty	11
Unsatisfactory result	2
Complicated procedure	12
Exclusion criterion overlooked	10
No baseline quantitative coronary analysis possible	3
Patients randomized	693
Deaths	5
Adverse event	25
Follow-up angiography refused	7
No follow-up quantitative coronary analysis possible	3
Patients with follow-up angiogram	653

the trial if angioplasty was not performed (4 patients with a change in lesion severity), was unsuccessful (11 patients whose lesion could not be reached or crossed), unsatisfactory (2 patients with >50% diameter stenosis after coronary angioplasty as assessed visually), or complicated by abrupt closure during the procedure with subsequent emergency bypass operation, or by periprocedural myocardial infarction with creatine kinase levels more than two times the upper limit and MB fraction >6% (12 patients). Thirteen patients were retrospectively excluded from the analysis, 10 because an exclusion criterion was overlooked and 3 because no baseline quantitative analysis was possible (Table 2).

Thus, 693 patients with successful coronary angioplasty, defined by the operator as <50% diameter stenosis on visual inspection of the postangioplasty angiogram, who met the inclusion criteria and who had an angiogram suitable for quantitative analysis were entered into the study and randomized. Follow-up angiography was scheduled for 26 ± 3 weeks after angioplasty, or earlier if warranted by symptoms. Of the 693 randomized patients, 653 (94%) had a follow-up angiogram suitable for quantitative analysis. Of the other 40 patients, 5 died before repeat angiography, 32 did not have a follow-up angiogram because of adverse experience (n = 25) or refusal (n = 7) and 3 had a follow-up angiogram that was unsuitable for quantitative analysis (Table 2).

Angioplasty procedure, follow-up and quantitative angiography. At the beginning of the procedure, all patients received a bolus of 10,000 IU of intravenous heparin. For prolonged procedures, an additional infusion of 5,000 IU/h was administered after 2 h, until the end of the procedure. Use of a calcium channel blocking agent was permitted for 48 h after coronary angioplasty. All patients received aspirin, 160 to 250 mg/day, starting the day before coronary angioplasty until 6 months of follow-up. Choice of the guiding catheters, guide wires, balloon type, inflation duration and pressure were left to the discretion of the operator.

Three angiograms were carried out for each patient immediately before coronary angioplasty, immediately after

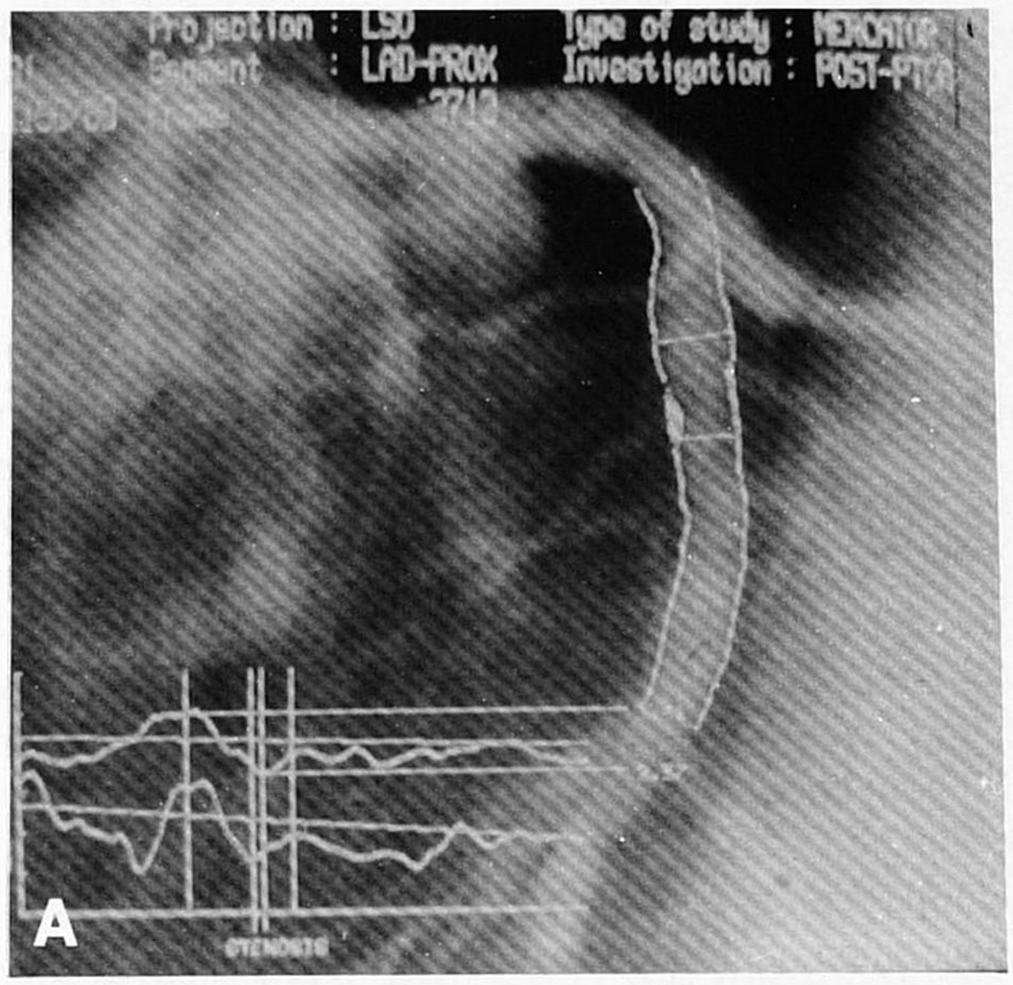


Figure 1. Example of quantitative coronary analysis of a lesion in the proximal left anterior descending coronary artery in the left superior oblique projection before (**A**) and after (**B**) coronary angioplasty. The diameter along the analyzed segment is represented in the diameter function curve (**upper curve**). The minimal lumen diameter is 0.90 mm before and 2.37 mm after angioplasty. The length of the stenosis is determined by curvature analysis and is depicted by two vertical lines. The reference diameter is determined where the minimal lumen diameter crosses the interpolated reference diameter line. The **white area** represents the atherosclerotic plaque and is defined as the difference between the detected and reconstructed edges.

coronary angioplasty and at follow-up. The angiograms were recorded so that they were suitable for quantitative analysis by the Cardiovascular Angiography Analysis System (CAAS), which has been validated and described in detail elsewhere (27,31–33). An example of an analysis before and after coronary angioplasty is shown in Figure 1. Postangioplasty values were obtained from the last angiogram re-

corded after removal of the guide wire. The initial procedure was considered complete when the guide catheter was removed. If the clinical condition required repeat angioplasty, the angiogram immediately before the repeat procedure was used to obtain follow-up values, irrespective of the timing of the repeat procedure (hours, days or weeks). To standardize the method of data acquisition and data analysis, and to ensure exact reproducibility of angiograms obtained before and after angioplasty and follow-up angiograms, special precautions were taken as described elsewhere (27,31–33).

The absolute values of the stenosis diameter and the reference diameter were measured by the computer using the known contrast-empty guiding catheter diameter as a scaling device. For that purpose, the catheter tips were retained for accurate measurement by a micrometer. To achieve maximal coronary vasodilation, intracoronary administration of either nitroglycerin, 0.1 to 0.3 mg, or isosorbide dinitrate, 1 to 3 mg, was performed in each artery of interest before and after angioplasty and at follow-up angiography. All contour positions of the catheter and the arterial segment were corrected for "pincushion distortion" introduced by the image intensifiers. Because the algorithm cannot measure total occlusions and lesions with Thrombolysis in Myocardial Infarction (TIMI) grade 1 perfusion, a value of 0 mm is substituted for the minimal lumen diameter and 100% for the percent diameter stenosis. In these cases, the postangioplasty reference diameter was substituted for the reference diameter before angioplasty or at follow-up, or both. For each dilated segment, the preangioplasty, postangioplasty and follow-up minimal lumen diameter and diameter stenosis are derived as the mean value from multiple matched projections.

Quantitative derived variables. The area (mm^2) between the actual and reconstructed contours at the obstruction site is a measure of the amount of *atherosclerotic plaque* (27). The *length of the obstruction* (mm) is determined from the diameter function on the basis of curvature analysis. *Symmetry* is defined as the coefficient of the left-hand distance and the right-hand distance between the reconstructed interpolated reference diameter and actual vessel contours, at the site of obstruction. In this equation, the largest distance between actual and reconstructed contours becomes the denominator, so that a perfectly symmetric lesion has a value of 1 and a severely eccentric lesion has a value of 0. To assess the extent of coronary bending, the *curvature* value at the obstruction site is computed as the average value of all the individual curvature values, along the centerline of the coronary segment, with the curvature defined by the rate of change of the angle through which the tangent to a curve turns in moving along the curve, and which for a circle, is equal to the reciprocal of the radius. The curvature value was determined by using the least foreshortened projection (in which the analyzed segment appeared longest between two defined landmarks) (Fig. 2).

Balloon/artery ratio was defined as the ratio using

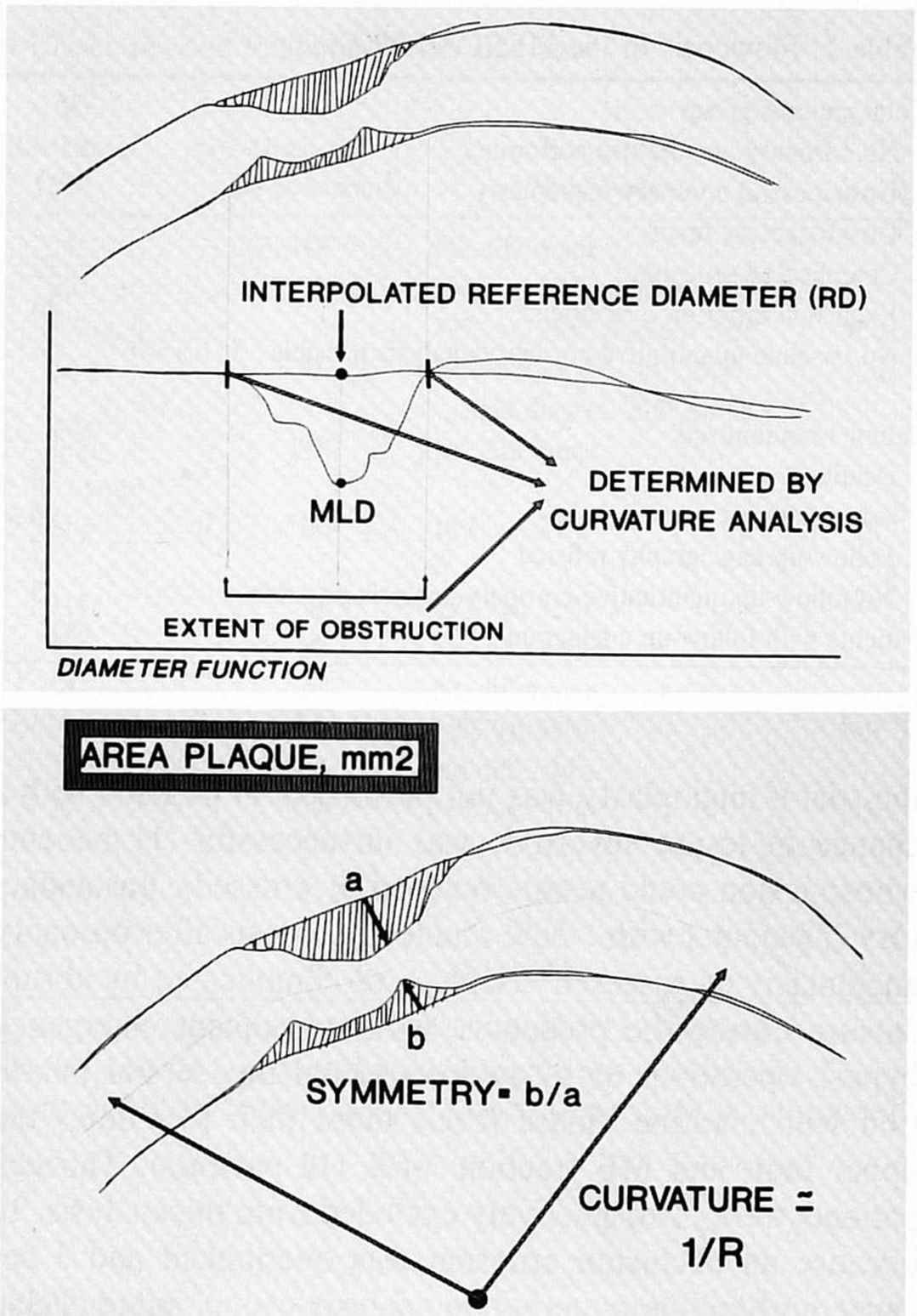


Figure 2. Top and **bottom panels** show the quantitative derived variables: curvature, symmetry, area plaque, lesion length. See text for definitions.

1) nominal size according to manufacturer, or 2) the measured reference balloon size, divided by vessel size (34). *Relative gain* was defined as the difference in minimal lumen diameter before and after coronary angioplasty, normalized for vessel size (interpolated reference diameter). *Stretch* was defined as the difference between the minimal balloon diameter (of the largest balloon used, inflated to the highest pressure applied) and minimal lumen diameter before coronary angioplasty, normalized for vessel size (34–36). *Elastic recoil* was defined as the difference between the minimal balloon diameter and the minimal lumen diameter after coronary angioplasty, normalized for vessel size (34–36). The *balloons* used for dilation were composed of 1) noncompliant material (polyethylene terephthalate or hydracross), or 2) compliant material (polyethylene, polyvinylchloride or polyolefin copolymer). *Relative loss* was defined as the difference in minimal lumen diameter after coronary angioplasty and at follow-up, normalized for vessel size (37).

In addition to quantitative measurements, qualitative assessment of certain lesion characteristics (calcification, presence of side branch in stenosis, location of stenosis in a bend) was also performed (38).

Definition of dissection. All postangioplasty angiograms were examined for the presence or absence of dissection, defined according to modified National Heart, Lung, and Blood Institute criteria as the presence of angiographically evident intimal or medial damage presenting either as a small radiolucent area within the lumen of the vessel (tear or flap, type A) or as an extravasation of nonpersisting or persisting contrast medium (type B or C) (10,39). A dissection was classified as type D in the presence of a spiral-shaped filling defect with delayed distal flow and as type E if a persistent lumen defect with delayed anterograde flow was seen on the final postangioplasty angiogram. A filling defect accompanied by a total coronary occlusion was classified as a type F dissection (Fig. 3 to 6).

Assessment of dissection. Each investigator was asked to assess and document the occurrence of dissection after the procedure. All films were reassessed by the angiographic core laboratory, which was empowered by the MERCATOR Angiographic Committee to revise the initial assessment of the investigator. Inter- and intraobserver variability of the two assessors (W.R.M.H., B.J.R.) for the assessment of dissection was examined in the angiographic core laboratory in an arbitrarily selected number of lesions. The coronary angioplasty films of 138 patients with 151 lesions (consecutive films reaching the core laboratory) were independently assessed for dissection by each observer on two separate occasions, 3 months apart, without knowledge of the results of the earlier assessment. In 271 (89%, kappa 0.75) of the 302 lesions, there was agreement on the presence or absence of dissection and 85% (kappa 0.66) agreement for the type of dissection between the two assessors. The intraobserver variability for the presence or absence and the type of dissection were, respectively, 87% (kappa 0.60) and 80% (kappa 0.48) for assessor 1 and 82% (kappa 0.58) and 76% (kappa 0.51) for assessor 2 (40).

If dissection is evident on the postangioplasty angiogram, the quantification of a coronary lesion can be hampered by consequent indecision; that is, the analysts may decide to include or exclude an extraluminal filling defect in the analysis (Fig. 7). As advised to the MERCATOR Angiographic Committee, the computer "decides" whether the extraluminal defect is included or excluded in the analysis, thereby avoiding subjective bias. If there is no clear separation between the lumen and the extravasation (large communicating channel), the computer includes the dissection in the analysis as the interpolated edge detection technique (making use of the weighted sum of first- and second-derivative difference functions applied to the brightness information using minimal cost criteria) will defect a small not significant difference in brightness. However, when the extravasation is distinctly separate from the true vessel lumen (small communicating channel), the computer excludes the dissection from the analysis as there will be a steep difference in brightness between the extravasation and the true lumen (Fig. 7).

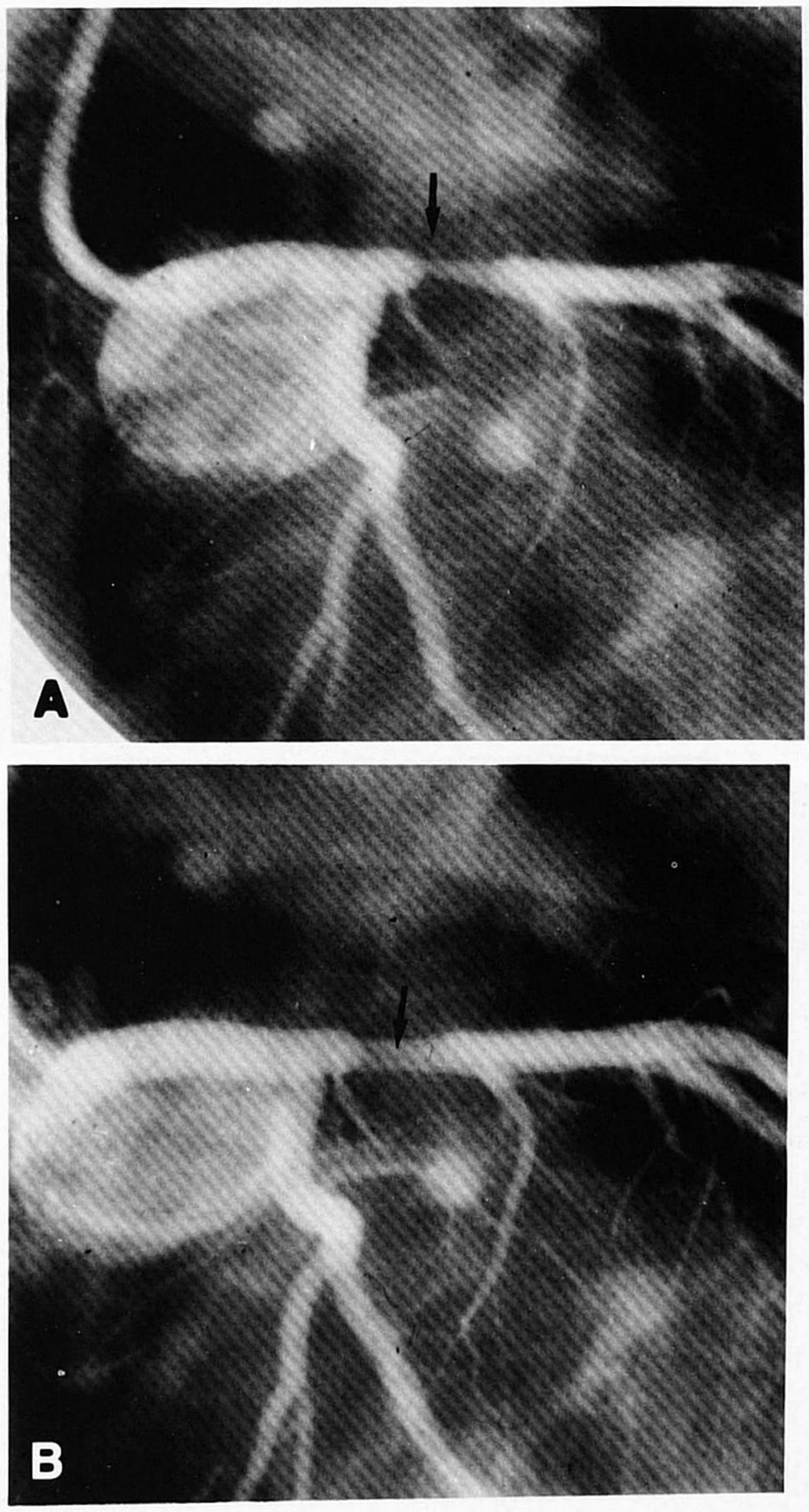


Figure 3. Stenosis in the proximal left anterior descending coronary artery before (**A**) and after (**B**) angioplasty with a typical example of a type A dissection. The **arrows** indicate the site of the lesion before angioplasty (**A**) and the site of an intimal flap after angioplasty (**B**).

End points. Restenosis was defined per lesion. Two different approaches were used to look at the restenosis process. 1) In the *categoric approach*, restenosis was considered to be present when the diameter stenosis was >50% at follow-up angiography because it is still common clinical practice to assess lesion severity in this manner. 2) In the *continuous approach*, which describes how the lesion "behaves" during follow-up, relative loss was defined as the absolute change in minimal lumen diameter, adjusted for vessel size, a procedure that allows comparison of vessels of different sizes.

Clinical outcome was defined for each patient, who was considered to have a dissection if dissection was visible on the postangioplasty angiogram in any dilated segment irrespective of procedural success. Full clinical follow-up was

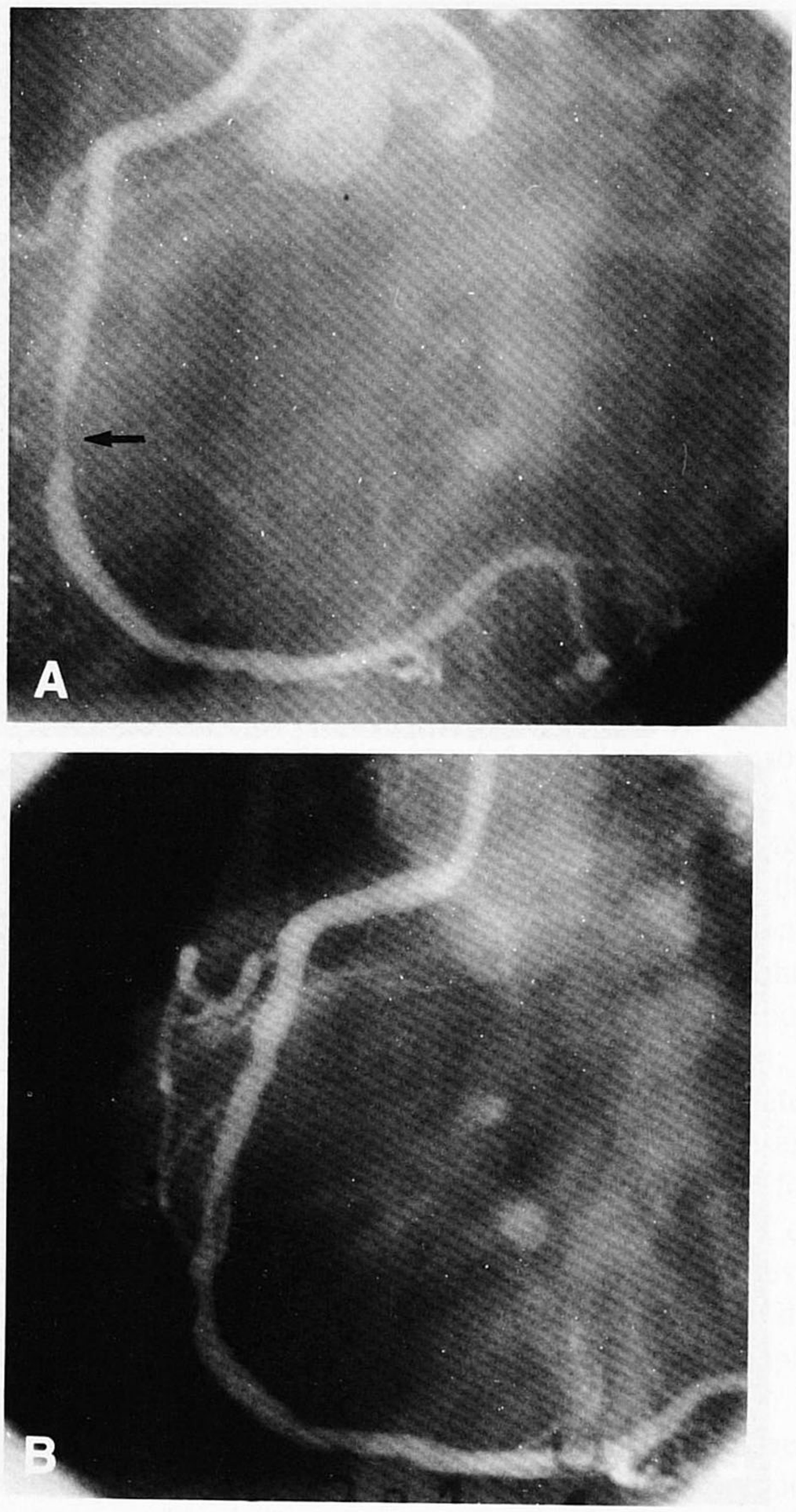


Figure 4. Stenosis in the mid right coronary artery before (**A**) and after (**B**) angioplasty with a typical type B dissection. The **arrows** indicate the site of the lesion before angioplasty (**A**) and the site of the extravasation of contrast material after angioplasty (**B**).

obtained in all 693 randomized patients during a 6-month follow-up period. Clinical status was ranked according to the most serious adverse clinical event that occurred, ranging from death (irrespective of cause), congestive heart failure functional class (New York Heart Association class III or IV), nonfatal myocardial infarction (defined as ECG changes, creatine kinase enzymes more than twice the upper limit of normal with MB fraction >6% of total creatine kinase, with or without symptoms), need for coronary revascularization (coronary artery bypass grafting, repeat coronary angioplasty, stent implantation or atherectomy at the same site or other site), recurrent angina requiring initiation of or an increase in medical therapy, or none of these (28). Only revascularization procedures that were carried out before the study end point (6 months ± 3 weeks) were included as clinical events (30).

Data analysis. Data were analyzed with the BMDP statistical software package (University of California, Berkeley, California 1990). A chi-square test was used to assess the differences in categoric variables. A one-way analysis of variance or Student *t* test was used to assess differences in continuous variables between two or more groups. p values < 0.05 were considered statistically significant. Patient, lesion and procedural variables were assessed for their relation to dissection. For that purpose, continuous variables were grouped into three equally sized subgroups (tertiles) and relative risks were calculated by comparing the subgroup with the highest percentage of dissection with the other two groups combined (reference group) (41). The 95% confidence levels were calculated to determine the precision of these estimates. A statistically significant difference at the 5% level is present where the 95% confidence intervals do not cross a value of 1. To rule out the influence on restenosis of differences in baseline lesion characteristics between the groups with or without dissection, a stepwise multivariate linear (dependent variable, relative loss) and logistic (dependent variable, >50% diameter stenosis) regression analysis was performed.

Results

An angiographically visible dissection was identified in 247 (32%) of the 778 lesions that were successfully dilated and had angiographic follow-up. In 242 lesions, the dissection was classified as type A (n = 82), B (n = 132) or C (n = 28). In only five lesions, it was assessed as type D (n = 3) or E (n = 2).

Patient-related variables and the risk of dissection. The relation between risk of dissection and patient-related variables is described in Table 3. For example, as age is a continuous variable, it was divided in tertiles with the highest frequency of dissection—36%—in the age group ≥62 years. The other two tertiles combined consisted of 514 lesions; in 153 (30%) of these, a dissection was seen on the postangioplasty angiogram. The relative risk of age ≥62 years for dissection was 1.19; that is, patients ≥62 years had 1.19 times the chance of having a dissection visible on the postangioplasty angiogram after successful coronary angioplasty than did patients aged <62 years. The 95% confidence interval of the relative risk for age ≥62 years was 0.97 to 1.48 (p = NS).

Absence of unstable angina and serum cholesterol level <5.7 mmol/liter at baseline were associated with a significantly higher incidence of dissection.

Lesion and procedure-related variables and the risk for dissection. The relation between risk of dissection and lesion and procedural variables is described in Table 4.

The frequency of any dissection was significantly higher with 1) a postangioplasty diameter stenosis >37%, 2) a lesion of intermediate length (≥5 to ≤6.7 mm), 3) an eccentric

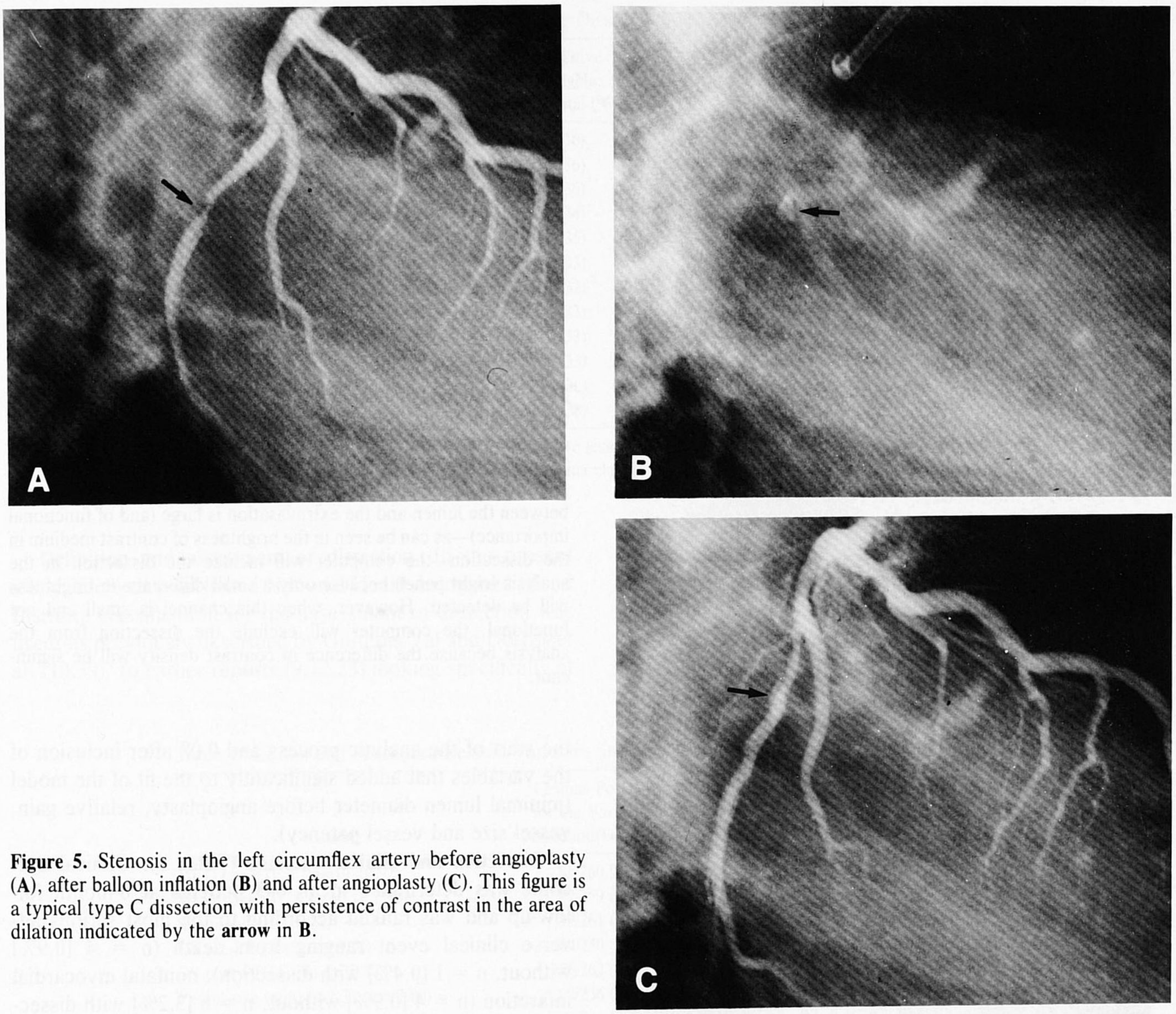


Figure 5. Stenosis in the left circumflex artery before angioplasty (**A**), after balloon inflation (**B**) and after angioplasty (**C**). This figure is a typical type C dissection with persistence of contrast in the area of dilation indicated by the **arrow** in **B**.

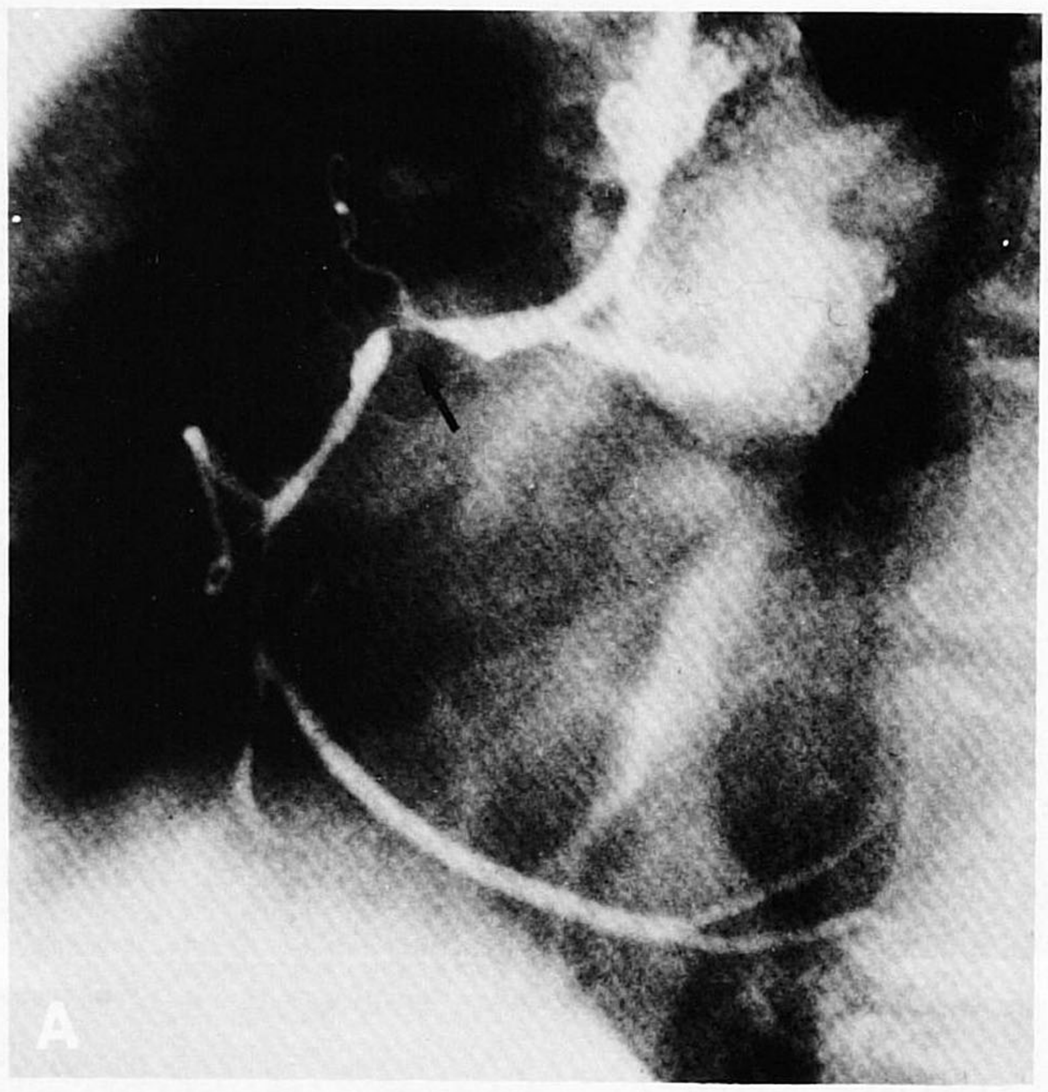
lesion (symmetry <0.23), 4) a lesion located in a more curved segment (curvature index ≥21), 5) a lesion located in the right coronary artery, 6) thrombus observed on the postangioplasty angiogram, 7) application of lower or higher inflation pressure (<7 or >9 atm), 8) noncompliant balloon material was used.

Multivariate logistic regression analysis was performed for all patient-lesion-procedural variables significantly associated with the occurrence of dissection in univariate analysis ($p < 0.05$). Of these variables, 1) absence of unstable angina pectoris, 2) more curved vessels, 3) eccentric lesion location in the vessel, 4) intermediate lesion length, and 5) noncompliant balloon material were retained in the model.

Dissection and restenosis (Table 5). When the restenosis cutoff criterion of ">50% diameter stenosis at follow-up" was used, then almost identical restenosis rates were seen for lesions with dissection (29%; cilazapril 25%, placebo 33%) or without dissection (30%; cilazapril 32%, placebo 29%). Similar rates were found if the type of dissection was grouped according to the National Heart, Lung, and Blood Institute classification with a restenosis rate of 33% for type A, 27% for type B and 32% for type C.

When absolute change in minimal lumen diameter during follow-up was used to define the restenosis process, the "relative loss" in lesions with dissection was 0.10 ± 0.22 (cilazapril 0.09 ± 0.20, placebo 0.13 ± 0.25) and in lesions without dissection was 0.10 ± 0.19 (cilazapril 0.10 ± 0.19, placebo 0.11 ± 0.19). If the type of dissection was subcategorized the relative loss was 0.15 for type A, 0.08 for type B and 0.10 for type C.

Multivariate linear and logistic analyses were performed to determine whether the observed differences between the groups with and without dissection with regard to baseline lesion, patient and procedural variables influenced restenosis according to the two approaches used. In both models, the regression coefficient for dissection was not influenced



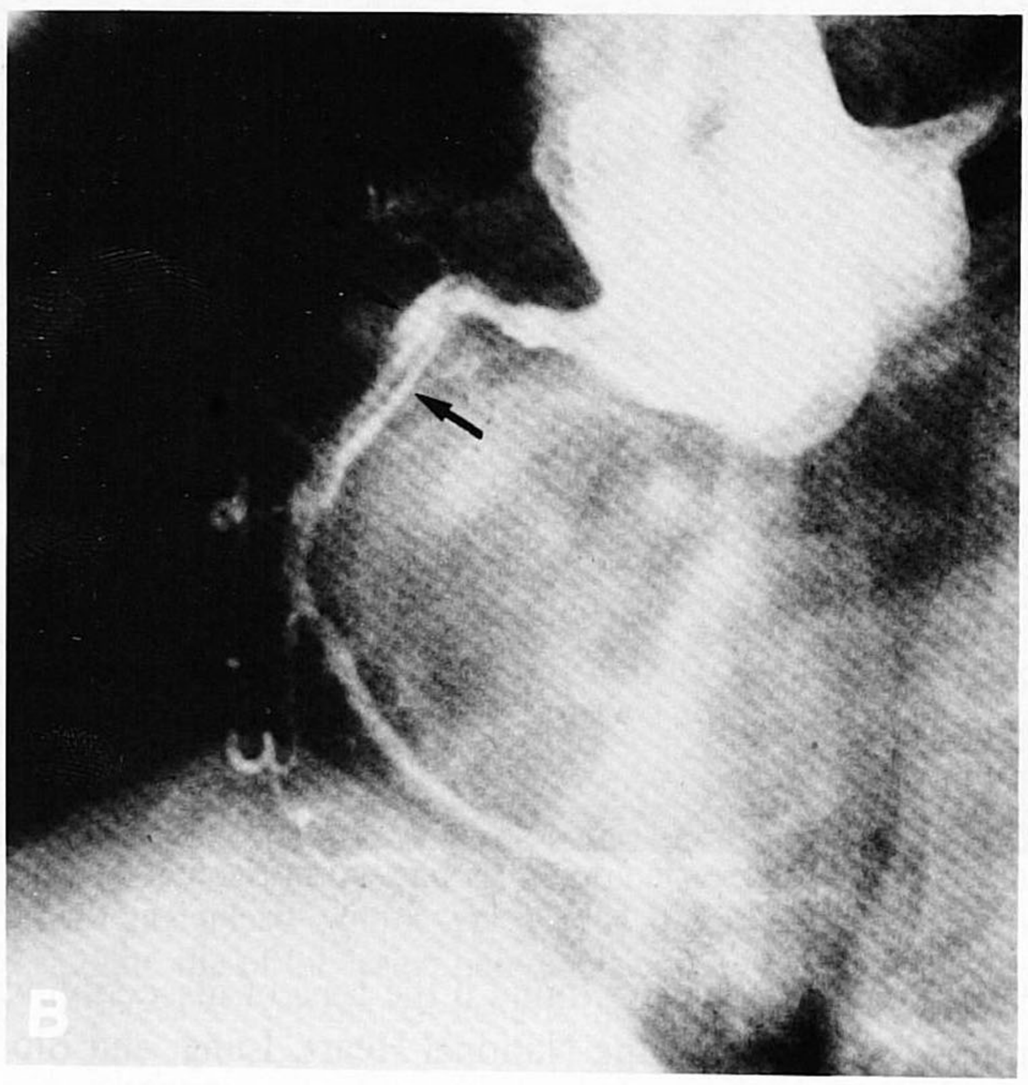


Figure 6. Stenosis in the proximal and mid right coronary artery before (**A**) and after (**B**) angioplasty with a typical type D spiral-shaped dissection associated with decreased flow. The **arrows** indicate the site of the lesions before angioplasty (**A**) and the site of the spiral-shaped dissection with decreased flow after angioplasty (**B**).

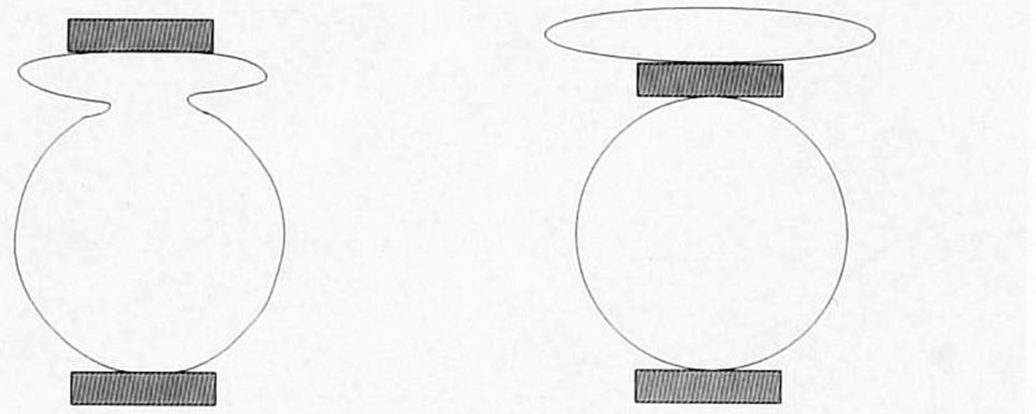


Figure 7. Method of quantitative analysis used when a dissection is not evident on the postangioplasty angiogram. Because a type A dissection is intraluminal, it will be analyzed as seen in the **left panel**. In contrast, type B to E dissections are extravasation outside the contrast-filled lumen. In cases where the communicating channel between the lumen and the extravasation is large (and of functional importance)—as can be seen in the brightness of contrast medium in the dissection—the computer will include the dissection in the analysis (**right panel**) because only a small difference in brightness will be detected. However, when this channel is small and not functional, the computer will exclude the dissection from the analysis because the difference in contrast density will be significant.

by the variables that were significantly associated with restenosis. In the linear model, the regression coefficient for the dissection variable was 0.02 at the start of the analysis process and 0.01 after inclusion of the variables that added significantly (relative gain, minimal lumen diameter after angioplasty and vessel dilated (nonright coronary artery vessel) to the fit of the model. In the logistic model, the regression coefficient for the dissection variable was 0.01 at the start of the analytic process and 0.08 after inclusion of the variables that added significantly to the fit of the model (minimal lumen diameter before angioplasty, relative gain, vessel size and vessel patency).

Dissection and clinical outcome (Table 6). Clinical outcome was determined in all 693 patients at 6-month follow-up and was ranked according to the most serious adverse clinical event ranging from death (n = 4 [0.9%] without, n = 1 [0.4%] with dissection), nonfatal myocardial infarction (n = 4 [0.9%] without, n = 8 [3.2%] with dissection), coronary revascularization (n = 73 [16.6%] without, n = 32 [12.7%] with dissection), recurrent angina requiring medical therapy (n = 88 [20%] without, n = 47 [18.7%] with dissection) to none of these (n = 272 [61.7%] without, n = 164 [65.1%] with dissection). No significant differences in clinical outcome between patients with or without dissection was observed if clinical outcome was evaluated according to the occurrence or nonoccurrence of either "hard events" (death, non-fatal myocardial infarction or coronary revascularization) (with dissection: placebo 17%, cilazapril 16%; without dissection: placebo 19%, cilazapril 18%) or "soft events" (recurrence of angina or no event) (p = 0.22).

Discussion

Two major problems arise in the exploration of a possible relation between an angiographically visible dissection after successful angioplasty and the long-term angiographic and clinical sequelae: 1) definition and assessment of dissection, and 2) definition and assessment of restenosis.

Table 3. Patient-Related Variables and Risk for Dissection

Variable	Lesions Positive for the Variable: Dissection/Total (%)	Lesions Negative for the Variable: Dissection/Total (%)	Relative Risk (95% CI)
Age (≥62 yr)	94/264 (36)	153/514 (30)	1.19 (0.97 to 1.48)
Female	47/129 (36)	200/649 (30)	1.19 (0.92 to 1.53)
Presence of diabetes type II	16/45 (36)	231/733 (32)	1.13 (0.75 to 1.70)
History of myocardial infarction	112/328 (34)	135/450 (30)	1.14 (0.93 to 1.40)
Never smoked	62/175 (35)	185/603 (31)	1.15 (0.92 to 1.46)
Not currently smoking	216/651 (33)	31/127 (24)	1.36 (0.98 to 1.88)
Single-vessel disease*	134/424 (32)	99/316 (31)	1.01 (0.81 to 1.25)
Single-site dilation	177/536 (33)	70/242 (29)	1.14 (0.91 to 1.44)
CCS class at baseline (I,II)†	134/411 (33)	113/365 (31)	1.06 (0.86 to 1.30)
No unstable angina	233/706 (33)	14/72 (19)	1.70 (1.05 to 2.75)
Duration of angina (≥305 days)‡	91/256 (36)	151/510 (30)	1.20 (0.98 to 1.48)
Cholesterol (<5.7 mmol/liter)§	90/239 (38)	147/499 (30)	1.28 (1.03 to 1.58)

*Not available for 38 lesions. †Not available for two lesions. ‡Not available for 12 lesions. §Not available for 40 lesions. CCS = Canadian Cardiovascular Society angina classification; 95% CI = 95% confidence intervals.

Definition and assessment of dissection. In the present study, the well established National Heart, Lung, and Blood Institute classification for the assessment of dissection was used, as previously described by Guiteras Val and Dorros et al. (10,39). In earlier reports (9,12,23) looking specifically at dissection and long-term follow-up, the assessment of dissection may well have been biased by knowledge of clinical variables because patients were assessed in a clinical setting by multiple assessors and inter- and intraobserver variability were not reported. As part of a multicenter study, we

Table 4. Lesion and Procedure-Related Variables and Risk for Dissection

Variable	Lesions Positive for the Variable: Dissection/Total (%)	Lesions Negative for the Variable: Dissection/Total (%)	Relative Risk (95% CI)
MLD pre-PTCA (mm) (<0.92)	85/260 (33)	162/518 (31)	1.05 (0.84 to 1.30)
MLD post-PTCA (mm) (<1.90)	82/259 (32)	165/519 (32)	1.01 (0.81 to 1.25)
Relative gain (≥0.33)	92/261 (35)	155/517 (30)	1.18 (0.95 to 1.45)
DS pre-PTCA (%) (≥64%)	84/250 (34)	163/528 (31)	1.09 (0.88 to 1.35)
DS post-PTCA (%) (≥37%)	100/262 (38)	147/516 (28)	1.34 (1.09 to 1.65)
Vessel size (mm) (≥2.35 to ≤2.80)	92/256 (36)	155/522 (29)	1.21 (0.98 to 1.49)
Length lesion (mm) (≥5 to ≤6.7)*	94/243 (38)	135/484 (28)	1.39 (1.12 to 1.72)
Atherosclerotic plaque (mm^2) (≥7.3)*	83/243 (34)	146/484 (30)	1.13 (0.91 to 1.41)
Symmetry index (<0.23)*	88/232 (38)	141/495 (29)	1.33 (1.07 to 1.65)
Curvature index (≥21)*	87/235 (37)	140/492 (28)	1.31 (1.05 to 1.63)
Totally occluded vessel pre-PTCA	18/51 (35)	229/627 (32)	1.12 (0.76 to 1.65)
RCA dilated	86/222 (39)	161/556 (29)	1.34 (1.08 to 1.65)
Proximal location in vessel	108/292 (37)	139/486 (29)	1.21 (0.98 to 1.51)
Calcified lesion	30/80 (38)	217/698 (31)	1.21 (0.89 to 1.63)
Side branch in stenosis	138/414 (33)	109/364 (30)	1.12 (0.91 to 1.37)
Lesion at bend point	23/65 (35)	224/713 (31)	1.13 (0.80 to 1.59)
Balloon artery ratio ≥1.2	83/246 (34)	164/532 (31)	1.09 (0.88 to 1.36)
Balloon artery ratio ≥1.1†	68/212 (32)	135/419 (32)	1.00 (0.78 to 1.27)
Noncompliant balloon material	143/401 (36)	104/377 (28)	1.30 (1.05 to 1.60)
Stretch ≥0.55†	79/213 (37)	124/418 (30)	1.25 (0.99 to 1.51)
Elastic recoil ≥0.27†	74/213 (35)	129/418 (31)	1.13 (0.89 to 1.42)
Thrombus post-PTCA	14/29 (49)	233/749 (31)	1.55 (1.05 to 2.30)
Maximal balloon pressure (<7 or >9 atm)	109/285 (38)	138/493 (28)	1.37 (1.11 to 1.68)
Total inflation time ≤145 s	80/165 (32)	167/533 (31)	1.04 (0.84 to 1.30)
Number of inflations ≥2 and ≤4	177/544 (33)	70/234 (30)	1.09 (0.86 to 1.37)

*Not available in 51 lesions with a totally occluded vessel. †Available in 631 lesions with an analysis of the inflated balloon at highest inflation pressure used. atm = atmospheres; MLD = minimal lumen diameter; PTCA = percutaneous transluminal coronary angioplasty; RCA = right coronary artery; other abbreviations as in Tables 1 and 3.

Table 5. Dissection After Successful Coronary Angioplasty With Angiographic Follow-Up and the Occurrence of Restenosis per Lesion Dilated: Categoric and Continuous Approach

	Restenosis			Dissection Type				
No.	None (n = 531)	Any (n = 247)	p	A (n = 82)	B (n = 132)	C (n = 28)	D (n = 3)	E (n = 2)
Continuous								
Loss (mm)	0.26 ± 0.48	0.28 ± 0.60	0.57	0.39 ± 0.65	0.23 ± 0.54	0.25 ± 0.55	0.41 ± 0.27	−0.11 ± 0.50
R loss	0.10 ± 0.19	0.10 ± 0.22	0.88	0.15 ± 0.24	0.08 ± 0.21	0.10 ± 0.21	0.16 ± 0.11	−0.04 ± 0.16
Categoric								
DS >50%	159 (30%)	72 (29%)	0.82	27 (33%)	36 (27%)	9 (32%)	0	0

DS = diameter stenosis at follow-up angiography; Loss = difference in minimal lumen diameter between postangioplasty and follow-up studies; R loss = relative loss (loss normalized for the vessel size).

prospectively collected lesion, patient and procedural variables to analyze, as an ancillary study, the relation of an angiographically visible dissection with restenosis and clinical outcome in all randomized patients. All baseline and follow-up films were screened, processed and analyzed at an off-line angiographic core laboratory without knowledge of clinical data. Interobserver and intraobserver variability for dissection (irrespective of type) were defined for the two assessors in the core laboratory (W.R.M.H., B.J.R.) with a kappa of 0.60 for assessor 1, 0.58 for assessor 2 and 0.75 between the two assessors. These kappa values indicates a satisfactory agreement between the two assessors and for each accessor in time (40).

Definition and assessment of restenosis. In virtually all reported studies on the relation between dissection and restenosis, visual estimation or hand-held caliper measurements were used to assess restenosis (8–20). Both of these methods are hampered by relatively wide interobserver and intraobserver variability (27–29). To avoid those pitfalls, in this study we assessed restenosis by quantitative coronary angiography using the CAAS-system, a well validated and extensively described method of analysis (27,31–33). In addition, previous reports represent, in most cases, the early experience of an institution and describe the long-term follow-up of patients who were not angiographically restudied at a predetermined time. The majority of these studies were retrospective analyses and involved a small number of patients (26).

The best definition for restenosis has been the subject of much debate (26). Of the different restenosis criteria proposed, the "50% diameter stenosis at follow-up angiography" is the most frequently used to assess restenosis because physiologic measurements demonstrate that this is the approximate value in animals with normal coronary arteries at which blunting of the hyperemic response occurred (42). This definition was applied to our data. Earlier studies (43) have shown that the reference diameter of a coronary artery is frequently involved in the restenosis process so that the use of percent diameter stenosis (whose calculation depends on the assumption of a "normal" reference diameter segment) may underestimate the change in the severity of a stenosis after coronary angioplasty. Furthermore, "the 50% diameter stenosis at follow-up" criterion tells us nothing about the behavior of the lesion after angioplasty. If this criterion is applied, lesions with a suboptimal angioplasty result will preferentially be identified as undergoing restenosis despite only a minor deterioration in lumen diameter. Our group has previously demonstrated that a change of ≥0.72 mm in minimal lumen diameter is an appropriate, objective method of assessing the degree of intimal hyperplasia during follow-up after coronary angioplasty (27,31,32,44). However, this criterion was historically assessed in vessels with an average reference diameter of 3.7 mm. Therefore it is best applied to vessels of comparable reference diameter. It would be unlikely to observe a loss ≥0.72 mm in coronary segments with a reference diameter of

Table 6. Dissection After Coronary Angioplasty per Patient and Clinical Outcome at 6 Month Follow-Up

	Clinical Event		Dissection Type					
	None (n = 441)	Any (n = 252)	A (n = 76)	B (n = 136)	C (n = 33)	D 3	E 3	F 1
Death	4 (0.9%)	1 (0.4%)	1 (1.3%)	0	0	0	0	0
NYHA III/IV	0	0	0	0	0	0	0	0
Nonfatal MI	4 (0.9%)	8 (3.2%)	4 (5.3%)	4 (2.9%)	0	0	0	0
Revasc	73 (16.6%)	32 (12.7%)	12 (15.8%)	18 (13.2%)	2 (6.1%)	0	0	0
Recurrent angina	88 (20.0%)	47 (18.7%)	16 (21.1%)	23 (16.9%)	7 (21.2%)	1	0	0
No event	272 (61.7%)	164 (65.1%)	43 (56.6%)	91 (66.9%)	24 (72.7%)	2	3	1

MI = myocardial infarction; NYHA III/IV = New York Heart Association functional class III or IV for congestive heart failure; Revasc = coronary revascularization procedure.

2 mm and a minimal lumen diameter of 1.4 mm. In other words, criteria based on the absolute change in minimal lumen diameter are limited because they do not relate the extent of the restenosis process to the size of the vessel. To circumvent this limitation, we used the change in minimal lumen diameter from after angioplasty to follow-up, normalized for the reference diameter (*relative loss*) as earlier reported by our group (37). This "sliding scale criterion," which adjusts for vessel size, allows the accurate regional assessment of the extent of the restenosis phenomenon in the entire coronary tree and also its relation to dissection.

Differences between lesions with and without angiographically visible dissection. None of the patient-related variables appear to be associated with the occurrence of dissection, except for *lower cholesterol levels* before coronary angioplasty and *absence of unstable angina*. Perhaps the atherosclerotic plaques in patients with low cholesterol levels are more fibrous and prone to tearing when stretched. It is surprising that unstable angina (which is much more frequently associated with acute complications, plaque rupture and thrombus formation than is stable angina) was associated with a lower dissection rate in our study. The definition of unstable angina used may describe a particular patient group with recent increase in the rate of plaque development, which is consequently "soft" and therefore more compliant, and less likely to tear than is atherosclerotic plaque in patients with chronic stable angina (21,22). In addition, because only successful dilations were included in the parent study, our data have a potential bias because patients in unstable condition have a higher acute complication rate.

Eccentric and more curved lesions are more prone to dissect during angioplasty than are other lesions. Balloon inflation in this setting is probably associated with unequal distribution of stretch and consequent shearing forces resulting in an intimal tear or dissection.

Intermediate *length of the lesion* was associated with more dissection. It could well be that long lesions are treated with more care (smaller balloon size, lower inflation pressures), as several reports (11,19,20) have suggested higher restenosis rates in long lesions. Because short lesions are easily covered by the normal balloon length, it could be that intermediate length lesions are intermediate and therefore yield more dissections.

The *right coronary artery* was more prone to dissection (especially the proximal part, with 41 dissections of 81 dilated lesions, as assessed with American Heart Association definitions [45]), than was the left circumflex or left anterior descending coronary artery. Lesions in the proximal right coronary artery have higher curvature values (mean = 30 vs. 20 for all other segments); such values constitute an independent risk factor for dissection and probably explain this observation.

Greater postangioplasty diameter stenosis was associated with more dissections. One explanation for this observation may be that an operator who detects a dissection during or after balloon inflation may terminate the angioplasty procedure to avoid further complications, believing the result to be acceptable although suboptimal.

Earlier reports focused attention on the relation between higher *balloon/artery ratio* and acute complications during coronary angioplasty, without any influence on the restenosis rates at 6 months (46,47). In the present study, no influence of the balloon/artery ratio on the occurrence of dissection was detected; the incidence of dissection was similar for a low (<0.9) or high (>1.1) balloon/artery ratio and irrespective of whether the balloon size stated by the manufacturer or the measured (by quantitative analysis) inflated balloon size was used. The balloon/artery ratio describes the relation between the normal vessel wall and inflated balloon. When the balloon/artery ratio is >1.3 the risk for complications is increased because of possible extensive injury to the normal vessel wall. However, in all cases (average minimal lumen diameter 1.02 mm, average balloon size 2.85 mm) the actual stenosis itself is 1 to 3 times "overstretched," with a consequent potential risk of dissection in every case.

The frequency of dissection was greater when a "*noncompliant balloon*" was used. The operator could determine the type of balloon used for dilation, it is impossible to say whether this observation reflects a real difference between the different balloon materials or that the decision of the operator to use a particular balloon depended on the eccentricity of the lesion, length of the lesion, clinical condition of the patient, vessel calcification and the like.

Sarembock et al. (48) demonstrated in an animal model that *high balloon inflation pressures* caused more mural thrombus, dissection and medial necrosis than did low inflation pressures. In our clinical study, low (<7 atm) pressure inflations were also associated with a higher incidence of dissection. Because there were no guidelines for pressure inflations during angioplasty, and routine practice varies center from center, it is not possible to draw a firm conclusion from this observation.

Thrombus after coronary angioplasty was associated with more dissection; however, the cause-effect relation is impossible to decipher because thrombus formation develops as a consequence of a dissection that is partially obstructing blood flow.

Of these variables, the right coronary artery, more curved vessels, eccentric location in the vessel, intermediate length and noncompliant balloon material emerged as the most important variables as they were retained in the multivariate logistic regression analysis that was performed to identify risk factors for dissection.

Dissection and restenosis. Multivariate linear and logistic analyses were performed to determine whether the observed differences between the groups with and without dissection with regard to lesion, patient and procedural variables influenced restenosis according to the two different approaches. As the regression coefficient for dissection was not influenced by the variables that were significantly asso-

ciated with restenosis in both models, it can be deduced that these discrepancies had no influence on restenosis.

Dissection and clinical outcome. Intimal tear or dissection has been reported to be an important predictor of ischemic complications after coronary angioplasty, but only a minority of patients will develop an acute ischemic event (49). Huber et al. (23) reported recently that patients with type B dissection have low rates of complication similar to those of patients without dissection. Patients with types C to F dissection had a significant increase in in-hospital complications. The present study includes only patients with a successful coronary angioplasty, defined as a <50% diameter stenosis on the postangioplasty angiogram. If the clinical condition required repeat coronary angioplasty, the angiogram immediately before the repeat intervention was used to obtain follow-up values, irrespective of the timing of the repeat intervention (hours, days or weeks). Although patients with dissection are considered to be at high risk for an ischemic complication during the in-hospital stay, similar or even slightly better clinical outcome was observed for patients with type B to F dissections in this study. Only 9 patients (1.5%) with an initially successful coronary angioplasty, had a repeat intervention or emergency coronary artery bypass grafting during the hospital stay. Five of these patients had a dissection (type A in three patients, type B in two) visible on the postangioplasty angiogram. Apart from possible bias by participating centers in excluding patients with severe diffuse disease or requiring emergency coronary angioplasty or multisite dilation, we have no explanation for this low in-hospital complication rate. Because type C to F dissections were detected in only 40 patients, strong conclusions regarding these types cannot be drawn in relation to long-term clinical outcome.

Limitations of the study. By definition, the MERCATOR trial included only patients with successful coronary angioplasty; thus no patient with important obstructive dissection was included in our study. This factor could have influenced our results. However, of the 42 patients who agreed to participate in the Mercator trial but were excluded from the analysis for the various reasons described under Methods, 12 patients had an "unwanted" type of dissection complicated by a myocardial infarction or requiring emergency bypass operation.

Coronary arteriography provides information on lumen contour, but not on diffuse vessel wall disease or changes that occur in the vessel wall due to coronary angioplasty. Despite this limitation, it has been used for >30 years as the ultimate diagnostic tool for coronary artery disease. Newer techniques such as intravascular ultrasound imaging can visualize the lumen and the vessel wall and thereby can detect dissections not visible on the coronary angiogram (50). Angioscopic devices demonstrate the lumen surface of the vessel intima and have detected intimal dissections in >90% of the cases after angioplasty whereas angiographic results were normal in 66% of cases (51). Angiographically visible dissections may be considered to be at the larger end of the dissection spectrum; although studies correlating intravascular ultrasound and angioscopic findings with angiographic results in large numbers of patients are still awaited.

Conclusions. Small hemodynamically insignificant but angiographically visible dissections are common after coronary angioplasty, occurring in 32% of successfully dilated lesions in this large series. No significant differences could be detected with regard to restenosis or long-term clinical outcome 6 months after successful coronary angioplasty whether such so-called therapeutic dissections were detected on the postangioplasty angiogram. New techniques, such as intravascular ultrasound or angioscopy, should help to improve understanding of the mechanism of dilation and the true occurrence of dissection, its role in the initiation of the healing process and its relation, if any, with the excessive hyperplastic response that occurs in many lesions.

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Appendix

Participants in the MERCATOR Study Group (Multicenter European Research Trial With Cilazapril After Angioplasty to Prevent Transluminal Coronary Obstruction and Restenosis)

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References

1. Bredlau CE, Roubin GS, Leimgruber PP, Douglas JS Jr, King SB III, Gruentzig AR. In-hospital morbidity and mortality in patients undergoing elective coronary angioplasty. Circulation 1985;72:5:1044–52.
2. Mata LA, Bosch X, David PR, Rapold HJ, Corcos T, Bourassa MG. Clinical and angiographic assessment 6 months after double vessel percutaneous coronary angioplasty. J Am Coll Cardiol 1985;6:1239–44.
3. McBride W, Lange RA, Hillis LD. Restenosis after successful coronary angioplasty. Pathophysiology and prevention. N Engl J Med 1988;318: 1734–7.
4. Waller BF. "Crackers, breakers, stretchers, drillers, scrapers, shavers, burners, welders and melters." The future treatment of atherosclerotic coronary artery disease? A clinical-morphologic assessment. J Am Coll Cardiol 1989;13:969–87.
5. Block PC, Baughman KL, Pasternak RC, Fallon JT. Transluminal angioplasty: correlation of morphologic and angiographic findings in an experimental model. Circulation 1980;61:778–85.
6. Castaneda-Zuniga WR, Formanek A, Tadavarthy M, et al. The mechanism of balloon angioplasty. Radiology 1980;135:565–71.
7. Sanborn TA, Faxon DP, Haudenschild C, Gottsman SB, Ryan TJ. The mechanism of transluminal angioplasty: evidence for formation of aneurysms in experimental atherosclerosis. Circulation 1983;5:1136–40.
8. Holmes DR, Vlietstra RE, Smith HC, et al. Restenosis after percutaneous transluminal coronary angioplasty (PTCA): a report from the angioplasty registry of the National Heart, Lung, and Blood Institute. Am J Cardiol 1984;53(suppl C):77C–81C.
9. Leimgruber PP, Roubin GS, Anderson HV, et al. Influence of intimal dissection on restenosis after successful coronary angioplasty. Circulation 1985;72:3:530–5.
10. Guiteras Val P, Bourassa MG, David PR, et al. Restenosis after successful percutaneous transluminal coronary angioplasty: the Montreal Heart Institute experience. Am J Cardiol 1987;60(suppl B):50B–5B.
11. Vandormael MG, Deligonul U, Kern M, et al. Multilesion coronary angioplasty: clinical and angiographic follow-up. J Am Coll Cardiol 1987;10:246–52.
12. Matthews BJ, Ewels CJ, Kent KM. Coronary dissection: a predictor of restenosis? Am Heart J 1988;115:547–54.
13. Black AJR, Anderson HV, Roubin GS, Powelson SW, Douglas JS Jr, King SB III. Repeat coronary angioplasty: correlates of a second restenosis. J Am Coll Cardiol 1988;11:714–8.
14. de Feyter PJ, Suryapranata H, Serruys PW, et al. Coronary angioplasty for unstable angina: immediate and late results in 200 consecutive patients with identification of risk factors for unfavorable early and late outcome. J Am Coll Cardiol 1988;12:324–33.
15. Fleck E, Regitz V, Lehnert A, Dacian S, Dirschinger J, Rudolph W. Restenosis after balloon dilatation of coronary stenosis multivariate analysis of potential risk factors. Eur Heart J 1988;9(suppl C):15–8.
16. Quigley PJ, Hlatky MA, Hinohara T, et al. Repeat percutaneous transluminal coronary angioplasty and predictors of recurrent restenosis. Am J Cardiol 1989;63:409–13.
17. Renkin J, Melin J, Robert A, et al. Detection of restenosis after successful coronary angioplasty: improved clinical decision making with use of a logistic model combining procedural and follow-up variables. J Am Coll Cardiol 1990;16:1333–40.
18. Rupprecht HJ, Brennecke R, Bernhard G, Erbel R, Pop T, Meyer J. Analysis of risk factors for restenosis after PTCA. Cathet Cardiovasc Diagn 1990;19:151–9.
19. Bourassa MG, Lespérance J, Eastwood C, et al. Clinical physiologic, anatomic and procedural factors predictive of restenosis after percutaneous transluminal coronary angioplasty. J Am Coll Cardiol 1991;18:368–76.
20. Hirshfeld JW Jr, Schwartz JS, Jugo R, et al. Restenosis after coronary angioplasty: a multivariate statistical model to relate lesion and procedure variables to restenosis. J Am Coll Cardiol 1991;18:647–56.
21. Detre KM, Holmes DR Jr, Holubkov R, et al. Incidence and consequences of periprocedural occlusion. The 1985–1986 National Heart, Lung, and Blood Institute Percutaneous Transluminal Coronary Angioplasty Registry. Circulation 1990;82:739–50.
22. de Feyter PJ, van den Brand M, Laarman GJ, van Domburg R, Serruys PW, Suryapranata H. Acute coronary artery occlusion during and after percutaneous transluminal coronary angioplasty. Frequency, prediction, clinical course, management, and follow-up. Circulation 1991;83:927–36.
23. Huber MS, Mooney JF, Madison J, Mooney MR. Use of a morphologic classification to predict clinical outcome after dissection from coronary angioplasty. Am J Cardiol 1991;68:467–71.
24. Nobuyoshi M, Kimura T, Ohishi H, et al. Restenosis after percutaneous transluminal coronary angioplasty: pathologic observations in 20 patients. J Am Coll Cardiol 1991;17:433–9.
25. Schwartz RS, Huber KC, Murphy JG, et al. Restenosis and the proportional neointimal response to coronary artery injury: results in a porcine model. J Am Coll Cardiol 1992;19:267–74.
26. Beatt KJ, Serruys PW, Hugenholtz PG. Restenosis after coronary angioplasty: new standards for clinical studies (editorial). J Am Coll Cardiol 1990;15:491–8.
27. Reiber JHC, Serruys PW. Quantitative angiography. In: Marcus ML, Schelbert HR, Skorton DJ, Wolf GL, eds. Cardiac Imaging. New York: WB Saunders, 1991:211–80.
28. Beaumann GJ, Vogel RA. Accuracy of individual and panel interpretations of coronary arteriograms: implications for clinical decisions. J Am Coll Cardiol 1990;16:108–13.
29. Flemming RM, Kirkeeide RL, Smalling RW, Gould KL, Stuart Y. Patterns in visual interpretation of coronary arteriograms as detected by quantitative arteriography. J Am Coll Cardiol 1991;18:945–51.
30. MERCATOR study group. Does the new angiotensin converting enzyme inhibitor cilazapril prevent restenosis after percutaneous transluminal coronary angioplasty? The results of the MERCATOR-study: a multicenter randomized double-blind placebo-controlled trial. Circulation 1992;86:100–11.
31. Reiber JHC, Serruys PW, Kooyman CJ, et al. Assessment of short, medium and long-term variations in arterial dimensions from computer assisted quantification of coronary cineangiograms. Circulation 1985;71: 280–8.
32. Serruys PW, Luijten HE, Beatt KJ, et al. Incidence of restenosis after successful coronary angioplasty: a time-related phenomenon. Circulation 1988;77:361–71.
33. Serruys PW, Rutsch W, Heyndrickx GR, et al. Prevention of restenosis after percutaneous transluminal coronary angioplasty with thromboxane A2 receptor blockade. A randomized double-blind placebo-controlled trial. Circulation 1991;84:1568–80.
34. Hermans WRM, Rensing BJ, Strauss BH, Serruys PW. Methodological

problems related to the quantitative assessment of stretch, elastic recoil and balloon-artery ratio. Cathet Cardiovasc Diagn 1992;179–85.
35. Rensing BJ, Hermans WRM, Beatt KJ, et al. Quantitative angiographic assessment of elastic recoil after percutaneous transluminal coronary angioplasty. Am J Cardiol 1990;66:1039–44.
36. Rensing BJ, Hermans WRM, Strauss BH, Serruys PW. Regional differences in elastic recoil after percutaneous transluminal coronary angioplasty: a quantitative angiographic study. J Am Coll Cardiol 1991;17(suppl B):34B–8B.
37. Hermans WRM, Rensing BJ, Kelder JC, de Feyter PJ, Serruys PW. Postangioplasty restenosis rate between segments of the major coronary arteries. Am J Cardiol 1992;69:194–200.
38. Ellis SG, Roubin GS, King SB III, Douglas JS Jr, Cox WR. Importance of stenosis morphology in the estimation of restenosis risk after elective percutaneous transluminal coronary angioplasty. Am J Cardiol 1989;63: 30–4.
39. Dorros G, Cowley MJ, Simpson J, et al. Percutaneous transluminal coronary angioplasty: report of complications from the National Heart, Lung, and Blood Institute PTCA Registry. Circulation 1983;67:4:723–30.
40. Fleiss JL. Statistical Methods for Rates and Proportions. 2nd ed. New York: John Wiley, 1981:212–36.
41. Rothman KJ. Modern Epidemiology. Boston: Little, Brown, 1986:115–25.
42. Gould KL, Lipscombe K. Effects of coronary stenosis on coronary flow reserve and resistance. Am J Cardiol 1974;33:87–94.
43. Beatt KJ, Luijten HE, de Feyter PJ, van den Brand M, Reiber JHC, Serruys PW. Change in diameter of coronary artery segments adjacent to stenosis after percutaneous transluminal coronary angioplasty. Failure of percent diameter stenosis measurements to reflect morphologic changes induced by balloon dilatation. J Am Coll Cardiol 1988;12:315–23.
44. Serruys PW, Strauss BH, Beatt KJ, et al. Angiographic follow-up after placement of a self-expanding coronary artery stent. N Engl J Med 1991;324:13–7.
45. Austen WG, Edwards JE, Frye RL, et al. A reporting system on patients evaluated for coronary artery disease. Report of the adhoc committee for grading of coronary artery disease, council on cardiovascular surgery, American Heart Association. Circulation 1975;51:7–40.
46. Roubin GS, Douglas JS Jr, King SB III, et al. Influence of balloon size on initial success, acute complications, and restenosis after percutaneous transluminal coronary angioplasty. A prospective randomized study. Circulation 1988;78:557–65.
47. Nichols AB, Smith R, Berke AD, Shlofmitz RA, Powers ER. Importance of balloon size in coronary angioplasty. J Am Coll Cardiol 1989;13:1094–100.
48. Sarembock IJ, LaVeau PJ, Sigal SL, et al. Influence of inflation pressure and balloon size on the development of intimal hyperplasia after balloon angioplasty: a study in the atherosclerotic rabbit. Circulation 1989;80: 1029–40.
49. Black AJR, Namay DL, Niederman AL, et al. Tear or dissection after coronary angioplasty. Morphologic correlates of an ischemic complication. Circulation 1989;79:1035–42.
50. Tobis JM, Mallery J, Mahon D, et al. Intravascular ultrasound imaging of human coronary arteries in vivo. Circulation 1991;83:913–26.
51. Uchida Y, Hasegawa K, Kawamura K, Shibuya I. Angioscopic observation of the coronary luminal changes induced by coronary angioplasty. Am Heart J 1989;117:769–76.