ELASTIC RECOIL, DISSECTION and RESTENOSIS
in patients treated by coronary balloon angioplasty

ELASTIC RECOIL, DISSECTIE en RESTENOSIS
in patienten die behandeld zijn met balloon dilatatie

PROEFSCHRIFT

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Cover Simplified presentation of how pharmacological agents could inhibit the restenosis proces

"Financial support by the Netherlands Heart Foundation for the publication of this thesis is gratefully acknowledged".

Aan Margriet,
en aan mijn ouders

CONTENTS

CHAPTER 1

GENERAL INTRODUCTION

Part of introduction has been published in 2 book chapters:

Restenosis following coronary angioplasty. Serruys PW, Rensing BJ, Luijten HE, Hermans WRM, Beatt KJ. In: Meier B, editor. *Interventional Cardiology*. Hogrefe & Huber Publishers, Toronto - Lewiston - Bern - Gottingen - Stuttgart. 1989;79-115.

Assessment of early and late success after PTCA. Hermans WRM, Foley D, Rensing BJ, di Mario C, Serruys PW. In: Faxon D, editor, *Practical angioplasty*, Raven Press. 1992;(in press)

GENERAL INTRODUCTION

In 1929, Forssman in Eberswald, Germany, inserted a catheter into his own left basilica vein and advanced it into his right atrium (1,2). This experiment was received with scornful criticism by his medical colleagues and was subsequently ignored for several years. In 1941, Cournand and associates and Richards rediscovered the "cardiac" catheter, employing it for the first time as a diagnostic tool (e.g. congenital and acquired (rheumatic) heart disease) (2). In 1964, Charles Dotter and Melvin Judkins developed a therapeutic purpose for the catheter by using an coaxial system of catheters to improve blood flow in patients with peripheral arteriosclerosis. However, they were criticized for their high incidence of complications (significant hematomas, distal emboli) (2,3). In 1974, Gruentzig modified the multiple catheter system of Dotter, with subsequent decreasing percentage of periprocedural hematoma. When used in the iliac and femoropopliteal arteries, the Gruentzig system achieved an initial patency of 86% and a 3 year cumulative patency rate of 73% (3). In 1976, Gruentzig miniaturized his peripheral balloon catheter to perform coronary angioplasty, initially in a canine model and later in human cadaver experiments. Then in 1977, in Zurich, Gruentzig performed the first percutaneous transluminal coronary balloon angioplasty (PTCA) in a human (4). Ever since, coronary balloon angioplasty has become a widely accepted treatment modality for patients with coronary artery disease, as it appeared to be safe and effective. Acceptance of coronary balloon angioplasty was given a major boost by the live demonstration courses in Zurich. In 1991 alone, more than 400.000 patients have been treated worldwide, and most likely the annual number will increase further. Major improvements in "angioplasty hardware" and operator experience, have resulted in a high primary success rate (more than 90%) and low complication rate (4-5% death, non-fatal myocardial infarction, acute bypass operation) despite extension of the indication to include patients with unstable angina, multivessel disease and totally occluded vessels (5).

Mechanism of coronary balloon angioplasty

Despite the therapeutic success of coronary angioplasty with a wider arterial lumen after the procedure, the exact mechanism of dilatation remains speculative and apparently involves multiple processes. Dotter, Judkins and, later on, also Gruentzig initially attributed the mechanism of balloon angioplasty to redistribution and compression of intimal atherosclerotic plaque (2,4). Data from angioplasty results in experimental models, human necropsy coronary arteries, and human vessels examined after successful or complicated coronary angioplasty procedures, revealed that plaque fracture, intimal atherosclerotic flaps, and localized medial dissection as the major

mechanism of balloon angioplasty (6-14). An additional mechanism appears to be stretching of plaque-free wall segments of eccentric atherosclerotic lesions (11,12). Recently, intravascular ultrasound imaging after balloon angioplasty have shown morphological patterns similar to previous histopathological morphology studies (15). An initial increase of the cross-sectional area is observed after coronary balloon angioplasty, but immediate or delayed elastic recoil (especially in eccentric type lesions) might reduce the coronary lumen towards predilatation and could be cause of early or late restenosis. The presence of elastic recoil has been demonstrated by in-vivo quantitative angiography and balloon ultrasound inflation catheters (BUIC) (14-19).

Risk of treatment with coronary balloon angioplasty

Patients treated with coronary balloon angioplasty are at risk for 2 major coronary events:

[1] Abrupt vessel closure

The reported incidence of acute coronary artery occlusion varies, depending on the definition applied, from 2% to 11% (20-22). It is the major cause of in-hospital coronary balloon angioplasty related morbidity and mortality, and has restricted application of this technique to centers where surgical standby can be provided or is readily accessible. The mechanisms of abrupt coronary artery occlusion are multifactorial and include:

1) Mechanical obstruction due to intimal dissection,
2) Elastic recoil following dilatation,
3) Platelet adhesion and aggregation with ensuing intracoronary thrombus formation,
4) Sub-intimal hemorrhage, and
5) Vasoconstriction or frank spasm of the disease free wall (7,12,16,17,23).

It is not always possible to distinguish between these mechanisms by angiography and they often occur in combination. However, it is likely that occlusive dissection accounts for the vast majority of abrupt coronary artery occlusion. Although acute coronary occlusion during coronary balloon angioplasty is unpredictable in the individual patient, it appears that female gender, unstable angina, multivessel disease, multiple lesions in same vessel, collateral flow from the lesion, intracoronary thrombus, severe narrowing, long lesion, ulcerated lesion. lesion at branch point, lesion at bend point are important pre procedural factors. Tear or dissection, remaining stenosis and

gradient of more than 20 mmHg are important post procedural factors (20,21,22).

[2] Restenosis or luminal narrowing after coronary balloon angioplasty

Restenosis or the recurrence of the stenosis after initially successful coronary balloon angioplasty is the major limitation of coronary balloon angioplasty, which restricts the long term benefit of the procedure. Restenosis occurs in 17% to 40% of all dilated lesions, this variability being mainly a consequence of 1) angiographic follow-up ranges between 57% to 100%, 2) time to follow-up ranges between 1 and 9 months, 3) different criteria of restenosis have been applied (angiographic, clinical, physiologic), and 4) visual assessment of the coronary angiogram is used in most studies (24). At present time, the restenosis process is not well understood. This is the reason why there have been at least 13 different "definitions", based on coronary angiographic findings, applied by various clinical investigators attempting to address the problem of restenosis through clinical studies in recent years (table 1).

Table 1 *Selection of criteria for angiographic restenosis in current use*

1	Loss of > 30% diameter stenosis from post-PTCA to follow-up (NHLBI I).
2	An immediate post-PTCA diameter stenosis < 50% and a diameter stenosis > 70% at follow-up (NHLBI II).
3	A return to within 10% if the pre-PTCA diameter stenosis (NHLBI III).
4	Loss at follow-up of at least 50% of the initial gain after PTCA (NHLBI IV).
5	Loss of > 20% diameter stenosis from post-PTCA to follow-up.
6	An immediate post-PTCA diameter stenosis < 50% that increase to > 50% at follow-up.
7	A diameter stenosis > 50% at follow-up
8	A diameter stenosis > 70% at follow-up .
9	Area stenosis > 85% at follow-up .
10	Loss of > 1 mm^2 in stenosis area from post-PTCA to follow-up.
11	A change of $\geq$0.72 mm in minimal luminal diameter from post-PTCA to follow-up.
12	A change of $\geq$0.50 mm in minimal luminal diameter from post-PTCA to follow-up.
13	Diameter stenosis > 50% at follow-up of a successfully dilated lesion (defined as diameter stenosis < 50%, and a gain of > 10% in luminal diameter, immediately after PTCA), excluding lesions with a < 10% deterioration in diameter stenosis since PTCA.

However, it seems that the pathological process of restenosis, is usually completed within 2 to 5 months after the procedure, and rarely continues after 6 months (25,26). In the last 10 years, attempts to retard the rate of this late complication of coronary balloon angioplasty have failed. Although many risk factors for restenosis have been identified (table 2) (27-31), most are difficult to influence and it seems to be impossible to reliably predict which patients or vessel segments will develop restenosis.

Table 2 *Factors predictive of restenosis*

Clinical Factors	Male
	Unstable angina
	No history of Myocardial Infarction
Lesional Factors	Bypass graft
	Initial lesion severity
	Residual percent diameter stenosis
	Lesion length > 10 mm
	Left Anterior Descending Artery
Procedural Factors	Long single inflation
	"Optimal" balloon-artery ratio (1.1-1.3)

Abstracted from ref. 27-31, pre-requisite for inclusion: study population comprised more than 250 patients, with an angiographic follow-up rate of 65% or more.

Despite many well designed and executed clinical trials of anti-thrombotic, anti-proliferative, anti-inflammatory, anti-spastic and lipid-lowering agents in the last 8 years (table 3)(32-37), a pharmacological solution has (yet) not been reached.

Table 3 *Pharmacological Interventions to prevent restenosis using drugs against:*

*	**Thrombosis** Heparin, hirudin, coumadin, acetylsalicylic acid, dipyridamole, sulfinpyrazone, thromboxane A2-synthetase inhibitor, thromboxane A2 receptor blocker, ticlopidine, prostacyclin, ciprostene, 7E3, fish oil, NSAID.
*	**Cell proliferation** Low molecular weight heparin, platelet derived growth factor antagonist (trapidil), angiotensin converting enzyme-inhibitor (cilazapril), colchicine, cytostatic agents, serotonin antagonist (ketanserin), angiopeptin.
*	**Inhibitor of inflammation** Corticosteroids, non-steroidal anti-inflammatory drugs.
*	**Coronary vasospasm** Nifedipine, diltiazem, verapamil.
*	**Lipid regulators** Fish oil, lovastatin.

Pathophysiology of restenosis after coronary balloon angioplasty

"Restenosis" or luminal narrowing after coronary balloon angioplasty refers to the process by which a blood vessel tends to renarrow following the mechanical injury imparted by a balloon (or other device). Recently, two restenosis models have been proposed to explain this very complex process to injury.

Forrester et al. hypothesized that restenosis is a manifestation of the general wound healing process expressed specifically in vascular tissue and occurs in 3 characteristic phases: 1) inflammation, 2) granulation and 3) extracellular matrix remodelling (38). As intact endothelium prevents platelet aggregation, a superficial endothelial injury leads to local platelet and leucocyte adhesion without release of the granules in the platelets. In case of a coronary balloon angioplasty - with intimal or medial injury -, the hemostatic system is activated and the granule's of the platelets are released. Thus, the inflammatory phase begins with coagulation of blood and fibronectin, while platelets aggregate at the wound surface, releasing promotor for local vasoconstriction, thrombus formation, further platelet aggregation, and growth factors (figure 1).

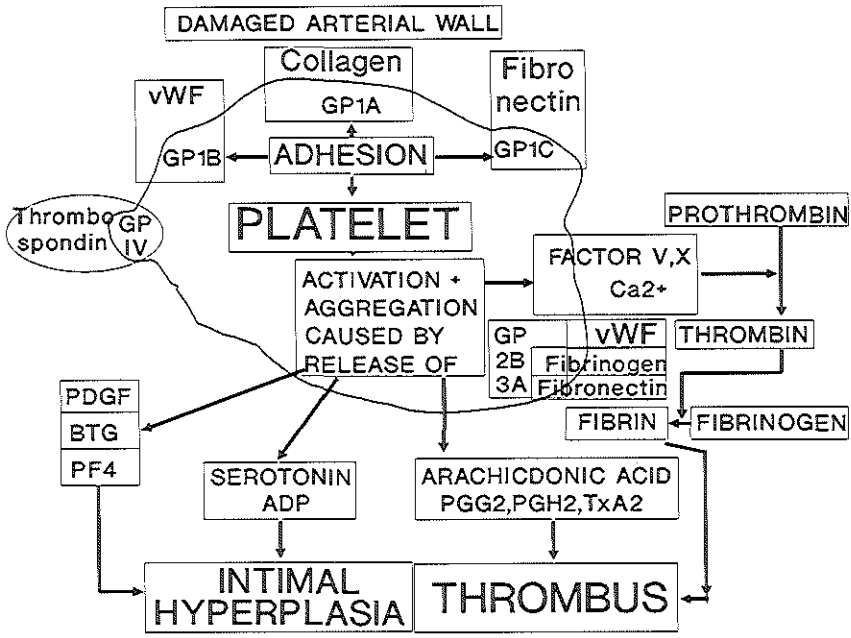

Fig.1 *Simplified presentation of platelet adhesion, activation and aggregation*

The granulation phase is marked by migration and proliferation of epithelial or endothelial cells from the wound margin and fibroblasts or smooth muscle cells from adjacent tissue, to cover the wound surface. The most prominent cell in intimal hyperplasia is the smooth muscle cell. Control of migration and proliferation is determined by the action of growth factors and their opposites (table 4).

Table 4 *Potential role of growth factors in coronary restenosis*

Growth factor	Potential Action in Restenosis
PDGF	Stimulates smooth muscle cell migration and proliferation
FGF	Stimulates endothelial cell and fibroblast proliferation
EGF	Replaces heparin on cell surface; promotes smooth muscle cell proliferation
IGF	Promotes smooth muscle cells proliferation and extracellular matrix production
TGF	Regulates matrix remodelling: possibly regulates other growth factors

PDGF = Platelet derived growth factor; FGF = Fibroblast growth factor; EGF = Epidermal growth factor; IGF = Insulin-like growth factor; TGF = Transforming growth factor

Smooth muscle cells has two phenotypes: 1) contractile (quiescent) phenotype in normal vascular media, 2) synthetic (secretory) phenotype in injured tissue with abundant synthetic organelles (such as free ribosomes, Golgi apparatus, and rough endoplasmic reticulum). In about 7 days, the phase of cellular migration and proliferation is slowed down and remodelling takes over, with production of large amount of chondroitin-sulfate and dermatan sulfate. By several months, the return of the contractile smooth muscle cell phenotype is paralleled by a change in the extracellular matrix: proteoglycans by collagen and elastin, and this finishes the wound healing process (38).

An alternative restenosis model, based on observations in a porcine coronary injury model, has been put forward by Schwartz et al., where platelets and thrombus play a central role (39). In response to arterial injury, platelets, fibrin and red blood cells accumulate at the injured site (thrombotic phase). This thrombus endothelializes, and mononuclear cells infiltrate on the lumen side of the vessel (recruitment phase). Cells, staining positive for alpha-actine (smooth muscle cells or myofibroblasts), form a thin cap just beneath the endothelial surface (proliferative phase). This cap thickens downward the media as the remaining thrombus material is resorb. The healing process is completed as all thrombus has been resolved and replaced by neointima. Since the smooth muscle cells first appear at the *luminal* side of the endothelialized thrombus, their origin is apparently not the media. From these observations, they concluded that the magnitude of the luminal narrowing process may derive more from the volume of local mural thrombus at the site of arterial injury than from uncontrolled cellular proliferation (39).

Two additional mechanisms of luminal narrowing at the angioplasty site are delayed elastic recoil and progression of the atherosclerotic plaque (12,40).

Approaches to detection of restenosis

Maintained success or its counterpart, restenosis, after an initial successful coronary balloon angioplasty, may be evaluated by:

1) Symptomatic criteria

Maintained improvement in quality of life is the goal of any therapeutic treatment modality, but as previously mentioned it is also the least objective evaluation of success. The reappearance of angina as the criterion of restenosis underestimates the angiographic rate of restenosis since the reported incidence of silent restenosis may be as high as 31% (41). Recently Califf et al. described that in studies with a high rate of angiographic follow-up, the probability that patients with symptoms had restenosis (positive predictive value) ranged form 48% to 92%, whereas the probability that

patients without symptoms were free of restenosis (negative predictive value) ranged from 70% to 98% (42). The low positive predictive value found in many of these studies may be explained by the presence of other mechanisms of angina, such as incomplete revascularization or progression of disease in other vessels. In view of the above considerations, the usefulness of symptomatic criteria for the detection of restenosis is at best limited.

The "paradox" of angiographic recurrent stenosis in the absence of clinical symptoms can be explained in part by looking more closely at the definition of restenosis used. If restenosis is said to be present when there is a loss of at least 50% of the initial diameter gain, a 60% diameter stenosis that is reduced to 10% by angioplasty assumes recurrence with a diameter stenosis of 35% at follow-up. It is not surprising that such a patient is likely to be asymptomatic, since a diameter stenosis of 35% is usually not hemodynamically significant.

2) Functional criteria

As far as detection of restenosis by noninvasive diagnostic tests is concerned, it can be said that in general an abnormal exercise ECG response or myocardial perfusion defect[s] on a thallium-201 scintigram are either associated with an angiographically demonstrable restenosis of the dilated segment or are the result of presence of additional disease (43-46). However, coronary collaterals to the myocardial region supplied by the dilated but restenosed vessel may provide adequate circulation to prevent exercise-induced thallium perfusion defects (47-51).

A) ECG exercise testing

Several studies have examined the ability of the exercise test to detect restenosis after coronary angioplasty. These studies have generally found that the presence of exercise induced ST-segment depression, angina on exercise, or both are not highly predictive of restenosis whether the test is performed early or late after angioplasty. The positive predictive value of early exercise testing ranges from 29% to 60%, and the corresponding value for late exercise testing ranges from 39% to 64% (42,52). These low values are most likely a consequence of incomplete revascularization. It is, however, also possible that the non-invasive test accurately demonstrates a functionally inadequate dilatation, despite the appearance of angiographic success.

B Thallium scintigraphy

The positive predictive value of thallium scintigraphy for detection of restenosis in series with a variable angiographic follow-up ranged from 37%-100% (42). Since coronary angiography is "the gold standard" for detection of restenosis in these

studies, the reported value of a non-invasive test is determined not only by the actual accuracy of the test but also by the completeness of angiographic follow-up. In studies with a high angiographic follow-up rate, the negative predictive value of thallium scintigraphy varies between 42% and 100%. Tomographic imaging of nuclear scintigrams may prove superior to planar imaging for the detection of restenosis (53). Of practical interest in this regard, a recent study (54), albeit in a small series of patients, suggests that exercise Tl-201 tomoscintigraphy with rest reinjection may be a useful means of detecting "restenosis".

3) Anatomic criteria

Although contrast angiography is still the "gold standard", intracoronary biopsies and intravascular ultrasound imaging emerge as two new modalities of investigation, of early and late assessment of any intervention.

A) Intravascular ultrasound

Intravascular ultrasound (IVUS) has the potential to offer new insights into the mechanisms, complications and long-term results of coronary interventions. However, before IVUS can be accepted as an alternative to arteriography, several significant limitations need to be overcome. In particular the size and relative inflexibility of the current devices prevent their routine use. In addition, the safety and accuracy of IVUS has yet to be demonstrated in clinical studies (18).

B) Histology

On-line in vivo histological assessment of biopsies taken with the atherectomy catheter is currently the only approach which can discriminate between classic atherosclerosis and fibrocellular hyperplasia. However, to what extent single biopsy samples represent the lesion as a whole is still undetermined. Although, this technique is only applicable in a subset of patients with a lesion suitable for atherectomy treatment, it does offer an additional perspective. Some authors have suggested, that there may be a relationship between the cellular density of the atherectomy specimen or growth rate, and migratory rate of these cells in culture, and the later development of restenosis (55-59).

C) Coronary Angiography

In view of the above, coronary angiography is still the most objective and reliable means of assessing the long term outcome of coronary interventions.

Visual qualitative assessment of cine-angiogram

Visual assessment of percentage diameter stenosis of a diseased coronary artery still remains the "gold standard" in more than 99% of centers performing coronary angiography (60,61). In addition, attempts to correlate closely the anatomy of a coronary stenosis and its physiologic significance by visual interpretation of cine-angiograms, are hampered be several serious shortcomings. The large intra-and interobserver variation (62-65), and lack of correlation with pathologic (66) and intra-operative (67) findings are well recognized. Furthermore, the reproducibility of visual lesion assessment is influenced by the severity of the coronary stenosis. In general, lesions between 20-80% diameter obstruction [moderate lesions] have a wider range of intra and inter observer variabilities than stenoses less than 20% or more than 80% (68). A recent report, where visual interpretation of coronary arteriograms was compared with quantitative coronary arteriographic assessment, confirmed these earlier findings that: 1) visual estimates of "moderately" severe stenosis were 30% higher than quantitatively measured actual percent diameter stenosis, 2) visual estimates diagnosed significantly more three-vessel disease, 3) visual interpretation significantly overestimated initial lesion severity and underestimated stenosis severity after angioplasty (69,70). The accuracy of visual lesion assessment of coronary cineangiograms is limited in the range of the intermediate severity in which minor luminal changes in moderate lesions is compounded by the fact that these minor changes have major hemodynamic consequences. While resting coronary blood flow is not dramatically altered until an obstruction of at least 85% of the diameter is present, maximal coronary flow is already diminished by obstructions as small as 30%, and marked impairment of coronary flow reserve [CFR] occurs with progressive diameter stenosis from 65-95% (71).

Quantitative coronary angiography

Since visual interpretation of the coronary angiogram is a poor means of predicting the physiological importance of obstructive coronary artery disease (70), automatic quantification systems have been introduced in recent years aimed at enhancing objectivity and reproducibility in the assessment of coronary artery dimensions. These computer programs analyze the coronary lesion either by 1) automated border detection of the segment of interest ("edge detection"), or 2) densitometric analysis of the radiographic image (using the concept that the density across an artery in a radiographic image is proportional to the cross-sectional area at that point) (72-74).

The Coronary Angiographic Analysis System (CAAS) has been in operation at

the Thoraxcenter since 1982 and has been rigorously and extensively validated (75,76). An example of an analysis is shown in figure 2.

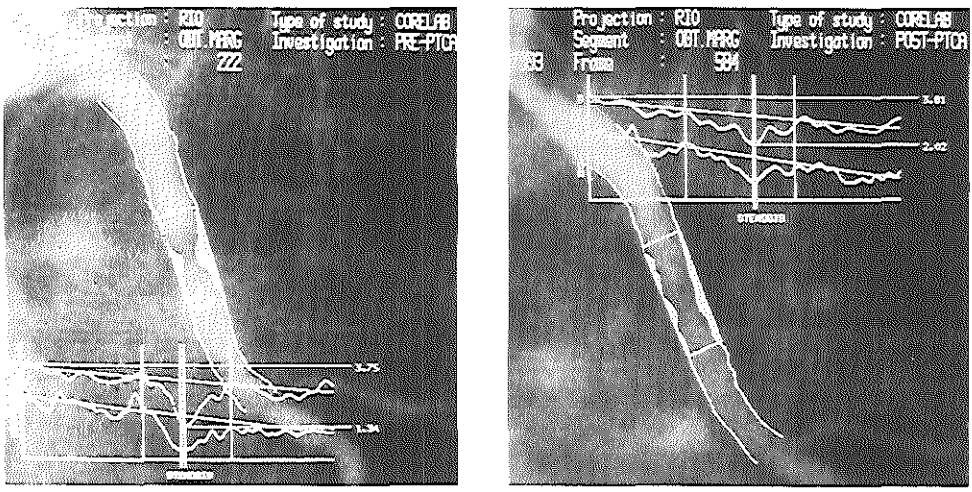

Figure 2 *Example of a stenosis in the marginalis branch of the left circumflex artery before (A) and after (B) dilatation.*

Essentially, the boundaries of a selected coronary segment are detected automatically (so called "edge detection") from optically magnified and videodigitized regions of interest (512 x 512 pixels) of an end diastolic cineframe. This step may soon be rendered unnecessary by the rapid development of on-line digital angiographic systems. Absolute diameter values are determined in mm using the guiding catheter (each individual catheter tip is retained and measured by micrometer) as a scaling device. A correction factor is then introduced for the so called " pincushion distortion " introduced by the image intensifier. The difficulty with selection of reference diameter is solved by using a computer derived or "interpolated" reference diameter, by which technique the computer generates the original disease - free dimension of the segment of interest. From these absolute measurements (minimal luminal diameter-MLD, maximal luminal diameter, mean luminal diameter and extent of obstruction) and the interpolated measurements obtained by the computer (symmetry, curvature, inflow / outflow angle, plaque area, roughness) many others may be derived eg. percent diameter stenosis, percent area stenosis, theoretical transstenotic pressure gradient, calculated poiseuille resistance and calculated turbulence resistance (72,76). The MLD is an unambiguous measurement of lesion severity and has the lowest long-term variability of all quantitative angiographic measurements of lesion severity.

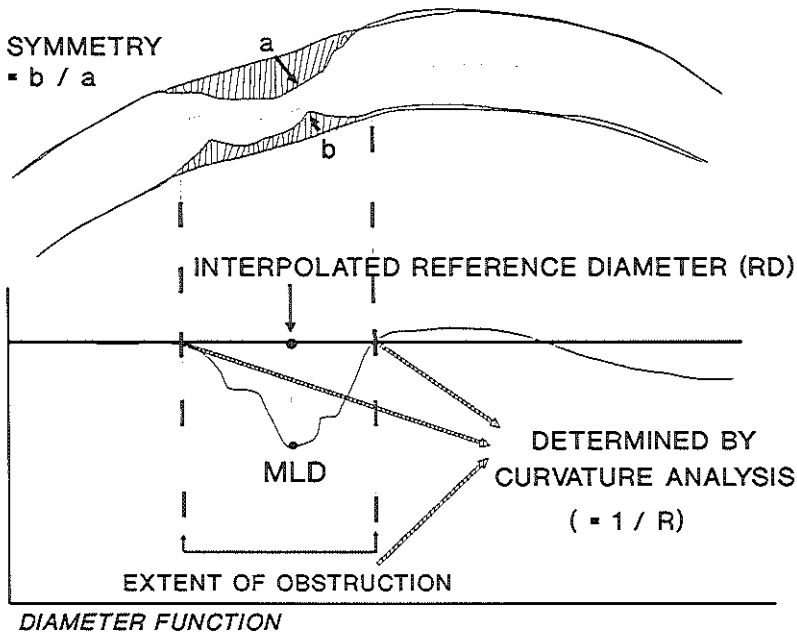

Figure 3 *Graphic representation of the quantitative angiographic measurements. The upper panel represents a stenosed arterial segments. The lower panel is the diameter function curve.*

Although quantitative, computer-based analysis methods have enhanced objectivity, some pitfalls still exist. For one, the presence of overlapping branches interferes with quantitative analysis of lesion severity from coronary angiograms. Also, various sources of variation in the angiographic data acquisition and analysis at different stages can be distinguished:

1) Pincushion distortion of image intensifier,
2) Differences in angles and height levels of x-ray systems,
3) Differences in vasomotor tone,
4) Variation in quality of mixing of contrast agent with blood,
5) Catheter used as scaling device (angiographic quality, influence of contrast in catheter tip on the calibration factor, size of catheter),
6) Deviations in size of catheter as listed by the manufacturer from its actual size,
7) Variation in data analysis (reference diameter, length of analyzed segment, frame selection) (95,96).

WHAT HAS BEEN LEARNED FROM STUDIES USING QUANTITATIVE CORONARY ANALYSIS ?

Timing of restenosis

Two virtually simultaneous studies addressing the issue of luminal changes in the months following coronary balloon angioplasty using coronary angiography at different pre-selected follow-up intervals, gave remarkably similar results (figure 4) (25,26). In the study carried out at the Thoraxcenter, the (mean) minimal lumen diameter increased slightly from 2.06 mm directly post angioplasty to 2.11 mm at 30 days and then decreased steadily to 1.93, 1.77, 1.69 and 1.82 mm at subsequent follow-up times (2,3,4,5 months). Nobuyoshi et al. restudied 229 patients at 24 hours, 1,3,6 and 12 months. Their findings were very similar to those from the Thoraxcenter. In addition, Nobuyoshi found that lesion progression after 6 months was unusual. These data demonstrate a striking resemblance to the pattern of intimal hyperplasia after vascular injury in animals, which reaches a peak at 4 to 12 weeks (79-81).

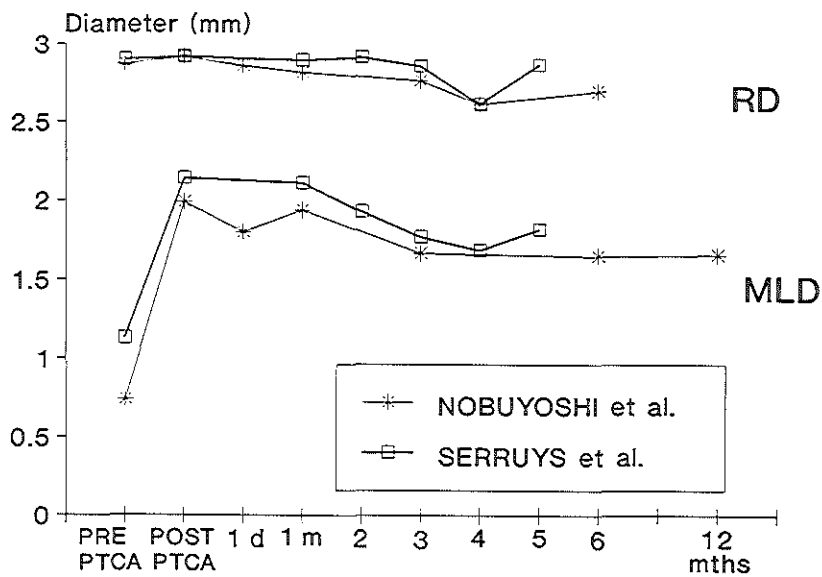

Figure 4 Minimal lumen diameter (MLD) and the interpolated reference diameter (RD) measurements as reported by Nobuyoshi et al. and Serruys et al. (25,26).

Absolute change in minimal lumen diameter, as measurement of the restenosis process

As a result of quantitative angiographic studies, a new concept for measuring restenosis has been introduced, as "clinical restenosis" ($\geq$50% diameter stenosis at follow-up) refers to the clinical decision making proces in the hospital (binary outcome: restenosis yes / no), the "restenosis process" (luminal re-narrowing as measured by

dimensional change after angioplasty) is used in angiographic restenosis studies comparing the effect of a new pharmacological agent with placebo or different interventions. The change in minimal lumen diameter from post angioplasty to follow-up angiography gives a reliable quantitative measurement of luminal narrowing (figure 5). It describes the magnitude of the reactive intimal hyperplasia after balloon trauma to the vessel wall.

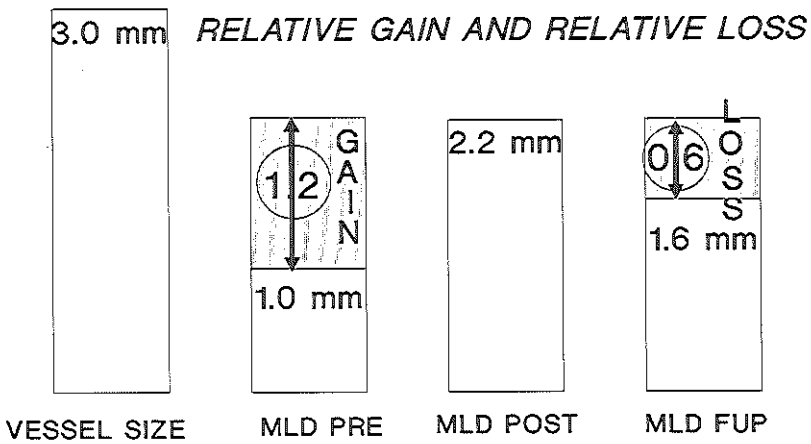

Figure 5 *Gain represents the accomplishment in minimal lumen diameter of the coronary angioplasty procedure (2.2 - 1.0 = 1.2 mm). Loss represent what is lost in minimal lumen diameter during the follow-up period (2.2 - 1.6 = 0.6 mm). Relative gain (1.2 / 3.0 = 0.4) and relative loss (0.6 / 3.0 = 0.2) is respectively gain and loss normalized for the (interpolated) reference diameter or vessel size.*

The continuous approach by measuring the change in minimal lumen diameter at follow-up has the advantage to detect the degree of benefit of new pharmacological agent or treatment. Beside that, the number of patients needed in a clinical trial can considerable be reduced, and by doing this the costs through the pharmaceutical industry to society. If a binary decision is used, 696 patients must be enrolled with complete angiographic follow-up to have an 80% certainty of detecting a reduction in the incidence of restenosis in a given population from 35% to 25% with 2p = 0.05. If on the other hand, a continuous variable is used, only about 100 patients would be required to demonstrate the same difference with the same statistical certainty. However, a small difference in minimal luminal dimension might be statistically significant, but its clinical relevance would have to be tested in a larger population (600 to 1000 patients). In addition, ancillary investigations such as intracoronary ultrasound or local biopsy are necessary to be able to distinguish between intimal proliferation, organized thrombus and elastic recoil (82).

OVERVIEW OF THE THESIS

The topic of this thesis is early and late luminal narrowing after percutaneous transluminal coronary balloon angioplasty as assessed by quantitative angiography, and the role of two possible risk factors: elastic recoil and dissection.

In *Chapter 2*, an review is given of the pharmacological agents that have been tested in the animal model and postangioplasty patients.

In *Chapter 3 and 4*, the methodological problems in the assessment of elastic recoil, stretch and balloon-artery ratio and the role of elastic recoil as a cause of luminal narrowing using quantitative methods are discussed. The 453 patients described in Chapter 3, represents the patients that were enrolled in the Thoraxcenter, in one of three following pharmacological restenosis prevention trials: 1) CARPORT (*Coronary Artery Restenosis Prevention On Repeated Thromboxane-antagonism*), 2) MERCATOR (*Multicenter European Research trial with Cilazapril after Angioplasty to prevent Transluminal coronary Obstruction and Restenosis*) or 3) PARK (*Post Angioplasty Restenosis prevention with Ketanserin*)).

In *Chapter 4* angiographic risk factors, including stretch and elastic recoil, for long term luminal narrowing (6 months) after a successful angioplasty procedure were investigated. To obtain independent predictors of a significant loss in minimal luminal diameter (MLD) - loss $\leq$ 0.72 mm - a multivariate logistic regression analysis was applied to 595 lesions with balloon measurements. Patients described in this chapter were enrolled in the CARPORT trial.

In *Chapter 5 and 6* the role of an *"unwanted"* and *"therapeutic"* type of dissection during and after percutaneous transluminal coronary balloon angioplasty are discussed. In Chapter 5, the role of qualitative and quantitative lesion morphology, in addition to clinical patient characteristics, in prediction of patients at high risk for major cardiac procedural or in-hospital cardiac events, was investigated. In this chapter, all 69 patients with a major procedural or in-hospital cardiac event - that were enrolled in CARPORT and MERCATOR trial - formed the study population. These patients were randomly matched to 267 patients (to the nearest week within the same hospital) without any major procedural and cardiac events from the same 2 trials. In Chapter 6, the relationship between an angiographically visible coronary dissection immediately after **successful** coronary balloon angioplasty and subsequent restenosis and long-term clinical outcome was investigated. The study population comprised all 693 patients who participated in the MERCATOR trial.

In *Chapter 7*, the angiographic morphology, as derived from quantitative coronary analysis, of the non-restenotic and restenotic lesion, was assessed in all 778 successfully dilated lesions with follow-up angiography, of 653 patients participating in the MERCATOR trial.

In *Chapter 8*, it was investigated whether luminal narrowing or restenosis after balloon angioplasty occurs only in a subset of patients cq. lesions or that it occurs to a certain extent in all dilated patients cq. lesions. For this study quantitative angiographic data of the CARPORT and MERCATOR were combined.

In *Chapter 9*, the risk for restenosis of the proximal left anterior descending artery as compared to lesions in the left circumflex or right coronary artery was investigated in all 1452 lesions of 1234 patients with 6 months follow-up angiography (follow-up rate 91%). In this study, quantitative angiographic data of the CARPORT and MERCATOR were combined.

In *Chapter 10*, an attempt was made to predict the absolute change in minimal luminal diameter at follow-up angiography with patient, lesion and procedural variables prospectively collected in the MERCATOR trial. Therefore a multiple linear regression analysis was applied to 778 lesion with the change in minimal lumen diameter from post angioplasty angiogram to follow-up angiogram as dependent variable.

In *Appendix I*, the quality control on cine-angiographic data acquisition and analysis in the 3 restenosis prevention trials - CARPORT, MERCATOR and PARK - are described.

In *Appendix II*, the results of the MERCATOR trial are presented. In this restenosis prevention trial, a novel angiotensin converting enzyme inhibitor, cilazapril, was compared to placebo, with respect to the amount of luminal narrowing at 6 months follow-up.

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CHAPTER 2

PREVENTION OF RESTENOSIS AFTER PERCUTANEOUS TRANSLUMINAL CORONARY ANGIOPLASTY: THE SEARCH FOR A "MAGIC BULLET"

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Prevention of restenosis after percutaneous transluminal coronary angioplasty: The search for a "magic bullet"

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Percutaneous transluminal coronary angioplasty (PTCA) is an accepted treatment for providing relief of angina pectoris in patients with single-and multivessel disease. Increased experience and advances in technology have resulted in a high primary success rate (90% to 95%) and a lower complication rate (4% to 5%). Despite the therapeutic success of coronary angioplasty, the exact mechanisms of dilatation remain speculative and involve multiple processes including stretching of the vessel at the site of the dilatation and disruption and fissuring of the plaque.[1] Angiographic renarrowing at the site of PTCA, frequently accompanied by recurrence of symptoms of angina, is a common phenomenon (30%) and has a negative bearing on the long-term results of PTCA. This usually occurs within the first 6 months after PTCA.[2,3] Although many of the risk factors for restenosis have been identified (Table I),[4-25] most of these are difficult to influence. Until now we have not found a technical or pharmacologic cure, and we are unable to predict which patients or vessel segments will have restenosis. The reason why a clinically significant restenosis occurs in only a minority of the dilated vessels (30%) remains an enigma. Although the typical restenotic lesion differs from the usual atherosclerotic plaque in architecture and lipid content, both contain smooth muscle cells and fibrous tissue,[26,27] and it is even likely that the factors responsible for restenosis are similar to those that effect de novo atherosclerosis. In some cases of "restenosis" it is conceivable that it is caused by progression of the preexisting atherosclerotic plaque.

An important step in the restenosis process is activation of the hemostatic system with platelet adhesion, platelet aggregation, and fibrin formation. This is followed by smooth muscle cell proliferation, which is mediated by growth factors produced by cellular constituents in the blood and damaged vessel wall.[28,29] Each of these steps could be sites of intervention that might halt the restenosis process. The drugs that could reduce or prevent restenosis in the animal model are listed in Table II. Some of these have been investigated in prospective randomized angioplasty trials and although efficacy has not been demonstrated, they continue to be used and prescribed in daily routine. In this review we will concentrate on the drugs (Fig. 1) that have been tested to prevent restenosis in the animal model (Table III) and in postangioplasty patients (Table IV).

Animal models are of limited value in restenosis research because it is impossible to create arterial stenoses in animals (e.g., pigs, rabbits, or dogs) that resemble human coronary artery disease (Table V). Most models use an inflated balloon to "injure" the intimal and medial layers of the vessel wall, although infused air has also been used. Some investigators have performed experiments in iliac or carotid arteries rather than in coronary arteries; others have fed the animals an atherogenic diet for brief periods of time to induce an "atherosclerotic lesion." Several studies in animals have examined the degree of platelet deposition after arterial injury to test the hypothesis that platelet aggregation and platelet-derived substances are responsible for the restenosis process.[29-31] Other studies use angiographic or histologic findings in damaged arteries to assess restenosis (Table IV). Recently a model of human restenosis

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Table I. Variables associated with higher restenosis rates in patients with follow-up angiography

Reference	*Year*	*No. of patients*	*Clinical*
Holmes et al.[4]	1984	557	Male sex Canadian class III-IV No previous MI Angina onset <2 mo Diabetes mellitus
Cowley et al.[5]	1985	557	Male sex
Leimgruber et al.[6]	1986	998	Old age Unstable angina Angina onset <2 mo
Kaltenbach et al.[7]	1985	333	Medication ?
Levine et al.[8]	1985	100	
Bertrand et al.[9]	1986	229	
Uebis et al.[10]	1986	100	
David et al.[11]	1984	191	Variant angina
Hollman et al.[12]	1986	536	Diabetes mellitus
Scholl et al.[13]	1981	45	Variant angina
Margolis et al.[14]	1984	216	Insulin-dependent diabetes mellitus
Marantz et al.[15]	1984	73	
Mata et al.[16]	1985	63	
Probst et al.[17]	1985	94	
Serruys et al.[18]	1985	28	
Roubin et al.[19]	1986	411	
Shaw et al.[20]	1986	97	High cholesterol Current smoker
Clark et al.[21]	1986	124	
Powelson et al.[22]	1986	50	
Urban et al.[23]	1987	91	
Bertrand et al.[24]	1989	437	
Ellis et al.[25]	1989	308	

BIP, balloon inflation pressure; CABG, coronary artery bypass graft; DS, diameter stenosis; MI, myocardial infarction; TSG, transstenotic gradient; CWP, coronary wedge pressure.
*In patients with totally occluded vessel.
†Early restenosis (<2 days).

was developed in the domestic crossbred swine fed a standard nonatherogenic diet.[32] Metallic foreign bodies were implanted percutaneously in porcine coronary arteries with oversized PTCA balloons inflated to high pressure. Results of histologic examination of lesions showed a marked proliferation of medial smooth muscle cells. This may be a useful animal model to test drugs used for treatment of restenosis, since it more closely resembles the response in human restenosis.

Hemodynamic or procedure-related	*Lesion-related*
Pre-PTCA TSG ≥40 mm Hg	Pre-PTCA DS > 70%
Post-PTCA TSG ≥20 mm Hg	PTCA on CABG
Post-PTCA TSG 15 mm Hg	LAD >RCA >LCX Post-PTCA DS >30% Absence of dissection Second PTCA PTCA on CABG
Inflation pressure <8 atm	Post-PTCA DS >30% Relative change <55% "Dynamic" coronary stenosis Length of pre-PTCA stenosis >2 mm
	Pre-PTCA DS >90% Post-PTCA DS >50% Concentric stenosis Multivessel PTCA Pre-PTCA DS ≥90% Post-PTCA DS >40% Absence of intimal tear Eccentric or calcified lesion
Post-PTCA TSG >18 mm Hg	Irregular lesion pre-PTCA
Maximum balloon pressure >7 atm	Large change in DS at PTCA
Balloon artery ratio ≤0.9	LAD or LCX >RCA Calcified stenosis Post PTCA DS >40%
Collaterals pre-PTCA	
Occlusion pressure >45 mm Hg	
	PTCA for total occlusion Multilesion PTCA in one vessel
More inflations* Higher EIP*	
	Presence of intimal disruption†
CWP ≥30 mm Hg	
	Presence of ergonovine-induced spasm before and after PTCA Stenosis at bend point of coronary artery

ANTICOAGULANTS AND ANTIPLATELET AGENTS

Platelets play an important role in the development of restenosis after PTCA.[33] Intact endothelium prevents platelet aggregation; however, after superficial injury a thin layer of thrombocytes attach themselves to the endothelium (platelet adhesion). If, however, there is deeper damage to the vessel wall, blood is exposed to collagen and other substances of the subintima, which is a potent stimulus for platelet aggregation that is mediated by the release of adenosine diphosphate, serotonin, thromboxane A_2, fibrinogen, fibronectin, and von Willebrand factor. These substances activate neighboring platelets via different metabolic pathways (thromboxane A_2, adenosine diphosphate, and a platelet-activating factor) and promote thrombosis. In addition, the release of several growth factors, including platelet-derived growth factor, epidermal growth factor, and transforming growth factor beta from thrombocytes, smooth muscle cells, endothelium, and macrophages, stimulates smooth muscle cells and fibroblasts to proliferate and migrate from the medial layer into the intima of the vessel wall. In some patients this response is excessive and is associated with formation of abundant amounts of connective tissue. This results in hyperplasia of the intima with a reduction in luminal diameter.

To prevent platelet deposition (which occurs within minutes of the procedure) and the associated release of smooth muscle cell mitogenic factors, antiplatelet therapy appears to be a logical approach. Experimental studies have demonstrated that the use of antiplatelet agents can decrease the extent of platelet deposition and acute thrombosis after angioplasty, with some agents reducing the rate of restenosis in the pig model (dipyridamole [2.5 mg/day] + acetylsalicylic acid [20 mg/kg/day], low-dose acetylsalicylic acid [1 mg/kg/day], anagrelide, intravenous nitroglycerin, and intravenous ibuprofen).[29, 34] Because only one of three pathways of platelet activation is blocked by current platelet-inhibitor therapy, it is not surprising that these agents are insufficient to prevent restenosis when tested in patients (Fig. 1).

Heparin. For many years heparin has been an integral aspect of the PTCA procedure since it binds reversibly with antithrombin, which results in increased activity of antithrombin. The antithrombin-heparin complex then binds with factor Xa and factor IIa resulting in an anticoagulant effect (believed to be the result of its IIa effect) and an antithrombotic effect (through its anti-Xa activity). Early discontinuation of heparin after angioplasty is associated with acute occlusion of the dilated arterial segment, suggesting that anticoagulation is important in the early stages after PTCA. However, the optimum duration of heparin therapy is still unknown.

A prospective trial conducted by the M-HEART study group[35] with 209 patients showed an inverse relationship between the duration of heparin therapy and the incidence of restenosis. This was not con-

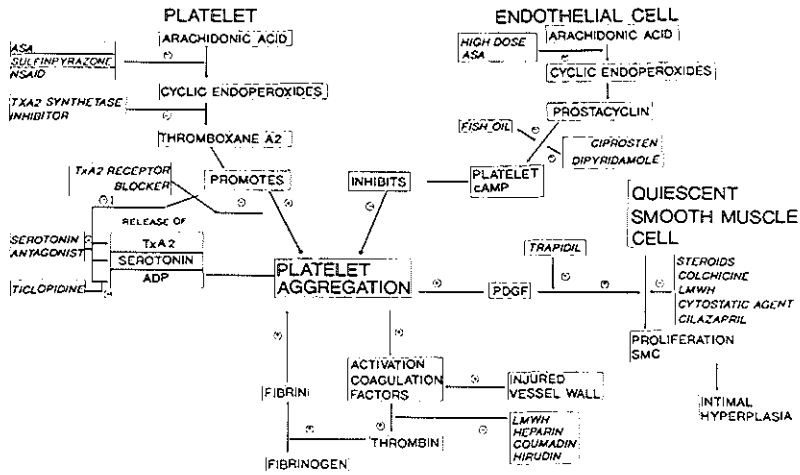

Fig. 1. Simplified schematic presentation of how the different drugs act on the different processes involved in the restenosis process (Modified from Fuster V et al. Prog Cardiovasc Dis 1987;22:325-46.) ASA, Acetylsalicylic acid; NSAID, nonsteroidal antiinflammatory drugs; TxA2, thromboxane A2; 7E3, antiplatelet glycoprotein receptor 2B/3A; ADP, adenosine diphosphate; LMWH, low molecular weight heparin; cAMP, cyclic adenosine monophosphate; IGF, insulin-like growth factor; FGF, fibroblastic growth factor; SMC, smooth muscle cell.

Table II. Mechanisms to prevent restenosis

Thrombosis
Heparin, hirudin, coumadin, acetylsalicylic acid, dipyridamole, sulfinpyrazone, thromboxane A_2 synthetase inhibitor, thromboxane A_2 receptor blocker, ticlopidine, prostacyclin, ciprostene, 7E3, fish oil, NSAID, ridogrel
Cell proliferation
Low-molecular-weight heparin, platelet-derived growth factor antagonist (trapidil), angiotensin-converting enzyme inhibitor (cilazapril), colchicine, cytostatic agents, serotonin antagonist (ketanserin), angiopeptin
Inhibitor of inflammation
Corticosteroids, nonsteroidal antiinflammatory drugs
Coronary vasospasm
Nifedipine, diltiazem
Lipid regulators
Fish oil, lovastatin

firmed in a randomized trial with 416 patients (469 stenoses) in Atlanta.[36] No differences in acute closure and restenosis were found in patients (all were without dissection; intimal flap inside or outside the lumen) randomly assigned to placebo or 18 to 24 hours of heparin after PTCA (all patients received acetylsalicylic acid for 6 months). Restenosis was defined as a narrowing of more than 50% of the vessel at the time of follow-up angiography, which was performed in only 58.4% of the patients treated with heparin and 64.5% of the patients given placebo. More bleeding complications were seen in the group of patients who were treated with heparin (8.2% vs 3.8%). Acute total closure was seen more frequently in the group given placebo (2.4%) than in the group treated with heparin (1.8%), and the restenosis rate was 41.2% with heparin and 36.7% with placebo.

Because *low-molecular-weight heparin* affects platelet aggregation and platelet-dependent thrombin generation to a lesser extent than "regular" heparin, it has fewer side effects and yet both forms are known to inhibit the proliferation of vascular smooth muscle cells (dose dependent) and thrombosis after endothelial injury in the rat.[37, 38] The mechanism of this inhibition is not clear.[39] Recently low-molecular-weight heparin has been used after transluminal angioplasty of rabbit iliac arteries.[40] Two groups were studied: the first group (n = 9) received low-molecular-weight heparin (10 mg/kg/day subcutaneously) immediately before transluminal angioplasty until follow-up angiography 1 month later, whereas the second group (n = 12) received a placebo. After 4 weeks all rabbits in the placebo group and three of nine rabbits in the group treated with low-molecular-weight heparin had a loss of more than 50% of the gain in diameter after transluminal

angioplasty. Histologic findings showed reduced intimal hyperplasia and no formation of thrombus in the group treated with low-molecular-weight heparin. A multicenter double-blind control trial with low-molecular-weight heparin (Enoxaparin) is currently underway in the United States. Patients without prior PTCA or recent myocardial infarction (within 5 days) are randomly assigned to placebo or low-molecular-weight heparin (30 mg subcutaneously) for 1 month, and all patients will undergo repeat angiography at 6 months. This will provide important information about whether long-term administration of low-molecular-weight heparin can decrease the rate of restenosis.

Hirudin. Newer anticoagulant drugs such as recombinant hirudin are becoming available. Hirudin prevents fibrinogen clotting, thrombin-catalyzed activation of factors V, VIII, and XIII, and thrombin-induced platelet activation. Hirudin has been shown to be more effective in preventing thrombosis than heparin (by quantifying the deposition of platelets and fibrinogen by means of the method of Dewanje in a swine model). This latter effect is probably due to the fact that hirudin is a more potent and specific thrombin antagonist.[41] Trials designed to test the efficacy of hirudin on early and late complications of PTCA are currently in the planning stages in Europe and the United States.

Coumadin. Before Gruentzig began his work at Emory University in Atlanta in 1980, he had been administering coumadin (a vitamin K antagonist responsible for inhibiting thrombin formation) to his patients after balloon dilatation. In Atlanta his view was challenged since there was evidence that antiplatelet drugs were effective in preventing thrombosis in venous bypass grafts. To test this new therapeutic approach a trial was begun[42] in which 248 patients were randomly assigned to either 325 mg acetylsalicylic acid daily or coumadin at a dose that resulted in a prothrombin time that was 2 to 2.5 times the normal value. In the group treated with acetylsalicylic acid (126 patients) restenosis was angiographically documented in 27% of the patients versus 36% of the patients treated with coumadin. A loss of >50% of the gain achieved at the time of PTCA or an increase in the stenosis of more than 30% (NHLBI IV) or development of positive (for ischemia) exercise test results if no angiogram was available were used as restenosis criteria. The results favored the acetylsalicylic acid strategy, but the difference was only significant for a subgroup of patients with a long history of chest pain (>6 months). In patients with poor compliance restenosis rates were 32% in the group treated with coumadin versus 20% in the group given acetylsalicylic acid.

In London a more recent randomized trial[43] with 110 patients investigated the effect of a combination of coumadin and verapamil compared with verapamil alone. The incidence of restenosis was 25% by lesion and 29% by patient in the group treated with coumadin and 33% and 37% in the control group (NHLBI IV criterion was used). Although the incidence of angiographic restenosis tended to be lower with coumadin, none of the differences were significant. A randomized trial to evaluate the efficacy of coumadin in the prevention of restenosis should be performed that would ensure adequate medication compliance with reliable and safe monitoring of prothrombin time.

Acetylsalicylic acid. Acetylsalicylic acid is a "popular drug" in restenosis prevention trials. In the animal model it reduces platelet-thrombus deposition in a dose of 1 mg/kg/day when given in addition to heparin. Angiographic restenosis has also been shown to be reduced when acetylsalicylic acid is used in addition to dipyridamole.[29, 44] Acetylsalicylic acid has the ability to inhibit platelet thromboxane A_2 synthetase and subsequent platelet activation by irreversibly blocking the enzyme cyclooxygenase, which is responsible for the conversion of arachidonic acid to thromboxane A_2. At high doses acetylsalicylic acid may be less effective, since it inhibits the production of prostacyclin (which prevents platelet aggregation) by endothelial cells.[45] However, it only partially inhibits platelet aggregation induced by adenosine diphosphate, collagen, or thrombin. Consequently platelet-derived growth factor and other mitogens may still affect proliferation of smooth muscle cells[33] (Fig. 1).

Acetylsalicylic acid has been studied in several prospective randomized trials. The first trial showed a reduction in the restenosis rate of 25% when acetylsalicylic acid (325 mg) was compared with coumadin.[43] Three trials compared different dosages of acetylsalicylic acid.[46-48] In a trial in Homburg/Saar, 203 patients were randomly assigned to either 1500 mg/day or 320 mg/day. In a preliminary report 25% of these patients had been restudied (6 months after PTCA). Results of follow-up angiography showed restenosis (>50% diameter stenosis) in 13 of 44 (31%) patients in the group treated with the lower dose compared with 9 of 42 patients (21%) in the group given the higher dose.[46] However, in a randomized trial in Atlanta with 495 patients, the effectiveness of two doses of acetylsalicylic acid (80 mg vs 1500 mg daily started the day before PTCA) in the prevention of restenosis and acute complications af-

Table III. The effect of drug therapy in the animal model for prevention of restenosis

Reference	*Year*	*Model*	*Drug*	*Dose*
Clowes and Karnowsky[37]	1977	Rat A. carotis	Heparin Placebo	5-14 days
Gordon et al.[39]	1987	Rabbit aorta	LMWH Hydrocortisone LMWH + hydrocortisone Placebo	2.5 mg/kg/day 1 mg/kg/day
Pow et al.[40]	1989	Rabbit A. iliaca	LMWH Placebo	10 mg/kg/day
Heras et al.[41]	1989	Pig A. carotis	Hirudin Heparin	1 mg/kg/hr 6 different doses
Faxon et al.[44]	1984	Rabbit A. iliaca	ASA + D Sulfinpyrazone Placebo	32-25 mg/day 100 mg/day
Sanborn et al.[54]	1986	Rabbit A. iliaca	TXA_2 synthetase inhibitor Heparin ASA	1 mg/kg/hr 500 U/kg 10 mg/kg
Liu et al.[62]	1990	Rabbit A. iliaca	Trapidil Placebo	60 mg/kg/day
Currier et al.[65]	1989	Rabbit A. iliaca	Colchicine Colchicine Placebo	0.2 mg/kg 0.02 mg/kg
Barath et al.[66]	1989	Rabbit aorta	Vincristine + actinomycin Placebo	0.075 mg/kg + 0.015 mg/kg
Powell et al.[67]	1989	Rats A. carotis	Cilazapril Placebo	10 mg/kg 5 different durations
Müller et al.[68]	1990	Rats A. carotis	Captopril Hydralazine Verapamil	100 mg/kg/day 8 mg/kg/day 100 mg/kg/day
Foegh et al.[70]	1989	Rabbit cardiac transplant	Angiopeptin Placebo	
Faxon et al.[72]	1984	Rabbit	Nifedipine Placebo	40 mg/day
Gellman et al.[80]	1990	Rabbits A. femoralis	Lovastatin Placebo	6 mg/kg/day

ASA, acetylsalicylic acid; D, dipyridamole; LMWH, low-molecular-weight heparin; TXA_2, thromboxane A_2.

ter PTCA was compared.[47] Results of follow-up angiography were available in only 166 patients (34%). In the group treated with the low dose of acetylsalicylic acid, 47% of the patients had restenosis >50% diameter stenosis in one or more sites) compared with 51% in the group treated with the high dose. There were no differences in success or acute complication rates. Thus restenosis was not influenced favorably by the use of a higher dose of acetylsalicylic acid.

A smaller trial compared the effects of acetylsalicylic acid in doses of 100 mg/day versus 1000 mg/day, started 1 day before PTCA until 6 months after PTCA.[48] In addition, all patients received calcium channel blockers and long-acting nitrates. Restenosis (clinically significant stenosis requiring repeat PTCA or coronary artery bypass graft) occurred in 7 of the 40 patients in the group treated with 100 mg acetylsalicylic acid (18%) and in 8 of the 39 patients in the group treated with 1000 mg acetylsalicylic acid (21%). The investigators concluded that restenosis is not favorably influenced by the use of high-dose versus low-dose acetylsalicylic acid. Another trial[49] designed to compare the effects of 100 mg acetylsalicylic acid with those of placebo was stopped prematurely after 40 patients (single blind) were enrolled because of reports showing the benefit of acetylsalicylic acid (combined with dipyridamole) in preventing acute thrombosis in dilated vessels and the need for urgent bypass surgery.[50] Results of follow-up angiography at 6 months (95% of the patients) in this particular trial showed an incidence of restenosis (>50% diameter stenosis) that was two times higher in the group treated with acetylsalicylic acid (33%) compared with the group given a placebo (14%). Although the difference seems impressive, it was not statistically significant because of the small numbers.

Animals Total	*Follow-up*	*Method*	*Effect*
45	7 days	Histology	Myointimal thickening less with heparin
16	2 wk	Histology	Ratio intimal/medial thickness in LMWH and hydrocortisone separately and synergistically lower than placebo
21	4 wk	Angiography Histology	Δ Luminal diameter (Post-PTCA)-(follow-up) = 1.1 mm placebo and 0.3 mm LMWH ($p < 0.001$)
55		Platelet deposition	Less platelet deposition with hirudin than heparin
25	4 wk	Angiography Histology	ASA + D and sulfinpyrazone reduce restenosis
70	30 min	Platelet deposition	Less platelet accumulation with TXA_2 synthetase inhibitor
17	4 wk	Arteriography Histology	Intimal thickness decreases with trapidil
34	4 wk	Arteriography (QCA) Histology	ΔLuminal diameter (Post-PTCA)-(follow-up) = 0.6 mm = 0.8 mm = 1.1 mm
36	3 days	Electron microscopy	Selective damage of proliferating smooth muscle cells
127	14 days	Histology	Intimal hyperplasia decreased with 70% given -6 → 14 days
43	Not reported	Histology	Captopril superior compared with others in reduction of intimal hyperplasia
20	6 wk	Histology	Intimal hyperplasia decreased by angiopeptin
18	4 wk	Angiography Histology	ΔLuminal diameter (Post-PTCA) (follow-up) = 0.9 mm = 1.2 mm
30	39 days	Arteriography Histology	Intimal hyperplasia decreased with lovastatin

In a well-designed trial at the Montreal Heart Institute and Toronto General Hospital,[51] 376 patients were randomly assigned to a combination of acetylsalicylic acid (990 mg daily) and dipyridamole (225 daily) or to placebo starting the day before PTCA until follow-up angiography 4 to 7 months later. More acute complications were seen in the placebo group, including 13 periprocedural myocardial infarctions in the placebo group versus three in the treated group ($p < 0.05$). However, no differences were observed in the restenosis rate (increase in diameter stenosis from <50% after PTCA to >50% at follow-up): 39% (127 patients) in the placebo group compared with 38% (122 patients) in the treated group. All patients received heparin until 12 hours after the procedure (500 U/hr) and diltiazem until follow-up angiography.

Chesebro et al.[52] randomly assigned 207 patients (297 stenoses) to either acetylsalicylic acid (975 mg/day) and dipyridamole (225 mg/day) or to placebo from the day before PTCA until 6 months later. There was no difference in the restenosis rate defined in a linear model based on the minimum lumen diameter obtained by quantitative angiography. There were fewer acute complications (occlusion, myocardial infarction, repeat PTCA, coronary artery bypass graft <48 hours) in the group treated with acetylsalicylic acid and dipyridamole (11% vs 20% in the placebo group) confirming the results of the Montreal/Toronto trial. It is clear from these data that although acetylsalicylic acid does not influence the incidence of restenosis, it definitely has a positive influence on acute complications during or immediately after angioplasty.

Dipyridamole. In a rabbit model treatment with acetylsalicylic acid and dipyridamole decreased

Table IV. The effect of drug therapy on restenosis in patients after successful coronary angioplasty

Reference	*Year*	*Drug*	*Dose*	*Patients Total*
Hirshfeld et al.[35]	1987	Heparin	Different duration	209
Ellis et al.[36]	1989	Heparin (18-24 hr) Dextrose	<2.5 normal PTT	416
Thornton et al.[42]	1984	Coumadin ASA	2-2.5 normal PTT 325 mg/day	248
Urban et al.[43]	1988	Coumadin + Verapamil Verapamil	>2.5 normal PTT Not reported	110
Dyckmans et al.[46]	1988	ASA ASA	1,500 mg/day 320 mg/day	203
Mufson et al.[47]	1988	ASA ASA	1,500 mg/day 80 mg/day	453
Schanzenbacher et al.[48]	1988	ASA ASA	1,000 mg/day 100 mg/day	79
Finci et al.[49]	1988	ASA Placebo	100 mg/day	40
Schwartz et al.[51]	1988	ASA +D Placebo	990-225 mg/day	249
Chesebro et al.[52]	1989	ASA + D Placebo	975-225 mg/day	207
White et al.[53]	1987	ASA + D Ticlopidine Placebo	650-225 mg/day 750 mg/day	236
Yabe et al.[55]	1989	TXA_2 synthetase inhibitor Placebo	600 mg/day	33
Kitazume et al.[56]	1988	ASA ASA + Ticlodipine ASA + Ticlodipine + Nicorandil	300 mg/day +200 mg/day +30 mg/day	280
Knudtson et al.[57]	1990	Prostacyclin + ASA + D ASA + D	5 ng/kg/min 325 + 225 mg/day	270
Raizner et al.[58]	1988	Ciprostene Placebo	120 ng/kg/min maximum 48 hr	311
Klein et al.[64]	1989	Ketanserin Not reported	0.1 mg/min for 24 hr	43
Corcos et al.[73]	1985	Diltiazem + ASA + D ASA + D	270 mg/day 650-225 mg/day	92
Whitworth et al.[74]	1986	Nifedipine + ASA ASA	40 mg/day	241
Slack et al.[75]	1987	Fish oil Placebo	2.4 gm/day	162
Reis et al.[76]	1989	Fish oil Placebo	6.0 gm/day	186
Milner et al.[77]	1989	Fish oil Placebo	4.5 gm/day	194
Dehmer et al.[78]	1988	Fish oil Placebo	3.2 gm/day	82
Grigg et al.[79]	1989	Fish oil Placebo	3.0 g/day	108
Sahni et al.[81]	1989	Lovastatin Placebo	20-40 mg/day	157
Rose and Beauchamp[84]	1987	Steroid Placebo	48 mg/day	66
Stone et al.[85]	1989	Steroid for restenosis	125 mg methylprednisolone/day 240 mg prednisone/week	102
Pepine et al.[86]	1990	Steroid Placebo	1.0 gm methylprednisolone	722

Fup, follow-up (% of successful PTCA); DS, diameter of stenosis; PTT, prothrombin time; NS, not significant; ASA, acetylsalicylic acid; TXA_2, thromboxane A2; D, dipyridamole.

Follow-up	*Method*	*Definition*	*Restenosis (%) Drug vs placebo significance*
Not reported	Angiography (4-12 mo)	>50% DS Fup (visual)	Longer heparin, less restenosis
61%	Angiography (3-9 mo)	>50% DS Fup (visual)	41% 37% p = NS
72%	Angiography (6-9 mo)	Loss >50% of gain	36% 27% p = NS
92%	Clinical	Stress test − → +	
77%	Angiography (5 mo)	>50% DS Fup	29% 37% Patient p = *NS*
98%	Clinical		25% 33% Site p = NS
40%	Angiography (6 mo) (preliminary)	>50% DS Fup	21% 31% p = *NS*
37%	Angiography (3-8 mo)	>50% DS Fup (visual)	51% 47% p = NS
100%	Angiography (6 mo)	Clinical	21% 17% p = NS
73%	Angiography (6 mo)	>50% DS Fup (visual)	33% 14% p = NS
100%	Clinical		
72%	Angiography (4-7 mo)	>50% DS Fup (QCA)	38% 39% p = NS
85%	Angiography (5 mo) (QCA)	Minimum diameter (Post-PTCA) (Fup)	Δ0.18 mm Placebo p = NS Δ0.14 mm ASA + D
75%	Angiography (6 mo)	>70% DS Fup (visual)	18% p = NS 29% 20%
100%	Angiography (>3 mo)	Loss >50% of gain	22% 53% p = NS
100%	Angiography (6 mo)	>50% DS Fup	38% 27% 16% p = 0.002
93%	Angiography (6 mo) (caliper)	>50% DS Fup or loss >50% of gain	27% 32% patient p = NS 22% 29% Site p = NS
80%	Angiography (6 mo) Clinical (MI,re-PTCA,CABG,Death)	>50% DS Fup (visual)	41% 53% Angiography p = NS 17% 34% Clinical p < 0.001
100%	Angiography (4-6 mo)	Not reported (QCA)	33% 29% p = NS
100%	Angiography	>70% DS Fup (visual)	15% 22% p = NS
82%	Angiography (6 mo)	Loss >50% of gain	29% 33% p = NS
91%		>50% DS Fup	
	Clinical	Stress test − → +	
85%	Clinical (6 mo)	Stress test − → +	16% 33% p < 0.05 Single vessel 67% 58% p = NS Multivessel
30%	Angiography (6 mo)	>70% DS Fup	34% 23% p = NS
100%	Clinical	Stress test − → +	
23%	Angiography (6 mo)	>50% DS Fup	18% 27% p = NS
100%	Clinical	Stress test − → +	19% 35% p < 0.01
100%	Angiography (6 mo)	>50% DS Fup (visual)	16% 36% p < 0.03 Site 19% 46% p < 0.007 Patient
94%	Angiography (3-5 mo) (caliper)	Loss >50% of gain	34% 33% p = NS Patient 29% 31% p = NS Lesion
50%	Angiography (3 mo)	>50% DS Fup	14% 47% p < 0.001
88%	Angiography (3 mo)	>50% DS Fup	33% 33% p = NS
53%	Angiography (6 mo)	>50% DS Fup	52% 54% p = NS Angiography
100%	Clinical	Stress test	58% 52% p = NS Clinical
74%	Angiography (4-8 mo) (caliper)	>50% DS Fup	40% 39% p = NS Lesion

Table V. Animal models used to test drugs for prevention of restenosis

Animal	Vessel	Method	Therapy	End point
	Artery	1. Balloon denudation	Antiplatelet	Platelet deposition
Rabbit	Coronary	of endothelium	Anticoagulant	(^{51}Cr or ^{111}In labeled)
Pig	Carotid	2. Infused air	Antiproliferative	Angiography
Dog	Iliac	1 or 2 with or without	Antiinflammatory	Visual
Rat	Aorta	diet high in cholesterol	Calcium antagonist	Quantitative
		3. Coil implantation	Lipid lowering	Histology
		4. Electrical stimulation		

platelet-thrombus deposition and restenosis after transluminal angioplasty by increasing platelet cyclic adenosine monophospate.[44] However, in clinical trials[51-53] no effect has been shown on the restenosis rate after angioplasty.

Sulfinpyrazone. In contrast to acetylsalicylic acid, sulfinpyrazone is a competitve (reversible) inhibitor of platelet cyclooxygenase, but the exact mechanism of its antithrombotic activity is not well understood. Faxon et al.[44] showed a reduction in restenosis with the use of a rabbit model. There is no clinical evidence to date to support a role for sulfinpyrazone in the prevention of restenosis after coronary angioplasty.

Thromboxane A_2synthetase inhibitor. Thromboxane A_2 is a potent aggregating agent and vasoconstrictor. A specific inhibitor of thromboxane A_2 can antagonize these actions while at the same time leaving prostacycling production of the vascular endothelium unaffected. In rabbits it was shown that a selective thromboxane synthetase inhibitor was more effective than heparin or acetylsalicylic acid in inhibiting platelet deposition after balloon angioplasty.[54] Another thromboxane A_2 synthetase inhibitor was tested in a small number of patients to prevent restenosis after PTCA.[55] It was given a minimum of 5 days before PTCA and was continued until follow-up angiography (>3 months later). Restenosis was defined as a >50% loss of the initial gain in luminal diameter. The results showed that 4 of the 18 patients (22%) given thromboxane A_2 synthetase inhibitor had restenosis versus 8 of the 15 patients (53%) in the placebo group. Besides inhibiting thromboxane A_2 synthetase, it is also possible to block the receptor of thromboxane on the platelet. Soon results will be available from a prospective European trial (Coronary Artery Restenosis Prevention On Repeated Thromboxane Antagonism) involving more than 700 patients treated with either a thromboxane A_2 receptor blocker or placebo until follow-up angiography 6 months after PTCA.

Ticlopidine. The mechanism of action of ticlopidine is not exactly known, but it is a potent platelet inhibitor. The optimum effect occurs 3 days after the first administration and lasts for at least several days. In a multicenter trial in the United States, patients were randomly assigned to ticlopidine (750 mg/day), to a combination of acetylsalicylic acid (650 mg/day) and dipyridamole (225 mg/day), or to placebo. Restenosis was defined as a diameter stenosis of 70% or more at follow-up angiography (6 months). There was no difference in the restenosis rate; in the 65 patients who received ticlopidine the restenosis rate was 29% compared with 18% in the 57 patients who received acetylsalicylic acid and dipyridamole. Among the 54 patients who received placebo, the restenosis rate was 20%. There was no difference in the acute complication rate.[53] In Japan data collected retrospectively showed a lower restenosis rate when patients received a combination of ticlopidine (200 mg/day), nicorandil (30 mg/day), and aspirin (300 mg/day).[56]

Prostacyclin or prostacyclin analogue. Prostacyclin is a potent naturally occurring platelet inhibitor and vasodilator. In a Canadian trial 270 patients were randomly assigned to placebo (136 patients) or prostacyclin (5 to 7 mg/min intravenously) (134 patients) just before PTCA up to 48 hours after PTCA.[57] All patients received 325 mg acetylsalicylic acid and 225 mg dipyridamole beginning before angioplasty until follow-up angiography 6 months later. Short-term administration of prostacyclin did not significantly lower the risk of restenosis: 27% in the treated group compared with 32% in the placebo group. Restenosis was defined as 50% or more narrowing at follow-up angiography or >50% loss of the immediate gain after angioplasty. Acute vessel closure and ventricular tachyarrhythmias were more common in the control group than in the patients who received prostacyclin.

Ciprostene. Ciprostene is a chemically stable analogue of prostacyclin. To study the effect of ciprostene during PTCA, 311 patients were randomly assigned shortly before PTCA (40 ng/kg/min) to ciprostene until 48 hours after PTCA (120 ng/kg/day) or to placebo. Acute closure occurred in three patients

in the placebo group and none in the ciprostene-treated group. Restenosis, defined as a diameter stenosis of 50% or more at the time of follow-up angiography, was present in 52 of the 126 patients (41%) treated with ciprostene and in 65 of the 122 patients (53%) given placebo. The clinical end points of this trial included death, myocardial infarction, repeat PTCA, or coronary artery bypass graft. In 30 of the 149 patients (20%) treated with ciprostene, one of these clinical end points was observed compared with 55 of the 147 patients (33%) in the placebo group. Although the clinical results were more favorable with ciprostene, there was no effect on the incidence of angiographic restenosis.[58]

Prostaglandin E_1. Inasmuch as the deposition of platelets after angioplasty in porcine carotid arteries was reduced significantly after infusion with prostaglandin E1 even more than with prostacyclin or dipyridamole, a study was attempted to determine the effect of intracoronary followed by intravenous prostaglandin E_1 on restenosis. Eighty patients were randomly assigned to an infusion of 20 to 40 ng/kg/min 12 hours before PTCA or placebo. Clinical follow-up showed abrupt occlusion in 3 of 40 patients in the placebo group compared with none in the prostaglandin E_1 group. An additional repeat PTCA was necessary in 4 of 40 given placebo compared with none in the group treated with prostaglandin E_1. No angiographic study has assessed the effect of prostaglandin E_1 on restenosis.[59]

ANTIPROLIFERATIVE DRUGS

Restenosis is characterized by migration and proliferation of smooth muscle cells in response to balloon injury. Although the mechanisms responsible for proliferation and migration of smooth muscle cells are not completely understood, it has been postulated that they are controlled by the balance between growth factors and growth inhibitors released from circulating blood cells, at local tissue sites, or both.[28, 60, 61] Interference with growth factor–mediated cellular hyperplasia may be beneficial in inhibiting smooth muscle cell proliferation and thereby reduce restenosis (Fig. 1).

Platelet-derived growth factor antagonist. Trapidil (triazolopyrimidine) has been shown to inhibit cellular proliferation induced by platelet-derived growth factor in cell culture and intimal thickening in damaged carotid arteries. In a model of atherosclerosis rabbits were assigned to placebo (n = 8) or trapidil (60 mg/kg/day) (n = 9). The medication was started 2 days before balloon dilatation of the external iliac artery and continued for 4 weeks. Follow-up angiography showed a greater luminal reduction in the control group than in the trapidil group ($p < 0.001$) compared with similar baseline values. Histologic findings showed significantly less intimal hyperplasia in the trapidil group compared with the placebo group.[62] A clinical trial in angioplasty patients seems warranted.

Serotonin antagonist. Serotonin, similar to platelet-derived growth factor, is released during platelet degranulation at the time of vessel injury and appears to directly stimulate proliferation of smooth muscle cells in addition to potentiating the effects of platelet-derived growth factor.[63] Therefore administration of a serotonin antagonist such as ketanserin may inhibit smooth muscle cell proliferation. Klein et al.[64] studied the effects of ketanserin on the incidence of early and late restenosis. Ketanserin was given intravenously (0.1 mg/min/24 hr) for 24 hours after PTCA to 21 patients. After 24 hours three patients in the placebo group had an occlusion compared with none in the control group. Follow-up angiography 4 to 6 months later showed no difference in restenosis rates: 29% in the control group and 33% in the ketanserin group. A large multicenter interventional trial (Post-Angioplasty Restenosis Ketanserin trial) with ketanserin has recently been started and will elucidate the question of whether a longer administration (6 months) has a beneficial effect on the incidence of restenosis.

Colchicine. Colchicine inhibits the proliferation and migration of smooth muscle cells and the release of chemotactants by leukocytes.[65] To study the effect of colchicine on restenosis, rabbits with atherosclerosis with >50% diameter stenosis underwent iliac transluminal angioplasty. Colchicine was started 2 days before transluminal angioplasty (0.02 mg/day or 0.2 mg/day) until follow-up angiography at 4 weeks. The high dose of colchicine significantly decreased the diameter stenosis at follow-up, although no effect was seen with the low dose. Clinical trials with colchicine are currently in progress. However, it is likely that the efficacy of the drug will be limited by a high incidence of side effects (abdominal pain, vomiting diarrhea, and bone marrow depression).

Cytostatic agents. After the disruptive action of balloon dilatation, a change in differentiation of smooth muscle cells (with a shift from the contractile to synthetic phenotype) is observed and accompanied by cell proliferation and extracellular matrix production, which is the basis for the restenosis process. Barath et al.[66] hypothesized that cytostatic agents may prevent restenosis by selective injury to active and proliferating smooth muscle cells without damaging the normal smooth muscle cells. In their study rabbits were divided into four groups: the first

group was a control group, the second group had only a balloon dilatation of the aorta, the third group received the cytostatic agents (vincristine, 0.075 mg/kg, and actinomycin D, 0.015 mg/kg), and the fourth group underwent balloon dilatation and received cytostatic agents. All rabbits were killed 3 days later. Electron microscopic findings showed that the cytostatic agents prevented smooth muscle cell proliferation without damaging the "normal" smooth muscle cells. The principle concern with these agents is the potential for serious side effects, because they are capable of damaging other rapidly dividing cells, for example, those in the gastrointestinal tract, bone marrow, and reproductive system. Recently it has become possible to administer the drug locally with a specifically designed infusion catheter, which should limit systemic toxicity.

Angiotensin-converting enzyme inhibitors. Several organs contain local angiotensin-converting enzyme (ACE) systems. It appears that both the production of angiotensin II and its interaction with specific angiotensin II receptors may take place in these tissues independent of the plasma renin-angiotensin system.[67] ACE is a membrane-bound enzyme present in the walls of large arteries and veins. Angiotensin II receptors are present in the smooth muscle cells in the media of the vessel wall. In chronic hypertension it has been shown that long-term administration of an ACE inhibitor can reduce medial hypertrophy. It has been postulated that the local ACE system plays an important role in the remodeling process after arterial injury. There is also evidence to support the role of angiotensin II as a mitogen responsible for intimal hyperplasia after PTCA. In rats, neointima formation was reduced by 80% 14 days after balloon dilatation of the left carotid artery when an ACE inhibitor was given either 6 days before, 1 hour before, or 2 days after angioplasty and continued until 14 days after angioplasty. This effect seems to be dose dependent and is synergistic with the effect of heparin. There was no effect with administration of a single dose or when it was discontinued 2 days after balloon dilatation.[67] Further study has shown that captopril (100 mg/kg/day) also reduced intimal hyperplasia to almost the same extent. Two other vasodilators, verapamil and hydrazaline, demonstrated a lesser effect.[68] These results indicate that hemodynamic effects on the vascular walls may influence the formation of intimal hyperplasia after balloon catheterization and that ACE inhibitors may reduce intimal hyperplasia through additional mechanisms related to inhibition of the angiotensin system. Currently a large multicenter randomized trial in Europe (Multicenter European Research Trial with Cilazapril After Angioplasty to Prevent Transluminal Coronary Obstruction and Restenosis) is underway to determine the effect of cilazapril on the incidence of restenosis. More than 700 patients have been randomly assigned to cilazapril or placebo starting 4 to 6 hours after PTCA, in addition to the standard therapy of 200 mg acetylsalicylic acid. After 6 months (or earlier if indicated by symptoms) follow-up angiography is performed. A similar trial with 1400 patients has recently begun in the United States, but with a different dosage schedule.

Angiopeptin. It has been known for a long time that hypophysectomy inhibits neointimal plaque formation in response to endothelial injury.[69] This suggests that an endocrine factor may be involved in plaque formation. Recently the effect of a newly synthesized class of pituitary growth hormone–inhibiting agents on vascular smooth muscle cell hyperplasia after endothelial cell injury in vivo has been investigated. These compounds are peptide analogues of somatostatin and have a high affinity for somatostatin receptors on pituitary cells and inhibit release of pituitary growth hormone. One of these agents, angiopeptin, was shown to inhibit vascular smooth muscle cell proliferation in response to a variety of vascular injuries. This seems to be due to a local effect directly on smooth muscle cells.[70] This new group of agents is currently undergoing investigation as an inhibitor of several variants of "accelerated atherosclerosis" (postangioplasty, cardiac transplantation, and coronary bypass surgery).

CALCIUM ANTAGONIST

Coronary spasm is frequently seen during and shortly after PTCA and may have a role in the pathogenesis of restenosis.[71] Calcium antagonists by inhibiting vasospasm may reduce the incidence of restenosis in an animal model,[72] and in two randomized trials[73, 74] calcium antagonists have not been shown to influence the incidence of restenosis.

Diltiazem. In a study from the Montreal Heart Institute,[73] 92 patients received diltiazem (270 mg) for 3 months, and all underwent recatheterization 5 to 10 months after balloon angioplasty or earlier if symptoms returned. All patients also received acetylsalicylic acid (650 mg) and dipyridamole (225 mg) for 6 months. Patients treated with diltiazem had a restenosis rate of 15% versus 22% in the patients not treated with diltiazem (restenosis was defined as stenosis of 70% or more at the time of the follow-up

angiography). The average decrease in diameter during follow-up was 4% in the diltiazem group and 7% in the control group. It was concluded that diltiazem had no effect on restenosis and that coronary spasm is not a major mechanism of restenosis.

Nifedipine. In a 6-month follow-up trial at Emory University in Atlanta,[74] 241 patients were randomly assigned to either nifedipine (40 mg/day) or placebo. All patients also received acetylsalicylic acid (325 mg/day). Restenosis was defined as a loss of more than 50% of the gain achieved at the time of PTCA. In patients who were compliant and underwent follow-up angiography (84 patients in both groups) there was no difference in restenosis rates: 29% in the nifedipine group and 33% in the placebo group.

LIPID-LOWERING DRUGS

Epidemiologic trials have shown that a diet rich in (n-3) polyunsaturated fatty acids (present in high concentrations in most salt water fish) may account for the low incidence of coronary disease in Eskimos. Animal research has shown that these polyunsaturated fatty acids inhibit atherosclerosis in general. This can be partly explained through a lowering of serum lipid levels and decreased aggregation of platelets by altering the balance between prostacyclin and thromboxane. In the last few years several trials have studied the effects of n-3 fatty acids in the prevention of restenosis after PTCA.

Slack et al.[75] showed that adding 2.4 gm of fish oil each day (rich in eicosapentaenoic acid) to the usual post-PTCA regimen of calcium channel blocker, nitrates, acetylsalicylic acid, and dipyridamole could reduce the incidence of clinical restenosis in patients with single-vessel disease (33% in the placebo group vs 16% in the group treated with fish oil). In 49 patients with multivessel disease, no influence could be shown. Reis et al.[76] showed that supplementing the normal diet with 6.0 gm of fish oil daily starting just before PTCA until 6 months later had no influence on the restenosis rate in 186 patients in whom PTCA was successful. Angiographic restenosis (70% diameter stenosis at a site previously dilated to less than 50%) was present in 34% of the group taking fish oil and 23% of the control group. However, repeat angiography was performed in only 68 patients (37%); almost all patients had a recurrence of chest pain, which contributed to selection bias at follow-up angiography. Milner et al.[77] found that the addition of 4.5 gm of fish oil each day to a normal diet in 194 patients had a positive influence on the clinical restenosis rate with 19% (16 of 84 patients) in the fish oil group versus 35% (35 of 99 patients) in the placebo group having a recurrence of chest pain. However, in the first week 11 of 95 patients stopped taking the medication because of side effects.

In Dallas[78] 82 patients were randomly assigned to acetylsalicylic acid and dipyridamole with and without 3200 mg (18 capsules) of eicosapentaenoic acid. Treatment was started 7 days before PTCA and was discontinued 6 months after PTCA. In all 82 patients a second angiogram (on average 3 to 4 months after PTCA) was obtained. Restenosis was defined as 50% or more narrowing of the dilatation site at follow-up angiography. Restenosis was seen in 46% in the placebo group and 19% in the treatment group. This trial suggests that n-3 fatty acids may effectively reduce restenosis in high-risk patients provided they comply with the treatment and are pretreated starting 7 days before PTCA. In Melbourne[79] 108 patients were randomly assigned to 10 capsules of fish oil or placebo. Medication was started the day before angioplasty and continued until 4 months after angioplasty. All patients also received acetylsalicylic acid and verapamil. Restenosis was defined as loss of >50% of the gain in luminal diameter at angioplasty (using caliper measurement). No difference in angiographically defined restenosis rates was observed: 34% in the group treated with fish oil versus 33% in the placebo group.

It is clear that a consensus cannot be reached. These conclusions are in part related to differences in the design of the individual studies. Although all studies were randomized, only in two studies were patients and investigators blinded to the n-3 supplement. Different dosages and formulations were used and patient compliance varied in the studies. There were also differences in the timing of initiation of therapy and variable methods (coronary angiography, stress test, or symptoms) for the detection of restenosis.

Cholesterol-lowering drugs. Hypercholesterolemia is a well-known risk factor for ischemic heart disease. Lipid modification is an important goal in secondary prevention in halting the progression of atherosclerosis in general and possibly after angioplasty. Recently it was shown that lovastatin reduces intimal hyperplasia after balloon angioplasty in rabbits with hypercholesterolemia.[80] However, two trials with postangioplasty patients in which the effects of lipid lowering on the incidence of restenosis[81, 82] after PTCA were tested yielded conflicting results.

In the first trial[81] 157 patients were randomly assigned to lovastatin or placebo for an unstated period of time. Only 50% of the patients underwent follow-up angiography at an average of 4 months after

PTCA (50 patients in the lovastatin group and 29 patients in the control group). Restenosis was defined as narrowing of 50% or more at follow-up angiography. Restenosis was seen in 14% of the sites in the lovastatin group and in 47% in the placebo group, suggesting a beneficial effect of lovastatin in this select group. In the second trial[82] aggressive treatment was used in 55 consecutive patients to lower cholesterol levels, including diet, colestipol, and lovastatin, starting on the day of PTCA. After 2 weeks the cholesterol level was reduced by 50%. To date 44 of the 55 patients have been restudied with a restenosis rate of 34%. There was no difference in cholesterol levels between patients with and without restenosis.

INHIBITORS OF INFLAMMATION

Corticosteroids. Corticosteroids have been suggested as a potential restenosis inhibitor.[83] Hydrocortisone can inhibit growth of vascular smooth muscle in culture.[39] However, in a randomized trial in which patients received placebo or corticosteroids from 48 hours before to 5 days after PTCA, there was no difference in restenosis rates (33% in both groups).[84] The same results were achieved when steroids were given as treatment to 102 patients with restenosis after PTCA.[85] In addition to acetylsalicylic acid, dipyridamole, and a calcium antagonist, patients received 125 mg methylprednisolone intramuscularly 1 day before the repeat PTCA and 240 mg prednisone for 1 week. Only the 54 patients undergoing follow-up angiography were analyzed. Restenosis was defined as >50% diameter narrowing at the site. Restenosis was found in 36% of the stenoses in the group treated with steroids compared with 40% in the group receiving standard treatment.

In a recent multicenter trial in the United States,[86] 850 patients were randomly assigned to methylprednisolone or placebo 2 to 24 hours before PTCA. In 71% of the patients follow-up angiography was performed. There was no difference between the two groups in the incidence of restenosis (defined as >50% diameter stenosis): 43% in the group treated with methylprednisolone versus 43% of the patients in the group given placebo. These trials showed that administration of corticosteroids has no influence on the incidence of restenosis.

Nonsteroidal antiinflammatory drugs. Ibuprofen is known to decrease platelet-thrombus deposition in polytetra fluoroethylene (PTFE)* arterial grafts. In a study of normal porcine common carotid arteries pretreated with heparin, balloon angioplasty was performed and followed by a bolus (12.5 mg/kg) and infusion (75 to 100 μg/kg/min) of ibuprofen or placebo. Quantitative ^{111}In-labeled autologous platelet deposition at the site of angioplasty was significantly reduced by ibuprofen.[87] Whether this will affect the risk of late restenosis is not known.

*Gore-Tex vascular graft, registered trademark of W.L. Gore & Associates, Inc., Elkton, Md.

FUTURE DEVELOPMENTS

Until now we have not found a drug that prevents restenosis in patients undergoing angioplasty. In the near future the results will be known of currently ongoing multicenter trials with a new ACE-inhibitor (cilazapril), serotinin antagonist (ketanserin), hirudin, low molecular weight heparin, angiopeptin and fish oil. Other promising drugs such as thrombin blockers, antagonists of smooth muscle cells, growth factor blockers, prostacyclin analogues, and monoclonal antibodies against platelet membrane receptors (GP IIb/IIIa) and the von Willebrand factor will be tested in clinical trials and may bring us closer to the solution of the restenosis problem.

CONCLUSION

Despite 13 years of clinical experience and research in the field of restenosis after PTCA, there have been no major breakthroughs in pharmacologic interventions. Assessment of the value of drug trials that have been performed in the past is extremly difficult because of differences in selection of patients, methods of analysis, and definition of restenosis. Recently our group has reviewed the influence of these three factors on the outcome and conclusion of restenosis studies.[88] Although there is no scientific proof that the tested drugs are effective, many clinicians continue prescribing them to "prevent restenosis."

Clinical and experimental research must continue to look for the elusive "magic bullet" that can prevent aggregation of thrombocytes, spasm, proliferation of smooth muscle cells, and atherosclerosis without any side effects and, if possible, in only one tablet! Moreover, the cost of this potential drug solution must be less expensive than repeating PTCA in 30% of all patients. It is clear that this magic drug has not been found, and in the meantime we will continue (re)dilating while we search for a pharmacologic or technical solution to the problem of restenosis.

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CHAPTER 3

METHODOLOGICAL PROBLEMS RELATED TO THE QUANTITATIVE ASSESSMENT OF STRETCH, ELASTIC RECOIL AND BALLOON-ARTERY RATIO

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Methodological Problems Related to the Quantitative Assessment of Stretch, Elastic Recoil, and Balloon-Artery Ratio

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The (inflated) balloon is important to determine the extent of stretch (theoretical maximal gain in diameter or area during PTCA), elastic recoil (the loss in diameter or area immediately after PTCA), and whether under- or over-sizing (balloon-artery ratio) of the dilated lesion occurred. In these assessments, the inflated balloon is used as scaling device with assumed uniformity along its entire length. In order to assess more accurately stretch, elastic recoil, and the balloon-artery ratio, the balloon diameter was measured over its entire length with edge detection and videodensitometry in 505 lesions (453 patients). With an average inflation pressure of 8.3 ± 2.6 atm a difference between the minimal and the maximal balloon diameter of 0.59 ± 0.23 mm was measured using edge detection and 1.70 ± 0.90 mm^2 difference in area using videodensitometry. This results in large variations in the calculated stretch, elastic recoil, and balloon-artery ratio depending on the site of the balloon chosen for assessment. The mean difference ± SD between stretch and elastic recoil assessed by edge detection and videodensitometry (using the minimal luminal diameter or area of the balloon) are respectively 0.00 ± 0.19 and 0.00 ± 0.24, suggesting that both methods are appropriate.

Key words: PTCA, balloon, QCA, recoil

INTRODUCTION

Percutaneous transluminal coronary angioplasty (PTCA) is an accepted revascularization procedure for treatment of patients with stable and unstable angina pectoris and for patients with single and multi-vessel disease [1,2]. Although earlier work has drawn attention to the process of in vivo inflation of the balloon, in vivo pressure-volume relationship [3], and in vivo pressure-diameter curves [4], the quantitative analysis of the inflated balloon at the site of the stenotic lesion has not been emphasized. Visual inspection of the inflated balloon led to the assumption that, with the use of a pressure as high as 20 atm, the balloon is fully and uniformly inflated to a diameter in accordance with the manufacturer's specification.

With the introduction of computer-based quantitative analysis systems—edge detection and videodensitometry—it became possible to measure the exact diameter and area of normal and stenotic arterial segments pre- and post-PTCA as well as the balloon diameter during full inflation. However, conflicting data has been published about the correlation of post-angioplasty analysis between the two techniques [5–20].

The inflated balloon has important clinical implications since it affects the extent of 1) stretch (theoretical maximal gain in diameter or area during PTCA), 2) elastic recoil (influence the immediate post-PTCA result) [4,21,22], and 3) under- or over-sizing of the lesion (important factor in the incidence of dissections) [23–26]. In the assessment of these three parameters, the inflated balloon is used as scaling device and is presumed uniform along its entire length. However, this assumption has never been critically analyzed.

The objective of this study was to determine (using two quantitative methods) whether the balloon diameter is uniform along its entire length. In the event of non-uniformity of the inflated balloon, guidelines will be

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proposed for the selection of the balloon diameter for future quantitative studies.

MATERIALS AND METHODS

Study Population and PTCA Procedure

The study population consisted of 453 patients (505 lesions) who had undergone successful PTCA at the Thoraxcenter between June 1989 and December 1989, defined as a less than 50% diameter stenosis on visual inspection of the post-PTCA angiogram. Patients with stable and unstable angina were included; patients with acute myocardial infarction (<7 days) and patients with total occluded lesions pre-PTCA were excluded. Mean age of the patients was 56 ± 10 yr. Of the 505 lesions dilated, 146 were located in the right coronary artery (RCA), 238 in the left anterior descending (LAD), and 121 in the left circumflex artery (LC).

Medications at the time of the procedure were intravenous heparin and acetylsalicylic acid. Choice of balloon type (compliant vs. non-compliant), inflation duration, total number of inflations, and inflation pressure were left to the operator. Coronary angiograms were recorded before and after angioplasty, and during dilatation with the largest balloon size at the highest inflation pressure applied.

Quantitative Coronary Angiography

The quantitative analysis of the stenotic coronary segments and the balloon at maximal inflation pressure was carried out by the Coronary Angiography Analysis System (CAAS), which has been validated and described in detail elsewhere [7,12,13]. Examples of analyses are shown in Figure 1.

Single identical views pre-PTCA, post-PTCA, and during balloon inflation were chosen for analysis. For this purpose, the largest balloon filled with contrast was filmed during the last inflation at maximum pressure. Contrast medium (Isopaque Cerebral 280 mg/ml, Nycomed AS Oslo) that is routinely used for arteriography of the carotid arteries was selected for its high radiopacity, which enhances the automated edge detection and videodensitometric analysis. This contrast medium has a low-viscosity and therefore does not need to be diluted. Special attention was given to avoid air bubbles in the balloon when filling with contrast medium.

Edge Detection

Any area sized 6.9 × 6.9 mm in a select cine-frame (overall dimensions 18 × 24 mm) encompassing the desired arterial segment was digitized by a high-resolution CCD camera with a resolution of 512 × 512 pixels and 8 bits of gray level. Vessel and balloon contours are determined automatically based on the weighted sum of the first and second derivative functions applied to the digitized brightness information along scanlines perpendicular to the local centerline directions of an arterial segment or inflated balloon. A computer-derived estimation of the original arterial or inflated balloon diameter at the site of obstruction is used to define the interpolated reference diameter. This technique is based on a computer-derived estimation of the original diameter values over the analyzed region (assuming there was no disease present) according to the diameter function. The absolute minimal values as well as the reference diameter are measured by the computer, which uses the known contrast-empty guiding catheter diameter as scaling device. To achieve maximal vasodilatation, either nitroglycerin or isosorbide dinitrate was given intracoronary for each coronary artery involved pre-PTCA and post-PTCA [7]. All contour positions of the catheters, the arterial segments, and the inflated balloon were corrected for pincushion distortion introduced by the individual image intensifiers.

Densitometric Analysis

Densitometry is based on the approximate linear relation that exists between the optical density of a contrast-enhanced lumen and the absolute dimensions of the arterial segment. Constitution of the relation between the path length of the x-rays through the artery or balloon and the brightness values requires a detailed analysis of the complete x-ray/cine/video chain, including the film development process [12,13,27]. For the first part of the chain, from the x-ray tube to the output of the image intensifier, we use Lambert Beer's law for the x-ray absorption and apply certain models for the x-ray source and the image intensifier. From the output of the image intensifier up to the brightness values in the digital image, we use a linear transfer function. The cross-sectional area of a vessel or balloon is then obtained as follows. The contours of a selected arterial segment or balloon (in a non-foreshortening view) are detected by automated edge detection as described above. On each scanline perpendicular to the local centerline direction of the vessel, a profile of brightness values is measured. This profile is transformed into an absorption profile by means of a simple logarithmic transfer function. The background contribution is estimated by computing the linear regression line through the background points directly left and right of the detected contours. Subtraction of this background portion from the absorption profile within the arterial contours yields the net cross-sectional absorption profile. Integration of this function gives a measure for the cross-sectional area at the particular scanline. By repeating this procedure for all scanlines, the cross-sectional area function is obtained. A reference densitometric area is obtained following the same principles as described above for the diameter measure-

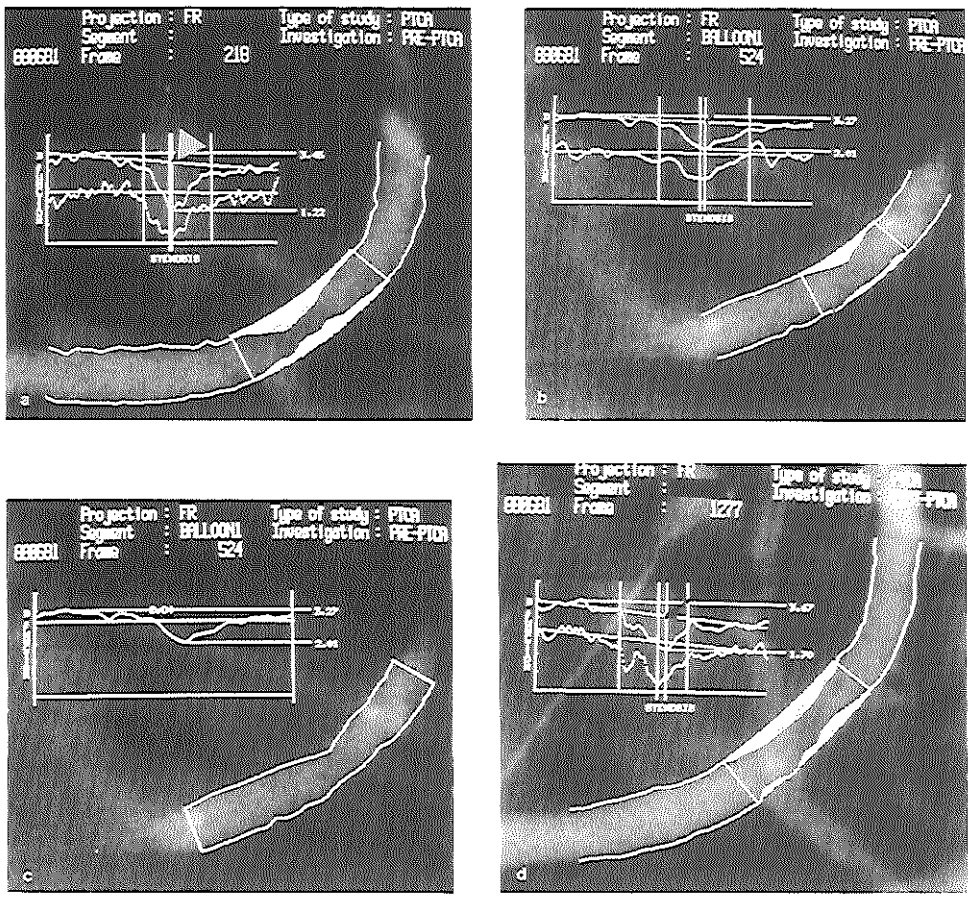

Fig. 1. Single frame angiogram of a mid portion of a circumflex artery. Superimposed on the video image are the diameter function curve (measured by edge detection [upper curve]) and the area function curve (measured by videodensitometry [lower curve]) of the severity of the obstruction before and after balloon dilatation (a,d) as well as of the balloon during maximal inflation (b,c). The interpolated reference diameter line is computed from the contours proximal and distal of the lesion. The reference diameter value is taken at the point coincident with the point of maximal narrowing (white arrow). The white areas are a measure for the "atherosclerotic plaque." b and c show the inflated balloon with an inflation pressure of 12 atm. The computer measured a minimal balloon diameter of 2.01 mm, a mean diameter over the entire length of the balloon of 2.84, a maximal diameter of 3.27, and a reference diameter of 2.99 mm (value not shown in figure). The nominal size of this balloon was 3.25 mm and was inflated at a maximum pressure of 12 atmospheres. These figures clearly show the non-uniform inflation process.

ments. It is clear that homogeneous mixing of the contrast agent and the blood must be assumed for the measurements to be correct. The complete procedure has been evaluated with cinefilms of Plexiglass^{R} of coronary obstructions [12,27].

Definitions of Quantitative Derived Morphologic Parameters

The area (mm^2) between the actual and reconstructed contours at the obstruction site is a measure of the amount of *atherosclerotic plaque* [12,28]. The *length of*

TABLE I. Quantitative Analysis of 505 Dilated Coronary Lesions and Inflated Balloons

	Pre-PTCA	Post-PTCA	*p* value
	Lesion		
Edge detection			
Minimal diameter (mm)	1.09 ± 0.31	1.83 ± 0.40	0.001
Reference diameter (mm)	2.70 ± 0.55	2.75 ± 0.51	0.001
Length lesion (mm)	6.5 ± 2.5	6.1 ± 2.6	0.001
Plaque area (mm^2)	7.09 ± 3.79	4.38 ± 3.32	0.001
Symmetry value	0.40 ± 0.24	0.35 ± 0.21	0.001
Curvature (units)	21.6 ± 10.9	20.4 ± 11.2	NS
Videodensitometry			
Minimal area (mm^2)	0.81 ± 0.79	2.63 ± 1.34	0.001
Reference area (mm^2)	5.98 ± 2.19	6.13 ± 2.33	0.001
	Balloon		
Edge detection		Videodensitometry	
Minimal diameter (mm)	2.37 ± 0.41	Minimal area (mm^2)	4.39 ± 1.61
Mean diameter (mm)	2.64 ± 0.40		
Maximal diameter (mm)	2.96 ± 0.44		
Reference diameter (mm)	2.75 ± 0.41	Reference area (mm^2)	6.09 ± 1.82
Nominal size (mm)	2.94 ± 0.39		

NS = Not significant.

the obstruction (mm) is determined from the diameter function on the basis of curvature analysis. *Symmetry* is defined as the coefficient of the left and 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. A symmetrical location of the lesion has a value of 1 and a severely eccentric located 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.

Assessment of Stretch, Elastic Recoil, and Balloon-Artery Ratio

Stretch was defined as the ratio between the inflated balloon diameter (mm) minus the minimal luminal diameter (MLD) of the vessel pre-PTCA and the reference diameter (RD) (mm) of the dilated segment, and this represents the maximum diameter of the vessel at the time of balloon inflation:

$$\frac{\text{balloon diameter} - \text{MLD pre-PTCA}}{\text{RD pre-PTCA}}.$$

As previously published [12,13] *elastic recoil* of the stenosis is defined as the ratio between the balloon diameter (mm) minus the MLD post-PTCA (mm) and the reference diameter of the dilated segment and this represents the early loss in diameter immediately following balloon inflation:

$$\frac{\text{balloon diameter} - \text{MLD post-PTCA}}{\text{RD pre-PTCA}}.$$

Balloon-artery ratio was defined as the ratio between the balloon diameter and the reference diameter pre-PTCA of the dilated segment and attempts to describe the extent of balloon under or over sizing of the normal segment of the vessel:

$$\frac{\text{balloon diameter}}{\text{RD pre-PTCA}}.$$

Assessment of stretch, elastic recoil and balloon-artery ratio were derived from videodensitometry by substituting diameter measurements with densitometrically measured area measurements.

Statistical Analysis

All continuous variables were expressed as mean values ± standard deviation (SD) (Tables I,II) and a *t* test was applied to these variables (Table I). A value of <0.05 was considered statistically significant.

TABLE II. Variation in the Extent of Stretch, Elastic Recoil, and Balloon Artery Ratio in 505 Dilated Lesions

	Stretch	Elastic recoil	BAR
Edge detection			
Minimal balloon diameter (mm)	0.49 ± 0.18	0.21 ± 0.15	0.90 ± 0.17
Mean balloon diameter (mm)	0.59 ± 0.18	0.31 ± 0.15	1.00 ± 0.17
Reference diameter of balloon (mm)	0.63 ± 0.18	0.35 ± 0.16	1.04 ± 0.18
Maximal balloon diameter (mm)	0.71 ± 0.20	0.43 ± 0.18	1.12 ± 0.20
Nominal size of balloon (mm)	0.71 ± 0.21	0.43 ± 0.18	1.12 ± 0.20
Videodensitometry			
Minimal area of balloon (mm^2)	0.67 ± 0.37	0.34 ± 0.32	0.81 ± 0.36
Reference area of balloon (mm^2)	0.98 ± 0.42	0.65 ± 0.36	1.12 ± 0.41
Nominal area of balloon (mm^2)	1.16 ± 0.54	0.82 ± 0.45	1.29 ± 0.51

BAR = Balloon-artery ratio.

To measure the strength of the relation between the nominal size and the measured balloon diameter, the product-moment correlation coefficient (r) and its 95% confidence intervals (CI) were calculated. The agreement between the two measures was assessed by determining the mean and the SD of the between-method difference as suggested by Bland and Altman [29]. This was done by computing the sum of the individual differences between the two measures to determine the mean difference and the SD. The same statistical method was applied to assess the relationship between the minimal cross-sectional area derived from edge detection and videodensitometry as well as of the inflated balloon.

To assess the relationship between several angiographic morphological variables (area plaque, curvature, length of the lesion, symmetry) and recoil, a univariate analysis was performed. To avoid arbitrary subdivision of data, cut off criteria for continuous variables were derived by dividing the data in three groups so that each group contained about one-third of the population. The group with the highest amount of recoil was then compared with the two other groups [30]. This method of subdivision has the advantage of being consistent for all variables and thus avoids any bias in selection of subgroups which might be undertaken to emphasize a particular point (Table III).

Analysis was carried out with a commercial statistical package (BMDP Statistical Software 1990).

RESULTS

Quantitative angiographic lesion characteristics of the 505 lesions dilated and of the balloon at highest inflation pressure used, are shown in Table I.

Lesion

The minimal luminal diameter increased from 1.09 ± 0.31 mm to 1.83 ± 0.40 mm after PTCA with an increase in minimal cross-sectional area from 0.81 ± 0.79 mm^2 to 2.63 ± 1.34 mm^2 ($p < 0.001$). There was a significant change in "interpolated" reference diameter after PTCA: 2.70 ± 0.55 mm pre-PTCA and 2.75 ± 0.51 mm post-PTCA, and in reference area: 5.98 ± 2.19 mm^2 pre-PTCA and 6.13 ± 2.33 mm^2 post-PTCA ($p < 0.001$).

Balloon

The average length of the balloon analyzed was 16.2 ± 3.7 mm; the tapered proximal and the distal part of the balloon were not included in the analysis (Fig. 1). The average inflation pressure used was 8.3 ± 2.6 atm, the number of inflations varied between 1 and 17 (mean 3.1 times), and the average inflation time was 255 ± 217 sec. As shown from Table I the balloon is not uniformly inflated over its entire length at the highest pressure used. Quantitative analysis showed a mean difference of 0.59 ± 0.26 mm between the maximal and minimal balloon diameter in case of edge detection and 1.70 ± 0.90 mm^2 between the reference area and minimal area by videodensitometry.

The manufacturer's size of the balloon used was 2.94 ± 0.39 mm (range 2.0 to 4.2 mm). The mean difference (± SD) in diameter (and the corresponding r and 95% CI) between the nominal diameter of the balloon and its in vivo measured diameter using *edge detection* were

0.66 ± 0.32 for the minimal balloon diameter
(r = 0.67; 95% CI = 0.62 to 0.72),
0.30 ± 0.29 for the mean balloon diameter
(r = 0.73; 95% CI = 0.69 to 0.77),
0.19 ± 0.31 for the reference balloon diameter
(r = 0.71; 95% CI = 0.66 to 0.75),
−0.02 ± 0.33 for the maximal balloon diameter
(r = 0.68; 95% CI = 0.63 to 0.72) (Fig. 2A–D).

Although the nominal size of the balloon during inflation is reached at the maximal balloon diameter, it appears

TABLE III. Influence of the Balloon Diameter or Area Used in the Univariate Analysis of Elastic Recoil

	Symmetry			Curvature			Area plaque			Length lesion		
Balloon	< 0.24 # 164	> 0.24 # 341	p	< 16 # 171	> 16 #334	p	< 5.1 # 170	> 5.1 # 335	p	< 5.2 # 168	> 5.2 # 337	p
Edge detection												
Minimal diameter	0.23	0.20	0.08	0.23	0.20	0.03	0.22	0.20	0.14	0.22	0.21	0.56
Mean diameter	0.33	0.30	0.15	0.33	0.30	0.03	0.34	0.30	0.001	0.32	0.31	0.26
Maximal diameter	0.45	0.43	0.25	0.45	0.42	0.07	0.47	0.42	0.001	0.45	0.43	0.21
Reference diameter	0.37	0.35	0.15	0.38	0.34	0.02	0.38	0.34	0.001	0.37	0.35	0.25
Nominal size	0.44	0.43	0.34	0.44	0.42	0.24	0.48	0.41	0.001	0.45	0.42	0.10
Videodensitometry												
Obstruction area	0.37	0.32	0.08	0.39	0.31	0.02	0.42	0.30	0.001	0.35	0.33	0.50
Reference area	0.69	0.63	0.11	0.72	0.61	0.001	0.77	0.59	0.001	0.70	0.62	0.04
Nominal area	0.85	0.81	0.40	0.88	0.79	0.05	1.01	0.72	0.001	0.89	0.79	0.02

that the balloon is not inflated at the theoretical diameter along its entire length.

The mean differences (± SD) in area (and the corresponding r and 95% CI), calculated using the cross-sectional area of the balloon, derived from the nominal size assuming a circular model of the balloon and from *videodensitometry* measurements, were

2.53 ± 1.56 for the minimal balloon area (r = 0.59; 95% CI = 0.53 to 0.64),
0.83 ± 1.42 for the reference balloon area (r = 0.70; 95% CI = 0.65 to 0.74) (Fig. 2E,F).

Stretch

Stretch measurement derived from edge detection varied between 0.49 ± 0.18—when the minimal value of the balloon diameter was chosen—and 0.71 ± 0.21 if the nominal size of the balloon or the maximal value of the balloon diameter was used. When videodensitometry is applied, stretch measurement varied between 0.67 ± 0.37—when the minimal value of the balloon area was chosen—and 1.16 ± 0.54 if the nominal area of the balloon (derived from the nominal balloon size) was used (Table II).

Elastic Recoil

Elastic recoil measurement derived from edge detection varied between 0.21 ± 0.15—when the minimal value of the balloon diameter was chosen—and 0.44 ± 0.18 if the maximal value of the balloon diameter was used. With videodensitometry, elastic recoil measurement varied between 0.34 ± 0.32 using the minimal value of the balloon area and 0.82 ± 0.45 using the nominal area of the balloon (derived from the nominal size) (Table II).

Table III shows the influence of the selected balloon diameter on the univariate analysis of elastic recoil. For each morphologic parameter, different levels of significance were observed. For instance, the degree of curvature was significantly related to the recoil phenomenon when the value of the minimal, mean, or reference balloon diameter was selected. However, the relation is no longer significant if the maximal value of the balloon diameter or the nominal balloon size was considered. The amount of area plaque is significantly related to the recoil phenomenon with less plaque giving more elastic recoil. This is of significance for all selected balloon diameters or areas except when the minimal value of the balloon diameter was selected.

Balloon-Artery Ratio

Balloon-artery ratio derived from edge detection varied between 0.90 ± 0.17 when the minimal value of the balloon diameter was chosen, and 1.13 ± 0.20 with the maximal value. With videodensitometry, the balloon-artery ratio varied between 0.81 ± 0.36 (with the minimal value of the balloon area) and 1.29 ± 0.51 when the nominal area of the balloon was selected (Fig. 3).

Comparison Between Edge Detection and Videodensitometry in the Assessment of Lesion Severity Pre- and Post-PTCA, of the Inflated Balloon, and of Stretch and Elastic Recoil

Lesion and balloon. The mean differences (± SD) between the minimal luminal cross-sectional area pre-TPCA, post-PTCA, and of the balloon derived from edge detection (assuming a circular cross-section) and measured by videodensitometry are 0.11 ± 0.50 mm^2, 0.11 ± 1.04 mm^2, and 0.16 ± 0.89 mm^2, respectively. (Fig. 4).

Stretch and recoil. Figure 5 shows the relationship between stretch and elastic recoil assessed by edge detection and videodensitometry using the minimal luminal diameter or area of the balloon. The mean difference (± SD) between the two measurements are respectively 0.00 ± 0.19 for stretch and 0.00 ± 0.24 for elastic recoil.

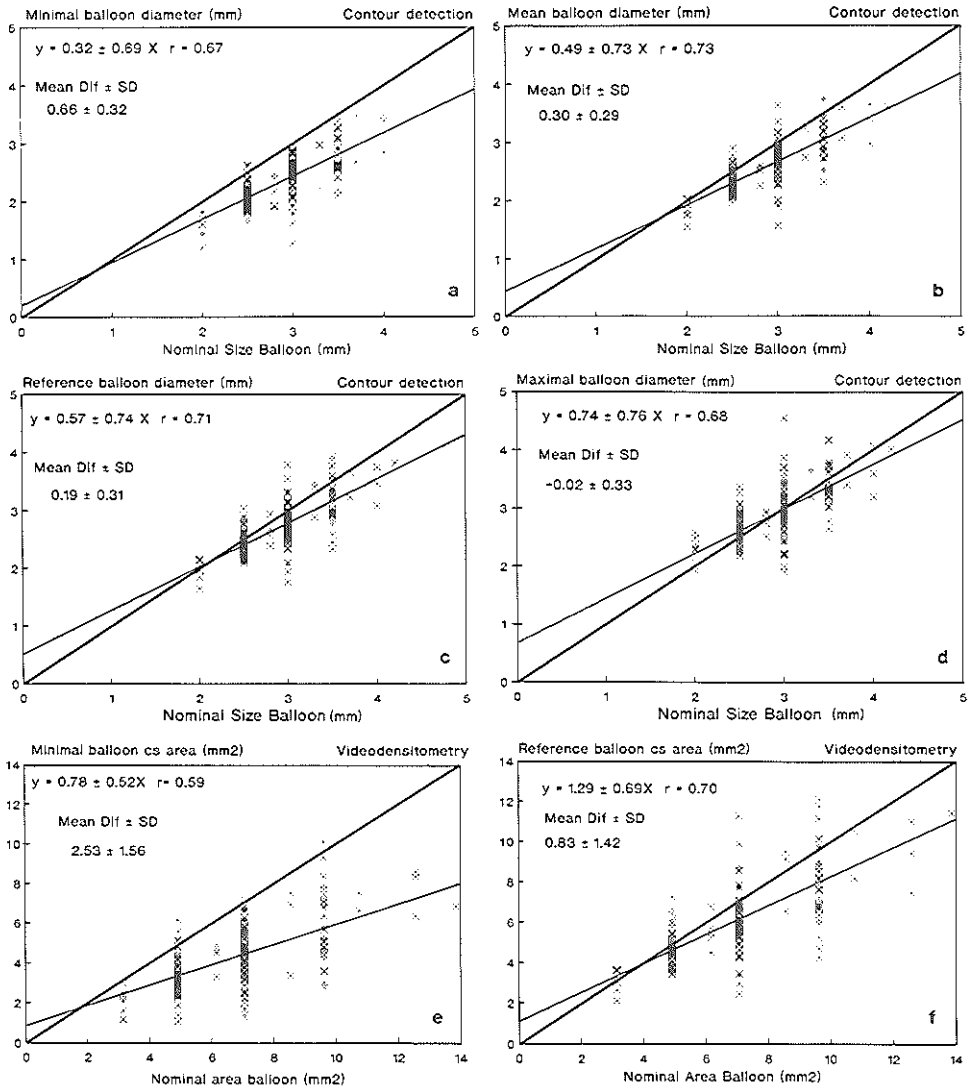

Fig. 2. Four different balloon diameters measured by edge detection versus the nominal size of the balloon (a–d) and two different balloon area's measured by videodensitometry versus the nominal area of the balloon (e,f). Mean Dif ± SD = Mean difference and standard deviation between the measured balloon diameter (area) and the nominal size (area) of the balloon. r = correlation coefficient with regression line.

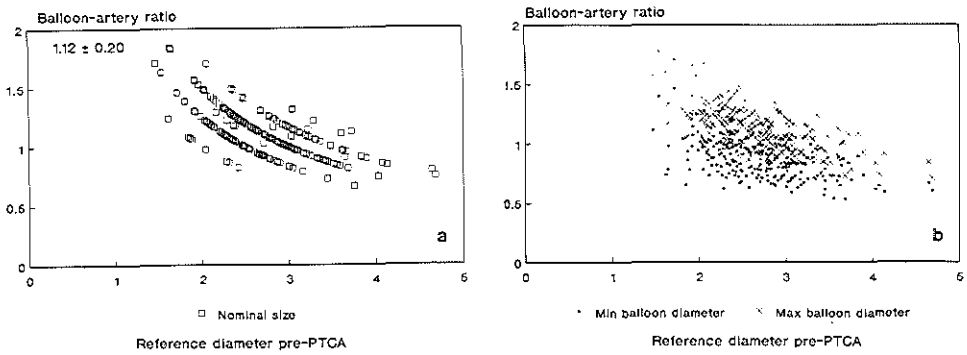

Fig. 3. The balloon-artery ratio vs. the reference diameter pre-PTCA. Depending on whether the nominal size (a) or the minimal or the maximal balloon diameter (b) is used, a single balloon inflation may be judged to be under sized (ratio < 1) or over sized (ratio > 1). Over sizing occurs more frequently in small vessels and under sizing more frequently in large ones.

DISCUSSION

This study showed that the balloon is not uniformly inflated at the highest pressure used. A maximal difference of 0.59 ± 0.26 mm in balloon diameter was measured at an average inflation pressure of 8.3 atm. Histologic studies have shown that the vast majority of atherosclerotic plaques in human coronary arteries are composed of dense fibrocollagenous tissue with varying amounts of calcific deposits and smaller amounts of intracellular and extracellular lipid ("hard plaques") [31]. Certain parts of plaques may restrict complete balloon expansion, which explains the pattern of non-uniformity. It has been the common clinical experience of many operators that some lesions will not yield even at inflation pressure up to 20 atm. Recently intravascular ultrasound images have confirmed this non-uniform inflation pattern during coronary angioplasty (personal communication, Dr. Jeffrey Isner).

Edge Detection and Videodensitometry

Ideally in the assessment of stretch and elastic recoil, the measurement of interest is the precise relationship between the cross-sectional area of the vessel and the balloon at the site of the obstruction. It might be assumed that at each stage of the procedure, the luminal area of the vessel at the stenotic site is not circular so that the geometric evaluation (assuming a circular model) of stretch and the recoil phenomenon might be misleading particularly after the disruptive effect of balloon angioplasty. As earlier reported, the use of edge detection may be limited in the analysis of dilated lesions immediately following angioplasty [9,13] because acute tears and dissections distort the anatomy. From a theoretical point of view, a videodensitometric approach seems to be the ultimate solution in measuring the vessel and balloon cross-sectional area in a single angiographic view. Although densitometry is independent of geometric shape, this technique seems to be more sensitive than edge detection to densitometric nonlinearities (x-ray scatter, image intensifier veiling glare, and beam hardening), oblique projection of the artery, and overlap with other structures, and its application is limited in the presence of branch vessels that may cause errors in the background correction technique and in situations where the x-ray beam is not perpendicular to the long axis of the vessel [16].

In the present study it was felt that the videodensitometric approach was used in relatively optimal condition since the inflated balloon was filmed in the least foreshortened view (for safety reasons), thereby avoiding large errors due to potential changes in background scatter and veiling glare. During inflation of the balloon, the surrounding coronary vessels were not opacified, thus minimizing the problems related to the background correction. However, the analysis of the lesion remains subject to the well known pitfalls (mentioned in the previous paragraph) encountered with the videodensitometric technique. Despite the well known technical limitations, the assessment of stretch and elastic recoil by videodensitometry did not significantly differ from the assessment derived from edge detection and both techniques might be used in the future on-line in the catheterization laboratory during coronary angioplasty.

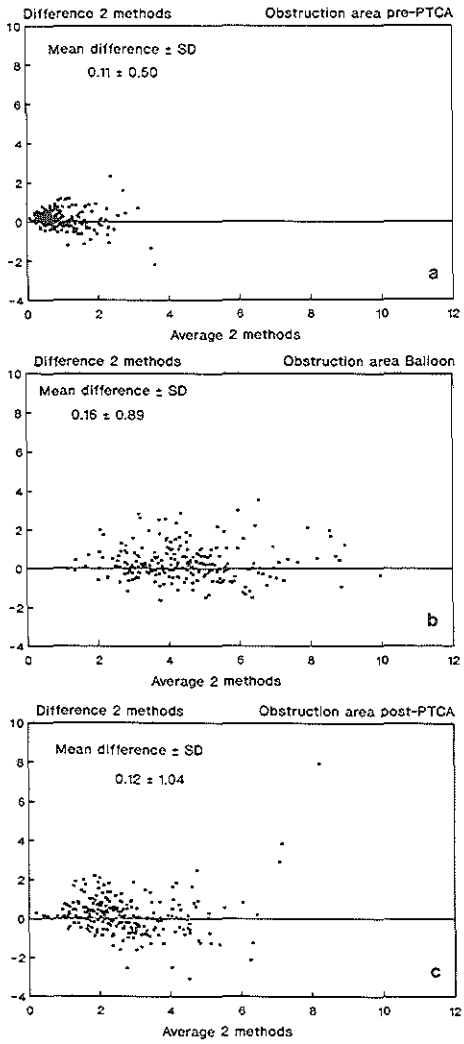

Fig. 4. The mean difference (± SD) between the mimimal luminal cross sectional area pre-PTCA (a), during balloon inflation (b), and post-PTCA (c) derived from edge detection and videodensitometry.

Compliant Vs. Non-Compliant Balloons

In this study, the choice to use a compliant or non-compliant balloon during PTCA was left to the operator. In 250 lesions a non-compliant balloon (209 balloons were made from polyethylene terephthalate [PET], nine balloons were made from polyolefin copolymer [POC], and 32 balloons were made from hydracross) was used for dilatation, and in 255 lesions a compliant balloon (236 balloons were made from polyethylene [PE] and 19 balloons were made from polyvinylchloride [PVC]) was used for dilatation. A significant difference was observed for the symmetry measurement (0.42 ± 0.25 in the non-compliant balloon group vs. 0.37 ± 0.23 in the compliant balloon group, $p < 0.03$) and for the highest balloon pressure used (9.0 ± 2.7 in the non-compliant balloon group vs. 7.6 ± 2.2 in the compliant balloon group, $p < 0.001$). Although no differences between the two groups in minimal lumen diameter or area pre-PTCA and post-PTCA, reference diameter or area pre-PTCA and post-PTCA, diameter stenosis or area stenosis pre-PTCA, nominal balloon size, calculated stretch, elastic recoil, and the balloon-artery ratio was observed, there was a significant difference in post-PTCA diameter stenosis—with a better result in the group where lesions were dilated with a compliant balloon type (diameter stenosis of 32% vs. 34% in the non-compliant balloon group). It is possible that this difference is caused by the type of lesions dilated (different symmetry) or due to the maximal balloon pressure used. A comparative study is warranted to investigate if this difference in post-PTCA result between the two groups is significant or that it reflects differences in selection.

Which Measured Balloon Diameter Should Be Used in the Quantitative Assessment of Stretch, Elastic Recoil, and Balloon-Artery Ratio?

It is clear from our study that the nominal size of the balloon listed by the manufacturer should not be used in the assessment of stretch and elastic recoil of the stenotic lesion or in the assessment of the balloon-artery ratio because the nominal size is not reached at the stenotic site even at an average pressure of 8.3 atm.

Stretch

To determine the actual amount of stretch at the obstruction, we propose to use the minimal diameter or area in the balloon during inflation as this persistent encroachment of the balloon during inflation presumably localizes the non-distensible part of the stenosis that restricts the dilatation. Even more accurate would be a superimposition of the two diameter functions of the dilated vessel and inflated balloon to continuously assess stretch over the entire length of the dilated lesion (Fig. 6).

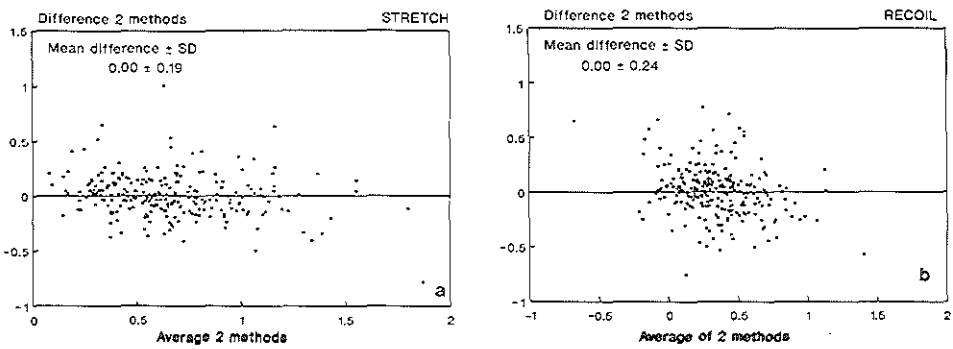

Fig. 5. a: The relation between stretch using edge detection and videodensitometry (the minimal luminal diameter or area of the balloon). b: The relation between elastic recoil using edge detection and videodensitometry (the minimal luminal diameter or area of the balloon).

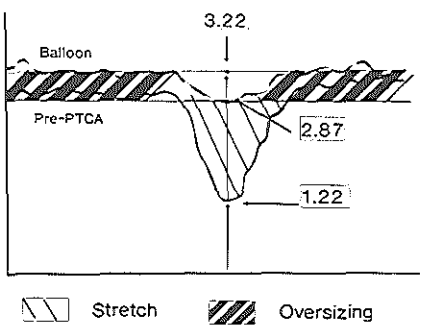

Fig. 6. In this example the minimal luminal diameter of the lesion pre-PTCA and during balloon inflation are 1.22 mm and 2.87 mm respectively. The interpolated reference diameter for the lesion is 2.87 mm and for the balloon 3.22 mm. The nominal size of the balloon is 3.5 mm. Theoretically the maximal gain is 3.50 − 1.22 = 2.27 mm. However, due to the atherosclerotic plaque in the vessel wall, complete balloon expansion was not achieved. Stretch of the lesion was (2.87 − 1.22) / 2.87 = 0.57. The upper line represents the diameter function curve of the balloon over the entire length of the balloon at maximum inflation pressure. The lower line represents the diameter curve pre-PTCA. The two interpolated reference diameter lines are also shown (see arrows). The difference between these two lines represents the balloon-artery ratio (/ / /). It is clear that in this example oversizing took place: the interpolated reference diameter of the balloon is 3.22 mm and of the stenosis 2.87 mm; this results in a balloon-artery ratio of 1.12. In this case, the minimal diameter of the balloon and the lesion are localized at the exact same spot; however, this is not always the case.

Elastic Recoil

Recently Monson et al. [4] studied in 27 patients the angiographic patterns of balloon inflation during PTCA. Videodensitometry was used to measure the diameter of the inflated balloon and of the lesion pre-PTCA and post-PTCA. They defined recoil as the ratio between the balloon diameter at 6 atm and the coronary diameter after angioplasty. They found that the nominal size of the balloon was almost never reached over the entire length of the balloon. Our data is in agreement with their observation (Table I).

Any analysis of factors affecting the recoil phenomenon will be greatly influenced by the selection of the value of the balloon diameter or area (minimal, mean, maximal, reference, or nominal) used for the calculation of the elastic recoil. Our group earlier reported that more elastic recoil was seen in asymmetric lesions (<0.37), lesions located in less angulated parts of the artery (<12.5 units), and in lesions with a small plaque content (<4.7 mm^2) [12]. In that latter study, the mean diameter (derived over the entire length) of the balloon was used. Table III shows the influence of the selected balloon diameter or area on the univariate analysis of factors affecting elastic recoil. From this table it is clear that small area plaque (<5.08 mm^2) and lesions located in less angulated parts of the vessel (curvature < 16.3 units) are significantly or not significantly affecting the recoil phenomenon of the lesion depending on the balloon diameter chosen for analysis.

To accurately assess the extent of elastic recoil at the site of severest luminal narrowing we suggest use of the minimal value of the balloon diameter or area as this measurement presumably reflects the narrowing persisting at the site of the stenosis during dilatation. Even more accurate would be a superimposition of the two diameter functions of the dilated vessel and inflated balloon to continuously assess elastic recoil over the entire length of the dilated lesion (Fig. 7).

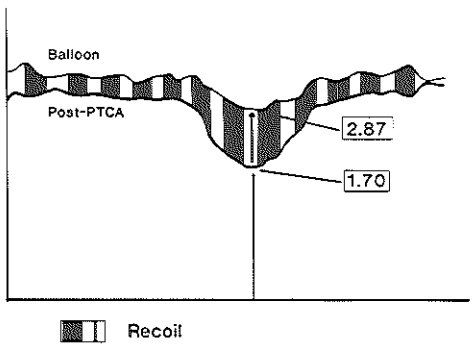

Fig. 7. The upper line represents the diameter function curve of the balloon; this shows what maximally was achieved during PTCA. The lower line represents the diameter function curve post-PTCA. //// = elastic recoil; represents what is lost in diameter immediately post-PTCA. Post-PTCA the minimal luminal diameter is 1.70 mm. Immediately post-PTCA (2.87 – 1.70) / 2.87 = 0.41 is lost due to elastic recoil. The ratio of elastic recoil is not necessarily at its maximum at the minimal obstruction site of the vessel.

Balloon-Artery Ratio

In the present study, the balloon-artery ratio derived from edge detection varied between 0.90 ± 0.17 (undersized) and 1.13 ± 0.20 (oversized) is selected (Fig. 3).

Roubin et al. [23] defined the balloon-artery ratio by estimating the so-called normal lumen of the coronary artery by direct visual comparison to the known diameter of the guiding catheter used. Then the patients were randomized to a (nominal) balloon size smaller or larger than this so-called normal lumen. They found more acute complications with a balloon size greater than the so-called normal lumen. Nichols et al. [24] compared the diameter of the inflated balloon to a normal artery (in most cases proximal of the stenosis (adjacent to the stenosis (user-defined). In this study, balloon sizes provided by the manufacturers were used. They concluded that the interventional cardiologist should approximate or slightly exceed the diameter of the normal arterial diameter in order to achieve optimal angiographic results with minimal dissections and minimal residual stenosis since oversized balloons (ratio > 1.3) caused a higher incidence of dissections.

Over- and under-sizing of the balloon with respect to the vessel dilated always refers to the non-diseased part of the vessel as over-sizing of the stenotic lesion itself always takes place (Fig. 6). So, in theory, the nominal size of the balloon and the non-diseased diameter pre-PTCA should be used for the balloon-artery ratio. However, the present data shows that although the nominal size of the balloon is reached during inflation (Table I) this maximal value represents only one point over the entire length of the balloon. The "reference diameter" of the balloon reflects the actual size of the balloon during inflation in the non-diseased part of the vessel. Therefore, we propose to use the reference diameter or area of the balloon in the quantitative assessment of the balloon-artery ratio.

CONCLUSIONS

Irrespective of the quantitative analysis technique, the balloon during inflation is not uniform over its entire length. This observation has major impact on the calculated values of stretch, elastic recoil, and balloon-artery ratio. As on-line quantification of the lesion before and during PTCA as well as of the inflated balloon is technical feasible during routine PTCA, our observation is of clinical significance and it could help to determine whether higher balloon pressures should be applied or a greater balloon size should be used to achieve an optimal short-term and long-term result of the angioplastied lesion.

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CHAPTER 4

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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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.

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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 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).

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

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.

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%)

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 standard 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.

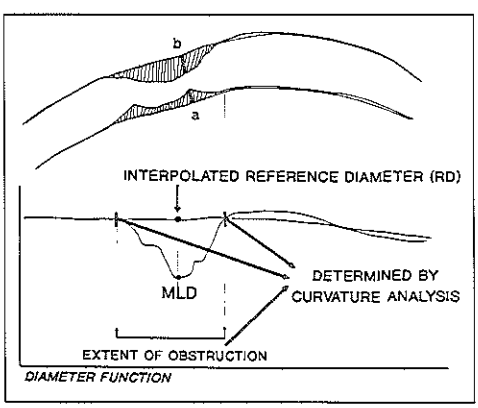

FIGURE 1. Graphic representation of quantitative angiographic measurements. *Upper panel* represents stenosed arterial segments. *Lower panel* is diameter function curve. Length of analyzed segment is depicted on *x axis*, and vessel diameter on *y axis*. Extent of obstruction = lesion length. Lesion 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.

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.

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

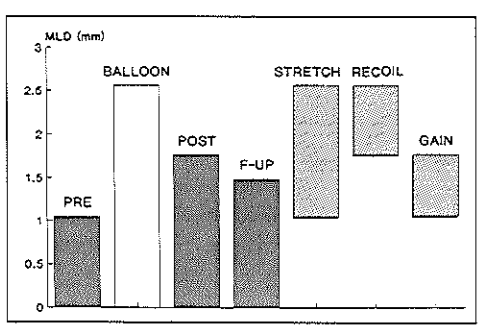

FIGURE 2. Graphic representation of terms used. Mean absolute values of variables are shown. Stretch, recoil and gain were normalized for vessel size (reference diameter) to correct for vessel size. BALLOON = balloon mean diameter; F-UP = follow-up MLD; MLD = minimal luminal diameter; POST = MLD after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

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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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CHAPTER 5

CAN MAJOR CARDIAC EVENTS DURING AND AFTER NATIVE CORONARY BALLOON ANGIOPLASTY BE PREDICTED FROM QUANTITATIVE AND QUALITATIVE ANGIOGRAPHIC LESION MORPHOLOGY AND CLINICAL CHARACTERISTICS ?

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Submitted

ABSTRACT

Background Major adverse cardiac events occur in 5 to 10% of all patients undergoing coronary balloon angioplasty. In this study prospectively collected clinical data, angiographic quantitative and qualitative lesion morphological assessment and procedural factors were examined to determine whether occurrence of these events could be predicted.

Methods Of 1442 patients undergoing balloon angioplasty for native primary coronary disease in 2 european multicenter trials, 69 patients experienced major cardiac adverse events and were randomly matched 1:3 with patients who completed an uncomplicated in-hospital course after successful balloon angioplasty (< 50% diameter stenosis by visual assessment).

Results Univariate analysis demonstrated that major procedural or in-hospital complications were associated with the following *pre-procedural* variables: 1) unstable angina (Odds ratio 3.11; 95% CI 1.72 to 5.61), 2) stenosis located in the mid segment of the artery dilated (Odds ratio 1.88, 95% CI 1.08 to 3.26), 3) lesion location at a bend of > 45° (Odds ratio 2.34; 95% CI 1.31 to 4.15) and with the following *post-procedural* variable: 1) dissection (Odds ratio 5.39; 95% CI 2.90 to 10.0). Multivariate logistic analysis was performed to predict the probability of major cardiac events. Considering only baseline pre-procedural factors, the model entered unstable angina (Odds ratio 4.13, 95% CI 2.01 to 8.52) and lesions located at a bend of > 45° (Odds ratio 2.33; 95% CI 1.15 to 4.74). If in addition post-procedural variables were added then unstable angina (Odds ratio 4.21; 95% CI 1.91 to 9.29) and dissection (Odds ratio 6.45; 95% CI 2.93 to 14.2) were the only independent predictors of major cardiac events.

Conclusion Thus, although computer assisted quantitative analysis systems have become the gold standard to assess the immediate and long term angiographic effect of coronary interventions, comprehensive measurements of lesion morphological characteristics didn't help to identify patients at higher risk for major acute in-hospital complications in this study.

INTRODUCTION

In the initial National Heart, Lung, Blood, Institute percutaneous transluminal coronary angioplasty (PTCA) Registry publication, which describes the immediate results of patients treated with PTCA, major cardiac events - i.e. death, myocardial infarction, coronary artery bypass grafting, repeat dilatation, - were reported in 13.6% of patients (1). Due to an increase in operator experience and improvement in radiographic equipment and balloon catheter design over the succeeding 5 years, this number dropped to 4 to 7 %, despite extension of the indications for coronary balloon angioplasty to include patients older than 70 years, and those with multivessel disease or with poor left ventricular function, prior bypass surgery and more severe and complex lesions (2,3,4,5,6). Many clinical factors such as - *multivessel disease, female gender, unstable angina, multiple lesion* - as well as qualitatively assessed lesion morphology - *eccentricity, presence of calcium, lesion length, stenosis at a bend point, stenosis at a branch point, thrombus, "complex lesions"* - have been suggested as predictors of a major procedural or in-hospital cardiac event (3,4,5,6,7,8,9).

As visual interpretation of coronary angiogram has a wide inter and intra-variability (10,11,12,13), quantitative coronary angiography systems are now the "gold standard" for geometric assessment of coronary abnormalities and for assessing the short and long term results of interventions (14,15,16,17). In addition to the degree of lumen narrowing, these quantitative coronary systems provide detailed lesion morphologic characteristics such as lesion length (mm), amount of atherosclerotic plaque (mm^2), eccentricity index, and curvature value (16).

The purpose of the present study was to investigate whether evaluation of lesion morphology by quantitative coronary analysis, in addition to qualitative assessment and consideration of baseline clinical characteristics, can identify patients or lesions at particularly high risk of major procedural or in-hospital adverse cardiac events. The identification of certain risk factors might be of considerable importance in patient and lesion selection for therapy by balloon angioplasty.

PATIENTS and METHODS

In total, 1442 patients were enrolled in 2 randomized double-blind placebo-controlled restenosis prevention trials (707 and 735 patients respectively) between December 1987 and June 1990. In the first trial, a thromboxane A2 receptor blocker (80 mg/day) and in the second trial, an angiotensin converting enzyme inhibitor (cilazapril, 5 mg bid), were investigated for their ability to prevent restenosis after native primary coronary artery disease. Unfortunately, neither of these trials, which are described in detail elsewhere, demonstrated any clinical or angiographic benefit from

the agent under investigation and therefore the total population was pooled (18,19).

Of the total number of recruited patients, 100 were excluded from the actual pharmacological trial because

1) the patient withdrew inform consent before the procedure (5 patients, all successful procedures without any procedural or in-hospital cardiac events),
   or the PTCA procedure was
2) not attempted (lesion severity had changed or due to equipment failure (9 patients)),
3) performed and successful (defined as one in which a greater than 20% change in luminal diameter is achieved, with the final diameter stenosis less then 50%) but an exclusion criterion had been overlooked by the investigator at the time of screening, and therefore these patients were retroactively excluded from the analysis (6 patients without any procedural or in-hospital cardiac events),
4) inability to reach or cross the lesion with the guide wire or with the balloon (43 patients with a totally occluded lesion or lesions with Thrombolysis In Myocardial Infarction (TIMI) grade I flow) and where treated medically or were put on a waiting list for bypass surgery,
5) unsuccessful: > 50% diameter stenosis on post-PTCA angiogram but without procedural complications (1 patients),
6) unsuccessful, with a diameter stenosis of > 50% on the post-PTCA angiogram accompanied by abrupt occlusion, dissection or thrombus, which resulted in ischemic complications which necessitated an emergency bypass operation or redilatation, or the patient suffered a myocardial infarction (18+15=33 patients)
7) successful but no quantitative analysis of the PTCA film was possible (3 patients) (table I).

For this study the population was formed by those patients who experienced major procedural or in-hospital complications, (defined as death, myocardial infarction (at least 2 of the following: typical anginal pain, electrocardiographic changes suggesting acute myocardial infarction, cardiac enzymes more than twice the upper limit of normal), the need for coronary artery bypass grafting or re-intervention) **after at least one balloon inflation**, regardless of the final result of the balloon angioplasty was considered successful or not (*Group I, n = 69 patients*). To assess the predictability of major cardiac events from baseline clinical, procedural and angiographic lesion characteristics, this patient group was compared with a control group made up of patients having successful coronary angioplasty without any major cardiac complications. Therefore, each patient in the study group was randomly matched 1 : 3 with control patients by date of angioplasty (to the nearest week in the same hospital) (*Group II, n = 207 patients*). Where multilesion dilatation was performed, the

Table I *Patients flowchart*

TOTAL PATIENTS GROUP	1442
Not included in intention to treat analysis of pharmacological trial:	
No coronary angioplasty performed	9
Exclusion criterion overlooked	6
Withdrawal inform consent	5
No quantitative analysis of baseline film possible	3
Failure to cross lesion or reach lesion with guide-wire or balloon	43
Unsuccessful angioplasty without clinical event	1
Procedural related myocardial infarction	15
Emergency bypass operation after attempted but failed angioplasty	18
PATIENTS WITH SUCCESSFUL CORONARY ANGIOPLASTY	1342
Repeat coronary interventions during hospital stay	14
Myocardial infarction during hospital stay	22
Adverse event or refusal for follow-up angiogram	78
PATIENTS WITH FOLLOW-UP ANGIOGRAM	1228

most severe lesion was used for comparing.

Each available cineangiogram was reviewed by 2 experienced interventionalists who were unaware of the clinical outcome.

PTCA procedure and angiographic analysis

At the beginning of the procedure all patients received a bolus of 10,000 IU intravenous heparin. For prolonged procedures, an additional infusion of 5,000 IU/hour was administered after 2 hours until the end of the procedure. Use of a calcium channel blocker was permitted for 24 hours post-PTCA. Choice of the guiding catheters, guide wires, balloon type, inflation duration and pressure were left to the discretion of the operator.

At least 2 different views, orthogonal if possible, were recorded in such a way that they were suitable for quantitative analysis by the Coronary Angiography Analysis System which has been validated and described in detail elsewhere (15,16,17).

The absolute 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 with a micrometer. To achieve maximal coronary vasodilation, either nitroglycerin 0.1 to 0.3 mg or isosorbide dinitrate 1 to 3 mg, was administered intracoronary to each affected coronary artery. All contour positions of the catheter and the arterial segment were corrected for "pincushion distortion" introduced by the image intensifiers. Since the algorithm cannot measure total occlusions or lesions with TIMI-1 perfusion, a value of 0 mm is substituted for the minimal lumen diameter and 100% for the percent diameter stenosis in such cases.

Definitions

PATIENT RELATED VARIABLES

The following patient related variables were recorded in the patient files: age, gender, duration of angina (days), cholesterol level (mmol/l), previous myocardial infarction, currently smoking, diabetes type I or II, extent of atherosclerotic disease (single or multivessel), Canadian Cardiovascular Society (CCS) angina classification and unstable angina (defined as pain at rest requiring treatment with intravenous nitrates) (20).

LESION RELATED VARIABLES

Qualitative lesion characteristics

The following qualitative lesion parameters were assessed: **A**) Vessel dilated (either right coronary artery, left anterior descending artery or circumflex artery), **B**) Location of the stenosis in the vessel dilated. Austen et al. divided the coronary tree in 15 different segments (21). This subdivision was used for location of the stenosis: *proximal*: corresponded with segment 1,6 and 11; *middle*: corresponded with segment 2,7,13 and 15; *distal*: correspond with segment 8,9,10,12 and 14) (figure 1) **C**) type of lesion, defined by a modified Ambrose classification 1) concentric, 2) eccentric (a stenosis asymmetrically positioned in the vessel in any non-foreshortened angiographic projection), 3) tandem lesion (2 discrete lesions in the same coronary segment, dilated simultaneously, as specified by the American Heart Association classification, 4) multiple irregularities (2 or more serial diffuse irregularities in the same coronary segment), 5) totally occluded vessel (21,22), **D**) a bend was considered present, if in any non-foreshortened projection, the balloon, in position to dilate, appeared to be

located in a portion of the vessel that had a 45° or greater angulation, at end diastole (23), **E**) presence of a side branch in the lesion to be dilated, **F**) presence of a side branch, separate from the actual lesion but within the dilated segment, **G**) presence of intra coronary thrombus - a filling defect within the lumen, surrounded by contrast material seen in multiple projections, in the absence of calcium within the filling defect, or the persistence of contrast material within the lumen, or a visible embolization of intraluminal material "downstream" (24), **H**) presence of calcification: defined as fixed radiopaque densities in the area of the stenosis to be dilated, **I**) type of lesion (A, B, C) according the American College of Cardiology / American Heart Association (ACC/AHA) Task Force (25).

Quantitatively derived lesion characteristics

The following quantitative measurements were obtained: minimal lumen diameter (mm), interpolated reference diameter (mm) and diameter stenosis (%) before coronary balloon angioplasty, lesion length (mm), eccentricity index of the lesion, area of atherosclerotic plaque (mm^2) and the curvature value (figure 2). Beside these variables, the CAAS system can calculate the "roughness" - as a measure for lesion irregularity - . However, we didn't use this information, as in our study, the "roughness" of the analyzed segment was computed, and not the "roughness" of the stenosis itself.

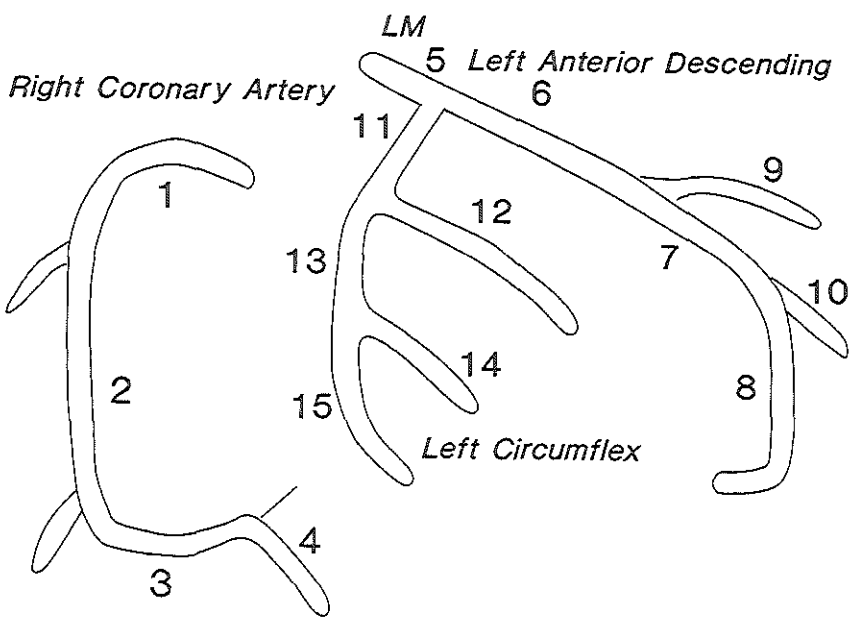

Figure 1 *Coronary tree divided in 15 segments (21)*

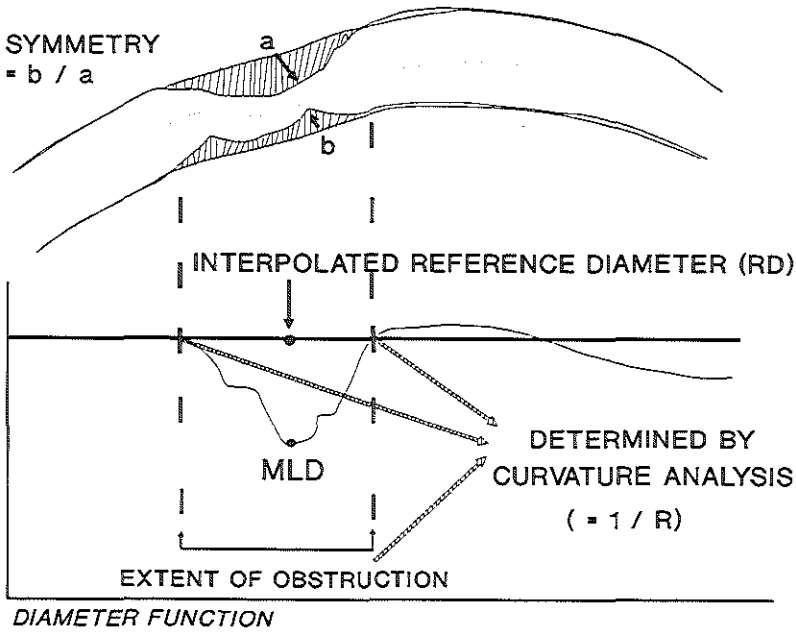

Figure 2 *See text for explanation*

PROCEDURAL RELATED FACTORS

Balloon-artery ratio is used to assess the suitability of the balloon size for the vessel segment and was defined as the ratio between the measured mean balloon size and the (interpolated) reference diameter of the dilated segment.

Coronary artery dissections were defined according to National Heart, Lung, and Blood Institute criteria as the presence of angiographically evident intimal or medial damage presenting either 1) as a small radiolucent area within the lumen of the vessel (tear or flap), 2) an extravasation of contrast medium without, or 3) with contrast staining, 4) a spiral-shaped filling defect with delayed distal flow, 5) persistent lumen defect with delayed antegrade flow, or 6) a filling defect accompanied by a total coronary occlusion (26,27),

Reproducibility of morphologic assessment

Inter observer variability of the 2 reviewers for the qualitative lesion assessment was examined 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 the diverse lesion morphology by each observer on two separate occasions, 3 months apart with blinding for earlier assessment. Interobserver discordance were as follows: lesion eccentricity: 21%, branch point location 29%, branch point location in dilated segment 19%, bend point location 14%, presence of

thrombus 2%, presence of calcification 10%, presence of dissection 11%, type lesion according ACC-AHA classification 25%.

Statistical analysis

Analyses were performed to test the hypothesis that clinical, qualitative and quantitative lesion morphologic and procedural characteristics are important determinants of major cardiac event. The risk of major cardiac adverse events for each variable was expressed as an odds ratio:

$$\frac{\text{Probability of an event, variable present}}{\text{Probability of no event, variable present}}$$

$$\frac{\text{Probability of an event, variable absent}}{\text{Probability of no event, variable absent}}$$

Continuous variables were dichotomized, by cutpoints derived by dividing the data into 2 groups, each containing roughly 50% of the population. This method of subdivision has the advantage of being consistent for all variables and thus avoids any bias in selection of subgroups that might be undertaken to emphasize a particular point. An odds ratio of 1 for a particular variable implies that the presence of that variable poses no additional risk for major event; odds ratio greater than 1 or less than 1 imply additional or a reduction in risk, respectively. The 95% confidence intervals were calculated to describe the statistical certainty. Multivariate analysis by multiple logistic regression was performed to identify variables independently correlated with the occurrence of major cardiac procedural or in-hospital adverse event, using only those variables significant at the $p < 0.10$ level in the univariate analysis. All these statistical analysis were carried out with a commercial statistical package (BMDP Statistical Software Package 1990).

RESULTS

Primary success, defined as a reduction in stenosis diameter to less than 50% on visual assessment, was achieved in (1342+6+5+3) 1356 patients or 94%. Myocardial infarction (as previously defined) occurred during or shortly after the procedure in 15 patients (or 1%) and in an additional 22 patients (or 1.5%) during the in-hospital stay. Emergency coronary bypass graft operation was necessary after attempted but failed

coronary balloon angioplasty in 18 patients (or 1.3%), and in a further 9 patients (or 1%) the indication for surgery occurred after the patient had left the catheterization laboratory. In 5 patients a redilatation was performed during the in-hospital stay. No patient died during the procedure or during the in hospital stay.

Clinical characteristics as predictors of major cardiac events

The clinical characteristics as related univariate predictors of major procedural or in-hospital coronary events are listed in table II. Patients with unstable angina experienced more coronary events than patients without unstable angina (Odds ratio 3.11; 95% CI, 1.72 to 5.61). Age, gender, duration of angina, serum cholesterol, history of myocardial infarction, diabetes type I and II, multi vessel disease and CCS angina class did not influence the risk for a major cardiac event.

Angiographic quantitative and qualitative lesion characteristics as predictors of major cardiac events

Lesion morphology (as evaluated by quantitative coronary analysis and qualitative assessment) as univariate predictors of major cardiac events are listed in table 3. Location of the target lesion in the mid segment of the coronary artery dilated (Odds ratio 1.88, 95% CI 1.08 to 3.26), or at a bend of > 45° (Odds ratio 2.34, 95% CI 1.31 to 4.15) were significant associated with more major cardiac events. No other lesion morphological characteristics, whether assessed qualitatively or by quantitative analysis, predicted the occurrence of major cardiac events. A trend was observed for type C lesion according ACC/AHA classification (Odds ratio 2.10, 95% CI 0.98 to 4.48).

Procedural predictors of major cardiac event

The presence of any type of dissection after the procedure was strongly associated with the subsequent occurrence of a major cardiac event (Odds ratio 5.39; 95% CI 2.90 to 10). Balloon-artery ratio was not found to be predictive of a major cardiac event. Thrombus post dilatation almost reached statistical significance (Odds ratio 4.31, 95% CI 0.94 to 19.80).

Table II *Patient, lesion and procedural related variables and the risk for major adverse cardiac events*

Variable	Patient Positive for the variable: event / total	Patient Negative for the variable: event / total	Odds ratio (95% CI)
History of MI	23 / 107	46 / 169	0.73 (0.41 to 1.30)
Currently smoking	10 / 45	59 / 231	0.83 (0.39 to 1.79)
Multivessel Disease	29 / 117	39 / 146	0.89 (0.51 to 1.51)
Diabetes	6 / 25	63 / 251	0.94 (0.36 to 2.46)
Age (< 58 yr)	35 / 136	34 / 140	1.08 (0.63 to 1.86)
Duration of angina (> 142 days)	35 / 137	31 / 135	1.15 (0.66 to 2.01)
Cholesterol (< 6.2 mmol/l)	34 / 129	27 / 132	1.39 (0.78 to 2.48)
CCS III,IV	47 / 169	21 / 100	1.45 (0.81 to 2.61)
Males	59 / 221	10 / 55	1.64 (0.78 to 3.46)
Unstable angina	29 / 69	39 / 206	3.11 (1.72 to 5.61)
Lesion Morphology			
Vessel dilated			
RCA dilated	15 / 67	54 / 209	0.83 (0.43 to 1.59)
LCx dilated	17 / 72	52 / 204	0.90 (0.48 to 1.69)
LAD dilated	37 / 137	32 / 139	1.24 (0.72 to 2.14)
Multiple site dilated	12 / 45	57 / 231	1.11 (0.54 to 2.29)
Total occlusion	8 / 24	61 / 252	1.57 (0.64 to 3.84)
Mid portion of vessel dilated	36 / 112	33 / 164	1.88 (1.08 to 3.26)
Lesion Morphology Quantitative Derived			
Symmetry index (< 0.34)[1]	30 / 121	32 / 132	1.00 (0.56 to 1.77)
MLD pre-PTCA (> 0.98 mm)	35 / 139	34 / 137	1.02 (0.59 to 1.76)

Table II *continued*

Variable	Patient Positive for the variable: event / total	Patient Negative for the variable: event / total	Odds ratio (95% CI)
DS pre-PTCA (< 62%)	35 / 136	34 / 140	1.08 (0.63 to 1.86)
Length Lesion (> 5.8 mm)[1)]	32 / 127	29 / 125	1.12 (0.63 to 1.99)
Vessel size pre-PTCA (> 2.53 mm)	37 / 140	30 / 134	1.25 (0.72 to 2.17)
Area plaque (> 6.1 mm^2)[1)]	35 / 127	26 / 125	1.45 (0.81 to 2.59)
Curvature index (> 19)[1)]	37 / 128	24 / 124	1.69 (0.94 to 3.05)
Lesion Morphology Qualitative Assessment			
Side Branch in area of balloon	46 / 186	20 / 80	0.99 (0.54 to 1.81)
Calcified lesion	9 / 33	57 / 233	1.16 (0.51 to 2.63)
Side Branch in stenosis	38 / 144	28 / 122	1.20 (0.69 to 2.11)
Eccentric located stenosis	36 / 130	31 / 137	1.31 (0.75 to 2.28)
Type C lesion	14 / 36	40 / 172	2.10 (0.98 to 4.48)
Bend > 45°	31 / 86	35 / 180	2.34 (1.31 to 4.15)
Procedural variables			
Balloon-artery ratio (> 1.02)	17 / 110	16 / 105	1.02 (0.48 to 2.14)
Thrombus post dilatation	4 / 7	61 / 258	4.31 (0.94 to 19.80)
Intimal tear or dissection	46 / 111	18 / 153	5.39 (2.90 to 10.00)

CCS = Canadian Cardiovascular Society Angina classification; MI = Myocardial Infarction, yr = year. Although clinical characteristics of (69+207=) 276 patients were analyzed, some were not known, and therefore in some variables the total number does not add up to 276. DS = Diameter Stenosis, LAD = Left Anterior Descending Artery, LCx = Left Circumflex Artery, MLD = Minimal luminal diameter, PTCA = Percutaneous Transluminal Coronary Angioplasty, RCA = Right Coronary Artery. Although 276 lesions were analyzed in total, some lesions could not be analyzed for certain variables. [1)] *not assessed in 24 lesions with total occlusion.*

Logistic regression analysis

In the preprocedural model which assessed the likelihood of major cardiac events for a patient using the variables known before angioplasty, - 1) unstable angina (Odds ratio 4.13, 95% CI 2.01 to 8.52) and 2) lesions located at a bend of > 45° (Odds ratio 2.33; 95% CI 1.15 to 4.74) were retained in the model. If in addition post-procedural variables were added then the following variables were retained in the model: 1) unstable angina (Odds ratio 4.21; 95% CI 1.91 to 9.29) and 2) dissection (Odds ratio 6.45; 95% CI 2.93 to 14.2) as independent predictors of the occurrence of major cardiac complications.

DISCUSSION

Despite the improvements in equipment and technique which have made it possible to cross and dilate more than 95% of the lesions attempted, the occurrence of procedural and in-hospital cardiac adverse events, due to acute or subacute vessel closure, continues to be largely unpredictable. The reported frequency of so called major cardiac adverse events depends on the time window applied - *after* the patient left the catheterization laboratory 1 to 2% or *during and after* the procedure 4 to 11% - . In the present study, major cardiac events were observed in 33 of (1356+33) 1389 patients (2.4%) during the procedure and in 36 of 1389 patients (2.6%) after the procedure. There are a number of potential explanations for the low percentage of major cardiac events during angioplasty in these 2 studies from which our population is derived. Although consecutive for each center, patients were being enrolled in clinical trials and therefore potential a selection bias in favor of those with single vessel disease and discrete lesions is introduced. Patients undergoing emergency angioplasty during the weekend or in the evening hours are usually not included in restenosis prevention trials for logistic reasons. In addition, no patients with evolving myocardial infarction or Q or non Q- wave myocardial infarction within two weeks of the angioplasty procedure. Also, in one of the trials, patients with type I diabetes were excluded. Ultimately of the 1389 patients enrolled in the two trials had one or two vessel disease, for whom the acute complication rate is generally lower than for these with multivessel disease. The percentage of in-hospital cardiac events of 2.6% correspond with what is known from the literature (4,5).

Risk factors of major procedural and in-hospital cardiac events

Ellis et al. in 1988 reported the results of 4772 procedures performed between April,1 1982 and March 31, 1986, and found, using multivariate analysis, seven

independent preprocedural factors related to abrupt vessel closure: stenosis length of 2 or more lumen diameter, female gender, stenosis at a bend point of 45 degrees or more, stenosis at a branch point, stenosis-associated thrombus (filling defect or staining), other stenoses in the same vessel, and multivessel disease (3). They concluded that, although an estimation of risk can be made before performing coronary balloon angioplasty, the most powerful predictors of closure can only be assessed during the procedure (post-PTCA percent diameter stenosis, intimal tear or dissection, prolonged post-PTCA use of heparin). The 1985-1986 NHLBI PTCA Registry study analyzed 1801 patients and revealed that baseline factors inherently associated with increased occlusion rates included triple vessel disease, high-risk status for surgery, and acute coronary insufficiency and lesion characteristics included severe stenosis before coronary angioplasty, diffuse disease or multiple discrete lesions, thrombus and collateral flow from the lesion. De Feyter et al. reported an acute coronary artery occlusion rate of 7.3% (of a total population of 1423), with unstable angina, multivessel disease and "complex lesions" as predictors for closure during or after the procedure. In all these studies, which involved large group of patients, lesion characteristics were visually assessed. No data are available on the predictability of major cardiac complications from quantitative coronary analysis, which has now has emerged as the "gold standard" for assessment of long term angiographic outcome of percutaneous transluminal coronary interventions (18,19). In addition to the "simple" quantitative parameters of minimal lumen (obstruction) diameter (mm), reference diameter (or vessel size) (mm) and percentage diameter stenosis, quantitative analysis computes length of the obstruction, area of atherosclerotic plaque (mm^2), symmetry index of the stenosis and curvature of the vessel. In this study, quantitative coronary analysis which had been applied to all cineangiograms of patients recruited for participation in the 2 restenosis prevention trials, was combined with assessment of qualitative lesion morphology and clinical characteristics to determine whether this thorough integrated approach could predict the occurrence of major cardiac events.

The present study is in agreement with earlier published studies as that unstable angina, lesion located at a bendpoint of more than 45°, and dissection were predictors of major procedural or in-hospital cardiac events.

Others have found that thrombus on the pre dilatation angiogram was predictive for a major cardiac event (3,4,5). However, thrombus was rarely seen on the pre dilatation angiogram in the present study, despite the fact that unstable angina, in which clinical syndrome the presence of intracoronary thrombus is frequently noted (27,28,29), was a risk factor for major cardiac event. It could well be that intravenous heparin, which the majority of the patients with unstable angina, in this study design, received, effectively dissolves almost completely the clot and therefore no thrombus is seen on the pre dilatation angiogram.

There is no obvious explanation why location of the target lesion in the mid segment of the coronary vessel was independently associated with a higher risk of major cardiac events in univariate analysis. However this variable was not entered in the logistic model.

It is disappointing that lesion morphology, as assessed by quantitative coronary analysis, was not of any help for the prediction of major cardiac events. Although inter and intraobserver variability potentially limits the qualitative assessment of lesion morphology, lesion located at a bend point of more than 45° was identified as having a greater risk for major cardiac event (10,11,12,13,31). The well described association of unstable angina with the occurrence of major adverse cardiac events is confirmed in this study and the location of the target lesion in a bend > 45° has previously been identified by Ellis as a risk factor for acute vessel closure. Location of a stenosis at a bend point is a predictor for major cardiac events has already been described by Ellis et al. Their explanation was that the balloon must necessarily tear an atherosclerotic fixed and rigid bend lesion as it straightens and stretches it. In addition, the maximal stress is several times greater when there is a geometric discontinuity in the object to which this stress is applied (3).

The most powerful predictor for major cardiac events is the occurrence of an intimal tear or dissection, which is not surprising as all patients experiencing peri procedural events, had either a type D, E or F dissection with flow limitations on their post dilatation angiogram (3,9).

From the literature, one would expect type C lesions (according ACC/AHA guidelines) to be a risk factor for major cardiac adverse events (25). In the present study type C lesions were not predictive for major cardiac adverse events although a clear trend was notable. Myler et al. reported recently that type C lesion had a angioplasty success rate of 90% instead of the low success rate of < 60% as described by the ACC/AHA Task Force (25,32). They concluded that it is more accurate to specify lesion morphology than to classify, as there are problems intrinsic to the coding scheme that makes it less useful in predicting outcome.

Limitations of this study

The study population of this retrospective analysis is formed by patients recruited for 2 multicenter restenosis pharmacological prevention trials in Europe. Although in both trials consecutive patients of the participating clinics were recruited, only 25% of all undergoing angioplasty patients were recruited because one or more specific exclusion criteria was found.

Coronary angiography, as a two dimensional silhouette of the vessel lumen, is inherently limited for the assessment of atherosclerotic plaque morphology as is been increasingly demonstrated by intravascular ultrasound techniques (33). It is

disappointed that even the use of objective quantitative analysis fails to provide insight to the prediction of major cardiac events from angiographic measurements and lesion morphology to facilitate patient and lesion selection for treatment by coronary balloon angioplasty. It is however possible that more sophisticated quantitative analysis systems might be more helpful in this regard or in other settings (34,35).

Notwithstanding that the CAAS system has been validated and extensively described in the literature, validation studies quantitatively derived lesion morphology such as lesion length, eccentricity, curvature and area of atherosclerotic plaque have not yet been performed (14,15,16). However, the computer estimation of the "original contour of the preatherosclerotic lumen" (interpolated reference diameter) is similar to that used by Crawford et al. (36). They demonstrated that the difference in area between the original lumen and the contours of the obstruction is a measure of the atherosclerotic plaque and this correlated with the cholesterol content in the corresponding human arterial specimen.

CONCLUSION

Although quantitative coronary analysis systems have become the "gold standard" for the assessment for long-term outcome of percutaneous interventions, lesion morphology derived from quantitative analysis does not help to identify lesions at high risk for major procedural of in-hospital events. Unstable angina, lesions at a bend point of more than 45°, and dissection were found to be predictive of major cardiac events. New techniques, such as angioscopy and intravascular ultrasound imaging may better characterize the atherosclerotic plaque and provide more profound understanding of the pathophysiological mechanisms of successful or unsuccessful coronary balloon angioplasty. Randomized trials where balloon angioplasty is compared with other devices will hopefully provide objective data for the stratification of patients and lesions at increased risk of major cardiac complications during and after coronary balloon angioplasty.

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CHAPTER 6

THERAPEUTIC DISSECTION AFTER SUCCESSFUL CORONARY ANGIOPLASTY: NO INFLUENCE ON RESTENOSIS OR ON CLINICAL OUTCOME: A STUDY IN 693 PATIENTS

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ABSTRACT

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: A) **categoric**, using the traditional cutoff criterion of > 50% diameter stenosis at follow-up, B) **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, recurrent angina requiring medical therapy, to none of the above.

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 164 (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 a dilated lesion without visible dissection on the post-balloon angioplasty angiogram.

INTRODUCTION

Percutaneous transluminal coronary angioplasty is an accepted revascularization procedure for treatment of patients with stable or unstable angina pectoris with single or multi-vessel disease (1,2). Despite the therapeutic success of coronary angioplasty, the exact mechanism of dilatation 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 dilatation 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 I, 8-20). This dissection 1) might result either 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 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. have demonstrated, using histopathologic examination, that deep arterial injury is associated with more extensive intimal proliferation (24). In addition, Schwartz et al. showed in a porcine model that the severity of vessel injury was strongly correlated with neointimal thickness (25). 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 suggested that the therapeutic type of dissection was associated with a trend towards lower restenosis rates (table I, 8-20,23). Thus, conflicting data have been reported. Most of these earlier studies had one or more methodological 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 a 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 without 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.

Table 1 *Studies where the relation between lesions with or without dissection and restenosis were examined.*

First Author (reference no.)	Year	Patients	Angio fup (%)	Definition restenosis	Restenosis (%)	Dissection (% of # lesions)	Restenosis with/without dissection
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) p=ns 19% vs 28% (gradient ≤15)p<0.05
Guiteras Val(10)	1987	181	98%	≥30% DS	28	45	56% vs 25% vs 21% severe mild none (p < 0.02)
Vandormael[1](11)	1987	209	62%	> 50% DS	82 (Symp) 30 (No Symp)	NR	No difference
Matthews(12)	1988	216	30%	loss >50% gain or lack of symptoms	21	30	18% vs 23% (p=ns)
Black[2](13)	1988	384	39%	> 50% DS	31[4]	34	29% vs 32% (p=ns)
de Feyter[3](14)	1988	179	88%	> 50% DS	32	25	No difference
Fleck[4](15)	1988	110	86%	MLCA > 1mm^2	58	31	No difference
Quigley[2](16)	1989	114	88%	> 50% DS	32	20	35% vs 31% (p=ns)
Renkin(17)	1990	278	47%[5]	> 50% DS	-	33	No difference
Rupprecht[4](18)	1990	676	70%	> 50% DS or loss >50% gain	29	NR	24% vs 30% (p=ns)
Bourassa(19)	1991	307	80%	> 50% DS with minimal 10% DS	36	41	33% vs 36% (p=ns)
Hirshfeld(20)	1991	694	73%	> 50% DS	40	39	40% vs 39% (p=ns)

[1] = multivessel dilatation; [2] = for restenosis; [3] = unstable angina; [4] = excluded total occlusions; [5] = angiography + exercise thallium scintigraphy; [6] only the ones with follow-up angiography. Angio fup = % of patients with angiographic follow-up; DS = Diameter Stenosis; Fup = follow-up; NHLBI National Heart Lung Blood Institute; Ref = Reference number; Sympt = Symptoms, MLCA = Minimal lumen cross-sectional area.

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 I). The results of the trial demonstrated that cilazapril, 5 mg twice a day, had no effect on restenosis or clinical outcome in the first 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 to revascularize 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 the trial if the angioplasty procedure 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 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 post angioplasty, or earlier, if warranted by symptoms. Of the 693 randomized patients, 653 (94%) had a follow-up angiogram suitable for quantitative analysis. Five patients died before repeat angiography, 32 patients did not have a follow-up angiogram because of adverse experience (25) or refusal (7) and in 3 patients the follow-up angiogram 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

Table 2 *Flowchart of the MERCATOR study.*

TOTAL PATIENT 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		7
No follow-up quantitative coronary analysis possible		3
PATIENTS WITH FOLLOW-UP ANGIOGRAM	653	

permitted for 48 hours after coronary angioplasty. All patients received aspirin 160 to 250 mg per day, starting the day before coronary angioplasty until 6 months 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 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 recorded 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 repeat procedure (hours, days or weeks).

To standardize the method of data acquisition, data analysis, and to ensure exact reproducibility angiograms obtained before and after angioplasty, and follow-up angiograms, special precautions were taken described elsewhere (27,31-33).

The absolute value of the stenosis diameter and the reference diameter

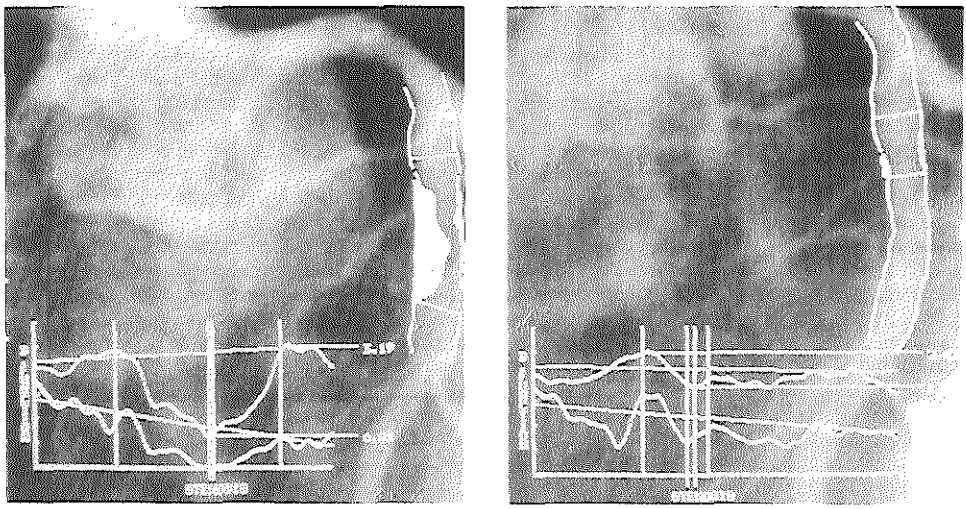

Figure 1 *Example of quantitative coronary analysis of a lesion in the proximal LAD in the LSO projection before (A) and after (B) coronary angioplasty. The diameter along the analyzed segment is represented in the diameter function curve (upper curve). The MLD is 0.83 mm before and 1.87 mm after angioplasty. The length of the stenosis is determined by curvature analysis and is depicted by 2 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.*

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, intra coronary 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 parameters 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 symmetrical 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 using the least foreshortened projection (in which the analyzed segment appeared longest between 2 defined landmarks) (Figure 2).

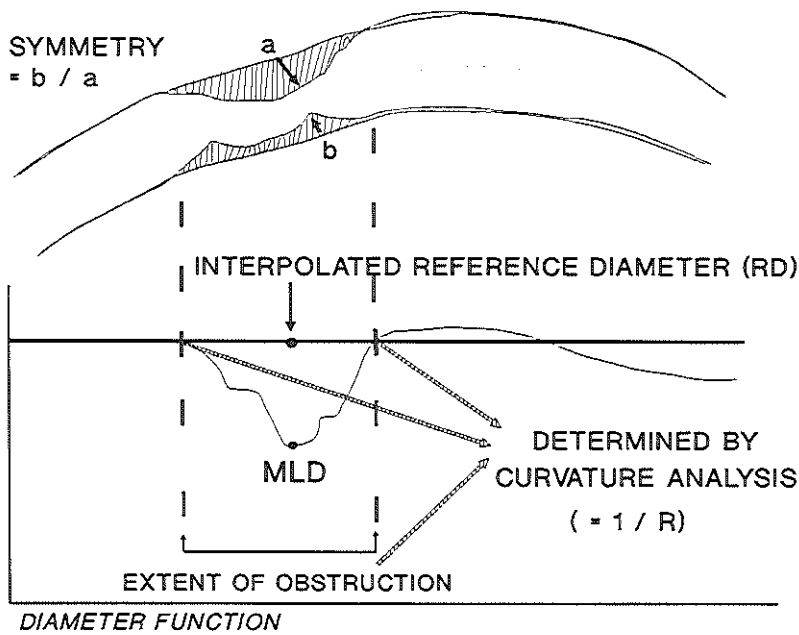

Figure 2. *See text for definitions.*

Balloon-artery ratio was defined as the ratio using 1) nominal size according to manufacturer, or 2) the measured reference balloon size, divided by the vessel size (34). **Relative gain** was defined as the difference in minimal lumen diameter before

and after coronary angioplasty, normalized for the 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 the 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 the vessel size (34-36). The **balloons** used for dilatation were composed of 1) non-compliant 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 the 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).

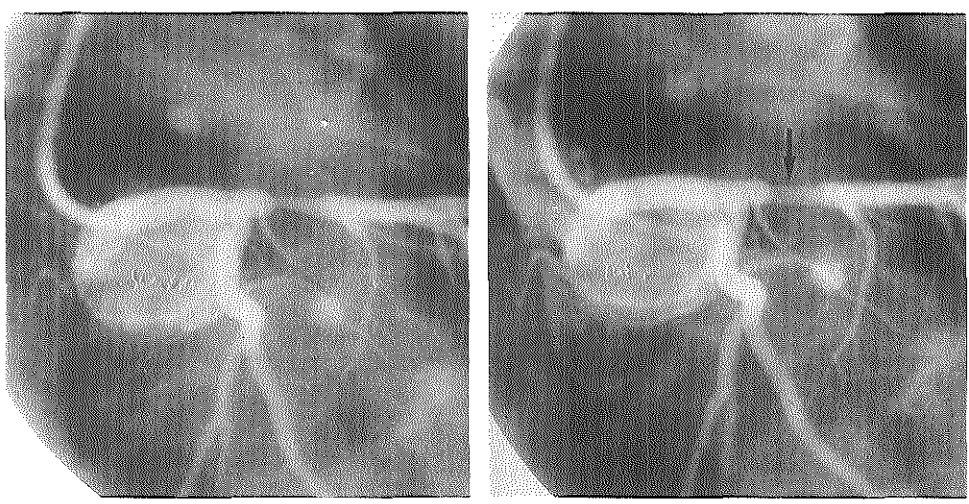

Figure 3 *Stenosis in the proximal left anterior descending artery before (A) and after angioplasty (B), with a typical example of a type A dissection. The arrow indicates the presence of an intimal flap on the post-PTCA angiogram.*

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 non persisting 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 antegrade flow was seen on the final post-coronary angioplasty angiogram. A filling defect accompanied by a total coronary occlusion was classified as a type F dissection (Figure 3 to 6).

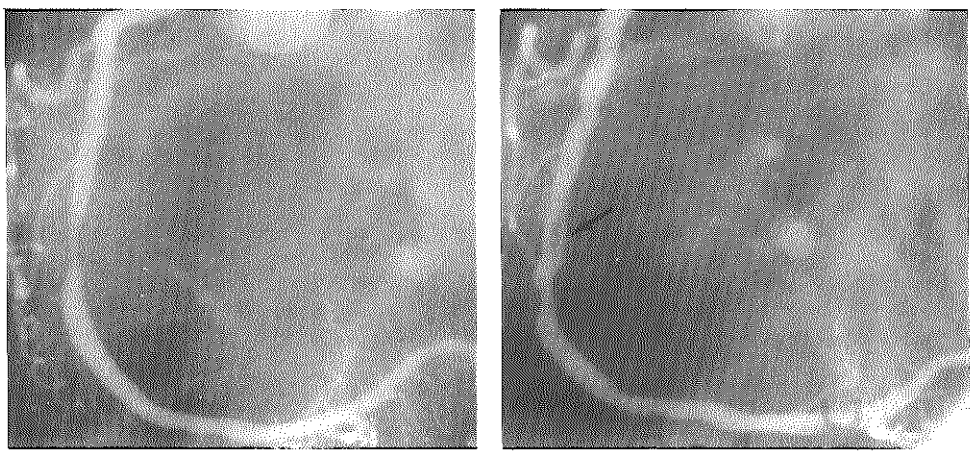

Figure 4 *Stenosis in the mid RCA before (A) and after angioplasty (B) with a typical type B dissection. The extravasation of contrast material is indicated by the arrow.*

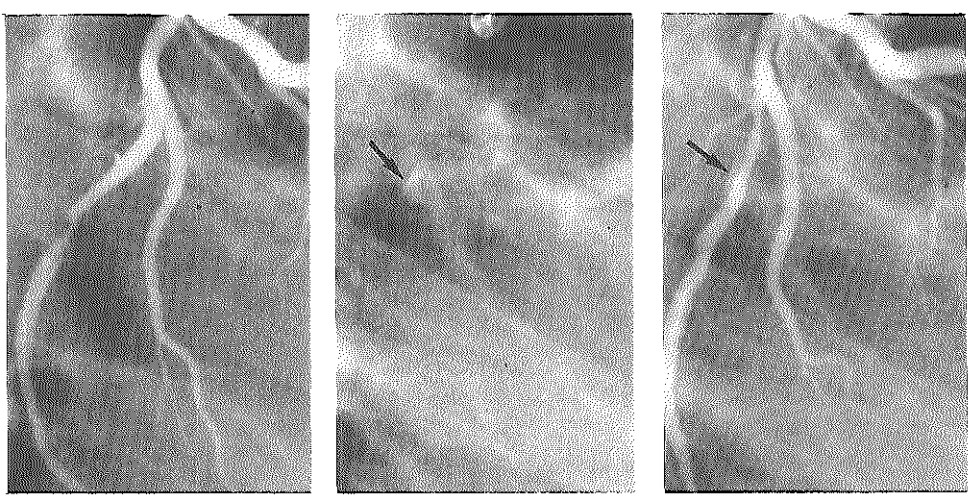

Figure 5 *Stenosis in LCx before PTCA (A), after balloon inflation (B), and after PTCA (C). This is a typical type C dissection, with persistence of contrast in the area of dilatation, indicated by the arrow.*

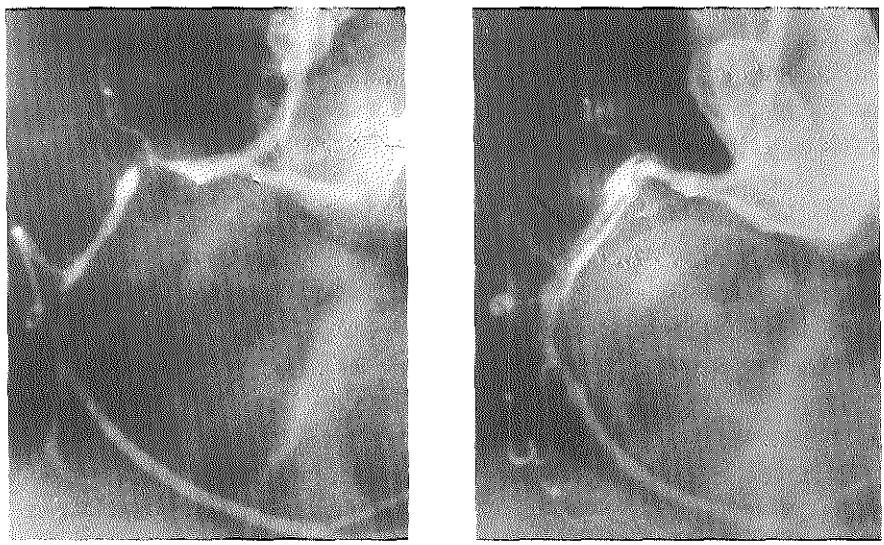

Figure 6 *Stenosis in the proximal and mid right coronary artery before (A) and after angioplasty (B) with a typical type D spiral shaped dissection associated with decreased flow.*

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 (WH, BR) 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 2 assessors. The intra observer 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 extralumen filling defect in the analysis (Figure 7). As advised to the Mercator Angiographic Committee, the computer "decides" whether the

extralumen 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 detect a small not significant difference in brightness. However, when the extravasation is distinctly separate from the true vessel lumen, (small communicating channel), the computer will exclude the dissection from the analysis as their will be a steep difference in brightness between the extravasation and the true lumen (Figure 7).

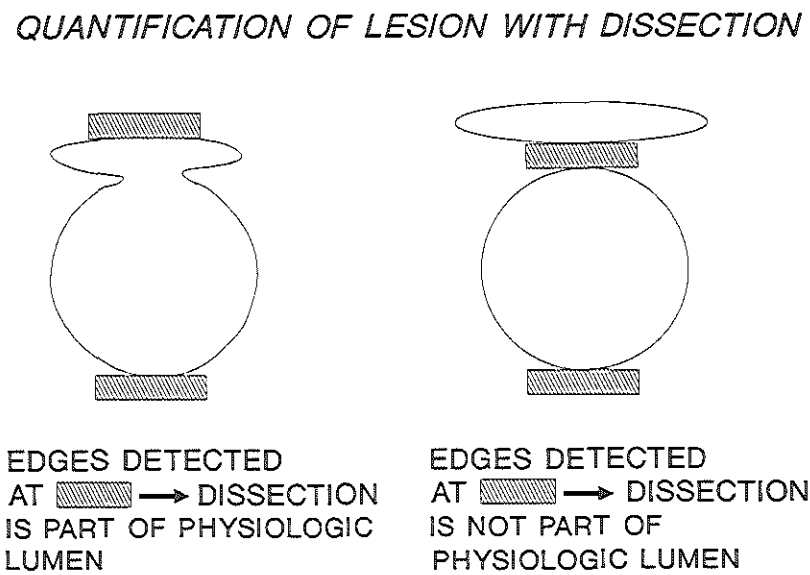

Figure 7 *This figure explains how the quantitative analysis is done, in case a dissection is present on the post angioplasty angiogram. As a type A dissection is intraluminal, this type of dissection will be analyzed as seen on the left side (A). In contrast, type B to E dissection are extravasation outside the contrast filled lumen. In cases where the communicating channel between lumen and the extravasation is large (and of functional importance) - as can be seen in the brightness of contrast in the dissection - the computer will include the dissection in the analysis (right side) as only a small difference in brightness will be detected. However, in cases where this channel is small and not functional, the "computer" will exclude the dissection from the analysis as the difference in contrast density will be significant.*

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 > 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 in any one of the dilated segments (irrespective of procedural success) a dissection was visible on the post angioplasty angiogram. Full clinical follow-up was 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 endpoint (6 months ± 3 weeks) were included as clinical events (30).

Data analysis Data was analyzed using 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 relationship 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 of differences in baseline lesion characteristics between the groups with or without dissection, on restenosis, 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 which were successfully dilated and had angiographic follow-up. In 242 lesions, the type of dissection was classified as type A (n = 82),B (n = 132) or C (n = 28). Only in 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 $\geq$ 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 $\geq$62 for dissection was 1.19, that is, patients $\geq$62years 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 $\geq$62 years was 0.97 to 1.48 (p=ns).

Absence of unstable angina and serum cholesterol level < 5.7 mmol/l 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 describes in table 4.

The frequency of any dissection was significantly higher with 1) a postangioplasty diameter stenosis > 37%, 2) a lesion of intermediate length ($\geq$5 to $\leq$ 6.7 mm), 3) an eccentric lesion (symmetry < 0.23), 4) a lesion located in a more curved segment (curvature index $\geq$21), 5) a lesion located in the right coronary artery, 6) thrombus observed on the postangioplasty angiogram, 7) application of low or high inflation pressure (< 7 or > 9), 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.

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 [*1)]	134 / 424	(32%)	99 / 316	(31%)	1.01	(0.81 to 1.25)
Single site dilatation	177 / 536	(33%)	70 / 242	(29%)	1.14	(0.91 to 1.44)
CCS-class at baseline [*2)] (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 [*3)] (≥305 days)	91 / 256	(36%)	151 / 510	(30%)	1.20	(0.98 to 1.48)
Cholesterol [*4)] (< 5.7 mmol/l)	90 / 239	(38%)	147 / 499	(30%)	1.28	(1.03 to 1.58)

*CCS = Canadian Cardiovascular Society angina classification, yr = years, [*1)] = not available for 38 lesions, [*2)] = not available for 2 lesions, [*3)] = n available for 12 lesions [*4)] = not available for 40 lesions, 95% CI = 95% Confidence Intervals.*

Table 4 *Lesion and Procedural-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)[*1] (≥5 to ≤6.7)	94 / 243	(38%)	135 / 484	(28%)	1.39	(1.12 to 1.72)
Atherosclerotic plaque (mm^2)[*1] (≥7.3)	83 / 243	(34%)	146 / 484	(30%)	1.13	(0.91 to 1.41)
Symmetry index [*1] (< 0.23)	88 / 232	(38%)	141 / 495	(29%)	1.33	(1.07 to 1.65)
Curvature index [*1] (≥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[*2] ≥1.1	68 / 212	(32%)	135 / 419	(32%)	1.00	(0.78 to 1.27)
Non compliant balloon material	143 / 401	(36%)	104 / 377	(28%)	1.30	(1.05 to 1.60)
Stretch [*2] ≥0.55	79 / 213	(37%)	124 / 418	(30%)	1.25	(0.99 to 1.51)
Elastic Recoil[*2] ≥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)
Max bal pressure <7 or >9 atm)	109 / 285	(38%)	138 / 493	(28%)	1.37	(1.11 to 1.68)
Total inflation time ≤145 sec	80 / 165	(32%)	167 / 533	(31%)	1.04	(0.84 to 1.30)
Number of inflation ≥2 and ≤4	177 / 544	(33%)	70 / 234	(30%)	1.09	(0.86 to 1.37)

*atm = atmosphere; DS = Diameter Stenosis; MLD = Minimal Luminal Diameter; PTCA = Percutaneous Transluminal Coronary Angioplasty; RCA = Rig Coronary Artery; RD = Reference Diameter; sec = seconds; [*1] = not available in 51 lesions with a totally occluded vessel; [*2] = available in 631 lesion with an analysis of the inflated balloon at highest inflation pressure used. RR = Relative risk 95%, CI = 95% confidence interval.*

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 0.10 ± 0.22 (cilazapril 0.09 ± 0.20, placebo 0.13 ± 0.25) or without dissections 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 analysis were performed to determine whether or not the observed differences between the groups with and without dissection with regard to baseline patient, lesion and procedural variables, influenced restenosis according to the 2 approaches used. The regression coefficient for dissection was not influenced 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 start of the analysis proces and 0.08 after inclusion of the variables then added significantly to the fit of the model (minimal lumen diameter before coronary 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 non-occurrence of either "hard events" (death, nonfatal myocardial infarction, coronary revascularization) - with dissection: placebo 17%, cilazapril 16%, without dissection: placebo 19%, cilazapril 18% - or "soft events" (recurrence of angina or no event) ($p = 0.22$).

Table 5 *Dissection after successful coronary angioplasty with angiographic follow-up and the occurrence of restenosis per lesion dilated.*

	RESTENOSIS			DISSECTION TYPE				
	NONE	ANY	P	A	B	C	D	E
No.	531	247		82	132	28	3	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
Categorical								
DS > 50%	159 (30%)	72 (29%)	0.82	27 (33%)	36 (27%)	9 (32%)	0	0

Loss = difference in mld between postangioplasty and follow-up, R Loss = Relative loss = loss / vessel size), DS = Diameter stenosis at follow-up.

Table 6 *Dissection After Coronary Angioplasty Per Patient and Clinical Outcome at 6 Months Follow-Up*

	CLINICAL EVENT		DISSECTION TYPE					
	NONE (n=441)	ANY (n=252)	A (n=76)	B (n=136)	C (n=33)	D (n=3)	E (n=3)	F (n=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
Coronary 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

NYHA = New York Heart Association class III/IV, MI = myocardial infarction, Revasc = coronary revascularization procedure

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.

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 Dorros and Guiteras Val et al. (10,39). In earlier reports, 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 intra-observer variability were not reported (9,12,23). As part of a multicenter study, we prospectively collected patient, lesion 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 (WH, BR) 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 assessor in time (40).

Definition and assessment of restenosis.

In virtually all the reported studies on the relation of 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 a group of patients who were not angiographically restudied at a pre-determined time. The majority of these studies were retrospective analyses and involved a small number of patients (26).

The best definition of choice 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 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 (which calculation depends on the assumption of a "normal" reference diameter segment) may underestimate the change in the severity of a stenosis after coronary angioplasty (43). Furthermore, "the 50% diameter stenosis criterion 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 $\geq$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 of $\geq$0.72 mm in coronary segments with a reference diameter of 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 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 dissections

None of the patient-related variables appear to be associated with the occurrence of dissection, except for **lower cholesterol levels** before coronary angioplasty and patients **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 this study. The definition of unstable angina used may describe a particular population 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 (21,22,45). In addition, because only successful dilatations 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. 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 have suggested higher restenosis rates in long lesions. Because short lesions are easily covered by the normal length of balloon, it could be that intermediate length lesions are intermediate and therefore yield more dissections.

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

Greater post angioplasty 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 determinate the angioplasty procedure to avoid further complications, believeing the result to be accepatable although suboptimal.

Earlier reports focussed 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 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 relationship of the normal vessel wall with the 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 consequent potential risk of dissection in every case.

The frequency of dissection was greater when a "**non-compliant 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 only the decision of the operator to use a particular balloon dependening on the eccentricity of the lesion, length of lesion, clinical condition of the patient, calcification and the like.

Sarembock et al. (48) demonstrated in the animal model that **high inflation pressures** caused more mural thrombus, dissection and medial necrosis versus low pressure. In this clinical study, low (< 7 atmospheres) pressure inflations were also associated with a higher incidence of dissection. Because there was 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 which is partially obstructing blood flow.

Of these variables, the right coronary artery, more curved vessels, eccentrically located in the vessel, intermediate length, and non- compliant balloon material emerged as the most important variables. They were retained in the multivariate logistic regression analysis that was performed to identify riskfactors for dissection.

Dissection and Restenosis Multivariate linear and logistic analysis were performed to determine whether the observed differences between the groups with and without dissection with regard to patient, lesion and procedural variables, influenced restenosis according to the two different approaches. As the regression coefficient for dissection was not influenced by the variables which were significantly associated 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 as an important predictor of ischemic complications after coronary angioplasty, but only the minority of patients will develop an acute ischemic event (49). Huber et al. reported recently that patients with type B dissections have low rates of complications similar to patients without dissection (23). Patients with type C to F dissection had an significant increase in in-hospital complications. The present study includes only patients with a successful coronary angioplasty, defined as < 50% diameter stenosis on the post angioplasty angiogram. If the clinical condition required repeat coronary angioplasty, the angiogram 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 (or 1.5%) patients with a 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 3 patients, type B in 2 patients) visible

on the post-coronary angioplasty angiogram. Apart from possible bias by participating centers in excluding patients with severe diffuse disease or requiring emergency coronary angioplasty or multi site dilatation, 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 can not be drawn in realtion to long-term clinical outcome in this setting.

Limitations of the study By definition, the MERCATOR trial only included successful dilated coronary angioplasty, thus no patient with important obstructive dissections 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 a variety of reasons describe under the Methods section, 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 where as angiography results were normal in 66% of cases (51). Angiographically visible dissections may considered to be at the "larger end of the dissection spectrum", although studies correlating intravascular ultrasound and angioscopic findings with angiography in large patient numbers are still awaited.

Conclusions Small hemodynamically insignificant angiographically visible dissections are 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 post-coronary angioplasty angiogram. New techniques, such as intravascular ultrasound or angioscopy, should help to improve understanding of the mechanism of dilatation 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 which occurs in many lesions.

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CHAPTER 7

MORPHOLOGICAL CHANGES DURING FOLLOW UP AFTER SUCCESSFUL PERCUTANEOUS TRANSLUMINAL CORONARY BALLOON ANGIOPLASTY: QUANTITATIVE ANGIOGRAPHIC ANALYSIS IN 778 LESIONS.

Further evidence for the restenosis paradox

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For the MERCATOR and CARPORT study group.

Submitted

ABSTRACT

Objectives and background. The purpose of this study was to determine if there are any morphological characteristics of lesions which renarrow - "*restenotic lesion*" - following successful coronary balloon angioplasty which are different from the appearance pre treatment, or, from the appearance of "*non-restenotic lesions*", which might provide some new insight into the restenosis phenomenon.

Methods. The study population consisted of 653 patients (778 lesions) with 6 months angiographic follow-up (94% angiographic follow-up rate), who were participating in the MERCATOR study. Detailed quantitative angiographic measurements, including the mean diameter of the vessel segment (mm) that was subjected to balloon dilation, were performed preangioplasty, postangioplasty and at follow-up using the cardiovascular angiographic analysis system, in order to provide some objective measurement of the actual extent of luminal changes in the months following coronary balloon angioplasty. Two different approaches for restenosis were used, 1) "*static criterion*" of > 50% diameter stenosis at follow-up, 2) "*dynamic criteria*" of $\geq$0.40 or $\geq$ 0.72 mm change in minimal lumen diameter between post angioplasty and follow-up.

Results. Both approaches identified more severe stenosis to be typical feature for "restenotic lesion" before angioplasty as compared with "non-restenotic lesion". No differences were observed in lesion length, balloon inflated vessel segment or roughness index before angioplasty in both groups. Conflicting data was found for the amount of atherosclerotic plaque, symmetry index, and curvature index.

The "restenotic lesion" at follow-up compared with its initial appearance gave conflicting results as to which approach was used. The "dynamic criteria" illustrate that the reference diameter and the mean diameter of the entire segment dilated are reduced during follow-up.

Conclusions. Two messages emerge from the study: 1) the restenosis process clearly involves the apparent normal vessel wall adjacent to the actual lesion, probably in response to the unavoidable injury caused by balloon dilatation, 2) the use of percentage diameter stenosis measurements depending on the assumptions of normality for a reference segment will therefore underestimates the true extent of the restenosis process and should be replaced in clinical angiographic studies by absolute luminal measurements.

INTRODUCTION

The introduction of percutaneous transluminal coronary balloon angioplasty, in 1977 by Andreas Gruentzig, has led to dramatic fundamental changes in the treatment of patients with stable and unstable angina pectoris with single or multi-vessel obstructive coronary artery disease (1-3). Despite the increasing therapeutic success of coronary balloon angioplasty with progressively lower acute complications rates, and improvement in, or disappearance of, anginal symptoms in the majority of patients treated, the exact mechanism of dilatation remains speculative and appears to involve multiple processes including "compression" of plaque, focal plaque "break", "fracture" or "tear" with or without localized dissection and, in eccentric lesions, "stretching" of the plaque-free wall with or without plaque compression (4-7).

The long term success of coronary balloon angioplasty has not, unfortunately, followed the same time trends and in spite of the investment of much effort, adjunctive pharmacological therapy and new catheter designs over the past decade, the frequency of lesion recurrence or *restenosis* remains broadly similar to early reports (8,9). Although there is a wide variation in the reported incidence of restenosis between the many published studies, the main source of variation is not in therapeutic approaches employed or the use of effective biological agents but because of bias in selection of patients for arteriographic follow-up, and differences in the criteria applied to the definition of the occurrence (or not) of restenosis (9,10).

The importance of the angiographic morphological appearance of coronary obstructions, in understanding the pathogenesis of acute ischemic syndrome, coronary atherosclerotic disease, restenosis and the response to thrombolytic therapy has previously been recognized (11-16). Quantitative coronary angiographic analysis systems have now supplanted visual assessment of the coronary cineangiogram and are now the "gold standard" for accurate, objective and reproducible geometric measurement of coronary luminal dimensions and for assessing, the short and long term outcome of interventions (17-20). In addition to the degree of luminal narrowing, these quantitative analysis systems can provide detailed assessment of lesion morphological characteristics such as minimal and mean lumen diameter (mm), vessel size (mm), diameter stenosis (%), lesion length (mm), and the amount of atherosclerotic plaque (mm^2) (17).

The purpose of this study was to determine, using a well validated quantitative coronary angiographic analysis system, whether there are any morphological characteristics of lesions which renarrow following successful coronary balloon angioplasty, the "restenotic lesion", which are different from the appearance pre treatment, or, from the appearance of "non-restenotic lesion", which might provide some new insight into the restenosis phenomenon.

METHODS

Study population. The study population consisted of all randomized patients enrolled in 26 centers for the MERCATOR trial. All patients gave informed consent and the study protocol was approved by the institutional review board. In this randomized double-blind placebo-controlled trial, a new angiotensin converting enzyme inhibitor, cilazapril, was investigated for its ability to prevent restenosis after primary coronary balloon angioplasty. Results of this aspect of the study are described elsewhere (20). In total, 693 patients with a successful coronary balloon angioplasty, defined as a < 50% diameter stenosis on visual inspection of the post-coronary balloon angioplasty angiogram, who met the inclusion criteria and who had an angiogram suitable for quantitative analysis, were randomized. In and exclusion criteria, and the reasons for non randomization are described elsewhere (20). Because treatment with the agent under investigation did not influence clinical or angiographic outcome, the placebo- and active treatment group were pooled, for the present study. Follow-up angiography was scheduled 24 ± 3 weeks after coronary balloon angioplasty, or earlier, if warranted by symptoms. Of the 693 randomized patients, 653 with 778 lesions (follow up rate: 94%) had a follow-up angiogram suitable for quantitative analysis.

Angioplasty procedure, follow-up and quantitative angiography. At the beginning of the procedure all patients received a bolus of 10,000 IU intravenous heparin. For prolonged procedures, an additional infusion of 5,000 IU/hour was administered after 2 hours and maintained until the end of the procedure. Use of a calcium channel blocker was permitted for 48 hours after coronary balloon angioplasty. All patients received 160 - 250 mg aspirin per day for 6 months. 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 prior to coronary balloon angioplasty, immediately after coronary balloon angioplasty and at follow-up. The angiograms were recorded so that they were suitable for quantitative analysis by the coronary angiography analysis system, which has been validated and described in detail elsewhere (17,19-22). Post coronary balloon angioplasty values were obtained from the final post coronary balloon angioplasty angiogram recorded after removal of the guide wire. The initial procedure was considered completed when the guide catheter was removed. If the clinical condition required re-coronary balloon angioplasty, the angiogram immediately prior to re-coronary balloon angioplasty was used to obtain follow-up values, irrespective of the timing of re-coronary balloon angioplasty (hours, days or weeks). Special precautions, as previously described elsewhere, were taken to standardize the method of data acquisition and to ensure exact reproducibility of before coronary balloon angioplasty, after coronary balloon angioplasty and follow-up angiograms (17,19-22). The absolute value of the stenosis

diameter as well as 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 with a micrometer. To achieve maximal coronary vasodilation, either nitroglycerin 0.1-0.3 mg or isosorbide dinitrate 1-3 mg, was administered intra coronary to each affected coronary artery before coronary balloon angioplasty, after coronary balloon 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. Since the algorithm cannot measure total occlusions and lesions with "thrombolysis in myocardial infarction" perfusion grade 1, a value of 0 mm is substituted for the minimal luminal diameter and for "balloon inflated vessel segment", and 100% for the percent diameter stenosis. In these cases the post-coronary balloon angioplasty reference diameter was substituted for the reference diameter pre-coronary balloon angioplasty and/or at follow up. For each dilated segment, the pre coronary balloon angioplasty, the post coronary balloon angioplasty and follow-up minimal luminal diameter, vessel size and diameter stenosis are taken as the mean value from multiple matched projections.

Definitions

Quantitatively derived lesion characteristics The following quantitative measurements were obtained before,after balloon angioplasty, and at follow-up (23):

1) *Minimal luminal diameter* (MLD, mm).
2) *Interpolated reference diameter* or vessel size (RD, mm). This measurement is independently generated by the computer using a technique of interpolation whereby the original disease-free vessel diameter is estimated using a combination of several diameter measurements proximal and distal to the actual stenosis. The advantage of this technique is that there is no user interaction and therefore an objective measurement is provided, rather than the arbitrary selection of a "normal" vessel segment proximal or distal to the lesion, as is the conventional approach.
3) *Percent diameter stenosis* (i.e. ((1 - MLD / RD) x 100%),
4) *Gain* in minimal luminal diameter (mm) is calculated as the MLD after coronary balloon angioplasty minus MLD before coronary balloon angioplasty.
5) *Relative gain* in minimal luminal diameter is calculated as the gain divided by the reference diameter and is used to compare the degree of luminal improvement achieved at intervention in vessels of different sizes. This may be considered as the angiographic correlate of vessel wall injury caused by intervention (24-31).
6) *Loss* is the change in minimal luminal diameter between the post coronary balloon angioplasty and follow up angiogram.
7) *Relative loss* is the loss in diameter between the post-coronary balloon

angioplasty and the follow-up angiogram normalized for the reference diameter. This parameter may be considered as the angiographic correlate of the thrombo-fibroproliferative healing response to the injury imparted at intervention (24-31).

8) *Lesion length* (mm), is determined from the interpolated diameter function and the actual luminal contour, on the basis of curvature analysis (figure 1).

9) *"Atherosclerotic plaque area"* (mm^2), is the area between the actual and interpolated contours at the obstruction site (figure 1).

10) *Eccentricity index* is calculated as the perpendicular distance between the reconstructed interpolated reference diameter and actual vessel contours at the site of obstruction. In this calculation the largest distance between actual and reconstructed contours is the denominator so that a concentric lesion has a value of 1 and a severely eccentric lesion has a value of 0 (figure 1).

11) *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 is determined using the least foreshortened projection (in which the analyzed segment was longest between 2 defined landmarks) (figure 1).

12) *Mean diameter of the segment dilated by the balloon or "balloon-inflated vessel segment" (BIVS):* To facilitate this particular measurement, each investigator was asked to cineangiographically record each balloon inflation. The extent of the actual vessel segment dilated is then identified by visual assessment and calipers and analyzed over its entire length by the automated edge detection system. The ultimate measurement of interest is the mean diameter (mm) of this segment (figure 2).

Definition of Restenosis Although it is our policy to assess the long term outcome following coronary balloon angioplasty and other interventions using a continuous approach to analysis and presentation of data (19,20), for the purposes of this study it is necessary to apply categorical criteria to identify the occurrence of restenosis or differentiate the "restenotic" from the "non-restenotic" lesion. To this end, restenosis is considered per lesion using 3 different categorical definitions: 1) > 50% diameter stenosis at follow-up, 2) $\geq$ 0.72 mm change in minimal lumen diameter between postangioplasty and follow-up, 3) $\geq$ 0.40 mm change in minimal lumen diameter between postangioplasty and follow-up. The relevance of using these criteria will be adressed in the Discussion.

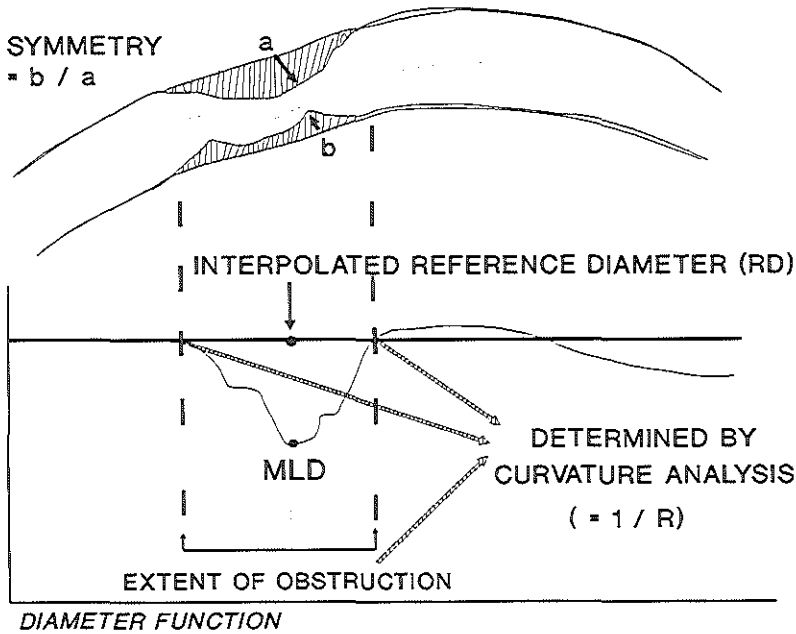

Figure 1 *See text for explanation.*

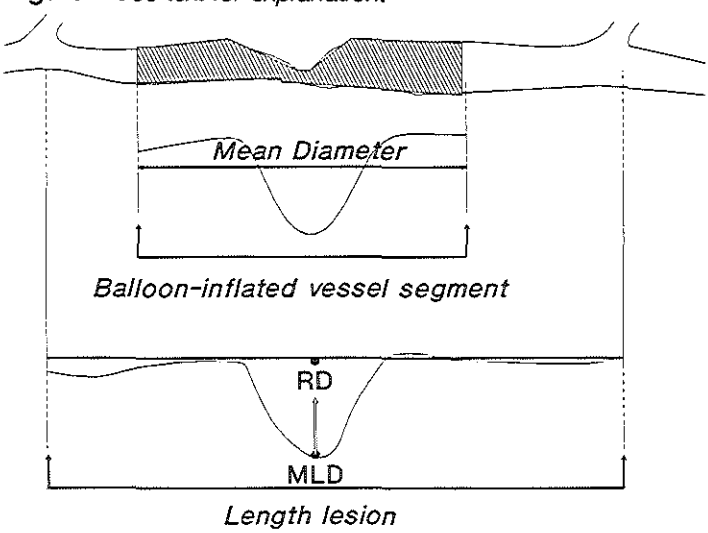

Figure 2 *A drawing of a stenosis in the mid portion of the left anterior descending artery. In addition to the regular analysis - from side brach to side branch -, the "balloon inflated vesssel segment" was determined by visual assessment of the part of the vessel that was submitted to the barotrauma of the inflated balloon. Therefore, the second analysis does not start at a side branch but at the proximal point where the balloon was inflated.*

Statistical methods

Values are shown as mean ± standard deviation (SD). Student t- test were used to assess differences in continuous variables of the restenotic lesion of its initial appearance and at follow-up, and of "restenotic" versus "non-restenotic" lesions. P-values less than 0.05 were considered statistically significant. Statistical analysis was carried out with a commercial statistical package (BMDP Statistical Software 1990).

RESULTS

Patient characteristics

The demographic characteristics of the 653 patients are shown in table 1. Mean age was 58 years (range: 33 to 77) and 542 or 83% of the patients were male. Follow-up angiography was performed after 164 ± 40 days (range 0 to 266 days). The vessel dilated was the left anterior descending in 46% (# 360) the right coronary artery in 29% (# 222), and the left circumflex in 25% (# 196) of lesions. Mild to moderate coronary disease predominated, with 63% having single vessel, 31% two vessel and only 6% exhibiting three vessel disease.

Table 1 *Patient characteristics.*

Age (yrs)	58	(33 - 77)
Male (%)	542	(83%)
Follow-up time (days)	164 ± 40	(0 - 266)
*Coronary Artery Disease (CAD)**		
1-vessel CAD	389	(63%)
2-vessel CAD	191	(31%)
3-vessel CAD	37	(6%)
Dilated vessel		
Right Coronary Artery	222	(29%)
Left Anterior Descending	360	(46%)
Left Circumflex	196	(25%)

Angiographic Measurements

(i) Overall pre-coronary balloon angioplasty, post-coronary balloon angioplasty and follow up results (Table 2):

Minimal luminal diameter increases from 1.02 ± 0.38 pre angioplasty to 1.78 ± 0.36 post angioplasty (gain is 0.76 ± 0.42 mm; range -0.22 to 2.34 mm) and is found to deteriorate again during follow up to 1.51 ± 0.57 mm (loss is 0.27 ± 0.52 mm; range -1.04 to 2.28 mm). Concomitantly, percentage diameter stenosis is reduced from 61 ±

14% before to 33 ± 10% immediately after coronary balloon angioplasty and increases to 44 ± 18% at follow-up. The vessel size does not change significantly during the study period: 2.62 ± 0.53 before angioplasty, 2.68 ± 0.50 post angioplasty and 2.70 ± 0.56 at 6 months follow-up angiography. The measured lesion length was similar pre-coronary balloon angioplasty and at follow-up as was eccentricity index, curvature value, and roughness value. However, the measured area of atherosclerotic plaque and the "balloon inflated vessel segment" was less at follow-up compared with pre dilatation.

Table 2 *Quantitative angiograhic data of 778 lesions*

	PRE-PTCA mean ± sd (range)	**POST-PTCA** mean ± sd (range)	**FOLLOW-UP** mean ± sd (range)
MLD (mm)	1.02±0.38 (0-2.20)	1.78±0.36 (0.7-3.3)	1.51±0.57 (0-3.1)
RD (mm)	2.62±0.53 (1.4-4.4)	2.68±0.50 (1.4-4.4)	2.70±0.56 (1-4.7)
DS (%)	61±14 (19-100)	33±10 (0-64)	44 ± 18 (5-100)
LL (mm)*)	6.1±2.2 (1-21)	5.8±2.2 (1.0-17)	6.2±2.4 (0.4-18)
Eccentricity *)	0.40±0.25 (0.02-1)	0.36±0.22 (0.01-1)	0.36±0.22 (0.01-1)
AP (mm^2)*)	6.5±3.6 (1-40)	4.1±3.0 (0.2-26)	5.4±3.5 (0.2-25)
Curvature*)	20±11 (1-89)	18±12 (1-95)	20±13 (1-95)
BIVS**)	2.23±0.63 (0-4.0)	2.46±0.44 (1-4.3)	2.37±0.64 (0-4.6)
Roughness**)	0.18±0.05 (0.1-0.5)	0.17±0.05 (0.1-0.5)	0.18±0.06 (0.1-0.6)

*AP = area plaque; BIVS = balloon inflated vessel segment; DS = (%) Diameter Stenosis ; LL = lesion length; MLD = Minimal Luminal Diameter (mm), RD = Reference Diameter (mm), *) not available for totally occluded vessels; before dilatation # 51 and at follow-up # 33. **) the inflated balloon was cine filmed # 652 lesions.*

(ii) Comparison of the morphology of the "restenotic lesion" with the "non-restenotic lesion", before, after PTCA and at 6 months (Table 3):

Differences in angiographic morphology of restenotic and non-restenotic lesions, pre and post-coronary balloon angioplasty and at follow up, are separately assessed for each of the three different restenosis criteria applied.

1) > *50% Diameter Stenosis at follow-up angiography*

Using this criterium as the "cut-off point" categorizes 231 lesions as progressing to restenosis ("restenotic lesions") giving a restenosis rate of 30%. Restenotic lesions are found to have a smaller minimal luminal diameter and a greater % diameter stenosis

than those which do not restenose ie. the restenotic lesion is more severe pre-coronary balloon angioplasty than the "non-restenotic". Furthermore the minimal luminal diameter immediately after dilatation is significantly larger for the non-restenotic lesion (1.81 vs. 1.70, $p<.001$). As no difference is observed in vessel size before and after the coronary balloon angioplasty procedure between the 2 groups, the diameter stenosis is concomitantly less in the "non-restenotic" (32% vs. 36%, $p<.0001$) than the restenotic lesion. In addition definition of restenosis by this criterium identifies the restenotic lesion to be less eccentric than the non-restenotic lesion pre and post-coronary balloon angioplasty and at follow up. Restenotic lesions are longer and have a greater plaque area at follow up than non-restenotic lesions (although the pre- and post-coronary balloon angioplasty lesion lengths are similar and the restenotic lesion has also greater plaque area pre-coronary balloon angioplasty). The mean diameter of the segment dilated is significantly less for the restenotic lesion at follow up while being similar to the non-restenotic lesion pre and post-PTCA. There is no difference in gain or relative gain, in mld, curvature value or roughness between the restenotic and non-restenotic lesions, as identified by the use of this criterium.

2) $\geq$ *0.72 mm criterion between post angioplasty and follow-up*

Application of this criterium for the identification of restenotic and non-restenotic lesions classifies 128 in the former category with a restenosis rate of 16%. As was found with the 50% diameter stenosis criterium, the restenotic lesion is more severe pre-coronary balloon angioplasty than the non-restenotic lesion (0.89 vs. 1.04mm and 67% vs. 59%). On the contrary, post-coronary balloon angioplasty a greater minimal luminal diameter and concomitantly smaller diameter stenosis is observed with the restenotic than the non-restenotic lesion. Consequently the gain in minimal luminal diameter is significantly greater for the restenotic lesion and despite a trend toward a larger vessel in the restenotic lesion group, the relative gain for this group is also significantly greater than for the non-restenotic lesion. As was uncovered by the use of the 50% diameter stenosis criterium, at follow up the restenotic lesion identified by this criterium is longer, has a greater plaque area, is less eccentric and the mean diameter of the dilated segment is less than the non-restenotic lesion. Lesion curvature and roughness do not differ significantly between restenotic and non-restenotic lesions at any point of comparison.

3) $\geq$ *0.40 mm criterion between post angioplasty and follow-up*

"$\geq$ 0.40 mm criterion" was observed in 255 lesions generating a restenosis rate of 33%. According to this criterium the restenotic lesion was also more severe than the non-restenotic lesion pre-coronary balloon angioplasty, with a MLD of 0.94 vs. 1.05 and a %DS of 64% vs. 59% respectively. In agreement with the 0.72mm criterium, the

Table 3 *Lesion morphology of restenotic versus non-restenotic lesions*

Restenosis criterion	> 50% DS fup			≥0.72 mm			≥0.40 mm		
	Absent # 547	**Present** # 231	**P**	**Absent** # 650	**Present** # 128	**P**	**Absent** # 523	**Present** # 255	**P**
Minimal Lumen Diameter (mm)									
pre-PTCA	1.06±0.37	0.91±0.39	*0.001*	1.04±0.37	0.89±0.43	*0.001*	1.05±0.37	0.94±0.40	*0.001*
post-PTCA	1.81±0.37	1.70±0.34	*0.001*	1.74±0.34	1.95±0.42	*0.001*	1.72±0.34	1.89±0.38	*0.001*
at fup	1.74±0.42	0.95±0.47	*0.001*	1.65±0.45	0.81±0.58	*0.001*	1.73±0.44	1.05±0.53	*0.001*
p (pre-fup)	*0.001*	*0.16*		*0.001*	*0.001*		*0.001*	*0.001*	
Vessel size									
pre-PTCA	2.62±0.55	2.63±0.48	*0.83*	2.61±0.54	2.70±0.51	*0.06*	2.61±0.55	2.63±0.52	*0.75*
post-PTCA	2.68±0.51	2.68±0.48	*0.92*	2.66±0.50	2.78±0.49	*0.02*	2.66±0.51	2.71±0.48	*0.22*
at fup	2.69±0.57	2.72±0.52	*0.40*	2.72±0.56	2.61±0.55	*0.06*	2.74±0.56	2.61±0.53	*0.001*
p (pre-fup)	*0.001*	*0.001*		*0.001*	*0.01*		*0.001*	*0.37*	
Diameter Stenosis (%)									
DSpre	59±14	65±14	*0.001*	59±14	67±16	*0.001*	59±13	64±15	*0.001*
DSpos	32±10	36±9	*0.001*	34±10	30±11	*0.001*	35±10	30±10	*0.001*
DSfup	35±10	65±15	*0.001*	39±13	69±21	*0.001*	36±12	59±20	*0.001*
p (pre-fup)	*0.001*	*0.79*		*0.001*	*0.33*		*0.001*	*0.001*	
Gain	0.75±0.41	0.80±0.43	*0.15*	0.70±0.38	1.06±0.48	*0.001*	0.67±0.38	0.95±0.44	*0.001*
Rel Gain	0.30±0.15	0.31±0.17	*0.32*	0.27±0.15	0.38±0.18	*0.001*	0.26±0.15	0.37±0.17	*0.001*
Loss	0.07±0.38	0.75±0.49	*0.001*	0.10±0.34	1.14±0.36	*0.001*	-0.01±0.29	0.84±0.40	*0.001*
Rel Loss	0.03±0.15	0.30±0.20	*0.001*	0.04±0.14	0.44±0.17	*0.001*	0.00±0.11	0.33±0.17	*0.001*

Table 3 continued

Restenosis criterion	> 50% DS fup			≥0.72 mm			≥0.40 mm		
	Absent # 547	**Present** # 231	**P**	**Absent** # 650	**Present** # 128	**P**	**Absent** # 523	**Present** # 255	**P**
Lesion Length (mm)									
pre-PTCA	6.0±2.2	6.2±2.4	*0.30*	6.1±2.2	6.1±2.2	*0.72*	6.1 ± 2.2	6.0±2.3	*0.59*
post-PTCA	5.7±2.2	5.8±2.3	*0.59*	5.8±2.2	5.8±2.2	*0.85*	5.9 ± 2.2	5.6±2.3	*0.09*
at fup	6.1±2.4	6.6±2.2	*0.01*	6.1±2.4	6.8±2.1	*0.001*	6.2 ± 2.4	6.2±2.3	*0.88*
p (pre-fup)	*0.68*	*0.03*		*0.55*	*0.002*		*0.26*	*0.22*	
Atherosclerotic plaque (mm^2)									
pre-PTCA	6.3±3.5	7.0±4.0	*0.02*	6.4±3.7	7.1±3.5	*0.07*	6.5 ± 3.7	6.6±3.5	*0.65*
post-PTCA	4.1±3.1	4.4±2.7	*0.21*	4.2±3.1	3.8±2.4	*0.15*	4.4 ± 3.1	3.6±2.5	*0.01*
at fup	4.6±3.1	7.7±3.6	*0.01*	5.1±3.4	7.4±3.4	*0.001*	5.1 ± 3.4	6.3±3.4	*0.001*
p (pre-fup)	*0.001*	*0.03*		*0.001*	*0.72*		*0.001*	*0.10*	
Symmetry Index									
pre-PTCA	0.39±0.24	0.43±0.26	*0.05*	0.40±0.25	0.40±0.25	*0.80*	0.39 ± 0.24	0.43±0.26	*0.03*
post-PTCA	0.35±0.22	0.39±0.24	*0.03*	0.36±0.22	0.38±0.24	*0.23*	0.34 ± 0.22	0.40±0.24	*0.001*
at fup	0.35±0.22	0.40±0.23	*0.01*	0.35±0.22	0.43±0.24	*0.01*	0.35 ± 0.21	0.40±0.24	*0.003*
p (pre-fup)	*0.02*	*0.22*		*0.001*	*0.36*		*0.01*	*0.26*	
Curvature Index									
pre-PTCA	20±11	19±10	*0.39*	20±11	20±10	*0.88*	20 ± 11	18±11	*0.04*
post-PTCA	18±12	18±12	*0.68*	18±12	18±11	*0.75*	19 ± 11	17±12	*0.22*
at fup	20±13	20±11	*0.91*	20±13	19±12	*0.41*	21 ± 13	19±12	*0.11*
p (pre-fup)	*0.25*	*0.08*		*0.30*	*0.75*		*0.16*	*0.17*	

Table 3 continued

Restenosis criterion	> 50% DS fup			≥0.72 mm			≥0.40 mm		
	Absent # 462	**Present** # 190	**P**	**Absent** # 545	**Present** # 107	**P**	**Absent** # 439	**Present** # 213	**P**
Balloon inflated vessel segment									
pre-PTCA	2.26±0.61	2.16±0.67	*0.06*	2.23±0.59	2.22±0.78	*0.88*	2.24±0.60	2.21±0.67	*0.50*
post-PTCA	2.47±0.44	2.43±0.45	*0.35*	2.43±0.42	2.59±0.48	*0.001*	2.44±0.44	2.50±0.44	*0.08*
at fup	2.49±0.49	2.09±0.85	*0.001*	2.47±0.48	1.89±1.03	*0.001*	2.51±0.49	2.10±0.81	*0.001*
p (pre-fup)	*0.001*	*0.25*		*0.001*	*0.001*		*0.001*	*0.06*	
Meangain	0.21±0.45	0.28±0.57	*0.11*	0.20±0.44	0.36±0.66	*0.001*	0.19±0.44	0.30±0.58	*0.02*
Meanloss	-0.02±0.29	0.35±0.73	*0.001*	-0.04±0.27	0.70±0.82	*0.001*	-0.07±0.27	0.40±0.67	*0.001*
Roughness of balloon inflated vessel									
pre-PTCA	0.18±0.05	0.18±0.06	*0.99*	0.18±0.05	0.19±0.05	*0.06*	0.18±0.05	0.19±0.05	*0.19*
post-PTCA	0.17±0.05	0.16±0.05	*0.15*	0.17±0.05	0.17±0.05	*0.98*	0.17±0.05	0.17±0.05	*0.99*
at fup	0.18±0.06	0.19±0.06	*0.06*	0.18±0.05	0.19±0.06	*0.48*	0.18±0.06	0.19±0.06	*0.49*
p (pre-fup)	*0.08*	*0.03*		*0.88*	*0.20*		*0.87*	*0.73*	

"at fup" = 6 Months Follow-up; Rel gain = relative gain; Rel loss = relative loss; pre-PTCA = before angioplasty; post-PTCA = after angioplasty.

post-coronary balloon angioplasty lumen is greater for restenotic than non-restenotic lesions, in terms of minimal luminal diameter (1.89 vs. 1.72 mm, $p<0.001$) and %DS (30% vs. 35%, $p<0.001$). The gain in minimal luminal diameter is therefore significantly greater (0.95mm vs. 0.67mm, $p<0.001$) for restenotic lesions and the relative gain is also significantly greater for restenotic lesions (0.37 vs. 0.26, $p<.001$). As with the previous two criteria, the mean diameter of the segment dilated at follow-up is less and the plaque area of restenotic lesions at follow up is significantly greater than for non-restenotic lesions. The restenotic lesion is less eccentric (0.35 vs. 0.43, $p<0.01$) as this was also observed by the 0.72 mm criterion. Lesion curvature and roughness do not differ significantly between restenotic and non-restenotic lesions at any point of comparison.

(iii) Morphology of the "restenotic lesion" at 6 months follow up compared with its pre-coronary balloon angioplasty appearance (Table 3)

In table 3 restenotic lesions, as separately identified by the three different criteria, are morphologically compared with their original appearance before coronary balloon angioplasty. For most of the angiographic characteristics measured, there is no agreement between the different criteria, indicating the total different group of lesions that are selected by each criterion.

According to the *">50% diameter stenosis criterium"* the minimal lumen diameter and the diameter stenosis of restenotic lesions is similar at follow-up than pre-coronary balloon angioplasty (0.95 vs. 0.91mm and 65% vs. 65%), greater vessel size (2.72 vs. 2.63mm) reference diameter of restenotic lesions is greater at follow up than pre-coronary balloon angioplasty (2.72 vs. 2.63mm, $p<.001$). In addition, restenotic lesions being longer (6.6 vs. 6.2mm, $p=.03$), and having greater plaque area (7.7 vs. 7.0mm^2, $p=.03$) at follow up than pre-coronary balloon angioplasty.

Use of the *"$\geq$0.72mm criterium"* identifies the reference diameter of restenotic lesions as being smaller (2.61 vs. 2.70mm, $p<.001$), the lesion itself as being longer (6.8 vs. 6.1mm, $p<.001$) and the mean diameter of the segment dilated as being less (1.89 vs. 2.22mm, $p<.001$) at follow up than pre-coronary balloon angioplasty. No significant difference is observed for lesion curvature and measured plaque area between pre-coronary balloon angioplasty and follow up.

Identification of restenotic lesions by the *"$\geq$0.40mm criterium"* reveals no significant difference between the caliber of the reference diameter, the lesion length, curvature index and plaque area of the segment pre-coronary balloon angioplasty and at follow up of restenotic lesions. The minimal lumen diameter is significantly less severe as is also reflected in a lower % diameter stenosis. Trends towards a smaller mean diameter of the segment dilated (2.10 vs. 2.21mm, $p= 0.06$) was observed.

DISCUSSION

The process of luminal narrowing after coronary interventions - restenosis - has clearly been shown by our group and others to a ubiquitous phenomenon occurring to a greater or lesser degree in all lesions and therefore is an unimodally (Gaussian) distributed phenomenon (32). The application of categorical cut-off criteria artificially divided lesions into two groups - those which restenose and those which do not -. In this study, we examine the applicability of 3 different restenosis criteria to the process of restenosis to address two frequent question in the search for some new insights to this response to vessel wall injury.

1)Are there angiographic morphological differences between lesions which progress to restenosis following successful coronary balloon angioplasty and those which do not ?.

2)Is there a change in angiographic morphology in either the "restenotic" or "non-restenotic lesion" from its baseline appearance to follow-up ?.

The categorical approaches used for the definition of restenosis

Vital in answering these questions is the definition of restenosis which will be used to determine which lesions fall into the category of "restenotic lesion". The definition of choice for restenosis has been the subject of much debate (9,10). Of the different restenosis criteria proposed, the "50% diameter stenosis at follow-up" is the most frequently used to assess "clinical restenosis", the rationale for which proclaims that a measure of stenosis severity should reflect coronary flow reserve and thus convey some functional and physiological meaning (33). However, this definition may exclude lesions which undergo a considerable degree of neoinitmal thickening after an optimal angioplasty result yet not cross the 50% diameter stenosis cut-off point, but include patients with only a mild degree of neoinitmal thickening which is sufficient to create a diameter stenosis >50% after a suboptimal angioplasty result. Therefore the application of this criterium, while being founded on sound physiological principles, provides no information on the behavior of the lesion since the coronary balloon angioplasty procedure and described as a "static" restenosis criteria (28).

In the past we have found that a loss in minimal lumen diameter of $\geq$0.72 mm to be a reliable indicator of angiographic progression of vessel narrowing (17,22,34). This value takes into account the limitations of coronary angiographic measurements with the cardiovascular-angiography analysis system and represents a worse-case scenario, without control of vasomotion or repetition of multiple matched views in *non-dilated* coronary artery obstruction with an average vessel size of 3.7 mm, by taken twice the long-term variability of repeat measurements.

As major criticism to the above 0.72 mm criterion arose in the literature, we have measured the variability of quantitative analysis of minimal lumen diameter of a *dilated*

coronary obstruction 24 hours after balloon angioplasty (35,36). However, special precautions were taken: 1) control of vasomotion with administration of 0.1 to 0.3 mg nitroglycerin or isosorbide dinitrate 1 to 3 mg for each coronary artery involved before and after angioplasty and at 24 hours, 2) repetition of multiple matched views (2.9), 3) all patients were fully anticoagulated for 24 hours so that the influence of thrombogenesis was effectively eliminated (average activated partial thromboplastin time between 80 to 120 seconds) and 4) average vessel size of 2.6 mm, which reflects the current population in recent multicenter restenosis prevention trials (19,20). The mean difference and the standard deviation of the minimal lumen diameter between post-angioplasty and 24 hours was 0.00 ± 0.20 mm. Therefore, if a change of $\geq$0.40 mm in minimal lumen diameter between the post-coronary balloon angioplasty and the follow-up angiogram was observed, restenosis was deemed to have occurred .

Our group has previously reported that the use of different categorical criteria identifies different lesions undergoing "restenosis" (14,34). The results of this study confirm this finding as illustrated by "restenosis rates" of 30%, 16% and 33% generated by application of ">50% diameter stenosis at follow up", "$\geq$.72mm loss in minimal luminal diameter during follow up" and ">0.40 mm loss in minimal lumen diameter during follow-up" respectively and the conflicting results of morphological comparisons between restenotic and non restenotic lesions and between the pre-coronary balloon angioplasty and follow-up appearance of restenotic lesions.

Morphology of the "restenotic lesion" versus the "non-restenotic" lesion:

The striking features of this comparison appear to be that lesions which progress subsequently to restenosis tend to be more severe pre-coronary balloon angioplasty, regardless of which criterion is applied. However, use of "dynamic criteria" demonstrate, furthermore, that lesions which "restenosed" were associated with a larger luminal gain and relative gain at coronary balloon angioplasty and had a greater post coronary balloon angioplasty minimal luminal diameter (and smaller % diameter stenosis) than those which do not progress to restenosis, whereas, in contrast, lesions which progressed to restenosis according to the ">50% diameter stenosis" criterion had a lesser post-coronary balloon angioplasty result and there was no difference between these lesions and those which did not progress to restenosis with respect to the gain or relative gain achieved at coronary balloon angioplasty. These striking discrepancies are not, in fact, all that surprising, since the "50% diameter stenosis" criterium cannot, by its nature, convey any measure of the degree of luminal renarrowing during follow up. Lesions which had a post-coronary balloon angioplasty diameter of less than but close to 50% (ie. technically successful coronary balloon angioplasty but perhaps classifiable as a "sub-optimal" result) will cross the 50% cut-off criterion for restenosis without necessarily undergoing very much luminal

renarrowing (for example 40% DS post coronary balloon angioplasty increasing to 55% at follow up) and, on the other hand, optimally dilated lesions may in fact undergo considerable renarrowing but not actually cross the 50% cut-off point (for example 10% DS post-coronary balloon angioplasty to 45% at follow up), therefore application of this criterion preselects the former type of lesion and conveys no measure of the degree of renarrowing and is therefore of questionable value in the context of important scientific research and restenosis prevention studies. Conversely, the main advantage of the other two criteria is that they do convey a measure of the extent of luminal renarrowing during follow up and the findings demonstrated by the use of these criteria in this study are very much in agreement with other recent reports by our group that the luminal gain at coronary balloon angioplasty is the greatest predictor of the subsequent occurrence of angiographic restenosis (28), that the relative gain is the greatest single determinant of luminal renarrowing (29), that the degree of luminal renarrowing (relative loss) is directly related to the degree of luminal gain at intervention (relative gain) (30) and a report of Schwartz et al. that there is a direct proportional relationship between arterial wall injury and intimal hyperplasia (24). Other groups have reported corroboratory angiographic findings regarding initial luminal gain at intervention and late loss during follow up, in the context of newer revascularization devices (37).

At follow up, as would be expected, restenotic lesions appear to be longer, have more plaque area, and are less eccentric than non-restenotic lesions, features which are in keeping with the hyperplastic response to wall injury and a process of luminal renarrowing. An additional, perhaps unexpected finding is that the mean diameter of the entire segment dilated (BIVS) is significantly less for restenotic lesions at follow up than is the case for non-restenotic lesions, whereas pre-coronary balloon angioplasty there was no significant difference in this measurement between the two groups of lesions, regardless of which criterion is applied. Furthermore, whereas there is an increase in this measurement from pre-coronary balloon angioplasty to post-coronary balloon angioplasty to follow up for the non-restenotic group there is a significant decrease for the restenotic group (except where restenosis is defined as 50%, but note that even in this group there is a significant decrease from post-coronary balloon angioplasty to follow up). Furthermore the reference diameter changes as defined by the "0.72mm criterion" confirm a previous reported by our group and others that the reference diameter decrease during follow up (14,28,38,39,40). However, in the present study the observed differences in reference diameter between post-angioplasty and follow-up are much smaller than in an previous publication of our group. Perhaps the standard administration of nitroglycerin or isosorbide dinitrate before each part of the procedure in the present study can partly explain this difference. It also concurs with a more recent report of the finding of whole artery restenosis in patients followed up

after directional atherectomy (40). Collectively these results appear to indicate that the presumably "normal" vessel wall adjacent to a dilated lesion becomes involved in the restenosis process, as a consequence of the injury imparted during intervention, since the inflated balloon is virtually always longer than the target lesion. The consistent findings with regard to the mean diameter of the dilated segment seem positively illustrative of this phenomenon of injury/restenosis with considerable and extensive renarrowing where there was substantial injury, greater luminal gain and relative gain and gain in BIVS in the restenosis group, and of beneficial vessel remodelling following mild but effective injury, less gain, relative gain and gain in BIVS in the non-restenotic group, yet the post-coronary balloon angioplasty result is reasonably well maintained to follow up (Table 3).

The use of percentage diameter stenosis measurements, relying on the arbitrary or non-arbitrary selection of a reference segment for its calculation, in the light of this information, cannot convey an estimate of the degree of luminal obstruction which is of sufficient accuracy for the purposes of important restenosis prevention studies. It is not surprising then that application of the ">50% diameter stenosis" criterion fails to identify lesions undergoing the greatest degree of luminal deterioration or loss/relative loss during follow up, additionally fails to highlight the greater luminal gain and relative gain achieved at coronary balloon angioplasty in lesions which subsequently developed restenosis and also the decrease in the mean diameter of the dilated segment and the reference diameter of these lesions from pre-coronary balloon angioplasty to follow up, as well as misleadingly demonstrating an actual increase in reference diameter.

Lesion morphology of the "restenotic lesion" compared with the original lesion

Irrespective of the criterion used, the "restenotic lesion" returns to its initial severity as reflected by the similar values of minimal lumen diameter and percent diameter stenosis (table 3). Depended on the restenosis criterion used, the vessel size decreases ($\geq$0.72 mm criterion), does not change ($\geq$0.40 mm criterion), or increases (> 50% Diameter stenosis). These findings reflect the different approaches - as explained earlier - to defining restenosis and the different groups of lesions selected by each criterion. Post-mortem studies have demonstrated, fibrocellular proliferation in vessel segments adjacent to target lesions presumably as a consequence of injury imparted during the dilatation proces. The proliferation was limited to the segments dilated whether or not they had been stenotic (38,39,40). In this study, the "balloon inflated vessel segment" seems to decrease, although individual large differences are observed. The restenotic lesion tended to become longer and had more atherosclerotic plaque, irrespective of the restenosis criterion used. Since in almost all cases the inflated balloon is longer than the stenosis, it is likely that the injury to the

vessel wall is not limited to the lesion itself and therefore the tissue will generate a lesion which is longer and or compromises of more plaque. Not surprisingly, the symmetry index remains unchanged from baseline to follow-up for restenotic lesions since the injury caused by balloon dilatation will be unequally distributed in eccentric lesions with a consequently unequal tissue response.

In the present study, the roughness measurement are reported of the "balloon inflated vessel segment" and not of the stenosis itself, as this analysis was not done at the time of the study. Mancini et al. has previously shown, using a different quantitative coronary system, that it is possible to distinguish between stable and unstable patients using the roughness of the stenosis (15).

CONCLUSIONS

Two messages emerge from the study: 1) the restenosis process clearly involves the apparent normal vessel wall adjacent to the actual lesion, probably in response to the unavoidable injury caused by balloon dilatation, 2) the use of percentage diameter stenosis measurements depending on the assumptions of normality for a reference segment will therefore underestimates the true extent of the restenosis process and should be replaced in clinical angiographic studies by absolute luminal measurements.

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CHAPTER 8

LUMINAL NARROWING AFTER PERCUTANEOUS TRANSLUMINAL CORONARY BALLOON ANGIOPLASTY FOLLOWS A NEAR GAUSSIAN DISTRIBUTION. A QUANTITATIVE ANGIOGRAPHIC STUDY IN 1445 SUCCESSFULLY DILATED LESIONS

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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

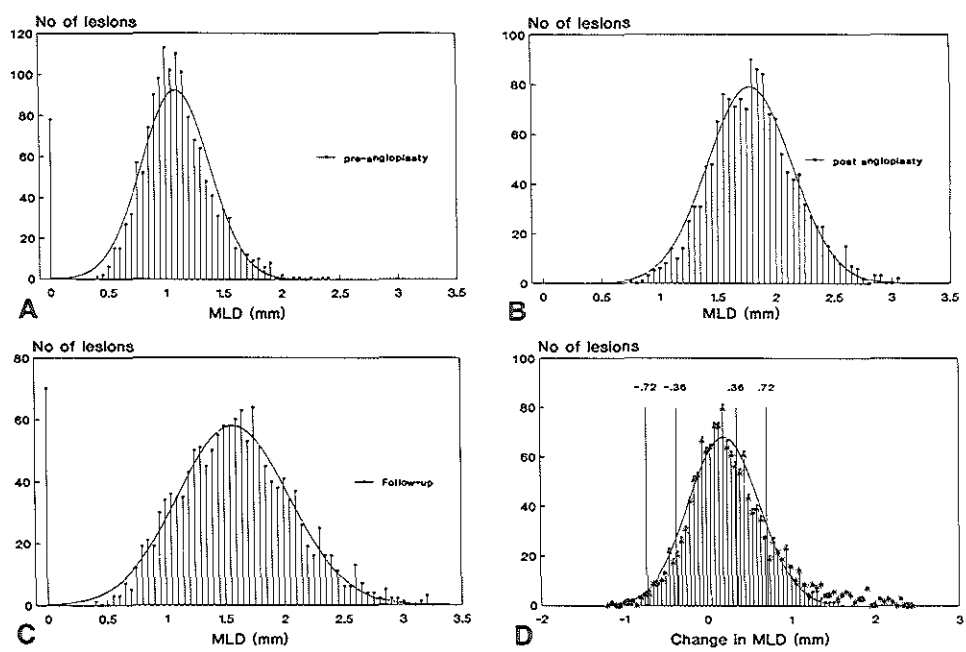
Minimal lumen diameter (mm)	
Before angioplasty	1.03 ± 0.37
After angioplasty	1.78 ± 0.36
Follow-up	1.50 ± 0.57
Reference diameter (mm)	
Before angioplasty	2.63 ± 0.54
After angioplasty	2.69 ± 0.52
Follow-up	2.70 ± 0.56
Change in minimal lumen diameter (mm)	
From before angioplasty to after angioplasty	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).



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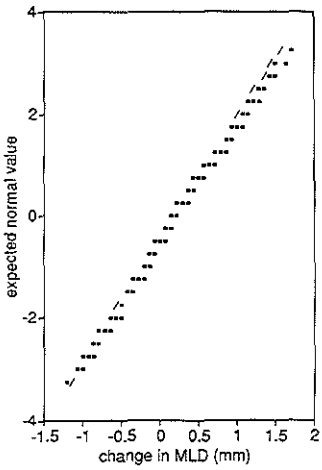

Figure 2. Normal probability plot of the change in minimal lumen diameter (MLD) from the postangioplasty angiogram to the follow-up angiogram, excluding lesions that had progressed toward total occlusion. The slashes depict the theoretic gaussian distribution; the squares are the values actually observed.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

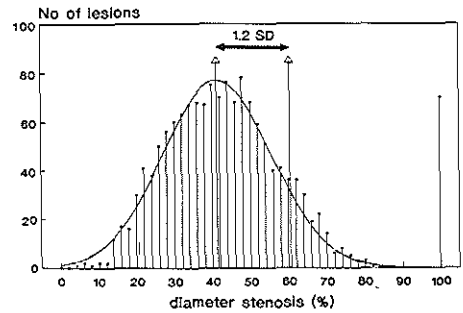

Figure 3. Histogram of percent diameter stenosis at follow-up angiography of 1,445 lesions. The curve superimposed on the histogram represents the theoretic gaussian distribution curves, given the mean values and SD of the study group, excluding total occlusions. Mean percent diameter stenosis excluding 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

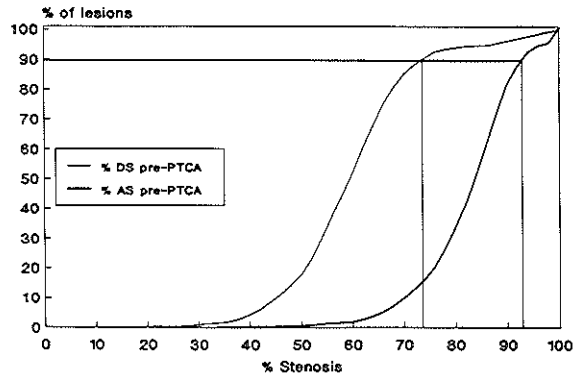

Figure 4. Cumulative distribution of percent diameter reduction (percent diameter stenosis [%DS], **thin curve**) and of percent area reduction (percent area stenosis [%AS], **thick curve**) for 1,445 lesions before angioplasty (pre-PTCA). Ninety percent of all lesions show a percent diameter stenosis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

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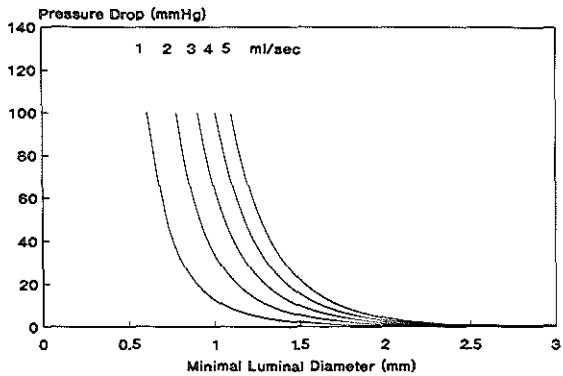

Figure 5. Theoretic pressure decreases calculated with the fluid dynamics equation derived by Gould (20) and Kirkeeide et al. (21) at assumed flows of 1, 2, 3, 4 and 5 ml/s, respectively. Reference diameter was assumed to be 2.6 mm and lesion length 6.5 mm.

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.

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.

We thank Jaap Pameijer for technical and logistic support.

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.

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CHAPTER 9

POSTANGIOPLASTY RESTENOSIS RATE BETWEEN SEGMENTS OF THE MAJOR CORONARY ARTERIES

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Postangioplasty Restenosis Rate Between Segments of the Major Coronary Arteries

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Conflicting data have been published regarding the rate of postangioplasty restenosis observed in diverse segments of the coronary tree. However, these studies may be criticized for their biased selection of patients, methods of analysis, and definitions of restenosis. In the present study, 1,353 patients underwent a successful coronary dilatation of ≥1 site. In all, 1,234 patients (91%) had a follow-up angiogram after 6 months, or earlier when indicated by symptoms. All films were processed and analyzed at the thoraxcenter core laboratory with the coronary angiography analysis system (automated contour detection). Restenosis was considered present if the diameter stenosis at follow-up was >50%. No differences in restenosis rates were observed between coronary segments using this categorical definition. A continuous approach was also used; absolute changes in minimal luminal diameter adjusted for vessel size were used in order to allow comparison between vessels of different sizes (relative loss). No significant differences were observed between the coronary segments with this continuous approach. These results suggest that restenosis is a ubiquitous phenomenon without any predilection for a particular site in the coronary tree.

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Ever since the introduction of percutaneous transluminal coronary angioplasty (PTCA)[1] as an alternative to coronary artery bypass grafting, this means of treatment has been plagued by the problem of restenosis, which has become an important field of investigation in interventional cardiology. During the last 14 years clinicians have searched extensively for factors increasing the risk of restenosis, and many patient-lesion-procedure-related factors have been put forward.[2,3] However, the cause and effect relation of these factors can be questioned, because these early studies were, in general, retrospective analyses with relatively small numbers of patients. In addition, these studies were fraught with methodologic problems; angiographic follow-up was incomplete, incidence of restenosis was influenced by the recurrence of symptoms, and time for restudy was not predetermined. Furthermore, the definition of restenosis varied between the different studies, and presence or absence of restenosis was assessed visually, a method known to be limited by inter- and intraobserver variability.[4,5] One risk factor for restenosis that led to controversy is the site of dilatation, with some studies finding a higher incidence of restenosis in the proximal left anterior descending coronary artery (LAD) as compared with the right or left circumflex coronary artery (LC) (Table I).[6–19] Recently, 2 multicenter restenosis prevention trials enrolled >1,400 patients who were analyzed at the same angiographic core laboratory. In 91% of these patients, follow-up angiography was performed, and the same quantitative coronary angiographic method of analysis was used.[5,20] The present study investigates whether the previously reported differences in restenosis rates in the 3 major coronary arteries could be confirmed in this large study group.

METHODS

The study population consisted of 1,442 patients with significant primary stenoses in native coronary arteries who were prospectively enrolled in 2 restenosis trials in Europe. Because no angiographic or clinical benefit of the 2 tested compounds could be demonstrated, the control and active treatment groups were pooled for the present study. PTCAs and follow-up films of all patients with successful dilations were analyzed at the thoraxcenter core laboratory. Informed consent was obtained in all cases before the PTCA procedure, and all patients were asked to return to the hospital for follow-up angiography. Patients with stable and unstable angina pectoris, and those with totally occluded vessel segments were included in the study. Pa-

TABLE I Summary of Restenosis Studies Demonstrating Conflicting Results as to the Site of Dilatation as a Risk Factor for Restenosis

Study	Year	Patients	Angio Fup (%)	Definition of Restenosis	Restenosis (%)	Coronary Artery	Statistical Analysis
Holmes[6]	1984	665	84	NHLBI I→IV	33.6	No difference	Multivariate
Kaltenbach[7]*	1985	356	94	DS Fup <20% DS pre	12	No difference	Univariate
				Decrease ≥50% of gain	16		
				↑ DS ≥30%	17		
Mata[8]†	1985	63	95	↑ DS >30% or DS >70%	23	LAD or LC > right	Multivariate
DiSciascio[9]†	1986	191	21¶	Decrease ≥50% of gain	58 1-VD 42 2-VD	No difference	Univariate
Leimgruber[10]	1986	1,758	57	>50% DS	30.2	LAD > right > LC	Multivariate
Myler[11]‡	1987	286	57	>50% DS	41	No difference	Multivariate
Val[12]	1987	181	98	↑ ≥30% DS	28	No difference	Multivariate
Vandormael[13]‡	1987	209	62	>50% DS	82 (Symp) 30 (No Symp)	LAD > right or LC Prox > Dist	Multivariate
Black[14]§	1988	384	39	>50% DS	31	No difference	Multivariate
de Feyter[15]‖	1988	179	88	>50% DS	32	LAD > right or LC	Multivariate
Fleck[16]*	1988	110	86	ΔMLCA > 1 mm^2 (QCA)	58	No difference	Multivariate
Quigley[17]§	1989	114	88	>50% DS	32	No difference	Multivariate
Renkin[18]	1990	278	47**	>50% DS	—	No difference	Multivariate
Rupprecht[19]*	1990	676	70	>50% DS or decrease >50% of gain	29.2	No difference	Multivariate
Present study	1991	1,353	91	>50% DS	31	No difference	Univariate
				Relative loss	0.11 ± 0.21		Analysis of variance

*Excluded total occlusions; †multivessel dilatation; ‡multilesion dilatation; §for restenosis; ‖unstable angina; ¶review of patients with clinical recurrence; **angiography + exercise thallium scintigraphy.
Angio Fup = % of patients with angiographic follow-up; Dist = distal; DS = diameter stenosis; LAD = left anterior descending; LC = left circumflex; ΔMLCA = change in minimal luminal cross-sectional area; NHLBI = National Heart, Lung, and Blood Institute; pre = before; Prox = proximal; QCA = quantitative coronary angiographic method of analysis; RCA = right coronary artery; Symp = symptoms; VD = vessel disease.

tients with developing myocardial infarctions and significant left main disease were excluded from the study. PTCA was successful if the final diameter stenosis was <50% on visual inspection of the angiogram after PTCA. PTCA was considered complete when the guiding catheter was removed from the groin. When recurrence of chest pain during the hospital stay led to coronary reintervention, the film before reintervention was used as the follow-up angiogram. If a follow-up angiogram was obtained before 3 months and if no definite restenosis had occurred, the patient was asked to undergo another coronary angiogram at 6 months.

Figure 1 describes the flow chart of all 1,442 randomized patients. Of the 1,353 patients with successful PTCA, 1,234 patients had a follow-up angiogram after 6 months, or earlier when indicated for symptoms.

Percutaneous transluminal coronary angioplasty procedure and angiographic analysis: At the beginning of the procedure, all patients received a bolus of intravenous heparin (10,000 IU). After 2 hours, an additional infusion of heparin (5,000 IU/hour) was administered until the end of the procedure. Use of a calcium antagonist for 48 hours was permitted. Choice of balloon type, inflation duration and pressure was left to the discretion of the operator.

Three angiograms were obtained of each patient (1 immediately before and 1 immediately after PTCA, and 1 at follow-up). The angiograms were recorded in such a way that they were suitable for quantitative analysis by the coronary angiography analysis system. An example of an analysis is shown in Figure 2. To standardize the method of data acquisition and to ensure exact reproducibility of angiograms after PTCA and at follow-up, measures were taken as described previously.[5,20]

All cineangiograms were quantitatively analyzed using the coronary angiography analysis system that has been validated and described in detail previously.[5,20] The absolute values of the stenosis diameter as well as the reference diameter are measured by computer using the known contrast-empty catheter diameter as a scal-

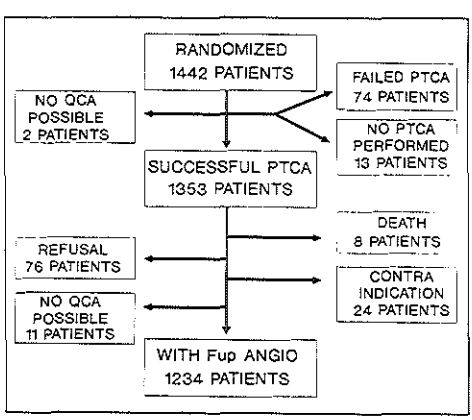


FIGURE 1. Flow chart of 1,442 randomized patients. In 74 patients, angioplasty procedure was unsuccessful, in 13, percutaneous transluminal coronary angioplasty (PTCA) was not performed, and in 2, quantitative analysis (QCA) was not possible. Angiographic follow-up (Fup ANGIO) was obtained in 1,234 patients (91%) after successful coronary angioplasty in 1,353.

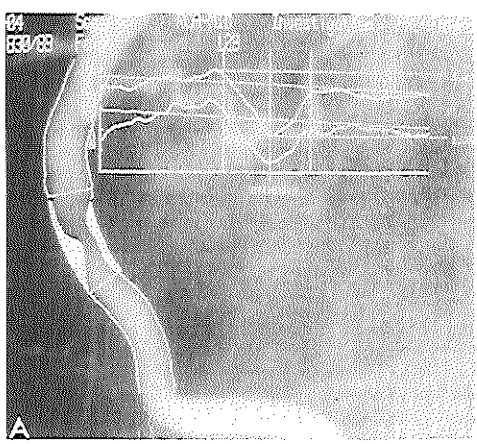
ing device. For that purpose, the catheter tips were retained for accurate measurement with a micrometer. To achieve maximal vasodilation, either nitroglycerin (0.1 to 0.3 mg) or isosorbide dinitrate (1 to 3 mg) was administered for each coronary artery involved before and after PTCA, and at follow-up angiography. All contour positions of the catheter and the arterial segment were corrected for pincushion distortion introduced by the image intensifiers. Because the algorithm is not able to measure total occlusions and lesions with Thrombolysis in Myocardial Infarction-1 perfusion, a value of 0 mm was substituted for the minimal luminal diameter and 100% for the percent diameter stenosis. In these cases, the reference diameter after PTCA was substituted for the reference diameter before PTCA or at follow-up. For each dilated segment, the minimal luminal diameter and diameter stenosis before and after PTCA, and at follow-up were taken as the mean value from multiple matched projections.[5]

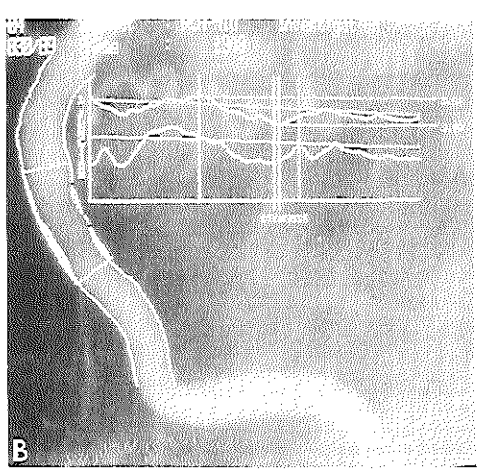
Definition of coronary segments: Austen et al[21] divided the coronary tree in 15 different segments (Figure 3). Because dilatation of the distal vessel segments did not occur frequently, it was decided to regroup these distal segments. The right coronary artery was divided in 4 segments: segment 1 corresponded with the proximal, segment 2 with the middle, and segments 3 and 4 were taken together as the distal right coronary artery. The LAD was divided in 5 segments; segment 6 corresponded with the proximal LAD, segment 7 with the middle LAD, and segments 8, 9 and 10 were taken together as the distal LAD. The LC was divided in 5 segments; segment 11 corresponded with the proximal LC, segments 13 and 15 were taken together as the middle LC, and segments 12 and 14 were taken together as the distal LC.

Definition of restenosis: CATEGORICAL APPROACH: Many criteria have been proposed by the National Heart, Lung, and Blood Institute to assess restenosis. The most frequently used criterion by clinicians is that restenosis is present when the diameter stenosis is >50% at follow-up angiography.[22] This definition was used for our data.

CONTINUOUS APPROACH: In addition to this arbitrary categorical approach for restenosis, we wanted to use absolute changes in minimal luminal diameter adjusted for vessel size, which allows for comparison between vessels of different sizes and is a reflection of how the lesion behaves during and after PTCA.

Relative gain depicts the increase in minimal luminal diameter normalized for the reference diameter during PTCA (minimal luminal diameter [before PTCA − after PTCA]/reference diameter before PTCA). Relative loss depicts the decrease in minimal luminal diameter normalized for the reference diameter (minimal lu-





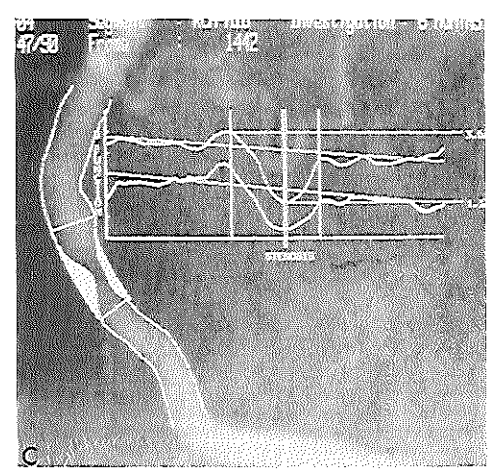


FIGURE 2. Single frame angiograms of same lesion of the right coronary artery before dilatation *(A)*, after dilatation *(B)* and at follow-up *(C)*. Arterial boundaries detected by system are shown on angiogram; *upper curve* represents diameter function curve. Minimal luminal diameter changes from 1.28 before to 2.58 mm after percutaneous transluminal coronary angioplasty. At follow-up 6 months later there is a decrease of minimal luminal diameter to 1.17 mm.

minal diameter [after PTCA − at follow-up]/reference diameter before PTCA) (Figure 4).

Data analysis: Data were analyzed using the biomedical-designed program statistical software package (University of California Press, Berkeley, California, 1990). A chi-square test was used to assess differences in categorical variables. A 1-way analysis of variance was used to assess differences in continuous variables among the 3 major coronary arteries and the 9 different segments of the coronary tree. A p value <0.05 was considered indicative of a significant difference.

RESULTS

The mean time to follow-up angiography was 165 ± 42 days. In 1,234 patients, 1,452 lesions were successfully dilated (1.2 lesions/patient). In 74 patients, a totally occluded vessel segment was dilated. In 1,137 patients, 1-vessel dilatation was performed, 93 had 2-vessel dilatation, and 4 had all 3 vessels dilated. The majority of stenoses were located in the LAD (684 lesions) compared with 414 lesions in the right coronary artery and 354 in the LC.

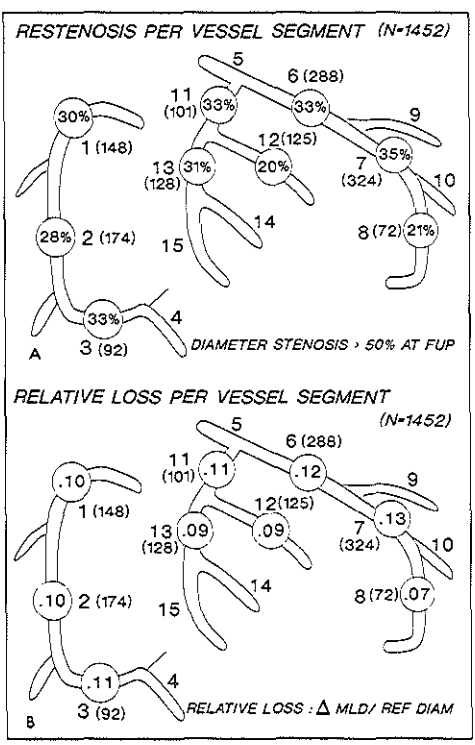


FIGURE 3. Coronary tree divided in 15 different segments with restenosis rate (using >50% diameter stenosis as criterion) for each segment (A), and relative loss per coronary segment (B) shown in *circles*. Between *brackets* are numbers of lesions dilated for that segment. FUP = follow-up. ΔMLD/REF DIAM = decrease in minimal luminal diameter normalized for reference diameter.

Table II lists the results of the quantitative measurements of the 1,452 lesions. The largest vessel was the right coronary artery, with an average reference diameter of 2.86 ± 0.55 mm. The LAD and LC had similar sizes: the average reference diameters were 2.54 ± 0.53 mm for the LAD, and 2.55 ± 0.50 mm for the LC (p <0.001). In addition, the average increases in minimal luminal diameter were 0.82 ± 0.37 mm in the right coronary artery, 0.71 ± 0.36 mm in the LAD, and 0.72 ± 0.35 mm in the LC. If these values were "normalized for the reference diameter" (relative gain), no significant differences were observed among either the 3 major coronary arteries (right coronary artery vs LAD vs LC; p = 0.44) or the different segments of the coronary tree (p = 0.77). During follow-up, the average losses in minimal luminal diameter were 0.26 ± 0.55 mm in the right coronary artery, 0.30 ± 0.48 mm in the LAD, and 0.25 ± 0.48 mm in the LC. If these values were normalized for the reference diameter (relative loss), no significant differences were observed among the 3 major coronary arteries (right coronary artery vs LAD vs LC; p = 0.13) or the different segments of the coronary tree (p = 0.19).

The restenosis rate, and relative gain and loss for the 3 major coronary arteries and the diverse vessel segments, using either the categorical or continuous approach, are listed in Table III. No significant difference in either approach was observed.

DISCUSSION

Several investigators have raised the question as to whether the dilated vessel constitutes a risk factor for the development of restenosis. They have reported conflicting results (Table I). The question is becoming even more relevant as new interventional techniques (such as stenting, atherectomy, laser photoablation and rotablation) have been "claimed" to be more effective than conventional balloon angioplasty in certain lesion types (long lesions and total occlusions), locations or vessels (right coronary artery, LAD, LC and bypass graft).[23]

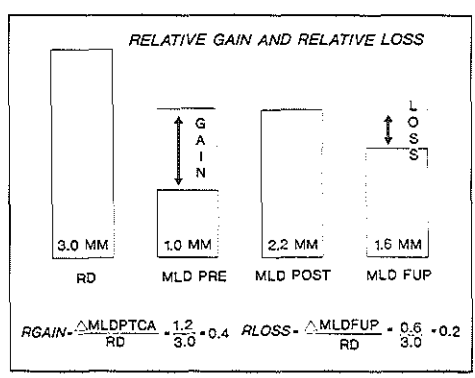


FIGURE 4. See text for explanation of relative gain (RGAIN) and relative loss (RLOSS). FUP = follow-up; MLD = minimal luminal diameter; POST = after; PRE = before; PTCA = percutaneous transluminal coronary angioplasty; RD = reference diameter.

although these new techniques have not yet succeeded in reducing restenosis rates.[24,25] Several explanations have been put forward to explain the increased risk for restenosis in the (proximal) LAD. Mata et al[8] believed that a high rate of "continuous success" needs an optimal selection of the balloon/artery ratio and optimal balloon pressure application. They suggested that anatomic or procedural factors were responsible for restenosis. Leimgruber et al[10] had 3 possible explanations. First, because they believed that the proximal LAD is

TABLE II Baseline Quantitative Angiographic Data per Vessel Segment Dilated

Coronary Artery	No.	Pre PTCA RD (mm)	Post PTCA RD (mm)	Follow-Up RD (mm)	Pre PTCA MLD (mm)	Post PTCA MLD (mm)	Follow-Up MLD (mm)
Total	1,452	2.63 ± 0.54	2.70 ± 0.52	2.70 ± 0.56	1.02 ± 0.38	1.77 ± 0.36	1.50 ± 0.57
Right	414	2.86 ± 0.55	2.93 ± 0.52	2.97 ± 0.58	1.08 ± 0.41	1.91 ± 0.37	1.65 ± 0.65
Proximal	148	2.99 ± 0.55	3.05 ± 0.51	3.07 ± 0.55	1.11 ± 0.45	1.96 ± 0.39	1.69 ± 0.63
Middle	174	2.82 ± 0.50	2.90 ± 0.50	2.94 ± 0.59	1.08 ± 0.41	1.91 ± 0.34	1.66 ± 0.65
Distal	92	2.71 ± 0.59	2.81 ± 0.56	2.85 ± 0.57	1.02 ± 0.35	1.83 ± 0.40	1.57 ± 0.66
LAD	684	2.54 ± 0.53	2.59 ± 0.49	2.58 ± 0.53	1.01 ± 0.36	1.72 ± 0.35	1.42 ± 0.53
Proximal	288	2.73 ± 0.52	2.78 ± 0.48	2.76 ± 0.53	1.08 ± 0.35	1.83 ± 0.35	1.53 ± 0.55
Middle	324	2.48 ± 0.47	2.52 ± 0.43	2.52 ± 0.47	0.97 ± 0.36	1.68 ± 0.32	1.35 ± 0.51
Distal	72	2.08 ± 0.44	2.14 ± 0.44	2.13 ± 0.42	0.87 ± 0.35	1.43 ± 0.29	1.29 ± 0.37
LC	354	2.55 ± 0.50	2.62 ± 0.46	2.61 ± 0.48	1.01 ± 0.36	1.73 ± 0.34	1.48 ± 0.51
Proximal	101	2.73 ± 0.47	2.75 ± 0.43	2.74 ± 0.44	1.06 ± 0.42	1.82 ± 0.32	1.52 ± 0.50
Middle	125	2.55 ± 0.50	2.64 ± 0.45	2.61 ± 0.50	1.00 ± 0.34	1.75 ± 0.32	1.52 ± 0.53
Distal	128	2.41 ± 0.49	2.50 ± 0.46	2.52 ± 0.48	0.98 ± 0.34	1.63 ± 0.34	1.41 ± 0.49

Values are means ± standard deviation.
LAD = left anterior descending; LC = left circumflex; MLD = minimal luminal diameter; Post = after; Pre = before; PTCA = percutaneous transluminal coronary angioplasty; RD = reference diameter.

TABLE III Restenosis Rate per Segment Using the Categorical Definition of > 50% DS at Follow-Up, and the Continuous Approach with Relative Gain and Loss

		DS (%) at Follow-Up > 50%			
	No.	Yes	No	Relative Gain	Relative Loss
Total	1452	444 (31)	1008 (69)	0.29 ± 0.16	0.11 ± 0.21
Right	414	123 (30)	289 (70)	0.30 ± 0.15	0.10 ± 0.22
Proximal	148	45 (30)	103 (70)	0.29 ± 0.15	0.10 ± 0.21
Middle	174	48 (28)	126 (72)	0.30 ± 0.15	0.10 ± 0.22
Distal	92	30 (33)	62 (67)	0.31 ± 0.15	0.11 ± 0.26
LAD	684	224 (33)	457 (67)	0.29 ± 0.17	0.12 ± 0.20
Proximal	288	95 (33)	193 (67)	0.29 ± 0.17	0.12 ± 0.19
Middle	324	114 (35)	210 (65)	0.29 ± 0.17	0.13 ± 0.21
Distal	72	15 (21)	57 (79)	0.27 ± 0.19	0.07 ± 0.15
LC	354	97 (28)	255 (72)	0.29 ± 0.16	0.11 ± 0.21
Proximal	101	33 (33)	68 (67)	0.29 ± 0.16	0.11 ± 0.18
Middle	125	25 (20)	100 (80)	0.30 ± 0.15	0.09 ± 0.21
Distal	128	40 (31)	88 (69)	0.28 ± 0.17	0.09 ± 0.21
p Value	(right vs LAD vs LC)	0.22		0.44	0.13
	(9 segments)	0.06		0.77	0.19

Values are means ± standard deviation.
Abbreviations as in Table I.

TABLE IV Relative Gain and Loss per Reference Diameter Group

						DS (%) at Follow-Up > 50%		
RD (mm)	No.	Absolute Gain (mm)	Relative Gain	Absolute Loss (mm)	Relative Loss	Yes	No	BAR
> 4.0 mm	18	0.72 ± 0.55	0.17 ± 0.13	0.13 ± 0.46	0.03 ± 0.10	6 (33)	12 (67)	0.77
3.5 to 4.0 mm	81	0.87 ± 0.47	0.24 ± 0.13	0.10 ± 0.50	0.03 ± 0.13	23 (28)	58 (71)	0.89
3.0 to 3.5 mm	222	0.83 ± 0.42	0.26 ± 0.13	0.33 ± 0.54	0.10 ± 0.17	71 (32)	151 (68)	0.97
2.5 to 3.0 mm	507	0.76 ± 0.40	0.28 ± 0.15	0.28 ± 0.52	0.10 ± 0.19	153 (30)	354 (70)	1.07
2.0 to 2.5 mm	454	0.72 ± 0.40	0.32 ± 0.17	0.28 ± 0.51	0.12 ± 0.23	148 (33)	306 (67)	1.20
< 2.0 mm	170	0.61 ± 0.34	0.34 ± 0.20	0.27 ± 0.46	0.15 ± 0.26	44 (26)	126 (74)	1.39
Analysis of variance		< 0.001	< 0.001	< 0.02	< 0.001	NS		

Values are means ± standard deviation.
BAR = balloon-artery ratio (size of the balloon according to manufacturer divided by the reference diameter before percutaneous transluminal coronary angioplasty); DS = diameter stenosis; NS = not significant; RD = reference diameter.

most often the largest artery, the 3.0 mm diameter balloons most frequently used at that time could have been undersized for the LAD and oversized for the right coronary artery and LC. This resulted in increased diameter stenosis after PTCA, which seems to be associated with a higher risk for restenosis. Second, a dilatation of the proximal LAD often involves the origin of the vessel and vessel branch points, and this factor also appears to be associated with an increased risk of restenosis. Third, the proximal LAD is well-recognized to develop "localized stenosis." Whether the same underlying mechanisms may predispose a patient to recurrence of lesions after angioplasty is unknown but well-conceivable.

Because balloon/artery mismatch was not identified as a predictor for restenosis in a group of patients with multilesion coronary angioplasty, Vandormael et al[13] suggested that the different anatomic and structural features of the proximal segment of the LAD compared with those of the proximal segment of the right coronary artery or LC may be responsible for the observation that dilatation of the proximal LAD is an independent risk factor for restenosis.

According to Califf et al,[3] 1 of the methodologic caveats for an increased rate of restenosis in the proximal LAD was that an ischemic response to exercise testing was more likely to be seen with proximal LAD lesions, thereby increasing the chance of preferential detection unless angiographic follow-up was complete. Also, a larger diameter of this vessel may have increased the risk that a satisfactory initial result was not achieved in earlier series, especially before the recent development of larger balloons to approach large vessels.

In the present study, no significant difference in the restenosis rate was found among the 3 major coronary arteries ($p = 0.22$) or the 9 coronary artery segments ($p = 0.06$) selected for the purpose of analysis. Our results contradict the earlier observations of Leimgruber and Califf and their coworkers that the proximal LAD is the largest vessel. In the present study, almost every segment of the right coronary artery has a larger diameter than the proximal LAD. An explanation for this discrepancy may be the differences in patient populations; availability of different balloon sizes (with diameters <2.0 mm as compared with those in the early days of PTCA when only balloon sizes of 3.7 mm were available) for dilatation may have affected PTCA of the proximal LAD. Another argument put forth in the early years that there was a mismatch between balloon catheters and proximal LAD is no longer valid, because in the present study, all patients underwent PTCA between December 1987 and December 1989 so that in all cases matched balloons were available. The differences in restenosis rates reported by these investigators are probably more related to the biased and incomplete angiographic follow-ups of these studies. In contrast, the present study has a 91% angiographic follow-up rate, and so the biased selection of symptomatic versus asymptomatic patients is virtually ruled out.

Definition of restenosis: The definition of restenosis has been the subject of much debate.[4] Of the different restenosis criteria proposed, >50% diameter stenosis at follow-up angiography is the most frequently used to assess restenosis, because physiologic measurements have shown that the threshold for chest pain is near a reduction of 50% of the lumen of a normal vessel.[22] This definition was applied to our data. However, earlier studies have shown that the reference diameter can be involved in the dilatation process so that the % diameter stenosis could underestimate the change in the severity of a stenosis after PTCA.[26] Furthermore, the 50% diameter stenosis criterion at follow-up reveals nothing about the way the lesion has behaved since the PTCA procedure. We have previously shown that a change ≥0.72 mm in minimal luminal diameter is an appropriate method to assess intimal hyperplasia after coronary PTCA.[5,20,27] However, this criterion was historically assessed in vessels with an average reference diameter of 3.7 mm.[5,20] Therefore, it should be applied to vessels of comparable reference diameter; it is unlikely to have a decrease ≥0.72 mm in coronary segments with a reference diameter of 2 mm, and a minimal luminal diameter of 1.4 mm. In other words, criteria based on the absolute change in minimal luminal diameter are limited because they make no attempt to relate the extent of the restenosis process to the size of the vessel. To circumvent this limitation it was proposed to use the change in minimal luminal diameter from after PTCA to follow-up, normalized for the reference diameter (relative loss). This sliding scale criterion that adjusts for vessel size allows for regional assessment of the extent of the restenosis phenomenon in the entire coronary tree. No difference in relative loss among the 3 major coronary arteries ($p = 0.13$) or the coronary segments could be observed ($p = 0.19$). Restenosis should thus be viewed as a ubiquitous phenomenon that is inducible to the same extent in every segment of the coronary tree. It must be emphasized that the relative gain (change in minimal luminal diameter from before to after PTCA, normalized for the reference diameter) and thus the stimulus for restenosis[28] were similar in every segment of the coronary tree.

Because the subdivision of the American Heart Association-coronary segments is somewhat arbitrary in that vessels of different diameters are grouped together, we reanalyzed the data by stratifying the lesions according to their reference diameters. Table IV lists the results. It appears that the larger the reference diameter is before PTCA, the smaller the relative loss is at follow-up; vice versa, the greatest value of relative loss is observed in the smaller vessels. This may be explained by oversizing of the balloon in these vessels. However, if the restenosis criterion of >50% diameter stenosis is used, then similar restenosis rates are found.

Potential limitation of the study: Our study population consisted mainly of patients with 1 dilatation site; 1,044 patients had 1 dilatation site, and 190 underwent dilatation of ≥2 sites. The high incidence of 1 dilatation site reflects the fact that the study population included in these 2 trials consisted predominantly of patients with 1-vessel disease, so that our findings may not be extrapolated to a population with multivessel disease. Nevertheless, in the subset of 93 patients with multivessel dilatation, the overall restenosis rate per lesion was also 31%. However, the relative gain and loss observed in

patients with 1- and 2-vessel dilatations differed statistically; a relative gain of 0.30 ± 0.16 was seen for 1-vessel dilatation versus 0.27 ± 0.16 for 2-vessel dilatation ($p < 0.04$), and a relative loss of 0.12 ± 0.21 for 1-vessel dilatation versus 0.08 ± 0.20 for 2-vessel dilatation ($p < 0.02$). Thus, in the population with 2-vessel dilatation, a reduced gain is associated with a reduced loss consistent with the concept that PTCA operators are less aggressive in their dilating strategy.

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CHAPTER 10

PATIENT, LESION AND PROCEDURAL VARIABLES AS RISK FACTORS FOR LUMINAL RENARROWING AFTER SUCCESSFUL CORONARY ANGIOPLASTY. A QUANTITATIVE ANALYSIS IN 653 PATIENTS WITH 778 LESIONS

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ABSTRACT

Background. The identification of variables predictive for restenosis could be helpful in the selection of lesions suitable for angioplasty and, if modifiable or controllable, potentially reduce restenosis. The purpose of this ancillary study of the MERCATOR trial, a double blind placebo-controlled trial to study the effects of cilazapril 5 mg twice a day, on restenosis and long-term clinical outcome, was to determine which, if any, patient,lesion or procedural factors were predictive of restenosis.

Methods. Quantitative coronary angiography was obtained in 94% of the 653 patients (778 successfully dilated coronary lesions) at angioplasty and at 6 months follow-up. Restenosis was defined as the mean loss in minimal lumen diameter at follow-up, as this reflects the magnitude of the fibroproliferative vessel wall reaction as a response to coronary balloon angioplasty.

Results. Stepwise multiple linear regression analysis was performed to identify independent predictors of restenosis. The following variables were retained in the model in order of significance: 1) relative gain (difference between the minimal lumen diameter pre and post-PTCA, normalized for vesselsize), 2) minimal lumen diameter post-PTCA, 3) dilatation of another vessel than right coronary artery. The overall prediction of the model was poor, where the predicted change in minimal lumen diameter was <0.1 mm, 0.1 to 0.3 mm, >0.3 mm, the corresponding percent correct classification was 30%, 52% and 55%.

Conclusion. The present study illustrates that the restenosis phenomenon cannot accurately be predicted by simple patient, lesion and procedural variables.

INTRODUCTION

The major limitation of the long term success of percutaneous transluminal coronary angioplasty (PTCA) is still restenosis (1-19). Fourteen years after its introduction by Andreas Gruntzig in 1977 as an alternative treatment modality for patients with asymptomatic or symptomatic coronary artery disease (20), more than 400,000 patients will be treated by PTCA worldwide in 1991, and most likely this number will increase further in future (21). Histological, experimental and clinical research has provided us with information that enables us to better understand the recurrence of successfully dilated coronary lesions. This untoward phenomenon is now recognized, by many researchers, as an intimal proliferation of smooth muscle cells together with an abundant matrix production (22-40).

Quantitative coronary analysis is the most reliable available method of assessing coronary arterial lumen changes over time and has demonstrated that the change in minimal lumen diameter between post-PTCA and follow-up angiography is the most non-ambiguous measurement to describe the continuous process of restenosis at present time (41-47).

Recent developments in pharmacological therapy and new percutaneous intracoronary revascularization techniques have failed to inhibit or prevent restenosis (47-55). On the other hand, a variety of patient - procedural - lesion related factors have been associated with an increased risk of restenosis (table 1, 1-15,18,19), however the ability to predict in individual cases which patient or lesion will be affected by restenosis, is poor.

A model that could predict which of the dilated lesions will re-narrow would be of value in many ways. 1) It could help to identify patients and lesions at high risk for lumen re-narrowing during the first 6 months. Such patients could then be offered another interventional technique or alternatively could be invited to participate in clinical trials of new pharmacological agents since they are at high risk. Their selection could potentially reduce the number of patients required in a study to evaluate new treatment. 2) It could provide more insight into the restenosis phenomenon by the identification of particular variables. 3) It might be helpful in the evaluation of new interventional devices.

The MERCATOR trial was set up to study the efficacy of a new angiotensin converting enzyme inhibitor, cilazapril, in the prevention of lumen re-narrowing after successful coronary angioplasty. All patients were asked to have a follow-up angiogram 6 months later or earlier if symptoms warranted. As an ancillary study, patient - lesion - procedural factors were prospectively collected to determine which, if any, were predictive for lumen re-narrowing at follow-up.

Table 1 *Summary of studies using multivariate analysis techniques to find variables with increased risk for restenosis.*

	Pts	Angio fup (%)	Definition restenosis	Restenosis (%)	Risk factors Patient	Lesion	Procedural
Holmes[1]	665	84%	NHLBI I or IV	34% pts	male severity angina no history of MI	bypass graft	-
Mata[2*1]	63	96%	↑ DS > 30% or DS > 70%	23% lesion	-	LAD or LCX > RCA % DS post-PTCA (40% vs 20%) calcified lesion	bar (0.9 vs 1.1)
Leimgruber[3]	1758	57%	> 50% DS	30% pts	unstable angina	LAD ↑ %DS post-PTCA gradient >15 mmhg	absence of intimal dissection
Myler[4*2]	286	57%	> 50% DS	57% pts 43% lesion	diabetes hypercholesterolaemie new onset angina current smoking	> 95% DS pre-PTCA	↑ max pressure
Guiteras Val[5]	181	98%	↑ ≥30% DS	28% pts 25% lesion	variant angina multivessel	↑ % DS post-PTCA low %DS Pre - Post	-
Vandormael[6*2]	209	62%	> 50% DS	50% pts	male diabetes	prox LAD longer lesions	-
de Feyter[7*4]	179	88%	> 50% DS	32% pts	worsening AP or post-MI AP	-	-
Fleck[8]	110	86%	MLCA > 1mm^2	44% lesions	-	-	-
Halon[9*4]	84	56%	> 70% DS	25%	-	multiple irregularities decrease coronary perfusion	-
Quigley[10*3]	114	88%	> 50% DS	32% pts	unstable angina hypertension diabetes	-	-
Renkin[11]	278	47%[*6]	> 50% DS	-	-	MLD post-PTCA	-
Rupprecht[12]	676	70%	> 50% DS or loss > 50% of gain	29% pts	unstable angina	↑ %DS pre-PTCA ↑ %DS post-PTCA	long single inflation
Bourassa[13]	376	66%	>50% DS + 10% ↑ post - fup	36% pts 35% lesion	severity angina	length > 10 mm % DS post-PTCA	-
Hirshfeld[14+15]	694	74%	≥50% DS	40% lesion	-	length > 10 mm vein graft LAD % DS pre-PTCA % DS post-PTCA	optimal BAR (1.1 - 1.

**1) multivessel; *2) multilesion; *3) restenosis; *4) unstable angina; *5) = patients with clinical recurrence; *6) = angiography + exercise thallium scintigraphy. Angio fup = % of successfully dilated patients with angio follow-up; AP = angina pectoris; bar = balloon artery ratio; DS = Diameter Stenosi*

METHODS

The study population consisted of 735 patients who were originally enrolled in 26 centers for the MERCATOR trial (Appendix I). The trial was carried out according to the declaration of Helsinki (1963), revised in Venice (1983). In this randomized double-blind placebo-controlled trial, cilazapril was investigated for its ability to prevent restenosis after primary coronary angioplasty. The results of the comparison between cilazapril and placebo have been reported elsewhere (48). All symptomatic and asymptomatic patients, aged 25 to 75 excluding women with childbearing potential, who had angiographically proven significant narrowing in one or more major coronary arteries and who signed informed consent before the PTCA-procedure, were considered to be eligible. Exclusion criteria were: PTCA performed to revascularize acute myocardial infarction, history of sustained hypertension, maintenance therapy of diuretics, Q-wave myocardial infarction before 4 weeks of study entry, previous and or failed PTCA at the same site, PTCA of a bypass graft.

Informed consent was obtained in 735 recruited patients before the PTCA procedure and were randomly assigned to cilazapril or placebo, but only 693 patients with a successful PTCA (defined as a visually assessed diameter stenosis of less than 50% post-PTCA) who met all in and exclusion criteria as stated in the protocol and formed the study population (figure 1). Clinical or angiographic benefit could not be demonstrated, so that the placebo and active treatment group could be pooled for the present study (48). Of the 693 randomized patients, 653 (or 94%) had a follow-up angiogram suitable for quantitative analysis and this forms the study population (fig 1).

TOTAL PATIENT 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		7
No follow-up quantitative coronary analysis possible		3
PATIENTS WITH FOLLOW-UP ANGIOGRAM	653	

Figure 1 *Patient flow chart.*

PTCA procedure and angiographic analysis At the beginning of the procedure all patients received a bolus of 10,000 IU intravenous heparin. After two hours, an additional infusion of 5,000 IU/hour was given until the end of the procedure. Use of a calcium channel blocker for 48 hours post-PTCA was permitted. Aspirin 160 to 250 mg per day was given for six months to all patients (56,57). Choice of guiding catheter, guide-wire, balloon type, inflation duration and pressure were left to the discretion of the operator.

Three angiograms were obtained in each patient, just before PTCA, immediately after PTCA and at follow-up. To standardize the method of data acquisition and to ensure exact reproducibility of PTCA and follow-up angiograms, specific precautions were taken as described elsewhere (16,41,44,47). To avoid potential coronary spasm, either nitroglycerin 0.1-0.3 mg or isosorbide dinitrate 1-3 mg, was given intracoronary for each coronary artery involved at pre-PTCA, post-PTCA 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. All cine-angiograms were quantitatively analyzed using the coronary angiography analysis system (CAAS), which has been validated and described in detail (41,44). All angiograms were processed and analyzed in a central core-laboratory. An example of an analysis is shown in figure 2.

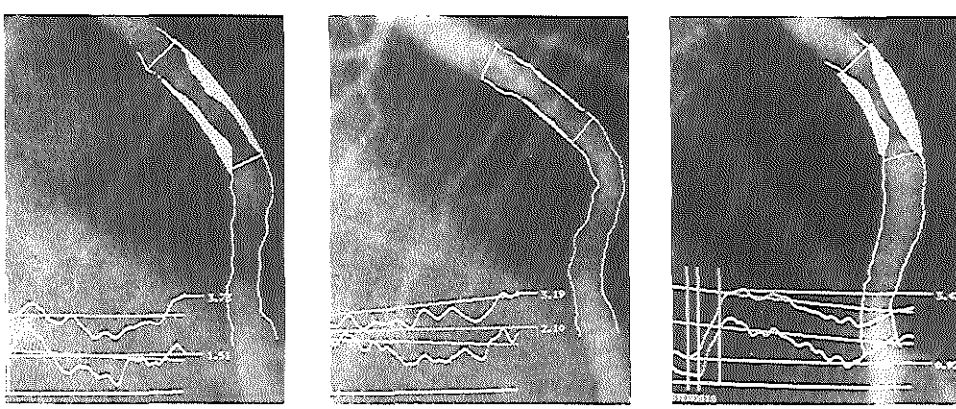

Figure 2 *A single frame of a narrowing in the LCx marginal branch before dilatation (A), after dilatation (B) and at follow-up (C). The diameter along the analyzed segment is depicted on the diameter function curve (upper curve). The MLD is 1.51 mm (A), 2.10 mm (B) and 0.92 mm (C) respectively. The length of the stenosis is determined with curvature analysis. The white area represents the atherosclerotic plaque.*

The follow-up coronary angiogram was performed at six months follow-up. If symptoms recurred within six months, coronary angiography was carried out earlier. If no definite restenosis was present and no revascularization procedure was performed and the follow-up time was less than 3 months, the patient was asked to undergo another coronary arteriogram at 6 months.

The absolute values of the stenosis diameter as well as the reference diameter are measured by the computer using the known contrast-empty catheter diameter as a scaling device. For that purpose the catheter tips were retained for accurate measurement with a micrometer. Since the algorithm is not able to measure total occlusions and lesions with TIMI-1 perfusion, a value of 0 mm was substituted for the minimal lumen diameter and 100% for the percent diameter stenosis. In these cases the post-PTCA reference diameter was substituted for the reference diameter pre-PTCA or at follow up. For each dilated segment, the pre-PTCA, the post-PTCA and follow-up minimal lumen diameter and diameter stenosis were derived from the mean value from multiple matched projections (41,44,47).

Patient, lesion and procedural risk factors The loss in minimal lumen diameter that occurred after angioplasty until follow-up angiography, per lesion dilated, was assessed for patient, lesion and procedural risk factors, prospectively recorded in each participating center. Some of the lesional factors (type of lesion, branch involved in stenosis, lesion located in bend, calcification of lesion, thrombus post-PTCA, dissection post-PTCA) were assessed by the core laboratory blinded for the code and clinical data. For each categorical variable, the change in minimal lumen diameter between post-PTCA and follow-up was determined in each category. Continuous variables were grouped into three equally sized subgroups (tertiles) and the loss in minimal lumen diameter between post-PTCA and follow-up was assessed in each tertile.

Patient-related factors are systemically present and therefore affect all dilated lesions: 1) age, 2) gender, 3) non-insulin dependent diabetes, 4) previous myocardial infarction, 5) history of smoking, 6) smoking at entry of the study, 7) extent of coronary atherosclerotic disease (single or multivessel), 8) number of sites dilated (1 or > 1), 9) angina CCS-class (0,1,2 versus 3,4), 10) pain at rest (yes or no), 11) unstable angina (defined as pain at rest requiring treatment with intravenous nitrates), 12) duration of angina (days), 13) medication taken and 14) cholesterol level at baseline (58).

Lesion-related factors are unique for each lesion: 1+2) minimal lumen diameter before and after PTCA, 3) relative gain (difference between the minimal lumen diameter before and after angioplasty, normalized for the vessel size), 4+5) % diameter stenosis

before and after PTCA, 6) vessel size, 7) lesion length (determined from the diameter function on basis of curvature analysis), 8) atherosclerotic plaque area before PTCA (defined as the area between the actual and reconstructed contours at the obstruction site), 9) eccentricity of the lesion before PTCA (symmetry index: defined as the coefficient of the left hand distance between the reconstructed interpolated reference diameter and actual vessel contours and the right hand distance between reconstructed and actual contours at the site of obstruction. In this equation the largest distance between actual and reconstructed contours becomes the denominator. A symmetrical lesion has a value of 1 and a severely eccentric lesion has a value of 0.), 10) curvature (bending) of the analyzed segment before PTCA (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 in the projection in which the analyzed segment appeared longest between 2 defined landmarks, the least foreshortened view), 11) patency of the vessel before PTCA, 12) vessel dilated (right coronary artery versus left anterior descending versus left circumflex), 13) location of lesion dilated in the vessel (proximal versus middle versus distal), 14) qualitative assessment of lesion morphology: a) type of lesion, b) involvement of side branch in lesion, c) balloon for dilatation located at a bend, d) calcification of lesion, e) dissection after PTCA, f) thrombus after PTCA (59,60,61,62).

Procedural-related factors are unique for each lesion: 1) minimal balloon diameter of the largest balloon with the highest pressure used, 2) balloon material used (compliant (PolyVinylChloride, PolyEthelyne, PolyOlefin Copolymer) versus non-compliant (PolyEthelyne Terphelate and Hydracross)), 3+4) balloon - artery ratio (size of the inflated balloon at highest pressure used (either measured or according size of manufacturer) divided by reference diameter of the analyzed vessel), 5) stretch (difference between minimal balloon diameter and minimal lumen diameter pre-PTCA, normalized for the reference diameter), 6) elastic recoil (difference between minimal balloon diameter and minimal lumen diameter post-PTCA, normalized for the reference diameter), 7) maximal balloon inflation pressure (atm), 8) total inflation duration (sec), 9) total number of inflations (63-65).

Statistical methods Statistical analysis was carried out with a commercial statistical package (BMDP Statistical Software 1990). Data are presented as mean ± 1 standard deviation. In univariate analysis, continuous variables were divided in 3 subgroups and compared with analysis of variance. Categorical or discrete variables were compared with the student t-test.

To obtain independent predictors for the loss in lumen diameter per lesion dilated, variables were entered in a stepwise multiple linear regression analysis in which the loss in lumen diameter between post-PTCA and follow-up was the independent variable. Stepwise multiple linear regression analysis was performed to assess the relationship between the variables mentioned in the "patients and methods" section (independent variables = X_i) and the loss in minimal lumen diameter from after angioplasty to follow-up angiogram (dependent variable = Y): $Y = \beta_0 + \beta_i x_i$ where β_0 is the intercept and β_i is th i^{th} regression coefficient. The standard BMDP criteria of F > 4 for inclusion and F < 3.9 for elimination were applied. Continuous variables were entered as such in the multivariate analysis, except variables with 2 of 3 tertiles showing approximately the same amount of loss in lumen diameter. These were entered as discrete variables (duration of angina, balloon-artery ratio, maximal balloon inflation pressure, total inflation time) (66). The code (placebo or cilazapril) of the treatment was forced into the model to rule out any influence of the investigational drug.

To determine how well the regression model performs in predicting restenosis according to 2 frequently applied restenosis criteria (1) $\geq$0.72 mm change in minimal lumen diameter between post-PTCA and follow-up (16,44,49), 2) > 50% diameter stenosis at follow-up and to describe the discrepancies of the 2 criteria, receiver operator characteristics (ROC) curves were constructed for each criterion. In these ROC curves sensitivity (true positive %) at different cut off points of predicted change in minimal lumen diameter is graphed as a function of 100% - specificity (false positive %).

RESULTS

Of the 693 randomized patients, 653 (94%) with 778 lesions (1.2 lesion / patient) had a follow-up angiogram suitable for quantitative analysis. The mean age was 58 ± 8 years and 82% of the patients were males. The average follow-up time was 164 ± 44 days. More than 62% of the patients had 1 vessel disease, 31% two vessel disease and only 6% had three vessel disease. There was an increase in overall minimal lumen diameter from 1.02 ± 0.38 mm before PTCA to 1.78 ± 0.36 mm post-PTCA and with subsequent decrease to 1.51 ± 0.57 mm at follow-up. Using categorical criterion, restenosis rate was 30% according to the > 50% diameter stenosis criterion and 18% if the criterion of $\geq$0.72 mm loss in lumen diameter at follow-up was used.

Variables predicitve for change in minimal lumen diameter during follow-up (table 2)

Patient related variables Statistically significant association was detected for 2 patient-related variables and loss in minimal lumen diameter between post-PTCA and

follow-up. A greater loss in minimal lumen diameter was observed in association with the number of sites dilated and duration of the angina, with a greater loss in minimal lumen diameter if only 1 site is dilated and if symptoms are of recent origin (Table 2A).

Lesion-related variables Statistically significant association was detected for 8 pre- or post-PTCA variables and loss in minimal lumen diameter between post-PTCA and follow-up. A greater loss in minimal lumen diameter was observed in association with A) *pre-procedural variables*: 1) lower values of minimal lumen diameter, 2) higher values of diameter stenosis, 3) occluded vessel, 4) lesions in left anterior descending artery, 5) calcified lesion and B) *post-procedural variables* 1) higher values for minimal lumen diameter after PTCA, 2) lower values for diameter stenosis after PTCA, 3) higher ratio of relative gain (Table 2B).

Procedural-related variables Statistically significant association was detected for 2 lesion-related variables and loss in minimal lumen diameter between post-PTCA and follow-up. A greater loss in minimal lumen diameter was observed in association with the total inflation time and stretch, with a greater loss in minimal lumen diameter with longer total inflation time and with more stretch (Table 2C).

Table 2: *Change in MLD per lesion*

Variable	#	Change in MLD (mm) (post-PTCA - Fup)	P-value
PATIENT RELATED VARIABLES			
Age (years)			
< 55	(n=256)	0.30 ± 0.58	
55 - 62	(n=263)	0.25 ± 0.50	0.5
> 62	(n=259)	0.26 ± 0.48	
Sex			
male	(n=649)	0.28 ± 0.53	0.21
female	(n=129)	0.22 ± 0.48	
Diabetes type II			
yes	(n=45)	0.32 ± 0.48	0.52
no	(n=733)	0.27 ± 0.52	

Table 2 *continued*

Variable	#	Change in MLD (mm) (post-PTCA - Fup)	P-value
History of Myocardial Infarction			
yes	(n=328)	0.28 ± 0.54	0.70
no	(n=450)	0.26 ± 0.50	
Ever smoked			
yes	(n=603)	0.25 ± 0.49	0.08
no	(n=175)	0.33 ± 0.59	
Currently smoking			
yes	(n=127)	0.21 ± 0.53	0.16
no	(n=651)	0.28 ± 0.51	
Extent of coronary artery disease (CAD)[1]			
single vessel	(n=424)	0.30 ± 0.51	0.11
multi vessel	(n=316)	0.23 ± 0.54	
Number of sites dilated			
1	(n=536)	0.30 ± 0.52	0.02
> 1	(n=242)	0.20 ± 0.50	
CCS-class at baseline[*]			
I,II	(n=441)	0.26 ± 0.52	0.68
III, IV	(n=365)	0.28 ± 0.51	
Pain at rest			
yes	(n=260)	0.29 ± 0.51	0.46
no	(n=518)	0.26 ± 0.52	
"Unstable angina"			
yes	(n=72)	0.29 ± 0.49	0.72
no	(n=706)	0.27 ± 0.52	

Table 2 *continued*

Variable	#	Change in MLD (mm) (post-PTCA - Fup)	P-value
Duration of angina (days)[2]			
< 86	(n=252)	0.33 ± 0.55	
86 - 305	(n=258)	0.29 ± 0.52	0.01
> 305	(n=256)	0.19 ± 0.48	
Medication			
none	(n=39)	0.34 ± 0.62	
mono	(n=195)	0.25 ± 0.53	
double	(n=369)	0.29 ± 0.52	0.34
triple	(n=175)	0.22 ± 0.47	
Total Cholesterol (mmol/l)[3]			
< 5.7	(n=239)	0.26 ± 0.53	
5.7 - 6.6	(n=254)	0.26 ± 0.51	0.97
> 6.6	(n=245)	0.25 ± 0.51	
LESION-RELATED VARIABLES			
MLD pre-PTCA (mm)			
< 0.92	(n=260)	0.36 ± 0.55	
0.92- 1.14	(n=258)	0.27 ± 0.51	0.0001
> 1.14	(n=260)	0.17 ± 0.47	
MLD post-PTCA (mm)			
< 1.60	(n=256)	0.16 ± 0.49	
1.60 - 1.90	(n=263)	0.25 ± 0.47	0.0001
> 1.90	(n=259)	0.40 ± 0.57	
Relative Gain at PTCA			
< 0.22	(n=258)	0.09 ± 0.43	
0.22 - 0.33	(n=259)	0.20 ± 0.48	0.0001
> 0.33	(n=261)	0.51 ± 0.55	

Table 2 *continued*

Variable	#	Change in MLD (mm) (post-PTCA - Fup)	P-value
% Diameter Stenosis pre-PTCA			
< 55	(n=252)	0.19 ± 0.45	
55 - 64	(n=276)	0.24 ± 0.48	0.0001
> 64	(n=250)	0.38 ± 0.61	
% Diameter Stenosis post-PTCA			
< 29	(n=258)	0.40 ± 0.50	
29 - 37	(n=258)	0.29 ± 0.48	0.0001
> 37	(n=262)	0.12 ± 0.54	
Vessel size (mm)			
< 2.35	(n=247)	0.26 ± 0.45	
2.35 - 2.80	(n=262)	0.30 ± 0.54	0.59
> 2.80	(n=269)	0.25 ± 0.56	
Length obstruction pre-PTCA (mm)[4]			
< 5	(n=241)	0.27 ± 0.47	
5 - 6.7	(n=243)	0.22 ± 0.48	0.41
> 6.7	(n=243)	0.26 ± 0.55	
Atherosclerotic area plaque pre-PTCA (mm^2)[4]			
< 4.7	(n=240)	0.24 ± 0.46	
4.7 - 7.3	(n=244)	0.23 ± 0.45	0.57
> 7.3	(n=243)	0.28 ± 0.58	
Symmetry index[4]			
< 0.24	(n=232)	0.22 ± 0.46	
0.24 - 0.45	(n=250)	0.26 ± 0.50	0.55
> 0.45	(n=245)	0.27 ± 0.53	

Table 2 *continued*

Variable	#	Change in MLD (mm) (post-PTCA - Fup)	P-value
Curvature analyzed segment[4]			
< 14	(n=234)	0.22 ± 0.45	
14 - 22	(n=235)	0.21 ± 0.43	0.66
> 22	(n=235)	0.19 ± 0.45	
Patency pre-PTCA			
total occlusion	(n=51)	0.54 ± 0.68	0.0001
patent	(n=727)	0.25 ± 0.50	
Vessel Dilated			
RCA	(n=222)	0.21 ± 0.59	
LAD	(n=360)	0.32 ± 0.49	0.05
LCx	(n=196)	0.24 ± 0.47	
Location of Vessel Dilated			
Proximal	(n=292)	0.27 ± 0.51	
Middle	(n=339)	0.28 ± 0.53	0.95
Distal	(n=147)	0.26 ± 0.52	
Qualitative lesion morphology assessment [4]			
Type Lesion			
concentric	(n=352)	0.23 ± 0.47	
eccentric	(n=295)	0.27 ± 0.54	
tandem	(n=38)	0.17 ± 0.43	0.42
multiple irregularities	(n=41)	0.31 ± 0.51	
Side Branch in stenosis			
yes	(n=413)	0.27 ± 0.51	0.94
no	(n=364)	0.27 ± 0.53	
Lesion located at bend point			
yes	(n=65)	0.24 ± 0.54	0.67
no	(n=713)	0.27 ± 0.52	

Table 2 *continued*

Variable	#	Change in MLD (mm) (post-PTCA - Fup)	P-value
Calcified Lesion			
yes	(n=80)	0.16 ± 0.47	0.04
no	(n=698)	0.28 ± 0.52	
Dissection post-PTCA			
yes	(n=247)	0.28 ± 0.60	0.57
no	(n=531)	0.26 ± 0.48	
Thrombus post-PTCA			
yes	(n=29)	0.34 ± 0.73	0.48
no	(n=749)	0.27 ± 0.51	
PROCEDURE RELATED VARIABLES			
Minimal Balloon Diameter (mm)			
< 2.15	(n=209)	0.23 ± 0.46	
2.15 - 2.51	(n=213)	0.30 ± 0.50	0.22
> 2.51	(n=209)	0.30 ± 0.52	
Balloon material			
Non-compliance	(n=400)	0.29 ± 0.51	0.20
Compliance	(n=377)	0.24 ± 0.53	
Balloon - artery ratio [5]			
< 0.98	(n=169)	0.22 ± 0.49	
0.98 - 1.11	(n=245)	0.30 ± 0.56	0.24
> 1.11	(n=217)	0.30 ± 0.49	
Balloon - artery ratio [6]			
< 1.05	(n=259)	0.23 ± 0.53	
1.05 - 1.20	(n=264)	0.33 ± 0.53	0.07
> 1.20	(n=255)	0.25 ± 0.49	

Table 2 *continued*

Variable	#	Change in MLD (mm) (post-PTCA - Fup)	P-value
Stretch			
< 0.43	(n=209)	0.10 ± 0.41	
0.43 - 0.55	(n=209)	0.31 ± 0.49	0.0001
> 0.55	(n=213)	0.41 ± 0.58	
Elastic Recoil			
< 0.15	(n=209)	0.32 ± 0.51	
0.15 - 0.27	(n=209)	0.26 ± 0.51	0.26
> 0.27	(n=213)	0.25 ± 0.52	
Maximal balloon Inflation pressure (atm)			
< 7	(n=219)	0.20 ± 0.51	
7 - 9	(n=285)	0.29 ± 0.54	0.09
> 9	(n=274)	0.30 ± 0.50	
Total inflation times (sec)			
< 145	(n=245)	0.20 ± 0.49	
150 - 240	(n=285)	0.29 ± 0.52	0.05
> 240	(n=248)	0.31 ± 0.55	
Number of inflations			
1	(n=94)	0.24 ± 0.43	
2 - 4	(n=544)	0.27 ± 0.53	0.88
> 4	(n=140)	0.27 ± 0.53	

** CCS = Canadian Cardiovascular Society classification (58), [1] not assessed in 38 lesions, [2] not assessed for 12 lesions, [3] not assessed in 40 lesions. [4] = not available in 51 total occlusions before PTCA [5] : measured balloon diameter in 621 lesions; [6] : balloon size according manufacturer*

Multiple linear regression analysis The stepwise multiple linear regression analysis showed that 1) relative gain, 2) minimal lumen diameter post-PTCA, and 3) dilatation of another vessel than right coronary artery were independently predictive for lumen narrowing at follow-up. Trial medication, which was forced into the model, had only a very small statistically insignificant contribution to the fit of the model (table 3).

To assess the value of the model at predicting the degree of lumen narrowing at follow-up, the percentage of correctly classified lesions was calculated for 5 intervals of predicted change in lumen diameter. Correct prediction by the model was poor, especially in the lower range. On average only 30% of lesions were correctly classified. On the other hand, lesions that showed moderate or more sever change were more predictable, although the percentage is still low (table 4). The information content of the model according to the ROC curves was best for $\geq$0.72 mm cut-off criterion (figure 3). These findings underscore the very poor predictability of lumen renarrowing after balloon coronary angioplasty and explains the discrepancies between the 2 restenosis criteria with > 0.72 mm decrease in minimal lumen diameter as an "active criterion" and the 50% diameter stenosis as a "static criterion".

Table 3 *Multivariate linear regression model for the prediction of change in MLD.*

	Coefficient	SE	F to remove
Intercept	-0.33		
Allocation to cilazapril	-0.04	0.04	1.73
Relative gain at PTCA	0.95	0.12	65.73
MLD after angioplasty	0.21	0.05	14.95
Vessel dilated (RCA vs LAD+LC)	-0.11	0.04	7.80

LAD = left anterior descending, LCx= left circumflex artery, MLD = minimal lumen diameter, PTCA = percutaneous transluminal coronary angioplasty, RCA = right coronary artery

Table 4 *Percentages of correct classification*

Interval of predicted change in MLD	Percent correct classification	
< 0.1 mm	91 / 300	30%
0.1 to 0.2 mm	20 / 82	24%
0.2 to 0.3 mm	19 / 72	26%
0.3 to 0.4 mm	7 / 64	11%
≥ 0.4 mm	97 / 260	37%

MLD = minimal lumen diameter

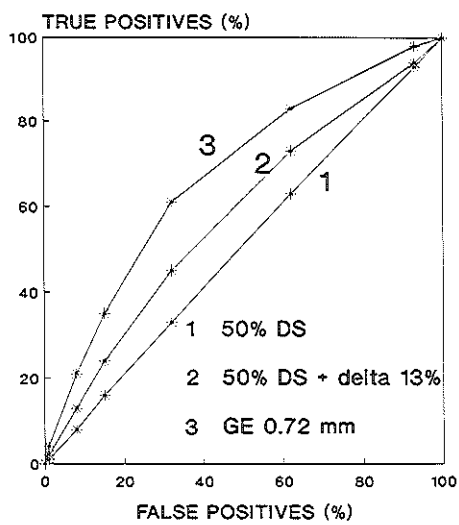

Figure 3 *Receiver operator curves for comparison of restenosis criteria at different cut-off points of predicted change in lumen diameter. The diagonal line is the line of identity or line of "no prognostic value". ROC curves on the line of identity have no prognostic value, those in the left upper corner are most informative. Solid curve: 0.72 mm criterion, normal curve 50% diameter stenosis criterion with a change in diameter stenosis at follow-up of at least 13%, dotted curve: 50% diameter stenosis criterion.*

DISCUSSION

Many different patient-procedural-lesion related variables have been proposed as being predictive of restenosis (table 1), with little agreement between the various studies. This may be due to deficiencies in their methodology relating to important

areas: (1) patient selection, 2) method of analysis 3) definition of restenosis (45). Most of the early studies were retrospective analyses of a small number of (symptomatic) patients not recatheterized at a predetermined time and used different arbitrary categorical definitions of restenosis.

ad 1,2) In the present trial, 94% of all randomized patients had follow-up angiography and thereby eliminating the bias in the assessment of the true change in lumen diameter of the dilated lesion at follow-up if only symptomatic patients would have follow-up angiography. All baseline and follow-up films were processed and analyzed at the same angiographic core laboratory using an automated interpolated edge detection technique (CAAS), which has been extensively validated and described in the literature, thereby reducing the inter and intra observer variability inherent to visual interpretation of coronary angiograms (41-44).

ad 3) Recently 2 published ancillary studies of restenosis prevention trials prospectively collected patient, procedural and lesional factors to determine which of these factors were predictive for restenosis. They identified different factors as predictive of restenosis despite using the same restenosis criterion (diameter stenosis > 50% at follow-up) (13-15). The criterion of a diameter stenosis > 50% at follow-up is the most frequently used, although of historical relevance (67), it does not differentiate between a suboptimal result immediately after PTCA and a minor deterioration at follow-up. For example: an increase in diameter stenosis of 35% from 10% post-PTCA to 45% at follow-up is not classified as restenosis, whereas an increase of only 6% from 45% post-PTCA to 51% at follow-up is. If distinction is to be identified between restenosis and a suboptimal result, one could add that a change of 13% in diameter stenosis between post-PTCA and follow-up should be present, as this reflects the long-term variability of the measurements. As restenosis is a continuous intralumen growth process - that can be measured by quantitative techniques in large scale populations - absolute change in MLD (or loss at follow-up) was chosen as the dependent factor for the assessment of risk factors for regrowth of the lesion (68). Although potentially useful because of the ability to compare vessels of different sizes, the change in MLD between post-PTCA and follow-up normalized for the reference diameter (relative loss) was not used in this analysis, as the relative loss is not independent from the vessel size (fig 4A). As loss in minimal lumen diameter during follow-up seems to be independent of the vessel size (fig 4B) this was chosen (69,70).

Predictors for lumen renarrowing during follow-up

Patient related factors Patients undergoing PTCA for recent onset angina exhibited greater mean loss in minimal lumen diameter during follow-up. Perhaps this is related to the tendency of lesions associated with new onset angina to be biologically more

active ("softer") and more compliant and therefore more amenable to the dilating forces of the balloon. Consequently, a better initial result is obtained with a greater " relative gain". Long presence of stable angina pectoris is associated with more calcification in the lesion and therefore less gain in minimal diameter can be achieved. Beside that less cells that can growth are present and therefore less intimal hyperplasia is presumably seen.

Patients with more than 1 site dilated during the same procedure has less mean loss in minimal lumen diameter during follow-up. A possible explanation could be that in addition to the culprit lesion, a less severe lesion is dilated, as it is not always clear which lesion is causing the anginal symptoms. As this results in an average minimal lumen diameter before dilatation that is higher and an average gain that is lower, the subsequent average loss will be lower.

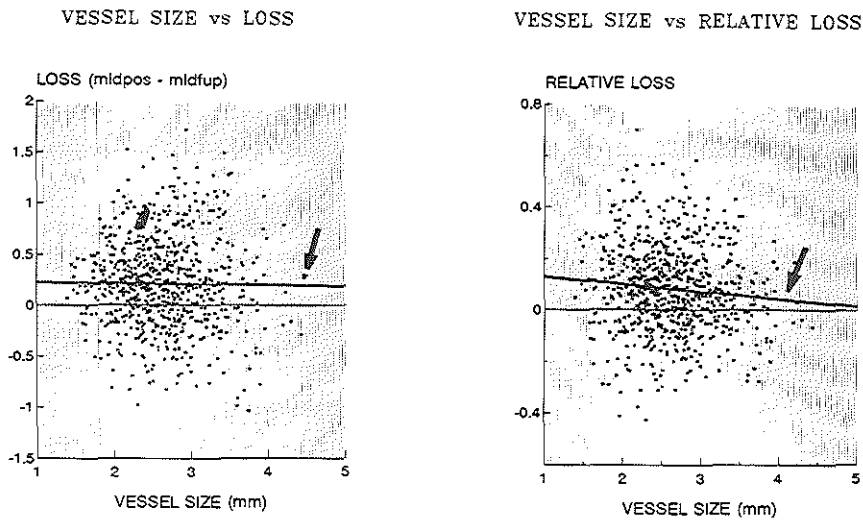

Figure 4 *Scatter plot, with on the X-axis the vessel size, and on the Y-axis the loss (A) defined as the change in minimal luminal diameter between post-PTCA and follow-up, and relative loss (B) defined as the change in minimal luminal diameter between post-PTCA and follow-up normalized for the vessel size. The arrow indicates the regression line.*

Lesion related factors The one factor most strongly associated with lumen renarrowing after angioplasty was "relative gain" achieved by the angioplasty

procedure. This is the ultimate paradox of treatment with coronary balloon angioplasty; the greater the initial "relative gain", the greater the subsequent loss. The final result or "relative gain" of an angioplasty procedure is the combination of permanent plastic and reversible elastic changes i.e. a combination of deep arterial injury and reversible stretch imposed on the diseased vessel wall. The more severe the stenosis is, the more deep arterial damage will occur, resulting in a more aggressive repair process. This phenomenon has been observed in animal models of arterial injury and is a perfectly logical consequence of the healing process (24,25,26).

In univariate analysis the separate variables were also highly significant: minimal lumen diameter before and after PTCA, diameter stenosis before and after PTCA, and the presence of totally occluded vessels, but only minimal lumen diameter post-PTCA, beside relative gain, was retained in the multivariate linear regression model.

High values of post-PTCA diameter stenosis has been reported to be associated with higher restenosis rates (table 1), although confusion could be caused by suboptimal dilatation (i.e. 49% diameter stenosis) in which case only a small loss (i.e. 2% increase in diameter stenosis) is required to exceed this categorical cut-off point of 50%. However, in our study *low* values of diameter stenosis post-PTCA is associated with more loss.

Totally occluded vessels have been reported to be associated with higher restenosis rates using "traditional" restenosis criteria (70,71), but was not retained as a separate factor in our analysis. This is due to the fact that total occlusions are part of the continuous variables minimal lumen diameter whcich is by means of the relative gain the most important predictor.

There has been many conflicting studies whether the vessel dilated is a risk factor for restenosis (table 1). In present study, univariate analysis shows a greater loss in minimal lumen diameter in the left anterior descending artery as compared to the right coronary or left circumflex artery (table 2B). In stepwise linear regression analysis, dilatation of another vessel than the right coronary artery consistuted an independent riskfactor predictive for loss. This is somewhat surprising, as recently our group has found no statistical significant difference in loss between the 3 major coronary arteries in 1452 dilated lesions, although a trend towards more (relative) loss in left anterior descending artery was observed (47,48,72). Those 1452 lesions were derived from two identical executed restenosis prevention trials using a similar methodologic approach. The observed loss in lumen diameter for respectively the CARPORT and MERCATOR trial were: 0.34 ± 0.63 and 0.21 ± 0.59 for RCA (vessel size 2.85 mm), 0.27 ± 0.46 and 0.32 ± 0.49 for LAD (vessel size 2.53 mm) and 0.28 ± 0.55 and 0.24 ± 0.47 for the LCX (vessel size 2.53 mm). Although similar loss during follow-up was observed for the LAD and LCX, the loss in the RCA was low in the MERCATOR trial and high in the CARPORT trial. We have no explanation for this contradictory

observation. In addition, the coefficient is 0.11, which means that 0.11 mm of what is lost can be explained by dilatation of the vessel and therefore is of limited value for the prediction of loss in the individual patient.

Calcified lesions are associated with less loss during follow-up. A possible explanation is that in these lesions less gain is achieved, as calcified lesions are difficult to dilate successfully.

Procedural related factors Higher total inflation times was associated with more loss during follow-up. This reflects an initial poor result after 1 to 3 dilatations and consequently more extensive deep arterial injury with perhaps prolonged sub-intimal ischemia due to pressure occlusion of vasa vasorum. This has been the observation in animal experiments (74).

Stretch was found to be highly significant in univariate analysis, although it was not retained in the stepwise linear regression analysis, as stretch was reflected in the variable (relative) gain (75).

Limitations As this is an exploring data analysis, no adjustments were made for multiple statistical comparisons. Therefore, it is possible that some of the relationships found in this paper has reached significance by chance alone. The multivariate model was developed and tested in the same population. Generally the model will be less accurate if assessment of fit is carried out in a different population. However the poor fit of the model even if tested in the same population underscores the poor predictability of the restenosis proces.

Conclusion Prediction of lumen narrowing with prospectively collected patient, lesion and procedural factors was shown to be poor. Only 3 variables were found to be independent determinants of the loss in minimal lumen diameter of the dilated lesions. The most important factor is 1) relative gain achieved during coronary angioplasty, 2) minimal lumen diameter after angioplasty, and 3) dilatation of not the right coronary artery. This finding seems to be a paradox, as every dilatation is aimed to achieve an increase in minimal lumen diameter. However it seems that the more gain is achieved during coronary angioplasty, the more the lesion can and will lose.

Maybe a more meaningful parameter to use in future restenosis prevention trials or testing of new interventional devices could be the minimal lumen diameter at follow-up, as it is not important for the patient what is lost in diameter as to what is left over.

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APPENDIX I

EXPERIENCES OF A QUANTITATIVE CORONARY ANGIOGRAPHIC CORE LABORATORY IN RESTENOSIS PREVENTION TRIALS

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SUMMARY

Quantitative coronary angiography is increasingly being used as the method of analysis for defining the endpoint in restenosis prevention trials as it is more accurate and reproducible as compared to visual assessment. However, large variations in data acquisition and analyses are possible and they should be minimized. In this chapter our experiences in an angiographic core laboratory in four restenosis prevention trials with approaches toward standardized angiographic data acquisition and analysis procedure are presented.

INTRODUCTION

Since its introduction more than 14 years ago [1], percutaneous transluminal coronary angioplasty [PTCA] has been attended by a 17% to 40% incidence of restenosis, typically developing within 6 months of the procedure [2-5]. Each year the number of patients undergoing PTCA has increased and now approaches the number treated with coronary artery bypass grafting [CABG]. In the last 10 years, experimental models have given us more insight into the restenosis phenomenon and pharmacological agents have been developed aiming to prevent or reduce restenosis. Many of these "experimental agents have been investigated in clinical restenosis prevention trials [4-7] and although these agents were able to reduce restenosis in the animal model, most of the clinical trials failed to demonstrate a convincing reduction in the incidence of restenosis in man. In these clinical trials, the primary endpoint has been either angiographic [change in minimal luminal diameter at follow-up; > 50% diameter stenosis at follow-up; loss > 50% of the initial gain] and / or clinical (death, nonfatal myocardial infarction; coronary revascularization; recurrence of angina requiring medical therapy, exercise test, quality of life]. The use of an angiographic parameter as a primary endpoint provides the necessary objectively whereby the patient population required for statistical analysis numbers between 500 and 700, whereas more than 2,000 patients are necessary if a clinical endpoint is used [6].

Despite the widespread and long-standing use of coronary angiography in clinical practice, as well as the outstanding improvement in image acquisition, the interpretation of the angiogram has changed very little and is still reviewed visually. However, visual assessment is a subjective evaluation with a large inter- and intra observer variability and can therefore not be used in important scientific studies for example restenosis prevention trials [8-9]. Quantitative coronary angiography has the advantage of being more accurate and reproducible in the assessment of lesion severity, than visual or hand-held caliper assessments. At the Thoraxcenter, the computer-assisted Cardiovascular Angiography Analysis System (CAAS) using an automated edge detection technique was developed and validated [8,10]. A typical example of the quantitative analysis of a coronary obstruction is presented in Fig. 1.

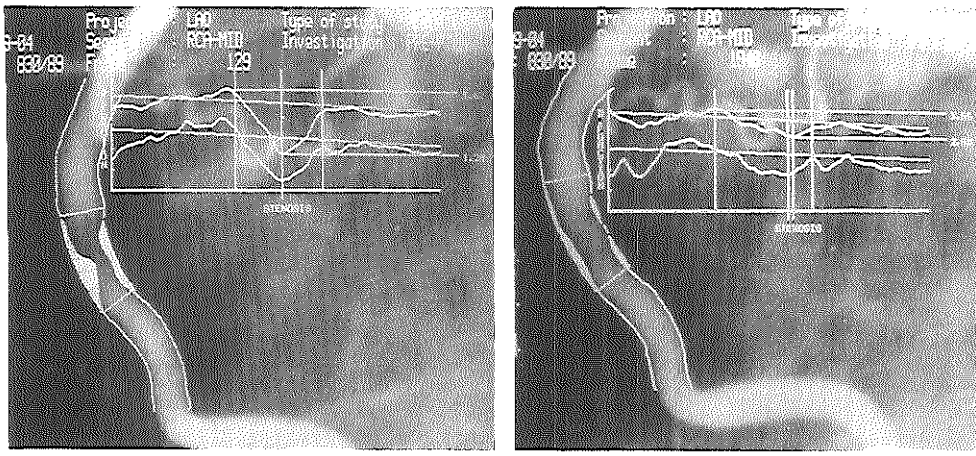

Figure 1 *Example of a quantitative analysis of a coronary obstruction of the mid portion of the right coronary artery: pre-PTCA (a), and post-PTCA (b). The upper curve represents the diameter along the analyzed segment, the lower curve represents the densitometric analysis along the analyzed segment. The minimal lumen diameter is 1.28 mm pre-PTCA (a), and 2.58 mm post-PTCA (b).*

Over the last 3 years, we have been the angiographic "core laboratory" (using the CAAS-system) in 4 restenosis prevention trials with recruitment of patients in Europe, United States and Canada (Table I). In order to obtain reliable and reproducible quantitative measurements over time from coronary (cine)-angiograms, variations in data acquisition and analyses must be minimized.

Table 1 *Angiographic Core Laboratory in 4 restenosis prevention trials (1988 - 1991)*

CARPORT	Coronary Artery Restenosis Prevention On Repeated Thromboxane antagonism. Intake and analysis complete, 707 patients, published: Circulation Oct 1991.
MERCATOR	Multicenter European Research trial with Cilazapril after Angioplasty to prevent Transluminal coronary Obstruction and Restenosis. Intake and analysis complete, 735 patients, publication pending.
MARCATOR	Multicenter American Research trial with Cilazapril after Angioplasty to prevent Transluminal coronary Obstruction and Restenosis. Intake complete, follow-up analysis pending, 1436 patients.
PARK	Post Angioplasty Restenosis Ketanserin trial. Intake complete, fup analysis pending, 703 patients.

In this chapter we present our experiences in the core laboratory with our approaches toward standardized angiographic data acquisition and analysis procedures as well as in qualitative or morphologic descriptions.

Table 2 *Potential problems with angiographic data acquisition and analysis*

1 Pincushion distortion of image intensifier
2 Differences in angles and height levels of X-ray system settings
3 Differences in vasomotor tone
4 Variation in quality of mixing of contrast agent with blood
5 Catheter used as scaling device (angiographic quality, influence of contrast in catheter tip on the calibration factor, size of catheter)
6 Deviations in size of catheter as listed by the manufacturer from its actual size
7 Variation in data analysis

1 Pincushion Distortion

Pincushion distortion of the image intensifier introduces a selective magnification of an object near the edges of the image as compared with its size in the center [Figure 2 A). An inaccuracy in the measurement of the minimal lumen diameter of the stenosis over time could be introduced if, for example, the stenosis after the angioplasty procedure is filmed in the center and at follow-up near the edges of the image intensifier. To overcome this potential problem, a cm grid has to be filmed in each mode of the image intensifier in all the catheterization rooms to be used before the clinic can start to recruit and randomize patients for a restenosis prevention trial. With this cm grid film, the CAAS system calculates a correction factor for each intersection position of the grid wires so that the pincushion distortion can be corrected for [Figure 2 B]. Fortunately, the newer generations of image intensifiers introduce significantly less distortion than the older ones from the early and mid 80's; the degree of distortion is even less when the lower magnification modes are used with multi-mode image intensifiers. At present time there are in our database pincushion correction factors of 557 different modes of magnification (82 clinics with 207 angiorooms) from all over Europe, United States and Canada.

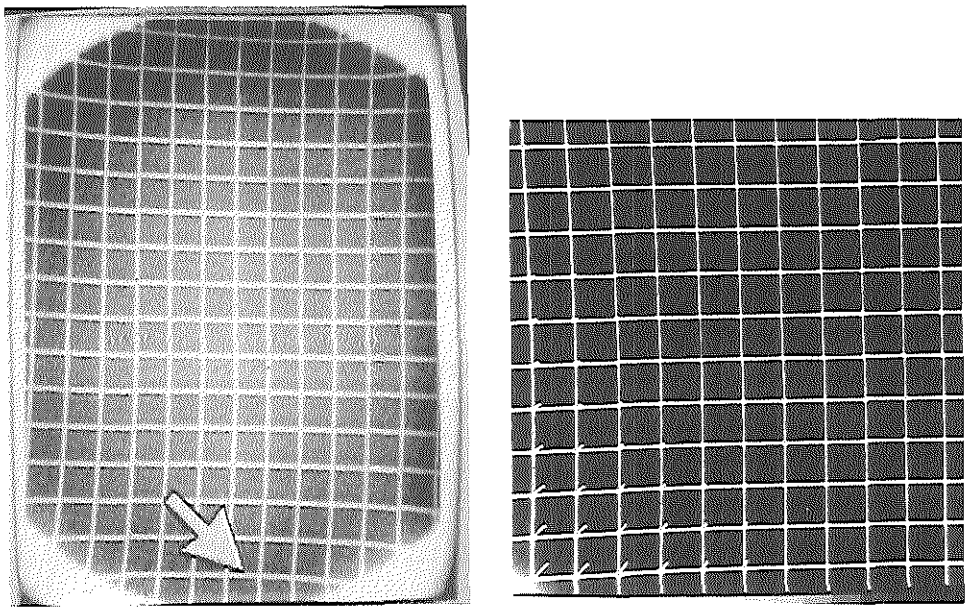

Figure 2 *Example of pincushion distortion introduced by the image intensifier (A, see arrow) and of the calculated correction factor with the use of the filmed cm-grid (b).*

2 Differences in angles and height levels of the X-ray gantry

As it is absolute mandatory to repeat exactly the same (baseline) views of the coronary segments in studies to evaluate changes in lumen diameter over time, we have developed at the Thoraxcenter an on-line registration system of the X-ray system parameters such as parameters describing the geometry of the X-ray gantry for a particular cine-film run (rotation of U-arm and object, as well as distances from isocenter to focus, table height) and also selected X-ray exposure factors (kV, mA). When repeat angiography is scheduled, the geometry of the X-ray system is set on the basis of the available data, so that approximately the same angiographic conditions are obtained. In a clinical study with repositioning of the X-ray system, it was found that the angular variability, defined by the standard deviation of the absolute differences of angular settings, was < 4.2 degrees and that the variability in the various positions of image intensifier and X-ray source was < 3.0 cm [8,11]. As on-line registration of the X-ray system settings is not available in all hospitals, we have developed a technician's worksheet that has to be completed during the PTCA procedure with detailed information of the procedure (view, catheter type, catheter size, balloon type, balloon size, balloon pressure, kV, mA, medication given) [fig III]. In this way minimization of

differences in X-ray settings at follow-up angiography is ensured. Furthermore, each center intending to participate in one of the trials is required to provide 2 sample cine-angiograms from each of its catheterization rooms for verification of their ability to comply to our standards.

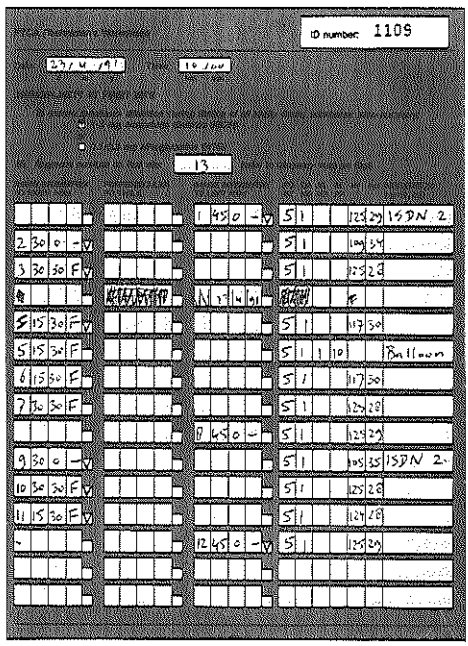

Figure 3 *Example of a page of the technician's worksheet*

3 Differences in vasomotor tone of the coronary arteries

As the vasomotor tone may differ widely during consecutive coronary angiographic studies, it should be controlled at all times. An optimal vasodilatative drug for controlling the vasomotor tone of the epicardial vessel should produce a quick and maximal response without influencing the hemodynamic state of the patient. Only nitrates and calcium antagonists satisfy these requirements. On isolated human coronary arteries calcium antagonists are more vasoactive but they act more slowly; in the in-vivo situation, however, the nitrates are more vasoactive than the calcium antagonists [12-15].

We have measured in 202 patients the mean diameter of a normal segment of a non-dilated vessel in a single view pre-PTCA, post-PTCA and at follow-up angiography 6 months later. In cases where a stenosis of the left anterior descending artery (LAD) had been dilated, a non-diseased segment in the left circumflex artery (LCx) was analyzed and vice versa; where dilatation of a stenosis in the right coronary artery

(RCA) was performed, a non-diseased segment proximal to the stenosis was used for analysis. All patients were given intracoronary (either 0.1 to 0.3 mg of nitroglycerin or 1 to 3 mg isosorbide dinitrate (ISDN)) before PTCA and before follow-up and all but 34 received similar dosage before the angiogram immediately after PTCA. Table 3 summarizes the results of the analyses; a decrease in mean diameter of -0.11 ± 0.27 (mm) was observed in the segments of patients studied without intracoronary nitrates post-PTCA, whereas a small increase was seen of +0.02 ± 0.21 (mm) in the group with intracoronary nitrates prior to post-PTCA angiography ($p < 0.001$). No difference in the mean diameter between pre-PTCA and follow-up angiography was measured.

In summary, the vasomotor tone should be controlled in quantitative coronary angiographic studies. This is only achieved by means of a vasodilator drug that produces fast and complete vasodilation without any peripheral effects. Therefore, we strongly advocate the use of 0.1 to 0.3 mg nitroglycerin or 1 to 3 mg of ISDN pre-PTCA, after the last balloon inflation before repeating the views used pre-PTCA and at follow-up angiography.

Table 3 *Influence of nitroglycerin on the mean diameter of non diseased segments in 202 patients in single projection*

Mean Diameter (mm)	Without Nitro Post-PTCA N = 34	With Nitro Post-PTCA N = 168	t-test
Pre-PTCA	3.12 ± 0.63	2.74 ± 0.63	
Post-PTCA	3.01 ± 0.64	2.75 ± 0.59	
Follow-up	3.18 ± 0.55	2.82 ± 0.63	
Delta (Post - Pre)	-0.11 ± 0.27	+0.02 ± 0.21	$p < 0.001$
Delta (Fup - Pre)	+0.06 ± 0.22	+0.07 ± 0.22	$p = ns$

4 Influence of contrast agent on vasomotor tone of epicardial coronary agents

Jost et al. have clearly demonstrated that the vasodilative changes in vessel dimensions due to contrast medium administration are significantly smaller with the use of a nonionic rather than ionic contrast medium [16]. Therefore, in quantitative coronary angiographic studies, nonionic contrast media with iso-osmolality should be applied.

It has been suggested to administer the contrast medium by an ECG triggered injection system. This is however not (yet) feasible during routine coronary angioplasty even in a setting of a clinical trial.

5. Catheter used as scaling device for measurements of absolute diameters

A Angiographic versus microcaliper measured size of catheter

The image quality of the (x-ray radiated) catheter is dependent on the catheter material, concentration of the contrast agent in the catheter and kilovoltages of the x-ray source. Reiber et al. in 1985 showed that there was a difference of +9.8% in angiographically measured size as compared with the true size for catheters made from nylon. Smaller differences were measured for catheters made from woven dacron (+0.2%), polyvinylchloride (-3.2%) and polyurethane (-3.5%) [17]. It was concluded that nylon catheters could not be used for quantitative studies.

B Influence of variation in contrast filling of the catheter on calibration

It was also demonstrated that catheters made from woven dacron, polyvinylchloride and polyurethane when flushed with saline had, identical image contrast qualities whereas differences in image contrast at various fillings (air, contrast with 3 different concentrations (Urografin-76, Schering AG, Berlin, Germany; 100% - 50% - 25%)) of the catheters acquired at different kilovoltages was seen [17].

In addition, we measured the calibration factor in 95 catheters from 15 different clinics to compare contrast with filled saline catheter. Figure 4 summarizes our results. In a considerable number of cases, a difference in calibration factor was present with an average calibration factor of 0.143 ± 0.020 (mm/pixel) for the flushed (contrast empty) catheter versus 0.156 ± 0.030 (mm/pel) for the catheters filled with contrast ($p < 0.001$). This means that with the use of a contrast filled catheter instead of a flushed catheter, the minimal luminal diameter will have an apparent increase in diameter value of ± 0.05 mm pre-PTCA, ± 0.15 mm post-PTCA and ± 0.20 mm for the reference diameter.

For this reason we strongly advise the clinics to flush the catheters before each cine-run to have an "identical flushed catheter" for calibration throughout the study period.

C Size of the catheter

Until recently only 7F and 8F catheters have been used for follow-up angiography and from earlier studies it is known which of the catheters are preferred for quantitative analysis [17,18]. However, 5F and 6F catheters are available and increasingly being used for follow-up angiography. Koning et al. have carried out a study to determine whether these catheters can be used for calibration purposes (Internal Report), (Table

4). They found that the differences between the true and angiographically measured diameters of the 5F and 6F catheters in all cases were lower for 6F than for the 5F catheters. Secondly, the Argon catheters showed the largest overall average difference, followed by the Edwards catheters and the 5F USCI catheter. The Cordis catheters, the 6F right Judkins Medicorp, the 6F Schneider and 6F USCI have the lowest average differences between the true and measured diameters. However, none of the catheters satisfy earlier established criteria [17], being that the average difference of the angiographically assessed and true diameter is lower than 3.5% and that the standard deviation of the measured diameters be smaller than 0.05 mm, under the following conditions: filled with 100% contrast concentration, filled with water, acquired at 60 kV and 90 kV. On the basis of these results, it was concluded that 5F or 6F catheters should not be used for QCA studies using the CAAS-system at the present time.

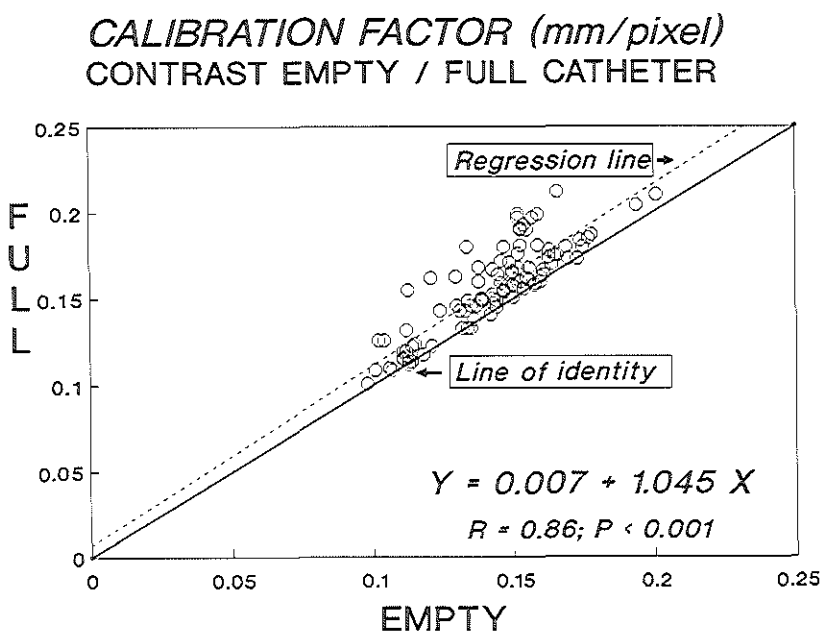

Figure 4 *Relationship between the calibration factor calculated using an contrast empty (flushed) catheter versus a contrast filled catheter. A considerable number of measurements with the contrast filled catheter are above the line of identity.*

Table 4 *Comparison of the true sizes of the 5F and 6F catheter segments with angiographically measured dimensions (measurements were averaged over the three different fillings (water, contrast medium concentrations of 185 and 370 mg I/cc), each at two different kilovoltages (60 and 90 kV).*

	TRUE SIZE (mm)	ANGIOGRAPHICALLY MEASURED SIZE (mm)	AVG DIF (%)
5F Catheters			
Argon	1.66	1.85 ± 0.09	11.3
Cordis	1.73	1.79 ± 0.15	3.2
Edwards	1.66	1.80 ± 0.08	8.5
Mallinckrodt	1.73	1.72 ± 0.14*	-0.8
Schneider	1.69	1.79 ± 0.07	6.1
USCI	1.61	1.75 ± 0.14	8.5
6F Catheters			
Argon	1.98	2.14 ± 0.07	8.1
Cordis	2.01	2.03 ± 0.11	1.1
Edwards	1.96	2.10 ± 0.07	7.1
Medicorp (left)	1.97	2.07 ± 0.04	5.1
Medicorp (right)	1.99	2.02 ± 0.10	1.6
Mallinckrodt	1.97	1.91 ± 0.15*	-2.9
Schneider	1.94	2.00 ± 0.09	3.0
USCI	1.99	2.06 ± 0.08	3.4

*Mean value ± standard deviation, * measurements of the Softouch tip will be more favorable*

6. Deviations in the size of the catheter as listed by the manufacturer

In our experience, the size of the catheter as specified by the manufacturer often deviates from its actual size, especially disposable catheters. If the manufacturer cannot guarantee narrow ranges for the true size of the catheter, all catheters should be measured by a micrometer. Therefore, all catheters used during the angioplasty procedure and at follow-up are collected, labelled and sent to the angiographic core laboratory for actual measurement.

As the actual measurement can be hampered by individual variation, we have evaluated the inter- and intraobserver variability of catheter measurements at the Core

Laboratory. A total of 96 catheters with different sizes (6F to 9F) were measured by 3 different analysts independent of each other. One month later, all three analysts measured the same catheters for a second time, unaware of the results from the first time (Table 5) . The intraobserver variability was excellent with a mean difference of less than 0.01 mm and a standard deviation of the difference of less than 0.03 mm for all catheter sizes. Similarly the interobserver variability between the 3 analysts showed a mean difference of less than 0.03 mm and a standard deviation depending on the size between 0.00 and 0.04 mm. We conclude that the catheter can be measured with an excellent accuracy and precision.

Table 5 *Intra- and inter-observer variability of 96 catheter diameter measurements with an electronic microcaliper*

INTRA-OBSERVER VARIABILITY

	n	Overall Mean	Mean of Diff	p-value	s.d of Diff
9F	30	2.75	0.008	NS	0.026
8F	114	2.56	0.009	NS	0.028
7F	132	2.25	0.001	NS	0.008
6F	12	1.94	-0.002	NS	0.006

INTER-OBSERVER VARIABILITY

	N	1 vs 2		1 vs 3		2 vs 3	
		Mean Diff	s.d. Diff	Mean Diff	s.d. Diff	Mean Diff	s.d Diff
9F	20	0.00	0.04	0.00	0.02	0.00	0.04
8F	76	0.00	0.03	0.00	0.02	0.00	0.03
7F	88	0.00	0.01	-0.01	0.02	0.00	0.02
6F	8	-0.02	0.03	-0.01	0.00	0.01	0.03

s.d = standard deviation; diff = difference

7. Variation in data analysis

Reference Diameter

Although the absolute minimal luminal diameter is one of the preferred parameters for describing changes in the severity of an obstruction as a result of an intervention, percent diameter stenosis is a convenient parameter to work with in individual cases. The conventional method of determining the percent diameter stenosis of a coronary obstruction requires the user to indicate a reference position. This selection of the reference diameter is hampered by observer variation. In arteries with a focal obstructive lesion and a clearly normal proximal arterial segment, the choice of the reference diameter is straightforward and simple. However in cases where the proximal part of the arterial segment shows combination of stenotic and ectatic areas, the choice may be difficult. To minimize these variations, the CAAS-system uses an interpolated or computer defined reference technique.

Length of Analyzed Segment

Anatomic landmarks such as bifurcations are used for the manual definition of start and end points of arterial segments so as to minimize the problem of non identical analyses. For that purpose, drawings are made by the investigator of all different views suitable for quantitative analysis, pre-PTCA, post-PTCA and at follow-up. In addition, a hard-copy is made of every drawing, to enable analysis of the exact same segments at follow-up angiography.

Frame Selection

Usually, an end-diastolic cineframe is selected for the quantitative analysis of a coronary obstruction to avoid blurring effect of motion. If the obstruction is not optimally visible in that particular frame (e.g. by overlap by another vessel) a neighboring frame in the sequence is selected. However, since a marker is not always present on the cine-film, the visually selected cine-frame may not be truly end-diastolic. Beside that, individual analysts may choose different frames even when the same selection criteria are followed. In addition, it is possible that the frames are selected from different cardiac cycles, in relation to the moment of contrast injection. Reiber et al. have critically assessed this problem in 38 films whether selection of the frame (3 frames preceding, 3 frames immediately following the frame and the same frame as chosen by the senior cardiologist as the reference end-diastolic frame, but one cardiac cycle earlier or later) resulted in a significant differences in the measurements. They found no significant difference in the mean and the standard deviation of the differences for the obstruction diameter, interpolated reference diameter, percent diameter stenosis, extent of the obstruction and area of atherosclerotic plaque

obtained in various frames with respect to the "select reference frame". Therefore, it is concluded that the selection of a true end-diastolic cineframe for quantitative analysis is not very critical and that in case of overlap it is possible to select a neighboring frame [19].

III QUALITY CONTROL IN THE MERCATOR TRIAL

In the MERCATOR-trial - a restenosis prevention trial with a new angiotensin converting enzyme inhibitor cilazapril - in which 26 clinics have participated, quantitative coronary angiography was used to determine the primary endpoint as defined by the rate and extent of restenosis. Before the clinics could start to recruit patients for the study, they had to supply 2 sample cinefilms for analysis to demonstrate that they could comply with the required standards. Of all participating clinics 1 or more cm-grid films of all modes of all image intensifiers were received at the core laboratory to allow correction for pincushion distortion of the image intensifiers. All clinics received a set of radiopaque plates to be able to make it clear on the film whether nitroglycerin or isosorbide dinitrate was given before the contrast injection, which field size of the image intensifier was used, the balloon pressure and balloon size used etc. In a period of 5 months (June 1989 - November 1989), a total of 735 patients were recruited with a minimum of 8 patients and a maximum of 56 patients per clinic. Five of the 735 patients were not included in the final analysis of the trial because their cinefilm could not be quantitative analyzed; in 1 patient the film developing machine broke down so that no post-PTCA film was available for analysis; in 2 patients analysis was not possible due to a large coronary artery dissection; in 1 patient no matching views were available and in 1 patient poor filling of the vessel had occurred (due to the use of a catheter with side holes) making comparison with the baseline film unreliable.

In 2 patients pre-PTCA, 34 patients post-PTCA and in 4 patients at follow-up angiography intracoronary nitroglycerin or isosorbide dinitrate had not been administered as assessed by the absence of the plate on the film and nothing had been recorded in the column "medication given during the procedure". In 26 patients, a 5 or 6 French catheter was used at the time of follow-up angiography. In 8% of the views pre-PTCA, 12% of the post-PTCA views and 12% of the follow-up views, the images had to be analyzed with a contrast-filled catheter because no flushed catheter was available. Figure 5 shows the average number of matched views available for QCA analysis per segment dilated.

QUALITATIVE ASSESSMENT

In addition to quantitative measurements, an angiographic core laboratory can assess qualitative or morphologic factors, such as type of lesion (according the AHA

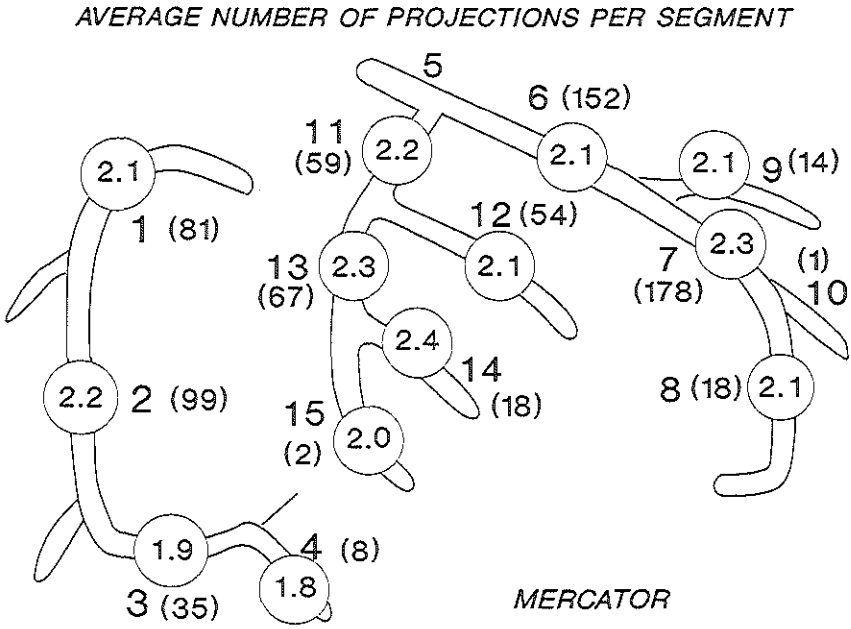

Figure 5 *The average number of matched projections (pre-PTCA, post-PTCA and at follow-up) that were used for quantitative analysis in the MERCATOR trial per segment are given in the circles. The numbers between the brackets are the total number of stenoses for that particular segment.*

classification), description of the eccentricity of the lesion and type of dissection after the procedure, using modified NHLBI criteria, to establish the roles of these descriptors in the restenosis process. Recently, we have studied the interobserver variability for the description of the lesion and the type of dissection [20,21]. Using the Ambrose classification there was an agreement of 80% between the two assessors of the core laboratory and for dissection there was an agreement of 87%. At the present time, no additional data is available but will become available in the near future,

CONCLUSION

The use of quantitative coronary angiography is an objective and reliable method to evaluate changes in arterial dimensions over time. An angiographic core laboratory plays a crucial role in minimizing the problems of data acquisition and data analysis as well as the overall quality of the trial. Beside that an angiographic core laboratory may help demonstrating the reproducibility of qualitative factors and their role in the occurrence of acute and late complications of PTCA.

Furthermore, in our experience it has been possible to standardize angiographic data acquisition from 82 different clinics in Europe, United States and Canada.

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APPENDIX II

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

MERCATOR study group

Circulation: 1992;86:100-10.

Does the New Angiotensin Converting Enzyme Inhibitor Cilazapril Prevent Restenosis After Percutaneous Transluminal Coronary Angioplasty?

Results of the MERCATOR Study: A Multicenter, Randomized, Double-Blind Placebo-Controlled Trial

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

Background. **Cilazapril is a novel angiotensin converting enzyme inhibitor with antiproliferative effects in the rat model after balloon injury.**

Methods and Results. **We conducted a randomized, double-blind placebo-controlled trial to assess the effect of cilazapril in angiographic restenosis prevention after percutaneous transluminal coronary angioplasty (PTCA). Patients received cilazapril 2.5 mg in the evening after successful PTCA and 5 mg b.i.d. for 6 months or matched placebo. In addition, all patients received aspirin for 6 months. Coronary angiograms before PTCA, after PTCA, and at 6-month follow-up were quantitatively analyzed. In 94% of 735 recruited patients, PTCA was successful and all inclusion and exclusion criteria were met. For the per-protocol analysis, quantitative angiography after PTCA and at follow-up was available in 595 patients who complied with the treatment regimen (309 control, 286 cilazapril). The mean difference in minimal coronary lumen diameter between post-PTCA and follow-up angiogram (primary end point) was -0.29 ± 0.49 mm in the control group and -0.27 ± 0.51 mm in the cilazapril group. Clinical events during 6-month follow-up, analyzed on an intention-to-treat basis, were ranked according to the most serious clinical event ranging from death (control, two; cilazapril, three), nonfatal myocardial infarction (control, eight; cilazapril, 5), coronary revascularization (control, 51; cilazapril, 53), or recurrent angina requiring medical therapy (control, 67; cilazapril, 68) to none of the above (control, 224; cilazapril, 212). There were no significant differences in ranking.**

Conclusions. **Long-term angiotensin converting enzyme inhibition with cilazapril in a dose of 5 mg b.i.d. does not prevent restenosis and does not favorably influence the overall clinical outcome after PTCA.** (*Circulation* **1992;86:100–110)**

KEY WORDS • **clinical trials** • **cilazapril** • **angiotensin converting enzyme** • **percutaneous transluminal coronary angioplasty**

Percutaneous transluminal coronary angioplasty (PTCA) was introduced by Andreas Gruentzig in 1977 as an alternative treatment for coronary artery bypass grafting (CABG) in patients with angina pectoris.[1] Increased experience and advances in technology have resulted in a high primary success rate (over 90%) and a low complication rate (death or nonfatal myocardial infarction, 4–5%).[2] However, the late restenosis rate (17–40%) still limits the long-term benefit of the procedure.[3–8]

The cause of restenosis is unclear, but factors such as platelet aggregation, formation of mural thrombi, intimal proliferation of smooth muscle cells, elastic recoil, and active vasoconstriction at the site of PTCA injury have all been implicated.[9–17] A decade of intensive clinical and pharmacological research has not succeeded in altering the restenosis rate.[18,19] Various treatments started shortly before or after PTCA and sometimes given for up to 6 months, such as intravenous administration of heparin, antiplatelet therapy (aspirin, dipyridamole, ticlopidine, prostacyclin, ciprostene, thromboxane A_2 receptor blocker), anticoagulants (coumadin), calcium channel blockers (nifedipine, diltiazem, verapamil), and other agents such as corticosteroids and colchicine, have failed to reduce the restenosis rate.[20,21] Fish oil and cholesterol-lowering agents have shown promise, although the published results are conflicting.[20,22]

Balloon angioplasty extensively damages the medial smooth muscle cells as well as the endothelial lining of

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

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the coronary vessel wall.[23] Recent data have shown that mitogens from platelets are not wholly responsible for initiating the proliferative response in balloon catheter-injured arteries, because smooth muscle cell proliferation occurred in the absence of platelets.[24] The smooth muscle cell proliferation was correlated with the severity of trauma inflicted by the denuding technique to the arterial wall, which would suggest a role for endogenous factors possibly released from damaged endothelial and smooth muscle cells.[12,25] The basic fibroblastic growth factor (bFGF) is one of the main factors, as it is released from disrupted cultured vascular cells and is a growth factor for smooth muscle cells in vitro and in vivo.[24,26] Platelet-derived growth factor (PDGF) may regulate the migration of smooth muscle cells from the media into the intima.[27,28] In this process, angiotensin II might act as a comitogen and stimulate increased proliferation of smooth muscle cells that have been activated to enter the cell cycle and have migrated to the subintima.[29] Based on the hypothesis that a local angiotensin system may regulate the vascular response to endothelial injury, Powell et al[30] examined the effects of various doses of the angiotensin converting enzyme (ACE) inhibitor cilazapril on neointimal proliferation in the rat carotid

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artery. Administration of a high dose resulted in an 80% reduction in neointima formation in this balloon-injured artery model.

The present multicenter, randomized, double-blind placebo-controlled trial was designed to test whether ACE inhibition can prevent late restenosis after PTCA in humans.

Methods

Study Population

All symptomatic and asymptomatic patients scheduled for PTCA with an angiographically proven, functionally significant narrowing in one or more major coronary arteries were considered for inclusion in 26 participating centers (see "Appendix"). A screening log was maintained in 17 participating centers. Between June 1989 and December 1989, 27% of patients screened in these centers were enrolled. Reasons for exclusion are listed in Table 1.

Treatment Allocation

The trial was carried out according to the Declaration of Helsinki (1963; revised in Venice, 1983). Informed consent was obtained in 735 recruited patients before the PTCA procedure. Patients were randomly assigned to cilazapril or placebo, but only 693 patients with successful PTCA (defined as a visually assessed diameter stenosis of <50% after PTCA) who met all inclusion and exclusion criteria as stated in the protocol continued the trial and formed the study population (Figure 1). Forty-two patients were excluded for the following reasons. 1) The PTCA procedure could not be performed (lesion not suitable). 2) The PTCA procedure was unsuccessful or unsatisfactory (either inability to reach or to cross the lesion or a diameter stenosis of >50% after PTCA, or abrupt occlusion not responding to intracoronary spasmolytic or thrombolytic therapy). 3) The PTCA procedure was complicated by myocardial

TABLE 1. **Screening Results of 17 Log-Keeping Clinics**

	n	%
Total number of screened patients	1,755	100
Number of recruited patients	478	27.2
Excluded from the trial	1,277	72.8
Reason for exclusion		
History of sustained essential hypertension	271	15.4
Previous and/or failed PTCA at the same site	268	15.3
Q wave MI <4 weeks before study entry	174	9.9
Follow-up coronary angiography unlikely	109	6.2
Logistic reasons	67	3.8
Significant concomitant disease	50	2.8
Older than 75 years	43	2.5
Dilatation of bypass graft	40	2.3
Primary perfusion therapy	39	2.2
No informed consent given	39	2.2
Current evidence or history of heart failure	28	1.6
Other reasons* (<1% each)	122	8.6

PTCA, percutaneous transluminal coronary angioplasty; MI, myocardial infarction; MERCATOR, Multicenter European Research Trial With Cilazapril After Angioplasty to Prevent Transluminal Coronary Obstruction and Restenosis; ACE, angiotensin converting enzyme.

*Participation in other trial; planned directional atherectomy procedure or stent implantation; left main disease; history of type II hypercholesterolemia; previous cerebrovascular accident; previous participation in MERCATOR; hypotension; contraindication to ACE inhibition/aspirin; women of childbearing potential; insulin-dependent diabetes; miscellaneous.

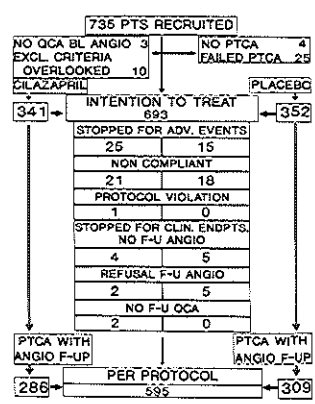

FIGURE 1. *Patient flowchart in MERCATOR (Multicenter European Research Trial With Cilazapril After Angioplasty to Prevent Transluminal Coronary Obstruction and Restenosis). Pts, patients; QCA, quantitative coronary angiography; BL, baseline; Excl, exclusion; PTCA, percutaneous transluminal coronary angioplasty; ADV, adverse; Clin endpts, clinical end points; F-UP, F-U, follow-up; ANGIO, angiogram.*

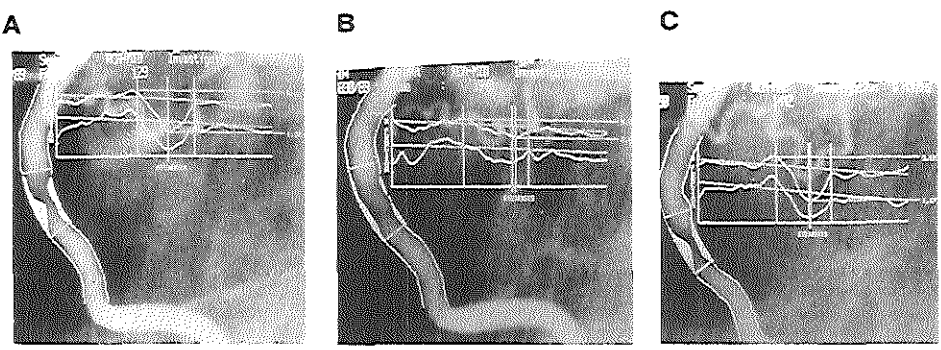

FIGURE 2. *Video images: Single frame of a narrowing in the right coronary artery before percutaneous transluminal coronary angioplasty (PTCA)* (panel A), *after PTCA* (panel B), *and at follow-up* (panel C). *Superimposed on the video image is the diameter function curve (upper curve) together with the interpolated reference curve. Minimal lumen diameter is 1.28 mm before PTCA, 2.58 mm after PTCA, and 1.17 mm at follow-up.*

infarction before the first drug intake (symptoms, ECG changes, and creatine kinase levels more than twice the upper limit of normal). Retroactively, patients were excluded from the study for the following reasons. 1) The baseline film could not be quantitatively analyzed. 2) The exclusion criterion was overlooked at the time of screening.

Trial medication was given for the first time in the evening after successful PTCA and consisted of either capsules of cilazapril (first evening, 2.5 mg; 5 mg b.i.d. thereafter) or matching placebo for 6 months. In addition, all patients received 75–125 mg aspirin b.i.d. before coronary PTCA until follow-up angiography.[31,32]

Follow-up Evaluation

Patients returned to the outpatient clinic after 1, 2, 4, and 6 months for an interview, a cardiac examination, ECG, laboratory tests, and a capsule count. Follow-up angiography was performed at the 6-month visit after the trial medication was discontinued. When symptoms recurred within 6 months, coronary angiography was carried out earlier. When no definite restenosis was present and the follow-up time was less than 3 months, the patient was asked to undergo another coronary angiogram at 6 months.

One to 4 days before follow-up angiography but after discontinuation of the trial medication, a symptom-limited exercise test was performed on a bicycle ergometer according to a standard protocol. The test was performed with the patient in a sitting position, starting with a work load of 20 W, which was increased by 20 W every minute. Exercise was continued until anginal symptoms, a drop in systolic blood pressure, severe arrhythmia, or an ST depression of more than 1 mm occurred or the patient stopped because of fatigue. A 12-lead ECG was recorded during exercise and recovery. ST changes were measured 80 msec after the J point.

PTCA Procedure and Angiographic Analysis

At the beginning of the procedure, all patients received a bolus of 10,000 IU intravenous heparin. After 2 hours, an additional infusion of 5,000 IU/hr was given until the end of the procedure. Use of a calcium channel blocker for 48 hours after PTCA was permitted. Choice of balloon type, inflation duration, and pressure were left to the operator.

For the purpose of the study, three coronary angiograms were obtained in each patient—one just before PTCA, one immediately after PTCA, and one at follow-up. Angiograms were recorded in such a way that they were suitable for quantitative analysis by the Coronary Angiography Analysis System (CAAS). An example of an analysis is shown in Figure 2. To standardize the method of data acquisition and to ensure exact reproducibility of post-PTCA and follow-up angiograms, measures were taken as described earlier.[21,33] All angiographic analyses, including qualitative assessment of certain lesion characteristics,[34–36] were performed at a core laboratory, which was blinded to treatment allocation and did not have access to clinical data.

As visual assessment of coronary angiograms is hampered by a large interobserver and intraobserver variability,[33,37] all cineangiograms were quantitatively analyzed using the CAAS system, which has been validated and described in detail.[33,38] The absolute values of the stenosis diameter as well as the reference diameter are measured by the computer, using the known contrast–empty catheter diameter as a scaling device. To achieve maximal vasodilatation, intracoronary nitroglycerin or isosorbide dinitrate was given for each coronary artery involved before PTCA, after PTCA, and at follow-up angiography. All contour positions of the catheter and the arterial segment were corrected for pincushion distortion introduced by the individual image intensifiers. Because the algorithm is not able to measure total occlusions and lesions with TIMI-1 perfusion, a value of 0 mm was used for the minimal lumen diameter and 100% for the percent diameter stenosis. In these cases, the post-PTCA reference diameter was used as the reference diameter before PTCA or at follow-up.

End Points

The primary end point of this study was the within-patient change in minimal lumen diameter as deter-

mined by quantitative angiography after PTCA and at follow-up. Post-PTCA values were obtained from the last post-PTCA angiogram made directly after removal of the guide wire. The initial procedure was considered finished when the guide catheter was removed. In the case that the clinical condition required repeat PTCA, the angiogram made before repeat PTCA was used to obtain follow-up values irrespective of the timing of repeat PTCA (hours, days, or weeks).

For each dilated segment, the minimal lumen diameter was taken as the mean value from multiple matched projections. Within-patient change was defined as the follow-up value minus the post-PTCA value. In the case that more than one segment was dilated (multivessel or multisite procedures), the mean change over all lesions dilated was taken as the end point. Secondary end points were restenosis rates, exercise test results, and clinical events. These were death (irrespective of cause), New York Heart Association class III–IV as a result of congestive heart failure, nonfatal myocardial infarction (symptoms, ECG changes, and creatine kinase enzymes above twice the upper limit of normal), coronary revascularization (CABG, repeat PTCA, stent implantation, or atherectomy at the same site or other site), and recurrent angina requiring initiation or increase in medical therapy, or none of the above. Only revascularizations that were done before the 6-month time window (6 months±3 weeks) were counted as a clinical event.

Statistical Methods and Analysis

As stated in the original protocol, the required sample size (200 evaluable patients per treatment group) was based on the assumption of a restenosis rate of 30% in the control group and of 15% (i.e., a 50% difference) in the cilazapril group (two-sided test with an α error of 0.05 and a power of 0.80). However, as more and more quantitative data became available, we realized that restenosis should be viewed as a continuous process. This is best measured by the mean overall change in absolute minimal luminal diameter instead of applying arbitrarily selected cutoff criteria of 50% diameter stenosis at follow-up or ≥0.72-mm change in minimal diameter between post-PTCA and follow-up. Consequently, the initial power calculations were changed during the trial in a protocol amendment with continuous data. With the assumption of a change of -0.40 ± 0.50 mm in mean minimal lumen diameter between postangioplasty and follow-up angiogram in the control group and -0.25 ± 0.50 mm (i.e., a 37.5% difference) in the active drug group (two-sided test with an α error of 0.05 and a power of 0.90), the minimal sample size was estimated to be 233 patients in each group. Thus, enough patients were recruited to detect a significant difference between the two treatment groups.

For statistical evaluation, intention-to-treat and per-protocol populations were defined. The intention-to-treat population comprised patients who fulfilled all inclusion and exclusion criteria and received at least one dose of test medication. The per-protocol population consisted of all compliant patients of the intention-to-treat population who had an analyzable follow-up angiogram. A patient was judged compliant if at least 80% of the test medication was taken and the test medication was not stopped more than 5 days before follow-up angiography.

To test the hypothesis that the mean change in minimal lumen diameter is equal in the two treatment groups, ANOVA was done with treatment and center as main factors and treatment times center as interaction term. As the change in minimal luminal diameter after PTCA follows a near-gaussian distribution, parametric tests were allowed to be used.[39] The treatment effect was defined as the difference in mean change in minimal lumen diameter between the two treatment groups. In addition, 95% confidence intervals of the treatment effect were obtained from the ANOVA.

Comparison of the clinical outcome was done for the intention-to-treat population. Each patient was assigned at the time of follow-up to the most serious applicable event on the scale described above. For comparison of the clinical outcome between the two treatment groups, standard nonparametric statistical methods were used.

Results

In total, 735 patients gave informed consent, and subsequently, 693 continued the trial and constituted the intention-to-treat population. Figure 1 shows the patient flowchart. Forty-two patients (23 patients randomly assigned to cilazapril and 19 patients to placebo) were not included in the trial for the following reasons. In four patients, no PTCA was performed because the lesion was no longer an indication for PTCA; in 25 patients, the outcome of the PTCA procedure was unsatisfactory (two patients with a post-PTCA diameter stenosis of >50% by visual assessment), unsuccessful (11 patients because of inability to cross the lesion), or complicated (four patients with emergency CABG, eight patients with sustained occlusion). Thirteen patients were excluded from the analysis (10 because a selection criterion was overlooked, three because no baseline quantitative analysis was possible). Of the remaining 693 patients, 352 were randomized to receive placebo and 341 were randomized to receive cilazapril.

Baseline Characteristics and Clinical Follow-up

Selected demographic and clinical characteristics of the two study groups are shown in Tables 2 and 3. In general, baseline characteristics were evenly distributed in the two groups except for patients with pain at rest and patients currently smoking, who were more frequently encountered in the control group.

Clinical follow-up was obtained for all 693 patients. During the course of the study, five patients died (control, two; cilazapril, three). The cause of death was cardiovascular in four cases and of other origin in one case. Nonfatal myocardial infarction was documented in 13 patients (control, eight; cilazapril, five); 17 patients underwent bypass surgery (control, eight; cilazapril, nine); repeat PTCA, atherectomy, or stent implantation was performed in 87 patients (control, 43; cilazapril, 44); and recurrent angina was observed in 135 patients (control, 67; cilazapril, 68). Finally, 224 (64%) in the control group and 212 (62%) in the treated group were event free at 6-month follow-up. Table 4 shows the number of events on a per-patient basis, with only the most serious event listed. Adjusted χ^2 test revealed no difference in ranking between the two groups.

During follow-up, 40 patients stopped their treatment because of adverse experiences (hypotension: control, one; cilazapril, nine; cough: control, none; cilazapril, four; rash: control, three; cilazapril, two; dizziness:

TABLE 2. Clinical Characteristics of the Intention-to-Treat Population

	Control patients (n=352)	Cilazapril patients (n=341)
Men (No.)	292 (83%)	282 (83%)
Age (years)	56±8 (32–74)	57±9 (35–74)
Ever smoked	269 (76%)	259 (76%)
Current smokers*	70 (20%)	49 (14%)
Non–insulin-dependent diabetes	20 (6%)	21 (6%)
One-vessel disease	228 (65%)	225 (66%)
Two-vessel disease	106 (30%)	99 (29%)
Three-vessel disease	18 (5%)	17 (5%)
Total cholesterol (mg/dl)	228±59	227±54
No angina present	30 (9%)	28 (8%)
Angina present	322 (91%)	313 (92%)
CCS class I	46 (13%)	53 (16%)
CCS class II	108 (31%)	103 (30%)
CCS class III	102 (29%)	100 (29%)
CCS class IV	66 (19%)	57 (17%)
Pain at rest*	133 (38%)	99 (29%)
Controlled by oral medication	92	64
Controlled by nitrates (i.v.)	28	15
Controlled by maximal medication	11	16
Continues at maximal medication	2	4
Duration of angina (days)	432±902	422±921
Previous MI	146 (41%)	142 (42%)
Previous CABG	6	7
Previous angioplasty	6	4
PTCA+CABG	1	1
No. of patients on		
Nitrates	246 (70%)	236 (69%)
Ca antagonists	228 (65%)	217 (64%)
β-Blockers	182 (52%)	180 (53%)
No medication	14 (4%)	19 (6%)
Monotherapy	89 (25%)	91 (27%)
Double therapy	180 (51%)	151 (44%)
Triple therapy	69 (20%)	80 (23%)

CCS, Canadian Cardiovascular Society angina classification; MI, myocardial infarction; CABG, coronary artery bypass graft; PTCA, percutaneous transluminal coronary angioplasty.
Values are mean±SD. *$p<0.05$.

control, two; cilazapril, three; gastrointestinal problems: control, three; cilazapril, four; other reasons: control, five; cilazapril, four). Nine patients stopped treatment because they had a clinical event (death: control, two; cilazapril, three; CABG: control, one; cilazapril, one; nonfatal myocardial infarction: control, two; cilazapril, none), and one patient became a protocol violator. Thirty-nine patients did not fulfill compliance criteria (control, 18; cilazapril, 21); in nine patients, no angiogram suitable for quantitative analysis could be obtained due to either refusal (control, five; cilazapril, two) or to technical reasons (absence of matched views or poor quality of the follow-up film: control, none; cilazapril, two). Thus, the per-protocol population consisted of 309 control patients and 286 patients treated with cilazapril.

TABLE 3. Angiographic Characteristics of Per-Protocol Population

	Control patients (n=309, 367 lesions)	Cilazapril patients (n=286, 342 lesions)
Vessel dilated		
RCA	103 (28%)	101 (30%)
LAD	173 (47%)	153 (45%)
LCx	93 (25%)	88 (25%)
Number of sites dilated		
One	305 (82%)	283 (82%)
Two	51 (15%)	51 (15%)
Three	8 (2%)	7 (2%)
Four	3 (1%)	1 (1%)
Lesion type		
Concentric	188 (51%)	179 (52%)
Eccentric	135 (37%)	108 (31%)
Tandem	3 (1%)	18 (5%)
Multiple irregularities	31 (8%)	25 (7%)
Total occlusion	10 (3%)	12 (4%)
Calcified lesion	45 (12%)	46 (14%)
Side branch in stenosis	213 (58%)	197 (56%)
Lesion at bend point	34 (9%)	48 (13%)
Thrombus after PTCA	10 (3%)	14 (4%)
Dissection*		
No*	262 (72%)	235 (69%)
Type A	32 (9%)	39 (12%)
Type B	57 (16%)	49 (15%)
Type C	12 (3%)	13 (4%)
Type D	1	1
Type E	0	2
Largest size balloon (mm)	2.88±0.41	2.83±0.65
Maximal pressure (atm)	8.3±2.5	8.0±2.7
Total inflation (seconds)	245±226	247±214
Balloon artery ratio	1.14±0.20	1.12±0.18

RCA, right coronary artery; LAD, left anterior descending coronary artery; LCx, left circumflex artery; PTCA, percutaneous transluminal coronary angioplasty.
Values are mean±SD. *Modified from Reference 35.

Angiographic Efficacy Analysis

Table 5 summarizes the quantitative angiographic findings in the per-protocol population. On per-protocol basis, the loss at follow-up in minimal lumen diameter was −0.29±0.49 mm in the control group and

TABLE 4. Ranking per Patient Based on Most Serious Clinical Event During 6-Month Follow-up

	Control patients (n=352)	Cilazapril patients (n=341)
Death	2 (<1%)	3 (<1%)
NYHA III/IV	0	0
Nonfatal myocardial infarction	8 (2.3%)	5 (1.4%)
Coronary revascularization	51 (14.5)	53 (15.5)
Angina recurrence	67 (19.0%)	68 (19.9%)
No event	224 (63.6%)	212 (62.2%)

NYHA, New York Heart Association classification for congestive heart failure.

TABLE 5. **Quantitative Analysis in the Per-Protocol Population**

	Control patients (n=309)	Cilazapril patients (n=286)
Obstruction diameter (mm)		
Before angioplasty	0.98±0.35	1.05±0.35
After angioplasty	1.77±0.34	1.80±0.36
Follow-up	1.48±0.54	1.54±0.54
Reference diameter (mm)		
Before angioplasty	2.61±0.54	2.66±0.51
After angioplasty	2.67±0.48	2.72±0.49
Follow-up	2.68±0.56	2.74±0.52
Difference in obstruction diameter (mm)		
After preangioplasty	0.79±0.42	0.75±0.37
Follow-up postangioplasty	−0.29±0.49	−0.27±0.51
Percentage stenosis (%)		
Before angioplasty	61.4±13.4	60.1±12.3
After angioplasty	32.9±9.0	33.0±10.0
Follow-up	44.2±18.0	43.5±17.2
Difference in percentage stenosis (%)		
After preangioplasty	−28.5±15.3	−27.1±13.7
Follow-up postangioplasty	11.3±18.2	10.5±18.0

Values are mean±SD.

−0.27±0.51 mm in the cilazapril-treated group (treatment effect, 0.023 mm; 95% CI, −0.06–0.11 mm). Figures 3 and 4 represent a cumulative frequency curve of the minimal lumen diameter and of the change in minimal lumen diameter observed in both groups. Adjustment for current smoking and pain at rest did not affect the results. When participating clinics were analyzed separately, the results were consistent.

Table 6 summarizes the restenosis rates in the per-protocol population per lesion according to seven frequently used restenosis criteria.

Bicycle Ergometry

Of 693 patients, 564 (81%) underwent exercise testing at follow-up. Reasons for not performing the test were death in five patients (control, two; cilazapril,

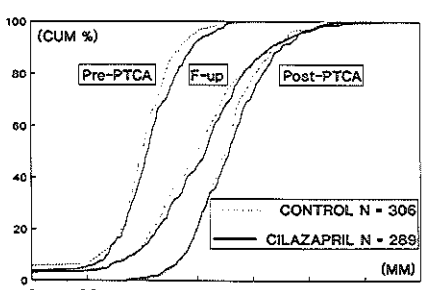

FIGURE 3. *Cumulative distribution curve (CUM %, cumulative percentage of patients) of the minimal lumen diameter before percutaneous transluminal coronary angioplasty (PTCA), after PTCA, and at 6-month follow-up (F-up) in both treatment groups.*

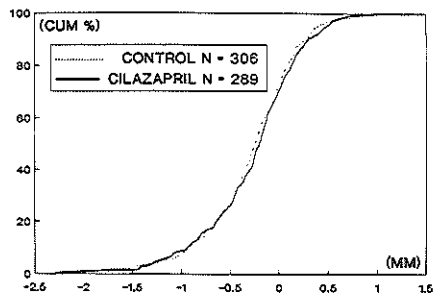

FIGURE 4. *Cumulative distribution curve of the change in minimal lumen diameter from before percutaneous transluminal coronary angioplasty (PTCA) to follow-up in both treatment groups. CUM %, cumulative percentage of patients.*

three), unstable angina in 58 patients (control, 30; cilazapril, 28), refusal in 18 patients (control, five; cilazapril, 13), adverse event in 23 patients (control, 11; cilazapril, 12), logistic reasons in six patients (control, four; cilazapril, two), and other reasons in 14 patients (control, five; cilazapril, nine). The exercise test was not performed according to protocol in five patients (control, four; cilazapril, one). Table 7 summarizes results of exercise testing in both groups. No difference in objective parameters was observed. Chest pain during exercise was reported in 74 patients (25%) receiving placebo and 42 patients (15%) receiving cilazapril (p=0.03). ST deviation (depression or elevation) of >0.1 mV associated with anginal symptoms was observed in 39 patients (13%) in the control group and 25 patients (9%) in the cilazapril group.

Discussion

Rationale for ACE Inhibition After PTCA

Over the past decade, it has been repeatedly demonstrated that treatment of chronic hypertensive rats with ACE inhibitors reduces the medial hypertrophy of muscular arteries.[40–42] Therefore, it has been postulated that the local renin–angiotensin system may participate in regulating the vascular response to arterial injury.

TABLE 6. **Restenosis Rates per Lesion According to Frequently Used Definitions**

	Control patients (n=309, 368 lesions)	Cilazapril patients (n=286, 342 lesions)
MLD (post-PTCA follow-up) ≥0.72	59 (16%)	56 (17%)
MLD (post-PTCA follow-up) ≥0.36	153 (42%)	129 (38%)
>30% DS increase in DS at follow-up	45 (12%)	42 (13%)
<50% DS after PTCA to >70% DS follow-up	25 (7%)	20 (6%)
DS follow-up <10% DS before PTCA	66 (18%)	55 (16%)
Loss of >50% of gain or >30% ↑DS	144 (39%)	125 (37%)
<50% DS after PTCA to >50% DS follow-up	103 (28%)	96 (28%)

MLD, minimal lumen diameter; PTCA, percutaneous transluminal coronary angioplasty; DS, diameter stenosis.

TABLE 7. Exercise Test Results of 564 Patients

	Control patients (n=291)	Cilazapril patients (n=273)	p
Maximum work load (W)	146±39	151±44	NS
Exercise time (seconds)	446±124	454±127	NS
Systolic blood pressure at peak exercise (mm Hg)	196±27	192±28	NS
Heart rate at peak exercise (beats per minute)	142±22	142±21	NS
Double product (mm Hg · 100/beats per minute)	279±65	275±66	NS
ST deviation >1 mm	102 (36%)	99 (37%)	NS
Anginal symptoms during test	74 (25%)	42 (15%)	0.03
Combination of ST >1 mm and symptoms	39 (13%)	25 (9%)	NS

This hypothesis has prompted the investigation of the role of angiotensin II after injury. For this purpose, the effect of the long-acting ACE inhibitor cilazapril on the proliferative response to arterial injury was examined by Powell et al[30] in an animal model. This inhibitor was selected because at a dose of 10 mg/kg/day, it lowered blood pressure over a 24-hour period and reduced the medial hypertrophy of hypertensive rats. Using the same dose of cilazapril, neointima formation was decreased by 80% and lumen integrity was preserved in normotensive rats in which the left carotid artery was subjected to endothelial denudation and injury by balloon catheterization.[30]

More recently, several groups have studied the effects of angiotensin II on smooth muscle cell proliferation in vitro as well as the influence of ACE inhibition on smooth muscle cell proliferation. Angiotensin II induced expression of several growth factor genes, such as genes encoding PDGF, transforming growth factor-β (TGF-β), and thrombospondin (TS).[43–46] These results demonstrate that, in cultured cells, angiotensin II induces messenger ribonucleic acids to encode several important growth factor genes and thus induces cell proliferation. Cilazapril or its active metabolite did not have a direct effect by itself, but the antiproliferative effect was mediated through angiotensin II. Consequently, the inhibition of angiotensin II production may prevent the proliferative response that occurs after PTCA in humans.

Trial Design: Quantitative Angiography as Primary End Point

The primary goal of a restenosis prevention trial is the improvement in short-term and long-term clinical outcome of patients having undergone a PTCA procedure. It is assumed that the improvement in clinical outcome is related to an anatomical phenomenon, namely, the prevention of the recurrence of the stenosis in the treated vessel. However, in trials testing pharmacological compound with possible anti-ischemic or antianginal effects unrelated to the postinjury hyperplasia, the clinical outcome might be misleading and obscure the reason for the observed improvement. Quantification of luminal dimension changes over time may provide insight into the biological and mechanistic effects on the treatment after PTCA. The appearance (or reappearance) of angina as a sole criterion of restenosis underestimates the angiographic rate of restenosis. The poor value of recurrent anginal symptoms as a marker of restenosis is confirmed by the low predictive value of symptoms found in many studies.[18] Similarly, the usefulness of ergometry to detect restenosis after PTCA has been questioned since several studies have found that the presence of exercise test–induced angina or ST segment depression/elevation or both are not highly predictive for restenosis when the test is performed early or late after PTCA.[18] A drug tested for its ability to prevent restenosis may be shown to be beneficial after PTCA by reducing angina during exercise testing and yet have no effect on intimal hyperplasia after balloon-induced injury.

In the present study, fewer patients in the cilazapril-treated group experienced anginal pain during exercise testing. This symptomatic beneficial effect was not corroborated by an increase in work load or in double product or by ST changes. It must be emphasized that this difference in behavior between the two groups remains unexplained and had no bearing on the general outcome of the trial.

TABLE 8. Prognostic Value of Minimal Lumen Diameter at Follow-up in the Per-Protocol Population Divided Into Five Equal Groups

MLD follow-up (mm)	Exercise test		Clinical outcome			
	<1 mm ST changes and no chest pain	≥1 mm ST changes and chest pain	MI	Reintervention	Angina	None
<1.10	70 (75%)	24 (26%)	5 (4%)	49 (41%)	24 (20%)	41 (35%)
1.10–1.39	88 (88%)	12 (12%)	1 (1%)	18 (15%)	25 (21%)	74 (63%)
1.39–1.63	103 (90%)	11 (10%)	2 (2%)	10 (8%)	31 (26%)	77 (64%)
1.63–1.91	99 (93%)	8 (7%)	1 (1%)	7 (6%)	21 (15%)	89 (75%)
≥1.91	111 (98%)	2 (2%)	1 (1%)	7 (6%)	18 (15%)	94 (78%)
Total patients	471	57	10	91	119	375

MLD, minimal lumen diameter; MI, myocardial infarction.

In contradistinction, the prognostic value of the change in sequential coronary angiogram has been largely underestimated as a surrogate end point for clinical atherosclerotic events. In the second phase of the pharmacological investigation, the main emphasis should be put on the pathophysiological mechanism of prevention of restenosis in the postinjury model, and the improvement in clinical outcome should be viewed as a secondary benefit dependent on the anatomical status.

When the patient population of this trial is stratified according to the minimal lumen values at follow-up, it appears that the percentage of patients having reached one of the predefined clinical end points is as high as 65% in the worst category (minimal lumen diameter at follow-up <1.10 mm), whereas the percentage of event-free patients ranges from 63% to 78% in the other categories (Table 8). It must be emphasized that 41% of the patients in the worst anatomical category had reintervention versus only 6% in the best anatomical category irrespective of the initial dilatation site. Besides the prognostic value, the anatomical results also have a clear functional impact because only 2% of the patients had a positive exercise test in the best anatomical category versus 26% of the patients in the worst anatomical category.[47]

Lack of Effect on Angiographic Restenosis

The lack of angiographic effect in MERCATOR (Multicenter European Research Trial With Cilazapril After Angioplasty to Prevent Transluminal Coronary Obstruction and Restenosis) might have been dilution because of the loss to angiographic follow-up. If cilazapril had an important effect on restenosis, then clinical events such as sudden death, etc., would have predominated in the placebo group. Inasmuch as such events lead to loss to angiographic follow-up, angiographic restenosis might have been underestimated in the placebo group but not in the cilazapril group. Dilution would also occur if patients who are completely asymptomatic refuse repeat angiography. This kind of distortion (bias) of the effect assessment in an angiographic restenosis trial cannot be avoided as a matter of principle. Because there was no difference in clinical events leading to loss to angiographic follow-up and because the percentages of patients who had angiographic follow-up was relatively high (cilazapril, 94%; control, 94%), we do not believe that the lack of angiographic effect of cilazapril observed relates to loss to angiographic follow-up.

Several explanations (which are not mutually exclusive) may account for the apparent failure of cilazapril to decrease the rate of coronary restenosis.

Dose Relation

The dose selected for this trial was based on pharmacokinetic data in healthy volunteers, demonstrating that a single dose of 5 mg cilazapril reduced the plasma ACE activity to virtually unmeasurable levels.[48,49] Pharmacokinetic data from hypertensive patients demonstrate that after a single dose of 5 mg cilazapril, the plasma angiotensin II concentration starts to return to baseline in 8–10 hours, although a sustained blood pressure reduction is achieved. Therefore, the dosage of 5 mg b.i.d. was chosen.

After the trial was designed, it was shown that inhibition of neointima formation is a dose-dependent phenomenon and that the dose required for inhibition of neointimal formation appears to be somewhat higher than for lowering blood pressure.[46] In the rat model, this dose relation for the antiproliferative effect of cilazapril is different from the dose relation for the antihypertensive effect. Thus, a possible explanation for the lack of effect in MERCATOR is that the dose used was too low, as the dose used in the rat model was 70 times higher (10 mg/kg/day). The ongoing American/Canadian sister trial to MERCATOR, MARCATOR, which is similar in design but randomizes between 1, 5, and 10 mg of cilazapril b.i.d., will give us the unique opportunity to further investigate this relation in humans. If the antihypertensive effect in the 10 mg–b.i.d. subset of patients does not materially differ from that in the two other arms of the trial (1 and 5 mg b.i.d.), although a direct antiproliferative effect is observed, further investigation of the role of the renin–angiotensin system in tissue proliferation after vascular injury seems warranted.

Time Relation

As in animal experiments, no major difference in inhibition of neointimal proliferation was observed whether the drug was given 1 hour before or within 2 days after the wall injury. It was assumed that ACE inhibition by cilazapril could be started immediately after PTCA.[30]

In experimental studies, the strongest inhibition of neointima formation was obtained when treatment was started 6 days before injury. It could be that a period of drug impregnation before injury might be required to obtain an inhibitory effect, although a significant but slightly attenuated effect was observed when it was started 2 days after injury.

Species Relation

Powell et al[46] compared the effects of high doses of cilazapril (10 mg/kg/day) and captopril (100 mg/kg/day) on neointimal proliferation in the rat carotid artery model. Both agents were highly effective and, in addition, concomitant heparin therapy appeared to exert a synergistic antiproliferative effect. Similarly, in the atherosclerotic rabbit iliac model, cilazapril (5 mg/kg/day) reduced the incidence of restenosis after balloon injury.[50] In contrast, Lam et al[51] found no benefit of high-dose cilazapril (20 mg/kg b.i.d.) in the porcine carotid artery injury model. Churchill et al[52] and Huber et al[53] could not demonstrate significant benefit of captopril or enalapril in preventing restenosis in the swine model. Despite the fact that all species show an effect on blood pressure, the postinjury proliferation in baboons and pigs was not clearly affected by cilazapril at the doses used, whereas rats, guinea pigs, and rabbits did respond.[54] Rakugi et al[55] have shown that vascular injury results in the induction of ACE in proliferating cells in the neointima and supports the role of the local renin–angiotensin system in restenosis. Although quite attractive, the close parallel between the muscular response to experimental arterial injury and the development of restenosis in humans after therapeutic angioplasty remains a working hypothesis. The response of atherosclerotic human arteries may be modulated by cellular and molecular influences that are not exactly

similar to those acting in nondiseased nonhuman arteries.

Alternative Pathways of Angiotensin II Production

Other enzymes besides ACE are known for their ability to metabolize angiotensin I to angiotensin II (chymase, tonin, and cathepsin). It could well be that these alternative pathways resulted in sufficient levels of angiotensin II to activate or to stimulate the restenosis process. Because no actual measurement was done of angiotensin I or II, it is difficult to say whether these alternative pathways were active. However, we found a significant decrease in blood pressure immediately after the first drug intake in patients randomized to cilazapril compared with patients taking placebo. This effect was maintained during the entire 6-month follow-up period. Thus, clinically, there was an effect of cilazapril by reducing blood pressure, presumably by lowering the level of angiotensin II. The use of an angiotensin II receptor blocker might be worth exploring,[56] as in this case all angiotensin II, irrespective of the metabolic pathway that is used, is blocked.

Possible Mitogenic Effect of Angiotensin I

Another explanation for failure of cilazapril to reduce restenosis is that as a logical consequence of the use of ACE inhibitors, the concentration of angiotensin I is increased, which has been shown to be mitogenetic for arterial muscle cells.[45] This unavoidable side effect of ACE inhibitors may, perhaps only in some species, annihilate their favorable actions exerted through angiotensin II suppression.

Relevance of Mechanism of Action

The most recent theory on restenosis put forward by Lindner and Reidy[12] indicates that bFGF released after disruption and cell necrosis of the endothelium and media is the factor that initiates the proliferation and duplication of the smooth muscle cells. These subsequently activated smooth muscle cells tend to migrate in the subintima of the vessel, where they are attracted by the PDGF stemming from the aggregated platelets: It is in this location and stage that angiotensin II acts on them as a comitogen. This complex interaction may be the predominant biological scenario in certain species such as rat and rabbit but may be inoperative in other species such as the baboon and guinea pig.

Recently, Forrester et al[17] hypothesized that restenosis is a manifestation of the general wound-healing process expressed specifically in vascular tissue. They list five different groups of growth factors: PDGF, FGF, EGF (epidermal growth factor), IGF (insulin-like growth factor), and TGF (transforming growth factor), each with a specific role and with possibly many interactions. It is of course possible that angiotensin II has only a minor role in this complex process and that ACE inhibition did not result in less angiographic restenosis.

In contrast, Schwartz et al[57] hypothesize that mural thrombus is the most important factor in the restenosis process: It is seen in all treated animals after injury; after 3 days it is covered by endothelium, and later on, smooth muscle cells start to grow downward toward the media, suggesting that neointimal cells are probably not derived from arterial media at the immediate injury site.

Conclusions

Long-term ACE inhibition with cilazapril in a dose of 5 mg b.i.d. does not prevent restenosis and does not favorably influence the overall clinical outcome after PTCA in patients. The results of the MARCATOR trial must be awaited to see whether a higher dose of cilazapril has any effect on angiographic restenosis.

Appendix

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SUMMARY

During the last decade, percutaneous transluminal coronary angioplasty (PTCA) has become widely accepted as a treatment modality for patients with ischemic heart disease. In 1991 more than 500.000 patients were treated by coronary balloon angioplasty and this number will soon exceed that treated by coronary artery bypass grafting. Balloon angioplasty accomplishes uncomplicated successful revascularization in more than 90% of patients. However, in approximately one third of patients re-interventions will be necessary within 6 months because of a return of the anginal symptoms after successful initial treatment. In most patients, this "**restenosis**" can be managed by repeat balloon angioplasty or by the use of one of the increasing range of interventional devices, which have been developed in attempts to reduce the number of patients who experience restenosis. Unfortunately neither new devices nor pharmacological interventions have thus far been able to provide a remedy for the prevention of restenosis following percutaneous coronary revascularizations.

The pathological process of "restenosis" is now viewed as an exaggerated healing response of the vessel wall to the injury caused during the therapeutic manoeuvre of balloon inflation, in which multiple elements play an important role, for example growth factors, platelets and smooth muscle cells to mention but a few. In the animal model, several pharmacological approaches have been applied to prevent restenosis with excellent results but these results have not (yet) been reproduced in clinical trials (*chapter 2*).

The ideal approach to evaluate and assess for restenosis is still an issue of much debate. At the present time, quantitative coronary angiography has emerged as the gold standard for objective angiographic evaluation of the immediate and the long term outcome of coronary balloon angioplasty in restenosis prevention trials as it overcomes the wide inter- and intra-variability of visual assessment of the cineangiograms. To minimize the variability in data analysis in these important trials the value of a central angiographic core laboratory for independent objective off-line analysis is now well recognized (*chapter 1, appendix 1*).

In this thesis the process of restenosis in a prospective fashion is examined, using detailed quantitative coronary angiography, as applied to two large European multicenter restenosis prevention trials. The effect of clinical angiographic and procedural factors, hypothesized to have some influence on the likelihood of adverse events following balloon angioplasty as well as on subsequent development of restenosis, were evaluated. In the **CARPORT** study, 707 patients were randomized to either placebo or a thromboxane antagonist prior to undergoing coronary balloon angioplasty and therapy continues for 6 months. The **MERCATOR** trial evaluated the efficacy of an angiotensin converting enzyme inhibitor cilazapril to placebo in 735

recruited patients who were randomized to receive treatment after successful coronary angioplasty (*appendix 2*). Neither trial could demonstrate any clinical or angiographic benefit of the agents being evaluated, so all the patients were considered as a single group for some of the ancillary studies which comprise this thesis.

Elastic Recoil of dilated lesions following coronary balloon angioplasty has been advanced as being of potential importance on the process of restenosis. In *chapter 3* technical difficulties in quantification of elastic recoil are addressed and an objective and practical approach is proposed. It is concluded that the minimal balloon diameter should be used for the assessment of elastic recoil, because this measurement localizes the non-distensible part of the stenosis that restricts the dilatation and therefore the ultimate angioplasty result. *Chapter 4* examines the actual effect of elastic recoil as well as other factors on restenosis. The amount of relative gain (difference in minimal lumen diameter between pre and post angioplasty, normalized for the vessel size) emerged as the most important predictor for restenosis, defined as a loss in minimal lumen diameter of equal or greater than 0.72 mm. This definition of restenosis is chosen since it represents the 95% confidence interval for long-term lesion measurement variability of the CAAS system. Ultimately, elastic recoil emerges as having no influence on restenosis.

In *chapter 5*, the influence of quantitative and qualitative angiographic lesion morphology, in addition to clinical characteristics, and the occurrence of major adverse cardiac events in the immediate postangioplasty period was investigated. Although quantitative coronary analysis techniques have become the "gold standard" for the assessment for long-term outcome of coronary angioplasty, lesion morphology derived from quantitative analysis did not help to differentiate between lesions at high risk for major procedural or in-hospital events. Multivariate logistic analysis, showed that unstable angina and lesions at a bend point of more than 45° were found to be pre-procedural predictors and dissection a post-procedural predictor of major adverse cardiac events during the initial hospital stay.

In *chapter 6*, the association between intimal dissection after successful coronary angioplasty and subsequent restenosis was examined. Dissection was assessed by the central angiographic core laboratory, blinded for clinical data, and according to National Heart, Lung, and Blood Institute criteria. Although dissection was visualized in 32% of all successfully dilated lesions, no differences were observed in the occurrence of restenosis, defined as diameter stenosis of more than 50% at follow-up or clinical outcome (death, myocardial infarction, coronary revascularization, recurrent angina requiring increase in medical therapy, or none of these). If restenosis was considered as the proportional loss of minimal luminal diameter during follow-up (relative loss) again dissection was not found to have any detectable influence.

In *chapter 7*, the angiographic morphology of the "restenotic lesion" was

considered and compared both with its initial morphology and also with the morphology of "non-restenotic lesions". The aim of this evaluation was to study the process of restenosis in terms of morphological changes occurring and in addition to examine the impact of using different definitions of restenosis on the information obtained. Further more an additional criteria for the occurrence of a significant deterioration in minimal lumen diameter is introduced, based on the post angioplasty lesion measurement variability of the CAAS system. It is clear that the restenosis process involves the entire vessel segment dilated at coronary balloon angioplasty and that the categorical "static" cut-off criterion of "50% diameter stenosis at follow-up does not clearly describe the restenosis process.

In *chapter 8*, 1445 lesions were studied before and after coronary angioplasty and at 6 months follow-up, to examine the distribution pattern of changes in angiographic lumen dimensions of healed lesions. Traditionally the restenosis proces has been defined using categorical criteria as seen in some of the chapters. In this chapter, it is demonstrated that the minimal lumen diameter before and after angioplasty and at follow-up angioplasty as well as the change in minimal lumen diameter and diameter stenosis between post angioplasty and follow-up, is distributed as a uni-model, approximate Gaussian fashion. The application of categorical restenosis criteria therefore merely selects a portion of the population as being separate and different when in reality it would appear that restenosis is a single process with no difference can be validly defined.

In *chapter 9*, the distribution of restenosis between segments of the major coronary arteries are examined in 1452 lesions using 1) "static" restenosis criterion > 50% diameter stenosis at follow-up or 2) "dynamic" restenosis criterion: relative loss". This study reveals an ubiquitous distribution of the restenosis phenomenon without predilection for any portion of the coronary tree.

In *chapter 10*, multivariate analysis of clinical, angiographic and procedural variables is performed to determine if it is possible to identify factors which might be associated with more luminal renarrowing after successful angioplasty. The relative gain, or proportional luminal improvement, at coronary balloon angioplasty emerged as the most powerful determinant of subsequent renarrowing although the predictive value of the multivariate model in individual cases was rather weak. These findings are in agreement with pathological and experimental studies which indicate that the healing response of the vessel wall is directly proportional of the injury caused at intervention. This undoubtedly illustrates the multifactorial nature of the restenosis process.

SAMENVATTING

Percutane transluminale coronaria angioplastiek (PTCA), dotteren of ballon dilatatie van vernauwingen in kransslagaderen, is een niet meer weg te denken behandelings-methode voor patiënten met ischemische hart- en vaatziekten. In 1991 werden meer dan 500.000 patienten wereldwijd op deze wijze behandeld en in sommige landen overtreft dit aantal inmiddels de chirurgische ingrepen. Ernstige complicaties zoals dood, hartinfarct of acuut chirurgisch ingrijpen treedt bij ongeveer 5% van de patiënten op; 95% verlaat het ziekenhuis de dag na behandeling. Echter 20 tot 40% van de patiënten krijgt binnen 6 maanden opnieuw (ernstige) angineuze klachten. Catheterisatie, waarbij de kransslagaderen door middel van röntgen-contrast zichtbaar worden gemaakt, laat in de meeste gevallen een terugkeer van de vernauwing(en) zien op dezelfde plaats als de eerdere vernauwing. Dit proces van terugkeer van de vernauwing wordt **restenose** genoemd. De meeste patiënten worden opnieuw behandeld met de dotter procedure. In een (nog) klein aantal patiënten wordt een nieuwe interventie techniek (atherectomie catheter,stent implantatie, laser, rotablator) toegepast. Deze nieuwe technieken hebben hun opmars gemaakt om te proberen het huidige restenose percentage na dotteren te verlagen. Evenmin als medicamenteuze behandeling is momenteel een van deze technieken in staat gebleken het restenosepercentage significant te verlagen (*hoofdstuk 2*).

Het "restenose proces" wordt gezien als een uit de hand gelopen herstel reactie van de vaatwand op de beschadiging door de dotter procedure. Diverse factoren zoals groei- en stollingsfactoren, bloedplaatjes en gladde spiercellen spelen hierbij een belangrijke rol.

Kwantitatieve angiografische analyse van de vernauwing in de kransslagader is "de gouden standaard" om restenose te beoordelen in multi-center restenose preventie studies, omdat deze techniek een betere inter- en intra-waarnemer variabiliteit heeft dan visuele beoordeling van de catheterisatie film van de kransslagaderen. Om variatie in film analyse te voorkomen, moet gebruik gemaakt worden van een centraal angiografisch laboratorium, dat geblindeerd is voor klinische gegevens (*hoofdstuk 1* en *appendix 1*).

De meeste gegevens (prospectief verzameld) in dit proefschrift zijn afkomstig van twee europese multicenter restenose preventie studies, die gebruik hebben gemaakt van kwantitative angiografische analyse, namelijk, 1) **CARPORT** (Coronary Artery Restenosis Prevention On Repeated Thromboxane-antagonism), een dubbel blind placebo gecontroleerd onderzoek in 707 patienten met GR32191 40 mg per dag (de behandeling werd voor de dotter procedure gestart en 6 maanden gecontinueerd), 2) **MERCATOR** (Multicenter European Research trial with Cilazapril after Angioplasty to prevent Transluminal coronary Obstruction and Restenosis), een dubbel blind

placebo gecontroleerde studie in 735 patienten met cilazapril 5 mg gegeven 2 keer per dag naast 160 tot 250 mg aspirine en gecontinueerd voor 6 maanden (de behandeling werd gestart 4 tot 6 uur na het einde van de ballon dilatatie) (*appendix 2*). In beide studies kon geen gunstige werking op het restenose proces van het geteste medicijn worden aangetoond, zodat alle patiënten als een groep behandeld werd bij sommige sub-studies.

Waarom bij sommige patiënten de vernauwing terugkeert en bij (de meeste) anderen niet, is onbegrepen. Uit de literatuur zijn een aantal risicofactoren bekend; factoren die als de patiënt ze bezit een hogere kans geven op het terugkeren van de vernauwing. Naast het bestuderen van de verschillende aspecten van restenose, worden in dit proefschrift twee factoren bestudeerd en hun relatie en invloed op (vroege en late) restenose beschreven, namelijk de rol van het terugveren van de vaatwand direct na ballon deflatie ("**elastic recoil**") en de aanwezigheid van zichtbare scheuren in de atherosclerotische plaque ("**dissectie**") na ballondilatatie, om op deze manier het restenose proces beter te begrijpen, en daardoor mogelijk te beïnvloeden.

In *hoofdstuk 3* worden de methodologische problemen beschreven bij de meting van "elastic recoil". De conclusie is dat bij de bepaling van de hoeveelheid "elastic recoil" gebruik gemaakt moet worden van de minimale ballon diameter omdat deze meting zeer waarschijnlijk het minst uitgezette punt localiseert van de vernauwing, waardoor de dilatatie beperkt wordt en daarmee het uiteindelijke resultaat.

In *hoofdstuk 4* wordt de rol van "elastic recoil" op het restenose proces bestudeerd. De hoeveelheid "relatieve winst" (gedefineerd als de winst in minimale luminale diameter tijdens ballon dilatatie, gecorrigeerd voor de grootte van het vat) blijkt de beste voorspeller te zijn voor restenose, gedefineerd als een verlies van 0.72 mm of meer in minimale luminale diameter gedurende follow-up. Dit vertegenwoordigd twee keer de standard deviatie van lange termijn variabiliteit van analyse van een vernauwing. Het blijkt dat "elastic recoil" geen invloed heeft op het restenose proces.

In *hoofdstuk 5* wordt de rol bestudeerd van kwantitative en kwalitative beoordeling van de morfologie van de vernauwing, naast klinische facoren, bij de voorspelling van ernstige klinische gebeurtenissen tijdens en vlak na de ballondilatatie. Alhoewel kwantitative analyse technieken de "gouden standaard" is voor de beoordeling van korte- en lange- termijn resultaten, blijkt de kwantitatief afgeleide morfologie van de vernauwing geen bijdrage te kunnen leveren om op deze manier vernauwingen te identificeren die meer risico geven op het krijgen van een ernstige klinische gebeurtenis tijdens de behandelings fase. Patiënten met onstabiele angina pectoris, vernauwingen gelocaliseerd bij een bocht in een vat met meer dan 45° en het zien van een dissectie na de ballon deflatie zijn factoren, die bij aanwezigheid een verhoogd risico geven op het krijgen van belangrijke complicaties.

In *hoofdstuk 6* wordt de rol van een dissectie na een geslaagde ballon dilatatie

en de relatie met restenose beschreven. Dissectie wordt beoordeeld door het centrale angiografische-core-laboratorium, dat geblindeerd was voor klinische gegevens en dat gebruik maakte van criteria volgens de "National, Heart, Lung, and Blood Institute". Dissectie werd gezien in 32% van alle met succes gedilateerde vernauwingen. Er is geen verschil in restenose tussen vernauwingen met en zonder dissecties, zowel als het "50% diameter stenose criterium" of indien het "relatieve verlies criterium" werd gebruikt. Ook werden er geen verschillen geconstateerd in klinische eindpunten als sterfte, hartinfarct, reïnterventie, terugkeer van angina pectoris met toename van de gebruikte medicatie.

In *hoofdstuk 7* wordt de angiografische morfologie van de restenotische vernauwing vergeleken met zichzelf vóór ballon dilatatie en met de niet gerestenoseerde vernauwing. Drie verschillende definities voor restenose worden gebruikt. Het belangrijkste resultaat van deze studie is dat de normale vaatwand, die naast de vernauwing ligt, ook betrokken raakt bij het restenose proces. Dit kan geconcludeerd worden uit de afname van de gemiddelde diameter van het "balloon inflated vessel segment".

In *hoofdstuk 8* worden het verloop van 1445 vernauwingen nagegaan vóór en ná ballon dilatatie en na 6 maanden, om te bepalen of restenose een ziekte is die alleen voorkomt in een bepaalde subgroep van vernauwingen of dat restenose in alle vernauwingen in meerdere of mindere mate voorkomt. Aangezien zowel de diameter stenose als het verschil in minimale luminale diameter na dilatatie en 6 maanden later een normale verdeling laten zien, kan hieruit geconcludeerd worden dat restenose gezien kan worden als de staart van een normaal verdeeld fenomeen, waarbij sommige vernauwingen een meer of minder arbitraire grens overschrijden, en niet als een aparte reactie die optreedt in sommige vernauwingen en niet in andere.

In *hoofdstuk 9* wordt de verdeling van restenose tussen de verschillende segmenten van de 3 belangrijkste kransslagaderen bestudeerd in 1452 vernauwingen, door gebruik te maken van het klassieke "50% diameter stenose criterium" of met de continue benadering van het restenose probleem "relatieve verlies". Ongeacht het criterium werd een gelijke verdeling van restenose gevonden zonder voorkeur voor een bepaald segment.

In *hoofdstuk 10* wordt gezocht naar factoren die restenose - het verlies in minimale luminale diameter - als een weerspiegeling van de grootte van de fibroproliferatieve vaatwand reactie als reactie op de dotter behandeling, zouden kunnen voorspellen. De relatieve winst in minimale luminale diameter was de belangrijkste voorspeller alhoewel de voorspellende waarde van het model in individuele patienten matig was. Deze bevindingen zijn in overeenstemming met dier experimentele en pathologische bevindingen die duidelijk laten zien dat er een relatie bestaat tussen de hoeveelheid beschadiging en de herstel reactie (restenose).

Curriculum Vitae

De schrijver van dit proefschrift werd geboren op 11 juli 1962 te Sluis. Na het behalen van het VWO diploma aan de Scholengemeenschap "St Eloy" te Oostburg in 1980, werd een jaar de opleiding tot fysiotherapeut gevolgd in Vlissingen. In 1981 werd begonnen met de studie Geneeskunde aan de Erasmus Universiteit Rotterdam. Tijdens zijn studie was hij enkele jaren werkzaam in het medisch-studenten-team van het Sophia Kinder Ziekenhuis. Het doctoraal examen werd afgelegd in 1986. Aan het eind van de studie, volgde nog een keuze co-schap van 4 maanden in "John's Hopkins" te Baltimore, waarna het artsexamen in november 1988 met goed gevolg werd afgelegd. Vanaf 1 januari 1989 tot 1 mei 1992 was hij werkzaam op het Thoraxcentrum en werkte mee aan verschillende restenose preventie studies, zowel in Europa als in Canada en de Verenigde Staten. Vanaf 1 mei 1992 is hij begonnen met de opleiding tot cardioloog in het Thoraxcentrum (opleider Prof. Dr. J.R.T.C. Roelandt), waarvan de eerste 2 jaar gevolgd worden op de afdeling Interne Geneeskunde in het Drechtsteden Ziekenhuis locatie Refaja te Dordrecht, met als opleider Dr. B.P. Hazenberg.

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