RESTENOSIS AFTER PERCUTANEOUS TRANSLUMINAL CORONARY ANGIOPLASTY. A QUANTITATIVE ANGIOGRAPHIC APPROACH

Cover: Distribution of the amount of luminal narrowing after coronary balloon angioplasty. The distribution is approximately Gaussian, suggesting that "restenosis" is the tail end of a normally distributed phenomenon rather than a seperate disease entity that occurs in some lesions but not in others.

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RESTENOSE NA PERCUTANE TRANSLUMINALE CORONAIR ANGIOPLASTIEK. EEN QUANTITATIEVE ANGIOGRAFISCHE BENADERING

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Aan mijn vader

Contents

Chapter 1

INTRODUCTION

The first report of a nonsurgical technique of dilating areas of obstructive atherosclerotic disease in the human arterial system was reported by Dotter and Judkins in 1964 [1]. The technique described was for peripheral arteries, and involved the passage of tapered dilating catheters of increasing diameter over a guidewire. This technique had a limited following and was never widely accepted as an established mode of treatment. In 1973 the use of a balloon dilatation catheter in humans was reported. This consisted of the passage of a double lumen dilatation catheter with a non-elastic balloon through an area of stenosis in the femoro-popliteal and iliac arteries. This balloon was then inflated to dilate the stenosis [2]. The late Andreas Grüntzig adapted this technique for use in human coronary arteries. In 1977 he first presented the experimental results of dilating coronary artery stenosis [3]. The first percutaneous transluminal coronary angioplasty in a human was performed by Andreas Grüntzig in Zürich in September 1977. This treatment modality for ischemic heart disease proved to be safe and effective and rapidly gained widespread acceptance. Since then the growth of angioplasty has been dramatic with an exponential growth pattern since its initiation in 1977. An estimated 900.000 procedures were performed worldwide in 1991. Increased experience and advances in technology have resulted in a high primary success rate (over 90%) and a low complication rate (death, non fatal myocardial infarction; 4-5%) [4]. However, the luminal narrowing process after a successful procedure still hampers the long term outcome of the procedure in a considerable percentage of patients.

Mechanisms of coronary balloon angioplasty

Dotter and Judkins [1] in their original description of the angioplasty procedure attributed the mechanism of balloon angioplasty to redistribution and compression of the atherosclerotic plaque. However the vast majority of atherosclerotic plaques in human coronary arteries are composed of incompressible dense fibrocollageneous tissues with varying amounts of calcific deposits and far less amounts of intracellular and extracellular lipid (hard plaques). Therefore it appears unlikely that plaque compression plays a major role in balloon angioplasty (figure 1).

Castaneda Zuniga suggested that angioplasty induced paralysis, by overstretching the vessel wall beyond its limits of elasticity, was the cause of permanent luminal widening after balloon angioplasty. This widening was associated with histopathological features of smooth muscle cell lysis and twisted nuclei [5]. These correlates of severe medial damage were not found in human post mortem arteries after recent dilatation [6,7]. In in vitro models of balloon angioplasty in rabbit iliac artery, rabbit aorta and pig carotid artery, only severe oversizing of the balloon produced impairment of vasoconstrictor responsiveness [8]. Since Roubin et al. showed that deliberate oversizing of the balloon leads to an increased complication rate [9] and that satisfactory initial

results can be obtained by conservative balloon sizing [9,10], severe oversizing of the angioplasty balloon is not common practice in angioplasty today. Therefore arterial paralysis must be questioned as an explanation for the luminal widening achieved by angioplasty in human coronary arteries.

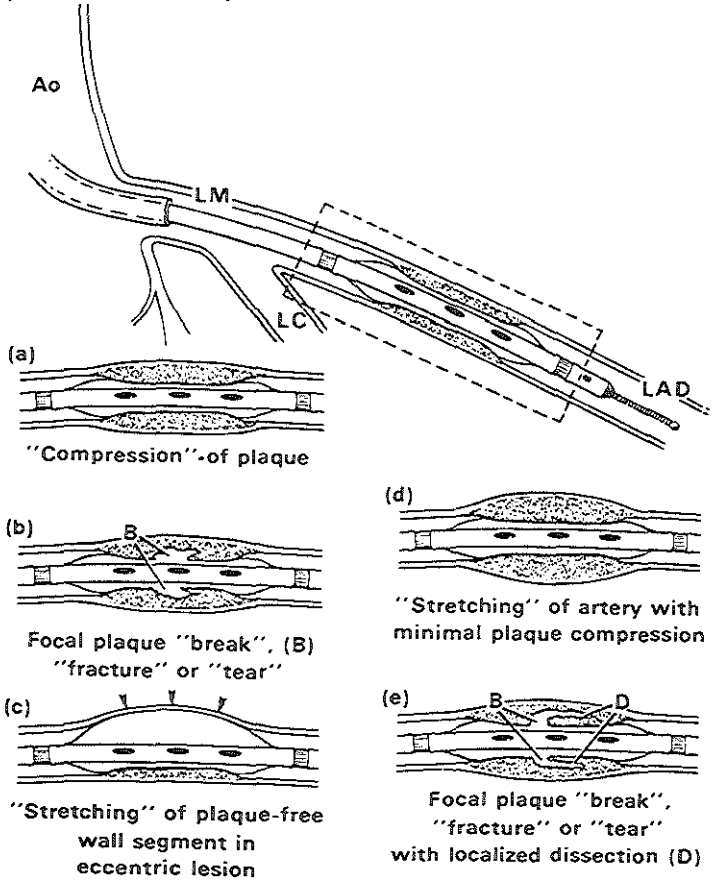

Figure 1. *Diagram showing possible mechanisms of coronary artery balloon angioplasty. Ao = aorta, LAD = left anterior descending artery, LC = left circumflex artery, LM = left main coronary artery. (from Waller, J Am Coll Cardiol 1985;6:1100)*

In an experimental rabbit model Sanborn found that localized aneurysm formation in addition to intimal splitting was responsible for the luminal widening after balloon dilatation of the artery [11].

It is now widely accepted that luminal widening of balloon angioplasty is caused by plaque fracture or splitting with or without localized medial dissection [7,12-18]. Plaque fractures, breaks and dissections within the plaque eventually extending to the

media improve luminal patency by creating additional channels for coronary blood flow (figure 1).

An additional mechanism of luminal widening as proposed by Waller et al.[19,20] seems to be the stretching of the plaque-free wall segment of an eccentric atherosclerotic lesion (figure 1). Balloon inflation in these type of lesions may result in preferential stretching of the non-diseased portion of the vessel wall circumference, while not affecting the relatively rigid remaining portions. Stretching of the plaque-free wall segment may result in an initial increase in coronary cross-sectional area but immediate or delayed elastic recoil might reduce the coronary lumen towards its predilatation state. The presence of immediate recoil has indeed been confirmed by in vivo studies using quantitative angiography and balloon ultrasound inflation catheters (BUIC) [chapter 2, chapter 3, chapter 4, 21-23].

Relatively few studies have been performed, studying the mechanism of balloon angioplasty in vivo. Jain et al. [24] describe three patterns of plaque dilation by examining pressure volume curves created while the balloon was being inflated. The first pattern was stretching of the plaque. After dilation these vessels would recoil and required several dilatations to achieve adequate dilation. The second pattern showed small incremental jumps in the pressure-volume curve. This was believed to reflect progressive compaction of the lesion. The third pattern was sudden yielding of the balloon at a given pressure. This pattern was angiographically correlated with dissection of the artery at the angioplasty site. Hjemdahl-Monsen et al. [25] found that in eccentric lesions more distention of the vessel wall was achieved at the same inflation pressures than in concentric lesions and that the former lesions showed more elastic recoil. Finally, on-line analysis with an intravascular balloon ultrasound inflation catheter (BUIC) shows that plaque fracture is the major contributor to improved luminal patency by balloon angioplasty [26].

Thus the weight of evidence indicates that the mode of action of angioplasty is by "controlled injury" of the vessel wall, with intimal and sometimes medial disruption. Elastic recoil could explain the "stubborn" character of some lesions at angioplasty.

Pathophysiology of luminal narrowing after coronary balloon angioplasty.

Despite widespread acceptance and use of coronary balloon angioplasty to treat severely narrowed coronary arteries in patients with symptomatic coronary heart disease, recurrence of stenoses at the angioplasty site remains a major problem. The frequency of clinical restenosis ranges from 17 to 47 percent depending on variations in definition (angiographic, clinical, physiologic).

It can be hypothesized that restenosis is a manifestation of the general wound healing process expressed specifically in vascular tissue. This process is very complex and

requires the interaction of an abundance of chemical substances and cells. The following is a speculative model of a largely unknown process and has recently been proposed by Forrester [27].

According to Forrester an analogy exists between wound repair, and the healing of coronary arteries after balloon damage [27]. The process begins with platelets aggregating at the damaged area. Aggregating platelets release substances that promote local vasoconstriction, further platelet aggregation and thrombus formation (e.g. thromboxane A2), and growth factors (e.g. Platelet Derived Growth Factor, PDGF) that activates mesenchymal cells in the vicinity of the injured site. Within a few hours monocytes appear. These monocytes also produce growth factors with chemotactic and mitogenic effects on local mesenchymal cells. An abundance of growth factors is now known and their actions and interactions are highly complex.

The next phase consists of cell migration into the damaged area. Endothelial cells from the wound margin migrate and proliferate to cover the wound surface. Smooth muscle cells begin to migrate and proliferate from adjacent tissue to the injured area. Smooth muscle cells migrating into and proliferating within the intima exhibit ultrastructural and functional properties equivalent to synthetic phenotype cells in culture; such cells show increased amounts of synthetic organelles, loss of capacity to contract and increased capacity to divide [28,29]. In contrast, cells of the contractile phenotype possess the opposite properties and make up most smooth muscle cells in normal vessels. Control of smooth muscle cell migration and proliferation is determined by the action of mitogens (e.g. PDGF) and opposing effects of inhibitors (e.g. heparin sulfates).

The third phase, extracellular matrix deposition and remodelling, continues for months. Smooth muscle cells slow their proliferation and begin to produce large amounts of extracellular matrix components. The injured blood vessel thus develops the histologic appearance of intimal hyperplasia: proliferating smooth muscle cells scattered through a loose extracellular matrix. By several months the return to contractile phenotype of the smooth muscle cells is parallelled by a change in extracellular matrix: proteoglycans are replaced by large bundles of type I collagen and elastin.

In Forrester's model restenosis is thought to result from migration and replication of medial smooth muscle cells into a developing neointima. An alternative model has recently been proposed by Schwartz et al. on the basis of observations in a porcine coronary injury model [30,31]. In their opinion 3 cellular stages can be identified as an obstructive neointima develops in response to arterial injury. In the thrombotic stage early after injury platelets, fibrin and red blood cells accumulate at the site of injury. In the recruitment stage, this thrombus endothelializes and mononuclear cells infiltrate on the lumen side of the vessel. In the proliferative stage cells staining positive for alpha actin (smooth muscle cells or myofibroblasts) appear on the luminal side of the

degenerating thrombus. These cells form a thin cap just beneath the endothelial surface. This cap thickens downward towards the media as the remaining thrombus material is resorbed. The healing process reaches completion when all thrombus material has been resolved and replaced by neointima and the mononuclear infiltrate has disappeared. The origin of the smooth muscle cells in this model is apparantly not the media at the site of damaged to the artery, since they first appear at the luminal side of the endothelialized thrombus. This model places mural thrombus in the center of the restenosis process. From their observations Schwartz et al. conclude 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.

Other mechanisms of luminal narrowing at the angioplasty site involve progression of atherosclerotic disease and gradual elastic recoil of an overstretched disease free wall in an eccentric lesion or return to predilatation state of a stretched concentric lesion, as proposed by Waller [32]. In chapter 2,3 4 and 5 the contribution of elastic recoil to luminal narrowing after balloon angioplasty will be extensively discussed.

Timing of restenosis

In 1988 two different studies, performing follow-up angiography at different pre selected follow-up intervals gave remarkable similar results and showed how lesions behave after angioplasty [33,34]. In the study carried out at the Thoraxcenter the 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 the subsequent follow-up times (2,3,4,5 months) [34,35]. Nobuyoshi and colleagues restudied 229 patients at 24 hours, 1, 3, 6 and 12 months [33]. Their findings were very similar to those from the Thoraxcenter (figure 2) Furthermore, lesion progression after 6 months was found to be unusual [33]. These findings show a remarkable resemblance with the peak of intimal hyperplasia after vascular injury in animals, which reaches a peak at 4 to 12 weeks [36,37].

Symptoms, function or anatomy as for the assessment of restenosis?

The incidence of late restenosis has remained much the same since the introduction of coronary angioplasty 14 years ago and a preventive treatment against restenosis still has to be developed. Primary success and restenosis after angioplasty may be defined by symptomatic criteria, like severity of angina pectoris, by functional criteria, such as provided by various exercise tests, or may be defined by anatomic criteria using histology, angiography or intravascular ultrasound. These three sets of criteria may be considered separately or may be interrelated.

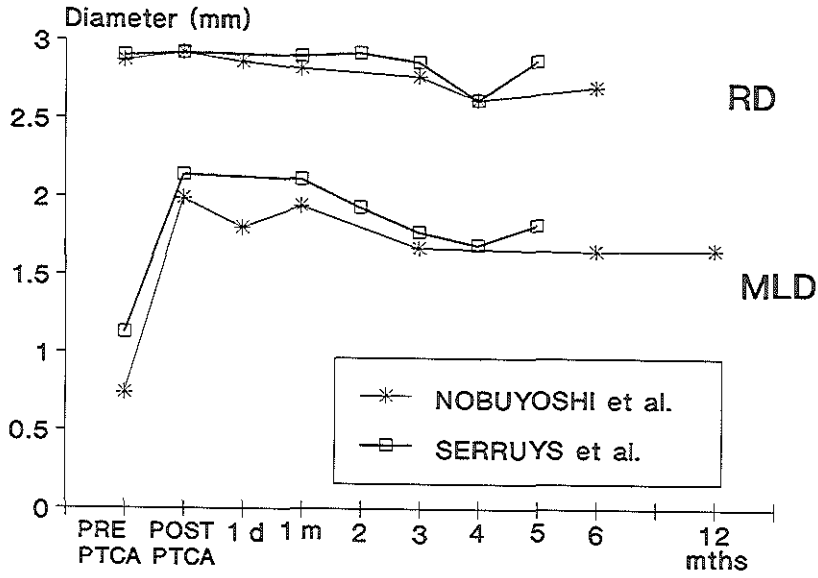

Figure 2. *Minimal lumen diameter (MLD) and reference diameter (RD) measurements as reported by Nobuyoshi et al. [33] and Serruys et al. [34,35].*

1) Symptomatic criteria.

Although the subjective improvement of symptoms after coronary balloon angioplasty is probably the most desirable end-point, it is also the least objective evaluation [38]. The frequency of symptomatic improvement appears to be lower than that of angiographic success: only 70% of the patients with a satisfactory angiographic result immediately post angioplasty exhibit such an improvement, probably due to incomplete revascularization in multivessel disease [39]. Furthermore, the reappearance of angina as criterion of restenosis underestimates the angiographic rate of restenosis as the reported incidence of silent restenosis may be as high as 31% [40]. In a recent review, Califf et al. [41] described that in studies with a high rate of angiographic follow-up, the probability that patients with symptoms had restenosis (i.e. the positive predictive value) ranged from 48% to 92%, whereas the probability that patients without symptoms were free of restenosis (i.e. the negative predictive value) ranged from 70% to 98%. 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.

2) Functional criteria

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 at exercise or both is not highly predictive of restenosis whether the test is performed early or late after angioplasty. The positive predictive values of early exercise testing range from 29% to 60%, and the corresponding values for late exercise testing range from 39% to 64% [41,42]. The low positive predictive value is most likely a consequence of incomplete revascularization, that is a significant stenosis at a site other than that dilated by angioplasty. It is, however, also possible that the non-invasive test is accurately demonstrating 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% [41]. 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 [43]. In studies with a high angiographic follow-up rate, the negative predictive value of thallium scintigraphy varies between 42 and 100% Potentially, tomographic imaging of nuclear scintigrams may prove superior to planar imaging for the detection of restenosis [44].

3) Anatomic criteria

a. Intravascular ultrasound

Intravascular ultrasound (IVUS) has been shown to yield detailed cross-sectional images of the arterial wall and, therefore, has the potential to offer new insights into the mechanisms, complications and long-term results of coronary interventions. Before IVUS can be accepted as an alternative to arteriography, several significant limitations need to be surmounted. 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. When these technical obstacles have been overcome and the clinical efficacy of this exciting new imaging modality has been established, its contribution to our understanding of the restenosis process will be invaluable.

b. Histology

In vivo histological examination, by taking biopsies from intracoronary lesions with an

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. Furthermore, this technique is only applicable in a subset of patients with a lesion suitable for atherectomy treatment. Some authors have suggested that there may be a relationship between the cellular density of the atherectomy specimen [45] or growth rate and migratory rate of these cells in culture [46-49] and the later development of restenosis.

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. The numerous studies already available on coronary restenosis using angiography, lack consistency in their methods and the definitions of restenosis used. Figure 3 illustrates this point. On the vertical axis of this "non scientific" figure, we have the names of the investigators, who have studied the restenosis problem, on the horizontal axis we have the restenosis rates observed in their studies. A restenosis rate ranging between 15 and 55% seems to emerge. However, we have to emphasize the following facts: the angiographic follow up ranges between 57 and 100%, the time to follow-up ranges between 1 and 9 months, 11 different criteria of restenosis have been applied and finally, visual assessment of the coronary angiogram was used in these studies.

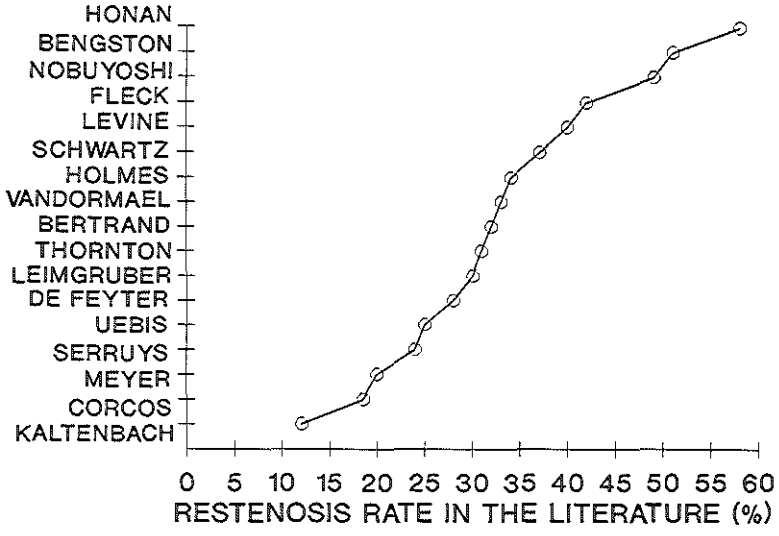

Figure 3. *Restenosis rates reported in the literature, applying 11 different restenosis criteria, different angiographic follow-up periods (1-9 months), while the percentage of patients undergoing repeat angiography varied (57-100%). In addition, different angiographic analysis techniques (visual or quantitative) were used.*

The variety of restenosis criteria in current use is shown in Table 1. As stated by Beatt et al. [50] most are entirely arbitrary, some are based on doubtful logic and some, although of some relevance for visual estimation of percent diameter stenosis, are unrealistic (e.g NHLBI II criterion) when applied to the more accurate values obtained from quantitative angiography. Most of the discrepancies between these studies can be attributed to 3 factors [50]: 1) selection of patients, 2) method of analysis and 3) the definition of restenosis used.

ad 1. In order to objectively asses the long term outcome it is necessary for all patients to be angiographically followed up at a predetermined time interval. This will avoid a selection bias in favor of symptomatic patients. The sample size of any clinical trial must be adequate to avoid type II error.

ad 2. A well validated system of analysis with known accuracy and variability must be employed. The use of a visual percent diameter stenosis measurement with its inherent inter- and intraobserver variability precludes meaningful results, and edge tracing by hand or other techniques that produce values not physiologically possible, are also unacceptable [51-53]. Videodensitometry may eventually provide the best measurement because the technique estimates the cross-sectional area of the lumen independent of geometric assumptions, but for technical reasons this method has not (yet) proven practical [54].

ad 3. The measured variable must be chosen so as to reflect the restenosis proliferative process and distinguish between the acute results of angioplasty (good or poor) and this proliferative process. We believe that the conventional assessment of percent diameter stenosis is not sufficiently discriminating in doing this and that definitions based on percent diameter stenosis measurement fail to identify lesions undergoing significant deterioration [50,55]. The >50% diameter stenosis at follow-up criterion may be of some relevance in determining a significant stenosis in human atherosclerotic vessels [56], but it tells us nothing about the dynamic behavior of the lesion since the angioplasty procedure. Furthermore, percent diameter stenosis criteria relate the minimal lumen diameter to the so called "normal" diameter of the vessel in the immediate vicinity of the obstruction. This assumes that there is a normal diameter, but diffuse intimal or subintimal thickening is frequently present in arteries with discrete stenoses (particular in multivessel disease). A coronary angiogram is not able to detect diffuse atherosclerotic disease. In addition, this "normal" area almost certainly is affected by the barotrauma of the balloon and will therefore also be involved in the reactive intimal hyperplasia and luminal narrowing [55]. This seriously questions the use of percent diameter stenosis as the index of restenosis.

Table 1. Criteria of restenosis in current use

1.	Reduction $\geq$30% in diameter stenosis (NHLBI I)
2.	An immediate post angioplasty diameter stenosis < 50% that increases to $\geq$70% at follow up (NHLBI II)
3.	A return to within 10% of the pre-angioplasty diameter stenosis (NHLBI III)
4.	Loss of at least 50% of the initial gain (NHLBI IV)
5.	As for 2 but for a diameter stenosis $\geq$50% at follow-up
6.	Reduction $\geq$20% in diameter stenosis
7.	A diameter stenosis $\geq$50% at follow-up
8.	A diameter stenosis $\geq$70% at follow-up
9.	Area stenosis $\geq$85%
10.	Loss $\geq$1 mm^2 in stenosis area
11.	Deterioration of $\geq$0.72 mm in minimal lumen diameter from post angioplasty to follow-up
12.	Deterioration of $\geq$0.5 mm in minimal lumen diameter from post angioplasty to follow-up

NHLBI = National Heart Lung and Blood Institute restenosis criterium

Quantitative angiography for the assessment of luminal narrowing after successful coronary balloon angioplasty

Attempts to correlate closely the anatomy of a coronary stenosis and its physiologic significance by visual interpretation of cineangiograms are hampered by several serious shortcomings. The large intra- and inter-observer variability [57-60], and lack of correlation with pathologic [61] findings of visually interpreted coronary cineangiograms are well recognized. Inter- and intraobserver variations from 8% to 37% in judging the location and severity of coronary obstructions from visual interpretations have been well documented in the literature. Furthermore, the reproducibility of visual lesion assessment is influenced by the severity and extent of the coronary stenosis. In general, visually assessed lesions between 20% and 80% diameter stenosis ("moderate lesions") have a wider range of inter- and intraobserver variability than stenoses less than 20% or more than 80%. The limitation that visual lesion assessment is not sufficiently accurate [62] for measuring small 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 altered until an obstruction of at least 85% is present, maximal coronary flow is already diminished by obstructions as small as 30% and marked impairment of coronary flow reserve occurs with progressive diameter stenosis above

65%. Quantitative angiographic analysis in the Carport trial (chapter 8) revealed that mean gain in lumen diameter achieved by angioplasty was 0.75 mm or 28% in diameter stenosis. Mean loss in lumen diameter at follow up was found to be -0.31 mm or 12% in diameter stenosis. It is clear that such small changes cannot be accurately assessed by visual interpretation of cineangiograms. A quantitative computer based analysis technique enhances objectivity, while it reduces the problem of high inter and intraobserver variability inherent to visual interpretation of the coronary cineangiogram [52,63].

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. The changes in minimal lumen diameter from post angioplasty to follow-up angiography gives a reliable quantitative measurement of luminal narrowing. It describes the magnitude of the reactive intimal hyperplasia after balloon trauma to the vessel wall. The minimal lumen diameter is an unambiguous measurement of lesion severity (simply the lowest point on the diameter function curve (figure 5)) and has the lowest long term variability of all quantitative angiographic measurements of lesion severity [64].

For the purpose of clinical trials a continuous measure of luminal reobstruction is preferable over a binary measure (restenosis yes/no). When the main concern is clinical decision making, however, a binary or categorical measure of restenosis provides clinicians with more workable information. Keeping in mind that an angiographic restenosis study assesses only the anatomical component of the restenosis problem, the threshold above which a loss in luminal diameter would have clinically significant functional or symptomatic consequences is not of great importance. Why then would one bother to try to define a threshold above which "significant" quantitative angiographic restenosis occurs? The possible benefit of a treatment (pharmacological or interventional) can be measured with much greater precision by comparing the absolute change in lumen diameter for each treatment group. For example, if treatment is expected to reduce the loss in lumen diameter from 0.4 ± 0.50 mm under placebo [34], to 0.25 ± 0.50 mm under active medication with a power of 90%, it can be calculated that 233 patients will be required per treatment group. The above treatment effect corresponds with restenosis rates (defined as loss in minimal lumen diameter of ≥ 0.72 mm) of 25% and 17.5% respectively (figure 4). When alternatively a categorical restenosis definition is used in order to demonstrate the same difference (with a power of 90%) in restenosis rates (7.5%), 620 patients per treatment group will be required. This is because a categorical end point does not take full advantage of the available information. In chapters 8 and 9 this continuous approach has been followed to study the possible beneficial effect of a thromboxane A2 receptor blocker on the restenosis process

and to find risk factors for the luminal narrowing process.

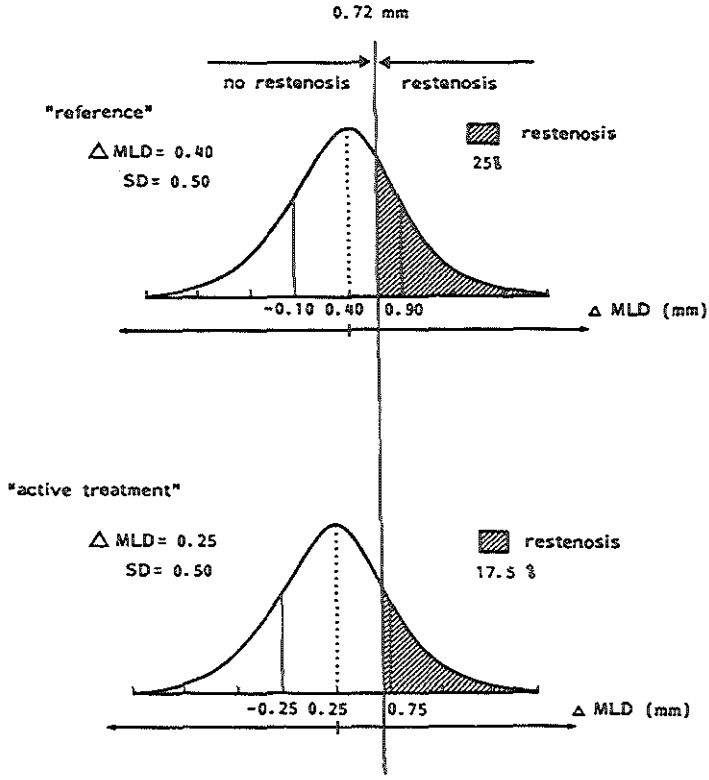

Figure 4. *Gaussian model of luminal narrowing after angioplasty in the reference group and in the treatment group, considering a 30% reduction in change in minimal lumen diameter (MLD) in the latter group. Under this Gaussian model one can calculate the corresponding restenosis rates (applying the ≥0.72 mm loss in MLD restenosis criterium). This restenosis rate (25%) is very close to the actually observed restenosis rates in the study of Serruys et al. [34]. Under this continuous model 233 patients per treatment group are required to show a 30% reduction in change in MLD with a power of 90%. If however a categorical model is applied then 620 patients per treatment group are required to show a decrease in restenosis rate from 25% to 17.5% (30%) with the same power.*

Description of the quantitative angiographic analysis system

a) Edge detection

The quantitative angiographic analysis system we applied is the Coronary Angiographic Analysis System (CAAS) and has been in operation at the Thoraxcenter since 1982. The system has been extensively validated and described in detail elsewhere [52,64]. Essentially, the contours of a selected coronary segment are detected automatically from

optically magnified and videodigitized regions of interest (512 x 512 pixels) of an end diastolic cineframe. Absolute diameter values (in mm) are determined using the guiding catheter as a scaling device (each individual catheter tip is retained and measured by micrometer). A correction factor for the selective magnification of an object near the edges of the image intensifier (pincushion distortion) is introduced. From the detected vessel contours, a diameter function is determined by computing the shortest distances between corresponding left hand and right hand contour positions (figure 5). The difficulty with selection of reference or "normal" diameter is solved by using a computer derived or "interpolated" reference diameter, by which technique the computer reconstructs the original "disease-free" dimension of the segment of interest, on the basis of diameter measurements proximal and distal to the obstruction. The interpolated reference diameter is then determined at the site of the minimal lumen diameter (figure 5). The interpolated technique allows for tapering of the vessel (figure 5). The area between the actual and reconstructed contours at the obstruction site is a measure for the amount of "atherosclerotic plaque" and is expressed in mm^2. The length of the obstruction site is determined from the diameter function on the basis of curvature analysis and expressed in millimeters. Using the reconstructed borders of the vessel wall, the computer can calculate a symmetry coefficient for the stenosis. A symmetrical lesion having a value of 1 and a severe eccentric lesion having a value of 0 (figure 5).

b) Densitometric procedure.

Constitution of the relationship between pathlength of the X-rays through the artery and the brightness value requires a detailed analysis of the complete X-ray/cine/video chain, including the film development process [65]. For the first part of the chain from the X-ray source 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 upto the brightness values in the digital image we use a linear transfer function. Details of this technique have been described elsewhere [66]. The cross-sectional area of a vessel is then obtained as follows. The contours of a selected arterial segment are detected as described above. On each scanline perpendicular to the centerline a profile of brightness values is measured. This profile is transformed into an absorption profile by means of a 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 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 each scanline, the cross-sectional area function is obtained. Calibration of the densitometric area values is accomplished by comparing the reference area calculated from the diameter measurements (assuming a circular

cross-section) with the corresponding densitometric area value.

Theoretically, densitometry seems the ultimate solution for the computation of a vessel's cross-sectional area from a single angiographic view [67-72]. Phantom studies have shown that densitometry is a very attractive, precise, and accurate technique for the assessment of the severity of coronary obstructions from only a single view in vitro. In particular if the cross-sectional shape is highly irregular as after angioplasty, densitometry is expected to be more reliable than edge detection methods. The in vitro measurement of radiographic phantoms however, cannot reproduce some of the sources of error of the videodensitometric approach in-vivo. Arterial branches overlapping or parallel to the analyzed segment impairing the measurement of the density of the lumen or of its background, patient structural noise inducing an inhomogeneous background, lack of orthogonality of the vessel with the radiographic beam, inhomogeneous filling of the vessel during injection are conditions which cannot be assessed in in vitro studies. Therefore Di Mario et al. (unpublished data) from our institution performed an animal study to validate and compare edge detection and videodensitometry techniques of the CAAS system in vivo. Phantoms with known circular lumina were implanted in the left coronary arteries of pigs and cineangiograms were obtained. Twenty eight cineframes were analyzed. Both edge detection and videodensitometry showed a good correlation with true phantom dimensions (minimal lumen diameter (MLD) and cross-sectional area (CSA)). Correlation coefficients for MLD measurements were 0.95 with a SEE of 0.12 for edge detection and 0.93 with a SEE of 0.19 for videodensitometry. Correlation coefficients for CSA measurements were 0.94 with a SEE of 0.24 for edge detection and 0.94 with a SEE of 0.31 for videodensitometry (figure 6). The mean differences between edge detection and densitometric MLD and CSA measurements and corresponding true phantom dimensions were calculated and considered an index of the accuracy of the measurements, while the standard deviation of the differences was considered an index of precision. For MLD measurements mean differences were -0.06 ± 0.14 mm for the edge detection technique and -0.11 ± 0.20 for the videodensitometry technique (difference not significant). For CSA measurements mean differences were -0.15 ± 0.30 mm^2 for the edge detection technique and -0.12 ± 0.31 mm^2 for the videodensitometry technique (difference not significant). These circular phantoms however, probably do not mimic true arterial obstructions since it is known that a large percentage of coronary lesions are non circular in particular immediately after balloon angioplasty [72]. Furthermore, some of the most important sources of non-linearity of densitometry such as scatter/veiling glare and beam hardening are difficult to correct for in vivo. The analyses in the Carport study showed that in approximately 10% of the pre-angioplasty cineframes, 2% of the post-angioplasty cineframes and 4% of the follow-up cineframes, videodensitometry failed to measure the lumen cross-sectional area because of the combined effect of low density of a severe stenosis, dense background and/or presence of parallel vessels interfering with the

background subtraction. Medium- and long term variability studies for videodensitometric assessment of lesion severity have not been performed for the CAAS system and are certainly a prerequisite before this technique can be applied for large scale restenosis prevention studies or atherosclerosis progression regression studies.

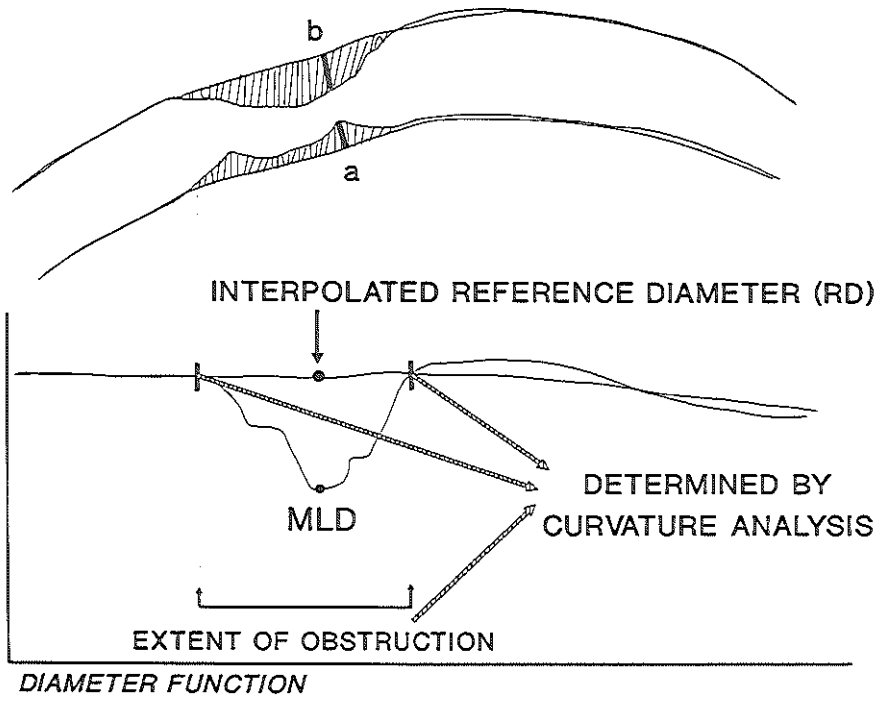

Figure 5. *Graphic representation of the quantitative angiographic measurements. The upper panel represents a stenosed arterial segments. The lower panel is the diameter function curve. The length of the analyzed segment is depicted on the X-axis and the vessel diameter on the Y-axis. MLD = minimal lumen diameter. Extent of obstruction = Lesion length. Lesion length is determined with curvature analysis of the descending and ascending limb of the diameter function curve at the site of the MLD. Eccentricity is determined the site of the MLD and calculated as a/b. The plaque area is depicted by the hatched part of the upper panel drawing.*

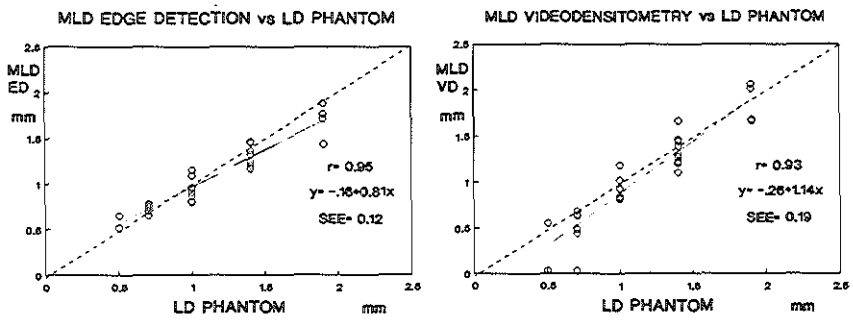

Figure 6a. *Lineair regression analysis of the phantom lumen diameter (LD) vs the minimal lumen diameter (MLD) measured with edge detection (left) and videodensitometry (right). The dashed line and the continuous line correspond to the line of identity and the regression line respectively.*

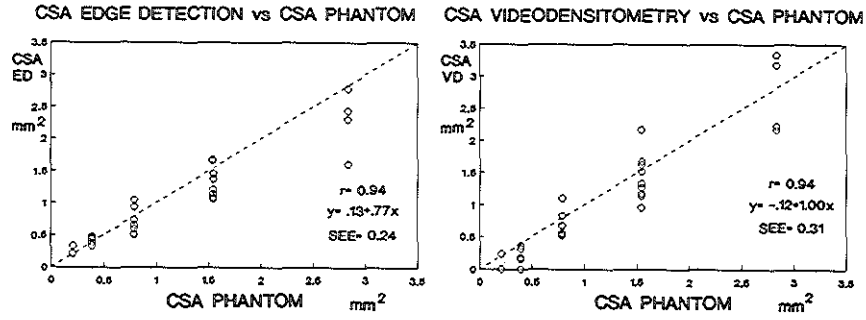

Figure 6b. *Lineair regression analysis of the phantom cross-sectional area (CSA) vs the CSA measured with edge detection (left) and videodensitometry (right). The dashed line and the continuous line correspond to the line of identity and the regression line respectively.*

Variability of angiographic data acquisition

For the interpretation of the quantitative coronary angiographic results from intervention studies, the total variability of the angiographic data acquisition and analysis procedure must be known. The source of variation and the approaches towards standardization for the technical aspects of the CAAS system are beyond the scope of this chapter. These are described in detail elsewhere [73,74]. The angiographic data acquisition is also hampered by various sources of variation. Measures taken to minimize the variation in data acquisition and analysis in the studies presented in the following chapters are discussed below and in Table 3.

1. On line registration of X-ray system settings
The angular settings of the x-ray system were recorded for every projection filmed at angioplasty and repositioned at follow-up angiography to correspond exactly to the projections used during angioplasty angiography

2. Preangiographic administration of vasodilative drugs
One of the most important variables in the quantitative assessment of arterial dimensions is the vasomotor tone. If no precautions are taken, the vasomotor tone may differ even during immediate consecutive coronary angiographic studies. The only way to achieve such control is by attempting to reach the ceiling of vasodilation of the vessels by means of a drug that produces fast and complete vasodilation. Such results seem to be obtained most reliably by the intracoronary administration of nitrates [75]. Therefore the same dose of intracoronary nitrates, either nitroglycerin 0.1-0.3 mg or isosorbidedinitrate 1-3 mg, was given before each angiographic study (pre angioplasty, post angioplasty and at follow-up angiography).

3. Use of nonionic and iso-osmolar contrast media
Adverse effects of conventional contrast media are related to single-valence cations, such as sodium and meglumine, to an imbalance in the ratio of sodium to calcium ions, to the high osmolality of the solutions and to their hyperviscosity [76]. Collective studies offer experimental and clinical evidence of the advantage of the low-osmolality agents in radiology [77,78]. Jost et al. have clearly demonstrated that the vasodilative changes in vessel dimensions due to the contrast medium administration are significantly smaller with use of a nonionic contrastmedium than with use of an ionic contrast medium [79]. Therefore, in quantitative coronary angiographic studies, nonionic contrastmedia with iso-osmolality should be applied. Because the data presented in this thesis originate from a multicenter trial it was unpractical to impose the use of 1 or 2 possible contrastmedia on all participating centers. Therefore it was requested to use the same type of contrastmedium at baseline and follow-up angiography.

4. Selection of catheter material

In the quantitative angiographic studies described in this thesis, the contrast catheters have been used for calibration. To determine the accuracy of such calibration measurements from coronary cineangiograms and the effects of catheter material, contrast filling of the catheter and kilovolt setting of the x-ray source on image quality of the irradiated catheter and thus on the accuracy of the measurements, Reiber et al. analyzed 4 catheter materials filmed under different conditions [80]. On the basis of their evaluation data it was concluded that woven dacron is the most suitable material for quantitative coronary angiographic studies. The polyvinylchloride and polyurethane catheters performed equally well, but slightly less than the woven dacron catheter. The nylon catheter should however not be used for these type of studies. Investigators in the studies described in this thesis were asked not to use nylon catheters.

5. Micrometer measurement of catheters following catheterization [80]

It has been our experience that the size of the catheter as specified by the manufacturer often deviates from the true size. If the manufacturers cannot guarantee narrow ranges for the size of the catheter, for example ± 0.05 Fr, its actual size should be determined with a micrometer following the catheterization. This problem is even more significant for the tip of a catheter, which is often hand-made and thus poorly specified. Most often the tip of the catheter is used for calibration. Films from all centers involved were requested to send the tips of all used catheters to the central core laboratory for film analysis. Prior to film analysis the exact size of the catheter was determined with a micrometer.

In addition, several other measures were taken to standardize the method of data acquisition and analysis of the preangioplasty, post angioplasty and follow-up angiograms. All cineframes to be analyzed were preferentially selected at end-diastole to minimize any possible blurring effect of motion and to limit foreshortening often observed during systole. In cases where the segment to be analyzed overlapped with other vessels or structures, the frame was selected at end systole or as near as possible to end-diastole. Before the post-angioplasty angiogram, totally radiopaque guidewires had to be removed to avoid interference with automated edge detection. The user defined beginning and end points of the analyzed segments in the coronary tree were identified according to the definitions of the American Heart Association [81]. Hard copies of the videoimage of the analyzed segment with the detected contours superimposed were made to ensure that the follow-up analysis was performed on the same coronary segment.

Table 3. Sources of variation in angiographic data acquisition and analysis

Sources of Error	Prevention
Patient related	
Patient size	...
Vasomotor tone	Standardized vasodilation
Vessel motion (blurring)	
Cardiac	End-diastolic frame
Respiratory	Held inspiration
Cyclic variation in diameter	End-diastolic frame
Geometric considerations	
Vessel curvature, stenosis irregularity, relation to other vessels or branches	Many projections
Technique related	
Different x-ray gantry settings between 1st and second film	On-line annotation of x-ray gantry settings
Foreshortening	Object of interest parallel to image intensifier
Insufficient mixing of contrast	At least 7F catheter, big bolus injection, with injection pump, isoviscous, isoosmolar contrast medium
Pincushion distortion	Lesion or segment of interest centrally located
Methodology related	
Edge detection algorithm	1st derivative: overestimation 2nd derivative: underestimation weighted sum 1st and 2nd derivative: precise
Calibration technique	Catheter tip caliper measurement
Pincushion distortion	Correction for each particular image intensifier

From de Feyter et al. Circulation 1991;84:414

Overview of the thesis

The central topic of this thesis is early (immediate and up to 24 hours) and late (6 months) luminal narrowing after percutaneous transluminal coronary balloon angioplasty as assessed by quantitative angiography.

In chapter 2 to 4 the role of elastic recoil as a cause of early luminal narrowing after balloon angioplasty is studied (up to 24 hours after angioplasty). In the studies described in chapter 2 and 4 videodensitometry was used to assess lesion severity before and after angioplasty because the balloon could only be filmed in 1 projection and videodensitometry offers the opportunity to accurately measure the cross-sectional area of a stenosis site in only 1 projection. It was assumed that edge measurements of performed in only 1 projection might be less accurate than the usual average value of MLD and cross-sectional area obtained from multiple projections. Therefore it seemed methodologically more correct to compare balloon measurements with lesion measurements in the same single projection using videodensitometry.
The 136 patients described in chapter 2 represent the first 136 consecutive patients in the Carport study in whom the balloon was filmed and in whom videodensitometry was possible in the same projection as the balloon was filmed in. In chapter 4 the same applied for the first 526 consecutive patients enrolled in the Carport trial. The patients described in chapter 3 were enrolled in a trial comparing the efficacy of recombinant hirudin to heparin with respect to 24 hour patency after balloon angioplasty. Only patients in whom a balloon was filmed in a non-foreshortened projection were analyzed and described in this preliminary report.

In chapter 5 angiographic risk factors, including stretch and recoil, for long term luminal narrowing (6 months) after a successful angioplasty procedure were investigated. To obtain independent predictors of a significant loss in MLD (loss $\geq$ 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.

One risk factor for restenosis that has been the subject of controversy in the literature is the site of dilatation, with according to some, a higher risk of restenosis in the proximal left anterior descending (LAD) coronary artery as compared to lesion in the right coronary artery and circumflex artery. In chapter 6 this was investigated in 1234 patients (follow-up rate 91%). For this study quantitative angiographic data of the Carport and Mercator trial were combined. The latter is a restenosis prevention trial comparing an ACE inhibitor (cilazapril) to placebo. In the Mercator trial neither angiographic nor clinical benefit of cilazapril could be demonstrated so both treatment groups (clazapril, placebo) could be pooled.

In chapter 7 it was investigated whether luminal narrowing or restenosis after balloon angioplasty occurs only in a subset of patients/lesions or that it occurs to a

certain extent in all dilated patients/lesions. For this study quantitative angiographic data of the Carport and Mercator trial were again combined.

In chapter 8 the results of the Carport trial are presented. In this restenosis prevention trial a thromboxane A2 receptor antagonist (GR32191B) was compared to placebo with respect to the amount of luminal narrowing at 6 months follow-up. Most of the data described in the thesis originate from this trial.

In chapter 9, we investigated which quantitative angiographic parameter best predicts the functional status of patients 6 months after successful coronary balloon angioplasty. Only patients with single vessel disease and a single site dilatation with quantitative angiographic follow-up were studied. Patients described in this study were enrolled in the Carport trial.

Finally in chapter 10, an attempt was made to predict the absolute change in lumen diameter at follow-up angiography with simple, independent, clinical, lesion related and procedure related variables collected in the Carport trial. Therefore a multiple linear regression analysis was applied to 666 lesions with the change in minimal lumen diameter from post angioplasty angiogram to follow-up angiogram as dependent variable.

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Chapter 2

QUANTITATIVE ANGIOGRAPHIC ASSESSMENT OF ELASTIC RECOIL AFTER PERCUTANEOUS TRANSLUMINAL CORONARY ANGIOPLASTY

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Quantitative Angiographic Assessment of Elastic Recoil After Percutaneous Transluminal Coronary Angioplasty

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

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

METHODS

Contour detection: The quantitative analysis of the stenotic coronary segments was performed with the computer-assisted Cardiovascular Angiography Analysis System (CAAS), which has been described in detail elsewhere.[6,7] To analyze a coronary arterial segment a 35-mm cine frame was selected. Electronically, a region of interest (512 × 512 pixels) encompassing the arterial segment to be analyzed was digitized with a high-fidelity videocamera. Contours of the arterial segments were detected automatically on the basis of the weighted sum of first and second derivative functions applied to the digitized brightness profile. From these contours the vessel diameter functions are determined by computing the shortest distance between the left and right contour positions (the upper curve in Figure 1). Conversion of the diameter measurements of the vessels to absolute values was achieved by using the contrast catheter as a

scaling device. To this end the contours of a user-defined portion of the optimally magnified catheter (optimal magnification factor $2\sqrt{2}$) are detected automatically and corrected for pincushion distortion caused by the image intensifiers. In arteries with a focal obstructive lesion and a clearly normal proximal or distal arterial segment, the choice of the reference region is straightforward and simple. However, in cases where the proximal or distal part of the arterial segment shows combinations of stenotic and ectatic areas, the choice may become difficult. To circumvent these problems, we implemented a method that is independent on a user defined reference region. This technique is denoted "interpolated reference diameter measurement."[8] The principle of this technique is the computer estimation of the original vessel diameter at the site of obstruction (Figure 1). The white areas in the figure are measures for the "atherosclerotic plaque" and are defined by the actual luminal contours and the reconstructed reference contours. The length of the obstruction site is determined from the diameter function on the basis of curvature analysis and expressed in millimeters. Using the reconstructed borders of the vessel wall, the computer can calculate a symmetry coefficient for the stenosis: a symmetrical lesion having a value of 1 and a severe eccentric lesion having a value of 0. Symmetry is defined as the coefficient of the left hand distance between the reconstructed and actual vessel contours and the right hand distance between reconstructed and actual contours at the site of obstruction. In this equation the largest distance between actual and reconstructed contours becomes the denominator. The curvature value at the obstruction site, as a measure for coronary bending, is computed as the average value of all the individual curvature values along the centerline of the coronary segment, with the curvature defined as the first derivative of the tangent as it moves along the centerline, which for a circle is equal to the reciprocal of the radius.

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

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

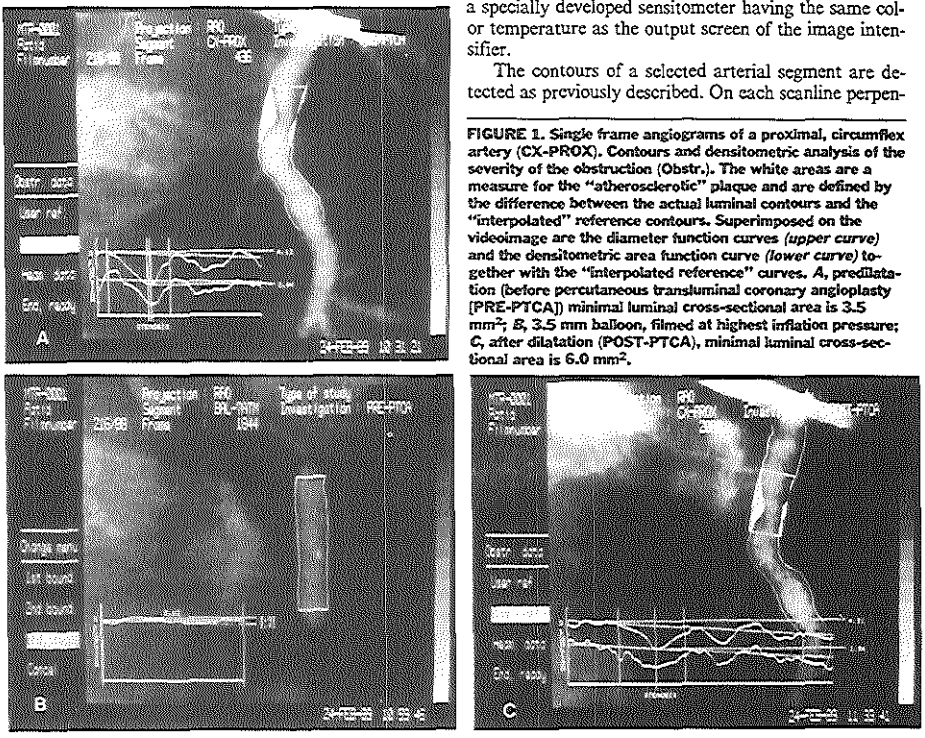

FIGURE 1. Single frame angiograms of a proximal, circumflex artery (CX-PROX). Contours and densitometric analysis of the severity of the obstruction (Obstr.). The white areas are a measure for the "atherosclerotic" plaque and are defined by the difference between the actual luminal contours and the "interpolated"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

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

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

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

RESULTS

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

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

TABLE I Recoil in 151 Coronary Arterial Narrowings

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

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

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

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

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

TABLE III Clinical Characteristics and Recoil in 136 Patients

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

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

TABLE IV Angiographic and Procedural Characteristics and Recoil of 151 Lesions

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

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

TABLE V Recoil in the Three Main Coronary Arteries

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

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

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

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

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

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

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

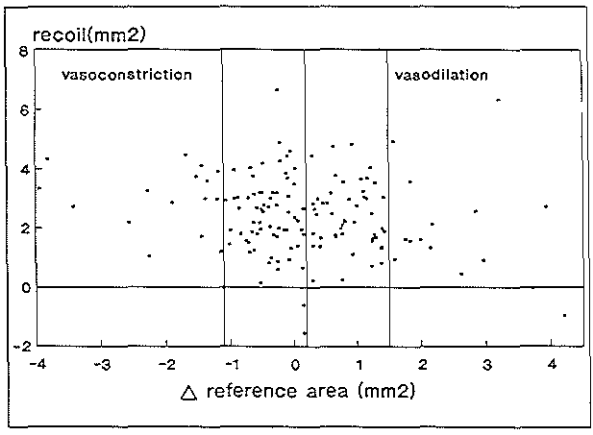

FIGURE 2. In this scatterplot the difference in interpolated reference area before and after percutaneous transluminal coronary angioplasty is plotted against the amount of recoil for each segment. The mean difference in reference area was 0.2 ± 1.3 mm² *(vertical lines in graph)*. The values are randomly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

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

DISCUSSION

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

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

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

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

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

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

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Chapter 3

IS RECOIL AFTER PERCUTANEOUS TRANSLUMINAL CORONARY ANGIOPLASTY AN INSTANTANEOUS PHENOMENON OR IS THERE ALSO A DELAYED COMPONENT?

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INTRODUCTION

It is a common clinical observation that in some lesions percutaneous transluminal coronary balloon angioplasty does not achieve a satisfactory result in the absence of a visible tear or dissection. This phenomenon has been investigated using quantitative angiography and intravascular ultrasound and has been attributed to elastic recoil of the vessel wall that was stretched within its limits of elasticity [1-5]. From pathologic and angiographic studies it is known that approximately 70% of atherosclerotic coronary lesions are eccentric [6,7]. This implies that part of the vessel circumference is free of atherosclerotic plaque and that this disease free portion will be preferentially stretched during balloon angioplasty with little damage to the atherosclerotic plaque [8]. Waller suggested that stretching of the plaque free wall segment may result in an initial increase in luminal diameter but that gradual relaxation or restitution of tone of this overstretched segment reduces the coronary lumen towards its predilatation state in hours to weeks after the angioplasty [8]. This study was undertaken to determine whether recoil is an instantaneous phenomenon occurring immediately after balloon deflation or a phenomenon with a delayed component as assessed 24 hours after a successful procedure.

METHODS

Patients. The study population consisted of 71 patients that underwent successful elective single vessel coronary balloon angioplasty defined as a less than 50% diameter stenosis on visual inspection of the post angioplasty angiogram. All patients gave informed consent and the study protocol was approved by the institutional review board.

Angioplasty procedure and 24 hour angiography. Coronary angioplasty was performed with a steerable, movable guide wire system via the femoral route. Details of the procedure have been described previously [9]. After the procedure the arterial sheaths were left in place overnight. The next day (range 17 to 29 hours after angioplasty), a repeat angiogram was obtained.

Three coronary angiograms were obtained in each patient, one just before angioplasty, one immediately after angioplasty, and one angiogram at 24 hours follow-up. The largest balloon used at its maximal inflation pressure was filmed in all patients in a single non-foreshortened projection. The 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. The exact same angulations of the x-ray equipment were repeated for each consecutive angiographic study. To minimize the influence of vasomotion on arterial dimensions either 1-3 mg isosorbide dinitrate or 0.1-

0.3 mg nitroglycerin was given intracoronary before the pre angioplasty, post angioplasty and 24 hour angiograms. 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 [10,11]. All angiograms were processed and analyzed in a central core-laboratory. Qualitative morphologic lesion variables were assessed by 2 experienced angiographers. Differences were resolved during a third review by consensus.

Quantitative angiography. All cineangiograms were analyzed using the computer assisted cardiovascular angiography analysis system (CAAS) which has been described and validated earlier [12-14]. 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 expressed in millimeters. In addition, this technique allows for the calculation of an eccentricity index of the lesion. The index ranges from 0 (severe eccentric) to 1 (perfectly symmetric) The area between the reconstructed "non-diseased" vessel contours and the actual contours is a measure of the amount of atherosclerotic plaque. In case of a total occlusion a value of 0 for the minimal lumen diameter and 100% for the percent diameter stenosis was substituted. Minimal lumen diameters and reference diameters were taken as the mean from matched angiographic projections from the pre-angioplasty, post angioplasty and 24 hour angiogram.

Assessment of elastic recoil. Elastic recoil was calculated as the difference between the minimal lumen diameter post-angioplasty and the mean balloon diameter divided by the interpolated reference diameter. The latter was done to correct for differences in size of the dilated segments.

RESULTS

The study group consisted of 71 patients, 55 male (77.5%) and 16 female. Mean age was 58 ± 8 years. The minimal lumen diameter pre angioplasty was 1.01 ± 0.37 mm and increased to 1.74 ± 0.32 mm ($p < 0.0001$, paired t-test) after angioplasty. At 24 hours, the average minimal lumen diameter was still 1.74 ± 0.37 mm. The interpolated reference diameter increased significantly from 2.68 ± 0.64 mm pre angioplasty to 2.76 ± 0.60 mm post angioplasty and 2.88 ± 0.61 mm at 24 hour follow-up angiography ($p < 0.005$, repeated-measures analysis of variance). Mean balloon diameter was 2.72 ± 0.41 mm. Figure 1 shows cumulative distribution curves of all individual data. Elastic recoil for the entire group was 0.38±0.14. Mean aortic blood pressure was 98.4 ± 17.5 mmHg pre angioplasty and 98.3 ± 13.6 mmHg post angioplasty. At 24 hours follow-up angiography the mean aortic blood pressure had decreased to 93.0 ± 14.8 mmHg.

Lesion and procedural characteristics.

Table 1 lists several lesion and procedural characteristics and the amount of elastic recoil. To avoid arbitrary subdivision of data, cut-off criteria for lesion length, symmetry, total inflation time and maximum inflation pressure were derived by dividing the data in 3 groups so that each group contained about one third of the population. The group with the highest amount of recoil was then compared to the 2 other groups wit an unpaired t-test. Lesions dilated with an oversized balloon and eccentric lesions showed more elastic recoil, although the latter did not reach a statistically significant level. Total inflation time, maximal inflation pressure, visible calcifications, a bend in the dilated segment of > 45°, lesion length of > 7 mm and vessel type did not influence the amount of recoil.

Figure 2 shows the quantitative angiographic measurements before angioplasty, after angioplasty and at 24 hours for eccentric and concentric lesions. Although the minimal lumen diameter immediately after angioplasty is lower for eccentric than for more concentric lesions, the minimal lumen diameter in both groups does not change in the first 24 hours. This suggests that recoil is indeed more pronounced in eccentric lesions, but also that recoil is an instantaneous phenomenon without a delayed component.

DISCUSSION

The presence of immediate recoil after percutaneous transluminal coronary angioplasty has now been confirmed by several in vivo studies using quantitative angiography and balloon ultrasound inflation catheters (BUIC) [1-5]. As predicted by Waller [8] some studies [1-3] showed that recoil was more pronounced in eccentric coronary arteries. In these type of stenoses, balloon inflation within the limits of elasticity, may result in preferential stretching of the non diseased portion of the vessel circumference. Deflation of the balloon will then immediately be followed by elastic recurrence of the vessel wall towards its predilatation state. In the present study this was again confirmed. However, the predicted slow restitution of tone with gradual recurrence of the lesion in the first hours to days after a successful procedure was not found in this study. The minimal lumen diameter in the total group as well as in the group with eccentric lesions did not change in the first 24 hours after balloon dilatation. As a result of greater immediate recoil, the minimal lumen diameter of eccentric lesions was lower in the eccentric lesion group at 24 hour group (figure 2). These findings suggests that recoil is an instantaneous phenomenon, occurring simultaneously with balloon deflation. Similar findings have recently been reported by Hanet et al [4].

An increase in interpolated reference diameter was observed in the first 24 hours. This might be caused by the cumulative effect of vasodilatory drugs administered during

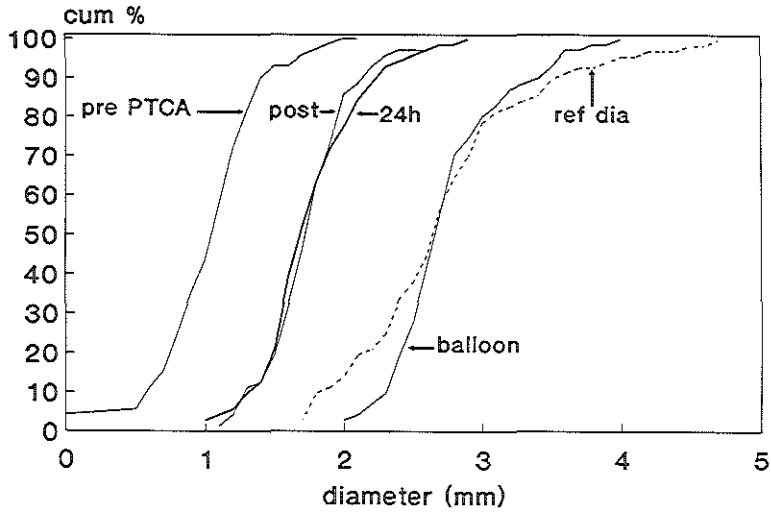

Figure 1. *Cumulative distributions of minimal lumen diameter (MLD) pre angioplasty, mean balloon diameter, MLD post angioplasty, MLD at 24 hours angiography (fat line) and interpolated reference diameter (dotted line). for the total group of patients.*

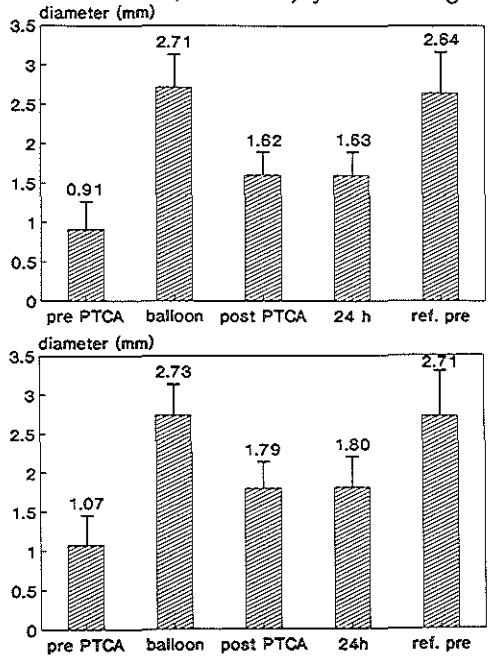

Figure 2. *Upper panel: Bar graph of mean (± 1SD) minimal lumen diameter (MLD) pre angioplasty, post angioplasty and 24 hours angiography, mean balloon diameter and interpolated reference diameter pre angioplasty for eccentric lesions (symmetry measure < 0.25). Lower panel: Bar graph of mean (± 1SD) minimal lumen diameter (MLD) pre angioplasty, post angioplasty and 24 hours angiography, mean balloon diameter and interpolated reference diameter pre angioplasty for more concentric lesions (symmetry measure* ≥ 0.25*).*

Table 1. Relationship between amount of elastic recoil and several procedural and lesional variables

	Variable present	Variable absent	p-value *
Balloon artery ratio > 1	0.46±0.13 (n=41)	0.28±0.08 (n=30)	0.0001
Symmetry < 0.25	0.41±0.17 (n=23)	0.35±0.14 (n=45)	0.08
Bend in dilated segment > 45°	0.35±0.13 (n=20)	0.39±0.15 (n=51)	0.28
Calcified segment	0.51±0.24 (n=6)	0.37±0.13 (n=66)	0.23
Length of stenosis > 7 mm	0.38±0.12 (n=25)	0.37±0.14 (n=43)	0.95
LAD dilatation	0.40±0.16 (n=35)		
RCA dilatation	0.33±0.10 (n=21) **		
LCX dilatation	0.40±0.14 (n=15)		
Total inflation time < 220 s	0.42±0.17 (n=24)	0.37±0.13 (n=47)	0.11
Max. inflation pressure > 8 atm.	0.35±0.12 (n=26)	0.39±0.14 (n=45)	0.25

* unpaired t-test, ** analysis of variance, p=0.25, LAD = left anterior descending artery, RCA = right coronary artery, LCX = left circumflex coronary artery, Max. = maximal

the course of the study. All patients received nifedipine 10 mg/2hours for the first 12 hours after the procedure. Thereafter they received 20 mg of slow release nifedipine 3 times during the second day after angioplasty. Before repeat coronary angiography all patients received an intracoronary dose of nitrates. The effect of the vasodilatory drugs is also reflected in a decrease in mean aortic pressure at 24 hours catheterization, while aortic pressure did not differ pre angioplasty and immediately post angioplasty. Hanet et al. [4] also found an increased reference diameter at 24 hour angiography. Subsegmental analysis in their series revealed that the increase was mostly dependent on the post-stenotic subsegments. Their explanation for this increase was that the reduction in transstenotic gradient and the resulting increase in perfusion pressure distal of the obstruction site causes a passive distension of the distal coronary segment.

Other explanations for early luminal narrowing.

Vasoconstriction at the dilatation site is a common cause of early luminal narrowing. As has been shown elegantly by Fischell and co-workers this can be rapidly reversed by an intracoronary injection of nitrates [15]. Since we gave intracoronary nitrates before the pre PTCA, post PTCA and 24 hour cine recordings, it seems unlikely that the amount of recoil observed was caused by vasomotion.

Platelet deposition and the formation of a non occlusive mural thrombus despite full heparinization, is not an uncommon finding in post mortem hearts obtained from patients who die in the first hours after angioplasty [16]. This has also been confirmed by angioscopy 15-30 minutes after PTCA [17]. However our post PTCA angiograms were made within minutes of the last dilatation. Although we cannot rule out the possibility that mural thrombus formation is partly responsible for the observed phenomenon, we feel it cannot explain the 40% decrease in luminal diameter found. Furthermore, if mural thrombus formation is a substantial contributor to earlier luminal narrowing, this would have been picked up at 24 hour angiography. Subintimal hemorrhage is also a cause of severe early luminal narrowing or acute closure, a process which is usually impossible to reverse and nearly always results in a failed PTCA. In this study only successfully dilated lesions were analyzed.

Deendothelialization of coronary arteries with loss of local endothelial derived relaxing factor function is a known cause of local vasoconstriction [18]. However, vasoconstriction after coronary balloon angioplasty is not a very common phenomenon if vasodilatory drugs are administered during the procedure [15]. Concomitant dilatory therapy with organic nitrates, as in the present study, might substitute for the local loss of endothelium at the dilatation site. Another explanation might be that damage to the arterial media and/or splinting of the vascular muscle by the atherosclerotic plaque, prevents the artery from contracting

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Chapter 4

REGIONAL DIFFERENCES IN ELASTIC RECOIL AFTER PERCUTANEOUS TRANSLUMINAL CORONARY ANGIOPLASTY: A QUANTITATIVE ANGIOGRAPHIC STUDY

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Regional Differences in Elastic Recoil After Percutaneous Transluminal Coronary Angioplasty: A Quantitative Angiographic Study

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The immediate result of percutaneous transluminal coronary angioplasty is influenced by both plastic and elastic changes of the vessel wall. To evaluate the amount of elastic recoil after coronary balloon angioplasty, the minimal luminal cross-sectional area of the largest balloon used at highest inflation pressure was compared with the minimal luminal vessel cross-sectional area directly after final balloon deflation in 607 lesions (526 patients). Elastic recoil was defined as the difference between balloon cross-sectional area and minimal luminal cross-sectional area of the dilated coronary segment immediately after balloon withdrawal. A videodensitometric analysis technique was used to avoid geometric assumptions on stenosis morphology directly after angioplasty.

Mean balloon cross-sectional area was 5.3 ± 1.6 mm^2 and minimal luminal cross-sectional area after angioplasty was 2.8 ± 1.4 mm^2. Reference areas before and after angioplasty did not differ (6.0 ± 2.6 and 6.2 ± 2.6 mm^2, respectively). Univariate analysis revealed that asymmetric lesions, lesions located in less angulated parts of the artery and lesions with a low plaque content showed more elastic recoil. Lesions located in distal parts of the coronary tree were also associated with more elastic recoil probably related to relative balloon oversizing in these distal lesions.

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Percutaneous transluminal coronary balloon angioplasty remains by far the most applied percutaneous coronary revascularization technique (1). Improvements in guide wire and balloon catheter design allow us to cross and dilate nearly every lesion in the coronary tree, with the exception of some chronically occluded lesions. However, the dilation process itself has not changed basically since the early days of balloon angioplasty and the mechanism by which luminal enlargement is achieved is still the subject of debate (2). Apart from plastic changes (dissection, intimal tear), the immediate result of a balloon angioplasty is also dependent on elastic properties of the vessel wall. We (3) reported earlier that elastic recoil after coronary angioplasty accounted for a nearly 50% decrease in luminal cross-sectional area immediately after balloon deflation. Because the disruptive action of the balloon on the vessel wall causes irregular and asymmetric luminal cross sections (4), cross-sectional area measurements based on automated edge detection techniques are potentially unreliable. Therefore, a videodensitometric analysis technique, which is theoretically independent of geometric assumptions on the shape of the stenosis, was used. This study was undertaken to determine the amount and the regional distribution of elastic recoil directly after balloon angioplasty with the use of a quantitative angiographic analysis technique.

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Methods

Study patients. The study group consisted of 526 patients (607 lesions) who had undergone successful coronary balloon angioplasty, defined as a <50% diameter stenosis on visual inspection of the postangioplasty angiogram. Patients with stable and unstable angina, as described previously (5), were included; patients with acute myocardial infarction were excluded. The mean age was 56 ± 12 years.

Coronary angioplasty. This was performed by the femoral route with a steerable, movable guide wire system (5). The choice of balloon type (compliant or noncompliant) and manufacturer, inflation pressure and inflation duration were left to the discretion of the operator.

Quantitative Coronary Angiography

Contour detection. All cineangiograms were analyzed using the computer-assisted angiographic analysis system (CAAS), which has previously been described and validated in detail (6,7). To describe briefly the important steps, any area of size 6.9 × 6.9 mm (512 × 512 pixels) in a selected cine frame (overall dimensions 18 × 24 mm) encompassing the

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desired arterial segment can be digitized with a high resolution digital camera. Vessel contours are determined automatically based on the weighted sum of first and second derivative functions applied to the digitized brightness information along scan lines perpendicular to the local centerline directions of an arterial segment. A computer-derived estimation of the original arterial dimension at the site of obstruction is used to define the interpolated reference diameter. The absolute values of the stenosis diameter and the reference diameter are measured by the computer using the known contrast catheter diameter as a scaling device. All contour positions of the catheter and the arterial segment are corrected for pincushion distortion introduced by the image intensifiers. The area between the actual and reconstructed contours at the obstruction site is a measure of the amount of "atherosclerotic plaque" and is expressed in square millimeters. The length of the obstruction is determined from the diameter function on the basis of curvature analysis and expressed in millimeters.

Using the reconstructed borders of the vessel wall, the computer can calculate a symmetry coefficient for the stenosis. Differences in distance between the actual and reconstructed vessel contours on both sides of the lesion are measured. Symmetry is determined by the ratio of these two differences, with the largest distance between actual and reconstructed contours becoming the denominator. Values for symmetry range between 0 for extreme eccentricity to 1 for maximal symmetry (that is, equal distance on both sides between reconstructed and actual contours). The curvature value at the obstruction site, as a measure for coronary bending, is computed as the average value of all the individual curvature values along the centerline of the coronary segment, with the curvature defined 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.

Densitometric procedure. Constitution of the relation between path length of the X-rays through the artery and the brightness value requires a detailed analysis of the complete X-ray/cine/video chain, including the film development process (8). For the first part of the chain from the X-ray source 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. Details of this technique have been described elsewhere (9). The cross-sectional area of a vessel is then obtained as follows. The contours of a selected arterial segment are detected, as described before. A profile of brightness values is measured on each scan line perpendicular to the centerline. This profile is transformed into an absorption profile by means of a logarithmic transfer function. The background contribution is estimated by computing the linear regression line through the background points directly to the left and right of the detected contours. Subtraction of this background portion yields the net cross-sectional absorption profile. Integration of this function gives a measure for the cross-sectional area at the particular scan line. By repeating this procedure for each scan line, the cross-sectional area function is obtained. Calibration of the densitometric area values is accomplished by comparing the reference area calculated from the diameter measurements (assuming a circular cross section) with the corresponding densitometric area value. The complete procedure has been evaluated with cine films of perspex models of coronary obstructions (8).

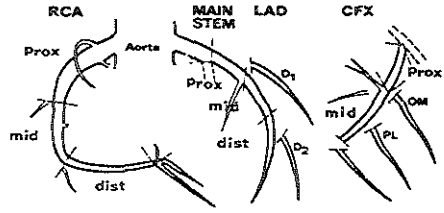

Figure 1. Map with the beginning and end points of the coronary artery segments. CFX = circumflex artery; D_1 and D_2 = first and second diagonal branches, respectively; dist = distal; LAD = left anterior descending artery; mid = mid portion; OM = obtuse marginal branch; PL = posterolateral branch; prox = proximal; RCA = right coronary artery.

Assessment of elastic recoil. Single identical views before and after angioplasty and during complete expansion of the largest balloon at highest inflation pressure were chosen for densitometric analysis. Mean balloon cross-sectional areas were calculated from diameter values, assuming a circular cross section at maximal inflation pressure. The same X-ray setting in terms of kilovoltage and milliamperes was used during the three cine recordings. Vessel segments were analyzed in the least foreshortened projection (that is, perpendicular to the incoming X-ray beam). The same amount of nitrates—either nitroglycerin, 0.1 to 0.3 mg, or isosorbide dinitrate, 1 to 3 mg—was given by intracoronary injection before the pre- and postangioplasty cine recordings. These agents were administered to maximally dilate the vessel and, hence, to control the varying influence of vasomotor tone on luminal dimensions. Elastic recoil was then calculated as the difference between the minimal luminal cross-sectional area after angioplasty and the mean balloon cross-sectional area (mm^2). The time between final balloon deflation and the postangioplasty cine recordings was usually <1 min. To compare the amount of recoil in different parts of the coronary tree, absolute values were normalized for reference area at the obstruction site. The beginning and end points of the major coronary segments are shown in Figure 1. The definitions are slightly modified from those of the American Heart Association (10).

Statistical analysis. The individual quantitative data were used to calculate mean values and SD. Univariate analysis of variance was performed for the continuous variables. A

Table 1. Quantitative Angiographic Analysis of 607 Lesions in 526 Patients

	Mean ± SD	
Minimal luminal cross-sectional area before angioplasty (mm^2)	1.0 ± 0.9	
Minimal luminal cross-sectional area after angioplasty (mm^2)	2.8 ± 1.4	$p < 0.0001$
Balloon cross-sectional area (mm^2)	5.3 ± 1.6	
Reference area before angioplasty (mm^2)	6.0 ± 2.6	NS
Reference area after angioplasty (mm^2)	6.2 ± 2.6	
Elastic recoil (mm^2)	2.5 ± 1.4	
Lesion length (mm)	6.5 ± 2.7	
Symmetry value	0.5 ± 0.3	
Plaque area (mm^2)	7.2 ± 4.4	
Curvature value (U)	17.5 ± 10.5	

probability value < 0.05 was considered significant. To avoid arbitrary subdivision of data, cutoff criteria for continuous variables were derived by dividing the data into 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 (11). This method of subdivision is consistent for all variables and thus avoids any bias in selection of subgroups that might be undertaken to emphasize a particular point.

Results

Angiographic lesion characteristics. The mean minimal luminal cross-sectional area predilation and postdilation and the balloon cross-sectional area for the 607 lesions are shown in Table 1. The mean minimal luminal cross-sectional area was 1.0 ± 0.9 mm^2 before and 2.8 ± 1.4 mm^2 after angioplasty. The mean balloon cross-sectional area was 5.3 ± 1.6 mm^2. The mean amount of elastic recoil was 2.5 ± 1.4 mm^2. These data indicate a nearly 50% loss of maximally achievable cross-sectional area directly after balloon deflation. Reference area before angioplasty was not changed significantly by angioplasty. Other quantitative angiographic lesion characteristics of the 607 lesions are shown in Table 1. Table 2 shows the grouping of the quantitative data for statistical analysis (based on the tertiles), the numbers in each group and the amount of recoil relative to vessel size. Asymmetric lesions, lesions with a small plaque area and lesions located in straighter arterial segments (low curvature value) were associated with significantly more elastic recoil.

Table 2. Quantitative Angiographic Variables and Elastic Recoil in 607 Coronary Lesions

	Yes (recoil/reference)	No (recoil/reference)	p Value
Lesion length <5.1 mm	200 (0.49)	407 (0.44)	NS
Symmetry <0.37	205 (0.50)	402 (0.43)	$p < 0.05$
Plaque area <4.7 mm^2	199 (0.55)	408 (0.41)	$p < 0.01$
Curvature <12.5 U	206 (0.51)	401 (0.40)	$p < 0.01$

Values indicate number of lesions and recoil normalized for reference diameter (recoil/reference).

Table 3. Regional Distribution of Elastic Recoil in 607 Coronary Lesions

	N	Recoil/ Reference Ratio		Balloon/ Artery Ratio	
LAD prox	118	0.43		0.90	
LAD mid	120	0.48	$p < 0.01$	0.97	$p < 0.01$
LAD dist	23	0.61		1.20	
LCx prox	39	0.41		0.80	
LCx mid	54	0.41		0.90	
Obtuse marginal	29	0.47	$p < 0.01$	0.93	$p < 0.01$
Posterolateral	24	0.54		1.10	
RCA prox	71	0.28		0.78	
RCA mid	76	0.38	$p < 0.01$	0.98	$p < 0.01$
RCA dist	50	0.40		0.98	

dist = distal; LAD = left anterior descending artery; LCx = circumflex artery; mid = mid portion; prox = proximal; RCA = right coronary artery.

Regional distribution of elastic recoil. Data on elastic recoil in the different parts of the coronary tree are summarized in Table 3. Data on diagonal branches and the ramus descendens posterior in left dominant systems are omitted because of the small number of segments dilated in this series (5 and 0, respectively). Recoil, normalized for vessel size, increased from proximal to distal parts for all three major coronary branches. This increase in elastic recoil corresponds to a significant increase in the balloon/artery ratio from proximal to distal parts of the coronary arteries.

Discussion

Mechanisms of lesion dilation in balloon angioplasty. Dotter and Judkins (12) in 1964 envisioned that balloon angioplasty worked by remodeling and compression of the atheroma because initial pathologic studies revealed little intimal destruction and no evidence of dissection. However, the vast majority of atherosclerotic plaques in human coronary arteries are composed of incompressible, dense fibrocollagenous tissue and therefore it appears unlikely that plaque compression plays a major role in balloon angioplasty. However Kaltenbach et al. (13) observed in an in vitro model a reduction in weight and thickness of the atherosclerotic vessel wall after pressure application. This reduction was more pronounced in lipoidotic plaques, suggesting that fluid expression from atherosclerotic tissue could play some role in the luminal widening achieved by angioplasty (13). According to Sanborn et al. (14), part of the angioplasty mechanism consists of stretching the vessel wall with a resulting fusiform dilation or localized aneurysm formation. If the lesion is eccentric, then the least diseased portion of the vessel wall will stretch (15).

Castaneda-Zuniga et al. (16) found that angioplasty induced paralysis by overstretching the vessel wall beyond its limits of elasticity and suggested this to be the cause of

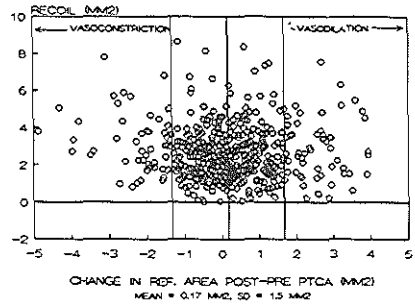

Figure 2. Is vasomotion part of the recoil phenomenon? Scatter plot of the difference in reference area after angioplasty from that before angioplasty (POST–PRE PTCA) against the amount of recoil for each of the 607 lesions (see text for explanation).

permanent luminal widening after balloon angioplasty. This widening was associated with histopathologic features of smooth muscle cell lysis and twisted nuclei. These correlates of severe medial damage were not found in human arteries examined post mortem after recent dilation (17,18). In in vitro models of balloon angioplasty in rabbit iliac artery, rabbit aorta and pig carotid artery, only severe oversizing of the balloon produced impairment of vasoconstrictor responsiveness (19). Because it is becoming clear that oversizing of the balloon leads to an increased complication rate (20) and that satisfactory initial results can be obtained by conservative balloon sizing (20,21), deliberate oversizing of the angioplasty balloon is not common in our institution. This is reflected by the mean balloon/artery ratio of 0.95 in our study. Thus, arterial paralysis must be questioned as an explanation for the luminal widening achieved by angioplasty in human coronary arteries. The most consistent finding after angioplasty is disruption and splitting of the neointima and localized intimal dissection (22).

Mechanisms of early restenosis. Early lesion recurrence after balloon angioplasty is most likely due to vasoconstriction, intimal flaps, mural thrombus formation or subintimal hemorrhage (23–27). Fischell et al. (26) showed that vasoconstriction after balloon angioplasty could be rapidly reversed by intracoronary injection of nitrates. Because we gave intracoronary nitrates before the pre- and postangioplasty cine recordings, it seems unlikely that the amount of recoil observed was caused by vasomotion. In Figure 2 the difference between the postangioplasty and preangioplasty reference area is plotted against the amount of recoil for each site. The values are randomly distributed around the mean value of 0.17 mm^2, suggesting the absence of vasoconstriction at the postangioplasty cine recording.

Despite full heparinization, platelet deposition and the formation of a nonocclusive mural thrombus are not uncommon findings in postmortem hearts obtained from patients who die in the first hours after angioplasty (27). Such findings have also been confirmed by angioscopy 15 to 30 min after angioplasty (28). However, our postangioplasty angiograms were made within minutes of the last dilation. Although we cannot rule out the possibility that mural thrombus formation is partly responsible for the observed phenomenon, we believe that it cannot explain the observed 50% decrease in luminal area. Subintimal hemorrhage is also a cause of severe early luminal narrowing or acute closure, a process that is usually impossible to reverse and nearly always results in failed angioplasty. In this study only successfully dilated lesions were analyzed.

Factors leading to elastic recoil. Eccentric lesions showed significantly more elastic recoil. This can be explained by the fact that in such lesions, a part of the vessel circumference is not diseased. The portion that is not diseased will be preferentially stretched by the balloon with subsequently more elastic recoil (15). Lesions with a high bending and a large bulk of atherosclerotic plaque showed less elastic recoil. It is known that dissections are more common in this type of lesion (24,29). The gross disruption of the vessel wall and the atherosclerotic plaque associated with an angiographically visible dissection might release the cicatrizing effect of the plaque that had chronically affected the media. Release of this force may allow the media to return to its more normal outer diameter and thus reduce some of the recoil effect.

Recoil relative to vessel size increases from proximal to distal parts of the coronary arteries. This phenomenon is due to the tendency of balloon oversizing in distal parts of the coronary tree (Table 3). If a vessel is stretched within its limits of elasticity, it will return toward its rest state along an elastic hysteresis loop. More stretch should thus give more elastic recoil. It is difficult to discern whether the oversizing is based on economic grounds (an extra balloon for a second distal site nearly doubles the cost of angioplasty disposable equipment) or is due to visual overestimation of smaller caliber vessels. In our series, a minority of 40 patients underwent multilesion dilation including a proximal and a distal segment. In 31 of these cases, the same balloon was used for the proximal and distal stenoses. Mean balloon cross-sectional area was 4.7 ± 1.2 mm^2 for the proximal stenosis and 4.6 ± 1.2 mm^2 for the distal stenosis (p = NS). Reference area was 5.8 ± 2.4 mm^2 for the proximal lesions and 4.6 ± 2.2 mm^2 for the distal lesions ($p < 0.01$). Balloon artery ratio was 0.85 ± 0.5 for these proximal lesions and 1.0 ± 0.5 for distal lesions ($p < 0.01$).

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Chapter 5

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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Abstract

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, we determined quantitative angiographic risk factors for angiographic luminal narrowing after balloon angioplasty, including stretch and elastic recoil at the dilatation site. Quantitative analysis was performed on 666 lesions in 575 patients at angioplasty and at 6 months follow-up. Stretch was defined as: balloon diameter - pre-angioplasty minimal lumen diameter (MLD) / reference diameter and recoil as: balloon diameter - post-angioplasty MLD / reference diameter. Multivariate analysis was applied to yield independent risk factors for luminal narrowing at follow-up. Predictors of absolute change in MLD (mm) were 1) relative gain at angioplasty (gain in mm normalized for reference diameter), 2) lesion length. To allow risk stratification, logistic regression analysis was applied using the loss in MLD as a binary outcome variable. A loss in MLD at follow-up of $\geq$0.72 mm was considered significant. Variables retained in the model were: relative gain > 0.3 (rate ratio: 2.9), relative gain 0.2 - 0.3 (rate ratio 2.1), stenosis length $\geq$6.8 mm (rate ratio: 1.7) and thrombus post 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 post angioplasty were found to be accompanied with more severe luminal narrowing at follow-up.

Keywords:
Angioplasty, Quantitative angiography, Loss in minimal lumen diameter, Restenosis.

INTRODUCTION

Luminal narrowing following 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 since 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 intra-observer 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 might 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 might leave a significant residual stenosis with a possible increased turbulence, platelet activation and restenosis [10].

In this study quantitative lesion measurements before angioplasty, after angioplasty, and at follow up were obtained and correlated with loss in minimal lumen 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 pre-angioplasty [6] and elastic recoil as the difference between mean balloon diameter and MLD post-angioplasty [9]. Both stretch and recoil were normalized for reference diameter to correct for the influence of vessel size and are therefore dimensionless.

PATIENTS AND METHODS

The study population consisted of 697 patients that 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 (GR32191B)

was investigated for its ability to prevent restenosis after primary coronary angioplasty. Follow-up on these patients was done 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 group 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 given in table I. A screening log was maintained in two centers to assess the relative frequencies of these exclusion criteria.

Table I. Reasons for excluding 1318 of 1614 screened patients in 2 of 6 centers.

Reason	No	(%)
Insufficient lead-in time*	235	(18)
Use of platelet inhibiting drugs or non steroid anti inflammatory drugs in 7 days preceding the study	352	(27)
Refusal to participate and/or undergo 6 months recatheterization	364	(28)
Currently taking 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)
Severe other disease	6	(0.5)
Participation in other trial	6	(0.4)
History of intolerance to aspirin	1	(0.1)
Under 21 years of age	1	(0.1)
Pregnant woman or woman likely to become pregnant during study	0	(0)
Total	1318	(100)

* Urgent referrals outside working hours.

Failure of the angioplasty procedure occurred in 48 patients (6.9%). Angioplasty success was defined as <50% residual stenosis by visual inspection of the post-angioplasty angiogram and no occurrence of in-hospital complications (death, acute myocardial infarction, repeat angioplasty, aorto coronary 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), 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 guide wire system via the femoral route. Standard available balloon catheters were used. Choice of balloon type and brand as well as inflation duration and inflation pressure were left to the discretion of the angioplasty operator. At the beginning of the angioplasty procedure all patients received 10000 International Units of intravenous heparin for the first two hours, afterwards 5000 International Units/hour for as long the procedure continued. All patients received 10 mg nifedipine every two hours for the first 12 hours after angioplasty. Thereafter they received 20 mg slow release nifedipine tablets 3 times during the second day after angioplasty.

Four coronary angiograms were obtained in each patient, one just before PTCA, one during maximal inflation of the largest balloon used, one immediately after angioplasty, and one angiogram at follow-up. The 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 the cathetertips 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 earlier [2,12]. All angiograms were processed and analyzed in a central core-laboratory (see appendix).

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

Quantitative angiography (figure 1). All cineangiograms were analyzed using the computer assisted cardiovascular angiography analysis system (CAAS) which has been described and validated earlier [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 expressed in millimeters. In addition, this technique allows for the calculation of an eccentricity index [9] of the lesion. The index ranges from 0 (severe eccentric) to 1 (perfectly symmetric). Since the algorithm is not able to measure total occlusions, a value of 0 mm was substituted for the MLD. In these cases the post-angioplasty reference diameter was substituted for the reference diameter pre PTCA. The mean change in MLD from post-angioplasty angiography to follow-up angiography and from pre-angioplasty to post-angioplasty was derived from matched angiographic projections. Balloon artery ratio was defined as the ratio of the mean balloon diameter measured in a non-foreshortened 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 - MLD pre-angioplasty / reference diameter), 2) elastic recoil (mean balloon diameter - MLD post-angioplasty / reference diameter) and 3) relative gain achieved by angioplasty (post angioplasty MLD - pre angioplasty MLD / 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 (inter observer concordance rate for the assessment of intracoronary thrombus in the corelab 89%).

Significant luminal narrowing. To predict significant luminal narrowing after PTCA, we chose a cut-off point above which significant deterioration in MLD is likely. We have found a change in MLD of $\geq$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 the CAAS system [14]. This variability reflects the long-term random variation in lesion measurements from coronary angiograms made at different catheterization sessions using the CAAS system. The use of 1 standard deviation would include 68.3% of the measurement variability, while the use of 2 standard deviations (2 x 0.36 = 0.72 mm) includes 95.5% of the measurement variability. 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 $\geq$50%diameter stenosis criterion.

Data analysis. Data were analyzed using the BMDP statistical software package (University of California, Berkeley, California 1990). 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 with restenosis) were entered in a stepwise multiple linear regression analysis to identify variables with an

independent contribution to the prediction of absolute loss in MLD as a continuous variable (see appendix).

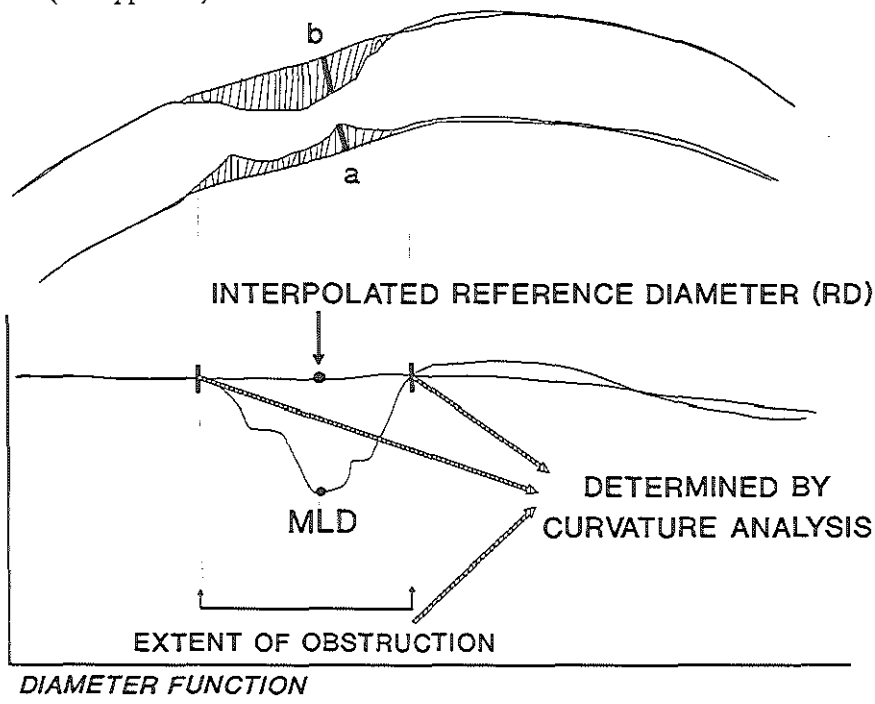

Figure 1. *Graphic representation of the quantitative angiographic measurements. The upper panel represents a stenosed arterial segments. The lower panel is the diameter function curve. MLD = minimal lumen diameter. Extent of obstruction = Lesion length. Lesion length is determined with curvature analysis of the descending and ascending limb of the diameter function curve at the site of the MLD. Eccentricity is determined the site of the MLD and calculated as a/b.*

To allow risk stratification, logistic regression analysis using indicator variables was subsequently applied, with the loss in MLD (using a loss of $\geq$0.72 mm as cut off value) and the 50% diameter stenosis 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 three equally sized subgroups (tertiles). Three subgroups were selected to enable assessment of trends in the incidence of $\geq$0.72 mm loss and because more subgroups would weaken the strength of associations. The incidence of a $\geq$0.72 mm loss was determined in each subgroup. If a trend for a higher incidence was present in each consecutive subgroup, then the subgroup with the lowest incidence was chosen as the reference group. If no trend for an increasing incidence of $\geq$ 0.72 mm loss in MLD was present in each consecutive

subgroup, the subgroup with the highest incidence was compared with the combined 2 other subgroups (= reference group).

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

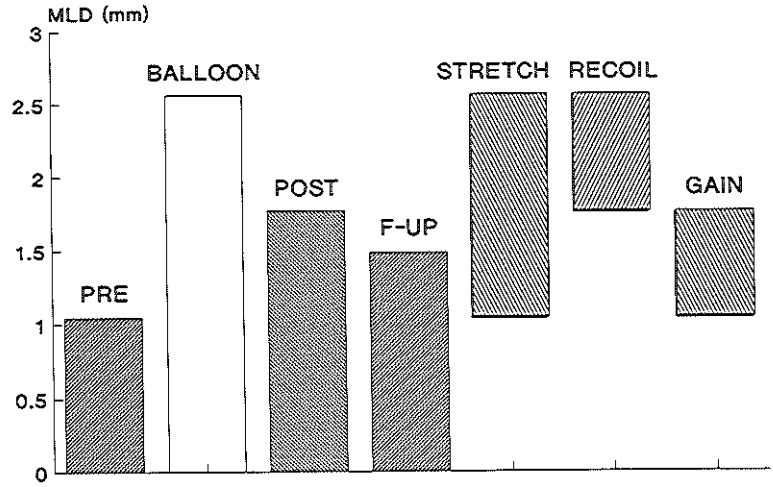

Figure 2. *Graphical representation of the terms used. In this graph the mean absolute values of the variables is shown. In the manuscript stretch, recoil and gain were normalized for vessel size (reference diameter) to correct for vessel size. pre = pre-angioplasty minimal lumen diameter, balloon = balloon mean diameter, post = post angioplasty minimal lumen diameter, F-up = follow-up minimal lumen diameter, MLD = minimal lumen diameter.*

RESULTS

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

Overall quantitative angiographic findings pre-angioplasty, post-angioplasty and at follow up angiography are presented in table III. Reference diameter was not different pre-angioplasty, post-angioplasty and at follow up (2.64$\pm$0.56 mm, 2.71$\pm$0.54 mm and 2.71$\pm$0.56 mm respectively), suggesting an accurate control of vasomotion during the three angiographic studies.

The incidence of significant luminal narrowing ($\geq$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).

Table II. Baseline characteristics

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

Univariate analysis

With univariate analysis (table IV) the following quantitative angiographic variables were associated with a loss in MLD of at least 0.72 mm: pre-angioplasty MLD, post-angioplasty MLD, gain in MLD obtained by angioplasty, length of the 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 post-angioplasty MLD for the 2 criteria and the absence of a difference in relative gain in the $\leq$50% diameter stenosis at follow-up group and the > 50% diameter stenosis group is explained in the discussion.

More stretching was accompanied by more recoil. The amount of recoil in the tertile with the highest amount of stretch ($\geq$ 0.65) was 0.42 as opposed to 0.25 in the combined other 2 tertiles of stretch (< 0.65)($p < 0.0001$, unpaired t test).

Multiple linear regression analysis.

The variables significantly related to $\geq$0.72 mm loss in MLD 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 $\geq$0.72 mm loss in MLD with univariate analysis, was not retained in the stepwise multiple *linear* regression model.

Table III. Quantitative angiographic data of 666 lesions

	Mean±SD	Range
Minimal lumen diameter (mm)		
pre-angioplasty	1.04±0.37	0.00-2.83
post-angioplasty	1.76±0.38	0.85-3.04
follow-up	1.48±0.59	0.00-3.15
Diameter stenosis (%)		
pre-angioplasty	60±13	33-100
post-angioplasty	34±9	6 - 76
follow-up	45±19	4 -100
Difference in Minimal lumen diameter		
post-angioplasty - pre-angioplasty (mm)	0.75±0.40	
post-angioplasty - follow up (mm)	0.28±0.52	
relative gain at angioplasty*	0.28±0.16	
Difference in % diameter stenosis		
post-angioplasty - pre-angioplasty	26±14	
post-angioplasty - follow-up	11±19	

SD=standard deviation, * see figure 2.

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 were: vessel dilated [15], total occlusion pre-angioplasty [16], angiographically determined thrombus pre angioplasty and post angioplasty, elastic recoil and balloon artery ratio. Thrombus pre- and post 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 out of 666 lesions pre angioplasty (5%) and in 16 out of 666 lesions post angioplasty (1.6%). 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 known to be 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 zero in these cases.

A relative gain at angioplasty of ≥ 0.3 had an adjusted rate ratio (RR) for developing a loss in MLD ≥ 0.72 mm of 2.9. This means that the risk for developing a loss of at least 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% confidence intervals (CI) 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 ≥ 6.8mm(RR 1.7, 95% CI 1.2 to 2.3), and thrombus post angioplasty (RR 2.6, 95% CI 1.1 to 6.2). Total occlusion pre angioplasty and use of active trial medication had no significant independent predictive contribution to a significant loss in lumen diameter (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, vesseltype and thrombus pre angioplasty were not retained in the final *logistic* regression model.

To assure that total occlusions did not unduly influence the results, the analysis was repeated excluding these lesions. Adjusted rate ratios were similar to those in the original analysis (relative gain 0.2-0.3: 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 (adjusted RR 1.3, 95% CI 1.1 to 1.4) and thrombus post-angioplasty (RR 1.8, 95% CI 1.0 to 3.1) were retained in the final model. The use of GR32191B 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 support 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 one factor most strongly associated with luminal narrowing in this study was the relative gain in MLD achieved by the angioplasty procedure. 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 (PDGF)) and vaso- and platelet-active substances. Extensive damage to the endothelial lining of the vessel, which

is always present after balloon dilatation, might 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 PDGF and 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 start 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 rabbits 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. have described an aggressive proliferative response in a porcine model as a result of severe stent oversizing [22]. 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 has recently also been demonstrated in a clinical stent study [23]. Implantation of an oversized stent was attended 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 attended 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 loss in MLD of at least 0.72 mm, probably due to an unequal distribution of thrombus post-angioplasty over totally occluded and patent arteries; 6 out of 36 (16.7%) total occlusions pre-angioplasty had a thrombus post-angioplasty versus 10 out 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 might 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% (12/36) ($\geq$0.72mm criterion). However, if total occlusions pre-angioplasty are left out of the analysis, a high relative gain and lesion length were still attended with a significant adjusted risk for a loss of at least 0.72 mm.

The fact that angiographically determined thrombus at the dilatation site pre angioplasty was not found to be a risk factor for a significant loss 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 post angioplasty is the angiographic proof that massive platelet aggregation, thrombin activation and fibrin formation has taken place with subsequent release of vasoactive substances [25] and growth factors involved in the fibroproliferative restenosis process.

Table IV. Univariate analysis of quantitative parameters and loss in MLD of ≥0.72mm.

	loss < 0.72 mm Mean ± 1 SD	loss ≥0.72 mm Mean ± 1 SD	P	≤50% DS at f-up Mean ± 1 SD	> 50 % DS at f-up Mean ± 1 SD	P
MLD pre-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 dia. pre-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
Lesion Length pre-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 post-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
loss 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

DS = diameter stenosis F-up = follow up, Gain = (MLD post PTCA - MLD pre PTCA) / reference diameter, MLD = minimal lumen diameter, PTCA = percutaneous transluminal coronary angioplasty, Recoil= (balloon diameter - MLD pre PTCA) / reference diameter, Stretch = (Balloon diameter - MLD pre-PTCA)/reference diameter, * subsequently entered in multiple linear regression analysis

Furthermore, a recent post mortem study has shown that part of early (<1 months) 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 $\geq$ 0.72mm loss in MLD. These findings correlate with the observations by Fischell et al who showed a relationship between the degree of arterial stretching and the severity of smooth muscle injury as determined by loss of vasoconstrictor responsiveness and histopathological examination [6], and, as emphasized above, 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 loss 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 an other report [8], that suggests that recoil might be a factor in luminal narrowing observed at follow-up. It might be that recoil is not an instantaneous phenomenon but rather exerts its effect over a longer period of time and could thus not be picked up by the post-angioplasty angiogram that was made within minutes after final balloon deflation.

Limitations. To allow risk stratification for loss in MLD with the use of multivariate analysis techniques, a cut-off 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 in the methods section. This criterion is not meant to be a restenosis criterion in this study, since that implies also some sort of functional measure of lesion severity at follow up. The commonly used definition of 50% diameter stenosis at follow-up is historically based on the physiological concept of coronary flow reserve introduced by Gould and others in 1974 and is taken because it represents the approximate value in animals with normal coronary arteries at which blunting of the hyperemic response occurs [28]. 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 is applied, lesions with a suboptimal angioplasty result will preferentially be selected (ie have to undergo a small loss in lumen diameter to be called restenosed). This is reflected by the lower post angioplasty MLD in the >50% diameter stenosis group (table IV) as compared to the > 50% diameter stenosis group. The mean percentage diameter stenosis post-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 28% in the group with a gain $\geq$ 0.3. This means that lesions with a small relative gain generally tend to have a poorer post angioplasty result and are close to the 50% diameter stenosis cut-off point. Furthermore, since the long term variability of diameter stenosis measurements using the CAAS system is 6.5% [14], a significant amount of lesions will be defined as restenosed while in fact no change has taken place. The mean post-angioplasty percentage diameter stenosis was 31% for those lesions fulfilling the $\geq$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 look at risk factors for change in luminal diameter, the 50% diameter stenosis criterion is inappropriate.

The definition of stretch was essentially the same as used by Fischell et al. in a series of in vitro experiments with isolated, perfused, non-diseased, whole vessel segments of rabbit aortas and dog carotid arteries [6]. In our population of diseased arterial segments, stretch was calculated as the difference between mean balloon diameter and MLD pre 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 took place during angioplasty.

The immediate luminal narrowing after balloon deflation that we attributed to elastic recoil could also be caused by spasm or non occlusive mural thrombus formation. It has been shown that the administration of intracoronary nitrates after angioplasty abolishes possible spasm [19,29]. Furthermore, the mean reference diameter post angioplasty was not different from the pre angioplasty value. Our post angioplasty angiogram was made within minutes after 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 lumen diameter.

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APPENDIX

Linear regression analysis

Stepwise multiple linear regression analysis was performed (BMDP statistical package, program 2R) 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 post-angioplasty angiogram to follow-up angiogram (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 applied.

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 0.72mm 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 into a model, one 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 applied. 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 an 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: $\text{rate ratio}^{(1 \pm 1.96/(bj/SE))}$

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Chapter 6

POST ANGIOPLASTY 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 mm² (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-

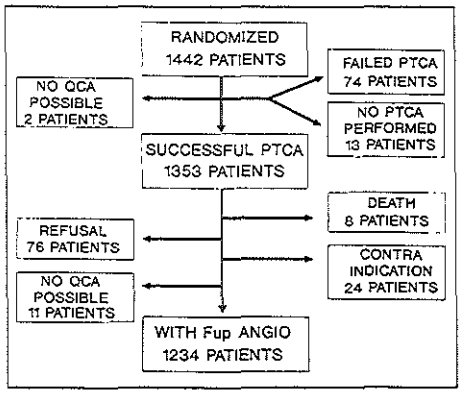


FIGURE 1. Flow chart of 1,442 randomized patients. In 74 patients, angioplasty procedure was unsuccessful, in 13, percutaneous transluminal coronary angioplasty (PTCA) was not performed, and in 2, quantitative analysis (QCA) was not possible. Angiographic follow-up (Fup ANGIO) was obtained in 1,234 patients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

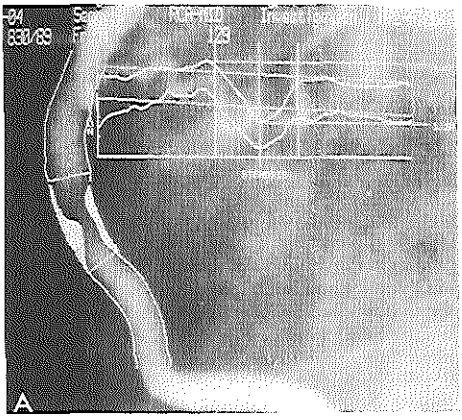
ing device. For that purpose, the catheter tips were retained for accurate measurement with a micrometer. To achieve maximal vasodilation, either nitroglycerin (0.1 to 0.3 mg) or isosorbide dinitrate (1 to 3 mg) was administered for each coronary artery involved before and after PTCA, and at follow-up 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-



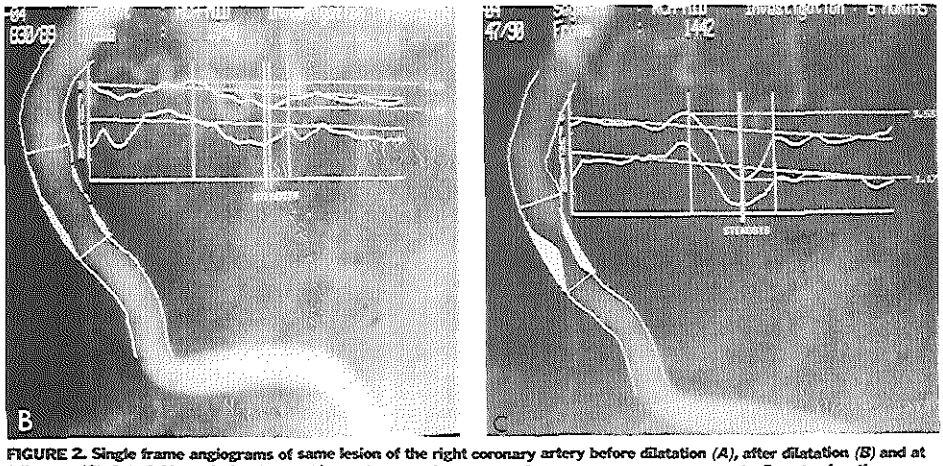


FIGURE 2. Single frame angiograms of same lesion of the right coronary artery before dilatation *(A)*, after dilatation *(B)* and at follow-up *(C)*. Arterial boundaries detected by system are shown on angiogram; *upper curve* represents diameter function curve. Minimal luminal diameter changes from 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.

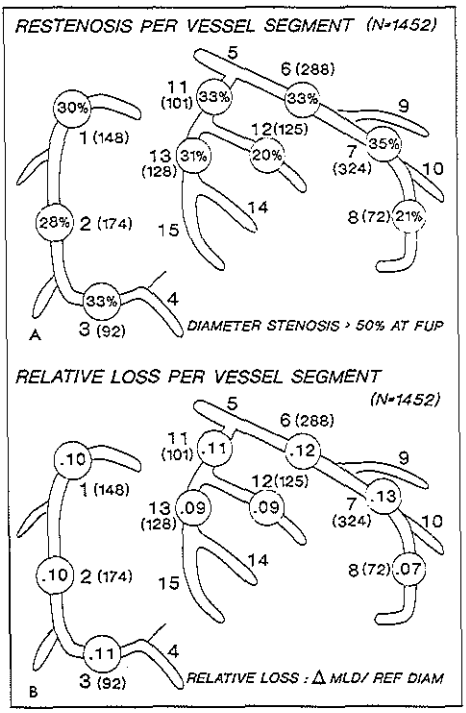


FIGURE 3. Coronary tree divided in 15 different segments with restenosis rate (using >50% diameter stenosis as criterion) for each segment *(A)*, and relative loss per coronary segment *(B)* shown in *circles*. Between *brackets* are numbers of lesions dilated for that segment. FUP = follow-up. ΔMLD/REF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

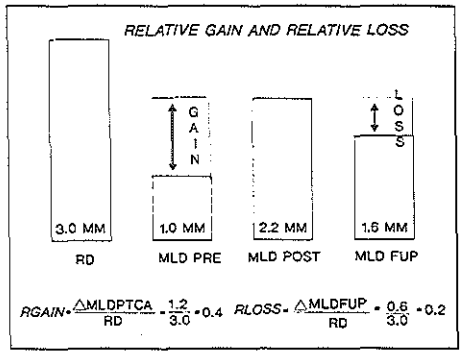


FIGURE 4. See text for explanation of relative gain (RGAIN) and relative loss (RLOSS). FUP = follow-up; MLD = minimal luminal diameter; POST = after; PRE = before; PTCA = percutaneous transluminal coronary angioplasty; RD = reference diameter.

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

	No.	DS (%) at Follow-Up > 50%		Relative Gain	Relative Loss
		Yes	No		
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

RD (mm)	No.	Absolute Gain (mm)	Relative Gain	Absolute Loss (mm)	Relative Loss	DS (%) at Follow-Up > 50%		BAR
						Yes	No	
> 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 7

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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Abstract

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 rather the tail end of a Gaussian distributed phenomenon, we studied 1445 successfully dilated lesions pre-angioplasty, post-angioplasty and at 6 months follow up. The original cohort consisted of 1353 patients of whom 1232 underwent repeat angiography with quantitative analysis (follow-up rate 91.1%). 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 pre-angioplasty (1.03±0.37 mm), post angioplasty (1.78±0.36 mm), at 6 months follow-up (1.50±0.57 mm) as well as the percentage diameter stenosis at 6 months follow-up (44±19 %) were assessed. Also the change in minimal lumen diameter from post angioplasty angiogram to follow-up angiogram was determined (0.28±0.52 mm). Seventy lesions progressed towards 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 cut-off point, rather than a separate disease entity occurring in some lesions but not in others.

Key words:

-Percutaneous Transluminal Coronary Angioplasty
-Restenosis
-Luminal narrowing
-Distribution

INTRODUCTION

For more than a decade investigators in the field in of coronary balloon angioplasty have assumed a Gaussian distribution of continuous (quantitative) angiographic parameters used to describe the severity of the coronary lesion before angioplasty, 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 percentage diameter stenosis at follow-up angiography 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 the present study we assessed the distributions of angiographic parameters of lesion severity, before angioplasty, after angioplasty, and at 6 months follow up in a large population. 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.

PATIENTS AND METHODS

The original study cohort consisted of 1427 patients in whom primary coronary balloon angioplasty was attempted between December 1987 and June 1990 and 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 1353 patients (primary success rate 94.8%), defined as a less than 50% residual stenosis by visual inspection of the post angioplasty angiogram of at least 1 lesion and no occurrence of in-hospital complications (death, acute myocardial infarction, 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 2 patients the angioplasty angiogram could not be analyzed due to technical deficiencies. A total of 1232 patients (91.1%) had a follow-up angiogram suitable for quantitative angiography and this forms the study population. Reasons for not completing the study were: late death (n=8), contraindication for repeat catheterization (n=24), refusal (n=76), while 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 via the femoral route. Standard available balloon catheters were used. Choice of balloon type and brand as well as inflation duration and inflation pressure were left to the discretion of the angioplasty operator. At the beginning of the angioplasty procedure all patients received 10000 IU of intravenous heparin for the first two hours, afterwards 5000 IU/hour for as long the procedure continued. All patients received 10 mg nifedipine every two hours for the first 12 hours after angioplasty. Thereafter they received 20 mg slow release nifedipine tablets

3 times during the second day after angioplasty.

Three coronary angiograms were obtained in each patient, one just before PTCA, one immediately after angioplasty, and an angiogram at follow-up. The angiograms were recorded in such a way that they were suited for quantitative analysis by the Cardiovascular Angiography Analysis System (CAAS). For calibration purposes the cathetertips 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 six months follow-up. If symptoms recurred within 6 months, coronary angiography was carried out earlier. If no definite restenosis was present and the follow-up time was less than 4 months, the patient was asked to undergo another coronary arteriogram at 6 months.

Quantitative angiography. All cineangiograms were analyzed using the computer assisted cardiovascular angiography analysis system (CAAS) which has been described and validated earlier [9,13]. In summary: Any area of size 6.9 x 6.9 mm (512 x 512 pixels) in a selected cineframe (overall dimensions 18 x 24 mm) encompassing the desired arterial segment is digitized with a high resolution CCD camera. Vessel contours are determined automatically based on 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 there is no disease present) is used to define the interpolated reference diameter. The absolute values of the stenosis diameter as well as 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. Since 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 % diameter stenosis and % area stenosis. In these cases the post angioplasty reference diameter was substituted for the reference diameter pre angioplasty or at follow-up angiography. The mean change in minimal lumen diameter from post angioplasty to follow up angiography and from pre angioplasty to post angioplasty was derived from matched angiographic projections. The percentage area stenosis was calculated using the measured minimal lumen diameter and interpolated reference diameter assuming a circular cross-section at the stenosis site.

RESULTS

Baseline characteristics. Table 1 summarizes the baseline characteristics of the 1232 patients with quantitative angiographic follow-up. These patients had 1445 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.

Table 1. Baseline patient and lesion characteristics.

Patiens	1232
Lesions	1445
Male sex	1002 (81%)
Age (years)	56 ± 9
Time to follow-up angiography (days)	165 ± 42
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 artery, LCX = left circumflex artery, RCA = right coronary artery.

Quantitative angiographic findings and distributions. Table 2 summarizes the quantitative angiographic data. Reference diameter was not significantly different pre-angioplasty, post-angioplasty and at follow-up, suggesting that vasomotion was accurately controlled during the 3 angiographic studies. Distribution plots of the minimal lumen diameter data are given in figure 1a to 1c. The distribution of the change in minimal lumen diameter from post angioplasty angiogram to follow up angiogram (loss in minimal luminal diameter) is depicted as well (figure 1d). A positive change corresponds to a decrease in minimal luminal diameter. If the restenosis criterion of $\geq$0.72 mm loss in lumen diameter is applied [3], 244 lesions (16.9%) were restenosed at follow-up. All distributions are more or less bell-shaped and follow the theoretical normal or Gaussian distribution for the given mean and standard deviation values if the totally occluded lesions are not taken into account (curves superimposed on the distributions).

Table 2. Quantitative angiographic data of 1445 lesions

	Mean ± 1SD
Minimal lumen diameter (mm)	
pre-angioplasty	1.02±0.38
post-angioplasty	1.77±0.36
follow-up	1.50±0.57
Reference diameter (mm)	
pre-angioplasty	2.63±0.54
post-angioplasty	2.70±0.52
follow-up	2.70±0.56
Difference in Minimal Lumen Diameter (mm)	
post-angioplasty - pre-angioplasty	0.75±0.41
post angioplasty - follow up	0.28±0.52
Diameter stenosis (%)	
pre-angioplasty	60.5±13.6
post-angioplasty	33.6±9.8
follow-up	44.2±18.7

SD=standard deviation

The distribution of the loss in minimal luminal diameter, excluding lesions that were totally occluded at follow-up (bars, figure 1d) is almost identical to the distribution including totally occluded lesions at follow up (asterisks, figure 1d) with the latter lesions showing a greater loss in minimal lumen diameter. This suggests that lesions progressing to total occlusion are not necessarily lesions with a poor or marginal angioplasty result and that a different mechanism of luminal 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 symmetrical and bell-shaped if lesions that progressed towards total occlusion were disregarded (figure 3).

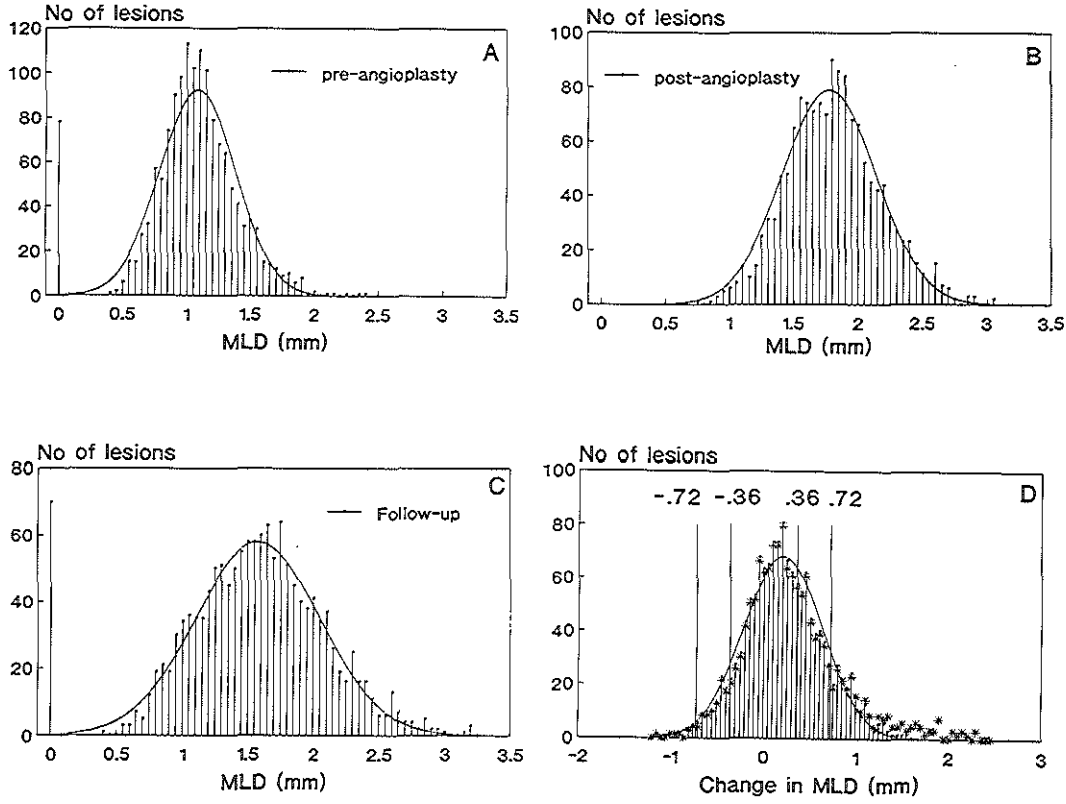

Figure 1. *Histograms of minimal lumen diameter (MLD) measurements of 1445 lesions The curves superimposed on the histograms represent the theoretical Gaussian distribution curves given the mean and standard deviation values of the quantitative angiographic measurements, excluding total occlusions.*
Figure 1a: histogram of MLD pre angioplasty,
Figure 1b: histogram of MLD post angioplasty,
Figure 1c: histogram of MLD at follow-up angiography,
Figure 1d: histogram of change in MLD from post angioplasty angiogram to follow-up angiogram. The asterisks denote the distribution of the change in minimal lumen diameter including those lesions that had progressed towards total occlusion. A positive change denotes a loss in minimal lumen diameter. The long term variability cut-off points are drawn in the histogram (see text for explanation).

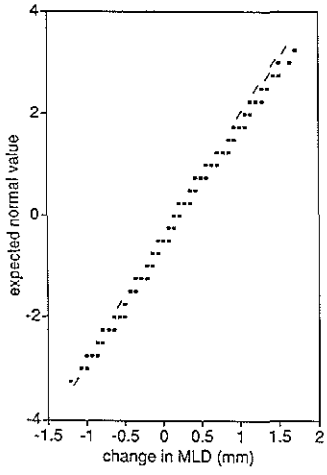

Figure 2. *Normal probability plot of the change in minimal lumen diameter (MLD) from post angioplasty angiogram to follow-up angiogram, excluding lesions that had progressed towards total occlusion. The slashes depict the theoretical Gaussian distribution. The squares are the actually observed values. A change greater than 0 corresponds to a loss in minimal lumen diameter.*

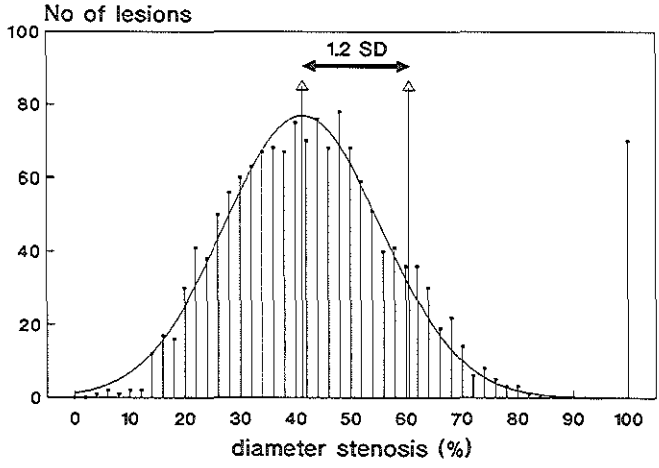

Figure 3. *Histogram of percent diameter stenosis at follow-up angiography of 1445 lesions. Mean percent diameter stenosis excluding total occlusions is 41.3 ± 14.5. Also indicated is the mean diameter stenosis pre angioplasty (60.5%). This limit marks 1.2 standard deviations to the right of the 41.3% 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 are added, 16.3% of all lesions demonstrate restenosis to at least the same severity as the mean stenosis severity prior to angioplasty. SD=standard deviation.*

Disregarding these total occlusions, mean % diameter stenosis at follow-up was 41.3 ± 16.1. The mean 60.5% diameter stenosis **pre-angioplasty** marks 1.2 standard deviations to the right on the bell shaped curve and thus the area under the curve located to the right of the 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 prior to angioplasty. If the >50% diameter stenosis at follow up criterion is applied, 444 lesions (30.7%) were restenosed.

Values of quantitative angiographic measurements. It is apparent from figure 4 that diameter stenosis measurements of more than 75% were very rarely encountered. In fact 90% of all lesions had a diameter stenosis of less than 74% (thin curve in figure 4). The corresponding calculated % area stenosis is represented by the fat curve in figure 4. Ninety percent of all lesions had an area reduction of less than 93%

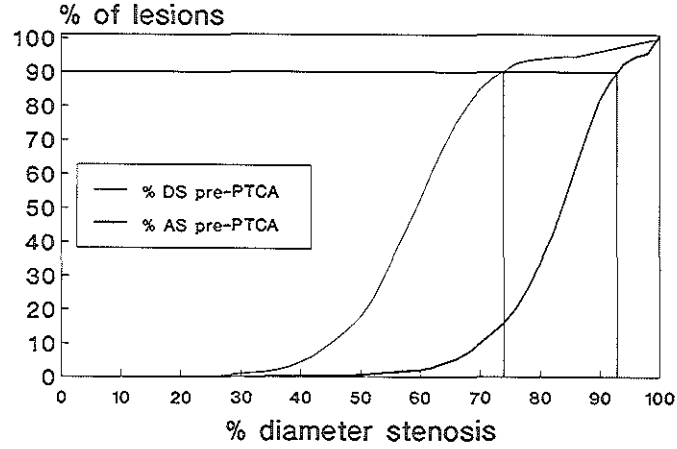

Figure 4. *Cumulative distribution of percent diameter reduction (percent diameter stenosis (%DS) thin curve) and of percent area reduction (percent area stenosis (%AS), fat curve) for 1445 lesions pre angioplasty. Ninety percent of all lesions show a % DS of less then 74%, which corresponds to 93% AS.*

Regression in lesion severity at follow-up angiography. Among the 1445 lesions analyzed, 429 showed an increase in minimal lumen diameter at follow-up (29.6%) (change < 0 mm, figure 1d). The long term variability of minimal lumen diameter measurements (i.e. 1 standard deviation of the difference of the means of 2 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 days 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 system. The use of 1 standard deviation would include 68.3% of the variability, while the use of 2 standard deviations (2 x 0.36 = 0.72 mm) includes 95.5% of the variability. Therefore an increase of more than twice the long-term measurement variability ($\geq$ 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 months follow-up period (figure 1d).

DISCUSSION

There is increasing evidence that reactive intimal hyperplasia is the underlying cause of luminal narrowing after successful balloon angioplasty. Post mortem studies and atherectomy specimen have revealed that medial smooth muscle cell migration and proliferation with the production of abundant extracellular matrix probably are the key factors in the luminal narrowing process after angioplasty [14-16]. Like most physical and biological phenomena this angiographicaly observed natural 'healing' process was found to be approximately Gaussian distributed.

Method of quantitative angiography and distribution of variables of lesion severity. In clinical medicine continuously distributed parameters of disease severity pose a problem because the decision on when or how to intervene has to be based on a more or less arbitrary cut-off point. For coronary stenosis severity, the 50% diameter stenosis value has emerged as a cut-off 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 a recently presented study [8] it was reported that the percentage diameter stenosis of lesions 4 months to 1 year after balloon angioplasty followed a bimodal distribution with the nadir between the 2 peaks at 50% diameter stenosis. This suggests that after balloon angioplasty 2 types of lesion behavior can occur, a restenosing- and a non restenosing reaction. If 2 different populations are present from the start, then it must be possible to isolate the restenosing patients before angioplasty. However, the prediction of restenosis with both invasive and non invasive tools is at most not very effective [18,19]. This finding has also far reaching consequences for the statistical analysis of angiographic restenosis data. The use of parametric statistical tests (eg t-test, analysis of variance) might no longer be appropriate.

In our population the distribution of percentage diameter stenosis was found to be unimodal and almost symmetrical and bell-shaped (figure 3). This discrepancy might be explained by the fact that quantitative angiography in the study of King et al. was carried out on-line in the catheterization laboratory with a non automated analysis technique and before clinical decision making was carried out. In that setting a percentage diameter stenosis around 50 is unwanted since it does not add information

for 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. at the 40th annual scientific session of the American College of Cardiology as an explanation for the bimodal distribution found in their series [8]. 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 pre angioplasty with a higher peak than expected (figure 1a) can be explained by lesion selection. Values around 1 mm correspond with diameter stenosis values in the range of 60 to 70%. These are generally the type of lesions selected for balloon angioplasty.

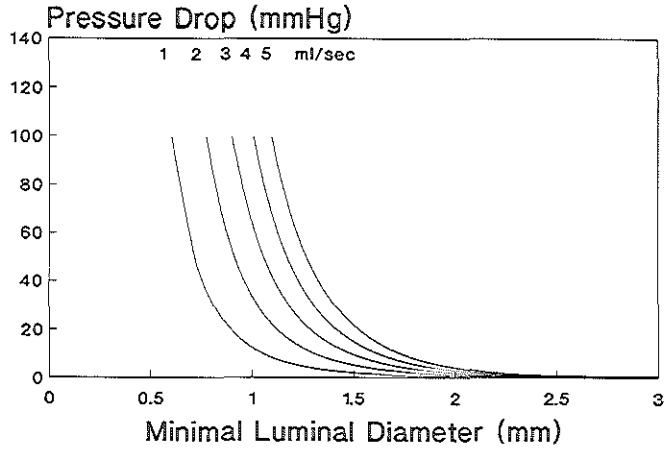

Figure 5. *Theoretical pressure drops calculated with the fluid dynamics equation derived by Gould and Kirkeeide [20,21] at assumed flows of 1,2,3,4 and 5 ml/sec respectively. Reference diameter was assumed 2.6 mm and lesion length 6.5 mm.*

Minimal lumen diameters smaller than 0.5 mm were not encountered. Figure 5 shows the theoretical pressure drop over a stenosis with a length of 6.5 mm (mean stenosis length in study) and an interpolated reference diameter of 2.6 mm (mean value in this study) at assumed flows ranging from 1 ml/second (rest) to 5 ml/second (maximal hyperemic flow). Pressure drops were calculated using the fluid dynamic equation derived by Gould and Kirkeeide [20,21]. Luminal diameters less than 0.5 mm are unrealistic from a fluid dynamics point of view since the pressure gradient over the stenosis necessary to maintain rest flow will be far beyond the physiological range (figure 5). Lesions that are approaching this severity will therefore show a severely reduced flow, become unstable and will eventually thrombose and occlude. For the same reason are diameter

stenosis measurements of more than 75% very rarely encountered. Only 10% of all lesions had a percentage diameter reduction pre angioplasty of more than 74% (figure 4). The highest pre angioplasty % diameter stenosis value encountered in this study (excluding total occlusions) was 86%. These at first glance low values of quantitatively measured diameter stenosis values correspond however with percentage area reduction values of more than 93! (figure 4). Therefore, visual stenosis severity scoring systems that allow classification of over 90% diameter reduction do not reflect the actual lesion severity and will describe lesions which are physiologically impossible. Furthermore, for accurate interpretation of studies using quantitative coronary angiography this discrepancy should be kept in mind.

Lesion progression towards total occlusion. From figure 1d and figure 2 it can be inferred that lesion progression towards total occlusion involves not only the near normally distributed luminal narrowing process, but that a part of the narrowing in lesions progressing towards total occlusion must be ascribed to a different process. Since lesions with a minimal lumen diameter of less than 0.5 mm are impossible because of the unphysiological high transstenotic pressure necessary to maintain blood flow (figure 5), it is likely that the last step in lesion progression towards 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. showed that platelet aggregation spontaneously occurs in partially obstructed coronary arteries [24]. Another explanation might be that a 'silent' thrombotic occlusion occurs early after an angiographic successful angioplasty. In the absence of an important collateral circulation one would then expect a high amount of myocardial infarctions in patients with a total occlusion at follow-up. Sixteen of the 70 totally occluded lesions at follow up were also totally occluded before angioplasty and were collaterally circulated. Of the 54 patent arteries pre angioplasty only 4 were infarct related during follow-up (enzyme elevation to twice normal and/or presence of new Q waves). Visible collateral circulation before angioplasty was present in only 8 of these 54 lesions (table 3). A slowly progressing lesion on the other hand could allow for a gradual build up of collateral circulation enabling a subsequent total occlusion to develop without myocardial necrosis.

Lesion regression. A definite increase in minimal lumen diameter (regression) was observed in 16 patients only (1.1%) (figure 1d). This finding is in concordance with earlier reported data [3]. True angiographic regression in the first months after angioplasty thus appears to be a rare phenomenon. On the other hand, Rosing et al. [25] described regression of the dilated lesion in 46 patients 3 years after successful angioplasty as compared to a 6 months angiogram. This finding can be ascribed to a late resorption of the extracellular matrix in the neointima [15].

Conclusion. The process of luminal narrowing after coronary balloon angioplasty is approximately normally distributed, with few lesions showing regression, most of the lesions showing no change and a considerable amount of the lesions 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 cut-off point, rather than a separate disease entity that occurs in some lesions but not in others. For comparison of the angiographic efficacy of pharmacological agents and new interventional devices, the use of change in minimal luminal diameter as end-point rather than restenosis rate is therefore recommended.

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Chapter 8

PREVENTION OF RESTENOSIS AFTER PERCUTANEOUS TRANSLUMINAL CORONARY ANGIOPLASTY WITH THROMBOXANE A2-RECEPTOR BLOCKADE. A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED TRIAL

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Prevention of Restenosis After Percutaneous Transluminal Coronary Angioplasty With Thromboxane A_2–Receptor Blockade

A Randomized, Double-Blind, Placebo-Controlled Trial

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Background. GR32191B is a novel thromboxane A_2–receptor antagonist with potent antiaggregational and antivasoconstrictive properties. We have conducted a randomized, double-blind, placebo-controlled trial to study its usefulness in restenosis prevention.

Methods and Results. Patients received either GR32191B (80 mg orally before angioplasty and 80 mg/day orally for 6 months) or 250 mg i.v. aspirin before angioplasty and placebo for 6 months. Coronary angiograms before angioplasty, after angioplasty, and at 6-month follow-up were quantitatively analyzed. Angioplasty was attempted in 697 patients. For efficacy analysis, quantitative angiography at follow-up was available in 522 compliant patients (261 in each group). Baseline clinical and angiographic parameters did not differ between the two treatment groups. The mean difference in coronary diameter between postangioplasty and follow-up angiogram (primary end point) was -0.31 ± 0.54 mm in the control group and -0.31 ± 0.55 mm in the GR32191B group. Clinical events during 6-month follow-up, analyzed on intention-to-treat basis, were ranked according to the highest category on a scale ranging from death (control, six; GR32191B, four) to nonfatal infarction (control, 22; GR32191B, 18), bypass grafting (control, 19; GR32191B, 22) and repeat angioplasty (control, 52; GR32191B, 48). No significant difference in ranking was detected. Six months after angioplasty, 75% of patients in the GR32191B group and 72% of patients in the control group were symptom free.

Conclusions. Long-term thromboxane A_2–receptor blockade with GR32191B does not prevent restenosis and does not favorably influence the clinical course after angioplasty. (*Circulation* 1991;84:1568–1580)

Percutaneous transluminal coronary angioplasty (PTCA) is increasingly being used as an alternative to coronary artery bypass graft surgery in patients with coronary artery disease. Although major improvements in angioplasty techniques have resulted in a high initial success rate, the late restenosis rate of 20–40% still limits the long-term benefit of the procedure.[1–5] For multivessel angioplasty, the restenosis percentage is even higher.[6] It is well known that restenosis after balloon angioplasty is a time-related phenomenon, occurring in the first months after balloon angioplasty.[5,7] Only very rarely does restenosis present itself more than 6 months after coronary angioplasty[8,9]; therefore, the follow-up period has been limited to the first six months after angioplasty in the current trial.

Deendothelialization and vascular disruption at the angioplasty site expose vessel wall smooth muscle cells and collagen directly to blood. This causes platelet adhesion, platelet aggregation, and activation of the clotting cascade. In addition, platelets may

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also activate leukocytes to release vasoconstrictor leukotrienes. These effects appear to be thromboxane mediated as inhibition of thromboxane reduces leukocyte activation.[10] Adhesion and aggregation of platelets at the postangioplasty plaque can lead to an early occlusion within the first 48 hours after angioplasty. Over the long term, platelet- and monocyte-derived growth factors stimulate smooth muscle cell proliferation, leading to the fibroproliferative reaction of the vessel wall in the first months after balloon angioplasty.[11–13] Apart from the proliferation process, organization of mural thrombi may also be the cause of restenosis.[14,15] Early platelet aggregation thus appears to play a pivotal role in the occurrence of postangioplasty thrombotic occlusion and the restenosis process.[16]

Thromboxane A_2 (TXA_2) is a potent platelet aggregational agent and vasoconstrictor released from activated platelets. Beyond the platelet-activating effect, TXA_2 also appears to have a more direct effect on vascular smooth muscle cell proliferation. Using primary cultures of smooth muscle from rat aorta, Hanasaki et al[17] demonstrated a mitogenic effect of thromboxane on smooth muscle cells, which occurs through binding to its specific receptor and may be suppressed by thromboxane-receptor blockade,[17] a promising approach to the inhibition of the effects of TXA_2.[18] TXA_2-receptor blockade prevents the deleterious actions of TXA_2 while sparing the beneficial synthesis of prostacyclin. GR32191B has been shown to be a potent and specific TXA_2-receptor–blocking drug that antagonizes the proaggregatory, vasoconstrictor, and bronchoconstrictor actions of TXA_2, as well as those of agents that act indirectly via TXA_2, such as collagen and arachidonic acid, and agents that directly stimulate the receptor, such as prostaglandin H_2 and the TXA_2 mimetic U-46619.[18,19] Although not affecting platelet adhesion, it potently inhibits the aggregation of platelets onto damaged blood vessels.[18,20] This property, together with the ability of the compound to inhibit the platelet-release reaction, indicates a potential clinical use of GR32191B in reducing early thrombotic events, late intimal hyperplasia, and subsequent restenosis after coronary angioplasty. The present multicenter, randomized, double-blind, placebo-controlled trial (Coronary Artery Restenosis Prevention on Repeated Thromboxane-Antagonism [CARPORT]) was carried out to evaluate the role of GR32191B in the prevention of late restenosis after PTCA.

Methods

All patients with angina and angiographically proven coronary artery disease who were scheduled for angioplasty were considered for inclusion at one of six participating centers (see "Appendix"). The trial was carried out according to the declaration of Helsinki, and specific exclusion criteria are given in Table 1. A screening log was maintained in two centers. At these two centers, 1,614 patients were screened from December 1987 through June 1989, and 72% were excluded (Table 1).

TABLE 1. Reasons for Exclusion for 1,318 of 1,614 Screened Patients at Two of Six Participating Centers

Reason	*n*	Total (%)
Insufficient lead-in time*	235	18
Use of platelet-inhibiting or nonsteroidal anti-inflammatory drugs within 7 days preceding the study	352	27
Refusal to participate and/or undergo 6-month recatheterization	364	28
Currently taking oral anticoagulant drugs	119	9
Angioplasty for restenosis	105	8
Acute myocardial infarction within 2 weeks preceding angioplasty	52	4
Bypass graft dilatation	39	3
History of obstructive airway disease	26	2
History of peptic disease or upper gastrointestinal bleeding	10	1
Previous participation in the trial	2	0.2
Severe other disease	6	0.5
Participation in another trial	6	0.4
History of intolerance to aspirin	1	0.1
Less than 21 years old	1	0.1
Pregnant woman or woman likely to become pregnant during study	0	0
Total	1,318	100

*Urgent referrals outside working hours.

Randomization and Treatment Protocol

Randomized, double-blind trial medication was allocated by telephone after the patient had been registered at the central allocation service. Trial medication consisted of either GR32191B for 6 months or control treatment with one dose of aspirin, followed by matching placebo.

One hour before angioplasty, patients allocated to GR32191B received 4 tablets of 20 mg GR32191B orally and an intravenous injection of a physiological salt solution. Patients allocated to control treatment received 250 mg i.v. acetylsalicylic acid and 4 placebo tablets. In addition to trial medication, all patients received a bolus of 10,000 units i.v. heparin at the beginning of the procedure. After two hours, 5,000 units/hr was given for as long as the procedure continued. Also, all patients received 10 mg nifedipine every 2 hours for the first 12 hours and 20 mg slow-release nifedipine tablets thereafter every 8 hours up to the second day after angioplasty.

In those patients in whom angioplasty was successful, either 40 mg GR32191B twice daily or placebo was started in the evening and continued until the end of follow-up. The final dose of trial medication was taken 1 hour before the follow-up angiogram. In addition, all participants were provided with paracetamol in 500-mg tablets for use as analgesic and were asked to avoid acetylsalicylic acid or nonsteroidal anti-inflammatory drugs while on trial medication.

Trial medication and paracetamol were packaged and supplied by Glaxo Group Research, which also prepared the random plan. Randomization was stratified by center.

Angioplasty Procedure and Follow-up Angiography

Coronary angioplasty was performed with a steerable, movable guide wire system via the femoral route. Choice of balloon type and brand as well as 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 angioplasty, one immediately after angioplasty, 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), using fixed-table systems and 35-mm cinefilm at a minimum speed of 25 frames/sec. All necessary details of the procedure were recorded in the case record form, and drawings of the segments to be analyzed were made by the investigators. Before the postangioplasty angiogram, radiopaque guide wires had to be removed to avoid interference with automated edge detection. For calibration purposes, catheter tips were cut off and sent with the cinefilm to the angiographic core laboratory. To standardize the method of data acquisition and to ensure exact reproducibility of postangioplasty and follow-up angiograms, measures were undertaken as has been described earlier.[5,21,22] A qualitative assessment of certain lesion characteristics was performed (see Table 2). Intracoronary thrombus was defined as the presence of a filling defect within the lumen, surrounded by contrast material seen in multiple projections in the absence of calcium within the filling defect, the persistence of contrast material within the lumen, or a visible embolization of intraluminal material downstream. Haziness was defined as a small radiolucent area within the lumen of the vessel disappearing with the passage of contrast material (type A dissection according to Dorros et al[23]). Intimal tear was defined as a filling defect within the lumen and dissection as contrast appearing outside the lumen, disappearing or persisting with the passage of contrast material (types B and C dissections according to Dorros et al[23]).

Follow-up Evaluation

After successful angioplasty, defined as at least one lesion successfully dilated (i.e., less than 50% diameter stenosis on visual inspection after the procedure) as judged by the investigator, patients returned to the outpatient clinic after 3 weeks and 3, 6, and 7 months for an interview, a physical examination, laboratory tests, a tablet count, and, except for the 6- and 7-month visits, a new supply of trial medication. Patients with an unsuccessful angioplasty discontinued trial medication and received the standard medical care. The follow-up clinical status of all patients, irrespective of PTCA success, was assessed 6 months after the procedure. In one of the participating centers (Rotterdam), platelet aggregation tests, using ADP and U-46619 (a TXA_2 mimetic) as aggregants, were carried out to assess pharmacological activity of the drug. At 6-month follow-up, 1–4 days before angiography, a symptom-limited exercise test was performed on a bicycle ergometer according to two different protocols. In Berlin, the test was performed with the patient in a supine position, starting with a work load of 25 W, which increased by 25 W every 2 minutes. In the other clinics, 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 1 minute. Exercise was continued until anginal symptoms, a drop in systolic blood pressure, severe arrhythmia, or a ST depression of more than 1 mm occurred. A 12-lead electrocardiogram was recorded during exercise and recovery. ST changes were measured 80 msec after the J point. Horizontal or downsloping ST segment depression associated with anginal symptoms was considered a positive response to the stress test. The follow-up coronary angiogram was performed at the 6-month visit. If symptoms recurred within 6 months, coronary angiography was carried out earlier. If no definite restenosis was

TABLE 2. Angiographic Baseline Data of Compliant Patients With Quantitative Angiographic Follow-up

	Control (n=261)		GR32191B (n=261)	
	n	%	n	%
Lesions (n)	320		316	
Lesions per patient (n)	1.23		1.21	
Vessels dilated				
LAD	167	52	146	46
RCA	90	28	99	31
LCx	63	20	71	23
Calcified lesion	19	6	32	10
Discrete	242	76	239	76
Asymmetry	133	42	134	42
Total occlusion	12	4	10	3
Tandem lesion	25	8	24	8
Side branch in stenosis	99	31	78	25
Side branch in dilatation site	178	56	193	61
Inflation duration (seconds)	138±92		133±90	
Maximum inflation pressure (atm)	9±2		9±2	
Balloon-to-artery ratio	1.10±0.22		1.06±0.22	
Thrombus visible after angioplasty	7		12	
Dissection	49	15	46	15
At balloon site	44		39	
Proximal of balloon	1		1	
Distal of balloon	4		6	
Intimal tear	37	12	26	8
Haziness	45	14	56	18

LAD, left anterior descending coronary artery; RCA, right coronary artery; LCx, left circumflex artery.

present and the follow-up time was less than 4 months, the patient was asked to undergo another coronary arteriogram at 6 months.

Quantitative Angiography

All cineangiograms were analyzed using the CAAS system, which has been described in detail.[24–26] 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 absolute values of the stenosis diameter as well as the reference diameter are measured by the computer using the known contrast catheter diameter as a scaling device. Because the algorithm is not able to measure total occlusions, a value of 0 mm was 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. In contrast, for a totally occluded vessel at follow-up angiography, a value was not substituted, so that the change in reference diameter from after angioplasty to follow-up was only calculated when an actual measurement was available.

Balloon-to-artery ratio was defined as the ratio of the mean balloon diameter measured in a single nonforeshortened projection and the reference diameter of the dilated segment in the same projection.

Assay of GR32191B and Platelet Aggregation Tests

Plasma samples of patients allocated to active drug treatment were taken before first drug intake and approximately 1 hour afterward. These samples were analyzed for GR32191B by high-performance liquid chromatography with fluorescence detection after solid-phase extraction on an advanced automated sample processor.

For the aggregation tests, blood was drawn from the patient by venipuncture. Nine parts of blood were mixed with 1 part 0.13 M sodium citrate solution. The blood was then centrifuged (15 minutes at 200*g* at room temperature), and the supernatant platelet-rich plasma (PRP) was carefully removed using a plastic Pasteur pipette and transferred to a separate plastic tube. The remaining blood was centrifuged for 10 minutes at 2,000*g* at room temperature to obtain platelet-poor plasma (PPP). PPP was then added to PRP to obtain PRP with a platelet count of 200×10^9 platelets/l. The PRP was stored at room temperature in full, capped tubes (contents, 5 ml) for 30–90 minutes. Aggregation was performed in a Payton twin-channel aggregometer at 37°C with a stirring speed of 900 rpm. Maximum and minimum light transmission was set up using PPP and PRP, respectively. Samples of 400 μl PRP were incubated in the aggregometer for 3 minutes at 37°C, and 40 μl of either the TXA_2 mimetic U-46619 (final concentration, 1 μM) or ADP (final concentration, 10 μM) was added. Aggregation was allowed to proceed to its maximum or a period of 5 minutes was allowed, whichever was longer. Aggregation was expressed as the peak response and represented in millimeters.

End Points

The primary end point of the present study was the within-patient change in minimal lumen diameter as determined by quantitative angiography after PTCA and at follow-up. Post-PTCA values were obtained from the last post-PTCA angiogram made before withdrawal of the guide catheter. The initial procedure were considered finished when the guide catheter was removed. In case evolution of the clinical condition required repeat PTCA (with reinsertion of guide catheter), the angiogram made before repeat balloon inflations was used to obtain follow-up values, regardless of the timing of repeat PTCA (hours, days, or weeks). Otherwise, the follow-up angiogram made according to protocol was used. For each dilated segment, the post-PTCA and follow-up minimal lumen diameters were taken as the mean values from multiple matched projections. Within-patient change (i.e., the primary end point) was defined as the follow-up minus the post-PTCA value. In case more than one segment was dilated (multivessel or multisite procedures), the change in minimal luminal diameter per patient was calculated as the average of the different lesions. Secondary end points were clinical events believed to be related to restenosis. These were death (regardless of cause), nonfatal myocardial infarction (at least two of the following: typical pain, electrocardiographic changes suggesting acute myocardial infarction, cardiac enzymes more than twice the upper limit of normal), coronary artery bypass graft surgery (CABG), and repeat angioplasty at the same site. Events were classified as "procedural" (i.e., onset of event or decision to perform another procedure taken while the guide catheter was still in place), "early" (i.e., onset within 24 hours of guide catheter removal), or "late" (i.e., onset more than 24 hours after guide catheter removal). Another secondary end point was the presence and severity of angina pectoris as assessed by the Canadian Cardiovascular Society classification at last follow-up.

Statistical Methods and Analysis

The minimal sample size was estimated at the outset of the study to be 233 patients in each group on 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[5] and -0.25 ± 50 mm (i.e., a 30% difference) in the active drug group (two-sided test with an α error of 0.05 and a power of 0.90).

In the comparison between treatment groups for the primary angiographic end point, patients included were those who had a successful initial angioplasty, had a quantitatively analyzable PTCA angiogram, had follow-up angiogram made while on trial medication, and were compliant with trial medication (had used at least 80% of their trial medication during the intervening period and had not discontin-

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TABLE 3. Clinical Baseline Data of 697 Patients Included in Analysis for Clinical End Points

	Control (n=346)		GR32191B (n=351)	
	n	%	n	%
Men (n)	276	80	279	80
Age (years)	56.9±9.0		56.6±9.0	
Ever smoked	259	75	280	80
Current smoker	40	12	57	16
Diabetes	28	8	29	8
History of hypertension	111	32	120	34
Lipids (mmol/l)				
Total cholesterol	6.2±1.1	(n=337)	6.2±1.2	(n=345)
LDL cholesterol	4.2±1.2	(n=240)	4.1±1.3	(n=251)
HDL cholesterol	1.1±0.5	(n=290)	1.2±0.5	(n=297)
CCS class				
I	37	11	42	12
II	111	32	116	33
III	141	41	140	40
IV	57	16	52	15
Pain at rest controlled by intravenous nitrates	43	12	48	14
Duration of angina (months)	2±44		24±45	
Previous MI	134	39	132	38
Previous CABG	7	2	12	3
Previous angioplasty	4	1	6	2
Patients on medication				
Nitrates	235	68	225	64
Calcium antagonists	208	60	222	63
β-Blockers	175	51	191	54
Monotherapy	97	28	104	30
Double therapy	151	44	156	44
Triple therapy	73	21	74	21

LDL, low density lipoprotein; HDL, high density lipoprotein; CCS, Canadian Cardiovascular Society angina classification; MI, myocardial infarction; CABG, coronary artery bypass graft surgery.

ued trial medication for more than 3 days). To test the null hypothesis that both mean changes in minimal lumen diameter are equal, an unpaired t test was used and a 95% confidence interval for the effect measure was obtained.

Comparisons for each clinical event were made on the basis of intention to treat (i.e., with inclusion of all patients who were randomized—defined as having taken at least their initial oral dose of trial medication—and regardless of angioplasty outcome or trial medication compliance). Also, the clinical status of each patient at the end of follow-up was ranked by assignment to the lowest applicable category of the following ordinal scale: 1, death; 2, nonfatal myocardial infarction; 3, status after CABG; 4, status after repeat PTCA; 5, presence of angina pectoris (Canadian Cardiovascular Society classification of 1 or higher); and 6, none of the above. The percentages of patients in each of these categories were compared between treatment groups on the basis of intention to treat. For all comparisons, the null hypothesis of no difference was tested by appropriate statistical tests.

Results

A total of 707 patients were randomized. Of these patients, 353 were randomized to receive GR32191B, and 354 were randomized to the control group. Selected demographic, clinical, and angiographic characteristics of the two study groups are shown in Tables 2 and 3. No baseline differences were observed between the two groups.

Figure 1 shows the patient flow and the reasons that subjects could not be evaluated with respect to quantitative angiographic restenosis. In 10 patients, angioplasty was not performed. One patient, who could not be treated because of radiographic equipment failure, was rerandomized 2 weeks later and retrospectively excluded as a protocol violator (previous participation in the trial was an exclusion criterion). Angioplasty was successful in 322 of the treated patients and 327 of the control group. Angioplasty was unsuccessful in 29 patients in the treated group and 19 in the control group. Thus, 322 treated patients and 327 control patients underwent successful angioplasty of at least one lesion and were eligible for follow-up angiography. Quantitative angiographic

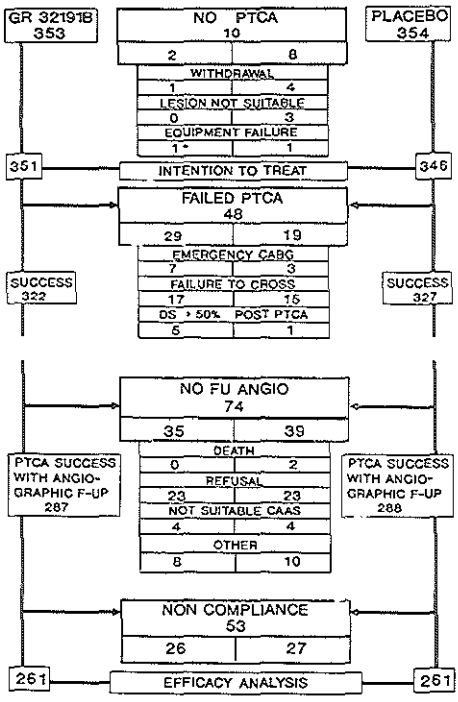

FIGURE 1. *Schematic of patient flow in Coronary Artery Restenosis Prevention on Repeated Thromboxane-Antagonism trial and reasons why no follow-up angiogram and/or quantitative angiography was obtained. Angio, coronary angiography; CABG, coronary artery bypass graft surgery; CAAS, coronary artery analysis system; DS, diameter stenosis; FU, follow-up; angioplasty, percutaneous transluminal coronary angioplasty. *Patient randomized twice and excluded from trial.*

follow-up as not available in 74 cases (35 treated and 39 control). In 18 cases, quantitative angiography could not be obtained for a variety of reasons: peripheral vascular problems (n=3), intercurrent noncardiovascular disease rendering repeat catheterization not desirable (n=9), one patient moved to another country, three patients underwent CABG without preoperative recatheterization, one cinefilm was lost, and one film was damaged during processing. Finally, 53 patients did not fulfill the compliance criteria and were excluded from the quantitative angiographic efficacy analysis (Figure 1).

Result of Angiographic Efficacy Analysis

Table 4 and Figure 2 summarize the quantitative angiographic findings of the efficacy analysis. At follow-up, the loss of minimal lumen diameter was identical in both groups: −0.31 mm (treatment effect, 0 mm; 95% confidence intervals, −0.09, 0.09). Figure

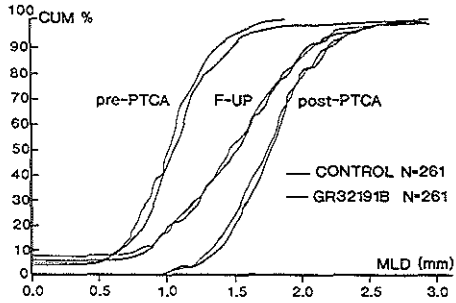

FIGURE 2. *Cumulative distribution curve of minimal lumen diameter before percutaneous transluminal coronary angioplasty (PTCA), post-PTCA, and at 6-month follow-up (F-UP) in both treatment groups. CUM %, cumulative percentage of patients; MLD, minimal luminal diameter.*

3 is a cumulative curve of the change in minimal lumen diameter observed in both groups. A loss of 0.72 mm or more[5,27] corresponds to restenosis rates of 19% in the control group and 21% in the treated group. Therefore, the relative risk for restenosis in the treated group with respect to the control group is 1.15 (95% confidence intervals, 0.82, 1.60).

Results of Bicycle Ergometry

Of 649 patient who had a successful angioplasty, 539 underwent exercise testing at follow-up. Reasons for not performing the test were death (2 patients), unstable angina (45 patients), inability to perform the

TABLE 4. **Quantitative Analysis of 636 Lesions in 522 Patients**

	Control (n=261)	GR32191B (n=261)
Obstruction diameter (mm)		
Before angioplasty	0.99±0.35	1.06±0.39
After angioplasty	1.77±0.34	1.79±0.33
Follow-up	1.46±0.59	1.49±0.58
Reference diameter (mm)		
Before angioplasty	2.64±0.57	2.70±0.50
After angioplasty	2.71±0.54	2.76±0.48
Follow-up	2.72±0.55	2.74±0.52
Difference in obstruction diameter (mm)		
After angioplasty minus before angioplasty	0.78±0.39	0.73±0.38
Follow-up minus after angioplasty	−0.31±0.54	−0.31±0.55
Percentage stenosis (%)		
Before angioplasty	62±13	61±12
After angioplasty	34±9	34±9
Follow-up	46±19	45±19
Difference in percentage stenosis (%)		
After angioplasty minus before angioplasty	−28±14	−26±14
Follow-up minus after angioplasty	12±20	11±19

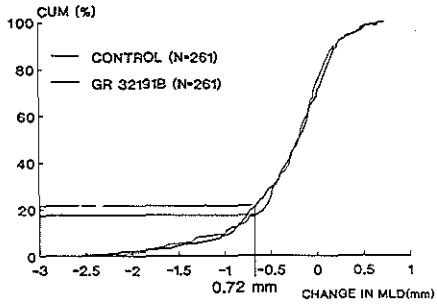

FIGURE 3. *Cumulative distribution curve of change in minimal lumen diameter from after angioplasty to follow-up in both treatment groups. CUM %, cumulative percentage of patients; MLD, minimal luminal diameter.*

test (19 patients), refusal (33 patients), and other (11 patients). Table 5 summarizes results of exercise testing in both groups. No difference in any parameter was observed at submaximal or maximal exercise. ST deviation (depression or elevation) of more than 0.1 mV (more than 1 mm) associated with anginal symptoms (considered positive) was observed in 47 patients in the control group and 55 patients in the GR32191B group.

Clinical Follow-up

Table 6 shows the total number of events during 6-month follow-up as well as the ranking of clinical status 6 months after angioplasty for all 697 patients randomized. Adjusted χ^2 test revealed no difference in ranking between the two groups. At 6-month follow-up, a comparable number of patients in both treatment groups were in each Canadian Cardiovascular Society class. Finally, 194 patients (56%) in the treated group and 197 (56%) in the control group were event and symptom free at 6-month follow-up.

TABLE 5. Exercise Test Results

	Control (n=262)		GR32191B (n=277)	
	n	%	n	%
Position				
Supine	98	38	110	40
Sitting	164	62	167	60
ST deviation >0.1 mV	102	39	117	42
Anginal symptoms during test	76	32	73	30
Combination of >0.1 mV segment deviation and symptoms	47	18	55	20
Maximum work load (W)	142±41		144±40	
Expected work load (W)	160±32		161±39	
Exercise time (minutes)	7.8±2.9		7.8±3.0	
Systolic blood pressure at peak exercise (mm Hg)	193±33		196±31	
Heart rate at peak exercise (min^{-1})	133±24		135±22	

Test performed in 539 of 649 patients with successful angioplasty.

Results of GR32191B Assay and Platelet Aggregation Tests

In four of the six participating centers, GR32191B plasma levels for patients allocated to the GR32191B group were analyzed before first drug intake and approximately 1 hour after first drug dose. GR32191B was not detected above the limit of quantification in the predose samples but was present in the postdose samples at concentrations ranging from 5 to 1,210 ng/ml, with a mean of 392±241 ng/ml, indicating that GR32191B was absorbed into the circulation after the oral administration of GR32191B.

During each follow-up visit of the Rotterdam patients, platelet aggregation tests were carried out using the TXA_2 mimetic U-46619 and ADP as aggregants. During the first three visits (3 weeks, 3 months, and 6 months after angioplasty), patients were on trial medication. The fourth visit (7 months after angioplasty) served as a control measurement. A total of 162 patients were tested at least one time during follow-up (Table 7). Mean ADP aggregation during visits 1, 2, and 3, expressed as peak response, was 116±12 mm (214 analyses) in the treatment group and 125±12 mm (203 analyses) in the control group (two-tailed t test, p=0.4). Mean U-46619 aggregation during visits 1, 2, and 3 was 10±21 mm (215 analyses) in the treatment group and 100±35 mm (203 analyses) in the control group (two-tailed t test, p<0.0001). This significant lowering of U-46619 aggregation in the treated group was observed in all except five patients during their 3-month test. These five patients showed U-46619 aggregation of more than 100 mm. At the 7-month assessment (patients off trial medication), mean U-46619 aggregation again rose to 80±42 mm (27 analyses) in the treatment group, which is not significantly different from the value of 99±32 mm (19 analyses) in the control group (two-tailed t test, p=0.8).

Bleeding Complications and Tolerability

Only mild bleeding events occurred in the trial. In-hospital bleeding events occurred in 18 patients (5%) in the control group and 15 patients (4%) in the treatment group (hematoma at puncture site of more than 5 cm, 14 versus 12 patients; prolonged bleeding at puncture site, three versus four; hematoma elsewhere, one versus none). During follow-up, four hematomas were reported in the control group and five in the treatment group. No cerebral bleeding or cerebral thrombotic events were encountered during the time course of the trial. Generally, the drug was well tolerated, and reported side effects were mild and evenly distributed in the two treatment groups. Total reported side effects were 40 in the control group and 44 in the treatment group (epigastric discomfort, 19 versus 20 patients; rash, 11 versus 12; nausea, six versus three; salivation, none versus two; headache, three versus six; fever, one versus one).

TABLE 6. Total Number of Events and Ranking Scale

	Total events during 6-month follow-up				Ranking of clinical status 6 months after angioplasty			
	Control (n=346)		GR32191B (n=351)		Control (n=346)		GR32191B (n=351)	
	n	%	n	%	n	%	n	%
Death								
Late	6		4					
All	6	2	4	1	6	2	4	1
Myocardial infarction								
Procedural	5		5					
Early	11		7					
Late	6		6					
All	22	6	18	5	22	6	18	5
Bypass graft surgery								
Procedural	3		7					
Early	5		2					
Late	18		18					
All	26	8	27	8	19	6	22	6
Repeat angioplasty								
Early	9		6					
Late	59		54					
All	68	20	60	17	52	15	49	14
CCS classification*								
IV	5	2	1	0.3	5	2	1	0.3
III	19	6	18	5	11	3	11	3
II	36	11	47	14	23	7	30	9
I	26	8	32	9	14	4	19	5
None	254	75	249	72	194	56	197	56

CCS, Canadian Cardiovascular Society angina classification. *For 687 patients alive at 6-month follow-up; secondary end point.

Discussion

Rationale for Selective Thromboxane Blockade in Prevention of Restenosis

At the time of the design of the trial in 1986, it was thought that platelet aggregation at the site of endothelial denudation and vascular disruption played a pivotal role in the pathogenesis of restenosis. Massive platelet deposition and aggregation at the dilatation site[13] could, on the one hand, lead to organization of a mural thrombus[28] and, on the other hand, trigger a fibroproliferative reaction of the vessel wall via the release of growth factors and chemotactic agents.

Balloon angioplasty causes a severe vascular trauma that can only be compared with spontaneous plaque rupture in unstable anginal syndromes,[29] with its known deleterious thrombotic consequences. Prevention of thrombotic events by blocking the TXA_2-induced aggregation with aspirin is known to be effective in unstable angina[30,31] and in the periangioplasty period.[32,33] Nevertheless, aspirin may still fall

TABLE 7. Platelet Aggregation Tests

Aggregation agent	Visit 1 (3 weeks)	Visit 2 (3 months)	Visit 3 (6 months)	Visit 4 (7 months)	Analysis of variance
ADP active (mm)	116±12	118±11	115±14	121±17	NS
n	81	72	61	26	
ADP control (mm)	124±13	126±11	127±11	118±11	p=0.03
n	81	69	53	19	
U46619 active (mm)	8±12	7±12	15±34	80±42	p<0.0001
n	81	72	62	27	
U46619 control (mm)	101±36	101±34	100±37	99±32	NS
n	81	69	53	19	

During visits 1, 2, and 3, patients were on trial medication.

short as the ideal agent because it is not sufficiently specific as an inhibitor of TXA_2 production.[34] Furthermore, by irreversibly acetylating cyclo-oxygenase and preventing the formation of the endoperoxide prostaglandin H_2, aspirin can block the production of "beneficial" prostaglandins such as prostacyclin as well as the "detrimental" TXA_2. A drug that preserved prostacyclin production while inhibiting the production or actions of TXA_2 might be expected to be superior to aspirin. This could be achieved either by a TXA_2 synthetase inhibitor or a TXA_2-receptor–blocking drug. However, no TXA_2 synthetase inhibitor is known to produce a complete blockage of TXA_2 synthesis. Furthermore, accumulating precursors of TXA_2, such as prostaglandin H_2, are also capable of inducing aggregation via the TXA_2-receptors.[35] In contrast, TXA_2-receptor blockade will antagonize not only the proaggregatory actions of TXA_2 but also those of agents that act indirectly via TXA_2, such as collagen, and agents that directly stimulate the TXA_2-receptor, such as prostaglandin H_2. A role for TXA_2-receptor blockade after PTCA has been suggested by an experimental animal model showing reduced intimal hyperplasia after balloon injury of rat carotids after treatment with GR32191 (M. Zimmerman, personal communication).

GR32191 (in doses of 0.125–1.0 mg/kg p.o) produced a dose-related antagonism of U-46619–induced platelet aggregation ex vivo, which at the 1-mg/kg dose persisted for more than 24 hours.[36] GR32191B has also been demonstrated to produce a long-lasting blockade of the TXA_2-receptor on vascular smooth muscle in vivo in humans.[36] Chronic dosing (17.5 mg b.i.d.) resulted in progressively increasing antagonism of U-46619–induced aggregation such that virtually complete inhibition was achieved over the entire 12-hour dosing cycle.[37] In healthy volunteers[37] as well as in our patients, the drug was well tolerated, and bleeding time was only slightly prolonged. Finally, GR32191 is entirely devoid of any agonistic actions.[38]

Trial Design

The design of CARPORT was based on four considerations, each of them having specific consequences. First, it was the underlying assumption that TXA_2-receptor blockade with GR32191B started before angioplasty would, at least in theory, affect both acute restenosis resulting from platelet aggregation–induced thrombus formation and chronic restenosis resulting from platelet aggregation–induced hyperplasia. Second, in view of the fact that patients in whom angioplasty did not succeed are not "at risk" for restenosis, trial medication was continued only in case PTCA was successful. Third, at this stage of the development of the therapeutic principle involved, it was considered necessary to establish the mechanism of action by direct observation of restenosis by angiography. As a consequence, the protocol included follow-up angiography regardless of clinical status. Within-patient change of minimal lumen diameter, as assessed by objective, quantitative measurements of coronary segments filmed in multiple matched projections, was chosen as primary end point. Furthermore, the number of patients was planned based on what was known about the reproducibility of this method rather than on the need to have sufficient power for detecting an effect on clinical outcome (which would have required a much larger number of patients). Fourth, it was considered unethical not to give any protection against acute thrombotic events during angioplasty to participating patients.[32,33] As a consequence, one dose of intravenous aspirin was given before PTCA to the control group before placebo was started.

Loss in Minimal Luminal Diameter as Primary End Point: A Noncategorical Approach

The reappearance of angina as a sole criterion of restenosis underestimates the angiographic rate of restenosis, and the value of recurrent anginal symptoms as a marker of restenosis is difficult to assess in many studies because the timing and completeness of angiographic follow-up often have been determined by symptomatic status.[39]

In the present trial, repeat catheterization with quantitative angiography was obtained in 88.5% of 649 patients with a successful angioplasty. A majority of patients (354 of 522, or 68%) were recatheterized in the 6-month (±2 weeks) time interval. The remaining patients underwent early recatheterization because of clinical suspicion for restenosis. Of the 522 compliant patients who had angiography at follow-up, 345 were angina free and 165 were symptomatic at follow-up. As shown in Figure 4B, there was considerable overlap between the change in minimal lumen diameter of patients with and of those without angina at follow-up angiography. This underscores that reappearance of angina is a poor proxy to the anatomic substrate at issue and confirms the poor predictive value of symptoms found in other studies,[39] which may be explained by the presence of other mechanisms for angina, such as incomplete revascularization or progression of disease in other vessels.

Several studies have examined the usefulness of ergometry to detect restenosis after angioplasty.[39] These studies have generally found that the presence of exercise-induced angina, ST segment depression, or both is not highly predictive of restenosis whether the test is performed early or late after angioplasty.[39] Figure 4B illustrates this for our data in a similar fashion as for angina. In view of the above, quantitative coronary angiography has emerged as the most reliable method for judging late results.

In studies evaluating the biology of restenosis, a continuous measure of the degree of lumen obstruction is preferable because any progression of the stenosis reflects the process of interest regardless of whether an arbitrarily defined threshold of obstruction is reached. Keeping in mind that an angiographic restenosis study assesses only the anatomic component of the restenosis problem, there is no

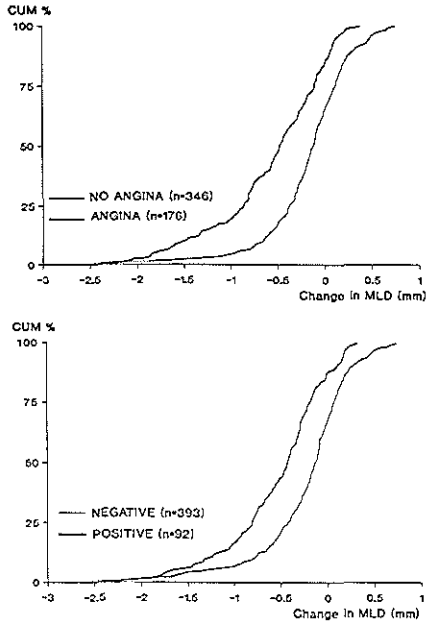

FIGURE 4. Top panel: *Cumulative distribution (CUM %) curve of change in minimal lumen diameter (MLD) for symptomatic and asymptomatic patients at follow-up angiography.* Bottom panel: *Cumulative distribution (CUM %) curve of change in minimal lumen diameter (MLD) for patients with positive ergometry and negative ergometry at follow-up angiography.*

threshold above which a loss of lumen diameter would have clinically significant functional or symptomatic consequences. Why, then, would one try to define a threshold above which there would be "significant" quantitatively determined angiographic restenosis? To define the threshold on consideration of reproducibility of the measurement in individual patients is also questionable. The expected benefit of a treatment can be measured with much greater precision by using the change in lumen diameter for the group. If it is assumed that treatment reduces the loss of lumen diameter from 0.4 mm under control conditions to 0.25 mm under active medication, 233 patients per treatment group are required for there to be a power of 90%. The above reduction corresponds with restenosis rates (defined as a loss of minimal lumen diameter of 0.72 mm or more) of 25% and 17.5%, respectively.[5,27] This difference, however, can be statistically detected only with 620 patients per treatment group (power, 90%). Thus, statistically, the quantitative outcome determined from direct measurements of continuous variables can be evaluated with only one third of the number of patients required for the categorical outcome. This is logical because categorical end points do not take full advantage of the available information.

Possible Explanations for Lack of Effect of GR32191B

In this trial, TXA_2-receptor blockade failed to demonstrate prevention of angiographic restenosis after angioplasty. Also, there was no apparent effect on overall clinical outcome. There are several possible explanations.

First, it could be hypothesized that the absence of benefit was due to poor absorption. In four participating clinics, plasma levels of GR32191B before first drug dose and 1 hour afterward confirmed an excellent gastrointestinal resorption of the drug in this group of patients with coronary artery disease who were fasting while awaiting an angioplasty procedure. Second, compliance could have been poor. Aggregation tests in one participating clinic showed that a 90% reduction of platelet aggregation via the TXA_2 pathway was achieved in the treated group throughout the entire study. This indicated that patients were taking their medication and that the drug was pharmacologically active. Third, it might be hypothesized that this substantial reduction in the aggregatory response of the platelet is still insufficient to prevent a substantial release of other factors involved in the initiation of the proliferative response.[13,40–42] In a recently published study, it was shown that GR32191 had no effect on primary aggregation induced by ADP, adrenaline, or platelet aggregating factor.[43] In the present study, GR32191 was found to inhibit only 70% of the total platelet deposition on deendothelialized rabbit aorta using ^{111}In-labeled human platelets from whole blood.[43] This was similar to the maximum inhibition achieved with prostacyclin and aspirin. Because several clinical trials with aspirin after balloon angioplasty have failed to prove a beneficial effect on restenosis,[32,44–46] it might be retrospectively inferred that a similar level of platelet inhibition would also fail to alter the restenosis rate. Furthermore, the magnitude of TXA_2-receptor blockade needed after balloon-induced vascular damage is not known. For example, a substantial increase in plasma levels of TXA_2 metabolite 11-dehydro-thromboxane B_2 from less than 50 to 174 pg/ml has been measured in the great cardiac vein after angioplasty of the left anterior descending coronary artery, despite pretreatment with aspirin.[47] One could question whether TXA_2-receptor blockade is effective in the face of such an increase, although it has been demonstrated that GR32191 can achieve a more-than-100-fold displacement to the right of the platelet aggregation concentration-effect curve for U-46619 in healthy subjects.[36]

More recently, it has been advocated that inhibition of platelet adhesion is a more efficient means to prevent subsequent aggregation of platelets.[48–51] However, it can be argued that complete inhibition of adhesion will cause untoward bleeding effects.

Finally, the pivotal role of the platelet in the initiation of the restenosis process might have been overestimated,[52] and antiplatelet therapy as the sole modality of treatment may be intrinsically insufficient to control the restenosis phenomenon.

Appendix

CARPORT Study Group

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KEY WORDS • percutaneous transluminal coronary angioplasty • restenosis • quantitative angiography • clinical trials

Chapter 9

WHICH ANGIOGRAPHIC PARAMETER BEST DESCRIBES FUNCTIONAL STATUS 6 MONTHS AFTER SUCCESSFUL SINGLE VESSEL CORONARY BALLOON ANGIOPLASTY?

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Abstract

To determine which quantitative angiographic parameter best describes functional status 6 months after coronary balloon angioplasty, we studied 350 patients with single vessel coronary artery disease who underwent a single site balloon dilatation. Sensitivity and specificity curves for the prediction of anginal status and exercise electrocardiography of 4 quantitative angiographic variables were constructed. The point of highest diagnostic accuracy for the variables was determined at the intersection of the sensitivity and specificity curves. Exercise electrocardiography was considered indicative for ischemia if horizontal or downsloping ST segment depression of $\geq$1 mm occurred. The points of highest diagnostic accuracy of the angiographic parameters were similar for both anginal status and exercise electrocardiography; 1.45 mm and 1.46 mm for the minimal lumen diameter measurements, 45.5% and 46.5% for the % diameter stenosis measurements at follow-up, -0.30 mm and -0.32 mm for change in minimal lumen diameter and -10% and -10% for the change in percent diameter stenosis at follow-up. Angiographic parameters reflecting a change in lesion severity at follow-up angiography were only slightly less accurate than parameters that describe lesion severity at follow-up. The large number of patients studied and the fact that the same optimal values for diagnostic accuracy of the various quantitative angiographic variables were obtained for the prediction of 2 different markers of ischemia suggests that these values reflect the lesion severity or increase in lesion severity in major epicardial vessels at which coronary flow reserve is unable to meet myocardial demands.

Key words:
-Percutaneous Transluminal Coronary Angioplasty
-Restenosis
-Functional Status
-Quantitative Angiography

INTRODUCTION.

Soon after the introduction of percutaneous transluminal coronary balloon angioplasty the vexing problem of restenosis became apparent. Approximately 30-40% of patients will show functional and/or angiographic signs of restenosis in the first months after a successful angioplasty procedure. A multitude of angiographic restenosis criteria have been developed over the last 12 years [1]. Restenosis criteria currently in use can be divided in those that describe the change in lesion severity from the post angioplasty situation up to the follow-up angiogram and those that merely describe lesion severity at follow-up angiography. An example of the first category is the loss in lumen diameter of more than 0.72 mm as proposed by Serruys [2], and an example of the latter category is the criterion of > 50% diameter stenosis at follow-up. Criteria that describe a change in lumen diameter may ignore the functional significance of the lesion at follow-up, especially in large vessels [3], whilst criteria that only describe the situation at follow-up will preselect lesions with a suboptimal result after angioplasty and thereby disregard the magnitude of the reactive intimal hyperplasia [1]. Recurrence of a flow-limiting stenosis can usually be identified by symptoms of chest pain similar to those that occurred before angioplasty. In addition to the medical history, exercise electrocardiographic testing is generally performed as a non invasive approach to confirm the recurrence of a coronary artery obstruction because it is a relatively simple, safe and inexpensive test. To determine which quantitative angiographic variable best predicts the functional status of the individual patient, we studied the recurrence of anginal complaints and positive electrocardiographic exercise testing 6 months after a successful angioplasty of a selected patient group with single vessel disease and single site dilatation. The functional parameters (recurrence of angina and positive exercise testing) were correlated with quantitative angiographic variables of change in lesion severity (change in minimal lumen diameter (MLD), change in percent diameter stenosis) and variables that merely describe lesion severity at follow-up angiography (MLD and percent diameter stenosis).

METHODS

Study population. The original patient group consisted of 697 patients that were enrolled in the multicenter CARPORT trial. A list of participating centers and investigators has been published previously [4]. Identical angiographic and clinical outcomes were observed in both randomization groups, so that the placebo- and active treatment group were pooled for the present study [4]. Selection criteria for this trial have been published previously [4]. Of the 697 patients, 649 had a successful procedure, defined as a less than 50% residual stenosis by visual inspection of the post angioplasty angiogram and no occurrence of in-hospital complications (death, acute myocardial infarction, bypass grafting, repeat angioplasty or symptom recurrence). Five hundred seventy five patients underwent subsequent follow-up angiography that was suitable for

quantitative analysis (follow-up rate 88.6%). Of these 575 patients, 350 had single vessel coronary artery disease and underwent a single site dilatation and therefore it was presumed that complete revascularization was achieved in this group of patients. All patients signed informed consent and the study protocol was approved by the institutional review boards of the participating centers.

Angioplasty procedure and follow up angiography. Coronary angioplasty was performed with a steerable, movable guide wire system via the femoral route. Details of the procedure have been described previously [4].

Three coronary angiograms were obtained in each patient, one just before angioplasty, one immediately after angioplasty, and one angiogram at follow-up. The 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 the cathetertips 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 [4-6]. All angiograms were processed and analyzed in a central core-laboratory. The follow-up coronary angiogram was performed at six months follow-up. If symptoms recurred within 6 months, coronary angiography was carried out earlier. If no definite restenosis was present and the follow-up time was less than 4 months, the patient was asked to undergo another coronary arteriogram at 6 months.

Quantitative angiography. All cineangiograms were analyzed using the computer assisted cardiovascular angiography analysis system (CAAS) which has been described and validated earlier [7-9]. 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. In case of a total occlusion a value of 0 for the minimal lumen diameter and 100% for the percent diameter stenosis was substituted. The mean change in minimal lumen diameter from post-angioplasty angiography to follow-up angiography and from pre-angioplasty to post-angioplasty was derived from matched angiographic projections.

Follow-up evaluation and bicycle ergometry. One to four days prior to follow-up catheterization each patient was seen in the outpatient clinic for an interview, physical examination and a symptom limited exercise test. Assessment of anginal complaints and test evaluation was documented at the individual centers prior to repeat angiography and thus without knowledge of the coronary anatomy. Typical anginal complaints were classified according to the Canadian Cardiovascular Society angina classification. The exercise test was performed on a bicycle ergometer according to two different protocols. In Berlin the test was performed in a supine position, starting with a workload of 25 watts which increased by 25 watts every 2 minutes. In the other 5 participating clinics the

test was performed in a sitting position, starting with a workload of 20 watts which was increased by 20 watts every minute. Exercise was continued until anginal symptoms, a drop in systolic blood pressure, severe arrhythmia, or a horizontal or downsloping ST segment depression of more than 1 mm developed. A 12 lead ECG was recorded during exercise and recovery. ST changes were measured 80 ms after the J point. Horizontal or downsloping ST segment depression in any lead of at least 1 mm, as measured with calipers, was considered a positive response to the stress-test.

Of the 350 study patients, 330 performed an exercise test at follow-up. Reasons for not performing the exercise test were: unstable angina: 14 patients, orthopedic problems: 5 patients and refusal: 1 patient. None of the patients used digitalis or showed a bundle branch block on the ECG, rendering the exercise ECG uninterpretable.

Restenosis criteria. Sensitivity and specificity for anginal status at follow-up and exercise testing at different cut-off points of continuous quantitative angiographic variables were determined. The angiographic variables were classified as either describing the lesion severity at follow-up angiography, "static variables": percent diameter stenosis and minimal lumen diameter, or as describing the change in lesion severity at follow-up angiography, "dynamic variables": change in percent diameter stenosis and change in minimal lumen diameter. In addition, diagnostic accuracy of six previously proposed definitions of restenosis was determined; (1) an increase in diameter stenosis of at least 30% by the time of follow-up angiography (National Heart, Lung and Blood Institute criterion 1 [NHLBI 1]), (2) an immediate post-angioplasty diameter stenosis of less than 50% increasing to greater than or equal to 70% at follow up (NHLBI 2), (3) an increase in stenosis severity to within 10% or less of the predilatation diameter stenosis at the time of follow-up angiography (NHLBI 3), (4) a loss of at least 50% of the gain achieved at angioplasty (NHLBI 4), (5) increase of lesion severity to more than 50% diameter stenosis at follow-up, (6) deterioration in minimal lumen diameter of at least 0.72 mm from immediately post-angioplasty to follow-up. The latter criterion is based on the long-term variability of minimal lumen diameter measurements using the CAAS system (0.36 mm). This variability is 1 standard deviation of the mean difference of 2 measurements of the same lesion filmed at 2 catheterization sessions on average 90 days apart [7]. This long term variability reflects the long-term random variation in lesion measurements from coronary angiograms made at different catheterization sessions using the CAAS system [7]. The use of 1 standard deviation would include 68.3% of the variability, while the use of 2 standard deviations (2 x 0.36 = 0.72 mm) includes 95.5% of the variability.

RESULTS

Table 1 summarizes the baseline characteristics of the 350 study patients. No differences were found in the proportion of patients with recurrent angina and ST

depression at exercise with respect to the vessel dilated (Table 2). The occurence of Q waves in the area supplied by the dilated artery as an indicator of prior transmural infarction (table 2) was low.

Table 1. Baseline characteristics of the study population.

No of patients	350
Male gender	285 (81.4%)
Age (years)	56 ± 9 (range 29-77)
Time to follow-up angiography (days)	172 ± 37
Dilated artery	
LAD	194 (55.4%)
RCA	92 (26.3%)
LCX	64 (18.3%)
History of previous MI	115 (32.9%)

Values as mean ± 1 standard deviation, LAD=left anterior descending artery, LCX=left circumflex artery, MI=myocardial infarction, RCA=right coronary artery.

Recurrent angina and quantitative angiography. At follow-up 102 of 350 patients (29%) had recurrent angina. Percentage correct classification of recurrence of angina (sensitivity) and percentage correct classification of absence of angina at follow up (specificity) as a function of cut-off points for the different quantitative angiographic variables are given in figure 1. The point of intersection of the sensitivity and specificity curves represents the cut-off point for which diagnostic accuracy was best. The "static" variables minimal lumen diameter at follow-up and percent diameter stenosis at follow-up, performed equally well with a sensitivity and specificity slightly above 70% at cut-off points of 1.45 mm and 46.5 % respectively. Parameters that reflect the change in lesion severity from directly post angioplasty to follow-up performed only slightly less favorable, with a sensitivity and specificity of just below 70% at cut-off points of -0.30 mm for the change in minimal lumen diameter and -10 % for the change in percent diameter stenosis. In order to compare the diagnostic accuracy of the different variables, receiver operator characteristic (ROC) curves were constructed (figure 3). Quantitative angiographic parameters denoting a change in lesion severity are only slightly less accurate than those that denote a static measurement of lesion severity at follow-up.

Positive exercise test and quantitative angiography. The exercise test result was abnormal in 116 patients (35%). Percentage correct classification for an abnormal test (sensitivity) and percentage correct classification for a normal test (specificity) as a

Table 2. Ischemia at follow-up and prior Q wave infarction by vessel type.

Proportion of patients with recurrent angina and		
LAD dilatation	28.9% (56 of 194 patients)	
RCA dilatation	28.3% (26 of 92 patients)	p=033*
LCX dilatation	31.3% (20 of 64 patients)	
Proportion of patients with ST depression of ≥1 mm at exercise and		
LAD dilatation	37.0% (67 of 181 patients)	
RCA dilatation	28.7% (25 of 87 patients)	p=091*
LCX dilatation	38.7% (24 of 62 patients)	
Proportion of patients with LAD dilatation and		
Q wave in ECG leads V1 to V5	10.3% (20 of 194 patients)	
Q wave in ECG leads II,III,aVF	17.0% (33 of 194 patients)	
Q wave in ECG leads V6,aVL	18.6% (36 of 194 patients)	
Proportion of patients with RCA dilatation and		
Q wave in ECG leads II,III,aVF	3.3% (3 of 92 patients)	
Q wave in ECG leads V1 to V5	32.6% (30 of 92 patients)	
Q wave in ECG leads V6,aVL	28.3% (26 of 92 patients)	
Proportion of patients with LCX dilatation and		
Q wave in ECG leads V6, aVL	20.3% (13 of 64 patients)	
Q wave in ECG leads V1 to V5	23.4% (15 of 64 patients)	
Q wave in ECG leads II,III,aVF	3.1% (2 of 64 patients)	

LAD=left anterior descending artery, LCX=left circumflex artery, RCA=right coronary artery. * Pearson chi-square test

function of cut-of points for the different quantitative angiographic variables are given in figure 2. It is clear that the diagnostic accuracy of exercise testing was lower than for anginal status at follow-up. The optimal combination of sensitivity and specificity was around 60% for all angiographic variables, with the "static" variables performing slightly better than the "variables of change" (figure 2). However, the cut-off points associated with the point of intersection of the sensitivity and specificity curves were similar to those obtained with anginal status. This was 45.5 % diameter stenosis at follow-up, 1.46 mm minimal lumen diameter at follow-up, a change of 10% in diameter stenosis and a change of 0.32 mm in minimal lumen diameter. ROC curves for the different quantitative angiographic variables are shown in figure 4.

Recurrent angina, positive exercise test and restenosis criteria in current use. Table 3 and 4 list the sensitivity, specificity and predictive values for recurrent angina and a positive exercise test of different previously proposed restenosis criteria. None of the criteria predicted recurrent angina and positive exercise testing with great accuracy. In particular a positive exercise test was very hard to predict with all angiographic restenosis criteria. Criteria that require a large change (NHLBI 1 and the $\geq$0.72mm criterion), and the NHLBI 2 criterium that requires an extraordinary high diameter stenosis at follow-up, had a low sensitivity. In fact the NHLBI 2 criterion is more a pre-

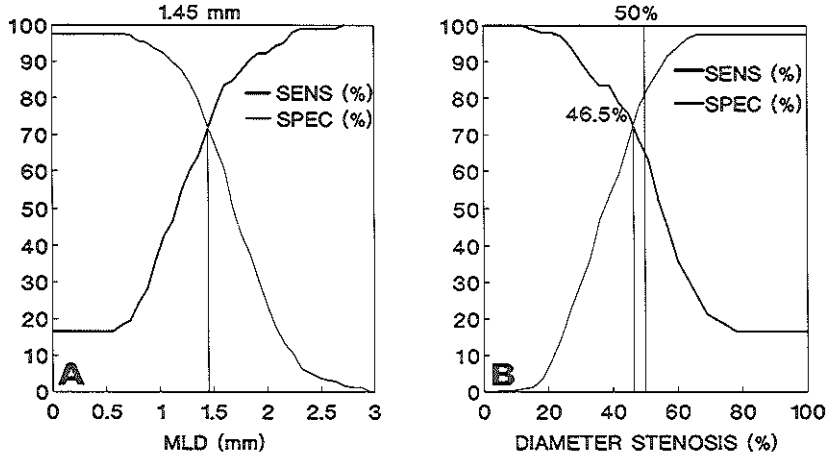

Figure 1a and 1b. *Percentage correct classification of recurrence of angina (sensitivity) and percentage correct classification of absence of angina at follow up (specificity) as a function of cut-off points for the different quantitative angiographic parameters. The point of intersection of the 2 curves denotes the cut-off point with the highest diagnostic accuracy. Where appropriate the 50% diameter stenosis and the $\geq$0.72mm loss in MLD restenosis criteria were drawn in the figure. Figure 1a: curves for minimal lumen diameter at follow-up. Figure 1b: curves for percent diameter stenosis at follow-up. MLD = minimal lumen diameter, Sens = sensitivity, Spec = Specificity*

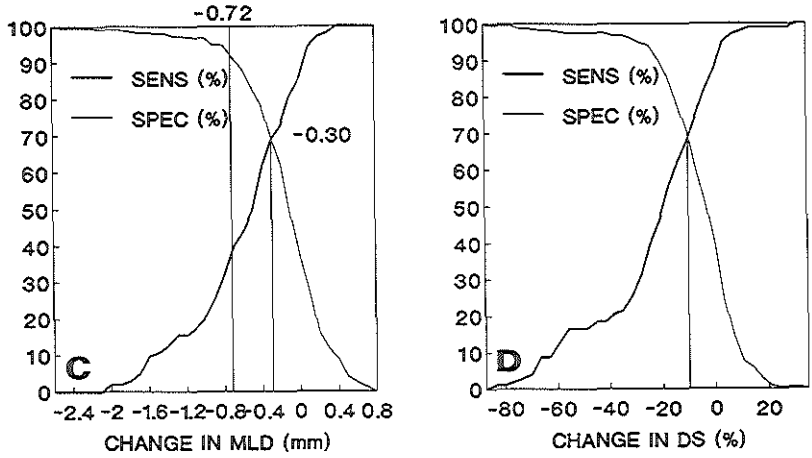

Figure 1c and 1d. *Legend as for figure 1a and 1b. Figure 1c: curves for change in minimal lumen diameter at follow-up. Figure 1d: curves for change in percent diameter stenosis at follow-up. DS = diameter stenosis, MLD = minimal lumen diameter, Sens = sensitivity, Spec = Specificity*

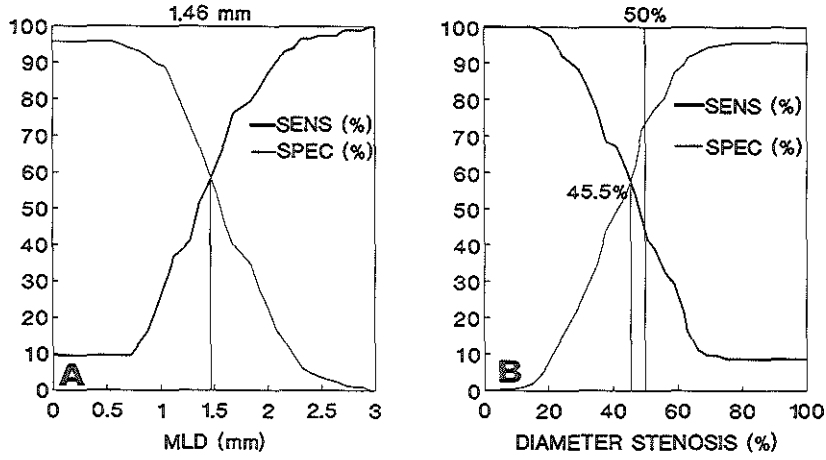

Figure 2a and 2b. *Percentage correct classification of positive exercise electrocardiography (sensitivity) and percentage correct classification of negative exercise electrocardiography (specificity) at follow up as a function of cut-off points for the different quantitative angiographic parameters. The point of intersection of the 2 curves denotes the cut-off point with the highest diagnostic accuracy. Where appropriate the 50% diameter stenosis and the ≥0.72mm loss in MLD restenosis criteria were drawn in the figure. Figure 2a: curves for minimal lumen diameter at follow-up. Figure 2b: curves for percent diameter stenosis at follow-up. MLD = minimal lumen diameter, Sens = sensitivity, Spec = Specificity*

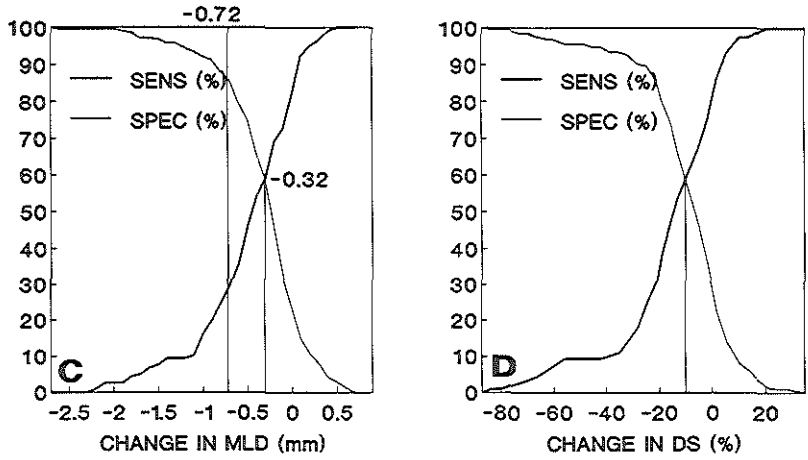

Figure 2c and 2d. *Legend as for figure 2a and 2b. Figure 2c: curves for change in minimal lumen diameter at follow-up. Figure 2d: curves for change in percent diameter stenosis at follow-up. DS = diameter stenosis, MLD = minimal lumen diameter, Sens = sensitivity, Spec = Specificity*

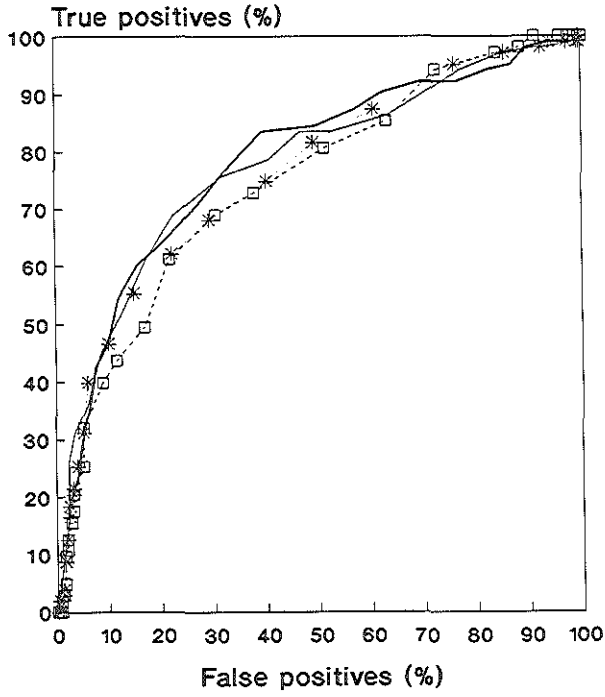

Figure 3. *Receiver-Operator Characteristic (ROC) curves for comparison of the diagnostic accuracy of anginal status at follow-up for minimal lumen diameter at follow-up (solid line), percent diameter stenosis at follow-up (normal line), change in minimal lumen diameter (dotted line with squares) and change in percent diameter stenosis (dotted line with asterisks).*

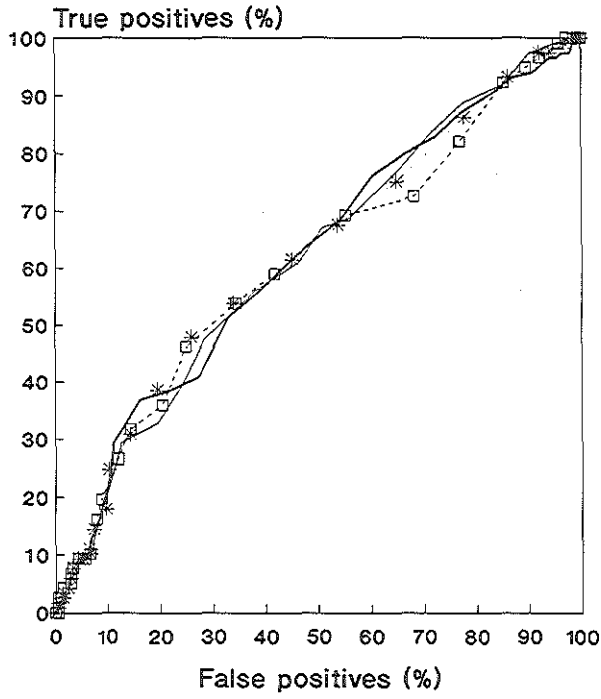

Figure 4. *Receiver-Operator Characteristic (ROC) curves for comparison of the diagnostic accuracy of exercise electrocardiography for minimal lumen diameter at follow-up (solid line), percent diameter stenosis at follow-up (normal line), change in minimal lumen diameter (dotted line with squares) and change in percent diameter stenosis (dotted line with asterisks).*

dictor of total occlusions since 22 of 26 lesions that fulfilled this criterion were totally occluded at follow-up. For the 330 patients that underwent exercise testing, 19 of the 22 lesions that fulfilled the NHLBI 2 criterium were totally occluded at follow-up. The NHLBI 3 and 4 criteria and the $\geq$50% diameter stenosis criterion performed better. The 50% diameter stenosis cut-off point lies close to the optimal cut-off point of 46.5% and is therefore one of the best predictors of recurrent angina or positive exercise testing, whereas the NHLBI 1 criterion (change in diameter stenosis $\geq$30%) and the $\geq$0.72mm criterion are clearly remote from the optimal cut-off points of -10% and -0.32 mm respectively (figure 1c, 1d and figure 2c, 2d).

Table 3. Diagnostic accuracy of different angiographic restenosis criteria for patients with recurrent angina.

	Criterion					
Characteristic	NHLBI 1	NHLBI 2	NHLBI 3*	NHLBI 4*	≥50%DS	≥0.72mm
Prevalence of restenosis	11.4% (40/350)	7.4% (26/350)	31.2% (109/349)	34.7% (121/349)	31.7% (111/350)	17.7% (62/350)
Sensitivity	28.4% (29/102)	20.6% (21/102)	60.8% (62/102)	64.7% (66/102)	63.7% (65/102)	39.2% (40/102)
Specificity	95.6% (237/248)	98% (243/248)	81% (200/247)	77.7% (192/247)	81.5% (202/248)	91.1% (226/248)
PVP	72.5% (29/40)	80.8 (21/26)	56.9% (62/109)	54.5% (66/121)	58.6% (65/111)	64.5% (40/62)
PVN	76.5% (237/310)	77.3 (243/314)	83.3% (200/240)	84.2% (192/228)	84.5% (202/239)	78.5% (226/288)

DS = diameter stenosis; NHLBI 1 to 4 = National Heart, Lung and Blood Institute restenosis criteria; PVP = predictive value for recurrent angina if criterion is fulfilled, PVN = predictive value for no angina at follow-up if criterion is not fulfilled. * = in 1 patient quantitative analysis was impossible pre-angioplasty, therefore these criteria could not be assessed in this patient.

Table 4. Diagnostic accuracy of different angiographic restenosis criteria for patients with positive bicycle ergometry at follow-up.

	Criterion					
Characteristic	NHLBI 1	NHLBI 2	NHLBI 3*	NHLBI 4*	≥50%DS	≥0.72mm
Prevalence of restenosis	11.2% (37/330)	6.7% (22/330)	30.7% (101/329)	34.7% (114/329)	31.2% (103/330)	17% (56/330)
Sensitivity	14.7% (17/116)	9.5% (11/116)	37.9% (44/116)	46.5% (54/116)	41.4% (48/116)	26.7% (31/116)
Specificity	90.7% (194/214)	94.9% (203/214	73.2% (156/213)	71.8% (153/213)	74.3% (159/214)	88.3% (189/214)
PVP	45.9% (17/37)	50% (11/22)	43.6% (44/101)	47.4% (54/114)	46.6% (48/103)	55.4% (31/56)
PVN	66.2% (194/293)	65.9% (203/308)	68.4% (156/228)	71.2% (153/215)	70% (159/227)	69% (189/274)

DS = diameter stenosis; NHLBI 1 to 4 = National Heart, Lung and Blood Institute restenosis criteria; PVP = predictive value for abnormal test if criterion is fulfilled, PVN = predictive value for normal test if criterion is not fulfilled. * = in 1 patient quantitative analysis was impossible pre-angioplasty, therefore these criteria could not be assessed in this patient.

DISCUSSION

Patient selection and methodological considerations. In this study we preferentially studied patients with single vessel disease and with a single lesion which was successfully dilated. In these patients only restenosis of this lesion can be held responsible for an abnormal ECG response at follow-up exercise testing or recurrent angina, whereas in multivessel disease the responsible lesion is not always easy identifiable. Moreover coronary angioplasty in multivessel disease will not result in complete revascularization in a considerable number of cases [10].

With conventional exercise protocols, ECG leads and ECG criteria, exercise testing is characterized by a high specificity and a moderate sensitivity [11]. Furthermore, its sensitivity increases with the extent of coronary artery disease, which implies a low sensitivity in patients with single vessel disease [12-14]. This explains the low predictive accuracy found in our population of patients with single vessel disease for the different restenosis criteria. These findings are comparable with the findings of Bengtson et al. [15] who found a sensitivity of 32 % and a specificity of 79 % for a positive exercise ECG.

It is known that diagnostic accuracy for restenosis of recurrent angina is better than for ST segment change [15,16]. From the data of Bengtson et al. [15] a sensitivity for recurrent angina of 59% and a specificity of 73% can be calculated. They applied the 50% diameter criterion for restenosis. Zaidi et al. [17] reported a sensitivity of 70% and a specificity of 66% for recurrence angina as a test for restenosis. Although the predictive accuracy of quantitative angiographic parameters was generally poor in the present study, it is remarkable that the points of intersection of the sensitivity and specificity curves were similar for 2 different markers of myocardial ischemia.

Angioplasty of the left anterior descending artery made up 55.4% of all procedures in this study. It might be argued that the large mass of potentially ischemic myocardium supplied by this artery in case of severe renarrowing, would render the findings of this study only applicable to LAD lesions. However no differences were found in the proportion of patients with recurrent angina and ST depression at exercise with respect to the vessel dilated (Table 2). Prior myocardial infarction is known to falsely increase the accuracy of exercise testing [18]. However the occurence of Q waves in the area supplied by the dilated artery (table 2) was low, indicating an only small possible influence on our findings.

Angiographic restenosis and functional status. Restenosis after a successful angioplasty procedure is now viewed as a fibroproliferative repair process in response to traumatic injury to the vessel wall [19,20]. We recently showed that luminal narrowing after angioplasty occurs to a certain extent in all dilated lesions [21] and that angiographic restenosis is the tail end of a normally distributed phenomenon. The restenosis rate is therefore dependent on the cut-off criterion applied. Generally 2 types

of angiographic restenosis criteria have been developed: criteria that denote the change in stenosis severity at follow-up angiography (e.g. the $\geq$0.72mm change criterion) and criteria that assess stenosis severity at follow-up angiography (e.g. the >50% diameter stenosis at follow-up criterion). From a functional point of view restenosis can be detected by recurrence of angina and by several noninvasive tests. These tests are aimed at detecting myocardial ischemia due to a flow limiting stenosis in an epicardial artery and give no information on the magnitude of the luminal narrowing process in the individual lesion. Angiographic restenosis criteria that give a static assessment of lesion severity at follow-up have the disadvantage of preselecting lesions with a marginal angioplasty result [1]. This means that these lesions have to undergo only a small deterioration to cross the cut-off point and be classified as "restenosed". Classically the 50% diameter stenosis criterion is applied to classify lesions or patients as "restenosed" at follow-up angiography after angioplasty. This criterion is historically based on the physiological concept of coronary flow reserve introduced by Gould and others in 1974 and is taken because it represents the approximate value in animals with normal coronary arteries at which blunting of the hyperemic response occurs [22]. Although the 50% diameter stenosis criterion is attractive because it links the angiographic appearance of a lesion with the clinical situation of the patient, it tells us nothing about the dynamic behavior of the restenosis process. Our findings underscore the significance of the 50% diameter stenosis criterion because the optimal cut-off point for prediction of functional status 6 months after coronary angioplasty was found to be close to this value (46.5% diameter stenosis).

Diagnostic accuracy of the *absolute* stenosis diameter (MLD) at 6 months follow-up however, was similar to the diagnostic accuracy of diameter stenosis measurements (figure 3 and figure 4) with a point of intersection of the sensitivity and specificity curves at 1.4 mm. This indicates that an absolute measure of stenosis severity is equally predictive of clinical status after angioplasty as a relative measurement. These values correspond well with the findings of Wilson et al. [23]. They found that coronary flow reserve dropped below 3.5 (the lower threshold of normal) at a minimal cross sectional area of 1.5 mm2 and a percent area stenosis of 75 which corresponds to a minimal lumen diameter of 1.4 mm and a percent diameter stenosis of 50% respectively. Wijns et al. demonstrated a steep increase in pressure drop over left anterior descending artery stenoses once a critical value of minimal cross-sectional area of 2.5 mm^2 was reached. This corresponds to a minimal lumen diameter of 1.78 mm [24]. The pressure measurements were made with a dilatation catheter across the stenosis (cross-sectional area of catheter: 0.64 mm^2). If this value is subtracted from the 2.5 mm^2 value, a minimal lumen diameter value of 1.54 mm emerges, which is close to the 1.45 mm found in the present study.

An approach that more closely reflects the magnitude of the reactive intimal

hyperplasia after angioplasty is applying criteria that describe the change in lesion severity at follow-up angiography. The major critique on this type of criterion is that they might disregard the functional significance of a lesion at follow-up. For instance a lesion with a post angioplasty percent diameter stenosis in the range of 0-15% can undergo a large deterioration and still not be flow limiting. Our study however, not only shows that the static parameters of minimal lumen diameter and percent diameter stenosis perform equally well in predicting clinical significance of a lesion 6 months after successful coronary angioplasty but also that the parameters of change in lumen diameter and change in percent diameter stenosis were only slightly less accurate in predicting the clinical significance of the lesions (figure 3 and 4). Therefore, parameters of change, apart from their usefulness in reflecting the magnitude of the reactive hyperplasia, also reflect nearly to the same extent as the "static" parameters, the clinical significance of the lesion at follow-up. The optimal cut-off point for the parameters of change was -0.30 mm for the change in lumen diameter and -10% for change in percent diameter stenosis with nearly equal diagnostic accuracies showing that absolute change in lesion severity (in mm) and relative change in lesion severity (in percentage) perform equally well in the prediction of recurrent angina or positive exercise ECG, 6 months after coronary angioplasty.

Limitations. First of all more sophisticated invasive and non invasive methods are available for the assessment of the functional significance of a coronary stenosis. It is known that exercise thallium scintigraphy has a higher diagnostic accuracy than electrocardiographic exercise testing [25]. The present data originate from a multicenter trial and therefore it is logistically difficult to standardize the methodology of radionuclide exercise tests or flow-reserve measurements in all participating centers. Exercise electrocardiographic testing on the other hand is inexpensive, safe and identical exercise protocols can be easily implemented in the participating centers. As proposed by Popma et al.[26], paired stress tests, (shortly after angioplasty and at 6 months follow up) should ideally be obtained, otherwise the interpretation of an ischemic exercise test at follow-up may be more difficult, especially in patients with multivessel coronary artery disease. Our study population consisted of patients with single vessel disease in whom complete revascularization was achieved. The absence of myocardial ischemia at hospital discharge after angioplasty, however, was not objectively confirmed by exercise testing. The diagnostic accuracy of quantitative angiographic parameters for the prediction of recurrent angina and an abnormal ECG response at exercise was not very high. However, the *absolute* values of sensitivity and specificity were not crucial to this study, but rather the point of intersection of the sensitivity and specificity curves. Finally all angiograms were preceded by an intracoronary dose of nitrates and not all patients were using vasodilatory drugs at the time of exercise testing. This might have shifted the points of intersection towards a higher minimal lumen diameter and lower percent diameter

stenosis.

Conclusion. The large number of patients studied and the fact that the same optimal values for diagnostic accuracy of the various quantitative angiographic variables were obtained for the prediction of 2 different markers of ischemia (anginal status and ST depression at exercise) suggests that these values reflect the lesion severity or increase in lesion severity in major epicardial vessels at which coronary flow reserve is unable to meet myocardial demands. Relative measurements (percent diameter stenosis) and absolute measurements (minimal lumen diameter) were found to be equally predictive of ischemia. Since the minimal lumen diameter is the most unambiguous measurement of lesion severity (independent of an arbitrary "normal" part of the artery), this measure can be a more reliable surrogate for clinical outcome than the classic percent diameter stenosis measurement in the many restenosis prevention trials with drugs and new devices currently underway or in the design phase.

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Chapter 10

LUMINAL NARROWING AFTER PERCUTANEOUS TRANSLUMINAL CORONARY ANGIOPLASTY. A STUDY OF CLINICAL, PROCEDURAL AND LESIONAL FACTORS RELATED TO LONG TERM ANGIOGRAPHIC OUTCOME

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Abstract

Background. The renarrowing process after successful coronary balloon angioplasty is now believed to be caused by a fibroproliferative vessel wall reaction. The magnitude of this process can be assessed by the change in minimal lumen diameter (MLD) at follow-up angiography. The aim of the present study was to find independent patient related, lesion related and procedural related risk factors for this luminal narrowing process. A model that accurately predicts the amount of luminal narrowing could be an aid in patient or lesion selection for the procedure, it could improve assessment of medium term (6 months) prognosis, modification or control of the identified risk factors could reduce overall restenosis rates and it could assist in the selection of patients at risk for a large loss in lumen diameter. This population could then constitute the target population for pharmacological intervention studies.

Methods and results. Quantitative angiography was performed on 666 successfully dilated lesions at angioplasty and at 6 months follow up. Multivariate linear regression analysis was performed to obtain variables with an independent contribution to the prediction of the absolute change in MLD. Diabetes mellitus, duration of angina < 2.3 months, gain in MLD at angioplasty, pre PTCA MLD, lesion length ≥ 6.8 mm and thrombus post PTCA were independently predictive of change in MLD. Overall prediction of the model was however poor, percentage correct classification for a change between -0.1 to -0.3 mm was approximately 10%.

Conclusion. Re-narrowing after successful PTCA is a process that cannot be accurately predicted by simple clinical, morphologic and lesion characteristics.

Key words:

PTCA, restenosis, quantitative angiography

INTRODUCTION.

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 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 [1-3]. Pharmacological agents aimed at reducing the absolute amount of intimal hyperplasia are currently being investigated in many clinical trials. In these trials it is presumed that the clinical outcome is related to an anatomical substrate, i.e. the prevention or reduction of reactive intimal hyperplasia after angioplasty.

If restenosis is viewed as an intraluminal growth process after a successful angioplasty, risk factors for restenosis should be risk factors for this growth process. The angiographically determined change in lumen diameter at follow-up is currently the only reliable indicator of the amount of reactive hyperplasia applicable to large study populations.

A model that accurately predicts the amount of luminal narrowing in the individual patient would be of value in several ways: First, it could be an aid in patient or lesion selection for the procedure because an accumulation of risk factors in the individual patient might indicate balloon angioplasty an unattractive means of revascularization; secondly, it could improve assessment of medium term (6 months) prognosis in the individual patient; third, modification or control of the identified risk factors could reduce overall restenosis rates; fourth, the model could assist in the selection of patients at risk for a large loss in lumen diameter. This population could then constitute the target population for pharmacological intervention studies because a larger mean loss in lumen diameter would permit the enrollment of a smaller number of patients in a study while maintaining an equal power. Therefore patient related factors, lesion related factors and procedural factors were correlated to the quantitative angiographic change in lumen diameter from post-angioplasty angiogram to follow-up angiogram in the present study.

METHODS

Study population. The study population consisted of 697 patients that were originally randomized in 6 European centers (see appendix) for the Carport trial [4]. In this randomized, double blind, placebo controlled trial a novel thromboxane A_2 receptor antagonist (GR32191B) was investigated for its ability to prevent restenosis after primary coronary angioplasty. Follow-up on these patients was done on a prospective basis and all patients agreed to undergo repeat angiography at 6 months. Identical angiographic and clinical outcomes were observed [4], so the placebo- and active treatment group were 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 inclusion. Exclusion criteria for trial participation and their relative frequencies have been published earlier [4].

Angioplasty success was defined as a less than 50% residual stenosis by visual inspection of the post-angioplasty angiogram and no occurrence of in-hospital complications (death, acute myocardial infarction, repeat angioplasty, aorto coronary bypass grafting or recurrence of symptoms), and was achieved in 649 patients (93.1%). Quantitative angiographic follow-up was available for 575 patients (88.6%) and this forms the study population (figure 1).

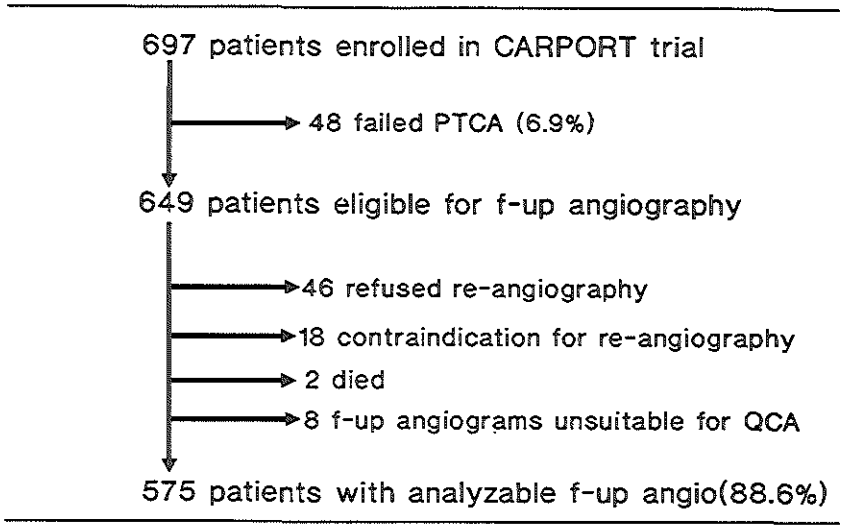

Figure 1. *Patient flow chart. PTCA=percutaneous transluminal coronary angioplasty, QCA=quantitative coronary angiography*

Angioplasty procedure and follow up angiography. Coronary angioplasty was performed with a steerable, movable guide wire system via the femoral route. Standard available balloon catheters were used. Choice of balloon type and brand as well as inflation duration and inflation pressure were left to the discretion of the angioplasty operator. At the beginning of the angioplasty procedure all patients received 10000 IU of intravenous heparin for the first two hours, afterwards 5000 IU/hour for as long the procedure continued. All patients received 10 mg nifedipine every two hours for the first 12 hours after angioplasty. Thereafter they received 20 mg slow release nifedipine tablets 3 times during the second day after angioplasty.

Three coronary angiograms were obtained in each patient, just before angioplasty, immediately after angioplasty, and at follow-up. To standardize the method of data

acquisition and to ensure exact reproducibility of the angiographic studies, measures were taken as described previously [5,6,7]. The angiograms were recorded in such a way that they were suited for quantitative analysis by the Coronary 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 the cathetertips were cut off for later measurement with a microcaliper. All angiograms were processed and analyzed in a central core-laboratory.

The follow-up coronary angiogram was performed at six months follow-up. If symptoms recurred within 6 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 4 months, the patient was asked to undergo another coronary arteriogram at 6 months.

Quantitative angiography (figure 2). All cineangiograms were analyzed using the computer assisted angiography analysis system (CAAS) which has been described and validated previously [8,9]. 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 (figure 2). The area between the actual and reconstructed contours at the obstruction site is a measure for the amount of atherosclerotic plaque and expressed in mm^2. The length of the obstruction is determined from the diameter function on the basis of curvature analysis and expressed in millimeters. In addition, this technique allows for the calculation of an eccentricity index of the lesion [10]. The index ranges from 0 (severe eccentric) to 1 (perfectly symmetrical). Since the analysis system cannot measure total occlusions, a value of 0 mm was substituted for the minimal lumen diameter and the post-angioplasty reference diameter was substituted for the reference diameter pre PTCA. The mean change in minimal lumen diameter from post-angioplasty angiography to follow-up angiography and from pre-angioplasty to post-angioplasty was derived from matched angiographic projections.

Potential risk factors studied. The loss in minimal lumen diameter was assessed for factors reported to be predictive of luminal narrowing after successful PTCA. For categorical variables the change in lumen diameter from post-angioplasty angiogram to follow-up angiogram was determined in each category. Continuous variables were grouped into three equally sized subgroups (tertiles) and the change in minimal lumen diameter assessed for each tertile.

Variables potentially predictive for luminal narrowing and eventually restenosis were divided in to 3 general categories. *Patient related factors* are present systemically and thereby affect all dilated lesions in a single patient. These include age, gender, diabetes, unstable angina (defined as pain at rest requiring treatment with intravenous nitrates), extent of atherosclerotic disease (single or multivessel), previous myocardial infarction,

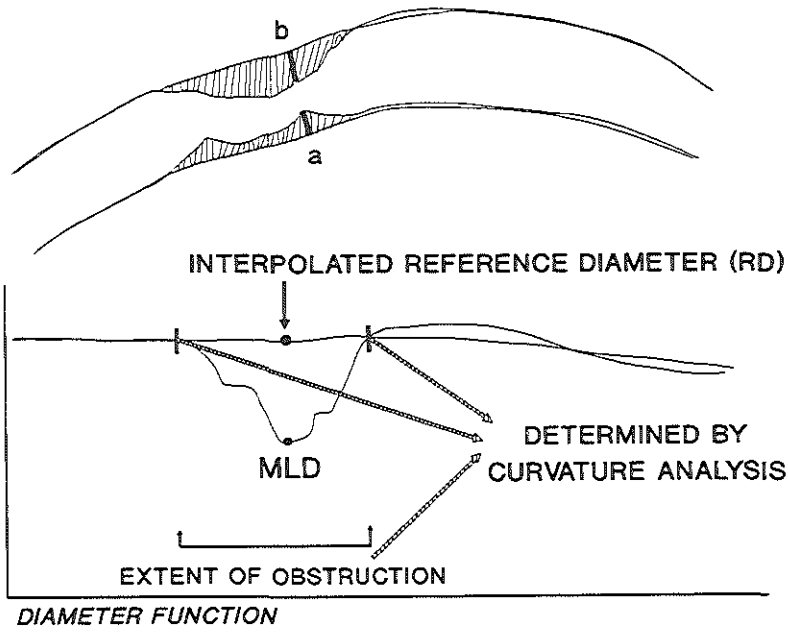

Figure 2. *Graphic representation of the quantitative angiographic measurements. The upper panel represents a stenosed arterial segment. The lower panel is the diameter function curve. The length of the analyzed segment is depicted on the X-axis and the vessel diameter on the Y-axis. MLD = minimal lumen diameter. Extent of obstruction = Lesion length. Lesion length is determined with curvature analysis of the descending and ascending limb of the diameter function curve at the site of the MLD. Eccentricity is determined the site of the MLD and calculated as a/b. The plaque area is depicted by the hatched part of the upper panel drawing.*

previous CABG, previous angioplasty at other site, platelet count, cholesterol level, lipoprotein cholesterol levels (HDL,LDL), glucose levels, history of smoking and continued smoking after the procedure. Because only 8 patients had type I diabetes, diabetes type I and II were pooled. *Lesion related factors* are characteristics unique to each lesion. The following factors were assessed: minimal lumen diameter pre-PTCA and post-PTCA, lesion length, eccentricity of the lesion, percentage diameter stenosis pre-PTCA and post-PTCA, presence of visible collateral circulation to the dilated vessel, total occlusion pre-PTCA, plaque area pre-PTCA (figure 2), vessel dilated (either left anterior descending artery, circumflex artery or right coronary artery), presence of dissection post-angioplasty (defined as filling defect within the lumen, disappearing with the passage of contrast material (type A dissection according to Dorros et al [11]) and

as contrast appearing outside the lumen, disappearing or persisting with the passage of contrast material (type B and C dissections according to Dorros et al.)), relative gain in lumen diameter achieved by angioplasty (defined as the difference in obstruction diameter before and after angioplasty divided by the interpolated reference diameter (vessel size)), presence of thrombus pre and post PTCA (defined as an intraluminal filling defect visible in all projections, a visible embolization of intraluminal material downstream or dye staining at the site of a total occlusion (inter observer concordance rate for the assessment of intracoronary thrombus in the corelab 89%)) and calcification of the lesion. *Procedure related factors* assessed were maximal measured balloon diameter, balloon-artery ratio (defined as the ratio of the quantitative angiographic diameter of the largest balloon at highest inflation pressure to the reference diameter), maximal inflation pressure, number of balloon inflations and total duration of balloon inflation.

Data analysis. The unit of analysis reported here is the stenotic lesion, not the patient. The primary outcome variable was the change in lumen diameter from directly post-angioplasty to follow-up angiogram. Data are presented as mean ± 1 standard deviation. In univariate analysis continuous variables that were divided into 3 subgroups were compared with analysis of variance and for the discrete variables with an unpaired Student's t-test.

To obtain independent predictors for the loss in lumen diameter, variables were entered in a stepwise multiple linear regression analysis in which the loss in lumen diameter was the dependent variable. Stepwise multiple linear regression analysis was performed (BMDP statistical package, program 2R) to assess the relationship between the variables mentioned in the 'Methods' section (independent variables = X_i) and the loss in minimal lumen diameter from post-angioplasty angiogram to follow-up angiogram (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 BMDP 2R 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 for each tertile. These were entered as discrete variables (lesion length $\geq$6.8 mm, cholesterol level $\geq$ 6.5 mmol/l, duration of angina < 2.3 months and percent diameter stenosis pre-angioplasty $\geq$56.5).

To determine how well the regression model performs in predicting restenosis according to 2 frequently applied restenosis criteria and to illustrate the discrepancies between the 2 criteria, receiver operator characteristic (ROC) curves were constructed for each criterion. The criteria applied were: change in lumen diameter $\geq$0.72mm at follow-up [5,8,12] and the classic criterion of an increase in diameter stenosis from < 50% post PTCA to $\geq$50% at follow up. The 0.72 mm 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 the CAAS system [8]. The use of 1 standard deviation would include 68.3% of the measurement variability, while the use of 2 standard deviations (2 x 0.36 = 0.72 mm) includes 95.5% of the measurement variability. The equivalent of the 0.72 mm value for diameter stenosis measurements is a change in diameter stenosis of 13%.

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 649 patients who had a successful angioplasty, 575 underwent satisfactory angiographic follow-up (follow-up rate 88.6%) and formed the study population. Baseline characteristics of the study population are summarized in table 1. A total of 666 lesions were successfully dilated. Restenosis rate was 32.6% (217 of 666 lesions) according to the >50% diameter stenosis criterion and 17.6% (117 of 666 lesions) if the criterion of $\geq$ 0.72 mm loss in lumen diameter was applied.

UNIVARIATE ANALYSIS

Patient related variables. Table 2A summarizes the changes in minimal lumen diameter for all analyzed patient related variables. Of the 18 patient related variables only 3, unstable angina, diabetes, and angina duration < 2.3 months, showed a significantly larger loss in minimal lumen diameter at follow-up. The high loss in lumen diameter associated with the presence of these variables was probably caused by lesions that progressed towards total occlusion at follow-up. Indeed, if totally occluded lesions at follow-up (n=42, 6.3%) were excluded from the analysis then a trend towards a higher loss in lumen diameter in the presence of one of these factors still existed, although not statistically significant: Diabetes: -0.27±0.39 vs -0.20±0.39 mm, p=0.18, unstable angina: -0.20±0.39 mm vs -0.18±0.39 mm, p=0.66, duration of angina < 2.3 months -0.24±0.37 mm vs -0.18±0.40 mm, p=0.09.

Lesion related variables (table 2B). The *pre-angioplasty* lesion related factors associated with a larger loss at follow-up were: smaller minimal lumen diameter, lesion length $\geq$6.8 mm, higher percentage diameter stenosis, larger plaque area, total occlusion and collateral circulation to the obstruction site (Table 2B). The *post-angioplasty* lesion related factors associated with a greater loss at follow-up were a larger post-angioplasty lumen diameter, lower percentage diameter stenosis post-angioplasty (ie a better angioplasty result), a higher relative gain achieved at angioplasty and thrombus post-angioplasty. Again, if total occlusions at follow-up were disregarded, the presence of total occlusions pre-angioplasty, collateral circulation and thrombus post-angioplasty were no

longer associated with a significantly higher loss in minimal lumen diameter (total occlusion -0.11±0.42 mm vs -0.20±0.39 mm, p=0.25, collateral circulation -0.23±0.41 mm vs -0.19±0.39 mm, p=0.34, thrombus post-angioplasty -0.25±0.39 mm vs -0.20±0.39 mm, p=0.67).

Procedure related variables. None of the procedural factors assessed was associated with a significantly greater loss in lumen diameter at follow-up (table 2C).

Table 1. Baseline characteristics

No of patients	575
Lesions	666
lesions/patient	1.16
Age (years)	56±9 (29-79)
Male gender (%)	464 (81%)
Follow up time (days)	172±41 (10-349)
Extent disease	
1 vessel	381 (66.3%)
2 vessel	156 (27.1%)
3 vessel	38 (6.6%)
MLD pre PTCA (mm)	1.04±0.37 (0-2.83)
MLD post PTCA (mm)	1.76±0.38 (0.85-3.04)
MLD f_up (mm)	1.48±0.59 (0-3.15)
% DS pre PTCA	60±13 (33-100)
% DS post PTCA	34±9 (6-65)
% DS f-up	45±19 (4-100)
Change in MLD at f-up (mm)	-0.28±0.52

%DS= percentage diameter stenosis, f-up=follow-up, LAD=left anterior descending artery, LCX=circumflex artery, MLD=minimal lumen diameter, RCA=right coronary artery.

Table 2A. Change in minimal lumen diameter per lesion for **patient related variables**

	Change in MLD at follow-up (mm)	P value
Age (years)		
< 52 (n=211)	-0.26±0.51	
52-61 (n=213)	-0.31±0.52	p=0.54
≥61 (n=242)	-0.31±0.57	
Sex		
male (n=533)	-0.28±0.50	p=0.11
female (n=133)	-0.37±0.65	
Diabetes I and II		
yes (n=56)	-0.56±0.77	p<0.001
no (n=610)	-0.27±0.50	
Unstable angina (pain at rest)		
yes (n=91)	-0.42±0.73	p<0.05
no (n=575)	-0.27±0.50	
Extent disease		
single vessel (n=401)	-0.31±0.55	p=0.45
multivessel (n=265)	-0.28±0.52	
Ever smoked		
yes (n=515)	-0.28±0.54	p=0.28
no (n=151)	-0.34±0.53	
Still smoking at follow-up		
yes (n=81)	-0.23±0.46	p=0.22
no (n=585)	-0.34±0.53	
previous MI		
yes (n=253)	-0.33±0.60	p=0.13
no (n=413)	-0.27±0.50	

Table 2A continued

	Change in MLD at follow-up (mm)	P value
previous CABG		
yes (n=20)	-0.22±0.42	p=0.45
no (n=646)	-0.30±0.54	
previous PTCA other site		
yes (n=11)	-0.25±0.57	p=0.77
no (n=655)	-0.29±0.54	
Duration of angina (months)		
<2.3 (n=210)	-0.37±0.59	
2.3-8.5 (n=227)	-0.26±0.50	p=0.06
≥8.5 (n=229)	-0.26±0.53	
Platelet count (10^6/ml		
<168 (n=216)	-0.30±0.56	
168-175 (n=220)	-0.27±0.50	p=0.48
≥175 (n=222)	-0.33±0.55	
Total cholesterol (mmol/l)		
<5.7 (n=225)	-0.32±0.56	
5.7-6.5 (n=217)	-0.34±0.58	p=0.15
≥6.5 (n=216)	-0.26±0.47	
HDL cholesterol (mmol/l)		
<0.93 (n=190)	-0.32±0.58	
0.93-1.2 (n=197)	-0.26±0.49	p=0.50
≥1.20 (n=188)	-0.31±0.54	
LDL cholesterol (mmol/l)		
<3.3 (n=166)	-0.36±0.59	
3.3-4.6 (n=169)	-0.31±0.52	p=0.11
≥4.6 (n=157)	-0.24±0.47	

Table 2A continued

	Change in MLD at follow-up (mm)	P value
Glucose (mmol/l)		
<4.8 (n=234)	-0.26±0.47	
4.8-5.6 (n=213)	-0.30±0.54	p=0.18
≥5.6 (n=210)	-0.35±0.61	
Hypertension		
yes (n=223)	-0.31±0.54	p=0.51
no (n=443)	-0.28±0.54	
AP class at baseline*		
I,II (n=290)	-0.27±0.49	p=0.25
III,IV (n=376)	-0.32±0.59	

CABG=coronary artery bypass grafting, HDL=high density lipoprotein, LDL=low density lipoprotein, MI=myocardial infarction, MLD=minimal lumen diameter, * Canadian Cardiovascular Society classification.

Table 2B. Change in MLD per lesion at follow-up for **lesion related variables**

	Change in MLD at follow-up (mm)	P value
MLD pre PTCA (mm)		
<0.9 (n=219)	-0.37±0.58	
0.9-1.15 (n=216)	-0.31±0.51	p<0.02
≥1.15 (n=228)	-0.22±0.51	
MLD post PTCA (mm)		
<1.65 (n=220)	-0.16±0.48	
1.65-1.9 (n=221)	-0.33±0.50	p<0.001
≥1.90 (n=225)	-0.39±0.55	
Relative gain at PTCA		
<0.2 (n=230)	-0.13±0.45	
0.2-0.3 (n=209)	-0.33±0.49	<0.001
≥0.3 (n=224)	-0.46±0.58	
Length obstruction (mm)		
<5.25 (n=229)	-0.23±0.46	
5.25-6.8 (n=195)	-0.24±0.51	p<0.01
≥6.8 (n=203)	-0.38±0.55	
Plaque area (mm2)		
<4.7 (n=208)	-0.21±0.45	
4.7-7.6 (n=212)	-0.29±0.53	p<0.03
≥7.6 (n=207)	-0.34±0.53	
Eccentricity		
<0.2 (n=210)	-0.31±0.52	
0.2-0.45 (n=205)	-0.26±0.50	p=0.42
≥0.45 (n=212)	-0.27±0.50	
% diameter stenosis pre-PTCA		
<56.5 (n=244)	-0.20±0.48	
56.5-64.5(n=210)	-0.35±0.54	p<0.001
≥64.5 (n=209)	-0.35±0.58	
% diameter stenosis post-PTCA		
<29.5 (n=217)	-0.40±0.57	
29.5-38 (n=225)	-0.32±0.53	p<0.001
≥38 (n=224)	-0.17±0.49	

Table 2B continued

	Change in MLD at follow-up (mm)	P value
Vessel size (mm) (reference diameter)		
<2.4 (n=240)	-0.30±0.53	
2.4-2.85 (n=214)	-0.30±0.51	p=0.91
≥2.85 (n=212)	-0.28±0.57	
Patency pre-PTCA		
total occlusion (n=36)	-0.54±0.87	p<0.01
patent (n=630)	-0.28±0.50	
Collateral circulation to obstruction site		
yes (n=122)	-0.39±0.64	p<0.05
no (n=544)	-0.25±0.49	
Thrombus pre PTCA		
yes (n=32)	-0.32±0.51	p=0.65
no (n=634)	-0.29±0.52	
Thrombus post PTCA		
yes (n=16)	-0.71±0.90	p<0.01
no (n=650)	-0.28±0.52	
Vessel dilated		
LAD (n=321)	-0.27±0.46	
LCX (n=154)	-0.28±0.55	p=0.36
RCA (n=191)	-0.34±0.63	
Calcified lesion		
yes (n=233)	-0.29±0.50	p=0.61
no (n=433)	-0.31±0.56	
Tandem lesion		
yes (n=25)	-0.27±0.39	p=0.82
no (n=641)	-0.29±0.54	
Dissection post PTCA		
yes (n=125)	-0.32±0.59	p=0.60
no (n=541)	-0.29±0.52	
Branch in stenosis		
yes (n=194)	-0.31±0.49	p=0.69
no (n=472)	-0.29±0.56	

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

Table 2C. Change in MLD per lesion at follow-up for **procedure related variables**

	Change in MLD at follow-up (mm)	P value
Maximal balloon diameter (mm)		
<2.35 (n=189)	-0.26±0.50	
2.35-2.7 (n=214)	-0.30±0.50	p=0.11
≥2.7 (n=192)	-0.35±0.55	
Balloon artery ratio		
<0.9 (n=201)	-0.27±0.55	
0.9-1.05 (n=201)	-0.29±0.53	p=0.17
>1.05 (n=193)	-0.36±0.54	
No. of inflations		
1 (n=178)	-0.29±0.47	
2-4 (n=254)	-0.30±0.51	p=0.55
>4 (n=234)	-0.35±0.57	
Maximal inflation pressure (atm)		
<8 (n=261)	-0.31±0.58	
8-10 (n=264)	-0.30±0.52	p=0.43
≥10 (n=141)	-0.24±0.50	
Total inflation duration (sec)		
<220 (n=202)	-0.30±0.54	
220-470 (n=230)	-0.28±0.52	p=0.69
>470 (n=224)	-0.27±0.48	

MLD=minimal lumen diameter

MULTIPLE LINEAR REGRESSION ANALYSIS

The stepwise multiple linear regression analysis showed 2 pre-angioplasty angiographic characteristics as predictive of luminal narrowing at follow-up, namely length of the stenosis and the minimal lumen diameter pre-angioplasty (table 3). Only 2 clinical variables and 2 one post-angioplasty variable, namely diabetes, duration of angina, the relative gain in lumen diameter achieved at angioplasty, and thrombus post angioplasty were found to be independently predictive for luminal narrowing following balloon angioplasty.

To rule out any influence of the investigational drug on our findings, the use of either the thromboxane A2 receptor blocker GR32191 or placebo was forced into model. Trial medication had only a very small, statistically unsignificant, contribution to the fit of the model (table 4).

In an attempt to assess how well the model predicted the amount of luminal narrowing at follow-up, the percentage of correct classified lesions was calculated for 5 intervals of predicted change in lumen diameter (table 4). Correct prediction by the model was poor, particularly in the range of predicted change from -0.1 to -0.4 mm. In fact only 10% of lesions in the middle 3 categories were correctly classified by the model. On the other hand lesions showing no change or regression and lesions showing large progression were more predictable. The information content of the model according to the ROC curves (figure 3) was optimal for the "loss of $\geq$0.72 mm" restenosis criterion. For the ">50% diameter stenosis" criterion the curve was very close to the line of "no prognostic value". If in addition to >50% diameter stenosis at follow-up also a loss of at least 13% in percent diameter stenosis (= twice the long term variability for diameter stenosis measurements, using the our analysis system) was required for a lesion to be classified as restenosis, a shift of the ROC curve to the left upper corner was apparent. These findings underscore the poor predictability of luminal narrowing and restenosis after balloon angioplasty and explain the differences between the restenosis criteria.

DISCUSSION

During 15 years of percutaneous transluminal coronary balloon angioplasty an abundance of clinical and experimental studies have been carried out in an attempt to elucidate factors that can predict the "Achilles heel" of coronary angioplasty, namely progressive luminal narrowing after a successful procedure. Although many clinical, procedural and lesion related factors have been linked to a higher angiographic restenosis rate, results of these studies are sometimes conflicting. As pointed out by Beatt et al [13], most of the discrepancies can be attributed to 1) patient selection, 2) the method of analysis and 3) the definition of angiographic restenosis employed.

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

Model	coefficient	SE of coefficient	F to remove
Intercept	0.40		
Relative gain at PTCA	-1.36	0.18	57.5
MLD pre PTCA	-0.19	0.07	6.7
Lesion length $\geq$6.8mm	-0.19	0.04	19.7
Diabetes	-0.34	0.07	20.7
Duration of angina			
<2.3 months	-0.11	0.04	6.2
Thrombus post angioplasty	-0.31	0.14	5.2
Allocation to GR32191B	0.03	0.04	0.5

MLD = minimal lumen diameter, PTCA = percutaneous transluminal coronary angioplasty. SE = standard error.

Table 4. Percentages of correct classification

Interval of predicted change in MLD	Percentage correct classification *
$\leq$-0.4 mm	98/197 (49.7%)
-0.3 to -0.4 mm	9/116 (7.8%)
-0.2 to -0.3 mm	13/123 (10.5%)
-0.1 to -0.2 mm	12/106 (11.3%)
>-0.1 mm	72/121 (59.5%)

MLD = minimal lumen diameter * = total amount of lesions is 663, because gain could not be calculated for 3 lesions that were located distal to a total occlusion pre PTCA and therefore the minimal lumen diameter is unknown.

Patient selection. To obtain objective, unbiased results, all patients should be recatheterized after a predetermined follow-up period regardless of their symptomatic status. Failure to perform angiographic follow-up in a majority of patients will introduce bias in the assessment of the true change in minimal lumen diameter at follow-up. The restenosis rate according to a more or less arbitrary cut-off point will be biased towards higher values if symptomatic patients or patients with unfavorable anatomy post-angioplasty are preferentially recatheterized. In this study 88.6% of all patients with a successful angioplasty had a follow-up angiogram performed within a predetermined time frame of 6 months.

Method of analysis. A well validated quantitative angiographic analysis system should be employed. Computer assisted automated edge detection techniques enhance objectivity and reproducibility and reduce the high inter- and intra-observer variability inherent to visual interpretation of the coronary angiogram [14,15]. The quantitative analysis system we applied for the analysis of the angiograms meets these requirements [13].

Restenosis criteria. The third factor influencing the restenosis rates is the restenosis criterion. The most frequently applied criterion in the literature is the > 50% diameter stenosis at follow-up criterion. This criterion is historically based on the physiological concept of coronary flow reserve introduced by Gould and others in 1974 and is taken because it represents the approximate value in animals with normal coronary arteries at which blunting of the hyperemic response occurs [16]. Although this criterion may be of some relevance in determining a clinically significant stenosis in human atherosclerotic vessels, it is a static measurement of lesion severity and tells us nothing about the dynamic behavior of the restenosis process. If the "50% diameter stenosis at follow up" criterion is applied, lesions with a suboptimal angioplasty result will preferentially be selected (ie have to undergo a small loss in lumen diameter to be classified as restenosed). Bourassa et al. [17] have recognized this shortcoming and thus considered lesions with $\geq$50% diameter stenosis at follow-up that did not show a change of at least 10% at follow-up as not "restenosed".

The predictive accuracy of the multivariate model for restenosis according to the 50% diameter stenosis criterion was very poor (figure 3). If in addition a change in percent diameter stenosis of at least 13% (twice the long term variability for percent diameter stenosis measurements) was required, then predictive accuracy of the model improved markedly, since lesions with a suboptimal angioplasty result did no longer unduly influence the restenosis rate. This requirement shifts the ROC curve to the left upper corner. A criterion that better reflects the dynamic behavior of the lesion after PTCA is the $\geq$0.72 mm loss in lumen diameter criterion as proposed by our group [5,8,12]. This criterion is not meant to be a restenosis criterion strictu sensu, since that implies also some sort of functional measure of lesion severity at follow up, but rather

an indicator of significant intraluminal growth as monitored angiographically.

Predictive factors for luminal narrowing after balloon angioplasty.

If restenosis is viewed as an intraluminal growth process after a successful angioplasty, risk factors for restenosis should be risk factors for this growth process. Therefore we determined risk factors for the absolute amount of quantitative angiographic luminal narrowing, rather than for the crossing of a more or less arbitrary cut-off point (eg 50% diameter stenosis or loss $\geq$0.72mm).

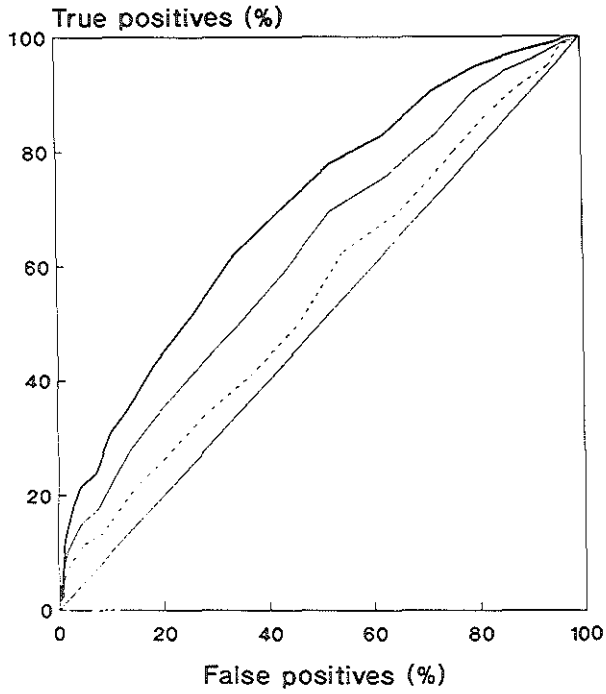

Figure 3. *Receiver operator characteristic curves (ROC curves) for comparison of restenosis criteria at different cut off points of predicted change in lumen diameter. The diagonal line is the line of identity or line of "no prognostic value". ROC curves on the line of identity have no prognostic value,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

A distinction should be made between lesions that progress towards total occlusion and lesions that remain patent at follow-up, since it is likely that part of the luminal narrowing observed in former lesions is caused by thrombosis and not only by the fibroproliferative process. The larger luminal narrowing in lesions in patients with diabetes, unstable angina, in totally occluded lesions, lesions with visible collateral

circulation and lesions with a visible thrombus post-angioplasty was largely determined by a higher incidence of total occlusions at follow-up.

Patient related factors. Diabetes, unstable angina and duration of angina shorter than 2.3 months were associated with more luminal narrowing at follow-up. If total occlusions at follow-up were disregarded, none of these variables showed significantly more narrowing. In multivariate analysis however, diabetes was independently predictive of luminal narrowing.

The assumption that risk factors for restenosis are similar to risk factors for atherosclerosis was not confirmed in the present study. Only diabetes was found to be independently related to the amount of luminal narrowing at follow-up. This finding has also been recognized by others [18-25]. In a recent study by Bourassa et al [17] using the same quantitative angiographic analysis system, diabetes was however not found to be predictive of restenosis. Other classic risk factors for atherosclerosis such as male gender, systemic hypertension, high cholesterol level and continued smoking after the PTCA, were not found to be related to luminal narrowing in the present study. The controversy regarding these risk factors is considerable, with many studies being positive for one or more patient related factors and many studies being negative [26,27].

Lesion related factors. *Pre-angioplasty variables.* In univariate analysis 5 pre-angioplasty variables were associated with more luminal narrowing at follow-up: minimal lumen diameter pre-angioplasty, percent diameter stenosis pre-angioplasty, length of stenosis, total occlusion pre-angioplasty, and collateral circulation to dilatation site. A relation between stenosis severity and restenosis rate has been shown previously [17,19,20,28]. It is conceivable that more severe lesions undergo more severe vessel wall damage during the procedure, a known trigger for the hyperplastic reaction [29-31]. In our multivariate analysis the pre-angioplasty minimal lumen diameter was found to be an independent determinant of subsequent loss in lumen diameter. In longer lesions more smooth muscle is possibly exposed to injury and platelet adhesion, which probably enhances the intimal hyperplastic reaction.

A relation between stenosis length and restenosis has also been described by others [17,32,33]. Total occlusion pre-angioplasty is a well known factor connected with total occlusion at follow-up [34,35] and thus a large loss in lumen diameter at follow-up. Because total occlusion pre-angioplasty is part of the continuous variables minimal lumen diameter and diameter stenosis pre PTCA, total occlusion pre-angioplasty was not found to be an independent predictor of loss in lumen diameter.

Collateral circulation to the dilatation site will be more abundant in case of a severe stenosis or total occlusion. Since the severity of the lesion (minimal lumen diameter) pre-angioplasty was found to be an independent determinant for the absolute loss in lumen diameter at follow-up, the presence of collaterals was not retained in the model.

No differences in luminal narrowing was observed for the 3 coronary arteries. Others [23,28,37-39] have reported a higher incidence of restenosis for the left anterior descending artery, a finding recently challenged by Hermans et al [40].

Post-angioplasty variables. Relative gain achieved at PTCA was both in univariate and multivariate analysis the strongest predictor (largest F to remove in final model) of luminal narrowing at follow-up. This variable probably best reflects the amount of damage inflicted upon the vessel wall by the angioplasty balloon. It is conceivable that more damage to the vessel wall with more deep arterial injury will result in a more aggressive repair process [1,29-31]. Other post-angioplasty variables that were related to more luminal narrowing at follow-up in univariate analysis were: higher minimal lumen diameter post-angioplasty, diameter stenosis post-angioplasty < 29.5% and visible thrombus post-angioplasty. Thus a better post-angioplasty result leads to more luminal narrowing or intimal hyperplasia at follow-up. Others have reported that a poorer post-angioplasty result was predictive of restenosis [17,20,22,28,36,41]. In general they applied the 50% diameter stenosis cut off point and, as discussed above, lesions with a poor post-angioplasty result will exceed this cut-off point with only minimal additional deterioration.

Because lesions with a low percent diameter stenosis and a large lumen diameter post- angioplasty were also the lesions that underwent a high relative gain at angioplasty and since this variable was the strongest independent predictor of the absolute amount of luminal narrowing at follow-up, percent diameter stenosis post-angioplasty and lumen diameter post-angioplasty were not retained in the multivariate analysis.

Thrombus post-angioplasty was retained in the multivariate model. Five of 16 lesions (31%) with a visible thrombus post-angioplasty were totally occluded at follow-up and therefore showed a greater overall loss in lumen diameter.

We did not find an association between coronary dissection immediately post-angioplasty and subsequent luminal renarrowing. Conflicting data have been reported concerning dissection and restenosis [21,22,42,43]. It is however clear that severe dissections are associated with a higher acute complication [44] and restenosis rate, the latter probably due to a poorer angioplasty result in combination with the 50% diameter stenosis criterion.

Procedure related variables. Balloon oversizing (balloon-artery ratio > 1.05) was not related to more luminal narrowing at follow-up. Some investigators found a positive effect of balloon oversizing on restenosis [28,41] others have not [17,45], however in a prospective randomized study, Roubin et al found a higher incidence of acute complications in case of oversizing but no difference in restenosis rate [44].

Limitations. Although this study suggests several factors that may be determinants of luminal narrowing after coronary balloon angioplasty it does not address the actual mechanism of restenosis. Vasomotion at follow-up angiography cannot be ruled out as

a possible cause of the observed luminal renarrowing in individual lesions, although intracoronary nitrates in appropriate doses were administered before each angiography. Mean reference diameter was not different before PTCA, after PTCA and at follow-up 2.64±0.56 mm, 2.70±0.53 mm and 2.70±0.56 mm respectively, suggestive of accurate control of vasomotion. Due to the relatively small sample sizes of some variables, ß error cannot be ruled out in this study. Furthermore, in performing multiple statistical comparisons, there is a risk that some of them may reach significance by chance alone. The multivariate model was developed and tested in the same population. Generally a 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 process.

Conclusion. Prediction of luminal narrowing with baseline clinical and quantitative angiographic was shown to be poor. Only 6 variables, namely minimal lumen diameter pre-angioplasty, relative gain at angioplasty, lesion length, diabetes, duration of angina and thrombus post-angioplasty were found to be independent determinants of the hyperplastic intimal reaction after balloon angioplasty. Control of these factors alone, if at all possible, will probably not result in a reduction of the amount of luminal narrowing and restenosis. Furthermore, since (elective) angioplasty is still a procedure performed to alleviate symptoms it seems not feasible to deny diabetics, patients with recent onset angina or patients with a severe lesion a balloon angioplasty procedure. Restenosis is obviously a process that cannot be predicted by simple clinical and morphologic patient or lesion characteristics. Therefore additional biochemical or histochemical factors [46] of importance in the restenosis process should be investigated and where possible tackled with appropriate pharmacological intervention.

The variable most strongly associated with the amount of luminal narrowing at follow-up was the relative gain at angioplasty. It must be noted that lesions with a large gain at PTCA not only can but also will undergo a larger loss in lumen diameter at follow-up. Because drugs currently under development to prevent restenosis after balloon angioplasty are designed to reduce the absolute amount of intimal hyperplasia, the highest possible benefit of a new drug treatment might be expected in lesions with the characteristics retained in the present multivariate model.

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Summary

Percutaneous transluminal coronary angioplasty has gained worldwide acceptance as a safe and effective alternative to coronary bypass grafting for the treatment of coronary artery disease [1]. Improvements in angioplasty hardware and x-ray equipment and increased operator experience have made it possible that by now approximately half of all coronary revascularization procedures are carried out with this technique in the United States. Also in the Netherlands this figure will be reached soon.

The major shortcoming of coronary balloon angioplasty is the recurrence of the stenosis at the site of balloon damage. Depending on the definition used 20 to 40% of all treated patients experience angiographic or clinical recurrence within the first months after a successful balloon angioplasty procedure [2]. Reinstatement of pharmacological therapy, a repeat angioplasty or surgical intervention are often necessary to alleviate symptoms or objective signs of myocardial ischemia. Apart from the psychological disadvantage of temporary revascularization and re-intervention(s) for a considerable group of patients, balloon angioplasty will also loose its financial advantage over surgical treatment if lasting revascularization can only be achieved after several procedures.

The cause of restenosis is largely unknown but is probably an exaggerated repair to injury process after severe barotrauma inflicted upon the vessel wall by the angioplasty balloon. A very complex process in which platelets, fibrin, thrombus, vasoactive substances, growth factors and smooth muscle cells are involved is likely responsible for this luminal narrowing after a successful coronary balloon angioplasty.

Many new coronary interventional devices and pharmacological agents have been developed and clinically tested over the last decade to tackle this "Achilles Heel" of coronary angioplasty. None of these new techniques or pharmacological treatments has so far consistently shown to be superior to balloon angioplasty or placebo medical treatment after balloon angioplasty [3,4].

The central topic of this thesis is early (immediate and up to 24 hours) and late (6 months) luminal narrowing after percutaneous transluminal coronary balloon angioplasty as assessed by quantitative angiography.

Most of the data on which the studies described in this thesis are based, originate from a randomized, double blind, placebo-controlled, multicenter european restenosis prevention trial, the CARPORT trial (Coronary Artery Restenosis Prevention On Repeated Thromboxane-antagonism trial). In this trial the novel thromboxane A2 receptor antagonist GR32191B was clinically tested against placebo for its usefulness in restenosis prevention. Objective quantitative angiography was performed pre-angioplasty, post-angioplasty and at 6 month follow up angiography, to assess the angiographic efficacy of the drug. All quantitative analyses were performed in a central core-laboratory

at Cardialysis in Rotterdam with the extensively validated Cardiovascular Angiography Analysis System (CAAS) [5]. Neither angiographic, nor clinical benefit of the compound could be demonstrated. The results of this trial are described in detail in chapter 8.

In the introductory chapter the requisites for accurate quantitative angiography in general and especially quantitative angiography for long term follow-up studies are described. The latter requires a high degree of standardization in acquisition and analysis of the coronary cineangiograms. This asks for a highly cooperative attitude of all angioplasty operators, technicians and nurses in the participating clinics. Nevertheless, all participants in Berlin, Nancy, Aalst (B), Brussels, Nieuwegein and Rotterdam succeeded in following the rigid protocol in almost all cases. Only 8 follow-up films were not made according to the protocol and could therefore not be analyzed [chapter 8]. Standardization of film analysis can, in our opinion, only be achieved if the analysis takes place in a central core-laboratory with strict guidelines for the analysts in order to minimize their influence on the automated edge detection process. Furthermore, central storage and reference facilities of the baseline quantitative data is of paramount importance for correct analysis of the follow-up angiograms. Over the last 3.5 years a professional quantitative angiographic core-laboratory has been set up at the Thoraxcenter/Cardialysis in Rotterdam that meets the logistic and technical requirements to accurately analyze and process the large amounts of cineangiograms produced in the frame of restenosis prevention trials, atherosclerosis progression-regression studies and studies with new interventional devices.

In chapter 2 to 4 the role of elastic recoil of the vessel after balloon angioplasty is studied. Diameters of the largest angioplasty balloon at its maximal inflation pressure were therefore measured with the CAAS system. In chapter 2 the amount of elastic recoil, defined as the difference in cross-sectional area of the balloon (mean 5.3 mm^2) and the post angioplasty cross-sectional area (mean 2.8 mm^2), was found to be approximately 2.5 mm^2, implying that almost 50% of the theoretical achievable cross-sectional area (i.e. the balloon cross-sectional area) is lost shortly after balloon deflation. The amount of recoil was more pronounced in eccentric lesions, this can be explained by the fact that in such lesions part of the vessel circumference is not diseased. This portion will be preferentially stretched by the balloon [6] with subsequently more elastic recoil.

Waller [7] suggested that recoil could follow a more protracted course, especially in eccentric lesions. In his view, overstretching of the plaque-free wall may result in an initial increase in luminal diameter, but gradual relaxation or restitution of tone of this overstretched segment reduces the coronary lumen towards its predilatation state in hours to weeks after the angioplasty. In chapter 3 we investigated whether recoil progresses in the first 24 hours after balloon angioplasty. In 71 patients with single vessel dilatation, a follow-up angiogram was made 1 day after the procedure. No difference in

minimal lumen diameter (MLD) at 1 day follow-up angiography was observed. It was therefore concluded that recoil is most likely an instantaneous phenomenon with no delayed component.

In chapter 4 it is described that the amount of recoil increases towards distal parts of the vessels. This increase was caused by oversizing of the balloon in distal, smaller, vessel segments.

In chapter 5 angiographic risk factors, including stretch and recoil, for luminal narrowing 6 months after a successful procedure were investigated. To obtain independent predictors of a significant loss in MLD (loss $\geq$ 0.72 mm), a multivariate logistic regression analysis was applied to 595 lesions with balloon measurements. The relative gain in MLD at angioplasty, defined as the difference in post angioplasty MLD and pre angioplasty MLD normalized for vessel size, was the most powerful predictor of a significant loss in lumen diameter at follow-up angiography. Relative risk for a relative gain > 0.3 was 2.9. This means that the risk for developing a loss of at least 0.72 mm with at least this relative gain is 2.9 times as high as it is for lesions with a relative gain of < 0.2. Other independent predictors were a relative gain between 0.2 and 0.3 (relative risk 2.1), a lesion length $\geq$6.8 mm (relative risk 1.7) and visible thrombus post angioplasty (relative risk 2.6). Stretch of the vessel wall was significantly related to luminal narrowing at univariate analysis but was not retained in the multivariate model. We concluded, since it is known that the amount of deep arterial injury is related to the restenosis process [8,9], that relative gain at angioplasty probably best reflects the amount of arterial injury inflicted upon the vessel wall at angioplasty.

Several investigators have sought predictors of restenosis [10]. A multitude of patient-, procedural- and lesion related variables have been found to predict long term outcome of an angioplasty procedure. But since these findings are based on different restenosis criteria and varying angiographic follow-up rates accurate comparison is difficult. One risk factor that has been the subject of controversy in the literature is the site of dilatation, with according to some, a higher risk of restenosis observed in the proximal left anterior descending (LAD) coronary artery as compared to lesion in the right coronary artery and circumflex artery. In chapter 6 this was investigated in 1234 patients (follow-up rate 91%) and we found neither a higher restenosis rate according to the classical 50% diameter stenosis criterion nor a greater loss in lumen diameter at follow-up angiography for proximal LAD dilatations. An explanation for the higher restenosis rates after LAD dilatation found by others might be the incomplete angiographic follow-up rate in their studies. An ischemic response to exercise is more likely to be seen with proximal LAD lesions, thereby increasing the chance of preferential detection unless angiographic follow-up is complete.

In chapter 7 the distributions of several quantitative angiographic parameters that reflect the restenosis phenomenon were determined. Both percentage diameter stenosis

at follow-up angiography and change in lumen diameter at follow-up angiography approximately followed a Gaussian or normal distribution. Therefore restenosis can be viewed as the tail end of a normally distributed phenomenon, with some lesions crossing a more or less arbitrary cut-off point, rather than a separate disease entity occurring in some lesions but not in others.

In chapter 8 the clinical and angiographic results of the Carport trial are extensively discussed.

In chapter 9, we investigated which quantitative angiographic parameter best predicts the functional status of patients 6 months after successful coronary balloon angioplasty. Accuracy of several quantitative angiographic parameters for the prediction of 2 different markers of myocardial ischemia, anginal status and ST depression of at least 1 mm at exercise electrocardiography, was determined. The cut-off points at which anginal status and exercise electrocardiography result were best predicted was 1.45 mm for the MLD at follow-up, 46.5% for the percent diameter stenosis at follow up, -0.30 mm for the change in MLD at follow-up and -10% for the change in percent diameter stenosis. Furthermore, parameters that depict a change in lesion severity at follow-up, were only slightly less accurate for the prediction of anginal status and exercise electrocardiographic result than parameters that merely describe lesion severity at follow up (MLD and percent diameter stenosis).

In chapter 10, an attempt was made to predict the absolute change in lumen diameter at follow-up angiography with simple, independent, clinical, lesion related and procedure related variables collected in the CARPORT trial. Therefore a multiple linear regression analysis was applied to 666 lesions with the change in minimal lumen diameter from post angioplasty angiogram to follow-up angiogram as dependent variable. It is now believed that the restenosis process is caused by a fibroproliferative vessel wall reaction after balloon trauma. The magnitude of this process can reliably be reflected by the change in minimal lumen diameter at follow-up angiography. Several variables with an independent contribution to the prediction of change in MLD were found. These were relative gain at angioplasty, obstruction diameter pre angioplasty, lesion length $\geq$6.8 mm, diabetes, duration of angina < 2.3 months and visible thrombus post angioplasty. However, correct prediction by the multivariate model was poor and modification or control of the risk factors will probably not influence the magnitude of the fibroproliferative reaction.

Restenosis is obviously a process that cannot be predicted by simple clinical, morphologic or procedural characteristics. Therefore, additional biochemical, histologic and cytologic factors of importance in the restenosis process should be investigated and where possible tackled with appropriate pharmacological intervention.

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Samenvatting

Percutane transluminale coronaria angioplastiek (PTCA, dotteren) is nu wereldwijd geaccepteerd als een veilig alternatief voor bypass chirurgie bij de behandeling van obstructief coronaria lijden [1]. Verbeterde röntgentechnieken, betere angioplastie materialen en toegenomen ervaring met de procedure zelf hebben het mogelijk gemaakt dat op dit moment de helft van alle revascularisatie procedures in de verenigde staten middels ballon dilatatie wordt verricht. In Nederland zal dit op korte termijn ook het geval zijn.

Ondanks het hoge primaire succespercentage van PTCA, zijn de resultaten op middellange termijn minder gunstig. Afhankelijke van de gebruikte definitie ontstaat bij 20 tot 40% van de patienten in de eerste maanden na een geslaagde procedure een nieuwe vernauwing (re-stenosering) op de plaats van de ballondilatatie [2]. De consequentie hiervan is dat patienten vaak opnieuw medische behandeling behoeven, hetzij met geneesmiddelen hetzij met een PTCA of bypass operatie. Een aanzienlijke groep patienten zal dus pas definitief geholpen zijn na meerdere ingrepen aan hun kranslagaders. Hierdoor zal de goedkopere PTCA behandeling in deze groep patienten het financiele voordeel op de bypass chirurgie verliezen, nog afgezien van het psychische trauma van slechts tijdelijke klachtenvermindering.

De oorzaak van restenosering is nog grotendeels onbekend maar berust waarschijnlijk op een overdreven wondgenezing na de locale beschadiging van het bloedvat door de dilatatie ballon. Bloedplaatjes, stollingseiwitten, thrombus, groeifactoren en gladde spiercellen lijken betrokken bij dit zeer ingewikkelde proces.

In een poging het restenose percentage te verlagen zijn de laatste jaren een aantal nieuwe methodieken ontwikkeld om vernauwingen in kranslagvaten op te heffen. Lasers, stents en apparaten die de atherosclerotische plaque wegsnijden zijn klinisch onderzocht maar zijn tot dusver niet succesvol gebleken. Ook is een heel scala van geneesmiddelen getest die op theoretische gronden de restenose vorming zouden kunnen voorkomen of afremmen. Ook op dit vlak is geen enkele vooruitgang geboekt [3,4].

Het centrale thema in dit proefschrift is vroege (tot 24 uur na de procedure) en late (tot 6 maanden na de procedure) bloedvatsvernauwing na een PTCA, zoals gemeten met behulp van een objectieve quantitatieve angiografische analyse techniek [5].

De meeste gegevens waarop de in dit proefschrift beschreven studies zijn gebaseerd zijn afkomstig van de CARPORT studie (Coronary Artery Restenosis Prevention On Repeated Thromboxane-antagonism). In deze studie werd met behulp van quantitatieve angiografie onderzocht of de nieuwe thromboxane A_2 receptor antagonist GR32191B minder bloedvatsvernauwing geeft in de eerste 6 maanden na een PTCA dan placebo behandeling. Zowel klinisch als angiografisch bood GR32191B geen voordeel boven placebo behandeling. De resultaten van deze studie worden uitgebreid besproken

in hoofdstuk 8.

In hoofdstuk 1 worden de benodigdheden voor nauwkeurige quantitatieve angiografische analyse van met name lange termijns follow-up studies beschreven. Dit vereist een hoge mate van standaardisatie bij zowel het maken van de coronair angiogrammen als bij de latere analyse. Dit vraagt een zeer coöperatieve instelling van alle betrokken cardiologen, technici en verplegend personeel in de deelnemende klinieken omdat het studie protocol vaak afwijkt van de plaatselijke gewoontes. Niettemin slaagden de deelnemers in de klinieken in Aalst (B), Berlijn, Brussel, Nieuwegein en Rotterdam er in om in praktisch alle gevallen het rigide protocol te volgen. Slechts 8 follow-up films waren niet volgens het protocol vervaardigd [hoofdstuk 8]. Naar onze mening kan standaardisatie van de film analyse slechts bereikt worden als alle analyses worden uitgevoerd door een centraal analyse laboratorium met strikte aanwijzingen voor de analisten, waardoor de menselijke en dus subjectieve invloed op het automatische analyse proces geminimaliseerd wordt. Bovendien zijn centrale opslag en referentie faciliteiten van de quantitatieve gegevens van de PTCA films onontbeerlijk voor goede analyses van de vervolg films, die pas ruim een half jaar na de PTCA film kunnen worden geanalyseerd. Gedurende de laatste 3,5 jaar is er in Rotterdam een professioneel laboratorium voor quantitatieve analyse van coronair angiogrammen opgezet dat voldoet aan de logistieke en technische eisen nodig voor de accurate verwerking en analyse van de grote hoeveelheid films die gemaakt worden in het kader van lange termijns angiografische studies.

In de hoofdstukken 2 t/m 4 wordt de rol van het elastisch terugveren (elastic recoil) na ballon deflatie besproken.

In hoofdstuk 2 werden de diameters van de in opgeblazen toestand gefilmde dilatatie ballonnen gemeten met behulp van quantitatieve angiografie. Elastic recoil werd gedefinieerd als het verschil in doorsnede oppervlakte van de ballon (gemiddeld 5.3 mm^2) en de doorsnede oppervlakte van het bloedvat ná de dilatatie (gemiddeld 2.8 mm^2). Dit betekent dat bijna 50% van de theoretisch haalbare bloedvatverwijding (dit is de doorsnede oppervlakte van de opgeblazen ballon) direct na het leegzuigen van de ballon verloren gaat. Er werd meer elastic recoil gevonden in bloedvaten waarbij de vernauwing aan één zijde van het vat gelocaliseerd was (excentrische vernauwingen). In dit type vernauwingen is een deel van de bloedvatwand niet aangedaan door de taaie atherosclerotische plaque en dit deel zal dus bij voorkeur opgerekt worden door de ballon [6]. Dit meer elastische deel zal dan ook meer recoil vertonen.

Waller [7] suggereerde dat elastic recoil in met name excentrische vernauwingen een meer verlengd verloop zou kunnen hebben. Overrekking van het plaque vrije deel van de bloedvatsomtrek zou naar zijn mening in eerste instantie resulteren in een toename van de luminale afmeting, maar langzame relaxatie en herstel van vaattonus zouden tot restenose in de eerste 24 uur na de dilatatie kunnen leiden. In hoofdstuk 3

werd onderzocht of recoil inderdaad een meer verlengd verloop kent. Bij 71 patienten werd 1 dag na de PTCA opnieuw een angiogram vervaardigd. Er werd geen verschil in minimale luminale diameter (MLD) gevonden na 1 dag vergeleken met de MLD direct na de procedure. Recoil lijkt dus een fenomeen dat ogenblikkelijk optreed zonder vertragings component.

In hoofdstuk 4 wordt beschreven dat elastic recoil toeneemt naarmate een meer distaal deel van een kransslagvat gedilateerd wordt. Deze toename kan echter verklaard worden doordat voor dilataties van de kleinere distale vaatgedeelten een relatief grotere ballon gebruikt werd dan voor de grotere proximale vaatgedeelten.

In hoofdstuk 5 werden angiografische risicofactoren onderzocht voor het optreden van vaatvernauwing 6 maanden na de PTCA. Om onafhankelijke voorspellers van een significante afname in MLD te verkrijgen, werd een multivariate logistische regressie analyse toegepast op 595 lesies waarbij ook de ballon diameter gemeten was. De toename in MLD bereikt met de ballon dilatatie, gedefinieerd als het verschil in MLD na de dilatatie en de MLD vóór de dilatatie was de sterkste onafhankelijke voorspeller voor een later significant verlies. Andere onafhankelijke voorspellers waren lange vernauwingen (langer dan 6.8 mm), en een zichtbare thrombus op het angiogram na de dilatatie. Het is bekend dat beschadigingen dieper in de wand van het bloedvat gerelateerd is aan een meer uitgesproken restenose reactie [8,9]. De toename in MLD door de ballon dilatatie zou dus een soor index kunnen zijn voor de uitgebreidheid en diepte van de vaatwandbeschadiging.

Sinds het begin van de PTCA is er gezocht naar voorspellers van restenose [10]. Een veelvoud aan factoren is beschreven. Maar omdat de bevindingen veelal gebaseerd zijn op verschillende restenose criteria, uiteenlopende tijdstipen van hercatheterisatie en wisselende percentages patienten met een vervolg angiogram, is vergelijking van deze bevindingen moeilijk. Eén risicofactor waarover in de literatuur controverse bestaat is de plaats van de dilatatie. Sommigen menen dat een hoger risico op restenose bestaat na dilatatie van het proximale gedeelte van de ramus interventricularis anterior (LAD) van de linker kransslagader in vergelijking met dilataties uitgevoerd in de rechter kransslagader of de ramus circumflexus van de linker kransslagader. In hoofdstuk 6 onderzochten we dit bij 1234 patienten (vervolg catheterisatie percentage 91%) en er werd noch een hoger restenose percentage gconstateerd volgens het klassieke 50% diameter stenose criterium noch een groter verlies in MLD bij vervolg angiografie 6 maanden na dilatatie van een proximale LAD lesie.

In hoofdstuk 7 werden van verscheidene quantitatieve angiografische parameters die het restenose proces weergeven de verdelingen onderzocht. Zowel het percentage vernauwing bij vervolg angiografie als het verschil in MLD van het post dilatatie angiogram en het 6 maanden vervolg angiogram waren normaal verdeeld. Hieruit wordt geconcludeerd dat restenose gezien kan worden als de staart van een normaal verdeeld

fenomeen, waarbij sommige lesies een meer of minder arbitrair afknotpunt overschrijden, en niet als een aparte reactie die optreed in sommige lesies en niet in andere.

In hoofdstuk 8 worden de klinische en angiografische resultaten van de CARPORT studie uitgebreid besproken.

In hoofdstuk 9 wordt beschreven welke quantitatieve angiografische parameter het best overeenkomen met de klinische status van patienten 6 maanden na een geslaagde éénvats ballon dilatatie. De waarden van de quantitatieve angiografische parameters waarop de aan- of afwezigheid van angina pectoris en de aan- of afwezigheid van een positief inspannings electrocardiogram het best werden voorspeld werd vastgesteld met behulp van sensitiviteit en specificiteit curves. Voor de MLD op 6 maanden was dit 1.45 mm, voor het percentage diameter vernauwing op 6 maanden was dit 46%. Voor de verandering in MLD van post angioplastie angiogram tot het 6 maanden vervolg angiogram was het afknotpunt -0.30 mm en voor de verandering in percentage diameter vernauwing was dit -10%. Bovendien waren de parameters die de verandering in ernst van de lesie, en dus het restenose proces, weergeven slechts weinig minder nauwkeurig bij de voorspelling van de functionele status dan de parameters die de ernst van de lesie bij vervolg angiogram weergeven.

In hoofdstuk 10 hebben we geprobeerd de absolute verandering in MLD van het angiogram direct na de PTCA tot het vervolg angiogram te voorspellen met behulp van eenvoudige klinische, angiografische en procedurele variabelen. Hiertoe werd een multipele liniaire regressie analyse toegepast op 666 gedilateerde kranslagvaten uit de CARPORT studie. Verschillende onafhankelijke voorspellers van het restenose proces werden geidentificeerd: relatieve winst in bloedvatafmetingen verkregen door PTCA, de ernst van de obstructie vóór de dilatatie, een vernauwing langer dan 6.8 mm, diabetes mellitus, een kortere duur van angineuze klachten vóórdat PTCA verricht werd en zichtbare thrombus op het angiogram direct na de dilatatie. Als met deze gegevens echter geprobeerd wordt de individuele verandering in MLD te voorspellen blijkt dit een zeer matig resultaat op te leveren. Restenose is dus zeer moeilijk te voorspellen met behulp van deze eenvoudige klinische, angiografische en procedurele factoren.

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Curriculum vitae

De schrijver van dit proefschrift werd geboren op 25 oktober 1962 te Nijmegen. Na het behalen van het Gymnasium ß diploma aan de Nijmeegse Scholen Gemeenschap werd in 1981 begonnen met de studie Geneeskunde aan het Rijks Universitair Centrum Antwerpen. Daar werd in 1984 de graad van kandidaat in de geneeskundige wetenschappen behaald. De studie geneeskunde werd daarna voortgezet aan de Erasmus Universiteit Rotterdam. In 1986 werd het doctoraal examen afgelegd en in 1988 het artsexamen. Tijdens de studie geneeskunde werkte hij als student assistent op de afdeling klinische epidemiologie van het Thoraxcentrum onder leiding van dr. J.W. Deckers.

Tussen oktober 1988 en december 1991 heeft de schrijver meegewerkt aan een aantal grote europese en amerikaanse restenose preventie studies onder leiding van prof. dr. P.W. Serruys. Sinds januari 1992 is hij begonnen aan de opleiding tot cardioloog (opleider, prof. dr. J.R.T.C. Roelandt) en volgt daartoe de 2 jarige stage Inwendige Geneeskunde in het Merwede Ziekenhuis in Dordrecht (opleider, dr. B.A. de Planque).

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