CLINICAL, ANGIOGRAPHIC AND HISTOLOGIC ASPECTS OF DIRECTIONAL CORONARY ATHERECTOMY

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KLINISCHE, ANGIOGRAFISCHE EN HISTOLOGISCHE ASPECTEN VAN DIRECTIONELE CORONAIRE ATHERECTOMIE

PROEFSCHRIFT

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Introduction and overview of the thesis

PART I: ANGIOGRAPHIC STUDIES

INTRODUCTION AND OVERVIEW OF THIS THESIS

The use of percutaneous transluminal angioplasty was initiated by Dotter and Judkins, with the introduction of tapered dilating catheters of increasing diameters in 1964 [1]. Almost a decade passed before Andreas Grüntzig reported the use of cylindrical high pressure balloons for the dilatation of atherosclerotic arteries [2]. In 1976, he miniaturized his peripheral balloon catheter to perform coronary angioplasty in a canine model and later in human cadaver experiments [3]. Then in 1977, in Zürich, Andreas Grüntzig performed the first percutaneous transluminal coronary angioplasty in a human [4]. Ever since, coronary balloon angioplasty has become an accepted treatment modality, as it appears to be safe and effective. Typically, PTCA was performed in patients with single vessel disease with a discrete stenosis in the proximal part of the coronary artery. After the introduction of the steerable balloon catheters in the early 80's and with increasing operator experiences, a rapidly increasing number of procedures were performed in Europe and across the Atlantic Ocean [5]. These improvements have resulted in a high primary success rate (>90%) and low complication rate (4-5%) despite extension of the indication to include patients with unstable angina, multivessel disease, bypass graft lesions, poor left ventricular function and totally occluded vessels [6]. In 1985, John Simpson [7] introduced a new transcatheter technique, directional coronary atherectomy, for the treatment of coronary lesions which removes obstructive tissue rather than dilates the lesion by a balloon. It was hypothesized that debulking of atherosclerotic tissue by atherectomy may reduce restenosis by 1) producing a large post-procedural lumen, 2) creating a smooth surface at the intervention site and 3) preventing elastic recoil. At September 7th 1989, John Simpson came to the Thoraxcentre in Rotterdam to introduce this novel interventional technique in Europe. Since the start of the Rotterdam atherectomy program, the clinical, histological and angiographic data of all patients were prospectively collected in the database and used for this thesis.
The central topic of this thesis are the acute and long-term clinical and angiographic outcome of directional coronary atherectomy and the response of the vessel wall after atherectomy.

Part I describes the angiographic observations after directional atherectomy. In particular, the concept of matching for quantitative angiographic and clinical characteristics is introduced and validated. Indeed, it is shown that matching may serve as a surrogate for the prediction of the outcome randomized trials comparing atherectomy with balloon angioplasty.

In chapters 1-3, some methodologic aspects of performing quantitative coronary analysis following directional coronary atherectomy are presented. Although quantitative coronary angiography has become the gold standard, the optimal method for the assessment of immediate and long-term results of coronary interventions has not been determined. Although edge detection remains the main form of analysis, its use may be limited particularly after dissections disrupt the anatomy of the vessel wall. Densitometry has been proposed as an alternative method because it theoretically is independent of the geometric shape. In chapter 2, we compared the results of minimal luminal cross-sectional area obtained by edge detection versus densitometry in 20 patients. In chapter 3, we integrated information obtained from edge detection, videodensitometry, lesion matching and pathology to assess the mechanism of directional atherectomy.

In chapters 4-7, the immediate and late results of directional atherectomy are reviewed and compared with the results of conventional balloon dilatation, stenting and rotating atherectomy. In chapter 4, the immediate angiographic results of atherectomy is compared with those of balloon angioplasty and stenting. In stead of the previously used historic controls, this comparative study uses the concept of lesion matching to individually match 51 atherectomy patients with angioplasty and stent patients. Matching is performed according to lesion location and reference diameter. In chapter 5, we have attempted to assess the utility of directional atherectomy, through a new quantitative angiographic index. Therefore, the utility index, which is the ratio between the final gain in diameter at follow-up and that what theoretically could have been achieved, is assessed in the initial 30 consecutive lesions treated by directional atherectomy which are matched with 30 angioplasty lesions. In chapter 6, the matching technique is further refined to include clinical and angiographic patient characteristics. Subsequently, we have attempted to assess late luminal renarrowing following atherectomy and angioplasty in 87 matched lesions. Relative gain and relative loss, being the angiographic correlates of vessel wall injury and neo-intimal hyperplasia, are assessed in both groups. In chapter 7, we have examined whether restenosis is related to the extent or mechanism of luminal improvement and we have explored the determinants of optimal atherectomy.

In chapter 8, the complimentary information of angiography, intravascular ultrasound and intracoronary ultrasound before and after directional atherectomy is used to characterize the mechanism of luminal enlargement and the vessel wall contour. Intracoronary ultrasound and coronary angioscopy findings in 26 patients are described and compared with those of angiography.

Part II addresses the clinical application of directional coronary atherectomy. In particular, the safety and efficacy of this procedure is assessed. The composite clinical endpoint which is used in this study to demonstrate the efficacy of atherectomy is the occurrence of any of the following: death, myocardial infarction, coronary artery bypass grafting and repeat percutaneous intervention. The advantage of such an analysis is that it only considers objective criteria which are evaluable in all patients.

In chapter 9-11, early and late follow-up of the first atherectomy procedures in two European centers are reviewed. The same quantitative angiographic analysis system, Coronary Artery Analysis System (CAAS), which has been extensively validated, was used for all quantitative analyses. In chapter 9, the acute clinical results of the first 113 procedures performed in Rotterdam and Brussel are described. In chapter 10, the long-term clinical follow-up of 150 patients is reported. In this analysis, the population was divided according to their clinical syndrome, i.e. stable or unstable angina, at the time of the index atherectomy procedure. In chapter 11, we have identified the clinical, angiographic and histologic predictors for restenosis. A dual approach to data analysis is taken in order to gain insight into factors affecting the clinical outcome and biological process. Therefore, multivariate analysis was performed to determine the correlates of residual lumen diameter at follow-up (angiographic outcome) and to characterize the determinants of late luminal loss (renarrowing process).

In chapter 12, the early and late results of directional atherectomy performed for restenosis within the coronary stent of 9 patients are examined. In addition, the retrieved tissue was studied for cell identification, proliferation rates and cell density using light microscopy, electron microscopy and immunohistochemical staining techniques. The results were compared with a control group of patients who had atherectomy for restenosis after earlier angioplasty, atherectomy or laser therapy.

Part III highlights the function of directional coronary atherectomy as a bridge between clinical care and experimental research. Atherectomy is the first percutaneous technique which allows us to harvest fresh atherosclerotic tissue from diseased human coronary arteries. Subsequent (immuno)histologic examination of this freshly obtained de-novo or restenotic plaque material may provide further insights into the mechanism of restenosis.

Chapter 13 provides an overview of the potential research applications. Some preliminary results of outgrowth of cultured smooth muscle cells are provided and compared with cultured medial cells from normal human umbilical arteries.

In chapter 14, the histopathologic characteristics of atherectomy specimens of stable and unstable angina pectoris are reported. Tissue samples of 93 procedures were examined using light microscopy for the identification of specific landmarks of the vessel wall to gain further insight into the histopathological substrate of stable and unstable angina.

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Part I

ANGIOGRAPHIC OBSERVATIONS

Chapter 1

EVALUATION OF THE CLINICAL USE OF DIRECTIONAL CORONARY ATHERECTOMY USING QUANTITATIVE CORONARY ANGIOGRAPHY

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INTRODUCTION

Quantitative Coronary Angiography (QCA has had a major impact in the field of interventional cardiology. Due to its superior accuracy and objectivity and improved interobserver and intraobserver variability, it has supplanted visual and hand-held calliper assessments of coronary arteriograms [1-3]. QCA is now the gold standard for the assessment of the coronary tree in the context of scientific research, although it has not yet gained widespread appeal for routine clinical use, because of expense and time constraints. To date there are two different techniques to quantitative angiographic stenosis measurement. The first one is based on the detection of luminal borders from orthogonal images to create a three-dimensional approximation of the diseased vessel while the second approach uses videodensitometry of the stenosis to extract three-dimensional information from a single angiographic view. Although this latter approach has particular advantages, we have favored the edge detection method because it provides absolute measurements, relatively insensitive to the image quality.

From a clinical viewpoint, the objectives of quantitative angiography are to obtain information that (1 contributes to the understanding of clinical syndromes, (2 facilitates decision-making, (3 helps to forecast future events (e.g. subacute occlusion, restenosis and (4 guides invasive therapy. It has been particularly useful in interventional cardiology as the only reliable means of assessing the short- and long- term effects of coronary interventions. In particular, the phenomenon of restenosis has been primarily described and researched most extensively on the basis of sequential QCA studies. At the Thoraxcenter in Rotterdam, we have been advocating the importance of QCA since the first publication of its use by our group in 1978 [4] and with subsequent and renewed vigour following our initial experience with QCA in the assessment of coronary interventions as reported in 1982 [5]. The system developed at the Thoraxcenter by Johan Reiber and colleagues, the Cardiovascular Angiographic Analysis System (CAAS, has been extensively and rigorously validated [6-8]. In our database, we have now collected information from 4,662 patients who have undergone several different forms of nonoperative coronary revascularization [1].

We have had to adapt the principles of QCA, which were initially designed for diagnostic studies to assess the extent of coronary artery disease, to more complicated and complex situations related to either the presence of a device, or the effect of an intervention, on the angiographic appearance of a damaged vessel. The introduction of several newer devices in the past 6 years, has presented a number of unique and unforeseen problems in image analysis and subsequent interpretation of important quantitative data. The emergence of digital subtraction angiography has allowed the "on-line" performance of QCA measurements in the catheterization laboratory, so that a technique previously confined to research applications has been transformed into a powerful analytical tool, directly

applicable to clinical decision making [9-12]. The immediate availability of QCA measurements during interventional procedures provides a unique opportunity for more accurate selection of appropriate interventional devices (eg. balloon or atherotome dimension, and for continuous monitoring and immediate evaluation of the result obtained.
The purpose of this chapter is to highlight the basic features of and information which can be provided by these two automatic computer assisted angiographic analysis systems and also to discuss some of the benefits and limitations of QCA in the analysis of the angiographic short and long-term sequelae of the various "devices" of interventional cardiology. Only close scrutiny of the analytical results, combined with ongoing communication between the angiographer, the analyst and the programmer, ensures that meaningful and useful data emerge from the use of QCA.

What information can be obtained from the use of automatic computer assisted angiographic quantitative analysis systems?

The prime aim of QCA is to provide precise and accurate measurements of coronary anatomy. The CAAS system can provide this information by two different methods: (1 detection of luminal borders (so called "edge detection", preferably in two orthogonal projections (to provide a three-dimensional approximation of the diseased segment which can then be converted into absolute values after calibration with an object of known diameter, such as the shaft of the guiding catheter; and (2 videodensitometry, an approach which assesses the relative area stenosis by comparing the density of contrast in the diseased and "normal" segment. The method by which the relative area stenosis is converted to absolute area stenosis measurements will be explained later in the chapter. The advantage of the information acquired by the densitometric method is that meaningful data can be obtained in a single projection, even if the cross-sectional shape is highly asymmetrical or eccentric. In contrast, area measurements derived from edge detection data (and specifically from minimal luminal diameter values, by definition, require an assumption of a circular cross-sectional lumen in the diseased arterial segment, which is at odds with the observations of several pathologic studies [13,14]. The limitations of both techniques will subsequently be discussed, and discrepancies in the results of these two methods following coronary interventions, will be presented later.
(1 Edge detection:
In our laboratory, the quantitative analysis of the stenotic coronary segments are carried out using the computer assisted Cardiovascular Angiographic Analysis System (CAAS, which has been described in detail elsewhere [2-7]. To analyse a coronary arterial segment a 35 mm cineframe is selected. Electronically a region of interest (512 x 512 pixels encompassing the arterial segment to be analyzed,

is digitized with a high fidelity videocamera. Contours of the arterial segments are detected automatically on the basis of the weighted sum of the 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. A computer-derived estimation of the original arterial dimension at the site of the obstruction is used to define the interpolated reference diameter. This technique is based on a computer-derived estimation of the original diameter values over the analyzed region (assuming there was no disease present according to the diameter function. Conversion of the diameter measurements of the vessel to absolute values was achieved by using the contrast catheter as a scaling devise, after correction for pincushion distortion. The minimal cross-sectional area of the narrowed segment and the interpolated percentage area stenosis are then derived by assuming a circular vessel cross-section and comparing the observed stenosis dimensions to the reference values.

The plaque area is a measure of the atherosclerotic plaque in this angiographic view, expressed in mm^2. This area is calculated as the sum of pixels between the computer-estimated predisease reference contours and the actual detected luminal contours of the obstructive lesion. Since measurement of area plaque is highly dependent on the length of the stenosis (which is subject to considerable variation and the determination of the reference contours of the artery in the presumed prediseased state, the usefulness of this parameter is debatable.

The symmetry value is a measure of the eccentricity of a particular lesion. A symmetry measure of 1 denotes a concentric obstruction; the number decreases (down to 0 with increasing asymmetry or eccentricity of the obstruction. Unfortunately, this parameter has not yet been validated against pathology and thus the pathologist and angiographer may not be referring to the same feature.

The curvature value is measured to assess the bend of the coronary segment analyzed. The view in which the vessel appears to be the least foreshortened (ie. the segment length is longest is chosen for the curvature analysis. The inflow and outflow angles are derived from the slope of the diameter function at the descending and ascending limb of the diameter function curve at the defined site of the obstruction.

The CAAS and the Philips digital cardiac imaging system (DCI have also attempted to convert information on angiographic parameters into functional data based on well-known fluid-dynamic equations [7].

The angiographic analysis is performed whenever possible using the average of multiple matched views with orthogonal projections.

(2 Videodensitometry:

To determine the changes in cross-sectional area of a coronary segment from the density profile within the artery, the calibration of the brightness levels in terms of the amount of X-ray absorption (Lambert Beer's Law is required. The

videodensitometric method used with our system, corrects for spatially variant responses in the imaging chain and for daily variations in the cine-film processing. Details of this technique have been described elsewhere [2-7]. Contours of the artery are detected by automated contour detection with the CAAS system as previously described. From the measured diameters along the analyzed segment, the diameter data described above are derived. On each scan line perpendicular to the centerline of the vessel, a profile of brightness is measured. This profile is transformed into an absorption profile by means of a simple logarithmic transfer function. The background contribution is estimated by computing the linear regression line through the background points directly left and right of the detected contours. Subtraction of this background portion from the absorbed profile within the arterial contours yields the net cross-sectional absorption profile. Integration of this function gives a measure for the cross-sectional area at the particular scanline. By repeating this procedure for all scanlines, the cross-sectional area function is obtained. A reference densitometric area is obtained following the same principles as described above for the diameter functions. 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. By this method, no assumption is made about the cross-sectional shape of the lesion in the most severely diseased segment of the vessel. Although densitometry is extremely attractive on a theoretical basis, numerous technical problems have limited its use. The major limitation is the strict requirement of an angiographic projection which is perpendicular to the long axis of the vessel (to prevent oblique "cuts" which would lead to overestimation of the luminal area, and the absence of overlapping, or closely parallel, sidebranches or other vessels, in the segment to be analyzed (which would interfere with the density of the lesion, due to background subtraction. Densitometry is also more sensitive than edge detection to densitometric nonlinearities (x-ray scatter, veiling glare and beam hardening and to inaccurate contrast filling of vessels.

Despite these limitations the results of a recent in vivo validation study suggest that videodensitometry can reliably measure vascular dimensions provided a sufficient care is taken to obtain a perpendicular incidence of the x-ray beam onto the examined coronary segment and b a homogeneous contrast filling of the vessel is obtained. The method was thoroughly validated in a porcine model where precision-drilled circular coronary stenosis phantoms (with diameters ranging from 0.5 to 1.9 mm and angiograms were analyzed using the edge detection and the densitometric technique of the CAAS system [5-8]. In this experimental application simulating a diagnostic coronary angiography, both analysis techniques showed a high accuracy and precision in the automatic measurement of the stenosis phantoms. In particular, the mean difference between minimal cross-sectional area, measured with videodensitometry, and true stenosis cross-sectional

area, was -0.12±0.31 mm². A limitation of videodensitometry, however, was its inability to distinguish accurately the very low density of some of the stenosis phantoms with the smallest diameter stenosis, from the background density.

Comparison of different digital and cineframe QCA measurement systems:

Recent developments in digital cardiac imaging systems have been directed towards on-line stenosis measurements during the procedure from video digitized images. By this approach the system will guide the operator in selecting the appropriate interventional technique (balloon, stent, atherectomy, in selecting the appropriate size of the device and in assessing the effect of the intervention thereby it will help to determine whether a better result may be achieved. At the Thoraxcenter during the last five years a large clinical experience has been accumulated through the application of the Philips DCI Automated Coronary Analysis System [10, 11]. A recent in vivo study of stenosis "phantoms" placed in porcine coronary arteries has confirmed that the accuracy, and precision, of the DCI on-line measurements are closely comparable to those obtained off-line using the CAAS system, with a mean difference between true "phantom" stenosis diameter and DCI minimal luminal diameter measurements of 0.08±0.15 mm, for stenosis diameters ranging from 0.5 to 1.9 mm [12]. We believe, therefore, that the data information presented here, mainly derived from the analysis of cine-film images, can now be immediately applied to guide the operator during diagnostic and interventional procedures. Over the past few years there has been a substantial amount of progress in the field of quantitative angiography. In particular, several new measurement systems have been developed and will be introduced in clinical practise in the near future. At the Thoraxcenter, we have had the opportunity to validate three systems with the cinefilm approach and one digital angiography system [12].

Technical considerations and limitations of QCA in clinical practise:

Firstly, the use of the catheter as a scaling device has certain limitations, such as those due to the out-of-plane position of the catheter with respect to the measured coronary segment, which require complex corrections. We believe, however, that many possible sources of inaccuracy can be easily minimized with the use of a strict protocol of calibration, including the measurement, with a micrometer, of the true size of the catheter, the avoidance of catheters with excessive tapering or poor radiopacity and the acquisition, before the coronary angiogram, of the catheter image (saline or blood filled in the same projection and field of view [15], positioning the catheter in the center of the radiographic image or operating a correction for pincushion distortion.

A second important technical point for all serial studies is the requirement for coronary vasodilation using agents of comparable efficacy for every study. In a recent study [16] the mean diameter of a normal segment of a nondilated vessel pre PTCA, post PTCA and at follow-up was analyzed in 202 patients. Thirty-four of these patients, who received intracoronary nitrate pre-PTCA, but not prior to

post-PTCA angiography exhibited a decrease in diameter of 0.11 mm versus the small increase of 0.02 mm in the group which did receive post procedural nitrate. Lack of control of vasodilator therapy at follow-up angiography may also partially explain an earlier observation, from our group, of a significant deterioration in the mean reference diameter at four months post angioplasty as several subsequent studies employing coronary vasodilators have produced contradictory information [17,18]. However, we still believe that in certain patients, the reference segment is involved in the restenotic process invalidating the use of percent diameter stenosis as an accurate measurement of lesion severity at follow up.

Third, the computer generated interpolated measurements may be unreliable for ostial lesions or lesions located at sidebranches. Manual contour correction may also be necessary when the angiogram is of poor technical quality which is, fortunately, relatively infrequent, with only 0.9% of films, from multicentre trials, being rejected due to poor technical quality [19].

A major *limitation* of edge detection (aside from the technical quality of the cinefilm represents its difficulty to accurately analyse the post angioplasty result. In particular, dissections are a frequent occurrence following PTCA and the resulting haziness, irregular borders or extravasation of contrast medium makes edge detection difficult. There is no ideal solution to this problem. If a dissection is present on the post-angioplasty angiogram, the analyst must decide whether to include or exclude the extraluminal filling defect in the analysis. As advised by the MERCATOR Angiographic Committee, the computer should "decide" whether to include or exclude the extraluminal defect in the analysis, thereby avoiding subjective bias. If there is no clear separation between the lumen and the extravasation (large communicating channel, the computer will include the dissection in the analysis as the interpolated edge detection technique will detect a small although not significant difference in brightness. However, in cases where the extravasation is distinctly separate from the true vessel lumen, (small communicating channel, the computer will exclude the dissection from the analysis as there will be a steep difference in brightness between the extravasation and the true lumen

QCA and Coronary Interventions:

Prior to a discussion of the use of directional atherectomy for coronary intervention, the utility of the information generated by QCA in general (and the CAAS system specifically must be addressed. Anatomic information, such as minimal luminal diameter, reference diameter and percentage diameter stenosis, represent the most useful and reliable information obtained by this system. The physiologic and clinical significance of any individual value can not be inferred, although the CAAS system can generate theoretical measures of resistance based

on the lesion characteristics and assumed coronary flow rates. Angiographic features of a particular lesion, which may be important to the clinical outcome such as ulceration or complex, ragged morphology have not been a focus of our research, in terms of their natural history in large populations undergoing coronary interventions.

Although the absolute minimal luminal diameter is one of the parameters of choice for describing changes in the severity of an obstruction as a result of an intervention, percent diameter stenosis is a convenient parameter to work with in individual cases. The conventional method of determining the percent diameter stenosis of a coronary obstruction requires the user to indicate a reference position. It is clear that this computed percent diameter stenosis will depend heavily on the position of the selected reference. In arteries with a focal obstructive lesion and a clearly normal proximal arterial segment the reference region is straightforward and simple. However, in cases where the proximal part of the arterial segment shows combinations of stenotic and ectatic areas, the choice may be very difficult. To minimize these variations, we have implemented many years ago an *interpolated* technique, which is operator-independent, to determine the reference diameter at the actual stenosis site without operator interference. The basic idea of this technique is the computer estimation of the original diameter at the site of the obstructive region (assuming there was no coronary disease present based on the diameter function. In this approach the reference diameter is taken as the value of the polynomial at the position of the minimal luminal diameter. The interpolated percent diameter stenosis is then computed by comparing the minimal diameter value at the site of the obstruction with the corresponding value of the reference diameter function. An important practical advantage that the arbitrary choice of the reference, either proximal or distal to the stenosis, is avoided representing a major advantage particularly in the analysis of repeated angiograms. On the other hand, this technique requires that the coronary segments are analyzed in a standard manner, i.e. from branch point to branch point, so that the length of the segments are approximately equal in repeated analyses.

Although different approaches to the analysis of a coronary artery obstruction have been described, it is impractible to compare the various systems quantitatively. In particular, the lack of data about accuracy and precision and the use of different parameters to describe the validation make such comparisons difficult. It goes without saying that comparisons of data from angiographic studies performed in various core-laboratories the procedure must be properly standardized and validated.

QCA and directional coronary atherectomy:

Few problems have been encountered in the angiographic analysis of lesions treated by directional atherectomy [20]. The radiopacity of the device, particularly when the support balloon is inflated, allows excellent visualization of the position of the eccentric cutting apparatus. The vessel luminal contours are typically smooth and much less ragged than after PTCA, facilitating the edge detection program. Despite the apparent smooth contours, however, similar discrepancy exists between analyses performed by edge detection and densitometry, as occurs post angioplasty [21], which suggests that the vessel wall assumes a less circular configuration as a result of atherectomy. As Baim's group has suggested, this may be due to preferential expansion of the bases of the atherectomy cuts [22].

Insights into the mechanism of atherectomy:

Using directional atherectomy, the atherosclerotic plaque is selectively removed as the cutting device is directed towards the protruding plaque. With plaque removal in stead of plaque disrupture with balloon angioplasty, it was initially hypothesized that a greater gain in luminal area can be achieved and may account for the main mechanism of action. In recent years, QCA of atherectomy-treated lesions has provided some insight into the mechanisms of lesion improvement. Penny et al have shown that an average of approximately 28% of the effect of atherectomy could actually be attributed to tissue removal, although the individual values had a wide range (7-92% [22]. The correlation between the volume of tissue retrieved and the change in luminal volume was poor. The authors concluded that the major component of luminal improvement was due to "facilitated mechanical angioplasty" resulting from the high profile of the device and the low pressure balloon inflations. Data from our angiographic core laboratory seems to support this hypothesis. The "Dottering effect" of the device accounted for 62% of the luminal improvement [23] in 10 patients who had QCA performed before, after crossing the lesion with the device and after atherectomy.

Longterm outcome after directional atherectomy:

In experimental work, Schwartz and colleagues have demonstrated a relationship between vessel wall injury induced by an intervention is related to a reparative process. This approach has become known as the biological approach and can be readily studied by quantitative coronary angiography using the loss in minimal luminal diameter as the angiographic parameter. In a matched comparative study [24,25], we found that atherectomy indeed resulted in a larger immediate gain when compared with balloon angioplasty (1.17 ± 0.29 to 2.44 ± 0.41 mm versus 1.21 ± 0.38 to 2.00 ± 0.36 mm; $p<0.001$. During follow-up however, this immediate favorable acute result is partially lost by a larger luminal loss so that at 6 months follow-up the minimal luminal diameter was not significantly different in the atherectomy group compared with the PTCA group (1.76 ± 0.62 versus 1.77 ± 0.59 mm.

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Chapter 2

EDGE DETECTION VERSUS VIDEODENSITOMETRY FOR QUANTITATIVE ANGIOGRAPHIC ASSESSMENT OF DIRECTIONAL CORONARY ATHERECTOMY

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The immediate efficacy of coronary atherectomy should be established by reproducible quantitative coronary analysis [1]. The name "directional atherectomy" suggests that the device can be selectively directed toward the plaque and that its cutting mechanism is potentially less disruptive on vascular architecture than other angioplasty modalities. As a result of this selectively debulking action, the vessel may assume a more circular configuration and cross-sectional area measurements obtained by edge detection and videodensitometry should become more comparable. Since the optimal method to analyse the immediate result after atherectomy has not yet been established this study was undertaken to determine whether videodensitometry and edge detection were equally acceptable methods in assessing the immediate results following atherectomy. Cine-angiograms of 20 patients who underwent directional coronary atherectomy were analyzed with a computer-based coronary angiography analysis system. The results of the cross sectional area derived from contour analysis and videodensitometry were compared before and after directional atherectomy.

From September 1989 through September 1990, 55 patients underwent directional coronary atherectomy at the Thoraxcenter. Patients were selected for atherectomy when an eccentric stenosis was present in a proximal coronary artery. This series consists of the initial 20 atherectomy patients (17 men, 3 women). Edge detection and videodensitometry were used to evaluate the immediate results of the atherectomy. All patients underwent a successful procedure without preceding or adjunct balloon angioplasty. The patients ranged in age from 42-76 years with a mean of 62 years. Coronary angiography showed single vessel disease in 14, two-vessel disease in 3 and three- vessel disease in 3 patients. The site of the obstruction was located in the left anterior descending coronary artery in 10 patients, in the circumflex coronary artery in 2 patients, in the right coronary artery in 6 patients and in a coronary artery bypass vein graft in 2 patients.

After administration of local anaesthesia, a 11 French sheath was inserted into the femoral artery. All patients received 250 mg acetosalicylatic acid and 10,000 U heparin intravenously. Intracoronary injection of isosorbide dinitrate was performed to relief any possible spasm. After the initial angiograms in multiple views were completed, a special 11 French guiding catheter was placed into the ostium of the coronary artery. Under fluoroscopy the guide-wire was advanced into the distal part of the artery. Then, the atherectomy device was slid over a guide-wire and positioned across the stenosis. After proper positioning the support balloon was inflated up to 0.5 atm, the cutter was retracted and balloon inflation pressure was increased to 2 to 3 atm. The driving motor was activated and the rotating cutter was slowly advanced to cut and collect the protruding atherosclerotic lesion in the collecting chamber located at the tip of the catheter. After each pass, the balloon was deflated and either removed or repositioned. On average, 6.7 (3-14) passes were performed across a stenosis. Atherectomy was

considered successful when the residual stenosis was $<50\%$ after tissue retrieval. After atherectomy the arterial and venous sheaths were usually left in place for 6 hours. Patients were monitored for 24 hours and electrocardiograms and cardiac enzyme levels were obtained twice a day. Nifedipine was given every 2 hours after the procedure and the patients were maintained on aspirin for one year.

The quantitative analysis of the stenotic coronary segments were carried out with the computer assisted Cardiovascular Angiographic Analysis System (CAAS), which has been described in detail elsewhere [2-7]. To analyse a coronary arterial segment a 35 mm cineframe was selected. Electronically a region of interest (512 x 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 the 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. A computer-derived estimation of the original arterial dimension at the site of the obstruction is used to define the interpolated reference diameter. This technique is based on a computer-derived estimation of the original diameter values over the analyzed region (assuming there was no disease present) according to the diameter function. Conversion of the diameter measurements of the vessel to absolute values was achieved by using the contrast catheter as a scaling devise, after correction for pincushion distortion. The minimal cross-sectional area of the narrowed segment and the interpolated percentage area stenosis are then derived by assuming a circular model and comparing the observed stenosis dimensions to the reference values. The angiographic analysis was done using the average of multiple matched views with orthogonal projections whenever possible.

To determine the changes in cross-sectional area of a coronary segment from the density profile within the artery, the calibration of the brightness levels in terms of the amount of X-ray absorption (Lambert Beer's Law) is required. The videodensitometric method used with our system, corrects for spatially variant responses in the imaging chain and for daily variations in the cine-film processing. Details of this technique have been described elsewhere [2-7]. Contours of the artery are detected by automated contour detection with the CAAS system as previously described. From the measured diameters along the analyzed segment, the diameter data described above are derived. On each scan line perpendicular to the centerline of the vessel, a profile of brightness is measured. This profile is transformed into an absorption profile by means of a simple logarithmic transfer function. The background contribution is estimated by computing the linear regression line through the background points directly left and right of the detected contours. Subtraction of this background portion from the absorbed profile within the arterial contours yields the net cross-sectional absorption profile. Integration of this function gives a measure for the cross-

sectional area at the particular scanline. By repeating this procedure for all scanlines, the cross-sectional area function is obtained. A reference densitometric area is obtained following the same principles as described above for the diameter functions. 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 the cine-films of perspex models of coronary obstructions [6].

The individual data for diameter and densitometric area measures were used to calculate the mean $\pm$ SD (table 2). Analysis of variance was performed to compare the area measurements derived from edge detection (assuming a circular cross-section) and densitometry before and after atherectomy and when significant differences were found, two-tailed paired t-tests were applied. A statistical probability of <0.05 was considered significant. To measure the strength of the relationship between the two methods of analysis, edge detection and videodensitometry, in the determination of minimal cross-sectional area, the product-moment correlation coefficient (r) and its 95% confidence intervals were calculated at two distinct times of study. The agreement between the two measures was assessed by determining the mean and the standard deviation of the between-method difference as suggested by Bland and Altman [8]. At each interval this was done by computing the sum of the individual differences between the two methods to determine the mean difference and the standard deviation.

In this study, the angiographic projection showing the severest narrowing was analyzed. The individual data obtained by edge detection and videodensitometry are presented in Table 1 and 2.

Table 1. Edge detection before and after directional atherectomy

	Pre-atherectomy	Post-atherectomy	p-value
Reference diameter (mm)	3.05 $\pm$ 0.55	3.40 $\pm$ 0.44	0.05
Obstruction diameter (mm)	1.08 $\pm$ 0.43	2.68 $\pm$ 0.42	0.000001
Diameter stenosis (%)	66 $\pm$ 10	20 $\pm$ 9	0.000001

On average, the reference diameter increased from 3.1 to 3.4 mm ($p< 0.05$); the obstruction diameter increased from 1.1 to 2.7 mm ($p<0.000001$); thus the interpolated diameter stenosis was reduced from 66% to 20% ($p<0.000001$). Quantitative analysis of the atherectomy device showed an increase of its diameter from 2.0 $\pm$ 0.2 mm to 3.4 $\pm$ 0.4 mm following inflation of the support-balloon. The minimal luminal cross-sectional area (MLCA) determined by densitometry was compared with the minimal luminal cross-sectional area measurements from edge detection which assumes a circular configuration. The comparative data before and after coronary atherectomy are shown in Table 2 and figures I and II.

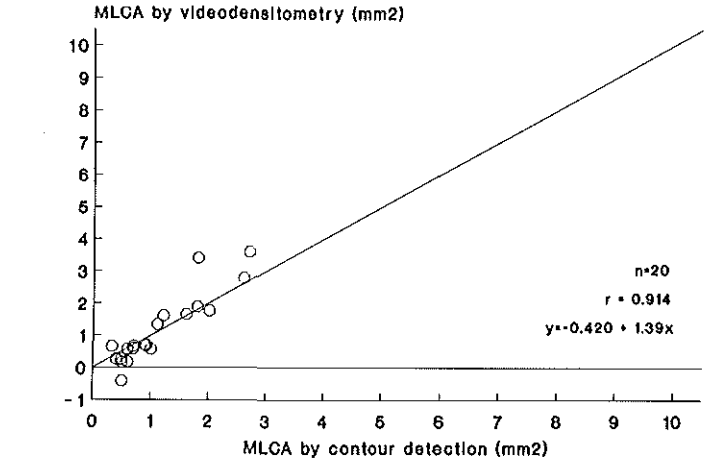

Figure I: Determination of the minimal luminal cross-sectional area (MLCA) by contour detection and videodensitometry before atherectomy. The line of identity is drawn. The correlation coefficient is 0.914 (95% confidence interval: 0.791-0.966). The regression equation was y = -0.420 + 1.39x.

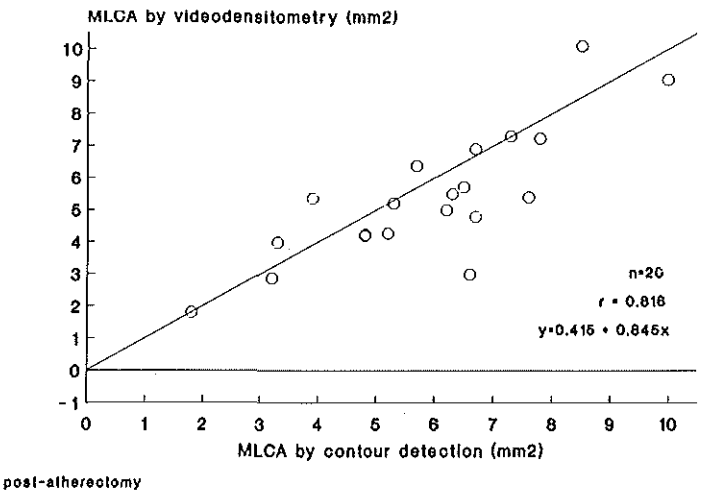

Figure II: Comparison of the post-atherectomy minimal luminal cross-sectional area (MLCA) as assessed by contour detection and videodensitometry. The line represents the line of identity. After atherectomy a slight deterioration in the relationship is found as is expressed by a lower correlation coefficient (0.816). The regression equation was: y = 0.415 + 0.845x.

The minimal luminal cross-sectional area increased after atherectomy from 1.12 ± 0.72 mm^2 to 5.91 ± 1.95 mm^2 ($p < 0.0001$). In patient 15, a coronary artery side branch ran parallel to the stenotic coronary artery and contributed to an increase in the background brightness value. Subtraction of this increased background contribution yielded a negative cross-sectional absorption profile at the site of the coronary artery obstruction. Before atherectomy, correlation coefficient was 0.914 (95% confidence interval: 0.791 to 0.966) indicating a reasonable linear relationship between the two techniques. However this deteriorated slightly following atherectomy resulting in a correlation coefficient of 0.816 (95% confidence interval: 0.584 to 0.924). The agreement between the two measurements is illustrated in Table 2 and Figures III and IV. The mean difference of the minimal cross-sectional area between the two methods before atherectomy was -0.01 mm^2 while this difference was slightly larger after atherectomy (mean difference 0.48 mm^2). The variability as determined by the standard deviation of the between-method difference was higher in the post-atherectomy analysis (1.21 mm^2) compared to the pre-atherectomy analysis (0.52 mm^2).

The use of quantitative angiographic analysis for assessing both the immediate and long-term results of interventional techniques appears mandatory. Whether edge detection or the videodensitometry should be used as the gold standard continues to be debated. Densitometry has been proposed as an alternative method of quantitative assessment of the severity of coronary stenosis. It is based on the linear relationship that exists between the optical density of a contrast enhanced lumen and the absolute dimensions of the arterial segment, and is therefore independent of the geometric shape. Discrepancies between edge detection and videodensitometry are most likely to occur when the shape of the vessel wall at the level of the stenosis deviates furthest from a circular configuration, since it is a basic assumption in the calculation of minimal luminal cross-sectional area by edge detection [2]. Previous angioplasty studies have shown discrepancies in the post-balloon analysis between edge detection and videodensitometry [2]. Since the cutting mechanism of atherectomy is expected to remodel the treated coronary artery into a more concentric and circular configuration, densitometry should correlate closely with the cross-sectional area measurements derived from edge detection.

Since comparing 2 methods in clinical practice should not only be limited to the assessment of the strength of the relation (correlation coefficient,r) [8], we also included the assessment of the degree of agreement or variability which is determined by the mean and the standard deviation of the between-method difference. This comparative study illustrates that a linear relationship exists between the 2 methods both before and after atherectomy. However it must be emphasized that the strength of the relationship deteriorates slightly after atherectomy.

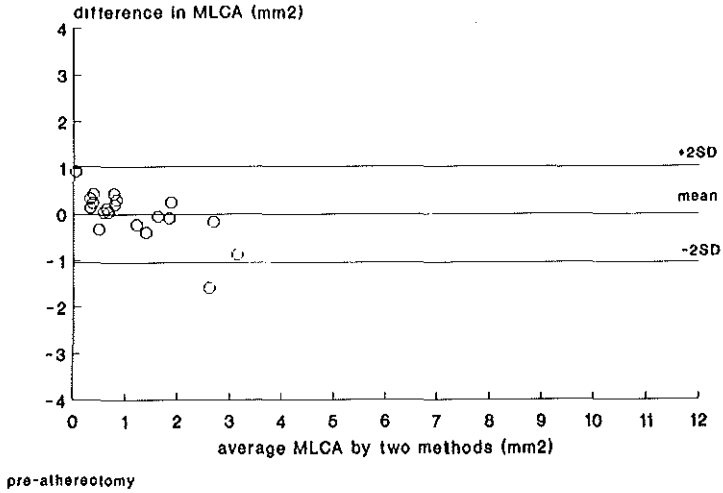

Figure III: Individual data of the average minimal cross-sectional area (MLCA) before atherectomy assessed by edge detection and videodensitometry versus the difference in cross-sectional area between the methods. The mean difference before atherectomy was -0.01 mm².

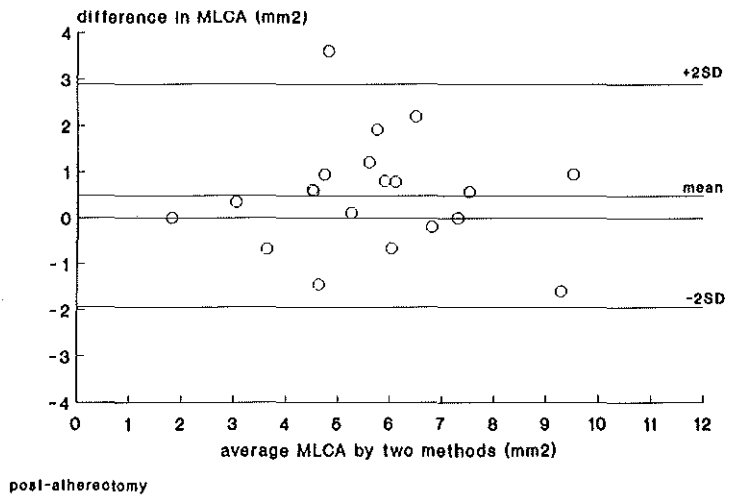

Figure IV: Comparison of the average minimal cross-sectional area (MLCA) after atherectomy by two methods (edge detection and videodensitometry) versus the difference in cross-sectional area between the methods. After atherectomy the difference was slightly higher (0.48 mm²). The variability was larger in the post-atherectomy analysis compared to pre-atherectomy.

Overall a good agreement exists between the two methods, although edge detection slightly underestimates the minimal luminal cross-sectional area before atherectomy and overestimates the minimal cross-sectional area after atherectomy.

Table 2. Minimal luminal cross-sectional area derived from edge detection and videodensitometry before and after coronary atherectomy

	Minimal cross-sectional area (mm^2) pre-atherectomy			Minimal cross-sectional area (mm^2) post-atherectomy		
pt	ED	VD	Difference	ED	VD	Difference
1	0.70	0.66	0.04	7.60	5.40	2.20
2	1.00	0.56	0.44	6.70	6.90	-0.20
3	0.40	0.26	0.14	6.20	5.00	1.20
4	0.50	0.16	0.34	7.30	7.30	0.00
5	1.10	1.33	-0.23	10.0	9.06	0.94
6	1.60	1.65	-0.05	6.60	2.99	3.61
7	0.60	0.56	0.04	3.20	2.86	0.34
8	0.92	0.67	0.25	4.81	4.22	0.59
9	0.49	0.25	0.24	4.80	4.19	0.61
10	2.70	3.58	-0.88	6.50	5.72	0.78
11	2.00	1.75	0.25	3.90	5.35	-1.45
12	0.70	0.58	0.12	5.70	6.37	-0.67
13	0.90	0.70	0.20	1.80	1.80	0:00
14	1.80	3.4	-1.60	3.30	3.98	-0.68
15	0.50	-0.42	-1.60	3.30	3.98	-0.68
16	0.50	-0.42	0.92	7.80	7.23	0.57
17	0.60	0.17	0.43	6.30	5.50	0.80
18	1.20	1.60	-0.40	8.50	10.1	-1.60
19	1.79	1.88	-0.09	5.30	5.20	0.10
20	0.33	0.65	-0.32	6.70	4.79	1.91
		mean $\pm$ SD:	-0.01 $\pm$0.52		mean $\pm$ SD:	0.48 $\pm$ 1.21

Quantitative coronary angiography shows that a similar discrepancy exists in the post-atherectomy analysis between edge detection and videodensitometry when compared with the results in a previous balloon angioplasty study [2]. This observation suggests that edge detection and videodensitometry are equally acceptable methods to assess the results of interventional techniques although

small differences exists in the post-interventional analysis. The possible explanation for those differences in the post-interventional analysis is the occurrence of trauma to the vessel wall by the devices. This obviously results in the formation of intimal flaps and dissections with subsequent distortion of the vessel configuration. Secondly the recoil phenomenon as assessed after balloon angioplasty may play an important role [9]. Stent implantation apparently counteract these influences by acting as a scaffolding device and by its self-expanding property [10,11]. This suggests that the cutting mechanism of atherectomy and the baro-trauma of angioplasty result in similar eccentric vessel contours.

In conclusion, despite small differences in minimal luminal cross-sectional area in the post-interventional results, edge detection and videodensitometry are equally acceptable methods. Atherectomy as well as angioplasty induce substantial trauma to the vessel wall which result in a non-circular vessel configuration. The smoothing process of stenting results in more circular vessel contours compared to angioplasty and atherectomy.

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Chapter 3

THE MECHANISM OF DIRECTIONAL CORONARY ATHERECTOMY

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ABSTRACT

An attempt to assess the mechanism of directional coronary atherectomy was made using different methods of analysis. Quantitative coronary angiography was used as the golden standard to assess the immediate results of atherectomy. A comparative quantitative analysis of atherectomy and balloon angioplasty was made. To determine whether the post-atherectomy cross-sectional area is close to a circle, we compared the area measurements obtained by edge detection with those obtained by videodensitometry. Finally, the extent of a 'Dotter' effect was established by quantitative angiography following crossing the stenosis with the atherectomy device. For the purpose of this study, the results of the first 113 successful atherectomy procedures were reviewed. In matched lesions, directional atherectomy induced a greater increase in minimal luminal diameter than balloon angioplasty (1.6 mm versus 0.8 mm;$p < 0.0001$). However, 62% of this luminal improvement is due to a 'Dotter' effect induced by the bulky atherectomy device. Following atherectomy only a slight difference in cross-sectional area measurements between edge detection and videodensitometry (mean difference: 0.28 mm^2) is found. Histologic examination of an atherectomized coronary artery shows a near-circular post atherectomy area geometry. In conclusion, directional atherectomy is a very effective device with a substantially better initial result than balloon angioplasty. However, insertion of this bulky device itself causes a luminal enlargement due to the 'Dotter' effect that accounts for 62% of the luminal improvement.

INTRODUCTION

Directional coronary atherectomy has been introduced as a novel percutaneous technique for the treatment of coronary artery disease. The exact mechanism through which directional atherectomy enlarges the vessel lumen is under extensive investigation. As its name indicates, 'directional' atherectomy selectively removes the atheromatous plaque as the cutting device is directed towards the encroaching plaque. With plaque removal instead of remodelling, a greater gain in luminal area is expected. Furthermore the luminal lining may become smooth and the vessel wall may assume a more circular configuration. Based on quantitative coronary analysis, we [1] and others [2] have suggested that a non negligible 'Dotter' effect is part of the "angioplastic" process. Whether this effect is an important determinant of the final result has not been firmly established. Together with quantitative coronary angiography, histopathologic examination of atherectomy specimens and postmortem examination may also shed light onto the mechanism of directional coronary atherectomy. Therefore, to elucidate some of the mechanism of directional coronary atherectomy, we have reviewed most of the quantitative coronary angiographic data (videodensitometry and edge detection) and histologic information collected in two institutions.

METHODS

Atherectomy procedure:
From September 1989 through July 1991, 113 patients underwent a successful directional coronary atherectomy at the Thoraxcenter and St Luc Hospital. A successful procedure is defined by tissue retrieval and a visually assessed post-procedural diameter stenosis $<50\%$. Using a standard over the wire technique, an 11 French guiding catheter is positioned in the coronary ostium. All patients received 250 mg acetosalicylatic acid and 10,000 U heparin intravenously. Intracoronary injection of isosorbide dinitrate was performed to relieve any possible spasm. The atherectomy device, either 6 or 7 French, is advanced through the guiding catheter, slided over a guide-wire and positioned across the stenosis. After proper positioning the support balloon was inflated up to 0.5 atm, the cutter was retracted and balloon inflation pressure was increased to 2 to 3 atm. The driving motor was activated and the rotating cutter was slowly advanced to cut and collect the protruding atherosclerotic lesion in the collecting chamber located at the tip of the catheter. After each pass, the balloon was deflated and either removed or repositioned. On average, 5.8 (3-14) passes were performed across a stenosis.

Quantitative coronary analysis:

Edge detection. The quantitative analysis of the stenotic coronary segments were carried out with the computer assisted Cardiovascular Angiographic Analysis System (CAAS), which has been described in detail elsewhere [3-7]. In essence, boundaries of a selected coronary artery segment are detected automatically from optically magnified and video digitized regions of interest (512 x 512 pixels) of a cine-frame. Each individual catheter is measured by a micrometer and used as a scaling device. Correction for pincushion distortion was performed. The computer-estimation of the original dimension of the artery at the site of the obstruction was used to define the interpolated reference diameter. The percentage diameter and area stenosis as well as the minimal cross-sectional area of the narrowed segment are then derived by assuming a circular model and comparing the observed stenosis dimensions to the reference values. The angiographic analysis was done using the average of multiple matched views with orthogonal projections whenever possible.

Videodensitometry. To determine the changes in cross-sectional area of a coronary segment from the density profile within the artery, the calibration of the brightness levels in terms of the amount of X-ray absorption (Lambert Beer's Law) is required. Details of this technique have been described elsewhere [3-7]. 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 the cine-films of perspex models of coronary obstructions [6].

Matching process:

Out of the initial cohort of 113 patients, fifty-one atherectomy patients (group A) were individually matched with 51 patients who underwent conventional balloon dilatation. The matching proces has been described earlier [1]. Briefly, the lesions were matched by location and quantitative angiographically determined reference diameter and minimal luminal diameter.

Edge detection versus videodensitometry:

In 29 patients (group B), edge detection and videodensitometry were used to evaluate the immediate results of the atherectomy. The change in minimal cross-sectional area before and after the procedure was determined by both methods and subsequently compared.

"Sham" atherectomy:

In 10 consecutive patients (group C) quantitative coronary angiography was performed before atherectomy, after crossing the stenosis with the device and after directional atherectomy.

Histopathology following atherectomy:

Post-mortem examination was available from 1 patient who died 2 days after a successful atherectomy procedure as a result of a delayed rupture of the right

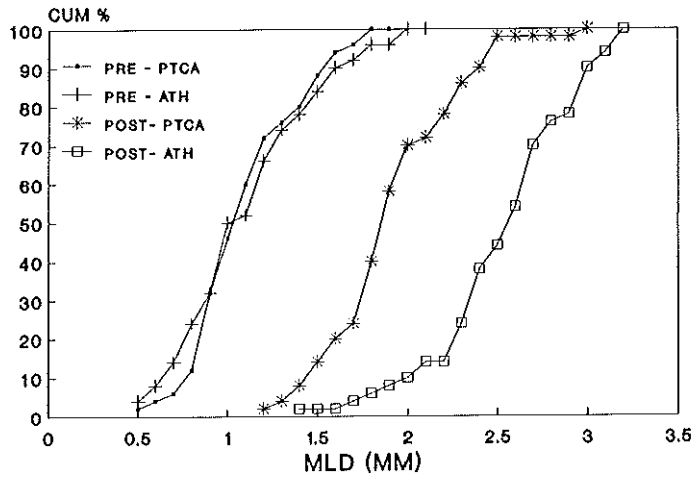

Figure I: Cumulative distribution of the minimal luminal diameter in 51 patients who underwent either atherectomy or balloon angioplasty. Atherectomy resulted in a superior immediate luminal improvement.

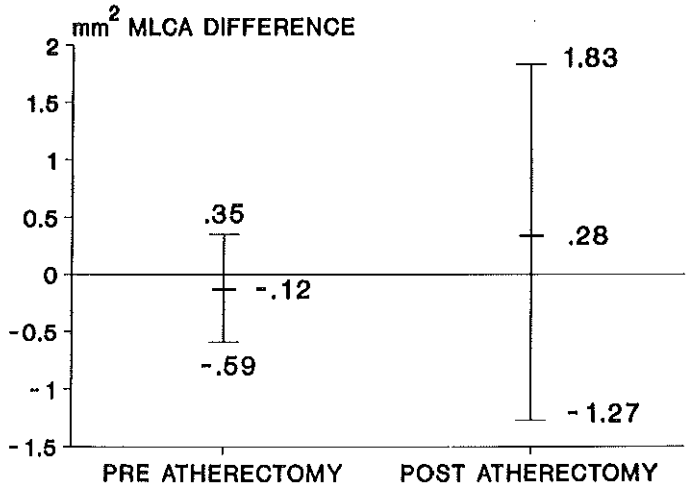

Figure II : Individual data of the average minimal cross-sectional area (MLCA) before and after atherectomy assessed by edge detection and videodensitometry versus the difference in cross-sectional area between the methods. The mean difference before atherectomy was -0.12 mm², this slightly increased to 0.28 mm² after atherectomy.

coronary artery which resulted in a tamponade leading to the death of the patient [8]. Post-mortem examination revealed a fissure of the atherectomized vessel.

RESULTS

Atherectomy versus balloon angioplasty:
The pre-procedural stenosis characteristics of the matched patients (group A) are summarized in table 1. The immediate efficacy of atherectomy and angioplasty as assessed by quantitative angiography are detailed in figure 1.

Table 1. Matched pre-procedural stenosis characteristics of 37 patients with successful coronary atherectomy compared to successful balloon angioplasty

	Pre-atherectomy	Post-atherectomy
Reference diameter (mm)	3.0 ± 0.6	3.0 ± 0.6
Minimal luminal diameter (mm)	1.1 ± 0.4	1.1 ± 0.3
Diameter stenosis (%)	64 ± 10	63 ± 9
Area plaque (mm^2)	9.1 ± 6.0	8.4 ± 4.6
Curvature value	15.9 ± 7.0	22.2 ± 13.1 *
Symmetry index	0.5 ± 0.3	0.5 ± 0.4

* = p-value <0.02.

As expected atherectomy and balloon angioplasty significantly improved the minimal lumen diameter (1.1 ± 0.4 mm to 2.7 ± 0.4 mm;$p<0.0001$ vs 1.1 ± 0.3 mm to 1.9 ± 0.4 mm;$p<0.001$). Immediately following atherectomy, the increase in minimal lumen diameter was superior compared to conventional balloon angioplasty (1.6 vs 0.8 mm;$p<0.0001$).
Edge detection versus videodensitometry:
In group B, the minimal luminal cross-sectional area (MLCA) as determined by densitometry was compared with the minimal luminal cross-sectional area measurements from edge detection which assumes a circular configuration. Analysis of variance was performed to compare the area measurements derived from edge detection and densitometry before and after atherectomy and when significant differences were found, two-tailed paired T-tests were applied. A statistical probability of <0.05 was considered significant. The agreement between the two methods was assessed by determining the mean and the standard deviation of the between-method difference as suggested by Bland and Altman [9]. The comparative data before and after coronary atherectomy in group B are shown in figure II. The minimal luminal cross-sectional area as determined by videodensitometry increased after atherectomy from 1.03 ± 0.77 mm^2 to 5.18 ± 1.64 mm^2 ($p<0.0001$). The mean difference of the minimal cross-sectional area

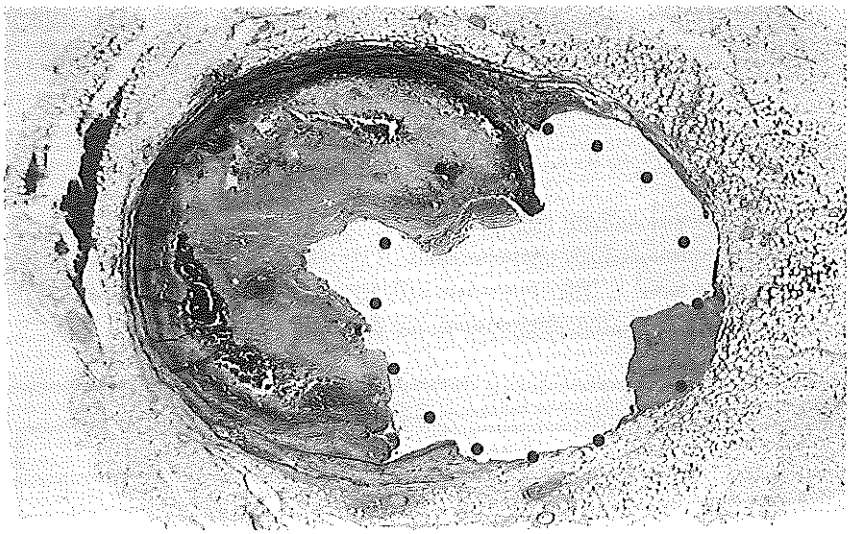

Figure III A: Histologic cross-section of the atherectomized coronary artery at the level of directional atherectomy (Haematoxylin-Azophloxine; original magnification x 12.). As indicated by the short and long axis measurements there is only a slight deviation from a circle. The arrow indicates the thrombus at the site of the fissure. (Reproduced from van Suylen (8) with permission).

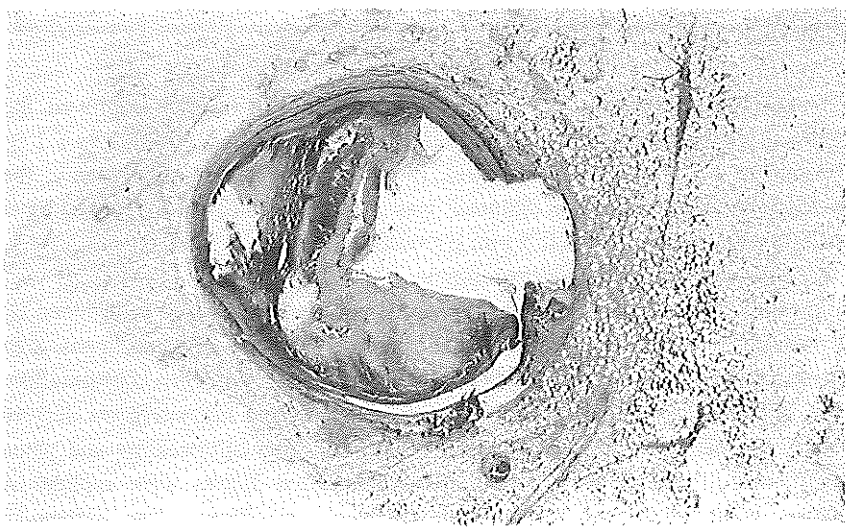

Figure III B: Histologic cross-section of the atherectomized artery following a single passage with the atherectomy device and subsequent excision of the atherosclerotic plaque (Haematoxylin-Azophloxine; original magnification x 12.). The directional cutting resulted in a small resection of quadrangular appearance. (Reproduced from van Suylen (8) with permission).

between the two methods before atherectomy was -0.12 mm^2 while this difference was slightly larger after atherectomy (mean difference 0.28 mm^2). The variability as determined by the standard deviation of the between-method difference was higher in the post-atherectomy analysis (1.55 mm^2) compared to the pre-atherectomy analysis (0.47 mm^2) suggesting that atherectomy induces a near-circular lumen area configuration. Quantitative analysis of the atherectomy device showed an increase of its diameter from 2.0 ± 0.2 mm to 3.4 ± 0.4 mm following inflation of the support-balloon.

"Sham" atherectomy:

The extent of the 'Dotter' effect as assessed by quantitative angiography in 10 consecutive patients of group C is summarized in table 2. The 'Dotter' effect accounts for 62% of the luminal improvement.

Table 2. Quantitative assessment of the "Dotter" effect during directional coronary atherectomy.

	Pre-atherectomy	Dotter effect	Post-atherectomy
Reference diameter (mm)	3.46 ± 0.36	3.34 ± 0.39	3.61 ± 0.31
Minimal luminal diameter (mm)	0.97 ± 0.32	1.85 ± 0.37	2.38 ± 0.33
Diameter stenosis (%)	71 ± 8	43 ± 8	34 ± 6

Histopathology:

A histologic cross-section of the atherectomized coronary artery of the patient who died after the procedure shows that all 3 layers of the vessel wall had been resected while the obstructive plaque remained unchanged (figure III).

DISCUSSION

In this report we used 4 different methods of analysis (edge detection, videodensitometry, matching and histology) to elucidate the mechanism of directional coronary atherectomy. Using our matching technique, we clearly showed that directional coronary atherectomy results in a superior immediate angiographic enlargement of the luminal area when compared to conventional balloon dilatation. These findings are in accordance with the observations reported by Muller et al [10]. Plaque removal and remodelling rather than remodelling alone can be accounted for this superiority. However, we demonstrate that the introduction of the bulky atherectomy device is associated with a substantial "Dotter" effect. This report shows that 62% of the luminal improvement is due to a "Dotter" effect and thus supports the findings of Penny et al [2] who could only retrieve 30% of the expected amount of atherosclerotic tissue which indicates the complementary role of the cutting action to the dilating action of the atherectomy device. Videodensitometry has been suggested as a superior

alternative to edge detection for the post-interventional analysis since it is independent of geometric shape. Comparing these two techniques of quantitative analysis provides information regarding the luminal area geometry after coronary atherectomy. Discrepancies between videodensitometry and edge detection are most likely to occur when the cross-section of the vessel wall deviates furthest from a circular configuration since this is a basic assumption using edge detection. Because atherectomy selectively removes the atherosclerotic plaque, it is expected that the vessel wall after atherectomy is less disrupted and therefore theoretically may assume a configuration which is close to a circle. Following atherectomy, only a small discrepancy in minimal luminal cross-sectional area between edge detection and videodensitometry is found which means that the post-atherectomy vessel lumen is close to a circle. Indeed, this study tends to demonstrate that atherectomy results in a relative circular lumen area configuration. This finding is at variance with the clover-leaf post-atherectomy lumen area configuration as proposed by Penny [2]. If this clover-leaf configuration as hypothesized by Penny et al [2] was a predominant feature following atherectomy, than our cross-sectional area measure derived from videodensitometry would be inferior to the measurement derived from edge detection since edge detection would overestimate the cross-sectional area: the largest diameter of this trilobated lumen would be interpreted as the diameter of a perfect circle, irrespective of the angiographic view in which it is filmed. Our study offers an alternative explanation for the change in vessel configuration after atherectomy: insertion of the bulky atherectomy device itself causes a lumen enlargement due to the 'Dotter' effect and a symmetrical stretching of the vessel wall as a result of its cylindric dimensions. Subsequent inflation of the support balloon with an increase in diameter from 2.0 mm to 3.4 mm and activation of the debulking device may lead to further luminal improvement by stretching of the non diseased vessel wall and excision of the encroaching plaque. Indeed we demonstrate that 62% of the luminal improvement achieved by directional atherectomy results from a 'Dotter' effect when crossing the stenotic lesion with the housing of the device. For ethical reasons protocol design including a balloon inflation of the support balloon has not been carried out, although it would presumably demonstrate that the balloon inflation with or without activation of the cutter also considerably contributes to the already observed amount of "Dotter" effect. Finally, the histologic cross section at the level of atherectomy (figure III) shows a relative circular post-atherectomy area geometry and not a clover-leaf geometry although directional cutting sometime results in a small resection of quadrangular appearance.

In conclusion, directional atherectomy results in a superior immediate angiographic result when compared to balloon angioplasty. However, using 4 different analytical approaches we demonstrate that a 'Dotter' effect accounts for 62% of the luminal improvement. Future developments should therefore be aimed at reducing the bulky design thereby limiting the need of balloon inflations.

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Chapter 4

COMPARATIVE ANGIOGRAPHIC QUANTITATIVE ANALYSIS OF THE IMMEDIATE EFFICACY OF CORONARY ATHERECTOMY WITH BALLOON ANGIOPLASTY, STENTING AND ROTATIONAL ABLATION

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ABSTRACT

Interventional cardiology has branched in two directions: devices that primarily dilate coronary stenoses and those that debulk coronary tissue. Presently the optimal coronary intervention has not been found. While awaiting randomized trials, a comparison based on matched quantitative coronary analysis may be useful to evaluate results of new interventional techniques. Therefore we compared 51 atherectomy patients with individually matched PTCA and stent patients. The lesions were matched according to stenosis location and reference diameter. Atherectomy and stenting resulted in larger gains in lumen diameter compared to conventional balloon angioplasty. The minimal luminal diameter was increased from 1.2 $\pm$ 0.4 mm to 2.6 $\pm$ 0.4 mm in the atherectomy group and from 1.2 $\pm$ 0.5 mm to 2.5 $\pm$ 0.4 mm in the stent group compared to an increase from 1.2 $\pm$ 0.3 mm to 1.9 $\pm$ 0.4 mm in the angioplasty group ($p < 0.00001$). Atherectomy and stenting resulted in a similar gain in minimal luminal diameter (1.4 mm versus 1.3 mm, p=NS).

In addition, atherectomy and stenting appear to be more effective devices in resisting elastic recoil due to an intrinsic dilating effect and tissue removal respectively.

In matched populations, directional atherectomy and stenting appear to be more effective intracoronary interventional devices than balloon angioplasty based on the immediate result. However, atherectomy is limited in smaller coronary vessels by its larger size.

INTRODUCTION

Directional atherectomy has recently been introduced as an alternative to conventional balloon dilatation [1]. It has been shown to be safe and effective when applied in human coronary arteries [2,3]. It was initially hypothesized that removal of the atherosclerotic plaque would result in a better immediate result with fewer acute complications and a reduced restenosis rate compared to conventional balloon angioplasty [4]. However, at the present time, it is difficult to compare the respective merits of various mechanical interventions since no randomized studies have been attempted. While awaiting these trials we utilized information from our quantitative angiography database to compare patients treated with various coronary interventions. Coronary lesions from 51 patients who underwent directional atherectomy were analyzed with the computer-based coronary angiography system and matched with similar lesions treated with balloon angioplasty, intracoronary stenting and rotational ablation. The immediate results from geometric assessment of the stenotic lesion by edge detection before and after atherectomy are presented and compared with the results of conventional balloon angioplasty, intra-coronary stenting and rotational ablation.

METHODS

Patient group:
From September 1989 through September 1990, 51 patients (43 men and 8 women) underwent an atherectomy procedure for symptomatic coronary artery disease. Three patients underwent two procedures and one patient had three procedures. The atherectomy procedure was successful in 54 of the 56 procedures (post-procedural diameter stenosis $< 50\%$). The mean age ($\pm$SD) was 58.2 ($\pm$10.1) years. At the time of atherectomy 21 patients were in New York Heart Association functional class IV, 11 in III and 19 in II. Coronary angiography showed single vessel disease in 39 patients, two-vessel disease in 8 and three-vessel disease in 4. The site of obstruction was located in the left anterior descending coronary artery in 31 patients, in the right coronary artery in 13 cases, in the circumflex artery in 9 cases and in the venous bypass graft in 3 cases.
Atherectomy Procedure:
After administration of local anaesthesia, a 11 French sheath was inserted into the femoral artery. All patients received 250 mg acetylsalicylic acid and 10,000 U heparin intravenously. Intracoronary injection of isosorbide dinitrate was performed to minimize any possible spasm. After initial angiograms in multiple views were made, a special 11 French guiding catheter was placed into the ostium of the coronary artery. Under fluoroscopy the guide-wire was advanced into the distal part of the artery. Then, the atherectomy device was directed over the

guide-wire and positioned across the stenosis. The support balloon was then inflated up to 0.5 atm, the cutter was retracted and balloon inflation pressure was increased to 2 to 3 atm. The driving motor was activated and the rotating cutter was slowly advanced to cut and collect the protruding atherosclerotic lesion in the collecting chamber located at the tip of the catheter. After every pass the balloon was deflated and either removed or repositioned. On average 6.1 $\pm$ 2.9 passes in multiple directions were performed across a stenosis. Atherectomy was considered successful when the residual stenosis was less than 50% after tissue retrieval. Following atherectomy, the arterial and venous sheaths were usually left in place for 6 hours. Patients were monitored for 24 hours and electrocardiograms and cardiac enzyme levels were obtained twice a day. Nifedipine was given every 2 hours after the procedure and the patients were kept on aspirin medication for one year.

Quantitative coronary angiography:

Quantitative analysis of the coronary segments was performed with the computer based Coronary Angiography Analysis System (CAAS), previously described in detail [5,6]. In essence, boundaries of a selected coronary artery segment are detected automatically from optically magnified and video digitized regions of interest (512 x 512 pixels) of a cine-frame. The absolute diameter of the stenosis in mm is determined using the guiding catheter as a scaling devise. Calibration of the catheter in absolute values (mm) is achieved by comparing the mean diameter of the guiding catheter in pixels with the measured size in millimeters. Each individual catheter is measured by a micrometer. To correct the detected contour of the arterial and catheter segments for pincushion distortion, a correction vector is computed for each pixel based on a computer- processed cineframe with a centimeter grid placed against the input screen of the image intensifier. Since the functional significance of a stenosis is related to the expected normal cross sectional area of a vessel at the point of obstruction, we use a computer-estimation of the original dimension of the artery at the site of the obstruction to define the interpolated reference area. The percentage diameter and area stenosis as well as the cross sectional area (mm^2) are then calculated. The length of the lesion (mm) is determined from the diameter function on the basis of a curvature analysis. Using the reconstructed borders of the vessel, the computer calculates the symmetry coefficient for the stenosis. The symmetry index ranges from 0 (totally eccentric stenosis) to 1 (symmetric). The degree of coronary bend is assessed by the curvature value at the obstruction site. This parameter 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.

Haemodynamic assessment:

The haemodynamic results were determined as described earlier [7,8,9,10].

Briefly, the theoretical pressure decrease was calculated using the arteriogram and digital computation, according to the formula: Pgrad = Q . (Rp + Q . Rt), where Pgrad is the theoretical transstenotic pressure decrease (mm Hg) over the stenosis, Q the mean coronary flow (ml/s), Rp the Poisseuille resistance and Rt the turbulence resistance. The theoretical trans-stenotic pressure decrease was calculated for a theoretical blood flow of 1, 2 and 3 ml/s. The Poiseuille and turbulence contributions to flow resistance were determined from stenosis geometry assessed by quantitative coronary angiography.

Matching process:

To avoid patient selection bias we selected populations with comparable base-line stenosis characteristics. The coronary artery tree was subdivided into 15 segments according to the American Heart Association guidelines. The lesions were individually matched according to stenosis location and reference diameter. Matching was considered adequate if the mean difference of the reference diameter between the groups were identical. Three patients who were treated for bypass graft stenosis and two patients with an unsuccessful procedure were excluded from the matching process. Thus 51 intra-coronary atherectomy lesions were individually matched with "twin" lesions treated by balloon angioplasty or self-expandable stent. The rotablator patient group was not individually matched since only 7 patients were included. Their results are represented as a group. Currently the Thoraxcenter angiographic registry contains quantitatively assessed stenosis data for 2300 patients either treated by angioplasty (n=1847), intra-coronary stenting (n=406), directional atherectomy (n=56) or rotational ablation (n=7).

Device profiles:

Atherectomy devices: In 50 of 51 atherectomy patients a 6 French catheter was used while in one case a 7 French atherectomy device was employed. The mean diameter of the atherectomy device was 2.1 mm by quantitative angiographic assessment.

Balloon-angioplasty: The transverse diameter of the deflated balloon is an important determinant as to whether a stenosis can be crossed. Currently used balloons have favorable profile characteristics as expressed by their small diameter (1.0 mm: ranging from 0.8 to 1.1 mm). The balloon sizes were matched to the reference diameter with the goal of achieving a ratio of 1:1 (inflated balloon diameter:artery diameter). The following balloon diameters were used in this study population: 2.0 mm (n=1), 2.5 mm (n=12), 3.0 mm (n=27), 3.4 mm (n=1), 3.5 (n=9) and 4.0 mm (n=1).

Stenting: The self-expanding stent is constrained on a small diameter-delivery catheter, but assumes its unconstrained larger diameter up to 6 mm when the constraining membrane is removed. The stent-catheter profile mounted on its delivery device is 1.57 mm [11]. In the 51 study patients the unconstrained diameters were 3.0 mm (n=5), 3.5 mm (n=29), 4.0 mm (n=9), 4.5 mm (n=1),

5.0 mm (n=3) and unknown in 4. The stent sizes were selected based on the size of the arterial segment, taking into account that the stent in its unconstrained form must have a diameter 0.5 mm. larger than the reference diameter of the stented vessel [11].

Rotational ablation: With rotational ablation the device consists of a rotating abrasive burr of variable profile characteristics (from 1.5 mm to 3.5 mm). In this series the largest burr size used was 2.25 mm. Choice of burr size was selected according to the reference diameter.

Quantitative assessment of the expansion ratio of the various devices:

Recently the concept of the expansion ratio has been addressed [12]. Briefly, the mechanism of all intra-coronary interventions may be divided in three stages. The first or "prefunctional stage", is characterized by the introduction of the device. The device is not yet operational and its intrinsic dimensions determine to which extent the device may be introduced into the coronary tree. During the introduction of a bulky device across a stenotic lesion, some degree of dilatation occurs as a direct result of a Dotter effect. The second or "operational stage", starts when the devices become operational and exhibit their specific mode of action (dilatation,cutting,ablation,vaporization). In becoming operational, the diameter of the device may expand (atherectomy, balloon, stent) or maintain its original dimensions (laser, rotational ablation). During this stage, the maximal effect of the device is achieved. The final result, after the removal of the device, is then determined by the recoil phenomenon and vascular reactivity. Consequently, the net luminal gain will be less than the initial gain when the device is operational.

To distinguish the acute effect of the various devices from the vascular reactivity and recoil phenomenon we subdivided the expansion ratio into the theoretical expansion ratio, which occurs during the "operational" stage, and the functional expansion ratio, which takes into account the elastic recoil phenomenon and describes the net result [13]. Both the theoretical and functional ratios were assessed for all interventional devices used in our study. The maximal achievable diameter of the vessel is calculated according to the diameter of the operational device while it is active. In case of balloon angioplasty and self-expandable stent, this corresponds to the diameter of the inflated balloon and to the unconstrained diameter of the self-expandable stent. For atherectomy, this was assessed by intra-coronary quantitative analysis during inflation of the support-balloon. The rotablator does not alter its diameter while operational. The post procedure diameter has been measured immediately following withdrawal of the device.

For example, when the diameter of an intra-coronary atherectomy device increases from 2.1 mm to 3.5 mm upon balloon inflation, the maximal achievable vessel diameter becomes 3.5 mm However the final luminal diameter at the end of the procedure measures 2.6 mm. Thus, the theoretical and functional expansion ratios are 1.7 (3.5/2.1) and 1.2 (2.6/2.1), respectively.

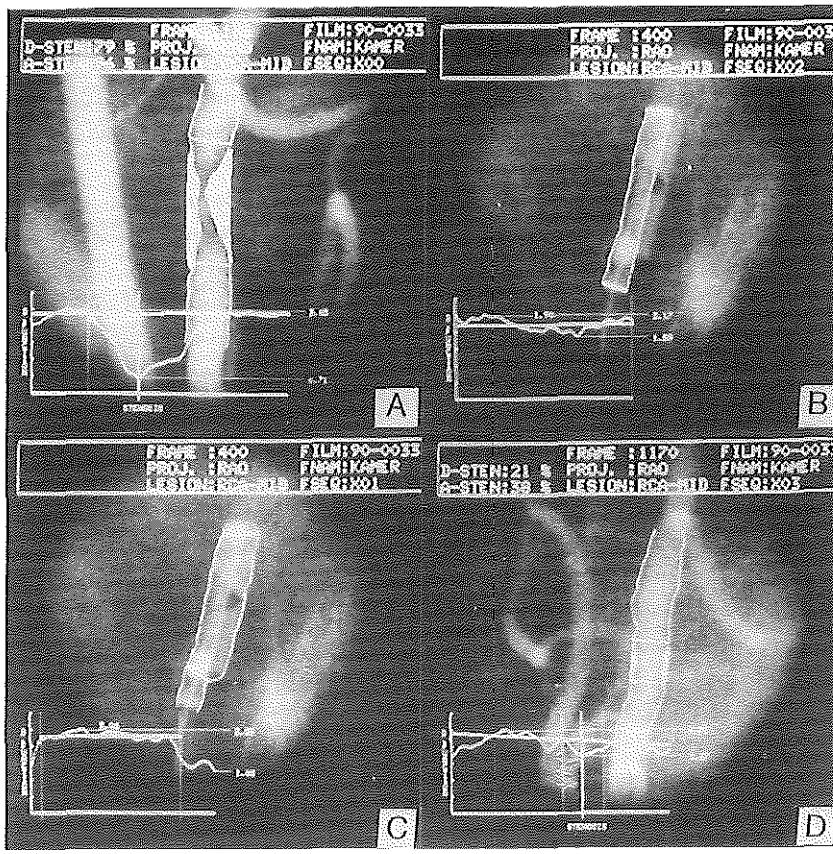

Figure Ia. Detected contours superimposed on the original video image for a representative right coronary artery stenosis, filmed in right (RAO) anterior oblique projection before directional atherectomy. The diameter function is shown at the bottom. The white area is a measure for the "atherosclerotic plaque". The minimal luminal diameter (verticle line) is 0.71 mm, corresponding to a diameter stenosis of 79% and an area stenosis of 96%.

Figure Ib. Contour analysis of the intra-coronary atherectomy device without inflated support balloon. This represents the first or "pre-functional stage" of an intra-coronary intervention which is characterized by the intrinsic diameter of the device.

Figure Ic. Contour analysis of the intra-coronary filmed atherectomy device with inflated support balloon. Beneath this is shown the diameter function. The mean diameter is 3.06 mm. This analysis represents the second or "operational stage" in which the atherectomy device exhibits its mode of action.

Figure Id. A single-frame angiogram of the right coronary artery filmed in RAO after directional atherectomy. The minimal luminal diameter increased to 2.27 mm, corresponding to a diameter stenosis of 21% and an area stenosis of 38%.

Statistical analysis.
All values are expressed as mean values ± 1 standard deviation. Morphologic and hemodynamic variables before and after atherectomy were compared by the paired Student's t-test. Comparisons of the severity of minimal luminal diameter, area plaque and diameter stenosis between the groups were performed using analysis of variance. If significant differences were found, the unpaired Student's t-test was applied. Differences were considered statistically significant at $p<0.05$.

RESULTS

Directional atherectomy:
Fifty-six lesions in 51 patients were studied and a mean of 1.4 angiographic projections per lesion were analyzed. The morphologic and hemodynamic data are presented in tables 1 and 2 respectively.

Table 1. Effect of directional coronary atherectomy on 55 obstructive lesions

	Pre-atherectomy	Post-atherectomy	p-value
Extent (mm)	6.4 ± 2.5	4.7 ± 2.1	<0.00001
Reference diameter (mm)	3.0 ± 0.6	3.2 ± 0.4	0.03
Minimal luminal diameter (mm)	1.1 ± 0.4	2.5 ± 0.5	<0.00001
Diameter stenosis (%)	63 ± 11	22 ± 15	<0.00001
Minimal cross-sectional area (mm^2)	1.1 ± 0.8	5.2 ± 1.8	<0.00001
Plaque area (mm^2)	8.8 ± 5.6	2.6 ± 2.1	<0.00001
Symmetry index	0.6 ± 0.3	0.7 ± 0.2	NS

The mean value for the minimal luminal diameter before and after atherectomy were 1.1 mm ± 0.4 mm and 2.5 mm ± 0.4 mm, respectively. This morphologic improvement was associated with a significant decrease in the calculated Poiseuille and turbulent resistance, as well as a theoretical trans-stenotic gradient decrease for a theoretical flow of 1 ml/s.
Atherectomy versus angioplasty and stenting:
Matching according to lesion distribution and reference diameter was considered adequate since the reference diameter was equal in all groups (3.0 ± 0.6 mm) while the mean difference for this parameter between the groups was 0.0 ± 0.1 mm. No pre-procedural differences were found between the atherectomy, PTCA and stent group in minimal luminal diameter (1.2 ± 0.4 mm vs 1.2 ± 0.3 mm vs 1.2 ± 0.5 mm), diameter stenosis (63 ± 10% vs 62 ± 10% vs 60 ± 12%), area plaque (8.8 ± 5.8 mm^2 vs 8.2 ± 4.5 mm^2 vs 8.4 ± 4.5 mm^2) and

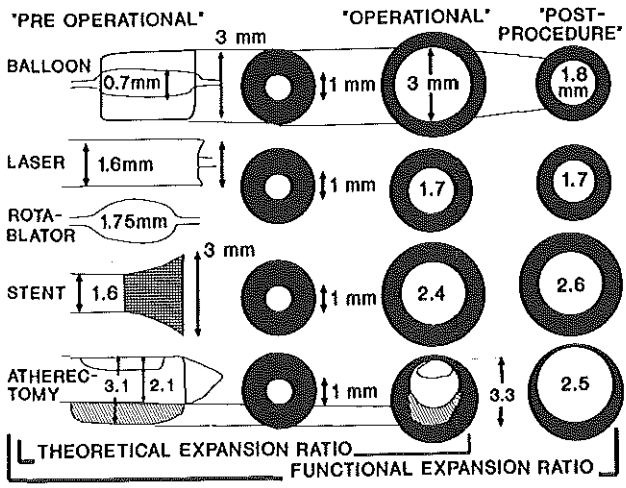

Figure 2. Schematic representation of the concept of functional and theoretical expansion ratio of the various intra-coronary intervention techniques. The first or "prefunctional stage", is characterized by the introduction of the device. In becoming operational some of the devices get expanded (atherectomy, balloon, stent) while others maintain their original dimensions (laser, rotational ablation). The end result is determined by the recoil phenomenon and vascular reactivity. After removing the device the maximal acute effect may be partially lost due to the elastic recoil of the vessel. The expansion ratio is subdivided into the theoretical expansion ratio, which is determined by the operational device, and the functional expansion ratio, which takes into account the elastic recoil phenomenon and describes the net result.

symmetry value (0.5 ± 0.3 vs 0.6 ± 0.3 vs 0.5 ± 0.2). Curvature value was less in the atherectomy group compared with the PTCA group (15.9 ± 7.0 vs 22.2 ± 13.1).

Table 2. Hemodynamic results immediately before and after directional coronary atherectomy

	Pre-atherectomy	Post-atherectomy	p-value
Poiseuille resistance (dynes s cm^{-5})	39.2 ± 124.8	0.30 ± 0.40	0.025
Turbulence resistance (dynes s cm^{-5})	20.6 ± 59.7	0.05 ± 0.17	0.013
Pressure gradient			
flow 1 ml/s	48.0 ± 154.5	0.40 ± 0.10	0.026
flow 2 ml/s	105.5 ± 380.9	0.60 ± 1.0	<0.01
flow 3 ml/s	197.5 ± 697.0	1.00 ± 1.60	0.042

Table 3 represents the changes in minimal luminal diameter, diameter stenosis and area plaque induced by presently available intra-coronary interventional devices as assessed by quantitative angiography in our institution. A significantly larger gain in lumen diameter was achieved by directional atherectomy and stenting compared with balloon angioplasty (1.4 mm and 1.3 mm versus 0.7 mm; $p<0.00001$). Rotational ablation resulted in the smallest luminal increment (1.2 ± 0.4 to 1.6 ± 0.1 mm).

Table 3. Comparative quantitative analysis of the immediate result of atherectomy, angioplasty and stenting

	Minimal luminal diameter (mm)	Area plaque (mm^2)	Diameter stenosis (%)
Atherectomy			
pre	1.2 ± 0.4	8.8 ± 5.8	63 ± 10
post	2.6 ± 0.4	2.6 ± 2.1	20 ± 11
PTCA			
pre	1.2 ± 0.3	8.2 ± 4.5	62 ± 10
post	1.9 ± 0.4*	5.3 ± 4.0	36 ± 11*
Stent			
pre	1.2 ± 0.5	8.4 ± 4.5	60 ± 12
post	2.5 ± 0.4**	3.5 ± 2.4**	20 ± 9**

*: $p<0.00001$ atherectomy vs PTCA, stent vs PTCA, **: p = not significant atherectomy vs stent

Quantitative analysis of the theoretical and functional expansion ratio:
Quantitative analysis of the intra-coronary atherectomy device shows a mean diameter of 2.1 mm which increases to 3.3 mm after inflation of the support balloon. Compared to the other devices, atherectomy has a larger catheter delivery system which limits the theoretical and effective expansion ratio (1.6 and 1.2 respectively). Balloon angioplasty and stenting give superior expansion ratios since they are introduced on smaller delivery systems. Rotational ablation had the lowest expansion ratio since the rotablator does not change in size while in operation (table 4).

Table 4. Quantitative assessment of the theoretical and functional expansion ratio of intra-coronary devices

	Balloon angioplasty	Self-expandable stent	Directional atherectomy	Rotational atherectomy
Device profile (mm)	1.0 (0.8 - 1.1)	1.6	2.1 (2.0 - 2.4)	2.0 (1.5 - 2.3)
Maximal achieved diameter (mm)	2.8 ± 0.5	3.3 ± 0.3*	3.3 ± 0.5	1.9 ± 0.4
Post-interventional diameter (mm)**	1.9 ± 0.4	2.5 ± 0.4	2.6 ± 0.4	1.6 ± 0.2
Theoretical expansion ratio	2.9	2.5	1.6	1.0
Functional expansion ratio	1.9	1.6	1.2	0.8

*: unconstrained stent diameter, **: assessed by quantitative coronary analysis

DISCUSSION

Over the past 5 years, there has been a rapid increase in the development of new interventional devices aimed to supplement conventional balloon dilatation. This progress in technology resulted in the introduction of directional coronary atherectomy, intra-coronary stenting, rotational coronary ablation and laser-assisted angioplasty. Clinical studies have demonstrated the feasibility and the safety of these interventions, however the relative efficacy of each technique remains to be assessed.

Edge detection versus videodensitometry:
The immediate efficacy of the various coronary interventions should be assessed by reproducible quantitative angiographic measurements [14]. Visual estimation of the stenosis severity alone results in unacceptable variation in the assessment of changes of coronary artery lesions. To obtain objective and reproducible values, a computer-assisted technique using automated edge detection or videodensitometry should be applied [15]. Whether edge detection techniques are inferior to videodensitometry remains an unresolved issue. A previous study from our group demonstrated that the edge detection method correlates well with densitometric analysis of the stenosis severity before angioplasty [5]. However after angioplasty, discrepancies between these types of measurements may be observed when using a single-plane view [16]. Recently we have shown that a linear relationship exists between the edge detection and videodensitometry both before and after atherectomy although the strength of this relationship deteriorates after atherectomy [17]. Therefore we felt justified to assess the immediate efficacy of coronary atherectomy by edge detection analysis.
Atherectomy versus angioplasty and stenting:
With an increasing number of interventional modalities, current indications and patient selection becomes difficult. This study demonstrates the important finding that atherectomy as well as stenting result in a larger increase in minimal luminal diameter compared to balloon angioplasty (1.4 and 1.3 mm versus 0.7 mm, $p < 0.00001$). In addition no differences in the post-interventional angiographic result were observed between atherectomy and stenting groups. This study confirms the findings of Muller [18] however, with our more refined matching technique, individual atherectomy lesions were directly compared to angiographically similar lesions treated by angioplasty or stenting. Although a randomized trial is the optimal method to compare the short and long-term results of new interventional techniques, matching based on quantitative analysis might become an acceptable alternative while awaiting these trials. Using this matching program we selected populations with comparable base-line stenosis parameters. The lesions were adequately matched since no differences were found in reference diameter, obstruction diameter, area plaque and symmetry index between the 3 groups. Whether the superior immediate results after atherectomy and stenting will be associated with a reduction in restenosis remains to be assessed in randomized trials.
Intra-coronary devices:
Expansion ratio is an important concept that relates the final effect of the intra-coronary device on the arterial diameter to the size of the catheter required to deliver this effect [12]. The maximal effect of the device may be partially lost due to the elastic recoil of the vessel. The expansion ratio has been subdivided into two components, theoretical and functional, to separate these influences [13]. Balloon angioplasty and stenting give extremely favorable theoretical and

functional expansion ratios (2.9 and 1.9 versus 2.5 and 1.6 respectively) since they may be delivered on low profile catheters. The directional atherectomy device is more limited by the size of the housing and collecting chamber. The dimensions of the rotational atherectomy device does not change during operation and therefore exhibits the lowest theoretical expansion ratio.

Although balloon angioplasty has the most favorable expansion ratio, the final result is profoundly influenced by the elastic recoil of the vessel [19,20]. Stenting and atherectomy appear to be more effective devices in resisting elastic recoil although the mechanisms are likely different. Stenting effectively prevents this recoil phenomenon presumably due to its scaffolding function and its intrinsic dilating effect [10,13]. By physically removing tissue, atherectomy appears to diminish the potential elastic recoil effect. However, the actual diameter of the atherectomy device limits its suitability in smaller coronary arteries.

Limitations:

There are several limitations of this study. First, it is an uncontrolled, retrospective observational study limited to a subset of patients who underwent a successful coronary intervention. Although matching for angiographic variables is a promising technique to assess the efficacy of intracoronary interventions, patient and procedure related variables should also be included in the analysis. Second, this study is based on the early experience with atherectomy and stenting. Future design changes and improved operator experience may further improve the immediate and long-term results. Finally, the efficacy of all intracoronary interventions will be limited by the restenosis problem which necessitates careful and complete angiographic follow-up. Thus controlled clinical trials are imperative in the future to determine the immediate angiographic result, the long-term efficacy of these interventions and if any benefit can be shown in particular patient subgroups.

Conclusions:

Quantitative angiographic assessment of the immediate result after directional atherectomy show significant improvement in stenosis geometry and hemodynamics. While awaiting randomized trials, matching based on quantitative analysis might become an acceptable alternative for objective and comparative assessment of various interventional techniques. In matched populations, directional atherectomy and stenting appear to be more effective intracoronary interventional devices than balloon angioplasty based on the immediate result however, atherectomy is limited in smaller coronary vessels by its larger size. Theoretically stenting has the most favorable characteristics as a dilating device although its clinical use is limited by its more complicated patient management.

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Chapter 5

COMPARATIVE QUANTITATIVE ANGIOGRAPHIC ANALYSIS OF DIRECTIONAL CORONARY ATHERECTOMY AND BALLOON CORONARY ANGIOPLASTY

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ABSTRACT

We have attempted to assess the "utility" of directional atherectomy, through a new quantitative angiographic index. This index can be subdivided into an initial gain component and a restenosis component. The *initial gain index* is the ratio between the gain in diameter during the intervention and the theoretically achievable gain i.e. the reference diameter. The *restenosis index* is the ratio between the loss at follow-up and the initial gain during the procedure. The net result at long term is characterized by the *utility index* which is the ratio between the final gain in diameter at follow-up and what theoretically could have been achieved. For this purpose, 30 coronary artery lesions were selected from a consecutive series of successfully dilated primary angioplasty lesions and were matched with the initial 30 successfully treated primary atherectomy lesions. Matching by stenosis location and reference diameter resulted in two comparable groups with identical pre-procedural stenosis characteristics. Atherectomy resulted in an increase in minimal luminal diameter twice larger than angioplasty (1.53 vs 0.77 mm;$p<0.0001$). At follow-up, however, there was a significant decrease in the minimal luminal diameter and a significant increase in percentage diameter stenosis in the atherectomy and angioplasty group (1.69 ± 0.58 vs. 1.57 ± 0.58 mm p=NS and 37 ± 18 vs. $47 \pm 18\%$ p=NS, respectively). The loss in minimal luminal gain was more pronounced in the atherectomy group when compared with the angioplasty group (0.92 ± 0.69 vs. 0.35 ± 0.51 mm; $p=0.0005$). Consequently, directional atherectomy resulted in a significantly higher initial gain ratio when compared with balloon angioplasty (0.84 versus 0.41;$p<0.00001$). At follow-up, the restenosis ratio and utility ratio were comparable in both groups (0.56 versus 0.62;p=NS and 0.29 versus 0.23;p=NS respectively). In matched populations, directional atherectomy is a very effective device with a substantially better initial result than can be achieved with balloon angioplasty. But it appears to be a potent stimulator of the restenosis process because at follow-up this initial favorable result is lost and the minimal luminal diameter is comparable to that after balloon angioplasty. Thus the final utility of directional coronary atherectomy is not significantly different from conventional balloon angioplasty.

INTRODUCTION

Restenosis after conventional balloon angioplasty remains the major limitation of this procedure [1-5]. Despite extensive efforts to elucidate this phenomenon our knowledge remains incomplete. In recent years studies have suggested that intimal hyperplasia is the major mechanism responsible for restenosis [6-9] and that lesion characteristics and regional flow dynamics are influencing this proliferative process [10]. Since improved operator experience and angioplasty techniques have not led to a reduction in restenosis rates, interventional cardiologists have designed new devices aimed at debulking instead of dilating the atherosclerotic plaque. Directional atherectomy is such a new technique with the potential advantage of creating smooth luminal surface. However early experience with atherectomy indicates that the restenosis rates are comparable to those following conventional balloon angioplasty although a randomized study has not been initiated [11-13]. Recently it has been demonstrated that the immediate results of atherectomy are superior to those achieved by balloon angioplasty [14]; whether this initial advantage can be maintained during follow-up and may ultimately result in a reduction of the restenosis rate remains to be assessed. Therefore, the present study was performed to determine whether this initial favorable result obtained with atherectomy affects the incidence of restenosis.

METHODS

Patient group:
From September 1989 through January 1991, 66 patients underwent 74 atherectomy procedures. For the purpose of this study, the initial 30 consecutive patients (23 men and 7 women) who underwent an angiographically successful procedure (post-procedural diameter stenosis $< 50\%$, with tissue retrieval) of a primary lesion in a native coronary artery were selected. The mean age ($\pm$SD) was 60.2 ($\pm$10.1) years. At the time of atherectomy 16 patients were in New York Heart Association functional class IV, 7 in III and 7 in II. Coronary angiography showed single vessel disease in 25 patients, two-vessel disease in 4 and three-vessel disease in 1. The site of obstruction was located in the left anterior descending coronary artery in 18 patients, in the right coronary artery in 7 cases, and in the circumflex artery in 5 cases.
Atherectomy Procedure:
After administration of local anaesthesia, a 11 French sheath was inserted into the femoral artery. All patients received 250 mg acetylsalicylic acid and 10,000 U heparin intravenously. Intracoronary injection of isosorbide dinitrate was performed to optimally vasodilate the vessel. After initial angiograms in multiple views were made, a special 11 French guiding catheter was placed into the ostium

of the coronary artery. Under fluoroscopy the guide-wire was advanced into the distal part of the artery. Then, the atherectomy device was directed over the guide-wire and positioned across the stenosis. The support balloon was then inflated up to 0.5 atm, the cutter was retracted and balloon inflation pressure was increased to 2 to 3 atm. The driving motor was activated and the rotating cutter was slowly advanced to cut and collect the protruding atherosclerotic lesion in the collecting chamber located at the tip of the catheter. After every pass the balloon was deflated and either removed or repositioned. On average 6.7 $\pm$ 2.9 passes in multiple directions were performed across a stenosis. Atherectomy was considered successful when the residual stenosis was less than 50% after tissue retrieval. Following atherectomy, the arterial and venous sheaths were usually left in place for 6 hours. Patients were monitored for 24 hours and electrocardiograms and cardiac enzyme levels were obtained twice a day. Nifedipine were given every 2 hours for 24 hours after the procedure and the patients were kept on aspirin medication for one year.

Follow-up evaluation:

After a successful atherectomy or angioplasty procedure (i.e. $<50\%$ post-procedural diameter stenosis on visual inspection), the patients were seen at the outpatient clinic. The follow-up coronary angiogram was performed within two weeks after an exercise test. Angiography was performed earlier if symptoms occurred within 6 months.

Quantitative coronary angiography:

Quantitative analysis of the coronary segments was performed with the computer based Coronary Angiography Analysis System (CAAS), previously described in detail [4,5,15,16]. In essence, boundaries of a selected coronary artery segment are detected automatically from optically magnified and video digitized regions of interest (512 x 512 pixels) of a cine-frame. The absolute diameter of the stenosis in mm is determined using the guiding catheter as a scaling device. Each individual catheter is measured by a micrometer and used as a scaling device. Correction for pincushion distortion was performed. The computer-estimation of the original dimension of the artery at the site of the obstruction to define the interpolated reference diameter. The percentage diameter and area stenosis as well as the cross sectional area (mm^2) are then calculated. The length of the lesion (mm) is determined from the diameter function on the basis of a curvature analysis (figure I). Symmetry is defined as the coefficient of the left hand distance between the reconstructed interpolated reference diameter and actual vessel contours and the right hand distance between reconstructed and actual contours at the site of the obstruction. The symmetry index ranges from 0 (totally eccentric stenosis) to 1 (symmetric). The degree of coronary bend is assessed by the curvature value at the obstruction site. This parameter 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

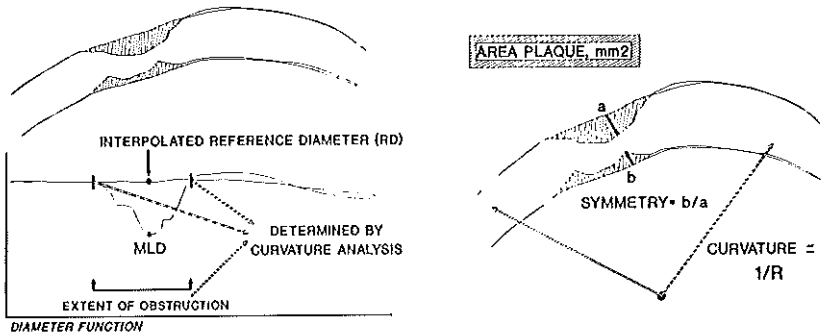

Figure I. Graphic illustration of the stenosis parameters obtained by quantitative coronary analysis. On the left, the y-axis represents the reference diameter and the vessel length is represented along the x-axis. The reference diameter and lesion length are determined by the diameter at the boundaries of the lesion which are defined by a curvature analysis. On the right, the curvature analysis is described. The curvature is defined by the rate of change of the angle through which the tangent of the curve turns and which for a circle is equal to the reciprocal of the radius (R).

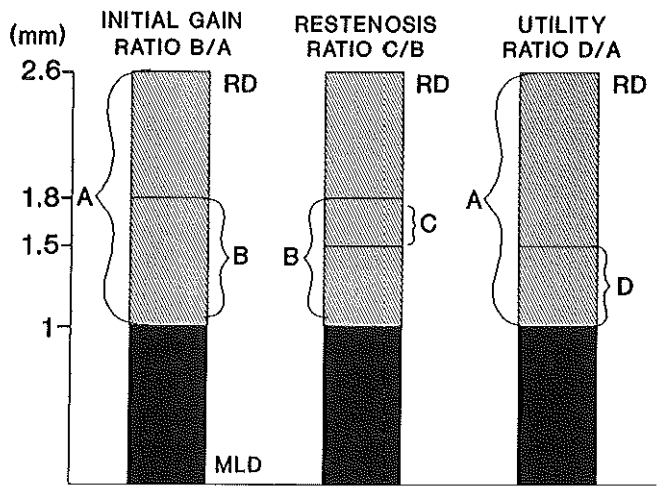

Figure II. Graphic illustration of the principle of the initial gain, restenosis and utility index. The initial gain index is represented by the ratio B/A; the restenosis index by the ratio C/B and the utility index by D/A. A represents the maximal achievable increase in minimal luminal; diameter (MLD), B the gain in MLD during the procedure, C the loss during follow-up, D the long-term result and RD the reference diameter.

moves along the centerline which for a circle is equal to the reciprocal of the radius. The area between the actual and reconstructed contours at the obstruction site is defined as the area plaque and is expressed in mm^2. To standardize the method of analysis of the interventional and follow-up angiograms, the following measures were taken [16]. First, the x-ray system was exactly positioned as was noted at the time of the intervention. Second, for all study frames to be analyzed were selected at end diastole to minimize foreshortening. Third, the user determined beginning and endpoint of a segment of a major coronary artery were identified according to the definitions of the American Heart Association [17]. Finally, Polaroid photographs were taken of the video image with the detected contours superimposed to ensure that the analysis was done on the same coronary segments in the consecutive angiograms. The balloon angioplasty patients were enroled in ongoing restenosis trials and therefore according to the protocol systematically received intracoronary nitroglycerine prior to angioplasty, following angioplasty and at follow-up catheterization whereas the atherectomy patients were less frequently given intra-coronary nitroglycerine at recatheterization.

Restenosis:

Two different criteria were used to define the restenosis rate. We have found a change in minimal lumen diameter of 0.72 mm. or more to be a reliable indicator of angiographic progression of vessel narrowing [4,15,16]. This value takes into account the limitations of coronary angiographic measurements and represents the long term variability for repeat measurements for a coronary stenosis using CAAS. The second criterion for restenosis chosen was an increase of the diameter stenosis from $<50\%$ after an intervention to $\geq 50\%$ at follow-up. The criterion was selected since clinical practice continues to assess lesion severity by percentage stenosis.

Assessment of initial gain, restenosis and utility ratio:

To compare the relative efficacy of various interventional techniques, it is critical to relate the procedural outcome and changes during follow-up to the maximal achievable result. Therefore we propose the use of the aforementioned ratios in the evaluation of intracoronary interventions. Briefly, quantitative angiographic changes following intra-coronary interventions may be divided in three stages as is summarized in figure II. The first or "operational stage", is characterized by the interaction of the operational device with the lesion. In becoming operational, the diameter of the device may expand (directional atherectomy, balloon, stent) or maintain its original dimensions (laser, transluminal extraction catheter, rotational ablation). During this stage, the maximal effect of the device is achieved and determines to which extent the minimal luminal diameter may be increased. The initial gain index represents the ratio between the achieved luminal improvement and the maximal achievable luminal improvement (reference diameter minus minimal lumen diameter (MLD) before intervention) and is

described by the following equation:

Initial gain index: change MLD at intervention / reference diameter - MLD pre intervention.

The initial gain index ranges from 0 (no effect) to 1 (no residual stenosis).
The second stage or "restenosis stage" starts during follow-up when biological processes determine the extent of intimal hyperplasia ultimately leading to a loss of luminal gain.
The restenosis index represents the ratio of the loss of lumen diameter improvement

during follow up and the achieved changes induced by the intra-coronary intervention and is described by the following equation:

Restenosis index: MLD post intervention- MLD follow up / change in MLD at intervention.

The restenosis index ranges from 0 (initial benefit intact) to 1 (initial benefit completely lost).
The utility index represents the ratio of the net gain in lumen improvement at follow-up and the maximal achievable luminal improvement and is described by the following equation:

Utility index: change in MLD at intervention - change in MLD at follow-up / reference diameter - MLD pre intervention.

The utility index ranges from 0 (no utility) to 1 (perfect result).
Matching process:
The coronary artery tree was subdivided into 15 segments according to the American Heart Association guidelines [18] and the lesions were individually matched according to stenosis location and reference diameter. The principles of matching are threefold: the angiographic dimensions of matched lesions are assumed to be "identical", the observed difference between the two "identical" lesions must be within the range of the CAAS analysis reproducibility of 0.1 mm (=1 SD)[5] and finally the reference diameter of the to be matched vessels are selected within a range of $\pm$ 0.3 mm (=3 SD; confidence limits 99%). To assess the immediate result of atherectomy and balloon angioplasty, 30 coronary artery lesions were selected by an independent technician from a consecutive series of successfully dilated balloon angioplasty lesions while complying with the selection criteria of matching. At the time of selection, the investigators were unaware of the 6-months angiographic outcome of these lesions and were thus blinded.

Matching was considered adequate if the mean difference of the reference diameter between the groups were equal to zero with a SD <0.3 mm [19]. Currently the Thoraxcenter angiographic database contains quantitatively assessed stenosis data for 2300 patients either treated by angioplasty ($n=1847$), intra-coronary stenting ($n=406$), directional and rotational atherectomy ($n=120$).

Statistical analysis:

All values are expressed as mean values $\pm$ 1 standard deviation. Comparisons of the severity of minimal luminal diameter, area plaque, diameter stenosis, curvature value symmetry index and length between the groups were performed using analysis of variance and the unpaired Student's T-test. Differences were considered statistically significant at $p<0.05$.

RESULTS

The pre-procedural stenosis characteristics of the matched patients are summarized in table 1. Matching for stenosis location and reference diameter resulted in comparable patient groups as far as severity of their lesions is concerned. Matching was considered adequate since the reference diameter was equal in both groups (3.03 $\pm$ 0.57 mm vs. 3.07 $\pm$ 0.55 mm; p=NS) while the mean difference for this parameter between the groups was 0.0 mm (sd 0.2 mm.).

Table 1. Matched pre-procedural stenosis characteristics of 30 patients with successful coronary atherectomy compared to successful balloon angioplasty

	Pre-atherectomy	Post-atherectomy
Reference diameter (mm)	3.03 $\pm$ 0.57	3.07 $\pm$ 0.55
Minimal luminal diameter (mm)	10.9 $\pm$ 0.37	1.15 $\pm$ 0.36
Diameter stenosis (%)	64 $\pm$ 10	63 $\pm$ 8
Area plaque (mm^2)	9.5 $\pm$ 6.4	8.4 $\pm$ 3.6
Curvature value	15.9 $\pm$ 7.0	22.2 $\pm$ 13.1*
Symmetry value	0.6 $\pm$ 0.2	0.5 $\pm$ 0.3
Length (mm)	6.8 $\pm$ 2.7	6.5 $\pm$ 2.6

*: $p<0.02$

Pre-procedural minimal lumen diameter in the atherectomy and angioplasty group were 1.09 $\pm$ 0.37 mm. and 1.15 $\pm$ 0.36 mm respectively. The other stenosis parameters (diameter stenosis, area plaque,symmetry index and length) did not differ significantly with the sole exception of the curvature value which was lower

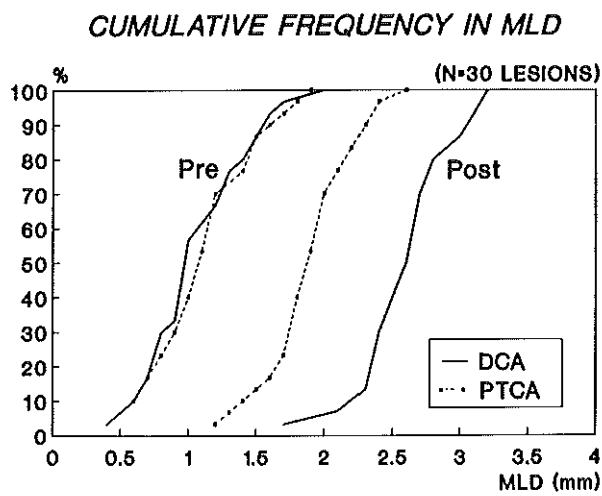

Figure III. Cumulative frequency of the immediate results of directional atherectomy and balloon angioplasty in 30 matched lesions. Directional atherectomy resulted in an increase in minimal luminal diameter (MLD) from 1.08 mm to 2.61 mm while angioplasty induced an increase from 1.15 to 1.92 mm. DCA = atherectomy, PTCA = angioplasty, pre = before intervention, post = after intervention.

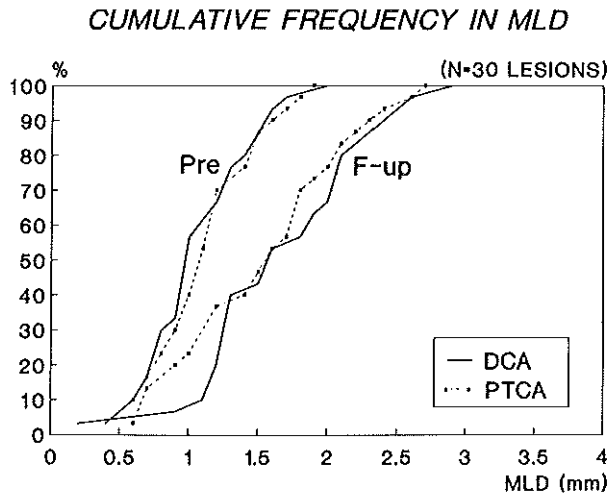

Figure IV. The cumulative frequency of the long-term results of directional atherectomy and angioplasty in this matched population. At 6 month follow-up the initial favorable result of atherectomy is lost when compared to balloon angioplasty. MLD = minimal luminal diameter, DCA = atherectomy, PTCA = angioplasty, pre = before intervention, F-up = at follow-up.

in the atherectomy group when compared with the angioplasty group (15.9 ± 7.0 vs 22.2 ± 13.1; $p<0.02$).

The immediate efficacy of atherectomy and angioplasty as assessed by quantitative angiography are detailed in table 2 and figure III. As expected, both atherectomy and balloon angioplasty significantly improved the minimal lumen diameter (1.08 ± 0.37 mm to 2.61 ± 0.33 mm;$p<0.0001$ vs 1.15 ± 0.36 mm to 1.92 ± 0.31 mm;$p<0.001$), but the increase in minimal lumen diameter was superior in the atherectomy group compared with the angioplasty group (1.53 vs 0.77 mm;$p<0.0001$). Accordingly, the initial gain ratio of atherectomy is also superior when compared with angioplasty (0.84 ± 0.36 vs. 0.41 ± 0.18;$p<0.00001$). The percentage diameter stenosis is thus reduced from 64 ± 10% to 19 ± 9% ($p<0.0001$) in the atherectomy group and from 63 ± 8% to 37 ± 10% ($p<0.001$) in the angioplasty group.

Table 2. Quantitative comparison of the immediate and long-term results of atherectomy with balloon angioplasty (n=30)

	Atherectomy	Angioplasty	t-test
Reference diameter pre (mm)	3.03 ± 0.57	3.07 ± 0.55	NS
Reference diameter post (mm)	3.24 ± 0.32	3.09 ± 0.56	NS
Reference diameter fup (mm)	2.81 ± 0.57	3.04 ± 0.65	NS
Minimal luminal diameter pre (mm)	1.08 ± 0.37	1.15 ± 0.36	NS
Minimal luminal diameter post (mm)	2.61 ± 0.33	1.92 ± 0.31	0.0000
Minimal luminal diameter fup (mm)	1.69 ± 0.58	1.57 ± 0.58	NS
Diameter stenosis pre (%)	64 ± 10	63 ± 8	NS
Diameter stenosis post (%)	19 ± 9	37 ± 10	0.0000
Diameter stenosis fup (%)	37 ± 18	47 ± 18	0.04
Difference in diameter stenosis (%)			
pre - post	45 ± 12	26 ± 12	0.0000
post - fup	18 ± 17	10 ± 17	NS

NS: non significant

At follow-up, all atherectomy and angioplasty patients included in this study underwent a 6-month control catheterization. Angiographic follow-up in the entire atherectomy and angioplasty populations were 95% and 92% respectively.

Angiographic analysis at follow-up (table 2 and figure IV) showed a decrease in minimal lumen diameter in both groups: from 2.61 ± 0.33 mm to 1.69 ± 0.58 mm in the atherectomy group and from 1.92 ± 0.31 mm to 1.57 mm ± 0.58 mm in the angioplasty group. Thus, the loss in minimal lumen diameter was more pronounced in the atherectomy group when compared with the angioplasty group (0.92 ± 0.69 mm vs 0.35 ± 0.51 mm; $p<0.0005$)
Accordingly, the percentage diameter stenosis increased from 19 ± 9% to 37 ± 18% in the atherectomy group and from 37 ± 10% to 47 ± 18% in the angioplasty group. The concomitant restenosis and utility ratios are tabulated in table III.

Table 3. Quantitative assessment of initial gain ratio, restenosis ratio and utility ratio after atherectomy and balloon angioplasty (n=30)

	Atherectomy	Angioplasty	t-test
Initial gain ratio	0.84 ± 0.36	0.41 ± 0.18	0.0000
Restenosis ratio	0.56 ± 0.55	0.62 ± 1.10	NS
Utility ratio	0.29 ± 0.33	0.23 ± 0.28	NS

NS: not significant, t-test: unpaired t-test

The percentage restenosis (detectable hyperplasia by quantitative coronary analysis) according to the 0.72 mm loss in minimal lumen diameter (which is twice the standard deviation of the long term variability of the minimal luminal diameter measurements using the coronary angiography analysis system (CAAS) criterion is 60% in the atherectomy group versus 36% in the angioplasty group. When restenosis is defined by an increase of diameter stenosis ≥50% at follow-up, the restenosis percentages are 20% and 16% (atherectomy versus angioplasty).

DISCUSSION

Coronary angioplasty is now an accepted form of treatment for patients with coronary artery disease. In the past years exponential growth in angioplasty has been partly the result of an increase of patients returning with restenosis. Despite extensive efforts in improving catheter equipment we are still unable to effectively reduce the rate of restenosis. Since no fundamental design-changes in balloon or balloon-derived catheter techniques are emerging, debulking techniques like directional atherectomy have been introduced in order to improve the angioplastic process and to presumably reduce the restenosis rate. The potential advantages of debulking atheromatous tissue over remodelling the plaque by balloon angioplasty include: minimize smooth muscle cell injury by wall stress, eliminate smooth muscle cells thereby reducing their proliferative potential, improve regional blood

flow and rheology by inducing less fissures or dissections, reduce radial stretch forces as applied with a dilating balloon and create larger gain in minimal luminal diameter. Indeed, recent studies have reported a larger increment in luminal improvement following atherectomy when compared with conventional balloon angioplasty [14] while other investigators observed a low incidence of post-procedural dissections [11,12,14].

Study design:

Whether atherectomy is superior to balloon angioplasty can only be assessed by a randomized study. This type of study would take several years during which continuing refinements and improvements of catheter systems would take place, rendering the comparison unreliable and open to criticism. Therefore, we proposed a matching technique based on stenosis location and reference diameter to compare the results of various intra-coronary interventional techniques. At present, this technique might be the best surrogate for a randomized trial when one tries to compare the short and long-term results of atherectomy with conventional angioplasty. Using our matching program we selected comparable stenotic lesions with respect to base-line characteristics (minimal luminal diameter, diameter stenosis,length, area plaque and symmetry index) as assessed by quantitative angiography. This study population reflects the base-line stenosis characteristics in patients treated by atherectomy [20] or balloon angioplasty [4,21].

Immediate results:

This study confirms the previous reports on improved luminal gain after atherectomy when compared with conventional angioplasty [14]. Atherectomy resulted in a two-fold increase in minimal lumen diameter from 1.09 $\pm$ 0.37 mm. to 2.61 $\pm$ 0.33 mm., compared with angioplasty (from 1.15 $\pm$ 0.36 mm to 1.92 $\pm$ 0.31 mm.). Accordingly, the percentage diameter stenosis decreased more dramatically after atherectomy than after angioplasty. This improvement in lumen gain by atherectomy may be due to three mechanisms: first, the introduction of the bulky device and subsequent inflation of the support balloon may result in a "Dotter effect", second its debulking action results in plaque removal rather than remodelling which finally reduces the extent of the elastic recoil phenomenon.

Restenosis:

Recurrence of a stenosis after an intra-coronary intervention may be assessed by clinical symptoms, stress testing or coronary angiography. Since symptoms and functional achievement at exercise testing have low predictive values in predicting restenosis, the diagnosis of restenosis should be based on reproducible quantitative angiographic measurements using a computer-assisted technique with either automated edge detection or videodensitometry. Furthermore, the definition of restenosis is a matter of ongoing debate. It has been shown by our group [4,22] as well as by others [3] that the determination of stenosis severity using percentage diameter stenosis does not reflect the changes following angioplasty

since the adjacent part of the dilated vessel may also be involved in the restenosis process or the reference diameter may be simultaneously reduced. Therefore, we selected minimal lumen diameter as a parameter for the morphologic changes after atherectomy or angioplasty.

The follow-up minimal luminal diameter for the atherectomy group is 1.69 mm compared with 1.57 mm for the balloon angioplasty group (p=NS). These findings are similar to previously documented late follow-up studies of coronary balloon angioplasty (1.69-1.82 mm) [4] and stenting (1.68 mm) [23]. Using the ≥50% diameter stenosis criterion, the restenosis rates after atherectomy and angioplasty are 20% and 16% respectively. Previous reports on restenosis after primary coronary atherectomy reported a restenosis incidence of 20% [11,12] using the ≥50% criterion.

Thus during follow-up, the initial greater gain in luminal diameter after atherectomy when compared with balloon angioplasty is totally lost. At follow-up the loss in minimal luminal diameter after atherectomy was 0.92 mm compared with 0.35 mm in the angioplasty group (p=0.0005). Although the minimal luminal diameter changes more dramatically in the atherectomy group when compared with the angioplasty group, both groups have an equal restenosis (0.56 versus 0.62;p=NS) and utility ratio (0.29 versus 0.23;p=NS) indicating that the relative changes are equal for both interventional techniques.

Animal and atherectomy studies [11-13,20] have demonstrated that fibrointimal hyperplasia may develop in coronary arteries previously treated by balloon angioplasty or atherectomy. Pathologic findings have raised a theory that deeper vascular injury is associated with a greater intimal proliferation. Injury beyond the subintimal level has been shown to be associated with more extensive intimal proliferation [24]. These data are supported by Webster [25] who found a greater smooth muscle proliferation after high inflation pressure with the same balloon size when compared to low pressures. Furthermore, an initial follow-up study after atherectomy indicates that this process may be accelerated when deep vessel wall components like media and adventitia are removed [13]. Additionally, atherectomy may lead to profound disrupture of the vessel wall architecture [26]. Finally, the introduction of the bulkier atherectomy device itself may potentially lead to a greater amount of vessel wall stretching when compared to the smaller balloon catheter system. All these influences may account for the greater cellular proliferation of the lesion treated by atherectomy.

Limitations:

There are several limitations of this study. First, it is an uncontrolled, observational study limited to a subset of patients with a successful coronary atherectomy or balloon angioplasty. This consecutive series of patients were studied by "blind" investigators unaware of the late angiographic results. Although matching for angiographic variables is a promising technique to assess the efficacy of intracoronary interventions, patient and procedure related variables

are not included in the analysis. Second, lesion complexity was not incorporated in the analysis. This is usually defined qualitatively [27] however, recently an objective and quantitative description of stenosis morphology has been introduced [28]. Further improvement in quantitative analysis may assess lesion morphology in a continuous scale fashion rather than assigning lesions to discrete categories. This type of analysis should be incorporated in future trials studying the efficacy of various interventional techniques. Third, this study is based on the early experience with atherectomy. Careful patient selection, future design changes and improved operator experience may further improve the immediate and long-term results. Thus controlled clinical trials are imperative in the future to determine the immediate angiographic result, the long-term efficacy of these interventions as well as the benefit, if any, in particular patient subgroups. These studies should also address the presumed time frame for restenosis after any particular intervention.

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Chapter 6

RESTENOSIS FOLLOWING DIRECTIONAL CORONARY ATHERECTOMY AND BALLOON ANGIOPLASTY: A COMPARATIVE ANALYSIS BASED ON MATCHED LESIONS

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ABSTRACT

Background. Directional coronary atherectomy has been introduced as an alternative technique for balloon angioplasty which may reduce the incidence of restenosis.

Objectives. Late luminal narrowing following directional atherectomy as assessed by quantitative coronary angiography and compared with balloon angioplasty.

Methods. A prospectively collected consecutive series of 87 successfully atherectomized native coronary artery lesions were matched with 87 coronary artery lesions selected from a consecutive series of lesions which had been successfully dilated by balloon angioplasty. Late angiographic analysis was performed in 158 lesions. The *net gain index*, represents the ultimate gain in minimal luminal diameter at follow-up, normalized for the vessel size. This index is the resultant of the *relative gain* attained during the procedure (the ratio of the change in minimal luminal diameter and reference diameter) and the relative loss observed during follow-up (the ratio of the change in minimal luminal diameter during follow-up and the reference diameter).

Results. Matching for clinical and angiographic variables resulted in two comparable groups with quite similar baseline stenosis characteristics. Atherectomy resulted in a more pronounced increase in minimal luminal diameter than balloon angioplasty (mean $\pm$ SD: 1.17 $\pm$ 0.29 mm to 2.44 $\pm$ 0.42 mm versus 1.21 $\pm$ 0.38 mm to 2.00 $\pm$ 0.36 mm;$p<0.001$), this favorable immediate result was subsequently lost during late angiographic follow-up so that the minimal luminal diameter at follow-up and the net gain index did not differ significantly between the two groups (1.76 $\pm$ 0.62 mm versus 1.77 $\pm$ 0.59 mm; $p=0.93$ and 0.18 $\pm$ 0.19 versus 0.17 $\pm$ 0.17;$p=0.70$). Consequently, the relative gain and relative loss were higher in the atherectomy group. For both techniques, the relative gain is linearly related to the relative loss but, the slope of the regression line is steeper for atherectomy suggesting that the relative loss is proportionally even larger for a given relative gain when compared to the balloon angioplasty group.

Conclusion. In matched populations, atherectomy induces a greater initial gain in minimal luminal diameter than balloon angioplasty however, the vascular wall injury induced by the device is of another nature (debulking versus dilating) which led to more relative loss over the follow-up period in the atherectomy group.

INTRODUCTION

Restenosis following intra-coronary interventions remains the most vexing limitation of these techniques [1-4]. In the past 5 years atherectomy, stenting and laser techniques have been introduced as an alternative or adjunct to balloon dilatation and as potentially safer techniques with better immediate and late results. Considerable difficulty exists in making valid comparisons between the different modalities with regard to outcome. We have previously shown that directional coronary atherectomy yields a superior immediate improvement in coronary luminal diameter than balloon angioplasty as judged by quantitative coronary angiography [4]. Because of the differing methods of action this discrepancy is not unexpected. Whether directional atherectomy indeed has a more favorable longterm result has not been proven. Therefore, we studied the longterm results following directional atherectomy and compared them with those of balloon angioplasty, as assessed by quantitative angiography. Since the restenosis phenomenon seems to be a systematic process affecting virtually every dilated stenotic lesion [2,3] it should therefore be assessed by a continuous analytical approach rather than applying categorical definitions of restenosis when the longterm results of two different types of interventions -such as directional coronary atherectomy and balloon angioplasty - need to be compared. For the purpose of this quantitative angiographic study, the initial consecutive 87 successfully treated de novo atherectomy lesions [83 patients) were matched (for clinical and quantitative angiographic variables) with 87 coronary artery lesions which were selected from a consecutive series of successfully dilated primary angioplasty lesions. Three recently conceived angiographic endpoints (minimal luminal diameter, relative gain versus relative loss and net gain index) at follow-up were assessed to compare the long-term results of directional coronary atherectomy and balloon angioplasty.

METHODS

Patient group:
From September 1989 through January 1992, 111 patients completed a six month follow-up period following 117 atherectomy procedures for coronary artery disease. Of these, 4 patients (4 lesions) had an atherectomy for bypass graft stenosis and 18 (19 lesions) underwent atherectomy for restenosis following a previous percutaneous intervention. For the purpose of this study, therefore, 89 patients (94 lesions) underwent an atherectomy procedure for native *de novo* coronary artery disease. However, during hospitalization one patient died as a result of tamponade [5], four patients (5 lesions) underwent emergency surgery following an unsuccessful procedure and one patient (one lesion) had surgery

because of presumed pericardial tamponade.

Ultimately, 83 patients with 87 *de novo* coronary artery lesions who underwent successful atherectomy were eligible for 6 month follow-up and were individually matched with patients undergoing successful balloon angioplasty. Late angiographic follow-up, and the final late comparative analysis, was obtained in 75 patients (90%) or 79 of 87 lesions (angiographic follow-up rate 91%) in each group. The mean age (±SD) of the 83 patients was 58 (±10) years. The site of obstruction (n=87) was located in the left anterior descending coronary artery in 56 cases, in the right coronary artery in 18 cases, and in the circumflex artery in 13 cases. Clinical and angiographic details of the matched groups are described in table 1.

Table 1. Patient and lesion demographics of the matched groups

	Atherectomy	Angioplasty	t-test
Lesion (no)	87	87	
Age (yr)	58 ± 10	57 ± 8	
% male	82	82	
Vessel treated (%)			
LAD	65	65	
RCA	19	19	
LCX	16	16	
Unstable angina (%)	43	43	
Diabetes (%)	3	3	
Hypercholesterolemia (%)	4	4	
Lesion length (mm)	6.4 ± 2.5	6.5 ± 2.4	NS
Area plaque (mm^2)	9.3 ± 6.8	9.2 ± 4.2	NS
Reference diameter (mm)	3.22 ± 0.60	3.18 ± 0.56	NS
Minimal luminal diameter (mm)	1.16 ± 0.38	1.19 ± 0.28	NS
Diameter stenosis (%)	64 ± 12	62 ± 8	NS
Reference area (mm^2)	8.72 ± 4.03	8.18 ± 2.75	NS
Area stenosis (%)	85 ± 10	86 ± 10	NS
Cross-sectional area (mm^2)	1.27 ± 0.94	1.11 ± 0.80	NS

Atherectomy Procedure:

The procedure was performed as described before [4], the atherectomy device was

directed over the guide-wire and positioned across the stenosis. The support balloon was then inflated up to 7.5 psi, the cutter was retracted and balloon inflation pressure was increased from 7.5 to 45 psi. The driving motor was activated and the rotating cutter was slowly advanced to cut and collect the protruding atherosclerotic lesion in the collecting chamber located at the tip of the catheter. After every pass the balloon was deflated and either removed or repositioned. On average 5.6 $\pm$ 2.2 passes in multiple directions were performed across a stenosis, resulting in tissue retrieval in all cases. Atherectomy was considered successful when the residual stenosis was less than 50% after tissue retrieval. Before and after the procedure, intracoronary nitroglycerine was administered to prevent coronary spasms. Pre-dilatation with a conventional balloon was performed in 2 patients and in 4 cases balloon angioplasty was performed following atherectomy for cosmetic reasons where there was persistent haziness after a successful atherectomy procedure. Following atherectomy, the arterial and venous sheaths were usually left in place for 6 hours. Patients were monitored for 24 hours and electrocardiograms and cardiac enzyme levels were obtained twice a day. Nifedipine was given every 2 hours for 24 hours after the procedure and the patients were maintained on aspirin medication for one year.

Follow-up evaluation :

After a successful atherectomy or angioplasty procedure (i.e. $<50\%$ post-procedural diameter stenosis on visual inspection), the patients were seen at one month for clinical evaluation at the outpatient clinic. An exercise test was performed within two weeks prior to the 6 month follow-up coronary angiogram. Angiography was performed earlier for symptomatic recurrence within 6 months.

Quantitative coronary angiography :

Quantitative analysis of the coronary segments was performed with the computer based Coronary Angiography Analysis System (CAAS), previously described in detail [1,4,6,7,8]. In essence, boundaries of a selected coronary artery segment are detected automatically from optically magnified and video digitized regions of interest (512 x 512 pixels) of a cine-frame. The absolute diameter of the stenosis in mm is determined using the guiding catheter as a scaling device. Each individual catheter is measured by a micrometer and used as a scaling device. Correction for pincushion distortion was performed. The computer-estimation of the original dimension of the artery at the site of the obstruction to define the interpolated reference diameter. The percentage diameter and area stenosis as well as the cross sectional area (mm^2) are then calculated. The length of the lesion (mm) is determined from the diameter function on the basis of a curvature analysis. Symmetry is defined as the coefficient of the left hand distance between the reconstructed interpolated reference diameter and actual vessel contours and the right hand distance between reconstructed and actual contours at the site of the obstruction. The symmetry index ranges from 0 (totally eccentric stenosis) to 1 (symmetric). The area between the actual and reconstructed contours at the

obstruction site is defined as the area plaque and is expressed in mm^2. To standardize the method of analysis of the interventional and follow-up angiograms, the following measures were taken [8]. First, the x-ray system was exactly positioned as was noted at the time of the intervention. Second, for all study frames to be analyzed were selected at end diastole to minimize foreshortening. Third, the user determined beginning and endpoint of a segment of a major coronary artery were identified according to the definitions of the American Heart Association. Finally, Polaroid photographs were taken of the video image with the detected contours superimposed to ensure that the same coronary segments were analyzed in the consecutive angiograms. At follow-up catheterization, the administration of intracoronary nitrates was recommended prior to angiography.

Categorical approach:

Two different criteria were used to define restenosis. We have found a change in minimal lumen diameter of 0.72 mm. or more to be a reliable indicator of angiographic progression of vessel narrowing [1,4,6-8]. This value takes into account the limitations of coronary angiographic measurements and represents the long term variability for repeat measurements for a coronary stenosis using CAAS. The second criterion for restenosis chosen was an increase of the diameter stenosis from $<50\%$ after an intervention to $\geq 50\%$ at follow-up since in clinical practice lesion severity is still assessed using percentage stenosis.

Continuous approach:

Three criteria were defined to assess the long-term efficacy of directional coronary atherectomy and balloon angioplasty using a continuous approach. We [2,9,10] and others [11] have found that the minimal luminal diameter at follow-up is associated with the onset of exercise induced thallium perfusion defects and symptoms. The second criterion relates - the gain achieved during an intervention and the observed loss during follow-up - to the vessel size, allowing a comparison between vessels of different sizes [9,12]. The relative gain is defined as the change in minimal luminal diameter (MLD) normalized for vessel size. The relative loss is defined as the change in minimal luminal diameter (MLD) during follow-up (fup) normalized for by vessel size.

Relative gain: MLD post - MLD pre / vessel size
Relative loss: MLD post - MLD fup / vessel size

The third criterion relates the final outcome of a procedure to the reference diameter. The net gain index represents the net gain in lumen improvement at follow-up normalized for vessel size and is described by the following equation:

Net gain index: MLD fup - MLD pre / vessel size. **(= relative gain-relative loss)**

Matching process:
The coronary artery tree was subdivided into 15 segments according to the American Heart Association guidelines and the lesions were individually matched according to stenosis location, reference diameter, minimal luminal diameter as well as the clinical parameters gender, anginal status, diabetes and hypercholesterolemia. Unstable angina was defined as chest pain at rest while hospitalized and treated with intravenous nitroglycerin and/or heparin. Hypercholesterolemia was defined as elevated levels of serum cholesterol >6.5 mmol/l requiring treatment with lipid lowering drugs [13). The principles of matching by quantitative angiography are threefold: (I) the angiographic dimensions of matched lesions are assumed to be "identical", (II) the observed difference between the two "identical" lesions must be within the range of the CAAS analysis reproducibility of 0.1 mm (=1 SD) and (III) the reference diameter of the lesions to be matched are selected within a range of $\pm$ 0.3 mm (=3 SD; confidence limits 99%) [4,14,15].
To compare the result of atherectomy and balloon angioplasty, 87 coronary artery lesions from a consecutive series of 2500 successfully dilated balloon angioplasty lesions (residual stenosis $<50\%$ on visual inspection) were selected by an independent analyst according to the above mentioned selection criteria of matching. These lesions were matched with the prospectively collected consecutive series of 87 successfully atherectomized native coronary artery lesions. Late comparative analysis between atherectomy and angioplasty was performed in 79 lesions since in the atherectomy group 8 lesions were lost to late angiographic follow-up. Consequently, the 8 twin matched angioplasty lesions were also not eligible for comparative follow-up analysis. At the time of selection, the analyst was unaware of the 6-months angiographic outcome of these lesions and was thus blinded. The Thoraxcenter angiographic database has now accumulated quantitative angiographic data on 2500 lesions treated by angioplasty, 535 lesion treated by intra-coronary stenting, 153 lesions treated by directional or rotational atherectomy and 73 lesions treated by laser angioplasty. Because neither angiographic, nor clinical benefit of the tested compounds could be demonstrated in the previous PTCA restenosis trials [8,10] the placebo and active treatment groups could be pooled for the present study.
Statistical analysis:
The unit of analysis reported here is the stenotic lesion, not the patient. All values are expressed as mean values $\pm$ 1 standard deviation. Comparisons of the severity of minimal luminal diameter, area plaque, diameter stenosis, symmetry index and length between the two groups were performed using analysis of variance and the paired student's t-test. Levene's test for variance was used to examine the equality of group variability and if significant difference was found, the Welch and Brown-Forsythe tests for equality of means were applied. The Bonferroni correction was applied for multiple comparisons. Linear regression analysis by groups was

performed (BMDP statistical package, program 1R) as a formal test for comparison of correlations and slopes. Differences were considered statistically significant where the p-value was less than 0.05.

RESULTS

Matching:
Baseline clinical and quantitative angiographic parameters of the matched population are listed in Table 1. No differences in gender, anginal status and stenosis location were observed. Minimal luminal diameter and reference diameter measurements were not significantly different in both groups; 1.16 ± 0.38 mm and 3.22 ± 0.60 mm for the atherectomy group and 1.19 ± 0.28 mm and 3.18 ± 0.56 mm for the angioplasty group (p=NS). The use of this matching technique resulted in the selection of patients treated by two different interventional techniques with similar clinical and preprocedural stenosis parameters (table 1). Figure 1 shows an example of two matched lesions which were treated by atherectomy or angioplasty.

Table 2. Quantitative comparison of the immediate and long-term results of atherectomy with balloon angioplasty in 79 stenoses

	Atherectomy	Angioplasty	t-test
Reference diameter pre (mm)	3.26 ± 0.62	3.23 ± 0.60	0.71
Reference diameter post (mm)	3.29 ± 0.41	3.23 ± 0.58	0.45
Reference diameter fup (mm)	3.02 ± 0.55	3.21 ± 0.63	0.05
Minimal luminal diameter pre (mm)	1.17 ± 0.29	1.21 ± 0.38	0.67
Minimal luminal diameter post (mm)	2.44 ± 0.42	2.00 ± 0.36	<0.001
Minimal luminal diameter fup (mm)	1.76 ± 0.62	1.77 ± 0.59	0.93
Diameter stenosis pre (%)	64 ± 12	62 ± 9	0.28
Diameter stenosis post (%)	25 ± 11	37 ± 10	<0.001
Diameter stenosis fup (%)	41 ± 17	45 ± 15	0.09
Relative gain	0.41 ± 0.20	0.25 ± 0.12	<0.001
Relative loss	0.23 ± 0.24	0.08 ± 0.16	<0.001
Net gain index	0.18 ± 0.19	0.17 ± 0.17	0.70

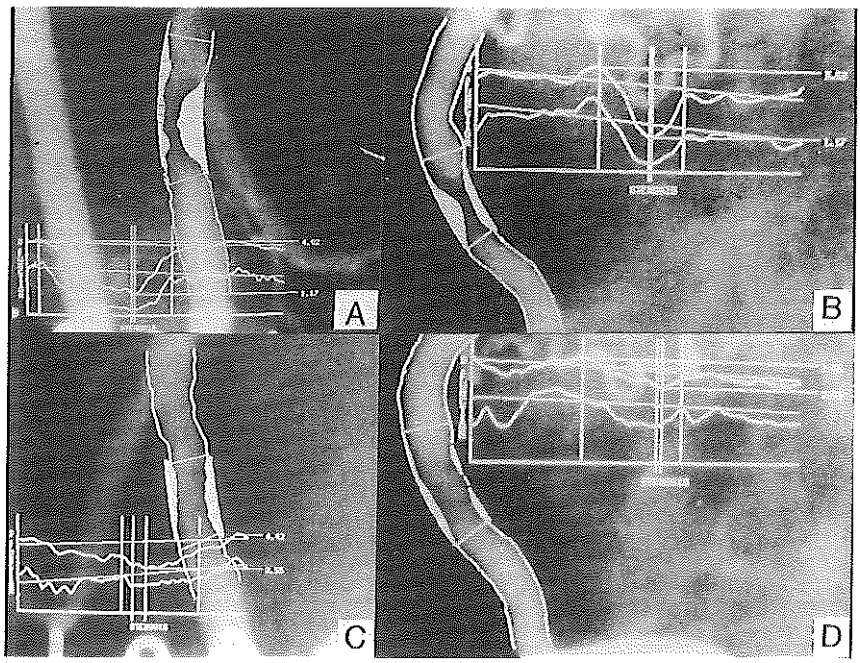


Figure 1. A representative example of an angiogram of matched lesions in the right coronary artery before atherectomy (A) or balloon angioplasty (B) and after atherectomy (C) or balloon angioplasty (D). Edge contour and densitometric analysis of the severity of the obstruction are superimposed. The graphs show the diagnostic diameter function (upper curve) and densitometric area function (lower curve). Lower vertical line is the minimal luminal diameter (1.17 mm in A and B). Outside vertical lines on the graph and the two lines on the angiogram are lesion boundaries. The mean reference diameter measured in the orthogonal projections is 3.55 mm (A) and 3.56 mm (B). There was a larger gain in minimal luminal diameter after directional atherectomy (C) than following balloon angioplasty (D).

Immediate results:

The reference diameter did not change significantly following either atherectomy or balloon angioplasty (3.26 ± 0.62 mm to 3.29 ± 0.41 mm in the atherectomy group versus 3.23 ± 0.60 mm to 3.23 ± 0.58 mm in the angioplasty group). Atherectomy resulted in a greater increase in minimal luminal diameter than balloon angioplasty with consequently greater "initial gain" (1.27 ± 0.48 mm versus 0.79 ± 0.34 mm;$p<0.001$) and post-procedural minimal luminal diameter (2.44 ± 0.42 mm versus 2.00 ± 0.36 mm;$p<0.001$) and concomitantly lower percent diameter stenosis (25 ± 11% versus 37 ± 10%;$p<0.001$). The relative gain following atherectomy was, accordingly, significantly greater than following balloon angioplasty (0.41 ± 0.20 versus 0.25 ± 0.12;$p<0.001$).

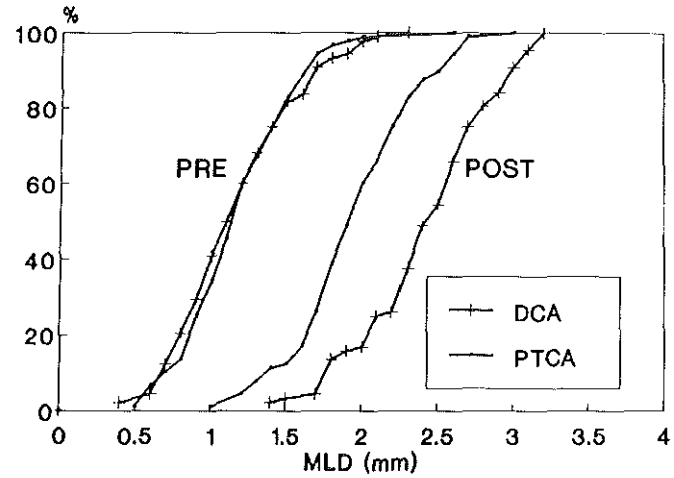
Table 3. Relative gain, relative loss and net gain per reference diameter group

Atherectomy group (n=79)							
Reference diameter	#	Absolute gain (mm)	Relative gain	Absolute loss (mm)	Relative loss	Net gain	RR (%)
< 2.5	8	1.68 ± 0.45	0.79 ± 0.16	1.40 ± 0.49	0.68 ± 0.27	0.11 ± 0.28	50
2.5 - 3.0	16	1.28 ± 0.54	0.46 ± 0.20	0.67 ± 0.49	0.24 ± 0.18	0.22 ± 0.21	25
3.0 - 3.5	27	1.15 ± 0.49	0.36 ± 0.15	0.51 ± 0.52	0.16 ± 0.16	0.20 ± 0.16	22
3.5 - 4.0	19	1.25 ± 0.38	0.34 ± 0.11	0.48 ± 0.55	0.13 ± 0.15	0.21 ± 0.18	26
> 4.0	9	1.26 ± 0.56	0.29 ± 0.14	0.99 ± 0.80	0.23 ± 0.19	0.06 ± 0.14	44
anova		0.1171	0.0000	0.0007	0.0000	0.1951	
Angioplasty group (n=79)							
Reference diameter	#	Absolute gain (mm)	Relative gain	Absolute loss (mm)	Relative loss	Net gain	RR (%)
< 2.5	10	0.59 ± 0.48	0.27 ± 0.21	0.24 ± 0.22	0.16 ± 0.19	0.11 ± 0.10	10
2.5 - 3.0	17	0.78 ± 0.24	0.27 ± 0.09	0.27 ± 0.38	0.09 ± 0.13	0.18 ± 0.18	18
3.0 - 3.5	27	0.88 ± 0.34	0.27 ± 0.10	0.42 ± 0.56	0.13 ± 0.17	0.14 ± 0.16	37
3.5 - 4.0	18	0.84 ± 0.33	0.23 ± 0.09	0.14 ± 0.64	0.04 ± 0.17	0.19 ± 0.17	39
> 4.0	7	0.66 ± 0.40	0.16 ± 0.10	-0.34 ± 0.37	-0.08 ± 0.09	0.23 ± 0.15	0
anova		0.1676	0.1272	0.0045	0.0194	0.7401	

RR = restenosis rate (i.e. diameter stenosis at follow-up ≥50%)

Long-term results:

Angiographic follow-up studies were performed in 90% of eligible patients in each group. Table 2 and figure II summarize the quantitative angiographic results at follow-up as analyzed according to a continuous and categorical approach. The



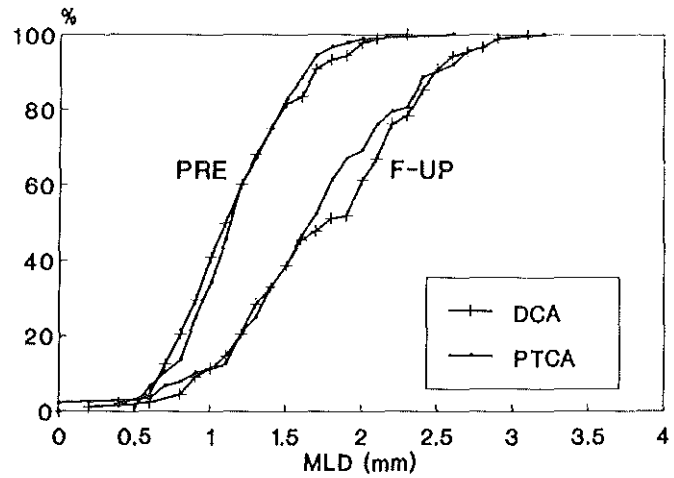
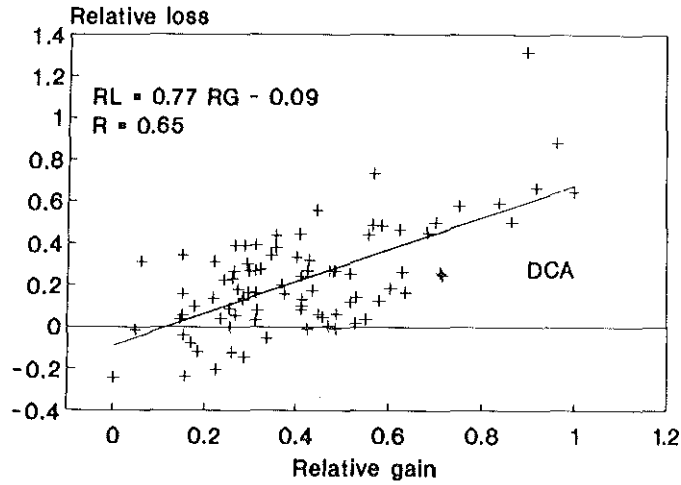


Figure II. Cumulative frequency curves to illustrate the immediate and follow-up effects in minimal luminal diameter (MLD) of directional coronary atherectomy as assessed by quantitative coronary angiography. Pre = before, post = after, f-up = at follow-up, DCA = directional coronary atherectomy, PTCA = balloon angioplasty.

minimal luminal diameter at follow-up for the atherectomy and angioplasty groups was not significantly different (1.76 ± 0.62 mm versus 1.77 ± 0.59 mm; p=0.93) nor was the net gain index (0.18 ± 0.19 versus 0.17 ± 0.17;p=0.70). The relative gain was greater in the atherectomy group compared with the balloon angioplasty group (figure III). A linear relationship exists between the relative gain and relative loss for each treatment group although the coefficient of correlation was superior in the atherectomy group (r= 0.64 versus r= 0.32). Thus, the amount of loss during follow-up is more clearly related to the gain achieved at intervention with respect to atherectomy. Furthermore, the slope of the regression line is steeper in the atherectomy group (0.75) when compared to the balloon angioplasty group (0.46), although this was not statistical significant (p=0.07) due to a large scatter in the angioplasty group. However, the relationship between relative gain and relative loss suggests that the vessel wall injury as well as the reactive hyperplasia is more intense for the same amount of gain. Finally, the vessel size plays an important role in the amount of relative gain and relative loss as described in table 3. It appears that the relative gain observed during the procedure and the relative loss at follow-up are both decreasing in vessels of increasing size.
As analyzed by the categorical approach using the >50% diameter stenosis criterion, 27% of the atherectomy and 29% of the angioplasty population had a restenosis (figure IV).

DISCUSSION

The ubiquitous phenomenon of restenosis has been the subject of much interest and attention since the introduction of percutaneous transluminal coronary angioplasty as a treatment for symptomatic coronary artery disease. Over the last few years, various new devices, including directional atherectomy [4,14-18], stenting [6,7,19], rotational ablation [20] and laser therapy [21] have been introduced to reduce the acute complication rate after balloon angioplasty and more importantly to lower the restenosis rate. Furthermore a variety of pharmacological agents [22,23] presumably liable to prevent restenosis have been tested in randomized clinical trials to reduce the restenosis rate. Unfortunately, none of these trials or device registries have been able to convincingly demonstrate a significant reduction in the restenosis rate. Many of these studies, however, have been fraught with methodological problems [24] and the interpretation of the results are confounded by the variety of definitions of restenosis used, rendering any comparison invalid.
Matching: comparing the comparable :
With the introduction of various new intracoronary devices it becomes critical to assess the relative merits of each system. We have introduced and validated the



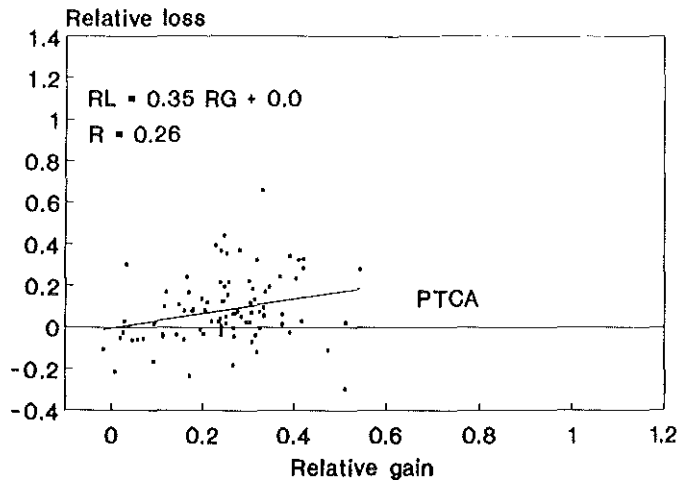


Figure III: Scatter histogram of values obtained for relative gain after atherectomy (DCA) or balloon angioplasty (PTCA) and relative loss during follow-up. A linear relationship emerges for both techniques however a higher coefficient of correlation ($r=0.65$ versus 0.26; $p<0.001$ versus $p=0.007$ respectively) and a steeper slope (0.77 versus 0.35; $p=0.07$) is found in the atherectomy group.

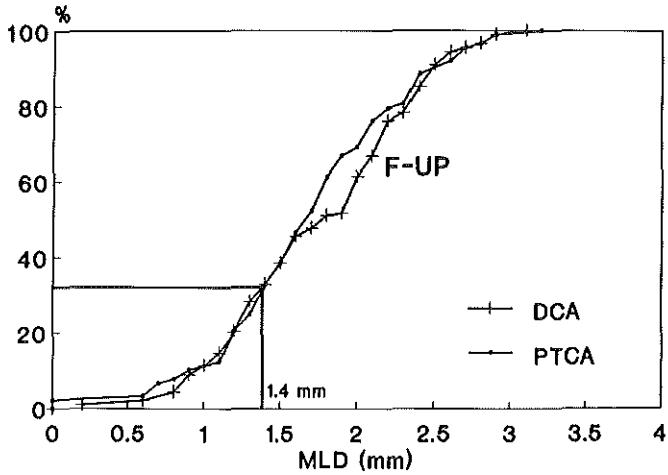
concept of matching as a surrogate for true randomized trials [4,14,15] anticipating their eventual results or at least allowing a more accurate calculation of power of upcoming randomized trials. The present study confirms that the longterm beneficial effect of directional atherectomy might be less pronounced than expected, and indeed important information may be derived by the evaluation of matched lesions which may be useful for the design of future randomized trials. For example, it can be calculated from this study how many patients should be included in a randomized trial in order to demonstrate a statistical difference in minimal luminal diameter between angioplasty and atherectomy. However, this should not preclude attempting a randomized trial which includes less patients (such as the CAVEAT trial) since subgroup analysis might nevertheless unravel a subset of patients (or lesions) who may especially benefit from the new intervention.

Dynamic versus static restenosis criteria :

Restenosis criteria currently in use can be divided into those which describe the change in lesion severity during follow-up (dynamic criterion) and those which merely describe lesion severity at follow-up (static criterion). Examples of the first category are the loss in lumen diameter of more than 0.72 mm as proposed by Serruys et al [4,6-8] and a change in percent diameter stenosis. Examples of the second category are the criterion of $>50\%$ diameter stenosis at follow-up and a minimal luminal diameter of more than 1.4 mm at follow-up [11]. In the present study we carefully selected comparable patient groups with identical stenoses by matching for clinical and angiographic parameters. However this technique does not reconcile the discrepancy arising out of the divergent immediate effects of two different interventional techniques rendering the dynamic restenosis criteria that describe a change in lesion severity from post-intervention to follow-up angiography inappropriate. Therefore a static restenosis parameter which describes the lesion severity at follow-up angiography should be used while comparing two different interventional techniques - such as directional coronary atherectomy and balloon angioplasty.

MLD at follow-up, the quantitative angiographic end-point :

Of all directly acquired measurements by quantitative coronary angiography, the absolute value of the minimal luminal diameter has been shown the greatest single determinant of the hemodynamic consequence of a stenosis and is therefore the only non-ambiguous, objective and reproducible parameter with which to describe the caliber of a coronary artery and changes therein following intervention [25]. In placebo-controlled restenosis prevention trials following PTCA, the change in minimal luminal diameter during follow-up has been traditionally used to assess the value of a new pharmacological strategy and this approach is justified since the luminal enlargement observed in the two arms of the trial were, by definition, comparable. Due to the different nature of the interventions applied here (ie. atherectomy versus angioplasty), the immediate



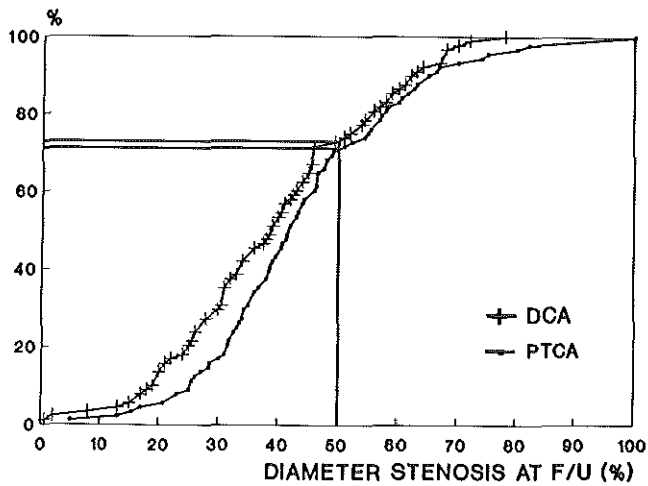


Figure IV: Static and dynamic assessment of long term angiographic outcome after atherectomy and balloon angioplasty as determined by 2 categorical cut off points; (A) MLD at follow-up = 1.4 mm and (B) diameter stenosis (DS) <50% at follow-up.

post-procedural results are different and no longer comparable. This is clearly shown in the cumulative distribution curve (figure II): atherectomy induces a larger gain in minimal luminal diameter than angioplasty which makes the immediate post-procedural characteristics dissimilar so that the loss during follow-up is no longer a helpful comparison of the long-term benefit. The most valid parameter for the comparison of two interventional devices is the minimal luminal diameter *at* follow-up because this static parameter, in itself, represents the final luminal improvement at follow-up. Moreover, the minimal luminal diameter at follow-up may have some *functional component*; in accordance with Danchin et al [11], we [26] found that a minimal luminal diameter of 1.45 mm correlates with the recurrence of angina pectoris (sensitivity and specificity of 72%). This information suggests that the absolute value of the minimal luminal diameter at follow-up may prove to be an even more useful parameter than parameters obtained by clinical examination or exercise testing.

In this study comparing two patient groups with similar clinical and preprocedural stenosis characteristics, using quantitative angiographic parameters of 158 coronary lesions, there was no significant difference in minimal luminal diameter at follow-up between the atherectomy and balloon angioplasty group.

Continuous versus categorical approach :Restenosis has been shown to be a proliferative response affecting virtually all lesions which have been subjected to the trauma of an intracoronary intervention [16,27-30]. Using quantitative angiography, our group previously demonstrated that a loss in minimal luminal diameter indeed occurs in all treated lesions, irrespective of localization in the coronary artery tree [12], and more importantly, that narrowing after balloon angioplasty follows a near Gaussian distribution [2]. Therefore, restenosis should be viewed as the tail end of an approximately Gaussian-distributed phenomenon rather than a unique disease entity, occurring in some lesions but not in others [2,3]. Given these facts, analysis with parametric statistical tests is appropriate and by using a continuous approach we may take advantage of all information made available by follow-up angiographic studies.

Relative gain as an 'injury score', relative loss as an index of neo-intimal hyperplasia:

The important observation that a greater gain in lumen (i.e. injury) is associated with a greater loss (ie repair) during follow-up has previously been described by Schwartz et al [31,32]. In a domestic swine stented model, which accurately mimics the proliferative nature of human restenosis, the extent of the proliferative response was strongly associated with rupture of the internal elastic lamina as induced by oversized and overpressurized balloon inflations, with, or without, coil implantation. In order to test this hypothesis in a clinical setting, we have substituted the concept of "injury score" and "neo-intimal hyperplasia" as observed in the animal model with the angiographically derived parameters of relative gain and relative loss. Quantitative angiographic analysis of 522 coronary

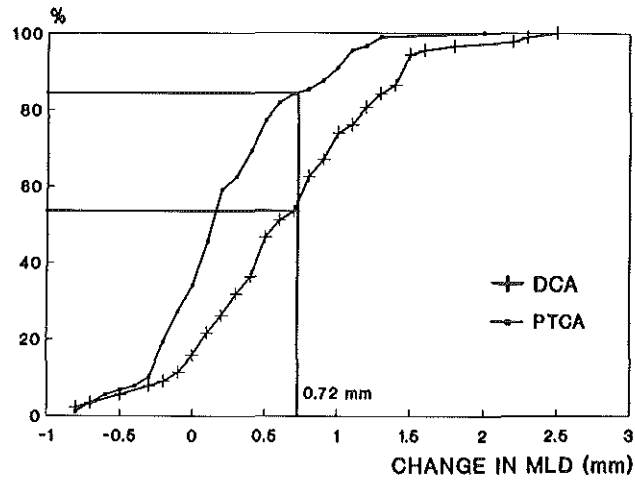


Figure IV C: Static and dynamic assessment of long term angiographic outcome after atherectomy and balloon angioplasty as determined by the third categorical cut off point; change of ≥ 0.72 mm in MLD during follow-up.

artery lesions [8] treated by balloon angioplasty with a 95% angiographic follow-up, reveals a linear relationship between relative gain and relative loss, although the coefficient of relation is low (0.4). The present study indeed confirms these observations for balloon angioplasty but unveils a stronger correlation between relative gain and relative loss for atherectomy, compared with balloon angioplasty. More importantly, the slope of the regression line is steeper in the atherectomy group than in the angioplasty group implying that not only is the relative gain greater in the atherectomy group but also that the reactive response (ie relative loss) is more pronounced after atherectomy than following angioplasty. As seen in figure III, the slope of the regression line between relative gain and relative loss, which reflects the inherent relationship between the degree of wall injury and the degree of repair represent an index of luminal renarrowing specific for each treatment modality (atherectomy, balloon angioplasty). Furthermore, the reference diameter emerged as a potentially important parameter which may affect the procedural outcome since it appears that the relationship between relative gain and relative loss is a function of the vessel size, with less gain during the procedure but also less loss during follow-up in larger vessels (table III). Indeed an earlier observation from our group [9,12] demonstrated that the relative loss is significantly smaller, in vessels with a reference diameter above 3.5 mm. This phenomenon might be related to less medial disrupture and a better artery/device ratio.

Limitations:

Several limitations of this study are to be acknowledged. First, it is an uncontrolled, observational study limited to a subset of patients with a successful coronary atherectomy or balloon angioplasty without inclusion of patient and procedure related variables. Second, this study is based on the relative early experience with atherectomy. Careful patient selection, future design changes and improved operator experience may further improve the immediate and long-term results. Controlled clinical trials, such as the CAVEAT trial, are imperative in the future to determine the immediate angiographic result, the long-term efficacy of these interventions as well as the benefit, if any, in particular patient subgroups. These studies should also address the presumed time frame for restenosis after any particular intervention.

Practical Implications :

At present debate still exists whether atherectomy should be performed while aiming at the maximal achievable result. On the one hand, studies have reported that "bigger is better" [33] while on the other hand controversy still exists regarding the influence of medial or adventitial tissue retrieval on the final restenosis rate [30,34,35]. Animal studies suggest a direct relationship between intimal hyperplasia and vessel wall injury at intervention. Introduction of quantitative angiographic correlates for these parameters in this clinical study, relative loss and relative gain respectively, clearly supports this hypothesis in the

context of directional atherectomy and balloon angioplasty. The biological control of the healing process has to be elucidated before we may take full advantage of the superior initial gain provided by this powerful interventional technique.

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Chapter 7

OPTIMAL USE OF DIRECTIONAL CORONARY ATHERECTOMY IS REQUIRED TO ENSURE LONG-TERM ANGIOGRAPHIC BENEFIT: A STUDY WITH MATCHED PROCEDURAL OUTCOME AFTER ATHERECTOMY AND ANGIOPLASTY.

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J Am Coll Cardiol accepted

ABSTRACT

Objectives. This study is designed to examine whether restenosis is related to the extent or mechanism of luminal improvement and to explore angiographic determinants for optimal atherectomy.

Background. Directional atherectomy induces a greater extent of acute gain and late loss but has not been found to yield a better late angiographic lumen than angioplasty in randomized trials. The difference in luminal renarrowing may be related to either the extent or the mechanism of acute gain. The design of previous studies has precluded the detection of a device specific effect on restenosis.

Methods. A retrospective analysis based on matching of a prospectively collected series of 80 native coronary arteries successfully treated with atherectomy with a prospectively collected series of 80 native coronary arteries successfully treated with balloon angioplasty. Angiographic analysis was performed in 160 lesions to explore whether a specific device related effect exists. Multivariate analyses were performed to determine the correlates of minimal luminal diameter at follow-up and late luminal loss and to identify the procedural characteristics for optimal atherectomy.

Results. Matching resulted in two comparable groups with equivalent baseline clinical and stenosis characteristics. By study design, atherectomy and angioplasty resulted in similar acute luminal gain (1.15 ± 0.44 mm vs 1.10 ± 0.40 mm;$p=0.50$). However, luminal loss was more pronounced after atherectomy and thus the minimal luminal diameter at follow-up differed significantly between the two groups (1.78 ± 0.57 mm vs 2.00 ± 0.56;$p=0.01$). Device type was retained in the multivariate analysis as an independent predictor of late minimal luminal diameter and luminal loss. Multivariate analysis identified vessel size and acute gain as determinants of optimal atherectomy.

Conclusions. Restenosis is not only the consequence of the extent of luminal improvement but also of the mechanism of vessel wall injury (debulking versus dilating). While performing atherectomy, the operator should strive for an optimal procedural result in order to accommodate an increased intimal hyperplastic response.

INTRODUCTION

It has been conclusively demonstrated that a large post-procedural diameter achieved at coronary intervention yields a greater long-term residual luminal diameter [1-11]. It has not been shown, however, whether this angiographic outcome is also related to the specific mechanism of the interventional device deployed. Thusfar, the design of coronary interventional studies has precluded the detection of a device specific effect on luminal renarrowing. In particular, previous studies have been confounded by the effects of unequal vessel size and acute luminal gain [3,4,7] which have been shown to be independent predictors of restenosis [4,5,9].

When we first studied the differences between restenosis after atherectomy and balloon angioplasty in a matched series [7], we observed a significant difference in luminal renarrowing between the two devices when deployed in vessels of similar size. Specifically, late loss was larger in the atherectomy than angioplasty group (0.68 mm vs 0.23 mm). While we believed that this effect was due to the superior immediate luminal gain with consequent greater luminal loss associated with atherectomy, we recognized that the difference in luminal renarrowing following atherectomy and angioplasty may relate to either the extent *or* the mechanism (debulking versus dilating) of luminal improvement ("vessel wall injury"). The purpose of this study is to extend our observations and to test the hypothesis that each device has unique properties with respect to luminal renarrowing which are independent of vessel size and lesion severity and luminal gain. Therefore, we compared the long-term angiographic outcome of directional coronary atherectomy and conventional balloon angioplasty in a prospectively collected series of 160 patients with comparable vessel size, lesion severity and acute gain. Multivariate analyses were performed to determine the correlates of minimal luminal diameter at follow-up and late luminal loss and to identify the angiographic characteristics for optimal atherectomy. The immediate and late changes in stenosis geometry were assessed by quantitative coronary angiography.

METHODS

Atherectomy patients:

From September 1989 through March 1993, 178 patients underwent 184 directional atherectomy procedures for native coronary or bypass graft lesions. Of these, 120 consecutive patients (who underwent 127 successful *stand-alone* procedures) had a 6 months follow-up angiography. For the purpose of this study, the late outcome of atherectomy was compared with that of angioplasty for consecutive native primary lesions. Therefore patients with restenotic lesions, lesions which underwent post-atherectomy adjunctive balloon angioplasty and

patients with a subacute coronary occlusion <24 hours were excluded. Of the 120 patients, 3 were treated for a lesion in a venous bypass graft and 13 had an atherectomy for 18 restenotic lesions after a previous angioplasty. Therefore, 104 patients who underwent 106 successful atherectomy procedures for native primary coronary artery disease were eligible for matching. Ultimately, 80 patients with 80 coronary artery lesions were individually matched with patients undergoing successful balloon angioplasty whereas the remaining 26 patients could not be matched. The clinical and angiographic details of the atherectomy and angioplasty groups are given in Table I.

Prior to atherectomy, patients had documented myocardial ischemia which required revascularization. Patients were selected for directional atherectomy when they presented with a stenosis in a proximal non-tortuous coronary artery with a presumed reference diameter >2.5 mm. All patients gave informed consent and were prospectively scheduled for 6-months angiography which was completed in 92% of the patients. The study was approved by the hospital's Institutional Review Board. All clinical and angiographic data were collected prospectively.

Balloon angioplasty patients were collected from the angioplasty database which contains clinical and angiographic details of 3072 patients who underwent 3736 angioplasty procedures and participated in previous angioplasty restenosis prevention trials in Europe and North America [8,12,13]. The mean age of these 3072 patients was 56 ± 9 years; 81% were men. The majority of the patients (52%) were treated for Canadian Cardiovascular Society class III or IV angina. In the entire angioplasty population, 47% of the dilated lesions were located in the left anterior descending coronary artery, 23% in the left circumflex and 30% in the right coronary artery. On baseline quantitative angiography, mean vessel size and minimal lumen diameter pre-angioplasty were 2.62 ± 0.53 mm and 1.09 ± 0.29 mm, respectively. The pre-angioplasty percentage diameter and area stenosis were 58 ± 10% and 84 ± 16%. Balloon dilatation in these 3736 lesions resulted in a post-angioplasty minimal lumen diameter and diameter stenosis of 1.77 ± 0.36 mm and 33 ± 8% respectively. At follow-up the minimal lumen diameter decreased to 1.53 ± 0.47 mm with a concomitant increase in diameter stenosis to 42 ± 14%. The loss index for these 3736 lesions was 0.30 ± 1.65. An angiographic and clinical follow-up rate of >90% was obtained. Because neither angiographic, nor clinical benefit of the tested compounds could be demonstrated in these restenosis trials the placebo and active treatment groups could be pooled for the present study.

Atherectomy and angioplasty procedure:

The procedure was performed as described previously [7,8,12-16]. Briefly, the atherectomy device was directed over a guide-wire and positioned across the stenosis. The support balloon was then inflated up to 7.5 psi, the cutter was retracted and balloon inflation pressure was increased to maximally 45 psi. The

driving motor was activated and the rotating cutter was slowly advanced to cut and collect the protruding atherosclerotic lesion in the collecting chamber located at the tip of the catheter. After every pass the balloon was deflated and either removed or repositioned. While an optimum angiographic result was sought for each lesion treated, the procedure was considered angiographically successful when the residual diameter stenosis was less than 50% after tissue retrieval. This classic definition of success should be viewed in the historical perspective, while nowadays a luminal gain of at least 0.7 mm or a post-atherectomy diameter stenosis $<20\%$ may be deemed necessary before considering the procedure as successful as recently observed in retrospective analyses [2] and as defined in the upcoming atherectomy trials (BOAT, OARS, EUROCARE).

Balloon angioplasty was performed with a steerable, movable guidewire system via the femoral route. Standard available catheters were used. Choice of balloon type, size as well as inflation duration and pressure was left to the discretion of the operator. Balloon dilatations were repeated until the severity of the obstruction was at least below 50% diameter stenosis as judged visually by the operator on coronary angiography. Following all interventions, the arterial and venous sheaths were usually left in place for 6 hours. Patients were monitored for 24 hours and electrocardiograms and cardiac enzyme levels were obtained twice daily. A calcium antagonist was given every 2 hours for 24 hours after the procedure and the patients were maintained on aspirin therapy for six months.

Quantitative coronary angiography:

Quantitative analysis of the coronary segments was performed with the computer based Coronary Angiography Analysis System (CAAS), which has been previously validated and described in detail [8,12,-17]. In particular accuracy and precision measurements for in-vivo phantom measurements are 0.09 and 0.23 [18]. In essence, boundaries of a selected coronary artery segment are detected automatically from optically magnified and video digitized regions of interest (512 x 512 pixels) of a cine-frame. The absolute diameter of the stenosis in mm is determined using the guiding catheter as a scaling device for calibration. The external diameter of each individual catheter is measured by a precision micrometer with a tolerance of 0.001 mm. Correction for pincushion distortion is performed. Computer-estimation of the original dimension of the artery at the site of the obstruction provides an interpolated reference diameter. The percentage diameter stenosis is then calculated. To standardize the method of analysis of the interventional and follow-up angiogram, the following measures are routinely applied. First, the x-ray gantry is exactly repositioned to the settings which were documented at the time of the intervention. Second, all study frames to be analyzed were selected at end-diastole to minimize foreshortening and blurring effects of systolic motion. Third, the user determined beginning and endpoint of a segment of a major coronary artery were identified according to the definitions of the American Heart Association [19]. Finally, Polaroid photographs were taken

of the video image with the detected contours superimposed to ensure that the analyses were performed on the same coronary segments. Intracoronary isosorbide dinitrate (1-3 mg) was given prior to and following intervention. Administration of intracoronary nitrates was recommended prior to angiography at follow-up catheterization.

Matching process:

To obtain patients with comparable pre- and post-procedural stenoses, lesions were matched according to reference diameter, pre-interventional minimal luminal diameter and post-interventional minimal luminal diameter. The analysis is thus independent of vessel size, lesion severity and extent of device-induced luminal gain. The process of matching has been previously described [7,16]. Briefly, the principles of matching by quantitative angiography are threefold: (i) the angiographic dimensions of matched lesions are assumed to be "identical", (ii) the observed difference between the two "identical" lesions must be within the range of the reproducibility of the CAAS analysis, 0.1 mm (=1 SD) and (iii) the reference diameter of the lesions to be matched are selected within a range of $\pm$ 0.3 mm (=3 SD; 99% confidence limits) [8,12,13].

Statistical analysis:

The unit of analysis reported here is the stenotic lesion, not the patient. All values are expressed as mean values $\pm$ 1 SD). Comparisons of the severity of reference diameter, minimal luminal diameter, diameter stenosis and area stenosis between the two groups were performed using the paired student's t-test. Levene's test for variance was used to examine the equality of group variability and if significant difference was found, the Welch and Brown-Forsythe tests for equality of means were applied. The Bonferroni correction was applied for multiple comparisons. Linear regression analysis by groups was performed (BMDP statistical package) as a formal test for comparison of correlations and slopes. Selected angiographic variables were evaluated by univariate regression analysis for their correlation with absolute luminal loss and for their correlation with minimal luminal diameter at follow-up. Independent contribution of variables was assessed by multivariate stepwise regression analysis using a commercially available statistical software package (SAS, SAS Institute Inc, Cary, North Carolina). Multiple linear regression analysis was utilized to account of the influence of pre-procedural minimal luminal diameter, acute luminal gain and vessel size in evaluating their contribution to the minimal luminal diameter at follow-up and late luminal loss. Differences between categorical variables were tested with the chi-square and Fisher exact tests as appropriate. A p-value less than 0.05 was considered statistically significant.

RESULTS

Outcome of the matching process (Table I):
Although 104 patients (106 atherectomy procedures) were eligible for the matching study, 24 patients (26 lesions) could not be matched with a twin balloon angioplasty patient. Therefore, the final analysis was performed on 160 patients treated by either directional atherectomy or balloon angioplasty. The baseline clinical and angiographic characteristics of the atherectomy patients were compared with those of the matched angioplasty group. The 160 patients were predominantly male with a mean age of 57 ± 11 years. Patients were predominantly treated for stable angina according to the American Heart Association classification. Atherectomy was preferentially performed in the left anterior descending (65% vs 25%) while the right coronary artery was more frequently treated by angioplasty (23% vs 56%;$p < 0.001$).

Table 1. Clinical and angiographic characteristics of the study population.

	Atherectomy		Angioplasty
	not-matched group (n=26)	matched group (n=80)	matched group (n=80)
Age (yr)	58 ± 12	57 ± 11	58 ± 10
Male (%)	70	81	91
Vessel treated (%)			
LAD	59	65	25
LCX	7	12	19
RCA	33	23	56
Unstable angina (%)	38	30	37
Previous infarction (%)	31	27	36
Previous CABG (%)	0	1	2
Diabetes (%)	4	2	6
Hypercholesterolemia(%)	24	15	20
Multivessel disease (%)	23	25	32
Reference diameter (mm)	3.64 ± 0.93	3.21 ± 0.49	3.22 ± 0.48
MLD (mm)	1.34 ± 0.52	1.16 ± 0.32	1.16 ± 0.28
Diameter Stenosis (%)	63 ± 12	64 ± 10	63 ± 9
Area Stenosis (%)	83 ± 17	84 ± 16	84 ± 17

LAD=left anterior descending coronary artery, LCX=left circumflex branch, RCA=right coronary artery, CABG=coronary artery bypass grafting, MLD =minimal luminal diameter.

The incidence of left circumflex artery lesions was similar in both groups (12% vs 19%). No differences between the groups were found for risk factors for

coronary artery disease or preceding cardiovascular events. By study design, no significant differences between the atherectomy and angioplasty groups were found in baseline quantitative angiographic parameters: mean vessel size (3.21 ± 0.49 vs 3.23 ± 0.48 mm), pre-procedural minimal luminal diameter (1.16 ± 0.32 vs 1.16 ± 0.28 mm) and percentage diameter stenosis (64 ± 10 vs 63 ± 9%) respectively. The baseline characteristics of the 26 unmatched atherectomy lesions revealed no difference in clinical profile between matched and unmatched patients. Although the percentage diameter stenosis and percentage area stenosis in the unmatched group was equal to the matched group, atherectomy was performed in larger vessels (reference diameter 3.64 ± 0.93 mm) with a concomitant larger minimal luminal diameter pre-procedure (1.34 ± 0.52 mm) than in the matched group. Matching with similar angioplasty lesions was not possible due to either a large acute lumen gain with concomitant low % residual diameter stenosis or because of large vessel sizes.

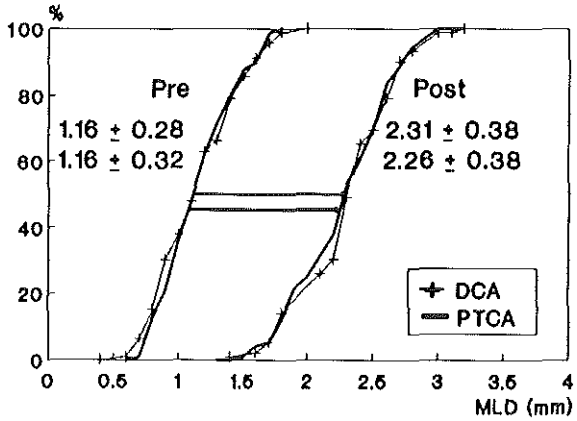
The 80 matched angioplasty patients had similar clinical and angiographic characteristics compared with the entire angioplasty population with respect to gender, age (56 vs 58 years) and diabetes (6% vs 7%). By virtue of matching with atherectomy lesions, the matched angioplasty group had bigger vessels (3.23 mm vs 2.62 mm) and minimal lumen diameters (1.16 mm vs 1.09 mm) than the entire angioplasty population, although their lesion severity was similar (% diameter stenosis 63% vs 58%).

Immediate angiographic outcome in matched patients (Table II):

By virtue of our matching protocol, the pre *and* post-procedural minimal luminal diameter in both groups were similar (2.31 ± 0.38 vs 2.26 ± 0.37 mm;$p=0.98$) and (2.31 ± 0.38 mm vs 2.26 ± 0.38 mm;$p=0.46$) respectively. Therefore, the acute luminal gain achieved with atherectomy was comparable with the gain achieved at angioplasty (1.15 ± 0.44 vs 1.10 ± 0.40 mm). Relative gain, defined as gain divided by vessel size, was similar in both groups. In figure I, the graphic display of the immediate results after atherectomy and balloon angioplasty are shown. As displayed, the matching process was adequate with superimposition of the distribution frequency curves of the minimal luminal diameter before and after atherectomy and angioplasty indicating similar pre- and post-procedural stenosis severity irrespective of the deployed device.

Late angiographic outcome in matched patients (Table II):

Angiographic follow-up was obtained in all patients. The restenosis rate according to the >50% diameter stenosis categorical criterion was comparable between the atherectomy and angioplasty group (28% vs 22%;$X^2=1.038$,$p=0.30$). Although a similar acute gain was achieved irrespective of the device used, the atherectomy patients had a significantly higher late loss during follow-up (0.53 ± 0.58 mm vs 0.26 ± 0.60 mm;$p<0.005$). Therefore, the residual minimal luminal diameter at follow-up was significantly smaller after atherectomy than after angioplasty (1.78 ± 0.57 mm vs 2.00 ± 0.56 mm;$p<0.001$)(figure I).



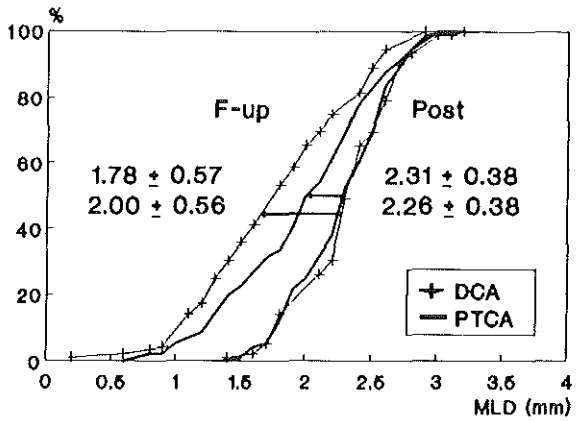


Figure 1: Cumulative frequency curves of the immediate and follow-up effects in minimal luminal diameter (MLD) of directional coronary atherectomy as assessed by quantitative coronary angiography. F-up = follow-up, pre = before atherectomy, post = after atherectomy.

Relative loss (loss divided by vessel size) and loss index (late loss divided by acute gain) were significantly higher after atherectomy indicating a more intense renarrowing process. A linear relationship was found between relative gain (injury) and relative loss (repair) in the two groups, with a steeper relative gain/relative loss regression line slope in the directional atherectomy group (0.56) than in the balloon angioplasty group (0.44) although this difference did not achieve statistical significance due to a wide data scatter (large standard error of the mean).

Table 2. Comparison of quantitative angiographic data in matched patients who underwent atherectomy or balloon angioplasty.

	Atherectomy (n=80)	Balloon angioplasty (n=80)	p-value
Reference diameter pre (mm)	3.21 ± 0.49	3.23 ± 0.48	NS
Minimal luminal diameter pre (mm)	1.16 ± 0.28	1.16 ± 0.32	NS
Minimal luminal diameter post (mm)	2.31 ± 0.38	2.26 ± 0.38	NS
Minimal luminal diameter f-up (mm)	1.78 ± 0.57	2.00 ± 0.56	0.01
Diameter stenosis pre (%)	64 ± 10	63 ± 9	NS
Diameter stenosis post (%)	28 ± 11	31 ± 10	0.02
Diameter stenosis f-up (%)	41 ± 18	38 ± 16	NS
Absolute luminal loss (mm)	0.53 ± 0.58	0.26 ± 0.60	0.005
Relative luminal loss	0.18 ± 0.21	0.08 ± 0.19	0.002
Loss index	0.52 ± 0.81	0.17 ± 0.68	0.004
Lesion length (mm)	6.73 ± 2.51	6.90 ± 2.34	NS
Curvature value	15.5 ± 6.9	12.7 ± 5.8	NS
Symmetry index	0.55 ± 0.25	0.44 ± 0.25	NS
Area plaque (mm^2)	9.33 ± 4.94	9.96 ± 4.45	NS

F-up = at follow-up, NS = not significant, pre = before intervention, post = after intervention.

Multivariate analysis of luminal loss and late residual diameter:

To characterize the luminal changes after directional atherectomy and balloon angioplasty according to a continuous approach, two multivariate stepwise models were generated in which (1) residual lumen at follow-up and (2) absolute loss were taken as the dependent variables.

Univariate predictors of *minimal luminal diameter at follow-up* were minimal luminal diameter post-intervention, device type and vessel size. In multivariate analysis, vessel size was found to have an independent positive influence on minimal luminal diameter at follow-up while device had a comparable negative influence on late residual lumen.

Therefore, it is apparent that the late results after successful interventions are superior in larger vessels and that there is a device effect on luminal renarrowing and late minimal luminal diameter at follow-up. The influence of vessel size may in part account for the results observed in new device studies because typically these devices are used in larger vessels. The multivariate model to predict residual late lumen was found to be: Minimal luminal diameter at follow-up = 1.28 + 0.22 vessel size - 0.23 Device (where angioplasty=0 and atherectomy=1).

Minimal luminal diameter after intervention, luminal gain, relative gain, minimal luminal diameter before intervention and device type were univariate predictors for *absolute luminal loss* during follow-up. Of these, luminal gain and device type were retained in the multivariate model to predict the renarrowing process. In multivariate analysis, the relationship between gain and loss is demonstrated as acute gain is found to exert a positive influence on late loss. In addition, pre-interventional minimal luminal diameter and device type were positively associated with luminal loss. This may indicate that the use of a bulky device is associated with an increase in late luminal loss because the use of the atherectomy device is associated with an additional late loss of 0.24 mm as compared with the use of the balloon. The model to predict absolute luminal loss in this population can be described by the following equation: Absolute loss = -1.0 + 0.64 Gain + 0.46 Minimal luminal diameter pre + 0.24 Device (where angioplasty=0 and atherectomy=1).

Optimal atherectomy:

Given the distinct renarrowing properties of the atherotome, we sought to identify which angiographic variables yield independent information for the prediction of late lumen. Therefore, the atherectomy population was divided into two groups according to the median post-atherectomy minimal luminal diameter. Table III summarizes the changes in stenosis geometry for all atherectomy procedures. A large post-procedural atherectomy lumen was associated with a large vessel (3.48 $\pm$ 0.70 mm vs 3.13 $\pm$ 0.54 mm;p=0.0001), a large minimal luminal diameter before atherectomy (1.29 $\pm$ 0.41 mm vs 1.11 $\pm$ 0.34 mm;p=0.02) and a large luminal gain (1.50 $\pm$ 0.39 mm vs 0.98 $\pm$ 0.42 mm;p=0.0001). The residual diameter stenosis for this group was 20 $\pm$ 8%. Although the late loss during follow-up was higher (0.86 $\pm$ 0.64 mm vs 0.42 $\pm$ 0.59 mm;p=0.004), the minimal luminal diameter at follow-up was larger in the group that underwent a favorable compared with the less favorable atherectomy (1.92 $\pm$ 0.62 mm vs 1.67 $\pm$ 0.56 mm;p=0.03). This preserved favorable long-term angiographic outcome was also reflected in the acute gain/late loss regression equation which showed a shallower slope in the optimal atherectomy group than in the suboptimal group (0.35 vs 0.45), although its difference did not reach statistical significance: loss = 0.33 + 0.35 gain (r=0.22;p=0.1173, optimal group) versus loss = 0.45 + 0.45 gain (r=0.32;p=0.02, suboptimal group). The restenosis rate, defined as diameter stenosis <50% at follow-up, was lower in the optimal than suboptimal

group (25% vs 34%) although it did not reach the level of significance.

Table 3. Optimal versus sub-optimal atherectomy: luminal changes after atherectomy per minimal luminal diameter post-atherectomy.

	MLD post >2.47 mm (n=53)	MLD post <2.47 mm (n=53)	p-value
Reference diameter pre (mm)	3.48 ± 0.70	3.13 ± 0.54	0.0001
Minimal luminal diameter pre (mm)	1.29 ± 0.41	1.11 ± 0.34	0.0208
Minimal luminal diameter post (mm)	2.78 ± 0.27	2.09 ± 0.28	0.0001
Minimal luminal diameter fup (mm)	1.92 ± 0.62	1.67 ± 0.56	0.0317
Diameter stenosis pre (%)	63 ± 10	65 ± 11	NS
Diameter stenosis post (%)	20 ± 8	32 ± 10	0.0001
Diameter stenosis fup (%)	39 ± 17	44 ± 18	NS
Gain (mm)	1.50 ± 0.39	0.98 ± 0.42	0.0001
Loss (mm)	0.86 ± 0.64	0.42 ± 0.59	0.0004
Relative gain	0.47 ± 0.20	0.34 ± 17	0.0004
Relative loss	0.28 ± 0.25	0.16 ± 0.21	0.0004
Net gain (mm)	0.63 ± 0.67	0.56 ± 0.60	NS
Loss index	0.59 ± 0.46	0.49 ± 0.96	NS

Fup = at follow-up, NS = not significant, pre = before intervention, post = after intervention.

Thus, these data indicate that optimal atherectomy seems to be related to not only to a large post-procedural lumen or large acute gain (procedural outcome) but also due to large vessel sizes (patient selection). Indeed *multivariate analysis* distinguished vessel size, luminal gain and pre-procedural minimal luminal diameter as independent predictors of minimal luminal diameter at follow-up and late loss. Figures II and III provide a three dimensional reconstruction of the regression planes for late lumen and late loss. The regression plane is the resultant of loss, gain and minimal luminal diameter pre-atherectomy. Vessel size may be seen as the fourth dimension which will shift the regression plane downward (late loss) or upward (late lumen) by 0.21 mm for every increase in vessel size by 1 mm. Both regression equations are: *minimal luminal diameter at follow-up* = 0.50 + 0.21 vessel size + 0.22 gain + 0.29 pre-procedural minimal luminal diameter. *Absolute loss* = - 0.50 - 0.21 vessel size + 0.78 gain + 0.71 pre-procedural minimal luminal diameter. Therefore, an optimal atherectomy (large late absolute lumen) is thus associated with large vessels, a large gain and a large initial lumen.

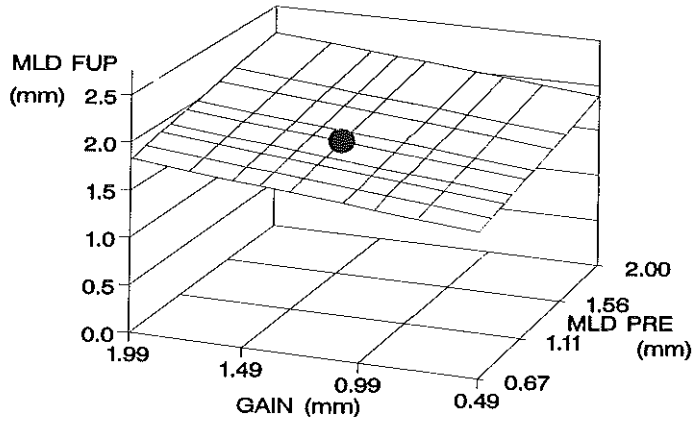


Figure II: Three dimensional representation of the linear regression model of minimal luminal diameter at follow-up (MLD fup) after atherectomy. MLD fup is represented on the Y-axis, gain at atherectomy on the X-axis and MLD pre on the Z-axis. The contribution of gain and MLD pre are represented by dividing the population in noniles. Positive relationships are found between gain and MLD fup and between MLD pre and MLD fup, which do not vary with vessel size. The dot in the center of the plane represents the median value for the luminal gain and MLD pre.

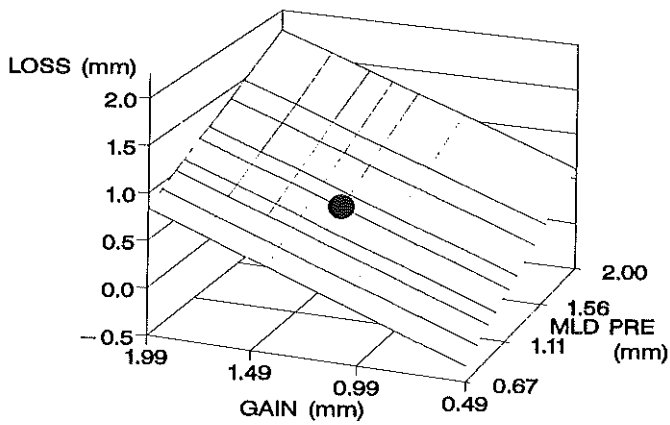


Figure III: Three dimensional representation of the linear regression model of luminal loss after directional atherectomy. Loss is represented on the Y-axis, gain at atherectomy on the X-axis and MLD pre on the Z-axis. The contribution of gain and MLD pre are represented by dividing the population in noniles. Positive relationships are found between gain and loss and between MLD pre and loss, which do not vary with vessel size. The dot in the center of the plane represents the median value for the luminal gain and MLD pre.

DISCUSSION

Restenosis has been shown in animal models to be the net result of injury inflicted on the vessel wall during an intervention and the subsequent biological healing response [20-22]. High pressure balloon inflation at angioplasty may yield excessive vessel wall damage with disruption of the internal elastic lamina and provoke an intense fibro-proliferative reaction. Low pressure balloon inflation and selective plaque removal by directional atherectomy potentially induces less vessel wall trauma. However, it is unknown whether atherectomy is less prone to induce an exuberant healing response after plaque *excision* than balloon *dilatation* for an equivalent degree of luminal enlargement measured on angiography. In order to explore the influence of a device effect on the renarrowing process we studied a matched patient population with similar baseline vessel and lesional characteristics and acute gain after atherectomy or angioplasty.

The major findings of this study are threefold: (1) in matched patients which underwent the same amount of luminal gain, atherectomy induces more subsequent luminal loss than angioplasty, (2) device type is retained in the multivariate model as a predictor of luminal renarrowing and (3) the benefit may not be sustained in the long-term if atherectomy is not performed optimally.

Matching.

Matching a study population with a reference patient group of similar characteristics can compensate for some of the limitations of nonrandomized studies [24]. Furthermore, it may serve as a surrogate for randomized trials [25]. Indeed, its analytical value in predicting the outcome of true randomized trials comparing angioplasty with atherectomy [7,10,11] and angioplasty with stenting [25,26] has been demonstrated. In the present study, patients were matched not only for vessel size and lesion severity but also for the acute luminal gain. Therefore, although the patients were treated with two different devices they have apparently undergone the same extent, albeit a partially different mechanism, of "vessel wall injury" inflicted by either the balloon or the atherotome. In this matching study, we found that device is an independent predictor of luminal loss (i.e. renarrowing process) and residual lumen at follow-up (i.e. angiographic outcome) which indicates that not only the extent of luminal gain but also the specific mechanism of action (debulking versus dilating) has an influence on restenosis. In non-matched observational studies, Kuntz et al [2,3,6] precluded, by virtue of their study design, the detection of an independent device effect because of the highly statistical differences between their device groups in acute luminal gain, which is known to be the strongest predictor for late outcome [3,9,10]. While prospective randomized trials are traditionally regarded as the methodology of choice for comparing long-term outcome of different interventional procedures such as CAVEAT, CCAT, BENESTENT and STRESS

[10,11,26,27], only an approach which includes matching for luminal gain will elucidate a specific device mechanistic effect on luminal renarrowing.

Multivariate analysis.

A comprehensive analysis of the restenosis phenomenon has recently demonstrated that the predictors of the residual lumen at follow-up and late luminal loss should be determined simultaneously to assess the restenosis phenomenon from a clinical outcome and biological process viewpoint [9,28,30]. The rationale for inclusion of device, vessel size, pre-interventional minimal luminal diameter and luminal gain for our multivariate analytical model was (i) to consider the potentially "confounding effect" of one variable on another and (ii) to use only absolute and not derived variables which accurately describe the lesion and can be modified by the clinician. The analysis of the late luminal changes of a matched population, indicated that device was an independent predictor of the renarrowing process and angiographic outcome. The cutting mechanism of the atherectomy device leads to more luminal loss with a smaller late lumen at follow-up compared to balloon angioplasty in patients who had similar post-procedural results. In the near future, this finding that the mechanism as well as extent of luminal improvement determines the subsequent renarrowing process should be analyzed prospectively and confirmed by multicenter studies.

The present results of our matched series may provide further insights into the atherectomy results of the CAVEAT and CCAT trials [10,11]. In these randomized trials, as in our matched atherectomy group, the moderate atherectomy procedural gain yielded a post-atherectomy minimal lumen of 2.31 mm (our matched DCA patients), 2.02 mm (CAVEAT) and 2.34 mm (CCAT). The greater luminal loss during follow-up ultimately led to late residual lumen diameters which were similar to those of the angioplasty group.

Optimal versus suboptimal atherectomy.

The present matching study identified a worse long-term outcome of atherectomy when the immediate results are comparable with angioplasty. This indicates that a moderate luminal gain achieved at atherectomy cannot compensate for an increased late luminal loss. In other words, if atherectomy is not optimally performed (large acute gain), the benefit may not be sustained in the long-term and the clinician should thus strive for a large luminal gain at directional atherectomy. To test this hypothesis we further analyzed our total atherectomy population and divided the angiographic results into two equal groups according to the distribution of the post-atherectomy lumen diameter. Indeed the patients who underwent an optimal atherectomy (post-atherectomy minimal luminal diameter 2.78 $\pm$ 0.27 mm and residual diameter stenosis of 20 $\pm$ 8%) had a significantly greater late lumen at follow-up (1.92 $\pm$ 0.62 mm vs 1.67 $\pm$ 0.56 mm;$p=0.03$) and a conventional restenosis rate of 25% versus 34%. In addition, we also observed a difference in the slope of the gain/loss regression line between the optimal and suboptimal groups (0.35 vs 0.45) although this difference did not

reach statistical significance. This trend towards less proportional loss with larger gains was also found in a preliminary analysis of the CAVEAT data which suggested a curvi-linear relationship between acute gain and late loss with a steeper slope for smaller gains and a shallower slope for larger gains [29]. Thusfar, the influence of optimal atherectomy on late angiographic outcome is not entirely resolved and further information will be provided by the imminent Balloon versus Optimal Atherectomy Trial (BOAT), Optimal Atherectomy Restenosis Study (OARS) and European Cardivólol Restenosis trial (EUROCARE). Although these will evaluate the effect of optimal atherectomy, BOAT and OARS are designed from the perspective "bigger is better" with emphasis on optimal performance while EUROCARE is designed from the perspective "the more you gain, the more you lose" and combines a large acute gain with a pharmacological agent to reduce late luminal loss. In other words, BOAT will increase the "doughnut's hole" while EUROCARE will also try to reduce the "doughnut" [9,21,28,30]. Ultimately the restenosis process may be controlled by the combination of a large luminal gain which will provide a large lumen at follow-up and pharmacological/biological/gene therapy to reduce the greater luminal loss.

Clinical implications.

The extent of luminal renarrowing is not only the consequence of the extent of luminal improvement but also of the mechanism of vessel wall injury (debulking versus dilating). While performing atherectomy, the operator should strive for an optimal procedural result in order to accommodate an increased intimal hyperplastic response.

Study limitations.

It could be argued that matching leads to a selection bias of the control group. Our data indicate, however, that the matched angioplasty lesions are a representative cohort of the angioplasty population with identical lesion severity as judged by percentage diameter stenosis. Furthermore, the matched angioplasty patients had similar lesion characteristics and outcome as the balloon angioplasty patients in the CAVEAT and CCAT trials [10,11]. Despite these angiographic similarities between the groups, a difference exists in lesion distribution which is similarly found by others [2,3,6]. This is due to dissimilar vessel sizes with smaller left anterior descending arteries than non left anterior descending vessels. Whether the left anterior descending artery is more prone to restenosis independent of vessel size has yet to be determined [5,6,9,23]. To our knowledge there is no pathophysiological evidence to suggest that one coronary artery should display an inherently more aggressive neointimal healing response to injury than others. Available information on the influence of lesion location on angiographic outcome is conflicting and merits further investigation, particularly with intravascular ultrasound imaging. The AHA/ACC lesion classification [31] was not used in this matching study because "it groups an array of lesions with a

heterogeneous morphology and dissimilar PTCA results" [15,16,32]. Quantitative morphologic assessment using automated edge detection derived length, symmetry index, curvature and in- and outflow angle values may overcome this limitation and also allows a continuous rather than categorical analysis [33].

This study did not assess the influence of recoil on the final outcome of the interventions however, previous studies have indicated that no significant difference in minimal luminal diameter 24 hours after angioplasty was observed [34] when appropriate measures where taken to control vasomotor tone [9]. This matching study however did take the difference in acute recoil which has been reported by Kimball et al [35] into consideration since matching was performed also for the post-procedural result.

Although matching seems a suitable statistical technique to explore such relationships, this study also indicates one of the limitations of matching. In order to find 80 angioplasty patients with similar pre- and post-intervention stenosis characteristics to be matched with the 80 consecutive atherectomy patients, 3637 angioplasty lesions were screened. This indicates that it is unlikely that a similar subanalysis could be performed to the CAVEAT and CCAT study groups.

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Chapter 8

ANGIOGRAPHIC, ULTRASONIC AND ANGIOSCOPIC ASSESSMENT OF THE CORONARY ARTERY WALL AND LUMEN AREA CONFIGURATION AFTER DIRECTIONAL ATHERECTOMY: THE MECHANISM REVISITED.

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Submitted

ABSTRACT

Objectives. The purpose of the present study was to use the complementary information of angiography, intravascular ultrasound and intracoronary angioscopy before and after directional atherectomy to better characterize the post-atherectomy appearance of the vessel wall contours and the mechanism of lumen enlargement.

Background. Directional coronary atherectomy aims at debulking rather than dilating a coronary artery lesion. The selective removal of the plaque may potentially minimize the vessel wall damage and lead to subsequent better late outcome. Whether plaque removal is the main mechanism of action has only be assessed indirectly by angiography and warrants further investigation using detailed analysis of luminal changes and vessel wall damage by ultrasound and direct visualization with angioscopy.

Methods. Twenty-six patients have been investigated by quantitative angiography, intravascular ultrasound and intracoronary angioscopy (n=19) before and after atherectomy. In addition all retrieved specimens were microscopically examined.

Results. Ultrasound imaging showed an increase in lumen area from 1.95 $\pm$ 0.70 mm^2 to 7.86 $\pm$ 2.16 mm^2 at atherectomy. The achieved gain mainly resulted from plaque removal since plaque + media area decreased from 18.16 $\pm$ 4.47 mm^2 to 13.13 $\pm$ 3.10 mm^2. Vessel wall stretching (i.e. change in external elastic lamina area) accounted for only 15% of lumen area gain. Luminal gain was higher in non-calcified (6.52 $\pm$ 2.12 mm^2) than in lesions containing deeply located calcium (5.19 $\pm$ 0.99 mm^2) and lowest in superficially calcified lesions (5.41 $\pm$ 2.41 mm^2).

Ultrasound imaging identified an atherectomy byte in 85% of the cases, while angioscopy revealed such a crevice in 74%. The complimentary use of the 3 technique revealed an underestimation of the presence of dissection/tear and new thrombus by angiography (10% and 4%) and ultrasound imaging (12% and 0%) compared with angioscopy (26% and 21%).

Conclusions. The combined use of angiography, ultrasound and angioscopy reveals that the post-atherectomy luminal lining is not as regular and smooth as seen by angiography. Luminal enlargement with atherectomy is achieved by plaque excision rather than arterial expansion.

INTRODUCTION

Directional coronary atherectomy has been introduced as an alternative interventional technique aimed at debulking rather than dispersing the protruding coronary artery plaque [1-13]. The selective removal of the plaque may potentially minimize the vessel wall damage by avoiding the induction of large dissections and promoting the restoration of a large regular vessel lumen. The potential mechanisms responsible for the luminal improvement achieved by directional atherectomy may include (i) plaque removal, (ii) vessel wall stretching, (iii) creation of dissections, (iv) normal vessel wall cutting, (v) plaque redistribution and (vi) plaque compression. Some of these features of directional atherectomy have been assessed in a limited number of angiographic and ultrasound studies but a comprehensive appreciation of all mechanisms involved in luminal gain after atherectomy has sofar not been performed. The introduction of intracoronary ultrasound imaging and coronary angioscopy in clinical practice permit detailed analysis of coronary artery lesion morphology and vessel wall damage in a manner not available with angiography [14-24]. In theory, the combined use of these three imaging techniques may provide insights into the working action of directional coronary atherectomy and may identify factors determining acute success and late outcome. The purpose of this study, therefore, is to use the complementary information of these imaging techniques to describe the vessel wall changes and lumen area configuration after directional atherectomy in order to elucidate the mechanism of atherectomy.

METHODS

Patients:
The study group comprised 26 patients who underwent directional atherectomy for symptomatic native coronary artery disease (Table I). There were 22 men and 4 women with a mean age of 57 $\pm$ 9 years. The majority of the patients (54%) was treated for unstable angina according to the Braunwald classification [25]. Four patients had a history of a myocardial infarction and 1 patient was treated for restenosis after a previous balloon dilatation. The majority of the lesions (65%) was located in the left anterior descending coronary artery.
Directional atherectomy was performed as previously described [6,7]. All patients had a successful procedure defined as an angiographic residual diameter stenosis of $<50\%$ on visual inspection. On-line quantitative coronary angiography (DCI Philips) before and after the atherectomy was performed to optimize device selection and to

assess the procedural result.

Intracoronary ultrasound imaging:

All patients underwent ultrasound imaging before and after atherectomy. The ultrasound images were obtained with a 4.3 F, 30 MHz ultrasound catheter (Cardiovascular Imaging Systems Inc., Sunnyvale, CA). The catheter was guided by simultaneous fluoroscopic monitoring. Ultrasound gain settings were adjusted for optimal visualization of the arterial wall-lumen interface in normal segments while saline injections were performed to improve the delineation of the leading edge echo when necessary.

Qualitative assessment of the ultrasound images was performed by a consensus of three observers using the integrated information acquired from a pullback manoeuvre [26-28] and comprised (i) plaque composition, (ii) plaque topography, (iii) the presence or absence of dissections and (iv) the presence or absence of an atherectomy byte. A lesion was judged as concentric when a thickening was circumferential along the entire vessel wall as opposed to an eccentric when a part of the vessel wall was disease-free. The following definitions were used to describe plaque morphology: *soft plaques*: more than 75% of the plaque area is composed of thickened intimal echoes with echodensity less than the reference adventitia. *Fibrous plaques*: more than 75% of the plaque area is composed of bright echoes, as bright or brighter than the reference adventitia, but without acoustic shadowing. *Diffuse calcific plaques*: bright echoes within a plaque with acoustic shadowing and occupying more than 180° of vessel wall circumference. *Mixed plaques*: when there is a combination of different types. The following definition was used to assess the presence of a *dissection*: a demarcated break in the linear continuity of the plaque with circumferential or longitudinal involvement of the internal elastic membrane. An atherectomy byte was defined as a rectangular excision into the (sub)intimal layer.

Quantitative measurements were made off-line from a videotape. *Lumen area* was defined as the area within the leading edge echo; *external elastic membrane area* was defined as the area within the media-adventitia boundary; *plaque plus media area* was defined as the difference between external elastic membrane area and luminal area [27]. Variability measurements including interobserver variability and the correlation between ultrasound measurements with circular phantoms and human coronary artery casts have been reported previously [29].

Coronary angioscopy:

In 19 patients the target artery was also evaluated by coronary angioscopy before and after atherectomy as previously described [19,30,31]. Unsuitable lesions for angioscopy included (i) proximal stenosis location (< 1.5 cm from the left main ostium) not allowing effective balloon inflation and (ii) excessive tortuosity not allowing visualization of the lumen. Angioscopy was performed with a 4.5 F

angioscope (Baxter-Edwards, Irvine, CA). During angioscopy the distal artery was flushed with Ringer lactate solution injected with a flow of 30 to 40 cc/min. To facilitate the review process a real-time fluoroscopy or cineangiography is combined with real-time angioscopy and ultrasound imaging by using split screen videotaping. Angioscopic images were assessed according to the recommendations of the European Working Group of Angioscopy [31]: *red thrombus* was defined as *lining or mural* thrombus when a red, predominantly mural, non-mobile, superficial mass adherent to the vessel surface was observed, as *protruding* when a red, intimal protruding, mobile or non-mobile mass adhered to the vessel wall was seen and as *occlusive* thrombus when a red intraluminal mass occluded completely the lumen. *Dissections* were distinguished into *small surface disruptions* (small, very mobile structures which are contiguous with the vessel wall) and *large dissections* (visible cracks or fissures on the luminal surface and/or large mobile or non-mobile structures which are contiguous with the vessel wall and of homogeneous appearance with the vessel wall). An *atherectomy induced byte* was defined as deep rectangular crevices extending into the wall in conjunctions with a mobile flap.

Quantitative coronary angiography:

Quantitative analysis of the coronary segments was performed with the computer based Coronary Angiography Analysis System (CAAS), previously described in detail [6,7,32-37]. In essence, boundaries of a selected coronary artery segment are detected automatically from optically magnified and video digitized regions of interest (512 x 512 pixels) of a cine-frame. The absolute diameter of the stenosis in mm is determined using the guiding catheter. The computer-estimation of the original dimension of the artery at the site of the obstruction allows to define the interpolated reference diameter. The percentage diameter stenosis is then calculated. To determine the changes in minimal cross-sectional area of the coronary artery segment from the density profile within the artery, videodensitometric algorithm was applied. 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. Intracoronary isosorbide dinitrate (1-3 mg) was given prior to and following atherectomy. At follow-up catheterization the administration of intracoronary nitrates was recommended prior to angiography. To standardize the method of data acquisition and data analysis and to ensure reproducibility of post-atherectomy and follow-up angiograms, measures were taken as previously described [34-36].

Histology:

The paraffin-embedded specimens were stained with haematoxylin-azophloxine as a routine stain. Von Kossa staining was used as a stain for calcium. The definitions of intima, media and adventitia have been described previously [38] and are in

accordance with the recommendations of the AHA Medical/Scientific Statement [39].

Statistical analysis:

All values are expressed as mean values ± 1 SD). The paired student's t-test was used to detect differences between continuous variables. Differences between categorical variables were tested with the chi-square and Fisher exact tests as appropriate. Differences were considered statistically significant where the p-value was less than 0.05.

RESULTS

Lesion morphology:

On *angiography*, the majority of the culprit lesions (88%) were considered type B lesions according to the AHA/ACC classification, 85% of the lesions were eccentric. None of the lesions were calcified or showed angiographic signs of thrombus (discrete filling defect surrounded by contrast in the absence of calcifications, or persistent contrast staining in the area of the stenosis).

Table 1. Patient and lesion characteristics.

Age (years)	57 ± 9
Gender (M/F)	22/4
Unstable Angina	14
Previous infarction	4
Previous PTCA	1
Lesion location LAD RCA LCX	 17 6 3
AHA/ACC classification type A type B type C	 3 (12%) 21 (88%) 0 (0%)

	Angiography	Ultrasound	Angioscopy
Eccentric	22 (85%)	20 (77%)*	**
Calcification	0 (0%)	14 (55%)	**
Thrombus	0 (0%)	0 (0%)	7 (37%)

*: eccentricity index ≤0.5 defined as minimal luminal diameter/maximal luminal diameter **: no value

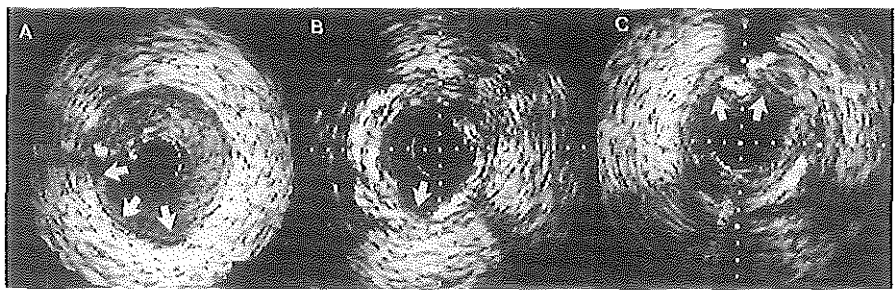

Figure 1. Intracoronary ultrasonic images of three patients illustrating the patterns of atherectomy bytes (white arrows). A: multiple bytes were performed in the normal vessel wall opposite to the atherosclerotic plaque. B: single atherectomy byte next to the treated lesion showing deposits of deep calcifications. C: pattern of two atherectomy bytes with a remaining part of the calcified plaque between both bytes. Apparently, the atherotome was unable to remove this piece of calcification.

The *intravascular ultrasound* catheter could be advanced through the stenosis in all 26 cases. In 18 patients the ultrasound probe was wedged into the stenosis. The majority of the lesions (58%) was characterized as soft lesions with minimal calcific depositions. One lesion was diffusely calcified with a calcific arch of $>180°$ while 10 patients (38%) exhibited focal calcifications either superficially (n=5) or deeply located (n=5).

Direct visualization of the vessel wall by *angioscopy* prior to atherectomy was performed in 19 patients and showed an irregular lesion in 12 patients. Yellow plaques were seen in 14 patients. Red masses suggestive of thrombus was noted in 7 patients (4 protruding and 3 lining thrombi). No flaps or dissections were observed.

Procedural results:

All 26 patients had successful atherectomy procedures that reduced the residual diameter stenosis to <50%. No balloon predilatation was performed. Atherectomy was performed with a 7 French atherotome in 84% of the cases and a mean of 8 ± 3 cuts were made in multiple directions. Although all atherectomy procedures were judged successful on angiography, 4 patients underwent an adjunctive balloon dilatation to optimize the final result. No major clinical complications (i.e. death, Q-wave myocardial infarction and coronary artery bypass surgery) were observed. In one patient a non-Q wave infarction (max. CPK 600 U/l) occurred due to a guiding catheter induced occlusive dissection of the right coronary ostium after a successful atherectomy. During coronary angioscopy, the majority of the patients experiences chest pain with concomitant electrocardiographic changes suggestive for ischemia.

Table 2. Quantitative angiographic and ultrasonic measurements of lesion severity and procedural result after directional coronary atherectomy.

	pre-atherectomy	post-atherectomy	p-value
Angiography			
Reference diameter (mm)	3.52 ± 0.52	3.70 ± 0.59	NS
Minimal lumen diameter (mm)	1.16 ± 0.43	2.85 ± 0.62	<0.0001
Diameter stenosis (%)	67 ± 11	23 ± 13	<0.001
Minimal cross-sectional area (mm^2)	1.20 ± 0.87	6.67 ± 2.70	<0.0001
Area stenosis (%)	88 ± 8	39 ± 20	<0.001
Ultrasound			
External elastic lamina area (mm^2)	20.11 ± 4.43	21.00 ± 3.91	0.02
Plaque + media area (mm^2)	18.16 ± 4.47	13.13 ± 3.10	<0.0001
Lumen area (mm^2)	1.95 ± 0.70	7.86 ± 2.16	<0.0001

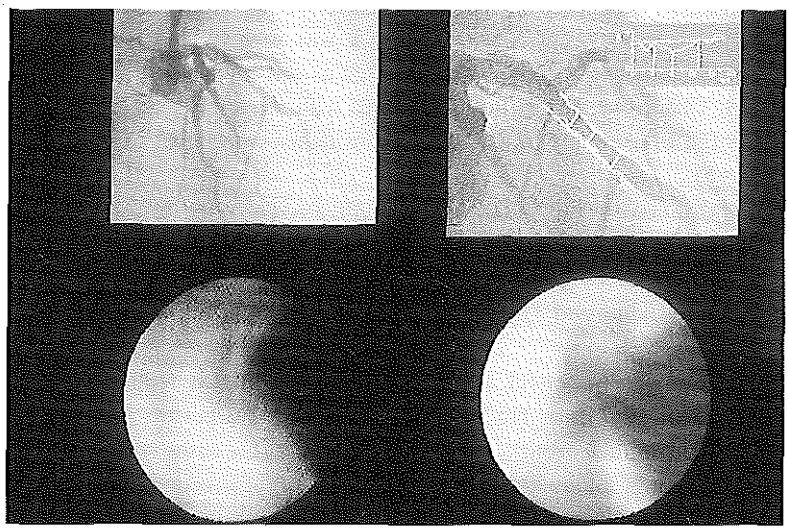

Figure II. Angiographic and angioscopic observations of an atherectomized stenosis in the mid portion of the left anterior descending coronary artery. Following atherectomy, the coronary artery wall had a smooth contour (left upper panel) while on-line quantitative coronary angiography shows a mild residual stenosis (right upper panel). On angioscopy, the proximal part of the artery had indeed a smooth wall configuration (right lower panel), however opposed to the angiographic findings, a small flap and a crevice suggestive for an atherectomy cut at the target lesion were seen (left lower panel).

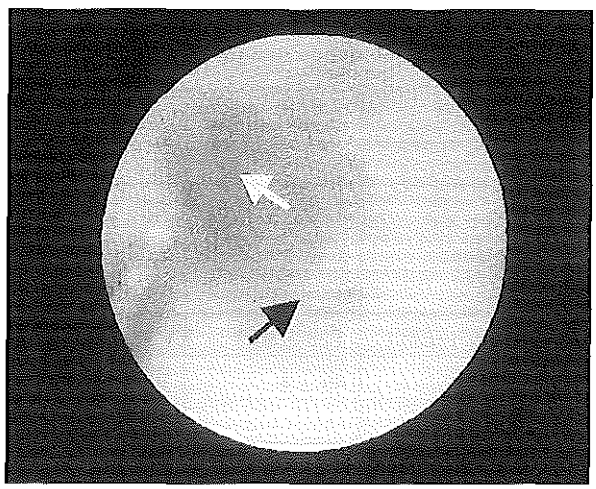

Figure III. Angioscopic illustration of the vessel wall configuration after directional atherectomy. The white arrow indicates the site of the excision which has formed a crevice into the wall. A small flap is observed at the site of the residual lesion (black arrow). The residual lesion contains yellow plaque material and has an irregular surface.

After balloon deflation, these abnormalities subsided and the chest pain disappeared.
Quantitative angiography (Table II):
The mean vessel size of this patient population was 3.52 ± 0.52 mm. Atherectomy induced an increase in minimal luminal diameter from 1.16 ± 0.43 mm to 2.85 ± 0.62 mm ($p<0.001$). After atherectomy, the diameter stenosis and area stenosis were 23 ± 13% and 39 ± 20% respectively. Correspondingly, the minimal luminal cross-sectional area as derived from videodensitometry also increased from 1.20 ± 0.87 mm^2 to 6.67 ± 2.70 mm^2 ($p<0.001$)
Quantitative ultrasound measurements:
External elastic membrane area, lumen area and plaque+media area at the normal reference segment proximal to the stenotic lesion did not change significantly during the procedure.

Table 3. Ultrasonic assessment of plaque reduction and lumen area gain achieved at atherectomy according its localisation and histological confirmation.

Plaque reduction (mm^2)			
Ultrasound	Histology		
	calcium	no calcium	
Subendothelial calcium	4.13 ± 2.11 (n=5)	- (n=0)	4.13 ± 2.11 (n=5)
Base of the plaque calcium	4.95 ± 1.36 (n=5)	3.85 ± 1.49 (n=5)	4.40 ± 1.46 (n=10)
No calcium	6.21 ± 4.75 (n=5)	5.62 ± 2.26 (n=6)	5.89 ± 3.47 (n=11)
	5.16 ± 3.16 (n=15)	4.88 ± 2.10 (n=11)	
Lumen area gain (mm^2)			
	calcium	no calcium	
Subendothelial calcium	5.41 ± 2.41 (n=5)	- (n=0)	5.41 ± 2.41 (n=5)
Base of the plaque calcium	5.19 ± 0.99 (n=5)	5.83 ± 1.57 (n=5)	5.51 ± 1.28 (n=10)
No calcium	6.34 ± 2.72 (n=5)	6.68 ± 1.66 (n=6)	6.52 ± 2.12 (n=11)
	5.69 ± 2.13 (n=15)	6.33 ± 1.61 (n=11)	

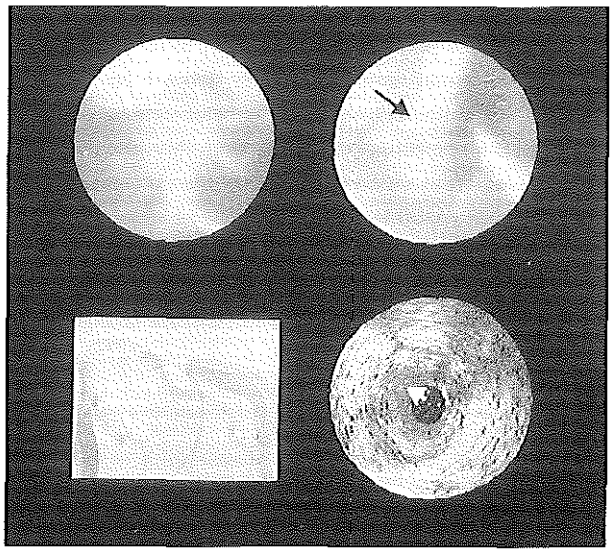

Figure IV. The combined use of angiography, ultrasound imaging and angioscopy in a patient who underwent directional atherectomy. The left upper quadrant illustrates the concomitant angiographic view showing a concentric lesion without evidence of thrombus. The right upper quadrant shows the enlarged lumen as assessed by ultrasound and shows the orientation of the atherectomy byte (arrow). The left lower quadrant shows the angioscopic view of the target stenosis before atherectomy with a thrombus present. After atherectomy, angioscopy identified an increase in lumen, a protruding flap without evidence of thrombus (right lower quadrant).

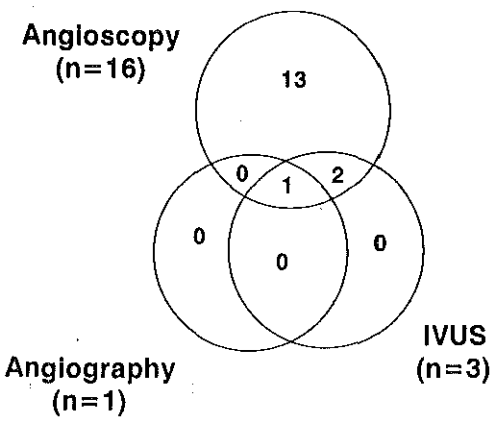

Figure V. Venn diagram to illustrate the complimentary information obtained by angiography, intracoronary ultrasound imaging and coronary angioscopy with respect to the detection of dissections. As shown, angiography and ultrasound imaging underestimate the incidence of dissections as compared with angioscopy.

No difference in external elastic membrane area between the reference and stenotic segment (20.94 ± 5.39 mm^2 vs 20.11 ± 4.43 mm^2;p=NS) was found, in other words no compensatory enlargement at the site of the stenosis could be documented. Directional atherectomy induced a significant increase in lumen area from 1.95 ± 0.70 mm^2 to 7.86 ± 2.16 mm^2 ($p<0.0001$) and a decrease in plaque plus media area from 18.16 ± 4.47 mm^2 to 13.13 ± 3.10 mm^2 ($p<0.0001$). The external elastic membrane area changed from 20.11 ± 4.43 mm^2 to 21.00 ± 3.91 mm^2 ($p=0.02$) which implies that vessel wall stretching is responsible for only 15% of the lumen area improvement achieved at directional atherectomy. The gain in lumen area was not dependent on lesion morphology (6.33 ± 2.05 vs 5.49 ± 1.68;p=0.30 soft vs mixed lesions) but did differ between calcified and non-calcified lesions; the change in lumen area varied with the location of calcium and was lowest in those lesions which contained (superficial) subendothelial calcium as compared to (deep) calcium at the base of the plaque (5.41 ± 2.41 mm^2 vs 5.51 ± 2.41 mm^2). Plaque reduction in cross-sectional lumen area was greatest in ultrasonic non-calcified lesions when compared with calcified lesions (5.89 ± 3.47 mm^2 vs 4.13 ± 2.11 mm^2). There were too few patients with three or four quadrant calcifications to assess the influence of the calcification arc on area improvement. Subsequent histological examination confirmed the presence of calcium in all plaques containing ultrasound evidence of superficial calcium (n=5) whereas it confirmed the presence of calcium in 50% in those cases with deep calcium (n=10). In addition, plaque reduction and lumen area gain were higher in those cases with histological evidence of calcium than those without calcium in the retrieved specimen (table III).

The post-atherectomy lumen area configuration (Figure I-IV):

Angiography after atherectomy revealed a smooth luminal lining in 19 patients, persistent haziness in 4, a dissection in 2 and thrombus in 1. *Ultrasound imaging* showed a regular lumen configuration in 4 of the 26 patients, an irregular configuration in 15, a subintimal tear in 4 (15%) and a dissection in 3 patients (12%). The appearance of a tear or dissection was not related and did not apparently contribute to lumen area gain as assessed by ultrasound because the gain in lumen area was not different in this group compared with patients without evidence of dissections/tears (5.81 ± 2.82 mm^2 vs 5.95 ± 1.68 mm^2;p=NS).

In 22 (85%) patients evidence of an atherectomy bytes were seen which resulted in a non-circular lumen area configuration. A clover-like post-atherectomy area configuration was never observed. Although the atherotome was directed towards the plaque in 1 patient the atherectomy bytes were made into the non-diseased area next to the plaque. *Coronary angioscopy* revealed an intracoronary thrombus after atherectomy in 11 patients (61%). In 4 of these patients (21%) this was a new thrombus while in the remaining 7 patients thrombus was already observed before

atherectomy. Dissections were observed in 5 patients (26%) and multiple or single subintimal flaps were seen in 9 (42%) and 2 (11%) patients. In 14 patients (74%) a crevice suggestive of an atherectomy byte was observed (figure III).

Complementary information of the three imaging techniques:

Figure V shows the frequency of dissections and thrombi detected by angiography, ultrasound and angioscopy. Angiography definitely underestimates the incidence of dissections (10%) compared with ultrasound (12%) and angioscopy (26%). The dissection seen on angiography was also detected by ultrasound and angioscopy, however, angiography detected only 33% of the dissections observed by ultrasound and 9% of the small and 0% of the big dissections noted by angioscopy. Although none of the big dissections visualized by angioscopy were demonstrated by ultrasound, all these patients had an irregular luminal contour on ultrasound examination. The incidence of post-atherectomy thrombus detected by angioscopy was 58% compared to 0% and 4% by ultrasound and angiography.

DISCUSSION

Because intra-coronary ultrasound imaging and coronary angioscopy permit detailed analysis of coronary artery lesion morphology and vessel wall damage in a manner not available with angiography, the complementary information obtained with these 3 imaging techniques is of pivotal value for the assessment of the mechanisms of luminal improvement during directional coronary atherectomy. The major findings of this study are threefold. First, the present study demonstrates that the combined use of quantitative angiography, coronary ultrasound imaging and intracoronary angioscopy may be applied safely in patients who underwent atherectomy for stable and unstable angina. Second, the main mechanism of action of atherectomy appears plaque reduction by excision rather than vessel wall stretching. Although selective plaque removal should in theory lead to a circular vessel lumen, ultrasound imaging in this series detected atherectomy bytes outside the plaque area and non-confluent bytes in the plaque. Subsequent direct visualization by angioscopy confirmed these bytes as vessel wall trenches. Therefore, the post-atherectomy vessel wall configuration is not circular or smooth as previously demonstrated in angiographic observations [3]. Whether this irregularity ultimately may facilitate the renarrowing process by allowing ingrowth of hyperplastic tissue within these areas remains to be assessed. Third, unlike the angiographic observations, detailed angioscopic imaging showed evidence of substantial vessel wall trauma leading to an irregular post-atherectomy lumen configuration with dissections, bytes and thrombi.

Plaque reduction:
The present study offers more detailed information on the mechanism of plaque reduction because, unlike in other studies, all lesions were crossed by the ultrasound device before and after atherectomy. Subsequently, plaque reduction was found to be the major determinant of the final luminal improvement achieved by directional atherectomy. These findings concur with those of other groups [22-24] and clearly differ from those of balloon angioplasty studies. These differences in action of devices may be of importance when examining the long-term results of various interventions. The present observations indicate that secondary to differences in luminal improvement, the renarrowing process after atherectomy may be of another nature (i.e. hyperplasia) than after balloon dilatation (i.e. recoil).
Vessel wall stretching:
Our observations indicate that although a significant plaque reduction occurred in most cases, accounting for most of the luminal gain, vessel wall stretching was the mechanism of luminal enlargement in some individual cases. In the entire group, vessel wall stretching, defined as the difference in external elastic membrane area before and after atherectomy, was found to a major contributor in the lumen area increase which is opposed to findings in previous angiographic studies [12,13]. This observation underscores the limitations of angiographic studies when assessing the mechanism of interventions.
Normal wall retrieval:
Disease-free wall excision, which is unique to atherectomy, indeed plays a role in the mechanism of lumen area enlargement. In the present patient population, ultrasound was the only technique which could determine whether the atherectomy bytes were appropriately targeted. Until now, this feature of atherectomy has not been highlighted with exception of a case report on the death of a patient due to coronary artery rupture [40]. There are two possible explanations for the occurrence of inappropriate directional cutting. First, device positioning was achieved under fluoroscopic guidance yielding a two-dimensional representation of the arterial geometry. Subsequent inappropriate positioning may well occur and not be visualized by angiography. Second, device rotation during cutting may have happened due to lesion characteristics or device under/oversizing. In our series, no stenosis characteristics were found to be predictive of the occurrence of disease-free vessel wall cutting while adequate device sizing was performed using digital quantitative angiography to estimate vessel size and lesion severity. In the cases with predominant disease-free wall oriented shaving, angiography showed a small residual stenosis after atherectomy and is thus of limited value in determining the post-procedural lumen area geometry. Additional passages with the atherotome to remove the plaque under angiographic guidance may in these cases be hazardous and our observations call for

the urgent need of ultrasound guided atherectomy to avoid this complication.

Compression and remodelling:

Whether the amount of plaque reduction represents tissue removal rather than redistribution can not be elucidated from this study since three-dimensional reconstruction of the stenosis was not performed routinely.

Dissections:

In a previous angiographic study, Hinohara et al [49] concluded that atherectomy resulted in a smooth vessel wall contour with less dissections than after balloon angioplasty. The present study offers the benefit of using the complementary information obtained by ultrasound and angioscopy and shows that these two imaging techniques more accurately detect dissections and irregular wall abnormalities. These findings are in agreement with observations of the GUIDE I trial in which dissections were seen in 40% by ultrasound compared to 19% by angiography [50]. In concert with these observations, the combined use of two imaging modalities may provide further insights into the origin of dissections. Indeed, our study indicates that dissections may be due to the specific cutting mechanism of atherectomy since the dissections were located at the site of the atherectomy bytes as visualized by angioscopy. Tenaglia et al [51] demonstrated the clinical significance of these observations and found that patients with an adverse outcome after atherectomy had a significant higher incidence of dissections compared to patients without adverse events. In keeping with these findings we have performed addition balloon dilatation after post-atherectomy ultrasound assessment in two patients to improve the atherectomy result thereby avoiding the risk of adverse events. The absence of such events in this population may reflect the advantage of such ultrasound guided atherectomy procedures.

Thrombus:

The detection of intracoronary thrombus by angiography has been hampered by the low resolution of the image intensifiers. Therefore it is understandable that direct visualization of the coronary vessel wall by angioscopy proved to be more accurate to identify thrombi than angiography [17,41-43]. Like dissections, the clinical significance of post-atherectomy thrombi resides in the high acute event rate associated with this finding [52] and therefore, the prevention or treatment of post-atherectomy thrombi may beneficially influence the short-term and late outcome after atherectomy. In particular, thrombi resection by atherectomy has been associated with less restenosis [53,54] while residual intraluminal thrombus is a potential stimulus for an augmented proliferative vessel wall response. Although angioscopy revealed post-atherectomy thrombi in 33% of the present patients, no acute events were seen. Whether subsequent intervention (thrombolysis, angioplasty) after the detection of thrombi results in a decrease in the restenosis rate remains to be determined.

Atherectomy for calcified lesions:
Although angiography did not detect the presence of calcium in any of the atherectomized lesions, 10 lesions contained focal deposits of calcium as demonstrated by ultrasound while 14 were calcified according to histological definitions. Although no statistical differences were detected in quantitative ultrasound measurements before and after directional atherectomy, a trend towards less plaque reduction and lumen area gain was observed in calcified lesions. More specifically, the localization of the calcium appears to be a determinant of the acute procedural result of atherectomy with less gain in those plaques with superficially located subendothelial calcium. Apparently, the cutting mechanism is less effective when the atherotome has to cut through areas containing calcium. The combined use of intravascular ultrasound and histology also provides evidence that directional atherectomy removes calcium. Specifically, all lesions that contained superficially located spots of calcium had histologic evidence of calcium in their atherectomy specimens whereas only 50% of the deeply situated calcium could be retrieved. Because acoustic shadowing of the calcium, the thickness of the calcium spots cannot be measured and therefore the amount of calcium removed can not be determined. These results suggest that micro-calcification of coronary artery lesions does not play a negative role when performing directional coronary atherectomy.
Post-atherectomy lumen area configuration:
Luminal renarrowing after new interventions remains an equally vexing problem than after conventional balloon angioplasty. Recent publications on longterm results after interventions with new devices such as stenting and atherectomy have taught us that the acute procedural result partially determines the late angiographic outcome [1,4,5,7-10]. However, even when an optimal angiographic procedural result after atherectomy or stenting is obtained, restenosis remains the major limitation of these procedures [1-11,36]. With the clinical application of ultrasound imaging and angioscopy, more detailed information regarding the effect of the disruptive process of an intracoronary intervention on the luminal geometry can be obtained. In particular, ultrasound imaging has been shown to be superior in detecting dissections than angiography [16,18] while angioscopy is more efficient in visualizing thrombus [41-43]. Subsequent analyses of such images may identify predictors for restenosis. Preliminary findings have indeed indicated that vessel wall stretching and tearing may lead to an increased fibro-proliferative response [44]. Also disruption of the internal elastic lamina leads to an enhanced luminal renarrowing process in human stented venous grafts [45] and swine stented coronary arteries [46-48].
Conclusions:
The complementary information of ultrasound imaging and coronary angioscopy have revealed further insight into the mechanism of directional atherectomy. In particular

atherectomy yields a less circular vessel wall area configuration with a higher number of dissections and more residual thrombi than detected on angiography. These results suggest that ultrasound and/or angioscopy may be used to guide atherectomy procedures thereby identifying an adverse angiographic outcome that may lead to serious clinical complications.

Limitations:

This study has several limitations. First, although at the outset of the study it was foreseen that all patients who would undergo atherectomy and had suitable anatomy for intracoronary angioscopy would be included in this prospectively collected series, it was not to perform angioscopy in some patients. Second, the size of the intravascular ultrasound catheter and the guidewire-artifact may have led to an underestimation of the number and orientation of the atherectomy bytes. Third, because a motorized pull-back procedure with three-dimensional ultrasonic reconstruction was not routinely performed, the extent of compression and remodelling could not be assessed.

Fourth, we recognize the relative small sample size of our study population which precludes further subgroup analyses. However, this pilot study does provide useful information on the working mechanism of atherectomy and the complementary information provided by the three imaging techniques. Finally, although the procedure was occasionally influenced by the ultrasonic and angiocopic information, it was not our intention to examine the impact of these imaging techniques on procedural outcome.

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Part II

CLINICAL OBSERVATIONS

Chapter 9

ONE HUNDRED THIRTEEN ATTEMPTS AT DIRECTIONAL CORONARY ATHERECTOMY: THE EARLY AND COMBINED EXPERIENCE OF TWO EUROPEAN CENTERS USING QUANTITATIVE ANGIOGRAPHY TO ASSESS THEIR RESULTS

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ABSTRACT

Directional coronary atherectomy has been introduced as an alternative for conventional balloon angioplasty when treating coronary artery stenoses with complex lesion morphology. To determine the immediate efficacy of coronary atherectomy in patients with such lesions, the first 113 attempts at directional atherectomy in two centers using quantitative angiography were reviewed in 105 patients. The lesions were classified as complex stenosis since 95% of the lesions had a symmetry index < 1.0 and a length of 6.83 ± 2.55 mm on average and an area plaque of 9.77 ± 6.69 mm^2. Procedural success defined as a residual stenosis $\leq 50\%$ after tissue retrieval was obtained in 90 (85.7%) of 105 patients. The primary angioplastic success rate, combining atherectomy and balloon angioplasty in case of failed attempt at atherectomy was 95.2%.

Coronary atherectomy was unsuccessful in 5 patients; three of these were referred for emergency coronary artery bypass grafting. Major complications (death, emergency surgery and transmural infarction) were encountered in 5.7% of the patients.

Assessed by quantitative coronary analysis, a residual minimal luminal diameter of 2.42 ± 0.52 mm and a diameter stenosis of $26 \pm 12\%$ were obtained immediately after directional coronary atherectomy.

We conclude that directional coronary atherectomy is particularly suitable for the treatment of stenosis with complex lesion morphology and is associated with acceptable complication rates. Randomized trials comparing atherectomy with balloon angioplasty are warranted to clarify the role of atherectomy in the treatment of lesions in the proximal part of the three major epicardial coronary arteries.

INTRODUCTION

Percutaneous transluminal coronary angioplasty was reported in 1978 by Gruentzig [1] as a non-operative technique for the treatment of single, discrete and proximal coronary artery stenosis in patients with symptomatic ischemic heart disease. Over the past decade improved technology and operator experience have led to a greater use of conventional balloon angioplasty with an excellent immediate success rate [2,3]. As indications for coronary angioplasty expand and more difficult anatomy is approached, the likelihood of acute complications has increased. Potential causes of an initial suboptimal and unsatisfactory angiographic result after conventional balloon angioplasty include arterial recoil, dissections and presence of thrombus. In the past 4 years, interventional cardiologists have designed new devices aimed at debulking the atherosclerotic plaque. Directional coronary atherectomy is such a new technique having the potential advantage of creating a smooth luminal surface by removing rather than remodelling the plaque. We report the immediate quantitative angiographic results of the initial 113 clinical applications of directional coronary atherectomy in two european centers using the same methodology to assess the efficacy of intra-coronary interventions. Patients were referred for elective transcatheter treatment of an angiographic complex lesion and selected for directional coronary atherectomy when they presented with a suitable coronary anatomy (a stenosis in the proximal part of a coronary artery with a reference diameter $\geq$ 2.5 mm). Quantitative coronary angiographic analysis (CAAS) was used to evaluate the immediate efficacy of directional atherectomy.

METHODS

Patient selection:
From September 1989 through April 1991, 105 patients underwent 113 attempts at directional coronary atherectomy at the two participating centers. Both medically stable and unstable patients were considered candidates for directional atherectomy when they presented with a large and eccentric coronary artery stenosis in the proximal part of an epicardial coronary artery with an anticipated reference diameter of at least 2.5 mm.
Coronary atherectomy:
The atherectomy procedure was carried out as previously described [4]. Briefly, all patients were pretreated with 250 mg acetosalicylatic acid and 10,000 U heparin intravenously. To prevent coronary spasm, intra-coronary isosorbide dinitrate was given. Following the initial angiograms, the atherectomy device was advanced using the over the wire technique and positioned across the stenosis. After proper positioning the support balloon was inflated up to 2 to 3 atm, the

driving motor was activated and the rotating cutter was slowly advanced to cut and collect the protruding intimal lesion in the collecting chamber located at the tip of the catheter. After each pass the balloon was deflated and either removed or repositioned. Atherectomy was considered successful when the residual stenosis was less than 50% and plaque material was present in the collecting chamber. Following atherectomy, the patients were monitored for 24 hours and electrocardiograms and cardiac enzyme levels were obtained twice a day. Nifedipine or nitrates were given every two hours for 24 hours after the procedure, and aspirin was given for one year. All atherectomy procedures were performed after obtaining informed consent.

Quantitative coronary angiography:

Quantitative analysis of the coronary segments was performed with the computer based Coronary Angiography Analysis System (CAAS), previously described in detail [4-8]. In essence, boundaries of a selected coronary artery segment are detected automatically from optically magnified and video digitized regions of interest (512 x 512 pixels) of a cine-frame (figure I and II). The absolute diameter of the stenosis in mm is determined using the guiding catheter as a scaling device. Calibration of the catheter in absolute values (mm) is achieved by comparing the mean diameter of the guiding catheter in pixels with the measured size in millimeters. Each individual catheter is measured by a micrometer. To correct the detected contour of the arterial and catheter segments for pincushion distortion, a correction vector is computed for each pixel based on a computer- processed cineframe with a centimeter grid placed against the input screen of the image intensifier. Since the functional significance of a stenosis is related to the expected normal cross sectional area of a vessel at the point of obstruction, we use a computer-estimation of the original dimension of the artery at the site of the obstruction to define the interpolated reference diameter. The percentage diameter and area stenosis as well as the cross sectional area (mm^2) are then calculated. The length of the lesion (mm) is determined from the diameter function on the basis of a curvature analysis. Symmetry is defined as the coefficient of the left hand distance between the reconstructed interpolated reference diameter and actual vessel contours and the right hand distance between reconstructed and actual contours at the site of the obstruction. The symmetry index ranges from 0 (totally eccentric stenosis) to 1 (symmetric). The degree of coronary bend is assessed by the curvature value at the obstruction site. This parameter 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. The area between the actual and reconstructed contours at the obstruction site is defined as the area plaque and is expressed in mm^2. The severity of a stenosis can also be expressed as a percentage area stenosis assuming circular

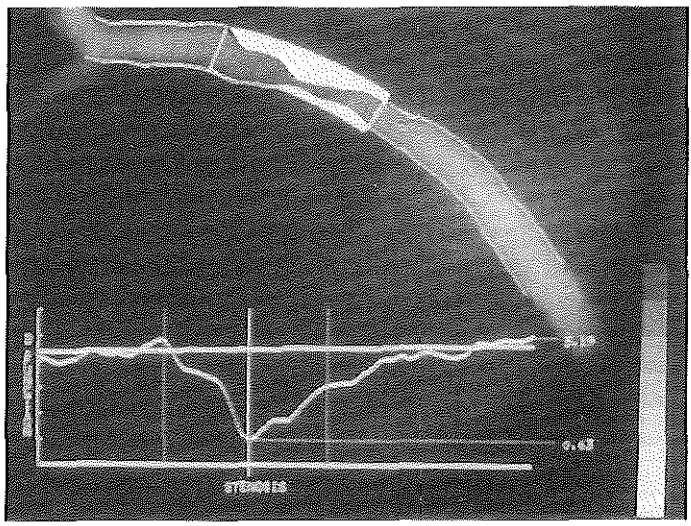

Figure I. Detected contours superimposed on the original video image for a complex lesion within a stent in a venous bypass graft, filmed in lateral (LAT) projection before directional atherectomy. The diameter function is shown at the bottom. The white area is a measure for the "atherosclerotic plaque". The minimal luminal diameter (vertical line) is 0.63 mm, corresponding to a diameter stenosis of 78% and an area stenosis of 95%.

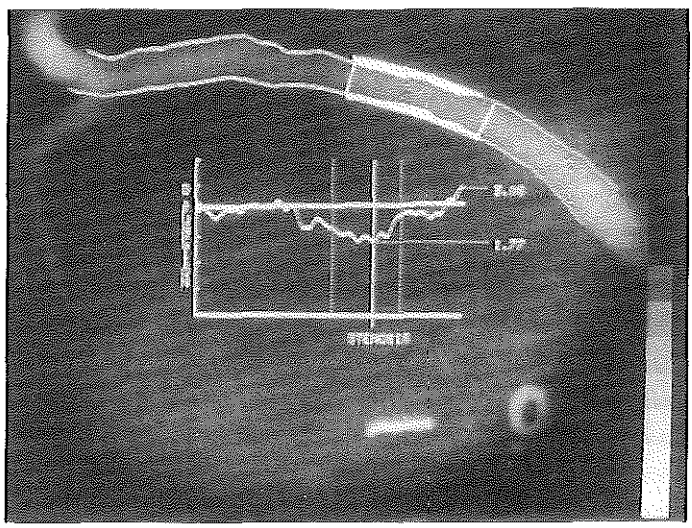

Figure II. A single-frame angiogram of the venous bypass graft filmed in LAT after directional atherectomy. The minimal luminal diameter increased to 1.77 mm, corresponding to a diameter stenosis of 33% and an area stenosis of 55%.

cross sections at the obstruction and reference position. Corresponding luminal areas (mm^2) were calculated by comparing the minimal area value at the obstruction with the reference value obtained following the interpolated diameter technique.

RESULTS

Technical success in crossing the stenosis with the atherectomy device was achieved in 95 of 105 patients (90.5%). In 10 patients atherectomy was not performed since the stenosis could not be reached by the atherectomy device; twice the guiding catheter could not be placed selectively in the coronary ostium and eight times the lesion could not be crossed by the atherectome itself. Nine of these patients underwent a successful conventional angioplasty procedure while one patient was electively referred for coronary artery bypass grafting. These 10 patients belonged to the cohort of the initial 25 patients treated by atherectomy in each center.

Clinical and lesion characteristics:

Of the 95 patients in whom directional coronary atherectomy was performed, 24% had a history of a previous balloon angioplasty (n=15), stenting (n=6) or coronary atherectomy (n=2), 24% had two or three-vessel disease and 41% had a previous myocardial infarction (table 1). Two patients had previously undergone a heart transplantation. At the time of atherectomy, 41 patients were in New York Heart Association functional class IV, 27 patients in class III, 26 patients in class II and one patient in class I. The target stenosis (n=103) in these 95 patients was located in the left anterior descending artery in 63 cases, in the left circumflex in 12 cases, in the right coronary artery in 24 cases and four times in a venous bypass graft.

Procedural results:

In all but 4 patients a 6 French atherectomy device was used. One patient was treated with a 5 French and in 3 patients a 7 French atherectomy device was used. On average 5.8 $\pm$ 2.8 passes in multiple directions were performed. The primary success rate as defined by a residual stenosis $<50\%$ and tissue withdrawal was 85.7% (90 of 105 patients). The primary angioplastic success rate, combining atherectomy and balloon angioplasty in case of failed attempt at atherectomy was 95.2% (100 of 105 patients). In five patients directional atherectomy was not successful; in one patient an obstructive dissection occurred which was successfully treated by a stent implantation, a second patient presented with a persistent total occlusion despite conventional balloon angioplasty and subsequent atherectomy. This patient was referred for elective coronary bypass grafting. Three patients were referred for emergency coronary artery bypass surgery because of guiding-catheter induced dissection

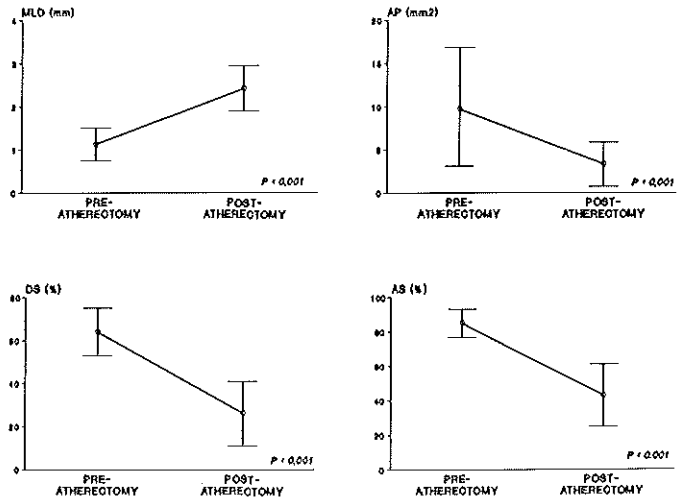

Figure III. Minimal luminal diameter, area plaque, diameter stenosis and area stenosis before and after coronary atherectomy. The minimal luminal diameter increased from 1.13 ± 0.38 mm to 2.42 ± 0.52 mm, the area plaque decreased from 9.77 ± 6.69 mm² to 3.32 ± 2.56 mm² and the diameter stenosis decreased from 64 ± 11% to 26 ± 15% and the area stenosis decreased from 85 ± 8% to 43 ± 18%.

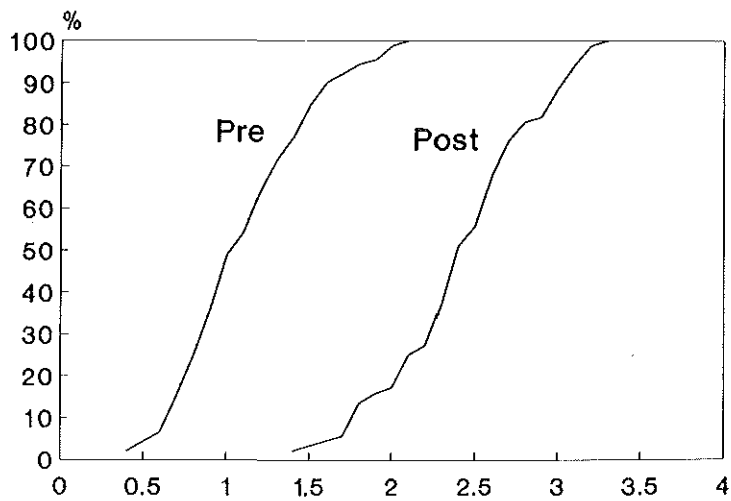

Figure IV. Cumulative frequency in minimal luminal diameter (MLD). Directional coronary atherectomy resulted in an increase of the minimal luminal diameter from 1.13 ± 0.38 to 2.42 ± 0.52 mm. Pre = before atherectomy, post = after atherectomy.

of the right coronary ostium (n=1), a total occlusion one hour after the atherectomy procedure which persisted despite emergency balloon angioplasty (n=1) and because of an obstructive dissection induced by the manipulation of the device into a curved coronary artery (n=1).

Table 1. Clinical and lesion characteristics of 95 patients treated successfully by directional atherectomy

Gender			*NYHA classification*	
Male	81		class I	1
Female	14		class II	26
History			class III	27
Prior infarction	43		class IV	41
Prior angioplasty	15		*Vessel disease*	
Prior stenting	6		One	67
Prior atherectomy	2		Two	22
Angina class			Three	6
Stable angina	54		*Target lesion*	
Unstable angina	41		LAD	63
			LCX	12
			RCA	24
			Graft	4

Quantitative angiography:
Quantitative angiographic analysis was performed on all successfully treated coronary lesions. The quantitative angiographic parameters which describe the complexity and the severity of the lesions are tabulated in table 2. With respect to lesion complexity, the length of the stenosis was on average 6.83 ± 2.55 mm while all but 5 lesions were found to be eccentric (symmetry index <1.0) according to quantitative angiographic definitions. The mean curvature value for all analyzed segments was 15.3 ± 7.5. The lesion severity can be characterized by the area plaque, area stenosis and minimal cross-sectional area. The mean value for the area plaque was 9.77 ± 6.69 mm^2 while the area stenosis averaged 85 ± 8% and the minimal cross-sectional area was 1.12 ± 0.75 mm^2.
The sequential changes in angiographic parameters before and after coronary atherectomy are shown in figure III and IV. The reference diameter did not change significantly (3.17 ± 0.64 mm to 3.26 ± 1.13 mm). As expected the minimal luminal diameter and mean cross-sectional area increased significantly (1.13 ± 0.38 mm to 2.42 ± 0.52 mm;$p<0.01$ and 1.12 ± 0.75 mm^2 to 4.84 ± 1.78 mm^2;$p<0.01$ respectively). Accordingly, the diameter stenosis and area

stenosis decreased significantly from 64 ± 11% to 26 ± 15% ($p<0.01$) and from 85 ± 8% to 43 ± 18% ($p<0.01$).

Complications:

Major complications (death, emergency coronary bypass grafting and Q-wave myocardial infarction) were observed in 5.7% of the patients (not mutually exclusive). One patient (0.9%) died three days after an angiographic successful procedure due to a delayed rupture of the atherectomized coronary artery and has been previously reported [9]. Three patients (2.8%) underwent emergency surgery and five patients (4.7%) sustained a transmural infarction either peri-operatively (n=3) or after an angiographically successful procedure (n=2). These last two patients developed an infarction due to an occlusion after a balloon angioplasty distal from the atherectomy site (n=1) and due to an embolization (n=1).

Minor complications (non Q-wave infarction, transient ischemic attack) were seen in 4 patients (3 and 1 respectively). No patients required blood transfusions or vascular surgery because of vascular problems at the femoral puncture site.

Table 2. Quantitative angiographic baseline stenosis characteristics of 113 successfully treated coronary artery lesions

Extent (mm)	6.83 ± 2.55
Symmetry index	0.53 ± 0.25
Curvature value	15.3 ± 7.50
Area plaque (mm^2)	9.77 ± 6.69
Area stenosis (%)	85 ± 7
Reference area (mm^2)	8.25 ± 3.30
Reference diameter (mm)	3.17 ± 0.64
MLCA (mm^2)	1.12 ± 0.75
MLD (mm)	1.13 ± 0.38
DS (%)	64 ± 11

DS = diameter stenosis, MLCA = minimal luminal cross sectional area, MLD = minimal luminal diameter.

DISCUSSION

The data from this study show a primary success rate of 85.7%. This success rate did not differ between the two centers and was markedly influenced by the learning curve effect since the 10 patients in whom the lesion could not be crossed by the device belonged to the cohort of the initial 25 patients treated by atherectomy in each center and therefore represent an inappropriate selection

process. Thus, the primary angioplastic success rate of 95.2% represents more closely the actual success rate and is comparable with other reports [10-13]. However, despite this experience, the procedure was unsuccessful in 5 patients. In three patients this was due to procedural and patient selection factors: 2 patients developed a guiding catheter induced dissection and in one patient the device caused a dissection while passing through a non-negotiable coronary artery bend.

Study design:

Patients with both stable (n=54) and unstable angina (n=41; typical ischemic chest pain associated with electrocardiographic changes) were selected for coronary atherectomy when they presented with a stenosis in the proximal part of an epicardial coronary artery. The clinical characteristics of this patient population do not differ significantly from those treated by balloon angioplasty [14,15] or stenting [16] at our institutions. However, this patient population is characterized by the high incidence of angiographic complex lesions when compared with balloon angioplasty patients. Meier et al [17] reported a mean lesion length of 4.6 mm in a conventional angioplasty patient population and they reported a higher complication rate in their patients with eccentric and long ($>$ 5.0 mm) stenoses. Quantitative coronary angiography in our patient population demonstrates a 95% incidence of asymmetric coronary artery stenoses with a long lesion (6.83 $\pm$ 2.55 mm), a large atherosclerotic plaque (area plaque = 9.77 $\pm$ 6.69 mm^2) which severely obstructs the coronary artery lumen (area stenosis = 85 $\pm$ 8%). Therefore, this patient population is characterized by a high incidence of angiographic complex lesions. We confirm the result of Hinohara [13] that coronary atherectomy achieves a high success rate in lesions with complex stenosis characteristics.

Mechanism:

Luminal improvement after conventional balloon angioplasty is created by compression or remodelling of the atheromatous plaque and by overstretching the vessel wall. Frequently many of the lesions are not effectively dilated because of elastic recoil of the vessel wall or incompressibility of the encroaching plaque. Furthermore, the barotrauma of the balloon may induce substantial damage to the vessel wall which may result in dissections or total occlusions. Recent studies report an incidence of acute coronary artery occlusion of 2 to 11% following conventional balloon angioplasty [14,18,19]. These studies have demonstrated that unstable angina and the complexity of the coronary artery lesion are important factors associated with risk of coronary artery occlusion [15,19,20]. Therefore, new techniques like directional atherectomy which remove rather than remodel the atheromatous plaque have been introduced to supplement conventional balloon angioplasty especially when treating complex lesions. Theoretically, these techniques have several advantages over dilating techniques. First, selective ("directed") plaque removal becomes possible with less dissections. Second, with

directional atherectomy plaque removal results in a superior luminal improvement when compared to balloon angioplasty [20,21] and finally, atherectomy induces less recoil of the arterial wall [20].

This study demonstrates the efficacy of directional atherectomy in treating coronary artery lesions with a complex morphology with a low incidence of acute occlusions (0.9%) when compared with balloon angioplasty. These results are in accordance with the observations of Hinohara [13]. Furthermore, atherectomy resulted in a large gain in luminal improvement when compared with historical [15] and matched [20,21] controlled angioplasty patients.

Complications:

Directional coronary atherectomy is associated with potential new problems due to the specific mechanism of atherectomy which may offset the wellknown incidence of complications observed with balloon angioplasty. Firstly, because the depth of the resection and precise spacial orientation of the device are not controlled it is possible to remove either medial or adventitial tissue. In recent studies [10,12,22] adventitia was identified in 30% of the resected specimen. The most feared complication after directional atherectomy is a coronary artery perforation. In our consecutive series this has been documented once (0.9%) three days after the procedure [9]. Improved operator experience and techniques with incorporation of intravascular imaging may avoid removal of vessel wall components. Secondly, directional coronary atherectomy may induce embolization of excised plaque material with subsequent development of a myocardial infarction. In this series myocardial infarction due to plaque embolization was observed in 3.7% of the patients (1 Q-wave infarction). This complication rate is not higher than that reported in large PTCA trials including stable and unstable patients [2,3,14,15,18,19]. Finally, acute coronary occlusion at the site of atherectomy occurred in 0.9% of the patients which is substantially lower than the reported 5 to 11% incidence after balloon dilatation [15,18,19].

Conclusions:

We confirm the results of other studies [10-13]: directional coronary atherectomy is technically feasible, is particularly suitable for the treatment of stenosis with complex lesion characteristics as assessed by quantitative coronary analysis and is associated with low complication rates. Success rates are further improved with adjunctive use of conventional balloon angioplasty for a failed atherectomy attempt. Randomized trials comparing atherectomy with balloon angioplasty are mandatory to clarify the specific role of atherectomy in the treatment of coronary artery disease.

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Chapter 10

ACUTE AND LONG-TERM OUTCOME OF DIRECTIONAL CORONARY ATHERECTOMY FOR STABLE AND UNSTABLE ANGINA

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ABSTRACT

The clinical efficacy and safety of directional coronary atherectomy for the treatment of stable and unstable angina was assessed in 82 stable and 68 unstable procedures. Therefore, clinical and angiographic follow-up were obtained in a prospectively collected consecutive series of 150 atherectomy procedures. Restenosis was assessed clinically and by quantitative angiography. The overall clinical success rate of atherectomy for unstable and stable angina was 88% and 91%, respectively. No significant differences were found for in-hospital event rates between the unstable and stable groups: death (1.5% vs 0%), myocardial infarction (10% vs 6%) and emergency bypass operation (3% vs 2%). These clinical events were related to the occurrence of abrupt occlusions (8.8% in stable and 6.1% in unstable angina;p=NS). Clinical follow-up was achieved in 100% of the stable and unstable patients at a mean interval of 923 and 903 days respectively. Two year survival rates were 96% and 97% in the unstable and stable populations. There were no significant differences with respect to bypass surgery and angioplasty, but event-free survival at 2 years was significantly lower in the unstable group (54%) than the stable group (69%). Quantitative coronary angiography did not detect any difference in luminal renarrowing during the 6 month angiographic follow-up period. Although directional coronary atherectomy can be performed effectively for unstable and stable angina, the long-term clinical outcome was less favorable in the unstable group. The overall higher incidence of adverse events in unstable patients occurred despite the *excision* of unstable plaque material, and may therefore reflect the inherent instability of the syndrome rather than the inability of atherectomy to establish a persistent success.

INTRODUCTION

Increasing operator experience has rendered directional coronary atherectomy a safe and successful treatment for patients with symptomatic coronary artery disease. However, the long-term outcome of atherectomy is still limited by unpredictable progression to recurrent stenosis. Although it was hypothesized that controlled plaque removal by the atherotome might lead to favorable short and long-term results, this was not confirmed in the two recently completed randomized trials, Coronary Angioplasty Versus Excisional Atherectomy Trial and Canadian Coronary Atherectomy Trial which compared atherectomy with balloon angioplasty [1,2]. Despite these findings, directional coronary atherectomy may be beneficial in particular patient groups.

The management of patients with unstable angina continuous to receive much attention, and conventional balloon angioplasty has assumed an important role in the treatment of this condition. However, most reported series demonstrated complication rates in excess of those seen in stable patients undergoing angioplasty [3-5]. This is thought to be related to the complex nature of unstable lesions where plaque ulceration and mural thrombus appear to be important [6-8]. Also it has been suggested that angioplasty in the context of unstable angina is associated with increased restenosis rates [9,10] although this has not been confirmed by others [3-5,11].

The potential for atherectomy to improve the outcome of unstable angina has not yet been determined. We therefore examined whether pre-procedural anginal status influenced immediate and late clinical progress in a prospective cohort of 143 patients undergoing 150 directional coronary atherectomy procedures in our institution.

METHODS

Patient selection:
Between September 1989 and January 1993, 143 patients underwent 150 directional coronary atherectomy procedures for stable and unstable angina. Patients were considered candidates for directional atherectomy when coronary angiography revealed a severe, eccentric non-calcified stenosis in the proximal non-tortuous part of an epicardial coronary artery with an anticipated reference diameter of at least 3.0 mm.

Clinical definitions:
Unstable angina was defined as chest pain at rest while hospitalized accompanied by electrocardiographical evidence of myocardial ischemia (ST segment or T wave changes) despite optimal medication including intravenous nitroglycerin and heparin amongst others without evidence of subsequent myocardial necrosis. All

other clinical syndromes of ischemic heart disease were considered *stable angina*. *Recent myocardial infarction* was defined as transmural (electrocardiographic Q-wave) or non-transmural (no Q-wave) when chest pain was associated with a peak CK elevation greater than twice the upper limit of normal values during the preceding 7 days.

Abrupt occlusion: a total occlusion of the coronary artery at any time during or after the atherectomy procedure, further classified as procedural occlusion (i.e. during the procedure) and subacute (i.e. after the procedure within 24 hours) in association with clinical or electrocardiographic evidence of ischemia.

Clinical endpoints:

The follow-up of all patient treated by atherectomy was started at the end of the procedure. The following clinical events were recorded:

Death: all death are considered cardiac unless they are documented to the contrary.

Myocardial infarction: defined as the development of new abnormal Q waves on the ECG or an enzyme change by more than two times the upper limit of normal creatinine kinase.

Table 1. Clinical characteristics of stable and unstable patients

	Unstable (n=68)	Stable (n=82)
Age (years)	58 ± 11	58 ± 10
Male gender	57 (84%)	66 (81%)
NYHA functional class		
II	-	33 (41%)
III	-	49 (59%)
IV	68 (100%)	-
Previous infarction	21 (31%)	16 (19%)
Previous PTCA	12 (18%)	17 (20%)
Multi-vessel disease	10 (15%)	14 (17%)
Target artery		
LAD	45 (67%)	57 (68%)
RCA	18 (26%)	15 (19%)
LCX	5 (7%)	10 (13%)

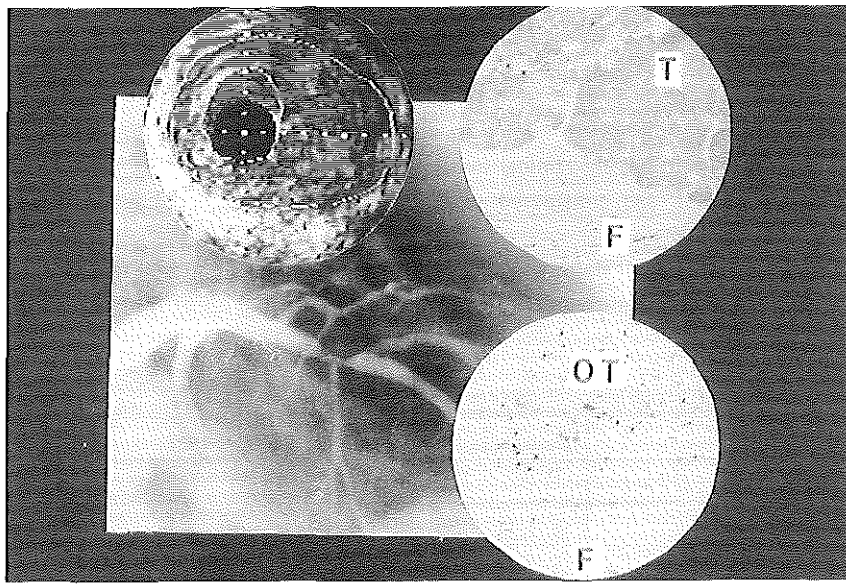

Figure 1. Coronary angiogram and histologic findings in an unstable patient before atherectomy. Coronary angiography showed an eccentric lesion with smooth borders located in the mid portion of the left anterior descending coronary artery. Intracoronary ultrasound imaging revealed an underlying eccentric plaque with heterogeneous echogenicity and without calcific deposits. Histopathological examination of the retrieved material disclosed areas of thrombotic material (T) with different degrees of organization (OT) in close apposition to moderately cellular fibrotic tissue (F).

Coronary artery bypass surgery: is classified as emergency, in-hospital elective and during follow-up.

Repeat angioplasty: defined as any re-insertion of a guiding catheter followed by a new angioplasty.

Atherectomy procedure.

The procedure was carried out as previously described [12-17]. Briefly, all patients were pretreated with 250 mg acetylsalicylic acid and 10,000 U heparin intravenously. To prevent coronary spasm, intra-coronary isosorbide dinitrate was given. Following the initial angiograms, the atherectomy device was advanced using the over the wire technique and positioned across the stenosis. On optimal deployment, the support balloon was inflated up to 2 to 3 atm, the driving motor was activated and the rotating cutter was slowly advanced to cut and collect the protruding intimal lesion in the collecting chamber located at the tip of the catheter. *Procedural success* was defined as a residual diameter stenosis of less than 50% after atherectomy with or without balloon angioplasty. *Clinical success* was defined as a procedural success without in-hospital adverse clinical events (death, myocardial infarction, bypass surgery). Following atherectomy, the patients were monitored for 24 hours and electrocardiograms and cardiac enzyme levels were obtained twice a day. Nifedipine or nitrates were given every two hours for 24 hours after the procedure, and aspirin was given for one year. All procedures were performed after obtaining informed consent.

Quantitative coronary angiography.

Quantitative analysis of the coronary segments was performed with the computer based Coronary Angiography Analysis System, previously described in detail [15-19]. In essence, boundaries of a selected coronary artery segment are detected automatically from optically magnified and video digitized regions of interest (512 x 512 pixels) of a cine-frame. The absolute diameter of the stenosis in mm is determined using the guiding catheter as a scaling device. Calibration of the catheter in absolute values (mm) is achieved by comparing the mean diameter of the guiding catheter in pixels with the measured size in millimeters. Each individual catheter is measured by a micrometer. To correct the detected contour of the arterial and catheter segments for pincushion distortion, a correction vector is computed for each pixel based on a computer- processed cineframe with a centimeter grid placed against the input screen of the image intensifier. Since the functional significance of a stenosis is related to the expected normal cross sectional area of a vessel at the point of obstruction, a computer-estimation of the original dimension of the artery at the site of the obstruction to define the interpolated reference diameter is used. The percentage diameter and area stenosis as well as the cross sectional area (mm^2) are then calculated. The length of the lesion (mm) is determined from the diameter function on the basis of a curvature analysis. The area between the actual and reconstructed contours at the obstruction site is defined as the plaque area and is expressed in mm^2. The

severity of a stenosis can also be expressed as a percentage area stenosis assuming circular cross sections at the obstruction and reference position. Corresponding luminal areas (mm^2) were calculated by comparing the minimal area value at the obstruction with the reference value obtained following the interpolated diameter technique.

Statistical analysis. Mean values and standard deviations are given for continuous variables. Comparisons of mean values were performed using a two-tailed paired t-test. Categorical variables were compared using chi-square tests with Yates' continuity correction applied were appropriate. A p-value of greater than 0.05 was considered non-significant.

RESULTS

Clinical and angiographic demographics:

Of the 150 procedures, 82 were performed for stable and 68 for unstable angina. Baseline clinical and angiographic characteristics are reported in Table 1. By study design, the unstable angina group contains only patients with New York Heart Association functional class IV angina. Similar baseline characteristics were found between the groups except that unstable patients sustained more infarctions before atherectomy. Most atherectomy procedures were performed in the left anterior descending coronary artery (68%) with more right coronary artery lesions in the unstable group. Most narrowings were primary stenosis although 19% of the patients underwent atherectomy for restenosis after previous angioplasty.

Procedural results.

In the group with unstable angina, *stand-alone atherectomy* was performed in 64 cases with a clinical success in 62 (97%). In one patient plaque embolization with subsequent side-branch occlusion occurred, and another patient underwent elective bypass surgery after an unsuccessful emergency atherectomy procedure. *Adjunctive balloon angioplasty* (n=4) after atherectomy was performed for the following angiographic complications: a nose cone dissection (n=2) and an abrupt total occlusion (n=2). When employed, balloon dilatation was angiographically successful in all cases, however one of these patients was subsequently referred for emergency coronary artery bypass surgery because of refractory threatening occlusion.

In the group with stable angina, *stand-alone atherectomy* was performed in 77 patients (94%). Clinical success was achieved in 76 (99%) as one patient underwent emergency bypass surgery for an occlusive catheter induced dissection. *Adjunctive balloon angioplasty* was performed in 5 patients to improve the post-atherectomy result. In this group no procedural abrupt occlusions were seen.

The procedural success rate for unstable and stable angina was 96% and 99% (p=NS), respectively.

In-hospital success and complications:
The clinical success rate defined as an angiographic success in absence of death, myocardial infarction or emergency or elective in-hospital bypass surgery was 88% (60/68 patients) for unstable angina and 91% (75/82 patients) for stable angina (p=NS).
Major clinical complications developed in 15 patients, usually related to the occurrence of an abrupt occlusion. In total the incidence of abrupt occlusion was 7.3% (8.8% vs 6.1% in the unstable and stable groups;p=NS). *Procedural occlusions* occurred in four (5.9%) unstable and one (1.2%) stable patient. In the unstable group, these were guiding catheter induced in 2 and nose-cone induced in 1 or occurred after dilatation of an occluded sidebranch (n=1). Three of these were treated by angioplasty and/or stenting. One patient was subsequently referred for emergency surgery after successful dilatation. One procedural occlusion (guiding-catheter induced) occurred in the stable group. *Subacute occlusions* occurred in 2 (2.9%) patients in the unstable and in 4 (4.8%) patients in the stable group (p=NS). All patients were immediately transferred back to the catheterization suite for subsequent successful balloon angioplasty but all except one suffered a myocardial infarction. Therefore, an *occlusion at the site of atherectomy* occurred in 4.4% of the unstable and 4.8% of the stable procedures (p=NS).
In-hospital death occurred in one unstable patient 3 days after a successful bail-out atherectomy. This patient developed cardiac tamponade secondary to a coronary perforation at the site of atherectomy.
Q-wave myocardial infarction occurred in 7 (10%) unstable and in 5 (6%) stable patients (p=NS). In the unstable group, 5 (71%) of the 7 infarctions were due to a (sub)acute occlusion, 1 patient had an unsuccessful emergency atherectomy after failed thrombolysis in the setting of an acute myocardial infarction and 1 patient had a plaque embolization that resulted in a sidebranch occlusion. Four (80%) of the 5 infarctions in the stable group occurred in the setting of a subacute occlusion.
Coronary bypass surgery was performed immediately in 2 patients in each group and on an elective basis in one patient in each group. All patients who underwent emergency surgery except one developed a transmural infarction.
Long-term clinical outcome:
Clinical follow-up was achieved in 100% of stable and unstable patients at a mean follow-up interval of 903 days in the unstable group and 923 days in the stable group. This analysis involved all patients including those with an unsuccessful atherectomy procedure. Event-free survival was defined as

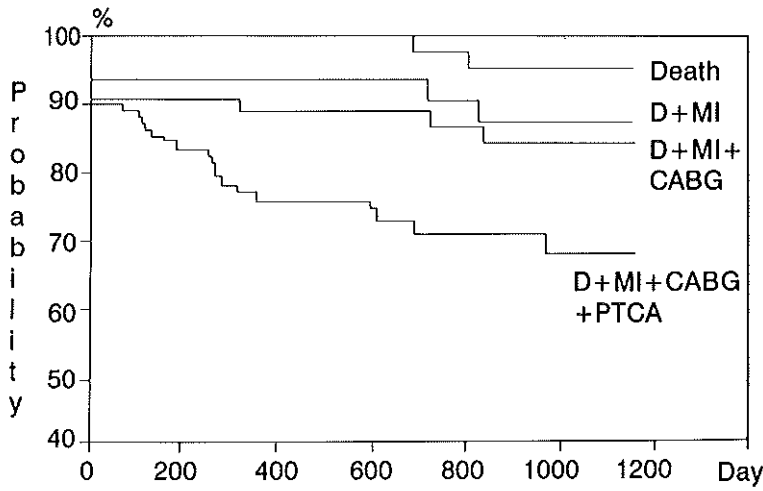

Figure II. Probability of survival and event-free survival after directional coronary atherectomy for stable angina. The Kaplan-Meier estimates of freedom from death (D); or death and myocardial infarction (MI); or death, myocardial infarction and coronary artery bypass grafting (CABG); or death, myocardial infarction and coronary artery bypass grafting (CABG) and repeat angioplasty (PTCA) are shown. The 2-year probability of freedom from death was 97%. The 2-year probability of freedom from death, MI, CABG and PTCA was 69%.

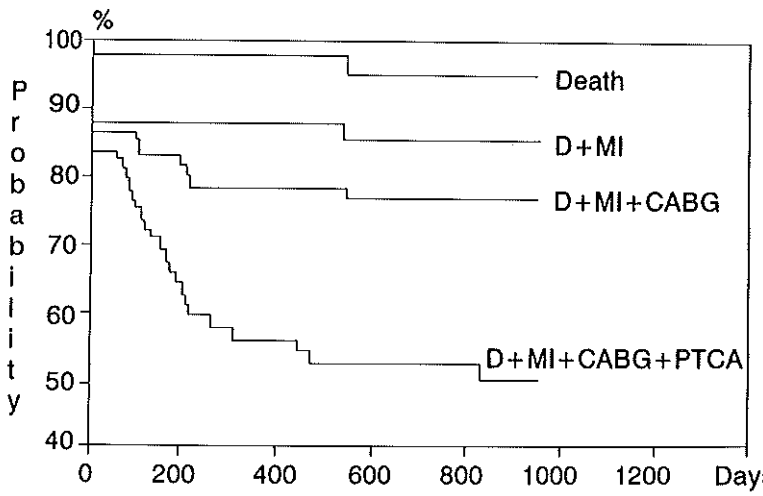

Figure III. Probability of survival and event-free survival after directional coronary atherectomy for unstable angina. The Kaplan-Meier estimates of freedom from death (D); or death and myocardial infarction (MI); or death, myocardial infarction and coronary artery bypass grafting (CABG); or death, myocardial infarction and coronary artery bypass grafting (CABG) and repeat angioplasty (PTCA) are shown. The 2-year probability of freedom from death was 96%. The 2-year probability of freedom from death, MI, CABG and PTCA was 54%.

survival in the absence of myocardial infarction, coronary bypass surgery or repeat transluminal intervention. Figures II and III show the initial and late freedom from events as assessed by the Kaplan-Meier analysis for the unstable and stable groups. One and two year *survival* were 98% and 96% in the unstable and 100% and 97% in the stable group. During follow-up, 1 (1.4%) patient from the unstable group died suddenly. Four (4.9%) patients from the stable group died during follow-up: one cardiac and 3 non-cardiac deaths. No other patients than those with a cardiac death suffered a *myocardial infarction*. *Coronary bypass surgery* for recurrent angina was performed in 5 unstable and 2 stable patients (7.5% vs 2.4%;p=NS). *Repeat angioplasty* was performed in 12 (17.9%) unstable and 15 (18.3%) stable patients including 4 patients who had an angioplasty for a lesion other than at the site of the index atherectomy. Thus at one and two years 57% and 54% of the unstable and 74% and 69% of the stable patients were event-free. The difference in event-free survival between the groups was statistically significant ($p < 0.02$).

Table 2. Quantitative angiographic analysis of the immediate and late effects of directional coronary atherectomy for unstable and stable angina.

	Unstable	Stable
Reference diameter pre (mm)	3.29 ± 0.59	3.17 ± 0.63
Minimal luminal diameter pre (mm)	1.17 ± 0.39	1.17 ± 0.40
Minimal luminal diameter post (mm)	2.38 ± 0.48	2.36 ± 0.58
Minimal luminal diameter fup (mm)	1.70 ± 0.49	1.66 ± 0.56
Diameter stenosis pre (%)	64 ± 11	63 ± 11
Diameter stenosis post (%)	28 ± 12	29 ± 15
Diameter stenosis fup (%)	46 ± 18	41 ± 18
Area stenosis pre (%)	85 ± 9	85 ± 7
Area stenosis post (%)	46 ± 12	47 ± 17
Area stenosis fup (%)	68 ± 17	62 ± 21
Absolute gain in lumen (mm)	1.20 ± 0.52	1.20 ± 0.57
Relative gain in lumen	0.39 ± 0.22	0.38 ± 0.21
Absolute loss in lumen (mm)	0.68 ± 0.68	0.74 ± 0.62
Relative loss in lumen	0.23 ± 0.27	0.25 ± 0.20

Quantitative angiography:
Follow-up angiography was performed in 92% of the unstable and 90% in the stable eligible patients. The results of quantitative angiographic assessment of atherectomy for unstable and stable angina are detailed in Table 2. No differences in reference diameter and lesion severity (minimal luminal diameter, diameter stenosis and area stenosis before atherectomy) were observed. Following atherectomy there was, as expected, a significant improvement in minimal luminal diameter, diameter stenosis and area stenosis for unstable and stable patients ($p<0.001$). The luminal gain achieved at atherectomy was identical for both groups (1.21 $\pm$ 0.52 mm vs 1.20 $\pm$ 0.57 mm;p=NS). During follow-up, both groups showed a comparable deterioration in luminal geometry, as reflected by a decrease in minimal luminal diameter and an increase in diameter stenosis. Using the 50% diameter stenosis criterion, restenosis occurred in 39% of unstable and 32% of the stable lesions (p=NS). At follow-up, no statistical difference in minimal luminal diameter between unstable and stable procedures for proximal left anterior descending artery lesions was found (1.68 $\pm$ 0.55 mm vs 1.61 $\pm$ 0.64 mm) nor was a difference in restenosis rates observed (30% vs 32%).

DISCUSSION

The aim of this study was to evaluate the immediate and long-term clinical and quantitative angiographic follow-up of patients undergoing directional atherectomy for stable and unstable angina in the same institution. To determine whether patients with unstable angina have a less favorable outcome than stable patients in terms of major complications both groups were evaluated at a mean follow-up period of 2 years. An additional analysis was performed to determine whether these two distinct clinical entities behave differently with respect to luminal renarrowing as assessed by quantitative angiography.
The major findings of this study are threefold. First, a similar high acute angiographic and clinical success rate was found for unstable and stable angina. Second, during a 2 year follow-up period, patients initially treated for unstable angina have a significantly lower event-free survival compared with stable patients. Third, quantitative coronary angiography revealed that luminal renarrowing after atherectomy for unstable angina was similar to that for stable angina patients and thus unstable patients have no higher incidence of restenosis.
Study design:
In single and multicentre angiographic follow-up series, directional atherectomy has been demonstrated to be a safe and effective alternative to coronary angioplasty in selected patients [1,2,12-17]. Multivariate analysis has revealed a limited number of lesion and procedural variables, but no clinical characteristics as independent, albeit weak predictors of restenosis [20]. In particular, anginal

status at the time of atherectomy (unstable vs stable angina) has not been found to correlate with late outcome. Recent balloon angioplasty data, however, suggest that unstable angina is associated with restenosis on univariate analysis [21,22] while recent onset angina was retained in the multivariate analysis model as a predictor for angiographic restenosis [21]. Whether these discrepancies between atherectomy and angioplasty data are due to the different mechanisms of action (debulking versus dilating) or could be due to selection bias or heterogeneity of the (un)stable population has not been determined and merits further investigation. Therefore, we assessed the clinical and angiographic outcome after atherectomy in these groups and demonstrated that our strictly defined homogeneous patient population, with objectively documented unstable angina, experienced more clinical complications during a two year follow-up period.

Immediate clinical outcome:

The association between the clinical anginal syndrome and the occurrence of (sub)acute complications after atherectomy has not been reported to date. The previous angioplasty experience of our group and others is of a less favorable clinical course after angioplasty for unstable angina compared with stable angina [3-5,28]. The present study concurs with these observations and indicates that atherectomy for unstable angina is related to a higher, although not statistically significant, incidence of (sub)acute occlusion when compared with stable angina (8.8% vs 6.1%;p=NS). Although an occlusion rate of 7.3% is higher than previously reported [12,29], this may be due to the higher incidence of unstable angina (45%) in the present study population. Popma et al [29] found an occlusion rate of 4.3% after directional atherectomy with a higher incidence in de novo lesions, right coronary artery stenoses and diffuse lesions. In addition Ellis et al determined other adverse angiographic lesion characteristics that increase the risk of acute complications [30]. The (sub)acute occlusion phenomenon after atherectomy in stable and unstable patients demands adequate bail-out strategies, and additional caution is appropriate with regard of the use of the bulky, stiff atherectomy device. The introduction of new, lower profile, atherectomy devices may further increase procedural success rates, particularly as the initially occurring nosecone-induced dissections have not been observed since their introduction.

The difference in acute complications between unstable and stable patients (12% vs 9% respectively; p=NS) indicate that the 11% clinical complication rate in the CAVEAT atherectomy patients may indeed be related to the clinical syndrome of unstable angina which was present in 66% of the population [1]. A higher incidence of immediate post-atherectomy complications in unstable patients is presumably related to the presence of complex coronary artery lesions [23-25]. These lesions contain more thrombus as observed at angioscopy [25], and confirmed by histology [26,27], and have more calcium [26], known to be associated with unsuccessful atherectomy procedures.

Long-term clinical follow-up:
The 2-year actuarial event-free survival rate after atherectomy was 54% for unstable and 69% for stable patients. The total population had a similar incidence and time-frame of events as reported previously by Fishman et al [31]. Complimentary to these findings, our study design allows us to analyse and explore the effect of unstable angina as the index cardiac syndrome on the long-term outcome after directional atherectomy. The present study indicates that atherectomy for unstable angina was associated with a less favorable long-term clinical follow-up. In particular, at one year 57% of the unstable patients were event-free compared to 74% of the stable patients. The majority of these adverse events consisted of revascularizations which occurred earlier in the unstable than stable patients. No differences in balloon angioplasty for angiographic restenosis was observed during follow-up in both groups while a trend towards more coronary artery bypass surgery in the unstable patients was found. These results strongly suggest that anginal status at the time of atherectomy had an impact on late clinical outcome. Differences in baseline patient characteristics could not contribute to these dissimilar follow-up results as the two patient groups were comparable apart from previous myocardial infarctions. The higher incidence of previous myocardial infarctions may reflect the inherent instability of the unstable coronary syndrome, likewise accounting for the higher incidence of acute and late events in such patients. It would appear that the syndrome of unstable angina is not wholly explained by lesion characteristics as excision of the unstable plaque by atherectomy did not yield a long-term clinical outcome similar to that of stable angina patients. These findings concur with the observations of Foley et al [32] that restenosis after balloon angioplasty for unstable angina is associated with an aggressive pattern of angina. A similar difference in clinical outcome has been reported for balloon angioplasty for stable and unstable angina [32,33]. Although these results suggest that there is no advantage of atherectomy over balloon angioplasty, a comparison with historical data should not be made because of clinical and angiographic differences between these populations.
Does unstable angina result in more restenosis?
A major finding of this study is that the luminal renarrowing process in the unstable group was similar to that of the stable group. At late angiographic follow-up, the residual lumen as expressed by minimal luminal diameter at follow-up was 1.70 $\pm$ 0.48 mm in the unstable and 1.66 $\pm$ 0.56 mm in the stable population. The frequency distribution curves for the minimal luminal diameter at follow-up are virtually superimposed confirming the lack of difference between the two groups. This is also confirmed with restenosis assessed as a categorical phenomenon defined by a diameter stenosis of $\geq$50%. Using this clinical definition, no statistical difference in restenosis rate was observed at 6 month angiography: 39% in unstable, and 32% in stable patients ($p=0.55$). These results are consistent with angioplasty reports [3-5,11,32] and confirm our previous

observation that clinical parameters are not independent predictors of late residual lumen or late loss after directional atherectomy [20]. The inconsistency between the long-term clinical and angiographic outcome may be related to the aggressiveness of the anginal pattern in unstable patients prompting repeat interventions at the time of restenosis [32].

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Chapter 11

CLINICAL, HISTOLOGIC AND QUANTITATIVE ANGIOGRAPHIC PREDICTORS OF RESTENOSIS FOLLOWING DIRECTIONAL CORONARY ATHERECTOMY: A MULTIVARIATE ANALYSIS OF THE RENARROWING PROCESS AND LATE OUTCOME

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ABSTRACT

Objectives: To characterize predictors of restenosis following successful directional atherectomy (DCA), we reviewed the clinical, angiographic and procedural data obtained during 132 consecutive procedures (125 patients).
Methods: Clinical and angiographic follow-up were obtained in a prospectively collected and consecutive series of 125 patients who underwent 132 atherectomy procedures for de-novo (89%) or restenotic (11%) lesions in native coronary arteries. Restenosis was assessed clinically and by quantitative coronary angiography. A dual approach to data analysis was taken in order to gain insight into factors affecting the clinical outcome and the vessel wall healing response. Therefore, multivariate analysis was performed (1) to determine the correlates of residual luminal diameter at follow-up (angiographic *outcome*) and (2) to characterize the determinants of the late luminal loss (renarrowing *process*).
Results: Clinical and angiographic follow-up after successful atherectomy were obtained in 100% and 95% respectively. Atherectomy achieved an acute luminal gain of 1.28 $\pm$ 0.48 mm (mean$\pm$SD) resulting in a minimal luminal diameter of 2.44 $\pm$ 0.47 mm. At follow-up the minimal luminal diameter decreased to 1.78 $\pm$ 0.64 mm. The angiographic restenosis rate was 28% if the traditional 50% percentage stenosis cut-off criterion was applied. Larger vessel size and post-atherectomy minimal luminal diameter and right coronary or circumflex lesions were independent predictors of a larger minimal luminal diameter (angiographic *outcome*). Luminal loss during follow-up (renarrowing *process*) was independently predicted by relative luminal gain and pre-procedural minimal luminal diameter.
Conclusions: In analyzing the long-term results of new interventional techniques, such as directional atherectomy, the late luminal loss during follow-up (renarrowing *process*) - which is characterized by the vessel wall healing response after an intervention - should be considered together with the residual luminal diameter at follow-up (clinical *outcome*). It is clear that whereas improved clinical outcome is associated with larger vessel size and post-procedural luminal diameter and non-LAD location, greater relative gain at intervention is predictive of more extensive luminal renarrowing.

INTRODUCTION

Directional coronary atherectomy is now accepted as a feasible alternative to conventional balloon angioplasty for the treatment of coronary artery disease [1-8]. While examining the long-term results of intracoronary interventions, two aspects must be considered: (1) the residual minimal luminal diameter at follow-up which determines the angiographic *outcome* and (2) the renarrowing *process* which can be characterized by the late luminal loss during follow-up which is initiated by the injury inflicted to the vessel wall during intervention. From a *clinical point of view*, Kuntz et al [9] have demonstrated that a large post-procedural lumen was the principal determinant for the best outcome at 6 months (i.e. a large lumen at follow-up) and they have advocated the motto that "bigger is better" [9]. Although this may be valid findings, the analysis was based on the relationship of the minimal luminal diameter after the intervention and at follow-up without taking the vessel size and proportional gain into account. The influence of these two parameter should be considered for two reasons. Firstly, the range of vessels treated in interventional experience is 2-5 mm, secondly restenosis rate has been reported to vary with vessel size [10,11]. Furthermore greater lumen increase at intervention has been shown to be associated with greater risk of coronary ectasia after atherectomy [12], acute complications [13] and increased luminal loss after angioplasty [14]. Studies have demonstrated that procedural luminal gain is the greatest single determinant of subsequent luminal loss [15-17]. Our group [15-17] has focused their attention on the renarrowing process and have reported the relationship between relative luminal gain and relative luminal loss (i.e. gain and loss normalized for the vessel size) as correlates of the biological response of the vessel wall after an intervention. This *"biological approach"* has unveiled the general biological law relating healing process to vessel wall injury and has been encapsulated in the following motto "the more you gain the more you lose".
The purpose of this study was to attempt to reconcile these apparently opposite viewpoints into a coherent methodologic approach by assessing the determinants of the angiographic *outcome* and renarrowing *process* in a consecutive series of patients treated by atherectomy.

METHODS

Patients:
One hundred thirty-one patients underwent 138 successful consecutive directional coronary atherectomy procedures at the Thoraxcenter (n=97) and at University of Louvain Hospital (n=41). Although all patients completed clinical follow-up, 6 patients did not undergo a 6 month angiographic follow-up (5%) and were

excluded from the study.

Atherectomy Procedure:

The procedure was performed as described previously [5,6,8,17]. On average 5.9 ± 2.8 (2 to 14) cuts in selected directions were performed across a stenosis. While an optimum angiographic result is sought for each lesion treated, the procedure was considered angiographically successful when the residual diameter stenosis was less than 50% after tissue retrieval. Patients were monitored for 24 hours and electrocardiograms and cardiac enzyme levels were obtained twice a day. A calcium antagonist was given every 2 hours for 24 hours after the procedure and the patients were kept on aspirin medication for six months.

Quantitative coronary angiography:

Quantitative analysis of the coronary segments was performed with the computer based Coronary Angiography Analysis System (CAAS), previously described in detail [8,16-21]. In essence, boundaries of a selected coronary artery segment are detected automatically from optically magnified and video digitized regions of interest (512 x 512 pixels) of a cine-frame. The absolute diameter of the stenosis in mm is determined using the guiding catheter. The computer-estimation of the original dimension of the artery at the site of the obstruction allows to define the interpolated reference diameter. The percentage diameter stenosis is then calculated. Intracoronary isosorbide dinitrate (1-3 mg) was given prior to and following atherectomy. At follow-up catheterization the administration of intracoronary nitrates was recommended prior to angiography. To standardize the method of data acquisition and data analysis and to ensure reproducibility of post-atherectomy and follow-up angiograms, measures were taken as previously described [17-19,21].

Restenosis:

Two different approaches (categorical versus continuous) were used to define restenosis. Using the categorical approach, the criterion chosen was an increase of the diameter stenosis from $<50\%$ after the intervention to $\geq 50\%$ at follow-up, as is generally applied in clinical practice. Using a continuous approach, minimal luminal diameter at follow-up (MLD fup), luminal loss during follow-up and relative loss (normalized loss for vessel size) were determined.

Luminal changes at intervention and during follow-up are calculated as follows:

Loss: MLD post - MLD fup **Relative loss:** (MLD post - MLD fup) / vessel size

Gain: MLD post - MLD pre **Relative gain:** (MLD post - MLD pre) / vessel size

Normalization of absolute luminal changes for the individual vessel size thereby eliminating the bias of vessel size has been previously described in detail [15-17].

Multivariate analysis approach:

The longterm angiographic luminal changes after successful directional atherectomy was thus evaluated using two separate multiple linear regression

analyses with minimal luminal diameter at follow-up or luminal loss respectively as the dependent variables.

Variables potentially predictive of restenosis were divided into three general categories. *Patient related variables* included age, gender, diabetes, hypertension, hypercholesterolemia (defined as elevated levels of serum cholesterol >6.5 mmol/l requiring treatment with lipid lowering drugs [22] and unstable angina (defined as pain at rest requiring treatment with intravenous nitrates and intravenous heparin).

Lesion related factors are characteristics unique to each lesion. The following factors were assessed: vessel size, pre-atherectomy minimal luminal diameter, post-atherectomy minimal luminal diameter, diameter stenosis before and after atherectomy, absolute gain and relative gain in minimal luminal diameter, treated vessel (left anterior descending coronary artery, left circumflex artery or right coronary artery), de novo versus restenotic lesion.

Procedure related factors assessed included: the center (Rotterdam or Louvain), number of atherectomy cuts, device size, device/artery ratio (defined as device size divided by the interpolated reference diameter) and the presence of media and/or adventitia in the excised specimens.

Statistics:

All continuous variables are expressed as mean $\pm$ 1 SD. A p-value <0.05 was considered as significant. Differences between variables measured before atherectomy, after atherectomy and at follow-up were assessed using one-way analysis of variance for repeated measurements. When the result was significant, paired t-tests were performed to find the significant differences. Selected angiographic and procedural variables were evaluated by univariate regression analysis for their correlation with absolute loss in luminal diameter during follow-up and for their correlation with minimal luminal diameter at follow-up. To avoid arbitrary subdivision of continuous variables, cutpoints were derived by dividing the data in two groups each containing roughly 50% of the total population. The groups were compared with use of two-group t-tests. Two-group t-tests for continuous variables and chi-square test for categorical variables were also used to compare the results from the two centers. Independent contribution of variables was assessed using a multivariate stepwise regression analysis with F-to-enter tests based on the mean square error criterion [23]. All analyses were performed using the BMDPC 90 statistical software.

RESULTS

Patient characteristics and procedural results (Table 1):

The present study population consists of 125 consecutive patients who underwent 132 coronary atherectomy procedures for symptomatic de novo ($n=117$) and

restenotic (n=15) native coronary artery disease. The mean age was 58 ± 10 years and the majority of the patients were males with single vessel disease. The target stenosis (n=132) in these 125 patients was located in the left anterior descending artery in 89 cases, in the left circumflex in 14 cases, in the right coronary artery in 29 cases. The clinical and immediate angiographic success as well as the complication rates for both centers have been described in detail elsewhere [5].

Table 1. Clinical demographics of 125 patients with 132 stenoses undergoing coronary atherectomy

Age (yr)	58 ± 10
Male gender (%)	82
Angina status (%)	
stable angina	60
unstable angina	40
Multivessel disease (%)	23
Restenotic lesions (%)	11
Angiographic follow-up (%)	93

The longterm results of the initial Rotterdam patients with a primary lesion were previously reported in a comparative study with balloon angioplasty [17]. All but 23 patients were treated with a 6 French atherotome, 21 were treated with a 7 French and 2 patients with a 5 French atherotome. The angiographic follow-up rate in the present study population is 95%. Of the six patients who did not undergo repeat angiography, 1 patient died 3 days after successful atherectomy [24], 1 patient had bypass surgery 7 days after the procedure for presumed tamponade while 4 asymptomatic patients refused angiography. At six months, 38 patients (31%) had recurrence of their anginal symptoms. Fifteen patients underwent either a balloon angioplasty, or repeat atherectomy (n=3) or stent implantation (n=1) for symptomatic restenosis of the previously treated segment. During the follow-up period, three patients were referred for elective coronary bypass surgery.

Quantitative angiographic analysis (Table 2,3):

Reference diameter did not change from pre to post procedure. The minimal luminal diameter increased from 1.16 ± 0.39 mm by 1.28 ± 0.48 mm resulting in a minimal luminal diameter of 2.44 ± 0.47 mm post-procedure. At follow-up, the minimal luminal diameter was 1.78 ± 0.64 mm (figure 1). Thus the late loss was 0.65 ± 0.64 mm. Likewise percent diameter stenosis decreased from 65 ± 11% pre-atherectomy to 26 ± 11% post-atherectomy and increased during

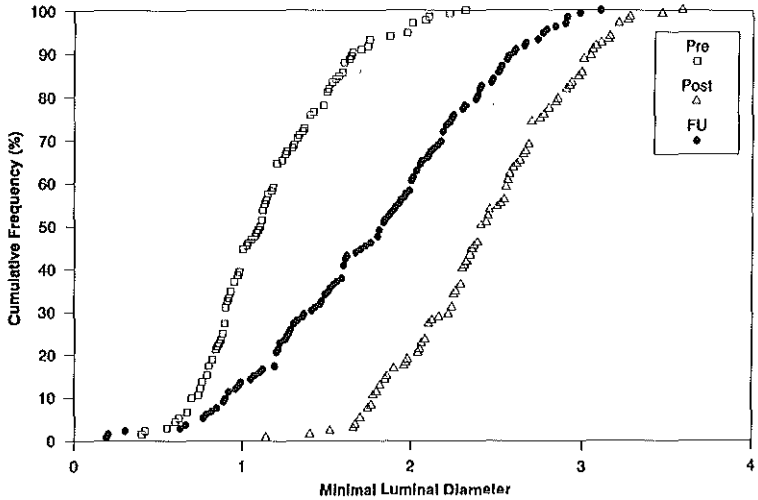

Figure I: Cumulative frequency curves to illustrate the immediate and follow-up effects in minimal luminal diameter (MLD) of directional coronary atherectomy as assessed by quantitative coronary angiography. Pre = before atherectomy, post = after atherectomy, f-up = at follow-up.

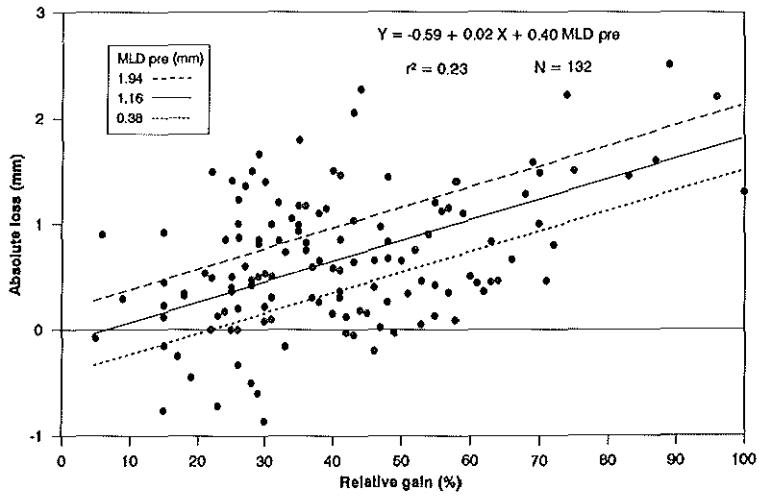

Figure IIa: Scatter histogram of values obtained for relative gain achieved at directional atherectomy and absolute loss during follow-up in 132 procedures. The three lines are projections of the two-variate linear regression when minimal luminal diameter before atherectomy (MLD pre) equals 0.38 mm (mean - 2 SD), 1.16 mm (mean) and 1.94 mm (mean + 2 SD) respectively.

follow-up to 41 ± 18% ($p<0.001$). The restenosis rate was 28% if the 50% diameter stenosis criterion was applied. Although no statistical difference was found in luminal loss or minimal luminal diameter at follow-up between patients with stable and unstable angina, a trend towards a larger minimal luminal diameter at follow-up was observed in the stable group. "Restenotic" lesions did not differ significantly from primary lesions with respect to luminal loss during follow-up nor with respect to retrieval of subintimal tissue. Subintimal tissue was excised (media (n=19) and/or adventitia (n=3)) and found to be related to the number of atherectomy cuts (5.7 ± 3.0 versus 7.5 ± 2.8;$p=0.04$) but not to the other procedural or angiographical variables.

Table 2. Quantitative angiography analysis of the immediate and late effects of directional atherectomy

Reference diameter pre (mm)	3.29 ± 0.64	
Reference diameter post (mm)	3.30 ± 0.50	NS
Reference diameter fup (mm)	3.02 ± 0.60	< 0.001
Minimal luminal diameter pre (mm)	1.16 ± 0.39	
Minimal luminal diameter post (mm)	2.44 ± 0.47	< 0.001
Minimal luminal diameter fup (mm)	1.78 ± 0.64	< 0.001
Diameter stenosis pre (%)	65 ± 11	
Diameter stenosis post (%)	26 ± 11	< 0.001
Diameter stenosis fup (%)	41 ± 18	< 0.001
Absolute gain in lumen (mm)	1.28 ± 0.48	
Relative gain in lumen	0.41 ± 0.19	
Absolute loss in lumen (mm)	0.65 ± 0.64	
Relative loss in lumen	0.20 ± 0.19	

f-up = follow-up, pre = before atherectomy, post = after atherectomy.

Univariate and multivariate analysis of residual lumen at follow-up: clinical outcome (Table 3,4):

A greater minimal luminal diameter at follow-up was associated with 1) vessel size >3.25 mm, 2) minimal luminal diameter after atherectomy >2.42 mm, 3) device/artery ratio ≤1.09, 4) pre-procedural minimal luminal diameter >1.11 mm, 5) device size >6 French and 6) lesion located in a vessel other than the left

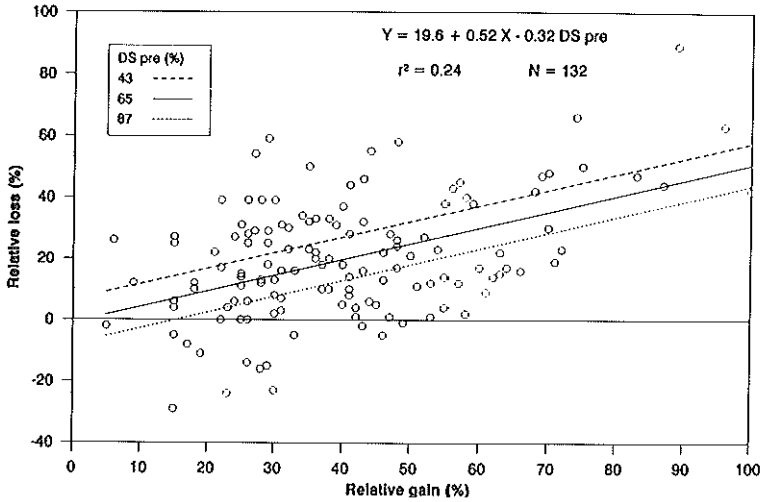

Figure IIb: Plot of the relative gain in lumen achieved at atherectomy versus the relative luminal loss during follow-up for 132 procedures. The three straight lines are projections of the two-variate linear regression when diameter stenosis before atherectomy (DS pre) equals 43% (mean - SD), 65% (mean) and 87% (mean + SD) respectively.

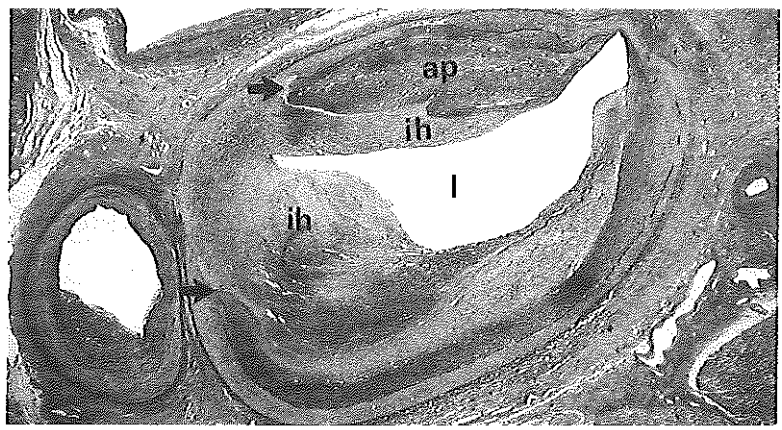

Figure III: Example of the biological process after directional coronary atherectomy. Histologic cross section of the circumflex branch of the left coronary artery at the site of directional coronary atherectomy 9 months before death. The site of the previous atherectomy shows that the initial underlying atherosclerotic plaque (AP) has been excised. The internal elastic membrane and media are disrupted (arrow), indicating that subintimal resection has occurred at atherectomy. The fibrocellular proliferation which developed after the procedure is histologically distinct from the underlying plaque and has the typical appearance of intimal hyperplasia (IH). Appreciate that this proliferative process is not only limited to the section were the plaque has been excised but also to the area which was exposed to the support-balloon. At the site of excision and subintimal disruption the proliferative response is substantially larger, however, balloon inflation, even with low pressures, also provokes a proliferative response.
Verhoeff van Giesson staining; original magnification x4.

anterior descending coronary artery. Multivariate stepwise regression analysis revealed that 1) vessel size, 2) minimal luminal diameter after atherectomy and 3) non-LAD lesions were independently predictive of minimal luminal diameter at follow-up.

The multivariate model can be described by the following equation: MLD at follow-up = 0.21 + 0.25 x vessel size + 0.37 MLD post - 0.25 x LAD (where LAD = 1 and non-LAD = 0).

Univariate and multivariate analysis of late luminal loss: biological approach (Table 3, figure II,III).

Relative gain >0.38, absolute gain > 1.29 mm, post-atherectomy minimal luminal diameter >2.42 mm, post-procedural diameter stenosis ≤26%, lesion located in the left anterior descending artery and device/artery ratio >1.09 were univariate predictors of a large absolute luminal loss during follow-up. The stepwise multiple regression analysis showed that 1) relative gain in lumen and 2) pre-procedural minimal luminal diameter were the only independent predictors of luminal loss during follow-up: absolute loss = -0.59 + 2 x relative gain + 0.399 x MLD pre (figure IIA). Similarly, if luminal loss was normalized for individual vessel size, multivariate analysis revealed that relative gain is the strongest independent predictor of relative loss (Figure IIB). It is readily appreciated that the wide scatter in the correlation plots implies that factors other than luminal dimensions (i.e. biological factors like diabetes or ultrastructural constituents like stellate cells and non-muscular myosin) clearly play a considerable part in the process of restenosis.

In the univariate analysis, the relationship between absolute loss and pre-procedural minimal luminal diameter is negative (Absolute loss = 0.76 - 0.094 MLDpre), however due to the confounding effect of relative gain ((MLDpost-MLDpre)/vessel size), the mathematical sign becomes positive in the multivariate analysis (Fig IIA: Absolute loss = -0.52 + 2 Relative gain + 0.399 MLDpre).

The reconciliation of outcome and process:

As appreciated in figure II a linear relationship exists between absolute gain and absolute loss and between relative gain and relative loss. Although some lesions show further luminal improvement during follow-up, the observed linear relationships imply that a greater luminal gain achieved at atherectomy is associated with a greater luminal loss during follow-up. On the other hand a satisfactory atherectomy result (large post-atherectomy minimal luminal diameter) is predictive of a better luminal diameter at follow-up. Although these results appear contradictory, the slope of the gain/loss relationship is clearly less than, and divergent from the identity line so that greater luminal gain is not fully offset by the subsequent loss. Thus a beneficial longterm angiographic *outcome* (a large minimal luminal diameter at follow-up) will be achieved despite an augmented biological renarrowing *process* (a greater luminal loss).

DISCUSSION

Late angiographic renarrowing as assessed by coronary angiography remains the major limitation of any coronary intervention. Neither pharmacological [22,25-27] nor alternative interventional techniques such as atherectomy [19,28-33] have been shown to abate the restenosis rate. Accepting therefore that restenosis as a healing response to vessel wall injury is inevitable after atherectomy, it is appropriate to investigate the possibility of detecting patient, lesion and procedural factors which might be associated with a favorable or unfavorable influence. In this study we have used a well validated quantitative angiography analysis system (CAAS) to objectively assess immediate and long-term angiographic outcome after atherectomy. The angiographic follow-up rate of 95% further enhances the validity of the conclusions. Furthermore, we have considered the luminal renarrowing *process* and the late luminal diameter (angiographic *outcome*) as parameters of equal interest in order to resolve currently conflicting views.

Pathophysiologic considerations:

Schwartz et al [34-36] have observed in experimental studies a strong positive correlation between vessel wall injury (i.e. rupture of the internal elastic lamina) and the subsequent neointimal hyperplastic response during follow-up. In order to test this hypothesis in a clinical setting, we have substituted the concept of "injury score" and "neo-intimal hyperplasia" used by Schwartz et al [34-36] with the angiographically derived parameters of relative gain and relative loss [15-17] so that the biological relationship between wall injury and the healing response could be more appropriately analyzed. It is crucial to elucidate whether the atherectomy procedure can to some extent escape the implacable consequences of the fundamental biological laws governing the healing response to wall injury. The scientific value of the relationship between relative gain and relative loss lies in the fact that this relationship constitutes a unifying approach which may characterize the intrinsic efficacy of a device independently from the vessel size in which it is operational.

Residual lumen at follow-up:

Of all directly acquired measurements by quantitative angiography, the absolute value of the minimal luminal diameter has been shown to be the greatest single determinant of the hemodynamic consequences of a stenosis, since this parameter affects blood flow by the fourth power term [37]. Moreover, the minimal luminal diameter at follow-up may have some functional component; we found that a minimal luminal diameter at follow-up of 1.45 mm correlates with the freedom from recurrence of angina [38]. Thus, from a clinical point of view, the largest minimal luminal diameter at follow-up is the goal for which to strive while performing intracoronary interventions [9]. Our study shows that a large reference diameter, a non-severe pre-procedural lesion, a large post-procedural diameter and presumably but not necessarily a bigger absolute gain at atherectomy are

associated with a large minimal luminal diameter at follow-up. Thus previous findings of Kuntz et al [9] are confirmed that greater lumen post-atherectomy provides greater late residual lumen. However, in addition we have found that a larger vessel of itself is predictive of a greater follow-up lumen. It is also noteworthy that the greatest acute procedural results were achieved in larger vessels in this as well as in other series [10,11,41]. In addition, a large relative luminal loss was observed in smaller vessels, in which greater relative gain had been achieved. This indicates that atherectomy appears more traumatizing and would, in our view, infallibly be associated with a poor longterm outcome, i.e. a small minimal luminal diameter at follow-up. We surmise that this general type of response to the atherectomy procedure may be unveiled in the recently completed CAVEAT trial, comparing balloon angioplasty and atherectomy [32].

The "restenosis" paradox:

The apparent paradox of greater luminal increase at intervention associated with greater luminal renarrowing during follow-up has now been demonstrated in several clinical studies [16,39,40]. In this study, the greatest determinant of luminal loss or relative loss was the relative luminal gain achieved at atherectomy. This finding is in agreement with published findings in studies of balloon angioplasty [15,16]. Based on these findings it would appear appropriate to use the relative gain/relative loss relationship as angiographic correlates for the injury/hyperplasia phenomenon described in experimental models [34-36] and in clinical research [4,6-9,11,13,14,18-20].

While others have focused on the *angiographic outcome* i.e. final minimal luminal diameter and found a reduced restenosis rate with increased luminal gain achieved with newer devices [9], our group is focusing in clinical studies mainly on the degree of renarrowing as a measure of the extent of the *"biological" renarrowing process* i.e. the development of intimal hyperplasia. This is the difference, as has been expressed by Schwartz et al [35] between the "doughnut and the doughnut hole". There is little doubt that a larger lumen at follow-up is clinically "better" for the patient and this parameter is of great importance in assessing the long-term *outcome* of therapy. However, in large clinical trials directed at the prevention of renarrowing, the effect of therapy must be measured by its restricting effect on the thickness of the "doughnut", which we believe is best encapsulated angiographically by the relative luminal loss during follow-up. As described in the present report, we believe that application of both approaches (residual lumen and renarrowing process) to the same population yield equal findings. The apparently conflicting viewpoints arise not from differences in therapeutic results but from differences in focus and approach. The coherent double approach to restenosis reveals that the clinician may achieve the best final *outcome* (large lumen at follow-up) by aiming for an optimal procedural result (large post-procedural lumen) particularly in large vessels. On the contrary, a large (relative) luminal loss is observed in small vessels in which a large relative gain is seen. This

indicates that the renarrowing *process* (luminal loss during follow-up) is augmented when a severe lesion in a small vessel is treated by atherectomy.
Whether subintimal tissue retrieval leads to an increased incidence in restenosis remains an unresolved issue with conflicting reports in the literature [42,43]. In this observational study, medial or adventitial tissue retrieval was not an independent variable related to more extensive luminal renarrowing although the frequency of retrieval of media and adventitia was only 20% compared with greater than 50% in other studies [2,43].
In the present study, no *clinical and procedural parameters* were found to be independent predictors of restenosis. In two recent multicenter restenosis trials [21,27] diabetes was the only patient related variable found to be independently related to the amount of renarrowing at follow-up. In our study, less than 10 patients with diabetes or hypercholesterolemia underwent atherectomy. Therefore, the predictive value of this variable cannot be evaluated in this study. Using univariate analysis, the device/artery ratio was found to be correlated with luminal loss however, this was not retained in the multivariate analysis. This observation underscores the necessity to strive for an optimal selection of the atherotome. With the clinical implementation of quantitative angiography, proper device selection (device/artery ratio 1.0 - 1.1) can be performed and the final result can be guided by these on-line measurements.
Compared to previously published data on luminal gain and loss after atherectomy, the acute luminal gain in this patient cohort *seems* low [9,11,32,33]. These differences may be secondary to the applied method of quantitative angiographic analysis. Specifically, it has been observed that measurements obtained by visual assessment tend to overestimate the severity of tight stenoses and underestimate the degree of milder ones [44-46] whereas the opposite has been reported of automated contour detection using well known phantom diameters [47]. Therefore, visual or calliper measurements will yield higher values for luminal gain achieved at intervention when compared with quantitatively assessed measurements. Nevertheless the relationship between gain and loss is maintained and similar to other reports [9]. Furthermore, a discrepancy between reference diameters will arise when comparing reports in which the average of the diameter of the vessel proximal and distal to the stenosis are used as the reference [9]. In order to avoid the bias introduced by the arbitrary selection of the user defined reference in the proximal and/or distal segment of the stenosis, we have implemented many years ago an *interpolated* technique, which is not user defined, to determine the reference diameter at the actual stenosis site [8,16-21].
Clinical implications:
Luminal renarrowing after successful atherectomy is a process that cannot be accurately predicted by simple clinical and angiographic parameters. In analyzing the long-term results of new interventional techniques, such as directional

atherectomy, the renarrowing *process* (luminal loss during follow-up) - characterized by the vessel wall healing response - is of equal importance as the angiographic *outcome* (minimal luminal diameter at follow-up) which conveys some index of the clinical outcome in the longterm. It is clear that whereas improved clinical outcome is associated with larger vessel size and post-procedural luminal diameter, greater relative gain at intervention is predictive of more extensive luminal renarrowing.

Limitations:

Several limitations of this study are to be acknowledged. First, it is an uncontrolled, observational study limited to a subset of patients with a successful coronary atherectomy.

Second, although angiography may detect luminal changes after intervention, it may not be the most reliable method to analyze the (biological) process taking place in the vessel wall itself. Because intravascular ultrasound provides an in vivo assessment of morphological changes in the vessel wall, this technique may provide more precise information, although reliable quantitative measures cannot yet be routinely obtained [48]. Third, it could be claimed that an acute gain of 1.28 mm represents a cautious approach to atherectomy leading to a modest angiographic result. However, the post-procedural luminal diameter in this series is comparable with other groups [32,33,49] although smaller than in the series of Kuntz et al [9]. This observation does not influence the conclusions of the present study because the linear relationship between (relative) gain and (relative) loss is maintained at all levels of (relative) gain. Four, luminal loss during follow-up may result not only from the biological proliferative response but may also be due to elastic recoil. From a methodologic aspect we have recommended a 15 minutes recovery time after balloon deflation before proceeding with the administration of intracoronary nitrates and assessment of the final angiographic result. Furthermore, it has been the experience of our group [50] and of others [51] that no further deterioration occurs in the 24 hours after balloon deflation if this methodologic premise is respected. Although the occurrence of elastic recoil was not studied presently, previous reports demonstrated a minimal, if any, elastic recoil after coronary atherectomy [6,52]. Finally, it should be appreciated that the predictive values of the models are weak due to a wide scatter of correlation plots. From a statistical viewpoint, the large standard error of the estimate found implies that other major biological determinants of late angiographic *outcome* and renarrowing *process* have not yet been unravelled. Because the restenosis process appears inherently not controllable, pharmacologic control of the proliferative response appears more than ever mandatory.

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Table 3. Categorical approach to assess correlates for renarrowing following directional coronary atherectomy by quantitative angiography

	MEDIAN	N	VESSEL SIZE(mm)	MLD pre (mm)	GAIN (mm)	REL GAIN	MLD post(mm)	LOSS (mm)	REL LOSS	MLD fup (mm)	DS fup (%)
VESSEL SIZE	≤ 3.25	67	2.80 ± 0.38	1.03 ± 0.34	1.30 ± 0.53	0.48 ± 0.21	2.34 ± 0.49	0.78 ± 0.60	0.25 ± 0.20	1.56 ± 0.58	43 ± 19
	> 3.25	65	3.79 ± 0.42 $	1.28 ± 0.40 $	1.26 ± 0.43	0.33 ± 0.12 $	2.54 ± 0.43 #	0.53 ± 0.66 #	0.15 ± 0.18 @	2.01 ± 0.63 $	39 ± 16
MLD PRE	≤ 1.11	68	3.03 ± 0.61	0.86 ± 0.16	1.45 ± 0.48	0.49 ± 0.20	2.31 ± 0.47	0.70 ± 0.66	0.23 ± 0.21	1.62 ± 0.66	45 ± 19
	> 1.11	64	3.56 ± 0.55 $	1.48 ± 0.30 $	1.10 ± 0.41 $	0.31 ± 0.12 $	2.57 ± 0.43 $	0.61 ± 0.61	0.17 ± 0.17	1.96 ± 0.57 @	36 ± 16 @
MLD POST	≤ 2.42	66	3.11 ± 0.57	1.04 ± 0.32	1.02 ± 0.38	0.34 ± 0.15	2.06 ± 0.28	0.44 ± 0.55	0.15 ± 0.19	1.62 ± 0.62	45 ± 18
	> 2.42	66	3.47 ± 0.66 @	1.27 ± 0.43 $	1.54 ± 0.43 $	0.47 ± 0.20 $	2.82 ± 0.27 $	0.88 ± 0.65 $	0.25 ± 0.19 @	1.94 ± 0.63 @	37 ± 17 @
DS PRE	> 65	62	3.39 ± 0.58	0.91 ± 0.26	1.47 ± 0.46	0.44 ± 0.17	2.38 ± 0.45	0.66 ± 0.69	0.20 ± 0.20	1.72 ± 0.68	45 ± 18
	≤ 65	70	3.20 ± 0.68	1.38 ± 0.36 $	1.11 ± 0.44 $	0.33 ± 0.14 #	2.49 ± 0.49	0.65 ± 0.60	0.20 ± 0.19	1.84 ± 0.60	37 ± 17 @
DS POST	> 26	65	3.43 ± 0.59	1.10 ± 0.43	1.11 ± 0.48	0.32 ± 0.14	2.20 ± 0.42	0.50 ± 0.63	0.14 ± 0.19	1.71 ± 0.68	46 ± 17
	≤ 26	67	3.15 ± 0.66 #	1.22 ± 0.43	1.45 ± 0.43 $	0.48 ± 0.20 $	2.67 ± 0.40 $	0.81 ± 0.61 @	0.25 ± 0.19 @	1.86 ± 0.60 $	36 ± 17 $
GAIN	≤ 1.29	67	3.35 ± 0.59	1.30 ± 0.40	0.90 ± 0.27	0.27 ± 0.10	2.20 ± 0.45	0.47 ± 0.59	0.15 ± 0.19	1.73 ± 0.69	43 ± 19
	> 1.29	65	3.23 ± 0.68	1.00 ± 0.32	1.67 ± 0.30 $	0.54 ± 0.16 $	2.68 ± 0.35 #	0.84 ± 0.63 $	0.25 ± 0.19 @	1.84 ± 0.54	38 ± 16

	MEDIAN	N	VESSEL SIZE(mm)	MLD pre (mm)	GAIN (mm)	REL GAIN	MLD post(mm)	LOSS (mm)	REL LOSS	MLD fup (mm)	DS fup (%)
REL GAIN	≤ 0.38	66	3.53 ± 0.56	1.37 ± 0.41	0.93 ± 0.31	0.26 ± 0.07	2.30 ± 0.52	0.50 ± 0.61	0.15 ± 0.18	1.80 ± 0.70	42 ± 19
	> 0.38	66	3.05 ± 0.63 $	0.94 ± 0.24 $	1.63 ± 0.34 $	0.55 ± 0.15 $	2.58 ± 0.36 $	0.81 ± 0.63 @	0.25 ± 0.19 @	1.77 ± 0.58	40 ± 16
LESION	RESTENOSIS	15	3.07 ± 0.68	1.17 ± 0.40	1.28 ± 0.31	0.43 ± 0.21	2.45 ± 0.45	0.79 ± 0.64	0.20 ± 0.20	1.65 ± 0.54	41 ± 15
	PRIMARY	117	3.32 ± 0.63	1.16 ± 0.40	1.28 ± 0.48	0.40 ± 0.18	2.44 ± 0.47	0.64 ± 0.64	0.20 ± 0.20	1.80 ± 0.65	41 ± 18
VESSEL	LAD	89	3.19 ± 0.64	1.12 ± 0.37	1.29 ± 0.49	0.42 ± 0.20	2.41 ± 0.46	0.75 ± 0.66	0.23 ± 0.20	1.67 ± 0.63	42 ± 18
	NOT LAD	43	3.48 ± 0.60 #	1.23 ± 0.44	1.26 ± 0.46	0.38 ± 0.16	2.49 ± 0.50	0.47 ± 0.55 #	0.14 ± 0.17 #	2.02 ± 0.61 @	38 ± 16
DEV SIZE (Fr)	≤ 6	111	3.22 ± 0.63	1.14 ± 0.38	1.24 ± 0.48	0.40 ± 0.19	2.38 ± 0.45	0.67 ± 0.63	0.21 ± 0.20	1.71 ± 0.63	42 ± 18
	> 6	21	3.67 ± 0.52	1.26 ± 0.44	1.47 ± 0.46 #	0.42 ± 0.17	2.75 ± 0.44 @	0.56 ± 0.67	0.15 ± 0.19	2.19 ± 0.56 @	37 ± 17
DEV/ART	> 1.09	69	2.82 ± 0.40	1.03 ± 0.35	1.30 ± 0.52	0.33 ± 0.12	2.34 ± 0.48	0.74 ± 0.61	0.24 ± 0.20	1.60 ± 0.58	43 ± 19
	≤ 1.09	63	3.80 ± 0.42 $	1.29 ± 0.39 $	1.26 ± 0.44	0.47 ± 0.21 $	2.55 ± 0.43 #	0.56 ± 0.66	0.16 ± 0.18 #	1.99 ± 0.65 $	39 ± 16
CUTS	> 5	64	3.36 ± 0.67	1.12 ± 0.36	1.29 ± 0.45	0.40 ± 0.19	2.41 ± 0.47	0.63 ± 0.68	0.19 ± 0.21	1.79 ± 0.67	43 ± 17
	≤ 5	68	3.22 ± 0.61	1.19 ± 0.42	1.28 ± 0.51	0.40 ± 0.19	2.46 ± 0.47	0.68 ± 0.60	0.21 ± 0.18	1.78 ± 0.61	39 ± 18

HISTOLOGY	MEDIA/ADV	22	3.08 ± 0.65	1.23 ± 0.48	1.19 ± 0.42	0.41 ± 0.20	2.43 ± 0.42	0.71 ± 0.60	0.22 ± 0.20	1.73 ± 0.73	43 ± 21
	INTIMA	110	3.33 ± 0.63	1.14 ± 0.38	1.30 ± 0.49	0.40 ± 0.18	2.44 ± 0.48	0.65 ± 0.65	0.20 ± 0.20	1.79 ± 0.62	41 ± 17
AGE	> 58.9	66	3.27 ± 0.58	1.07 ± 0.39	1.38 ± 0.45	0.43 ± 0.16	2.46 ± 0.49	0.67 ± 0.55	0.21 ± 0.17	1.79 ± 0.63	41 ± 18
	≤ 58.9	66	3.31 ± 0.70	1.24 ± 0.38 #	1.18 ± 0.48 #	0.38 ± 0.20	2.42 ± 0.44	0.64 ± 0.72	0.20 ± 0.22	1.77 ± 0.66	41 ± 17
GENDER	FEMALE	24	3.27 ± 0.74	1.14 ± 0.39	1.31 ± 0.53	0.43 ± 0.22	2.44 ± 0.49	0.65 ± 0.71	0.19 ± 0.23	1.80 ± 0.68	38 ± 20
	MALE	108	3.29 ± 0.62	1.16 ± 0.40	1.28 ± 0.47	0.40 ± 0.18	2.44 ± 0.49	0.66 ± 0.62	0.20 ± 0.19	1.78 ± 0.64	42 ± 17
ANGINA	STABLE	80	3.23 ± 0.63	1.14 ± 0.41	1.33 ± 0.46	0.43 ± 0.18	2.46 ± 0.46	0.65 ± 0.60	0.20 ± 0.18	1.82 ± 0.63	39 ± 18
	UNSTABLE	52	3.39 ± 0.63	1.19 ± 0.39	1.21 ± 0.51	0.37 ± 0.19	2.40 ± 0.46	0.67 ± 0.70	0.20 ± 0.22	1.73 ± 0.66	44 ± 18
CENTER	ROTTERDAM	91	3.18 ± 0.57	1.19 ± 0.39	1.24 ± 0.47	0.41 ± 0.20	2.42 ± 0.52	0.71 ± 0.60	0.22 ± 0.18	1.71 ± 0.55	41 ± 17
	BRUSSELS	41	3.52 ± 0.64 #	1.09 ± 0.40	1.37 ± 0.50	0.39 ± 0.15	2.47 ± 0.45	0.53 ± 0.70	0.17 ± 0.22	1.94 ± 0.79	41 ± 17

Gain = absolute luminal gain, Dev size = device size, Dev/Art = device/artery ratio, DS = diameter stenosis, Fr = french, MLD = minimal luminal diameter,
Rel gain = relative luminal gain.
Student t-test: # = $p<0.05$; @ = $p<0.01$; $ = $p<0.001$.

Chapter 12

DIRECTIONAL ATHERECTOMY FOR TREATMENT OF RESTENOSIS WITHIN CORONARY STENTS: CLINICAL, ANGIOGRAPHIC AND HISTOLOGIC RESULTS

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ABSTRACT

Objectives: The safety and long-term results of directional atherectomy in stented coronary arteries were determined in 9 patients (10 procedures). In addition, proliferation rates and cell density of restenosis tissue removed at specific intervals of time were studied to better characterize the development of restenosis.
Methods: In 9 patients (10 procedures) directional atherectomy was performed 82-1179 days for restenosis within a stented coronary segment. The tissue was subsequently studied for the presence of intimal hyperplasia, extent of proliferation and cell density. A control (non-stented) group consisted of 13 patients who had restenosis tissue removed 14-597 days following an initial procedure (PTCA, atherectomy or laser).
Results: The atherectomy procedures within the stent were all technically successful. In one case a small fragment of the stent was removed. For the entire group, the post atherectomy result was similar to the initial result after stenting (2.31 ± 0.38 mm versus 2.44 ± 0.35 mm). Five patients had follow-up 44-131 days after atherectomy, and three of the patients had diameter stenosis $> 50\%$. Three patients required reintervention (surgery, $n=2$; repeat atherectomy and then laser angioplasty, $n=1$).

Intimal hyperplasia was identified in 80% of the specimens after stenting and in 77% after PTCA or atherectomy. No differences were seen in tissue removed from stenting versus PTCA/atherectomy. In three stented patients (47-143 days after stenting) 70-76% of the intimal cells showed morphologic features of a contractile phenotype by electron microscopy. Evidence of ongoing proliferation (PCNA antibody studies) were absent in all specimens studied. Although large individual variability was present in the maximal cell density of the intimal hyperplasia, there was a trend toward a reduction in cell density over time.
Conclusions: Atherectomy can be safely performed for restenosis in stented coronary arteries with excellent initial results. However, restenosis continues to limit the late effectiveness after atherectomy. Intimal hyperplasia is a non-specific response to injury regardless of the method and accounts for about 80% of cases of restenosis. This preliminary study suggests that smooth muscle cell proliferation and phenotypic modulation towards a contractile phenotype are early events and largely completed by the time of clinical presentation of restenosis (ie. < 2 months). Cellularity results suggest that lesions may be predominantly cellular, matrix or a combination at a particular time after a coronary procedure.

INTRODUCTION

Restenosis remains the major limitation of percutaneous transluminal coronary angioplasty (PTCA), occurring in 20-40% of patients within the first 6 months after angioplasty [1]. The implantation of stents in coronary arteries or saphenous vein bypass grafts as an adjunct or alternative to PTCA was initially proposed to prevent late restenosis [2]. However restenosis has now been documented in a significant number of patients in the first 6 months following stenting [3,4]. The optimal method to prevent restenosis or to treat its occurrence (or recurrences) after PTCA or coronary stenting is unknown. No pharmacological treatment has been consistently successful in reducing restenosis rates after PTCA [5]. Although restenosis occurs with the use of mechanical devices other than PTCA, no randomized trials have yet been reported to determine if more favorable restenosis rates result from their use. Directional atherectomy is one of these alternative mechanical devices for nonoperative coronary vascularization. In selected patients excellent post procedural results have been documented [6]. Furthermore, since the tissue can be removed, it offers a unique opportunity to study the histological features of the restenosis tissue.

In the past two years, we have collected data from 10 procedures performed for restenosis within a stented coronary segment that were treated with directional atherectomy. The purpose of this study was twofold: 1) to determine the feasibility, safety and late results of directional atherectomy for treatment of restenosis within coronary stents and 2) to assess the tissue removed from the restenotic lesion that caused the narrowing within these stents. Although restenosis after PTCA has been characterized by proliferating smooth muscle cells associated with extracellular matrix formation, we were particularly interested if differences existed in restenosis after stenting. In addition, since the temporal changes in the histological pattern following PTCA are largely unknown and have been studied in only a limited number of patients [7], we wanted to study the proliferation rates and cell density of restenosis tissue removed at specific intervals of time to better characterize the development of restenosis. For the pathological studies, we have compared tissue retrieved by coronary atherectomy in 9 patients with restenosis in stented arteries with tissue obtained from 13 patients with restenosis after PTCA or previous atherectomy without adjunct stenting.

METHODS

The stent study population consisted of 9 patients who underwent 10 separate atherectomy procedures within the stent. Five of the patients were treated in Rotterdam, 2 patients in Belgium, 1 patient in United States and 1 patient in Toulouse, France. The clinical characteristics are presented in Table 1. Five of

the procedures were performed in stents placed in bypass grafts and the other 4 stents were implanted in native vessels (Table 2). Six of the stented vessels contained the Wallstent® (Schneider, Zurich) which is a self expandable stainless steel woven mesh stent [3,4]. Two patients had been implanted with a Palmaz-Schatz™ stent (Johnson and Johnson, Warren, New Jersey) which is a balloon expandable stainless steel tubular stent [8]. One patient had received a Wiktor™ stent (Medtronic, Minneapolis), a tantalum balloon expandable stent with a helical coil design [9]. Five of the patients were stented for primary lesions. The remaining 4 patients were originally stented for restenosis after PTCA. Two of these patients (Patient 4 and 9) had multiple restenoses and one of these patients (Patient 4) underwent a second atherectomy procedure within the stent for a restenosis recurrence after the initial atherectomy. All patients were treated with anticoagulation 42-124 days following stenting. Atherectomy was performed within the narrowed stent 82-1179 days post stenting. Three of the patients had separate PTCA procedures for stent-related problems prior to the atherectomy. Patient 1 initially underwent PTCA for restenosis 97 days after stenting and then required an atherectomy procedure 47 days later for a second restenosis within the stent. Patient 4 underwent balloon angioplasty for restenosis 210 days after stent implantation and then atherectomy 156 days later (366 days after stenting). Due to restenosis, a second atherectomy procedure was done 96 days after the first atherectomy (462 days after stenting). Patient 8 had a symptomatic acute occlusion five days after stenting. After recanalization with intracoronary streptokinase and PTCA, he had an uneventful recovery until he experienced recurrence of angina 5 months later due to restenosis within the stent. Patient 9 received a second stent for a different lesion in the bypass graft 570 days after the first stent. A lesion subsequently developed in the initial stent and was treated by atherectomy 1179 days after the first stent implantation (609 days after the second stent). Following atherectomy, two patients remained on anticoagulation.

For the histological evaluation of the tissue, we selected a control group which consisted of all patients in the Thoraxcenter experience who underwent an atherectomy procedure for restenosis after PTCA, atherectomy or laser (n=13) (Table 5). This group consisted of 11 men and 2 women, and the ages ranged form 40-71. The interval of time between the most recent intervention and atherectomy for restenosis ranged from 14-597 days.

Angiographic Analysis:

All cineangiograms were analyzed using the computer assisted cardiovascular angiography analysis system (CAAS) which has previously been discussed in detail [10]. The important steps will be briefly described. Any area of size of 6.9 X 6.9 mm in a selected cineframe (overall dimensions 18 X 24 mm) encompassing the desired arterial segment can be digitized by a high resolution CCD-camera with a resolution of 512 X 512 pixels and 8 bits of gray level. Contours of the desired segment are determined automatically, based on the

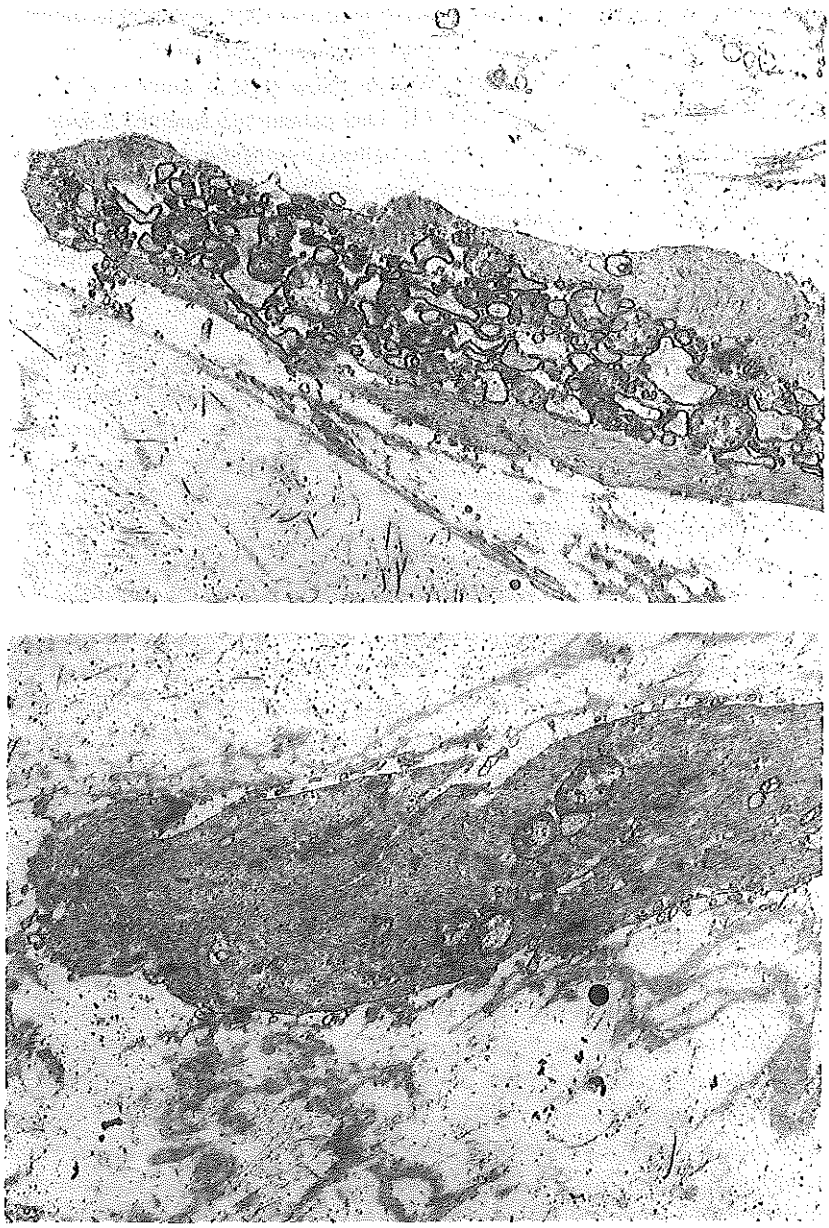

Figure 1: Transmission electron micrograph showing A) a smooth muscle cell with the synthetic phenotype. There are abundant cytoplasmic organelles including endoplasmic reticulum, Golgi apparatus, and ribosomes. Only a few myofilaments are present and are located in the periphery of the cell. B) Contractile smooth muscle cell cytoplasm consists mostly of myofilaments and a few mitochondria.

weighted sum of the first and second derivative functions applied to the digitized brightness information along scanlines perpendicular to the local centerline directions of the vessel segment of interest. A computer-derived estimation of the original dimension at the site of the narrowing is used to define the interpolated reference diameter. This technique is based on a computer-derived estimation of the original diameter values over the analysed region (assuming there was no narrowing present) according to the diameter function. The absolute diameter of the stenosis as well as the reference diameter are measured by the computer which uses the diameter of the guiding catheter as a calibration factor, after correction for pincushion distortion.

Tissue Analysis:

Following extraction of the tissue with the Simpson coronary atherocath^{R}, the specimens were carefully removed from the housing chamber of the catheter, washed with 0.9% saline and cut into pieces of approximately 1 mm by 1-2 mm. Representative pieces were fixed in 10% buffered formalin for light microscopy studies. The specimens were processed according to standard procedures and then paraffin sections were stained with haematoxylin and azophloxine, and with Van Gieson. Three to five slides were prepared at various levels through the paraffin block. The tissue was specifically assessed for the presence of intimal hyperplasia and atherosclerotic plaques according to the definitions of Johnson et al [11]. Intimal hyperplasia was defined as highly cellular tissue consisting of randomly arranged stellate and spindle cells in an abundant, collagen containing extracellular matrix. Atherosclerotic plaques consisted of dense fibrous tissue with abundant collagen, scattered fibroblasts and occasional mononuclear cells, including lymphocytes and macrophage/foam cells.

Immunohistochemical studies:

In deparaffinized sections, immunostaining was performed with monoclonal antibodies directed against alpha-smooth muscle cell actin (Sigma, St. Louis, Missouri) using an indirect conjugated peroxidase procedure. Proliferating cells were identified immunocytochemically using a monoclonal mouse anti-human proliferating cell nuclear antigen antibody (PCNA) (DAKO-PCNA, PC10, Glostrup, Denmark). This antigen is a DNA polymerase auxiliary protein, and is expressed during G1, S (DNA synthesis), and G2 phases of the cell cycle [12-14] but not in the quiescent G_0 phase. Small intestinal mucosa served as positive control for PCNA staining.

Electron Microscopy:

Representative pieces were fixed in a solution of glutaraldehyde-formaldehyde (4CF-1G). Postfixation was done with OsO_4. The specimens were then embedded in epon and ultrathin sections were stained with uranyl acetate and lead citrate. All specimens contained smooth muscle cells in an abundant

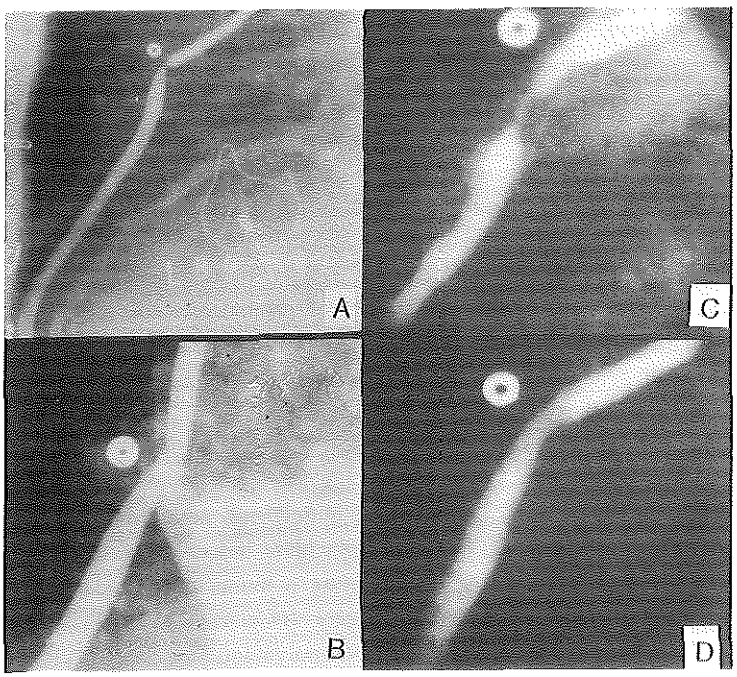

Figure II: Stenosis in proximal bypass graft prior to stenting (A), immediate result after stenting (B), restenosis in stent distal to original site of stenosis (C), immediate result after atherectomy within the stent (D).

extracellular matrix. Cells were assessed as either contractile or synthetic type smooth muscle cells based on the following morphologic features [7]. The synthetic cells were characterized by extensive cytoplasmic organelles, including endoplasmic reticulum, Golgi apparatus and ribosomes), and by peripheral location of myofilaments (Figure 1a). The cytoplasm of the contractile cells consisted mostly of myofilaments and a few mitochondria (Figure 1b). Cells were counted in multiple fields (at least 150 cells in total) and classified according to these criteria into two phenotypes.

Cell Density of Intimal Hyperplasia:

In haematoxylin and azophloxine stained sections, areas of intimal hyperplasia were identified and cell number was assessed in several fields by a computerized morphometry system (IBAS, Kontron, Oberkochen, Germany). The maximum value recorded was used for the determination of cell density which was expressed as cell number/ mm^2 intimal tissue. Specimens without intimal hyperplasia were excluded from this measurement since this part of the study was specifically designed to look for temporal changes in cellularity occurring in intimal hyperplasia formed in response to the coronary procedure.

RESULTS

(1) Clinical:

All atherectomy procedures were technically successful (residual stenosis $< 50\%$ with retrieval of tissue) and there were no procedural complications other than a transient ischemic attack that occurred during a PTCA of a separate lesion in one patient. The only technical problem occurred with the Wiktor™ stent. Following the procedure, the configuration of the stent was disrupted although no complications ensued. Tiny fragments of the tantalum wire were observed in the atherectomy material. All of the patients experienced immediate improvement in their symptoms. At late follow-up (4-15 months), patient 2 had died following bypass surgery for restenosis after atherectomy and patient 5 had died due to end stage renal failure. Two other patients required additional interventions for recurrence of symptoms due to restenosis after atherectomy. Patient 1 underwent bypass surgery 6 months after the atherectomy and Patient 4 was treated with excimer laser therapy. Five of the patients remained in NYHA Class I-II.

(2) Quantitative Angiography (Table 3):

Immediately after placement of the stent there was an overall significant increase in the minimal luminal diameter and a significant decrease in the percentage of the diameter with stenosis (changing from a mean [$\pm$SD] of 1.12 ± 0.36 to 2.44 ± 0.35 mm and from $63\pm9\%$ to $21\pm10\%$, respectively; $p<0.001$). However, at follow-up prior to the atherectomy, all of the lesions had deteriorated to an overall value of 0.99 ± 0.24 mm and $64\pm7\%$, respectively. The immediate

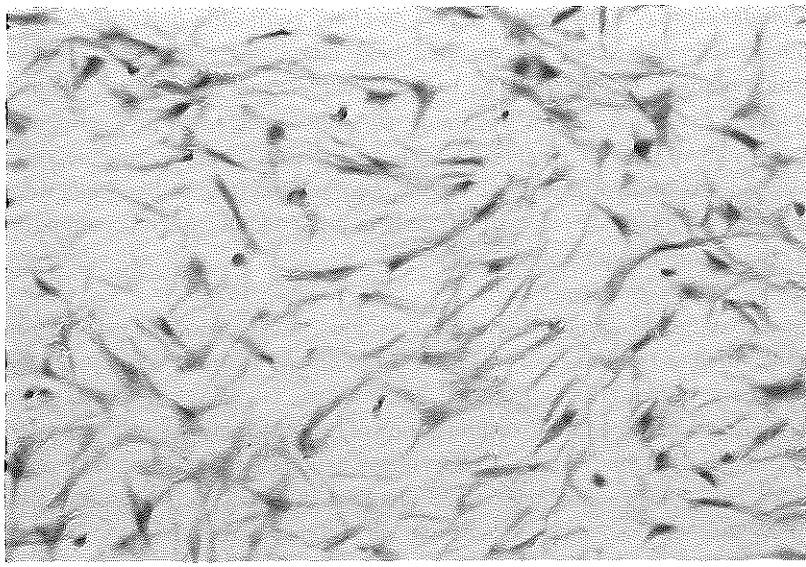

Figure III: Haemotoxylin-azofluoxine stained section of tissue removed from a stent 89 days after stenting. The section has the typical appearance of intimal hyperplasia (highly cellular tissue consisting of randomly arranged stellate and spindle cells in a loose extracellular matrix). (original magnification 25x)

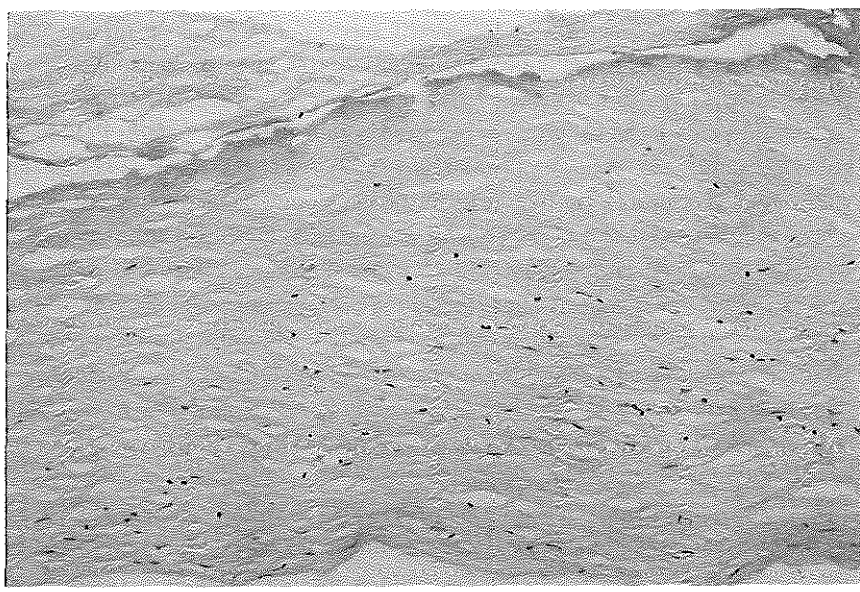

Figure IV: Haemotoxylin-azofluoxine stained section of tissue removed from a stent 156 days after stenting. No intimal hyperplasia was present. The tissue consisted of a few cells embedded in an abundant, collagen containing extracellular matrix. (original magnification 10x).

result after atherectomy was similar to the acute stenting results (2.31±0.28 mm, 27±10%). Late follow-up after atherectomy was only done in 5 of the lesions, with significant deterioration (loss of ≥0.72 mm) occurring in three lesions. An example of the angiographic appearance of the lesion pre and immediately post stenting, at follow-up/pre-atherectomy and post-atherectomy is shown in Figure 2.

(3) Histology:

(i) After Stenting (Table 4): The characteristic feature in tissue obtained in 8 of the lesions was intimal hyperplasia defined as a proliferative cellular response associated with a matrix of loose connective tissue. The area of intimal hyperplasia was typically sharply demarcated from the underlying sclerotic plaque. However the cellularity, amount of collagen, and extracellular matrix of the intimal hyperplasia varied between patients (Figure 3 and 4). In eight of the lesions, the main cell type within the lesions was identified as smooth muscle cells based on presence of SMC specific alpha actin. Specific staining for endothelial cells and macrophages was negative in two specimens tested although lymphocytes were identified in tissue from Patient 3. No giant cells as evidence of a foreign body reaction were identified in any tissue specimen. In three of the specimens prominent capillary ingrowth was evident. In two specimens, the internal elastic lamina and adjacent media were identified (Figure 5). No evidence of adventitia was recovered.

Ultrastructural studies in three of the stented patients (patients 1, 6 and 8) showed that the majority (70-76%) of intimal cells were contractile in morphology. No differences could be appreciated at the different time intervals. No differences were found in the histology or immuno-chemistry between lesions (primary vs de-novo), vessel (native vs bypass graft) or types of stents.

(ii) After PTCA/Atherectomy (Table 5): In the control PTCA/atherectomy group, the histologic appearance of the tissue was indistinguishable from the stent tissue. Intimal hyperplasia was evident in 10 of the thirteen specimens, and again various stages of cellularity were evident. Media was obtained in 3 of the specimens (22%). No evidence of adventitia was recovered.

(4) Proliferation studies (Table 5 and 6):

In all specimens studied, no cells could be identified that reacted with the antibody to PCNA.

(5) Cell Density:

The maximal cell density of the intimal hyperplasia in both the stent and control groups is shown in Figure 6. Although large individual variability was present, there was a trend towards a reduction in cell density of the intimal hyperplasia over time.

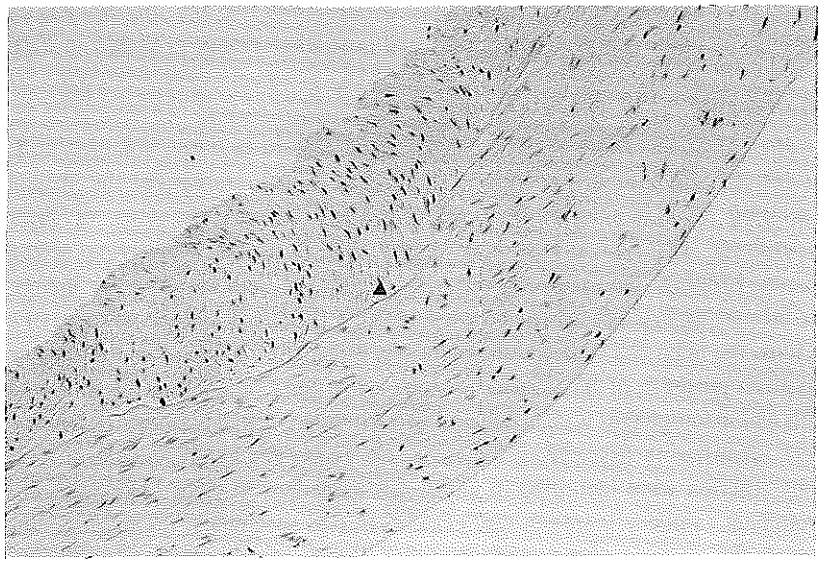

Figure V: Haemotoxylin-azofluoxine stained section of tissue removed from a stent 82 days after stenting. The presence of the media is indicated by the internal elastic lamina (arrow) and the typical architecture of the smooth muscle cells in the media. (original magnification 10x).

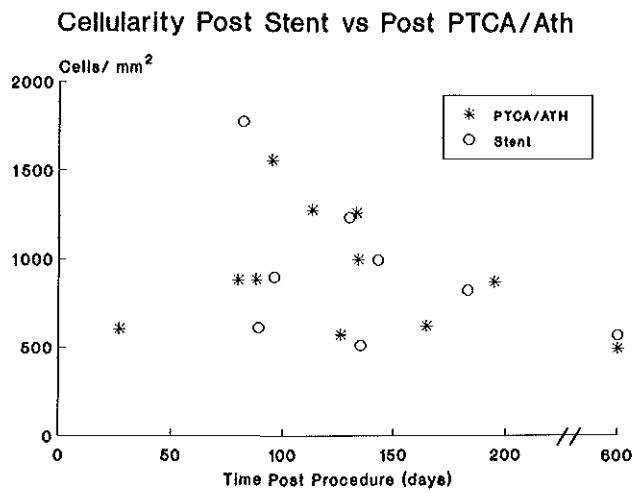

Figure VI: Maximal cell density (cell number/mm^2) in restenosis lesions following stenting, and PTCA of atherectomy. The x-axis represents the number of days after the procedure. Only restenosis lesions with intimal hyperplasia were evaluated. There is a trend towards decreasing cellularity over time in these lesions although considerable individual variability is evident.

DISCUSSION

Restenosis persists as an important limitation to all forms of non-operative coronary revascularization, despite increasingly more complex forms of interventions such as stenting, atherectomy and laser-assisted therapy. It remains to be established whether any mechanical method can effectively treat (and prevent recurrent) restenosis after coronary balloon angioplasty or stenting. We studied the efficacy of directional atherectomy in 10 cases as a procedure to prevent recurrence of restenosis. This study illustrates in a limited number of patients that directional atherectomy can be safely performed within a coronary stent and provide immediate results comparable to the initial stenting procedure. In fact, atherectomy may be a safer procedure in stented than in nonstented vessels since the wires appear to limit the depth of the cutter into the vascular wall and thus reduce the possibility of perforation. However it is still possible to remove media (as in Patients 3 and 6) either between the stent wires or if the stent wire has penetrated the internal elastic lamina. Restenosis occurred in both cases of medial resection. The problem of removing or disrupting part of the stent should be particularly of concern when the restenosis occurs immediately proximal to the lesion and the cutter can abut against the proximal part of the stent. Although the immediate results of atherectomy were excellent, the recurrence of restenosis in three of the patients less than 3 months after the atherectomy procedure emphasizes that atherectomy alone will not prevent the restenosis problem. The aggressive nature of the restenosis process, reflected in the brief period preceding recurrence of symptoms after the atherectomy, is in accordance with several series which have shown an association between the time from initial angioplasty to recurrence and the risk of second restenosis [15,16]. Similarly, a recent PTCA (< 4 months) predicted recurrent restenosis treated with directional atherectomy in a study where the restenosis rate was 44% [17].

Histological evaluation of the tissue retrieved from restenosis lesions (after stenting, PTCA, atherectomy or laser) confirms the findings of previous studies that 1) in atherectomy specimens, intimal hyperplasia is the characteristic feature in 75-80% of cases, and that the remaining 20-25% of cases contain only atherosclerotic plaque material without the features of intimal hyperplasia [11] and 2) smooth muscle cells are the predominant cell type found in restenosis lesions [18-20]. It is unclear whether the absence of intimal hyperplasia in restenosis lesions is due to a sampling error by the atherectomy catheter or another mechanism of restenosis such as elastic recoil or inadequate initial dilatation. If larger studies confirm this observation, the clinical importance is that restenosis interventional trials (pharmacological or mechanical) with the intention to prevent smooth muscle cell proliferation and the formation of intimal hyperplasia, can

only potentially affect approximately 75% of the restenosis population at risk. Future study designs may consider this in the determination of sample size for restenosis trials. In addition our study also illustrates that intimal hyperplasia predominates in restenosis tissue, regardless of the initiating procedure, with no unique features attributable to stenting in general or to a particular type of stent. This underscores the fact that intimal hyperplasia is a nonspecific response to vascular injury regardless of the method of damage [21,22].

The temporal sequence of events in the formation of intimal hyperplasia following coronary intervention remain largely unknown: Results from our study suggest that:

1) Smooth muscle cell proliferation is an early event, and barely detectable 2 months after the procedure:

To date, there is no data on the cell proliferation rates in humans following balloon angioplasty although the use of cyclin to label proliferating cells in human de-novo atherosclerotic plaques has previously shown a labelling index ranging from less than 1% to greater than 4% [23,24]. Our results, showing no proliferative activity in the smooth muscle cells 82 days to 700 days post stenting, suggest that smooth muscle cell proliferation is an early and limited process after vascular injury in humans. This is similar to the results following vascular balloon denudation in animals in which SMC proliferation is first observed 48 hours after vascular injury and peak proliferation occurs at about 1 week which is followed by a rapid decline reaching base-line values by a month after the vessel injury [25]. Due to the limited period of SMC proliferation early after coronary angioplasty, pharmacological agents designed to reduce proliferation may only be required in the first two months after the procedure rather than the six months usually prescribed.

2) The vast majority of smooth muscle cells modulate towards the contractile phenotype early after the procedure:

Therefore only a relatively small percentage of the smooth muscle cells (ie. those with the synthetic phenotype) appear to be responsible for the synthesis of extracellular matrix proteins since in-vitro studies have shown that the production of proteoglycans and collagen is 5 fold and 26-45 fold higher, respectively, in the synthetic phenotype [26,27]. In our study, synthetic type smooth muscle cells only comprised 24-30% of the overall smooth muscle cells in the three patients who had atherectomy performed 135-183 days post stenting. In contrast, Nobuyoshi et al identified "synthetic" type smooth muscle cells as the predominant cell type in the first 6 months and thereafter, the "contractile" type smooth muscle cell was dominant [7]. This earlier predominance of contractile smooth muscle cells in our study may be due to differences in methods of assessment (electron microscopy versus less reliable light microscopic features in Noboyoshi's series) or possibly related to differences in procedures (stenting versus PTCA alone). Interestingly, in a balloon-injury model in rats, Kocher et al observed a similar phenotypic

change (toward a contractile type) as in our study in lesions 75 days after injury, based on the ratio of smooth muscle to nonmuscle actins that had returned to levels of normal medial (contractile) SMCs [28].

3) Lesion cellularity decreases as a function of time but with a large interindividual variability:

As a consequence, lesions may be predominantly cellular, matrix or a combination at a particular time after a coronary procedure. Restenosis has been regarded as a process that is largely completed by 6 months after a procedure. Although cellular proliferation and matrix synthesis are recognized as the components of the restenosis lesion, the remodelling of the vessel wall after vessel injury is not understood and the relative contribution (and possibly the preeminent role) of the matrix components (proteoglycans and collagen) has not been appreciated. An inverse relationship appears to exist between the cellularity of the intimal hyperplasia lesions and the number of days following a procedure (although large individual variability is present).

A temporal relationship between the cellularity of the intimal hyperplasia lesions appears to exist (although large individual variability is present). Since cellular proliferation appears to be an early event, the cellularity of the lesion is primarily related to the amount of synthesized matrix. The wide range of cell density at a particular interval of time may be related to either inherent biological variability or possibly sampling error. The total amount of matrix present at a particular time is related to the synthesis and resorption of the particular component. The turnover of proteoglycans is unknown although the limited data shows low collagen and elastin turnover in experimental models of hypertension [29]. The individual variability in cell density emphasizes the differential importance of matrix deposition in individual lesions. Clearly determining the composition and extent of the matrix synthesis during remodelling of the vessel after atherectomy, stenting or PTCA is an important step in the understanding of the restenosis process and should lead to new and synergistic pharmacologic approaches beyond control of smooth muscle cell proliferation which appears to be an early and difficult process to limit.

Study Limitation:

This study is primarily limited by the relatively small amount of tissue extracted by the atherectomy catheter, which causes a potential sampling bias error. In particular, the device may not have removed the region of intimal hyperplasia containing the highest cell density or high cell proliferation or possibly even may have completely missed areas of intimal hyperplasia in specimens that only showed old atheroma. Therefore the findings from this study with respect to the remodelling of the lesion over time should be confirmed in larger studies.

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Table 1. Clinical Characteristics

Patient	Age	Sex	Previous MI	Previous CABG	Smoker	Hyper-cholesterolemia	DM	Hypertension
1	56	M	1986	1982	-	-	-	+
2	58	M	-	-	-	+	-	-
3	41	M	-	-	-	-	-	+
4b	55	M	Inferior,1977	1977/1983	-	+	+	-
5	64	M	-	1986 / 1987	+	+	+	+
6	67	F	Posterior	1986	-	+	-	-
7	67	M	-	1989				
4a	55	M	Inferior, 1977	1977 / 1983	-	+	+	-
8	44	M	Inferior, 1989	-	-	+	-	-
9	76	M	Inferior, 1974	1974	-	+	-	-

MI= myocardial infarction, DM= diabetes mellitus, CABG= coronary artery bypass surgery

Table 2. Stent Characteristics

Patient	Stent Vessel	Stent Type (mm)	Stent Diameter	Reason For Stent	Time to Atherectomy	Present Status (NYHA Class)
1	CABG	Wallstent	3.5	Primary	47 days (144)	surgery for restenosis
2	LAD	Palmaz-Schatz	3.0	Restenosis	82 days	surgery for restenosis
3	LAD	Palmaz-Schatz	3.5	Primary	89 days	I
4b	CABG	Wallstent	3.5	Restenosis	96 days (462)	laser angioplasty
5	Circumflex	Wallstent	3.5	Primary	130 days	dead (renal failure)
6	CABG	Wallstent	4.0	Primary	135 days	I
7	CABG	Wallstent	4.0	Primary	143 days	II
4a	CABG	Wallstent	3.5	Restenosis	156 days (366)	see above
8	RCA	Wiktor	3.5	Restenosis	183 days	I
9	CABG	Wallstent	5.0	Restenosis	609 days (1179)	II

CABG= bypass graft, ( ) represents number of days after the stent procedure in cases where additional procedures were required

Table 3. Angiographic Results

Patient	Reference Diameter (mm)	Pre Stent MLD (mm)	DS (%)	Post Stent MLD (mm)	DS (%)	FU-S (days)	Stent Follow-Up MLD (mm)	DS (%)	Post Atherectomy MLD (mm)	DS (%)	Ath Follow-Up MLD (mm)	DS (%)	FU-Ath (days)
1	2.37	1.07	56	1.95	22	49 (144)	0.91	62	2.58	8	0.63	74	131
2	2.84	1.15	59	2.67	5	82	1.19	56	2.26	24	1.89	39	14
3	3.14	1.84	49	2.84	14	89	1.34	58	2.18	32	1.34	58	44
4b	3.1					96	0.90	58	2.33	47	-		
5	3.1	1.1	60	2.1	19	130	1.30	59	2.37	25	-		
6	2.9	0.6	72	2.0	38	135	0.63	78	1.77	32	2.46	22	186
7	2.25	0.75	78	2.55	30	143	0.70	69	2.1	29	-		
4a	3.1	1.2	61	2.8	15	156 (366)	1.03	66	2.81	21	0.9	58	96
8	3.33	0.96	71	2.36	28	183	1.11	62	2.34	29	2.37	20	75
9	2.75	1.40	64	2.71	21	609	0.81	71	2.4	22	-		
Mean	2.89	1.12	63	2.44	21		0.99	64	2.31	27	1.79	39	
(±SD)	(0.35)	(0.36)	(9)	(0.35)	(10)		(0.24)	(7)	(0.28)	(10)	(0.67)	(19)	

MLD= minimal luminal diameter, DS= diameter stenosis, - not done, FU-S = follow-up after stenting, ath=atherectomy

Table 4. Histology Results

Patient	Duration Post Procedure	Intimal Hyperplasia	Media	Adventitia	Actin	PCNA
1	47 days (144)	-	-	-	++	-
2	82 days	+	+	-	NA	NA
3	89 days	+	-	-	++	-
4b	96 days (462)	+	-	-	++	-
5	130 days	+	+	-	NA	NA
6	135 days	+	-	-	++	-
7	143 days	+	-	-	++	NA
4a	156 days (366)	-	-	-	++	-
8	183 days	+	-	-	++	-
9	609 days (1179)	+	-	-	++	-

Duration post procedure refers to the most recent procedure. ( ) represents number of days since stent implantation when another more recent procedure was required. + present, - not present, NA= not assessed

Table 5. Histology Results of Restenosis after PTCA/Atherectomy

Patient	Age	Sex	Vessel	Procedure	Duration Post Procedure	Intimal Hyperplasia	Media	Adventitia	PCNA
1	66	F	LAD	PTCA	14 days	-	+	-	-
2	51	M	LAD	Ath	27 days (58)	+	-	-	-
3	66	M	RCA	PTCA	56 days	-	-	-	-
4	67	M	LAD	PTCA	80 days	+	-	-	-
5	60	M	CX	PTCA	88 days	+	-	-	NA
6	75	M	LAD	PTCA	95 days	-	-	-	NA
7	56	M	LAD	PTCA	113 days	+	+	-	NA
8	52	M	LAD	PTCA	126 days (201)	+	-	-	NA
9	40	M	LAD	Ath	133 days	+	-	-	-
10	71	F	LAD	PTCA	134 days	+	+	-	NA
11	49	M	LAD	Laser	165 days	+	-	-	NA
12	64	M	LAD	Ath	195 days	+	-	-	NA
13	58	M	RCA	PTCA	597 days	+	-	-	NA

LAD= left anterior descending artery, CX= circumflex, RCA= right coronary artery, NA= not assessed

Part III

HISTOLOGIC OBSERVATIONS

Chapter 13

HISTOLOGIC CHARACTERISTICS OF TISSUE EXCISED DURING DIRECTIONAL CORONARY ATHERECTOMY IN STABLE AND UNSTABLE ANGINA PECTORIS

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Histologic Characteristics of Tissue Excised During Directional Coronary Atherectomy in Stable and Unstable Angina Pectoris

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Unstable angina is an acute coronary syndrome associated with substantial short- and medium-term morbidity and mortality.[1] The understanding of the pathogenesis of this syndrome has been based largely on postmortem studies of coronary arteries[2] and supported by indirect evidence of coronary thrombosis in relation to the syndrome.[3–5] Because directional coronary atherectomy is unique in extracting intact atheromatous tissue during coronary recanalization, it may facilitate the study of the processes taking place in the vessel in different coronary syndromes. In the present study the histopathologic characteristics of atherectomy samples retrieved in 93 patients with stable or unstable angina pectoris were compared and related to different clinical variables.

We studied 93 patients who underwent directional coronary atherectomy providing histologic material at the Thoraxcenter during the period from 1989 to 1992. After the coronary atherectomy protocol was approved by the Thoraxcenter Institutional Review Board, informed consent was obtained in all patients before intervention. Directional coronary atherectomy was performed using the femoral approach. An average of 6 ± 3 passes in multiple directions were performed across the stenosis.

Clinical variables recorded included age, sex, previous myocardial infarction, current stable or unstable angina pectoris, previous coronary intervention and risk factors for coronary artery disease (history of hypercholesterolemia, non-insulin-dependent diabetes mellitus, cigarette smoking, hypertension and coronary artery disease in the family). Primary unstable angina was defined as continuous or intermittent chest pain at rest requiring hospitalization, associated with electrocardiographic evidence of myocardial ischemia but without associated increase in cardiac enzymes. The time interval between the onset of chest pain and the atherectomy procedure was 7 ± 5 days.

The obtained specimens were fixed in 10% formalin. Routine processing for light microscopy and hematoxylin-azophloxin and Verhoeff-van Giesson staining was performed. All specimens were reviewed by 2 independent observers who were unaware of the clinical data. The recommendations in the American Heart Association Medical/Scientific Statement on the definition of the intima of human arteries and of its atherosclerosis-prone regions[6] were followed in collecting information regarding intimal constituents. Medial tissue was identified on the basis of parallel arrangement of smooth muscle cells, embedded in collagen and frequently associated with a fragment of the internal or external elastic lamina. Adventitia was recognized by the presence of coarse bundles of dense collagen inter-

TABLE I Characteristics of the Study Population

	Stable	Unstable	p Value
Clinical Variables			
Age (years, mean ± SD)	57.89 ± 10.38	56.84 ± 10.85	NS
Previous myocardial infarction	13/48 (27%)	21/45 (47%)	0.05
Male sex	39/48 (81%)	37/45 (82%)	NS
Serum cholesterol ≥ 8 mmol/L	3/48 (6%)	3/45 (7%)	NS
Diabetes mellitus	1/48 (2%)	—	
Systemic hypertension	12/48 (25%)	10/45 (22%)	NS
Cigarette smoking	18/48 (37%)	16/45 (36%)	NS
Family history of coronary disease	6/48 (12%)	9/45 (20%)	NS
Previous coronary intervention	13/48 (27%)	11/45 (24%)	NS
Angina class (NYHA)	II:22, III:26	II:3, IV:42	
Histologic Variables			
Dense fibrous tissue	40/48 (83%)	39/45 (86%)	NS
Loose fibrous tissue	12/48 (25%)	5/45 (11%)	NS
Neointimal hyperplasia	14/48 (29%)	17/45 (38%)	NS
Cholesterol clefts	4/48 (8%)	4/45 (9%)	NS
Necrotic debris	3/48 (6%)	6/45 (13%)	NS
Calcium deposits	9/48 (19%)	18/45 (40%)	0.042
Thrombus	1/48 (2%)	10/45 (22%)	0.007
Macrophages	6/48 (12%)	9/45 (20%)	NS

NYHA = New York Heart Association.

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mingled with elastin fibers, sometimes in association with fragments of the external elastic lamina and media. Fibrous tissue was classified as dense when composed of acellular or poorly cellular connective tissue formed predominantly by dense collagen, and classified as loose when the tissue fragments showed a moderate cellularity and collagen bundles separated by accumulations of extracellular matrix. Neointimal hyperplasia was defined as fibromuscular connective tissue showing a random orientation of spindle-shaped and stellate cells embedded in abundant extracellular matrix. Cholesterol crystal clefts, necrotic debris and calcium deposits were recorded independently. No special staining was used to identify calcium. The presence of macrophages was recorded only when these formed clusters or when they were present in unusually high number. Thrombus and intraplaque hemorrhage were identified as amorphous material, in close apposition with atheromatous material, frequently showing collections of leukocytes between layers of fibrin. Areas consisting mainly of fibrin and not clearly related to the plaque that could have formed during the procedure were not recorded. The Verhoef-van Giesson staining was used to discriminate between fibrin and dense collagen. Organization was judged when infiltration by cellular elements, e.g., smooth muscle cells, fibroblasts and capillary sprouts, was observed, and graded from I to III on the basis of the number and characteristics of infiltrating cellular elements.

In the 43 patients with unstable angina, lesion morphology was classified according to the criteria proposed by Ambrose et al[7] by 2 independent cardiologists unaware of the result of the histopathologic studies. Complex lesion morphology was recorded when eccentric lesions with overhanging or ragged edges, or lesions with multiple irregularies were noted. In case of disagreement, the opinion of a third cardiologist was taken into account.

Mean values ± SD are presented for continuous variables. Comparison of mean values was performed using 2-tailed unpaired t tests. Discrete variables were compared using chi-square tests, and Yates' continuity correction was applied when indicated. Statistical significance was accepted at the 5% level.

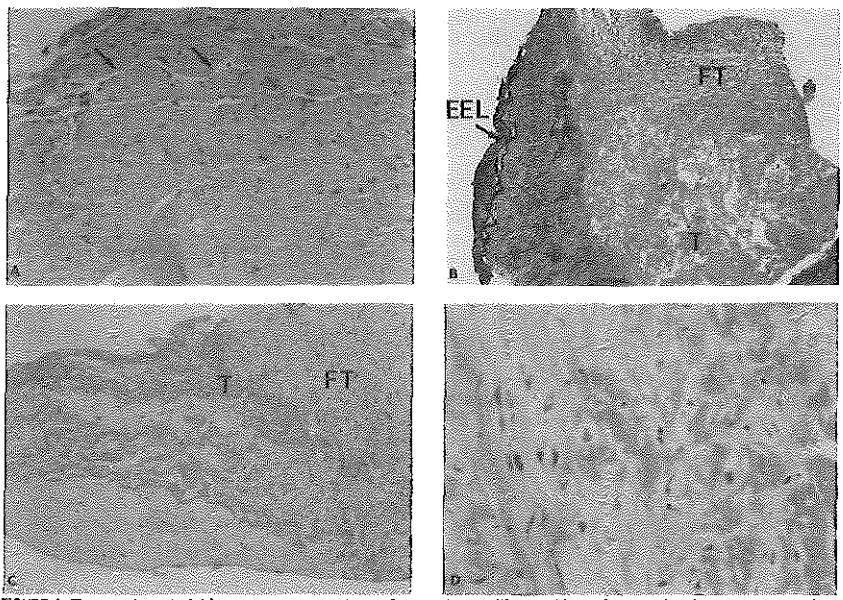

FIGURE 1. Thrombotic material in atherectomy specimens from patients with unstable angina showing different stages of organization. *A*, early organization 5 days after the onset of angina at rest showing lacunar spaces *(arrows)* in the thrombotic bulk that are partially covered by endothelial cells (confirmed by positive staining with lectin immunochemistry using Ulex europeus). *B*, large area of thrombus (T) *(yellow)* 7 days after the onset of angina at rest in close association to newly formed fibromuscular tissue (FT) and showing partial infiltration by myofibroblasts. Fragments of external elastic lamina (EEL) *(arrow)* and media are evident, indicating that deep vessel resection occurred during atherectomy. *C and D*, advanced thrombus organization by fibromuscular tissue 2 days after the onset of angina at rest. Although virtual incorporation to the vessel wall has taken place, it is possible to identify strands of thrombotic material surrounded by connective tissue *(D)*. *A, C and D*: hematoxylin-azophloxin; *B*: Verhoeff-van Giesson (original magnification: *A*, ×60; *B and C*, ×30; and *D*, ×125 — reduced by 37½).

No significant differences were found in the clinical characteristics of both groups, with the exception of a higher prevalence of previous myocardial infarction in the unstable group (13 of 48 [27%] and 21 of 45 [47%] in stable and unstable patients, respectively; p = 0.05) (Table I). Several associations between clinical variables were observed in the patient population. The mean age of male patients was significantly lower than that of female patients (56 ± 10 vs 64 ± 11 years; p = 0.004). Patients with hypercholesterolemia frequently belonged to families with a history of coronary artery disease (67 vs 13% in other patients, p = 0.003).

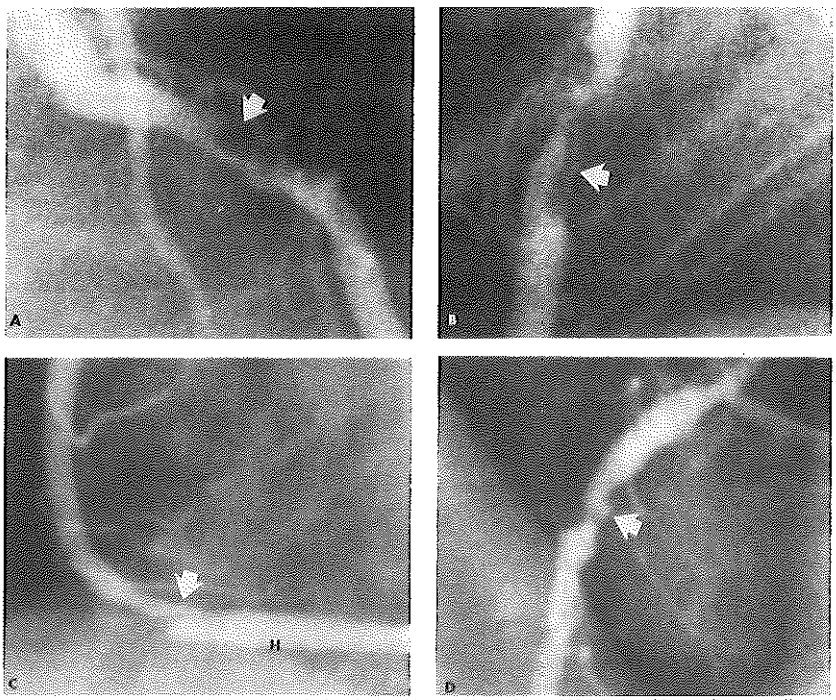

FIGURE 2. Complex angiographic morphology in 4 patients with unstable angina and histologic evidence of coronary thrombosis. *A to D* shows complex eccentric lesions with overhanging edges *(arrows)*.

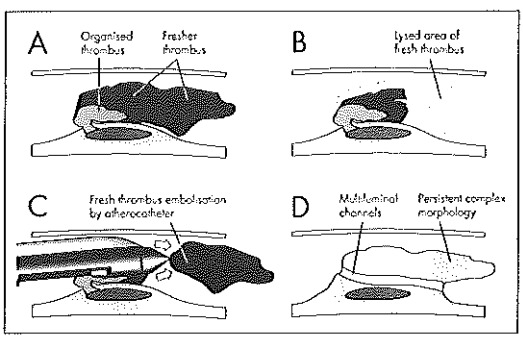

FIGURE 3. Mural thrombosis in unstable angina, and histologic findings in atherectomy specimens. *A*, episodic thrombus growth has been proposed as a characteristic feature of unstable angina, yielding areas of different degrees of organization. Fresher areas of thrombus may have been missed in atherectomy specimens due to spontaneous lysis and concomitant treatment with intravenous heparin *(B)*, or by dislodgement and embolization of the more labile fraction of thrombus by the atherocatheter *(C)*. In some cases, complex angiographic morphology may have resulted from persisting irregularities or multiluminal channels in relation to the recanalization of prior episodes of plaque ulceration *(D)*.

Twenty-four patients had a previous history of coronary intervention, including 14 balloon angioplasties, 6 stent implantations, 3 atherectomy procedures and 1 excimer laser angioplasty. The mean time interval between previous intervention and atherectomy was 147 ± 108 days.

The most striking difference between the syndromes was the presence of foci of thrombus or intraplaque hemorrhage in 10 of 45 (22%) unstable and only in 1 of 48 (2%) stable patients (p = 0.007). Only 1 of these patients had had a previous coronary intervention. All the samples showed some degree of cellular organization (including the presence of endothelial cells covering newly formed channels or capillary vessels present in thrombotic mass originating from the surrounding tissue), the appearance of smooth muscle cells or myofibroblasts, and the presence of thrombotic material embedded in fibrocellular tissue, the latter characteristic suggesting that the masses of fibrin and platelets derived from an episode of thrombosis or plaque hemorrhage were being integrated in the atheromatous plaque (Figure 1, A to D). Thrombus was apposed to fibrous tissue in all cases, without endothelial cells in the interface between both. A lack of relation between the time interval from the onset of angina at rest to atherectomy and the degree of thrombotic organization was evident. Likewise, the relation between angiographic morphology and the presence of thrombus in the retrieved tissue did not reach statistical significance. Complex angiographic morphology was noted in 17 of 45 unstable patients (37%) (Figure 2). Thrombus or plaque hemorrhage was present in 6 of these patients (35%) and in 4 of those with non-complex angiographic morphology (14%) (p = NS).

Calcium deposits were also observed more frequently in patients with unstable (18 of 45 samples, 40%) than stable (9 of 48 samples, 19%) angina (p = 0.042). No significant differences were found with regard to the presence of fibrous tissue, cholesterol clefts, necrotic core or clusters of macrophages. In the overall population, complex atheromatous samples (containing dense fibrous tissue, calcium deposits and necrotic debris) were obtained in older patients (58 ± 10 vs 51 ± 12 years, p <0.031). Necrotic debris was observed in 7 of 34 cigarette smokers (21%) versus 2 of 59 nonsmokers (4%) (p = 0.019). Macrophages were identified in 4 of 15 (27%) and 5 of 78 (6%) samples with and without necrotic debris, respectively (p = 0.05).

Neointimal hyperplasia was observed in 17 of 24 patients (71%) with previous coronary intervention and in 14 of 69 patients (20%) with primary lesions (p = 0.0001). Neointimal hyperplasia had identical characteristics in patients with previous balloon angioplasty, stenting, atherectomy or laser angioplasty. Particular attention was paid to the 14 patients with primary lesions showing typical neointimal hyperplasia. When compared with other primary lesions, no relation to the type of coronary syndrome was observed: 6 patients had stable and 8 unstable angina pectoris (p = NS). Likewise, no association with sex, coronary artery disease risk factors or previous myocardial infarction was found. However, the mean age of patients with primary lesions showing neointimal hyperplasia was significantly lower than that of patients with primary lesions and other histologic characteristics (51 ± 13 vs 59 ± 10 years, p = 0.017).

The retrieval of atheromatous material during directional coronary atherectomy has created new possibilities in the study of coronary syndromes. Although limited by lesion selection and sampling characteristics,[8] the collection and analysis of the removed tissue has the considerable advantage of allowing the pathologic assessment of coronary artery disease "in-vivo," thus avoiding the selection bias inherent in postmortem studies. To our knowledge, the present work represents the first comparative study of the histopathologic substrate of 2 different coronary syndromes using atherectomy retrieved material.

Primary unstable angina is considered to be an acute thrombotic syndrome[2–5] occurring predominantly in patients with widespread coronary artery disease.[9] Coronary thrombosis does not result initially in transmural myocardial necrosis because of incomplete, episodic vessel obstruction, intermittent spontaneous vessel recanalization, or the presence of well-developed collateral anastomoses.[3,4] Different observations suggest that the associated mural thrombus is very rich in platelet aggregates and has a layered appearance.[2]

In the present study a higher prevalence of mural thrombus and plaque hemorrhage in unstable angina was also observed: thrombus was identified in atherectomy samples obtained from the ischemia-related coronary lesion of 22% of unstable and in only 2% of stable patients. This figure is lower than the prevalence of thrombus suspected in angiographic studies[3] but similar to that reported in a necropsy study of patients with unstable angina.[9] It is remarkable that no statistical relation between complex angiographic morphology and presence of thrombus in the tissue retrieved could be found, although several explanations can be given for this. The persistence of complex angiographic morphology in the long term has been reported in 57% of cases by Haft and Al-Zarka.[10] A complex angiographic morphology may also result from multiluminal channels that are frequent in atheromatous plaques of unstable patients[11] (Figure 3D). Unstable angina may also result from changes in plaque geometry secondary to intraplaque hemorrhage, which may be difficult to differentiate from mural thrombus during the study of isolated fragments of the arterial wall.

An interesting finding is that all samples containing thrombus or intraplaque hemorrhage material showed different degrees of cellular organization that, on the grounds of the time scale of thrombus organization observed in experimental models,[12] bore no relation to the time interval between the onset of chest pain and atherectomy. This may suggest that the onset of coronary thrombosis or plaque hemorrhage had preceded the development of angina at rest by several days or weeks. The retrieved organizing thrombus may thus correspond to either an episode of plaque hemorrhage or to a first episode of subocclusive thrombosis that after episodic growth or rethrombosis led to the development of symp-

toms[2] (Figure 3A). The absence of fresh thrombus in these samples could be due to spontaneous lysis and inhibition of further thrombosis by continued systemic heparinization (Figure 3B) or embolization of that labile fraction of thrombus during catheter manipulation (Figure 3C).

These observations may have implications for therapeutic and diagnostic approaches in unstable patients. The low prevalence of observed thrombus and the degree of organization or embedded thrombus in the atheromatous plaque may explain the therapeutic failure of thrombolytic agents in primary unstable angina.[13,14] One should clarify whether some of the angioscopic characteristics of coronary thrombus observed in unstable patients, such as the characteristic greyish appearance reported by Mizuno et al[5] could be related not only to platelet-rich thrombus, but also to organizing characteristics of thrombus, since it is well known that the macroscopic appearance and color of thrombus shifts progressively toward a pale, whitish color as organization increases.[15]

The cause of the initial event in the development of mural thrombosis, plaque rupture or fissuring, remains controversial. In this study, macrophages, which have been identified in areas of the fibrous cap that are prone to rupture,[16] were not observed preferentially in unstable plaques but preferentially in plaques with necrotic core. Only fibrous tissue was found in close association with thrombus, an observation that may be relevant to the kind of initiating thrombogenic stimuli. Although no endothelium could be identified in the area covered by thrombus, no firm conclusions can be drawn from this because experimental studies have shown that endothelial cells are rarely observed 3 days after being engulfed by mural thrombosis.[12]

The higher prevalence of calcium deposits in unstable plaques may be related to the frequent existence of severe and widespread coronary artery disease in unstable patients.[11] A proportional relation between complex atheroma and age was also evident in the overall study population, in agreement with the current knowledge of the sequence of events leading to the progression of coronary artery disease.[17]

Our results also support previous observations in coronary atherectomy specimens showing that neointimal hyperplasia constitutes the pathologic substrate of restenosis after coronary intervention,[18] irrespective of the revascularization technique used previously. Typical atherosclerotic tissue was also retrieved in a substantial number of restenotic lesions, although this is probably due to the sampling characteristics of the device or in circumstances where restenosis was due to mechanisms other than neointimal hyperplasia.[8] In accordance with a previous study,[19] neointimal hyperplasia was also found in a substantial number of primary lesions. We noted that these patients were significantly younger than others with typical primary atherosclerotic lesions, a fact that may have particular relevance since fibromuscular neointimal proliferation has been reported as the pathologic substrate for coronary artery disease in the young, resulting in sudden death.[20] The ultimate meaning of this observation as to the natural history of atherosclerosis remains unclear. Neointimal hyperplasia represents an unspecific vessel wall response to different kinds of injury that lead to accelerated forms of atherosclerosis. Whether the presence of this type of tissue in primary lesions of young, symptomatic patients is a reflection of less-known factors initiating the atherosclerotic process (e.g., viral endothelial injury, genetical predisposition) remains hypothetical.

Histologic studies based on atherectomy specimens are biased by selective plaque sampling,[8] although in the present study this limitation was partially overcome by routinely performing multiple cuts in different sectors of the vessel. Case selection may have occurred since only vessels judged suitable for the technique were treated (e.g., coronary atherectomy was performed in only 1 patient with total occlusion). The differentiation between mural thrombosis and foci of plaque hemorrhage is strongly limited by the analysis of isolated fragments of atheroma. Atherectomy was performed in stenoses that were identified on the grounds of clinical, angiographic and electrocardiographic data as ischemia-related stenoses. However, this "culprit lesion" approach may not have been free from a number of confounding factors, including the persistence of complex angiographic morphology from a previous event[10] (Figure 3D), and the development of myocardial ischemia "at a distance" by a different coronary narrowing.

Despite these limitations, the results of the present study emphasize the use of directional coronary atherectomy as a means of investigation during its therapeutic use. The identification of such features as an increased prevalence of organized thrombus in patients presenting with unstable angina, and of neointimal hyperplasia in primary coronary lesions of younger patients contributes further to our knowledge of the processes that take place in the coronary arteries during the natural history of coronary syndromes.

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Chapter 14

DIRECTIONAL ATHERECTOMY: COMBINING BASIC RESEARCH AND INTERVENTION

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Directional atherectomy: Combining basic research and intervention

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In 1985 Simpson et al.[1] first described the percutaneous transluminal removal of atheromatous material from peripheral arteries by means of a novel catheter system. The technique was given the term "directional atherectomy," denoting the selective excision of obstructive luminal atheroma to distinguish it from surgical endarterectomy. Initial experience indicated that directional atherectomy could be performed safely and effectively and might be an attractive alternative to conventional balloon angioplasty in certain circumstances.[2,3] Developments in the atherectomy catheter and the design of suitable guiding catheters allowed the extension of the technique to the coronary arteries in 1986.[4] Recently, directional coronary atherectomy has undergone comparison with coronary balloon angioplasty in a multicenter prospective, randomized trial, the CAVEAT study. After brief discussion of the technical aspects and clinical use of directional atherectomy, this article will focus on the application of atherectomy as a route to research.

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TECHNICAL DETAILS

The Simpson AtheroCath (Devices for Vascular Intervention, Redwood City, Calif.) incorporates a rigid metal cylinder a short distance from the distal tip (Fig. 1). This cylinder is windowed longitudinally on one side and carries an eccentric balloon on the other. Within the cylinder is a cup-shaped cutter that can travel the length of the window; the cutter is advanced and retracted by a hollow drive cable. The most distal part of the cylinder serves as a collection chamber. Proximally, the drive cable connects with a hand-held, battery-operated motor that spins at

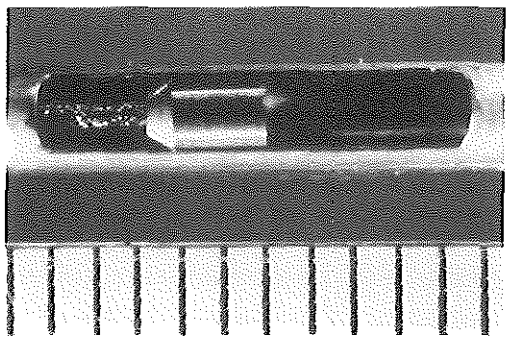

Fig. 1. Simpson Atherocath. In window of cutter housing, cutter and drive cable are visible. Guide wire has been withdrawn. *Bar scale,* 1 mm.

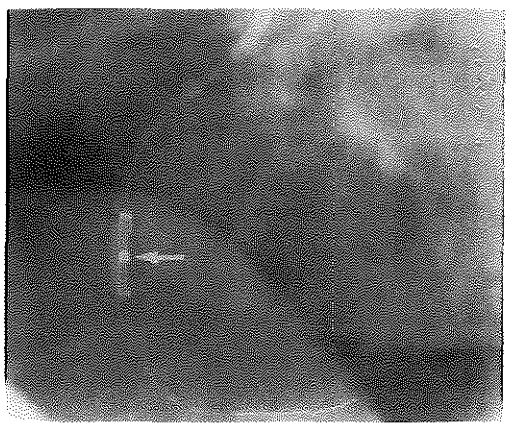

Fig. 2. Directional atherectomy device deployed in right coronary artery, 45° left anterior oblique projection. Eccentric balloon is inflated with contrast, opposing cutter housing to vessel wall. Rotating cutter is clearly visible *(arrow).*

±2,000 rpm. To position the Atherocath, a conventional 0.014-inch guide wire is passed through the cable lumen and manipulated across the lesion. The device can then be advanced. For coronary use preshaped, nonangled guiding catheters are first introduced. On retraction of the cutter, low-pressure inflation of the eccentric balloon holds the window firmly against the selected area of atherosclerotic plaque. Material intruding into the window is then shaved off and pushed into the collection chamber by the advancing cutter (Fig. 2). After withdrawal of the device from the patient, specimens are flushed back into the window from where they can be extracted (Fig. 3). The amount of tissue retrieved varies widely but from peripheral lesions approaches 100 mg in weight[5] and from coronary lesions approximately 20

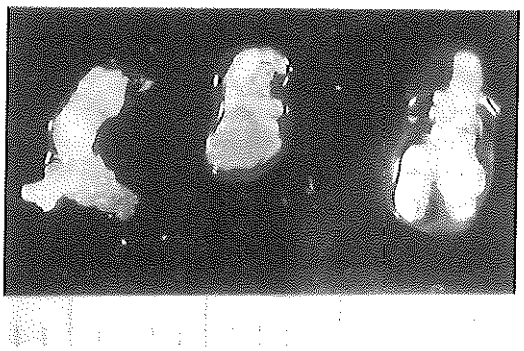

Fig. 3. Macroscopic appearance of tissue retrieved during directional coronary atherectomy. *Bar scale*, 1 mm.

mg.[5,6] The rigidity and bulk of the cutting and collection system (≥5F) limits coronary use to the proximal and middle sections of relatively large vessels (≥2.5 mm); the largest device (11F) may not be sufficient to allow satisfactory apposition in large peripheral arteries.

CLINICAL APPLICATIONS

There is debate regarding the most appropriate niche for atherectomy in vascular intervention; several reports have focused on the therapeutic potential of the technique in peripheral and coronary arteries.[2-4,7,8] It is proposed that atherectomy may be advantageous in dealing with complex lesions often seen in unstable angina, where conventional balloon angioplasty can be associated with suboptimal results. Threatened or abrupt occlusion resulting from balloon-induced dissection can be managed by using directional atherectomy to excise the intimal flap, a bail-out role, but this is controversial. Originally, atherectomy was thought less likely to provoke restenosis on the basis of leaving a smoother vessel lumen with fewer dissections. This is probably not the case, but the increased initial luminal gain compared with conventional balloon angioplasty may better accommodate subsequent restenosis.

RESEARCH APPLICATIONS

Directional atherectomy has created the potential for new directions in both clinical and laboratory research (Fig. 4). Indeed, among the new interventional devices, atherectomy is unique in providing the means to investigate pathophysiologic phenomena by using human vascular tissue. First, the tissue retrieved by the device can be subjected to histopathologic examination. Traditionally, the pathologic features of atherosclerosis in human beings have been studied by using material excised in the operating theater or autopsy suite. What directional atherectomy now offers is access to fresh vascular tissue for immediate fixation and examination in situations where precise details of the current and previous medical history and clinical investigations are available. Thus histopathologic appearances can be reliably related to different clinical pictures; primary atherosclerosis and restenosis, stable and unstable angina, for example.

Second, this tissue constitutes a source of cells for experimental work. Of necessity, investigations of mechanisms at cellular level in atherosclerosis, restenosis, and acute coronary syndromes have been performed in animal models to date. Studies have identified the vascular smooth-muscle cell as having a pivotal role in the response to injury of the vessel wall.[9] Smooth-muscle cells disaggregated or cultured from tissue excised at atherectomy can be examined with electron microscopy to identify subcellular organelles and myofibrils and with immunohistochemistry or electrophoresis to identify cytoskeletal proteins such as smooth muscle cell alpha-actin, to comment on cell phenotype. The distinction between the contractile and synthetic phenotypes of the vascular smooth-muscle cell in culture is shown diagrammatically in Fig. 5. Important behavioral properties of the smooth-muscle cell, migration, proliferation, and extra-cellular matrix synthesis, can be examined in

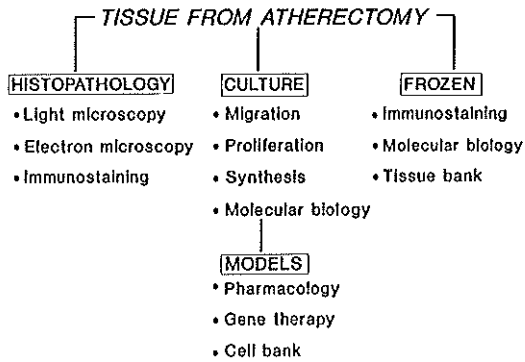

Fig. 4. Directional atherectomy: possible directions of research based on basis of retrieved tissue.

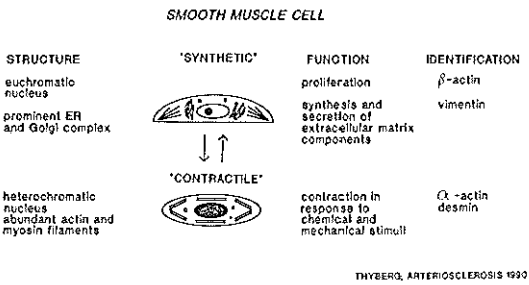

Fig. 5. Diagrammatic representation of differences in smooth-muscle phenotype: synthetic and contractile forms. (Adapted from Thyberg et al. Arteriosclerosis 1990;10:966.)

vitro. Also, cultured human vascular cells may be used as experimental models in the assessment of pharmacologic agents and the investigation of genetic processes in the cell, including the effects of genetic manipulation.

Third, tissue can be frozen pending characterization with molecular biologic techniques. Transcription, the process by which the genetic code is conveyed to the synthetic apparatus of the cell, and translation, the interpretation of the genetic message and consequent production of specific proteins (Fig. 6), can be unravelled by using monoclonal antibodies to recognize protein products and Northern blotting or in situ hybridization with selective radiolabeled gene probes to identify different messenger ribonucleic acid (RNA) chains (Fig. 7).

Histopathologic studies. A number of reports have been generated by this aspect of directional atherectomy. Material excised from primary atherosclerotic lesions in peripheral vessels bore the typical appearance of dense, fibrous plaque with occasional cholesterol crystals.[10] Two thirds of restenotic lesions in the periphery displayed the characteristic feature of the vascular response to injury, neointimal hyperplasia, but this feature was also found in approximately one third of primary lesions.[10,11] Coronary artery histologic features were similar; virtually all restenotic lesions revealed neointimal hyperplasia, a feature seen nevertheless in a third of primary lesions.[6] In our own series neointimal hyperplasia (Fig. 8) indeed correlated significantly with prior intervention, usually conventional balloon angioplasty, and was detected

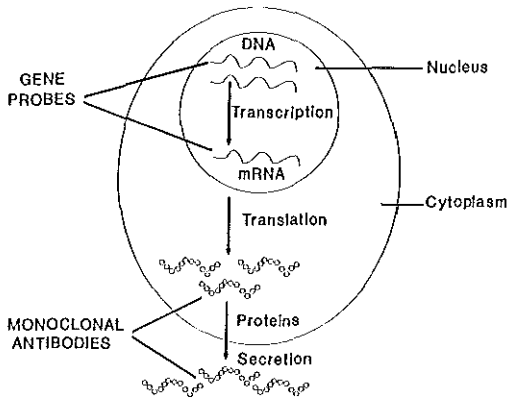

Fig. 6. Diagrammatic representation of route from genomic DNA to protein synthesis. Indicated are points at which different agents act to identify specific processes.

in 20% of primary lesions (Table 1). The presence of neointimal hyperplasia in a substantial proportion of primary atherosclerotic lesions is consistent with the suggestion that spontaneous intramural injury in the form of plaque rupture occurs commonly, often apparently without serious clinical consequence,[12] and confirms that the primary atherosclerotic plaque is far from inert. What cannot yet be drawn from the literature is whether or not the primary atherosclerotic plaque demonstrating this evidence of vascular injury can distinguish subgroups of patients with a different pattern of symptoms, rapid onset or crescendo angina pectoris, for example.

Neointimal hyperplasia in plaque tissue testifies to recent or ongoing cellular proliferation. The proliferative status of intimal smooth muscle cells in fresh tissue obtained at directional atherectomy can be documented by using a monoclonal antibody to a cyclin, the proliferating cell nuclear antigen (PCNA), thus identifying cells in the S, G_1, and G_2 phases of the cell cycle.[13] By this means a recent report confirmed that low rates of proliferation do exist in primary atherosclerotic lesions,[14] in agreement with the histologic data regarding neointimal hyperplasia. In a brief series of patients undergoing directional atherectomy for restenosis in coronary and venous bypass graft stents, compared with patients receiving atherectomy for restenosis postballoon angioplasty, anti-PCNA labeling indicated that smooth-muscle cellular proliferation may wane within a relatively short period of time after coronary interventions: 47 days after stent implantation and 14 days after balloon angioplasty.[15]

There is continuing interest in the role of thrombotic mechanisms in vascular events. In peripheral vessels adherent or incorporated thrombus was a common finding in relation to primary atherosclerotic lesions but less so in relation to restenotic lesions.[10,11] Although thrombus was not commented on in a report of 73 coronary specimens,[6] a recent communication described the presence of thrombus in 18 of 19 complex coronary lesions.[16] Our own group, examining 93 consecutive coronary atherectomy specimens, noted that the presence of organized thrombus within the plaque (Fig. 9) was related to unstable angina (Table I). The proportion of cases was small, 10%, but in these patients the degree of organization of the thrombus allows us to estimate with some confidence that spontaneous plaque rupture took place 7 to 10 days previously. Given accurate clinical details, the comparison of primary atherosclerotic lesions demonstrating either organized thrombus or neointimal hyperplasia, with lesions showing neither of these features, provides fresh insights into the pathophysiologic nature of the plaque in diverse coronary syndromes.

The features of the tissue excised at atherectomy may have further bearing on subsequent clinical outcome. Garratt et al.[17] examined the depth of resection during coronary atherectomy and related this to the subsequent development of restenosis; deep cuts were suggested to be a risk factor for restenosis in

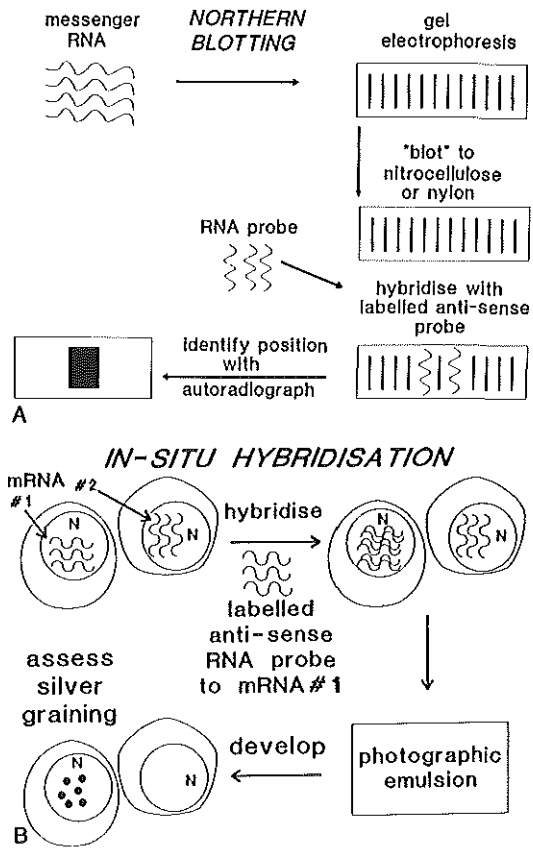

Fig. 7. Diagrammatic representation of techniques of **(A)** Northern blotting and **(B)** in situ hybridization.

venous grafts and in already restenotic lesions but not in primary lesions. In material from 125 peripheral and 39 coronary procedures, observation of a highly cellular intima, identification of the internal elastic lamina and the presence of arterial media were found to be predictive of restenosis after atherectomy.[18] Analysis of specimens from 377 coronary atherectomies revealed that the presence of lesion thrombus and incision into the adventitia were the two factors associated with procedural complications such as vessel occlusion, myocardial infarction, perforation and distal embolization in vein grafts.[19]

Information can also be obtained regarding other forms of vascular intervention. In 33 patients undergoing directional atherectomy for restenosis subsequent to balloon angioplasty, atherectomy, or laser angioplasty, Waller et al.[20] noted that the histologic appearances were similar regardless of the initial technique.[20] The enterprising use of directional atherectomy in 21 patients immediately after either

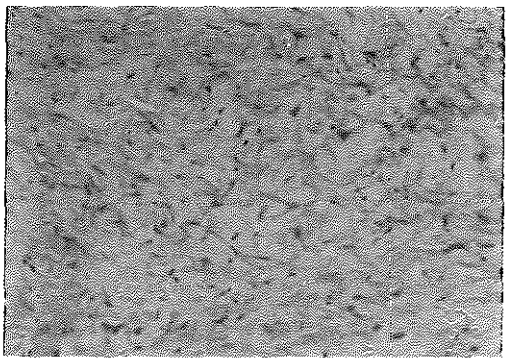

Fig. 8. Section of primary atherosclerotic coronary artery plaque excised at directional coronary atherectomy demonstrating neointimal hyperplasia. (hematoxylin-azofloxin stain; ×450).

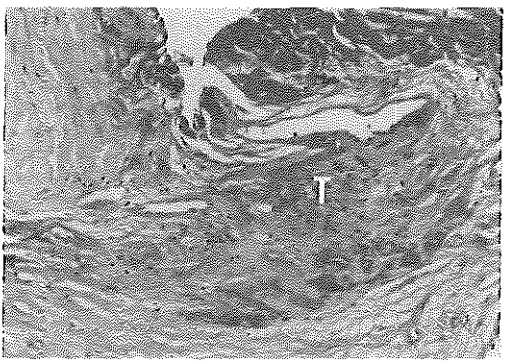

Fig. 9. Section of atherosclerotic coronary artery plaque excised at directional coronary atherectomy demonstrating organized thrombus *(T)*. (hematoxylin-azofloxin stain, ×400).

Table I. Frequencies with which neointimal hyperplasia was found in relation to lesion type and organized thrombus was found in relation to symptoms in coronary artery plaque tissue excised from 93 patients at directional atherectomy

	Primary lesion	*Restenosis*
Neointimal hyperplasia	14/69 (20%)	17/24 (71%)
	$p < 0.001$, X^2 test	
	Stable angina	Unstable angina
Organized thrombus	1/48 (2%)	10/45 (22%)
	$p < 0.01$, X^2 test	

Nd:YAG ("hot-tip"), holmium:YAG, or excimer laser angioplasty allowed Isner et al.[21] to describe the pathologic effects of the three modes of laser, which ranged from charring several cell layers thick with the first to a mildly basophilic, serrated appearance, one cell layer deep with the last.[21] Findings such as these may be useful when considering both the procedural result and the longer-term outcome of laser thermal and photoablation and may influence changes in clinical practice.

Studies using directional atherectomy are enhanced by the use of quantitative angiography where

edge-detection analysis in particular provides useful information on plaque geometry in relation to both the effect of the procedure[22] and histopathologic data. Conceptually, the marriage of directional atherectomy and intravascular ultrasonography is very attractive. High-quality images of the vessel wall will help to assess the separate contributions of the three modes of action of the atherectomy device: the "Dotter" effect, the effect of balloon inflation, and the effect of the cutter. Also, examination of tissue retrieved may prove useful in corroborating the information provided by intravascular ultrasonography with regard to the components and architecture of the vessel wall. In a similar manner, different types of thrombus, or features of the plaque such as fissuring, revealed by angioscopy, can be sought in atherectomy samples.

Cell and cell culture studies. Bauriedel et al.[23] were the first to embark on cell-based investigations with atherectomy material and demonstrated that cells disaggregated from atherectomy specimens could be identified as smooth-muscle cells by their staining with monoclonal antibodies to smooth-muscle cell alpha-actin.[23] An extension to this work included electron microscopic and electrophoretic studies of peripheral arterial atherosclerotic material.[24] The mixed phenotype of the intimal smooth-muscle cells (Fig. 5), revealed by the presence of peripheral myofilaments together with dense perinuclear organelles, was consistent with the findings of studies of vascular injury in experimental animal models, and the distribution of cytoskeletal proteins, predominantly beta-, alpha- and gamma-actin and vimentin was similar to that found in studies of surgically excised human tissue. Immunofluorescence microscopy applied to sections of tissue obtained from coronary arteries at atherectomy revealed that vimentin-positive smooth-muscle cells of synthetic phenotype were also positive for cytokeratins 8 and 18.[25] Cytokeratins are proteins found in fetal and neonatal but not adult vascular smooth-muscle cells, indicating that a subset of the coronary lesion smooth-muscle cells in this study had the characteristics of immature, dedifferentiated cells commonly associated with proliferative properties.

The material obtained at directional atherectomy can be exploited by using the technique of cell culture in the further use and investigation of the small pieces of tissue retrieved. Bauriedel et al.[23] were also the first to describe the cultivation of fibroblast-like cells from atherectomy tissue explants.[23] It was subsequently reported that cells isolated from primary atherosclerotic and restenosing lesions in both peripheral and coronary arteries behaved differently in initial cell culture and early subculture.[26, 27] Restenosis cells demonstrated more rapid growth, attributed to a significant subpopulation of small, low-adhesive proliferative cells that featured less among the cells of primary atherosclerotic origin. Two other findings were of particular interest. First, primary cells in culture did not respond to platelet-derived growth factor (PDGF), whereas restenosis cells responded by increasing their growth. Second, primary lesion cells proliferated in response to medium conditioned by restenosis cells, allowing the authors to propose an autocrine growth-promoting (non-PDGF) function of smooth-muscle cells in restenosis lesions in human beings, a mechanism previously suggested in animal studies. In a more recent study, this group describes their examination of cells cultivated from peripheral and coronary primary atherosclerotic and restenotic lesions by using a computer-assisted cell motion analysis system.[5] Cell outgrowth was not related to any clinical parameter, including the type of lesion, but restenosis cells were found to display increased migratory activity during initial outgrowth in culture (Table II), which in conjunction with their earlier findings regarding proliferation, led the authors to emphasize the importance of these aspects of cell behavior in the restenosis process.

Table II. Migratory velocity of smooth-muscle cells cultured from primary and restenotic coronary and peripheral arterial lesions excised at directional atherectomy

Cell source	*Migratory velocity*
Primary	
Coronary	19.4 ± 5.1 (n = 7)
Peripheral	21.1 ± 2.5 (n = 12)
Restenotic	
Coronary	46.2 ± 3.6 (n = 5)
Peripheral	48.0 ± 3.0 (n = 6)

Values are expressed as mean ± SEM. Units are $\mu m/hr$ (adapted from Bauriedel G, et al. Circulation 1992;85:554-64).

Our own group has also sought to use initial and extended cell culture as a means of examining the behavior of human coronary smooth-muscle cells obtained at directional atherectomy. Confluent cells cultured from retrieved tissue and electron micrographic images of these cells reveal appearances consistent with a mixed contractile/synthetic phenotype (Fig. 10). In agreement with the report of Dartsch et al.[26] with respect to peripheral vascular lesions, we found that smooth-muscle cells cultured from restenotic coronary lesions demonstrated accelerated growth compared with cells from primary atherosclerotic coronary lesions that had a growth pattern similar to young control human umbilical artery medial

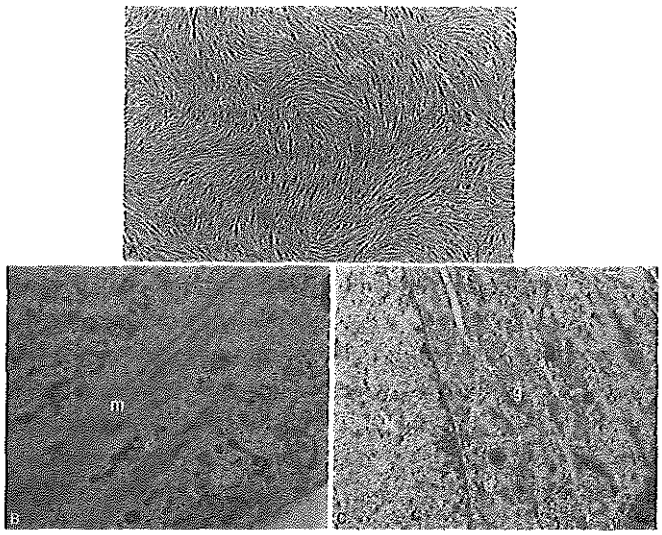

Fig. 10. **A**, Confluent cultured cells derived from tissue retrieved at directional coronary atherectomy; typical "hill-and-valley" culture morphologic features. Electron microscopic features of smooth-muscle cells from coronary artery atherosclerotic plaque tissue excised at directional atherectomy. **B**, peripheral myofibrils *(m)*. **C**, perinuclear *(N)* organelles, endoplasmic reticulum *(e)*, golgi bodies *(g)*, and numerous ribosomes are visible.

cells (Fig. 11). Although we were also unable to relate growth in culture to any clinical parameter, a factor favoring successful initial smooth-muscle cell outgrowth was the presence of organized thrombus in the atherectomy specimen (Table III), hinting at links between complex lesions, unstable angina, and restenosis. Further, coronary cells derived from both types of lesion demonstrated increased extracellular matrix production compared with the umbilical artery cells[27] (Table IV), consistent with the concept that extracellular matrix synthesis is a property of the adult vascular smooth-muscle cell important in both primary atherosclerosis and restenosis.

Cultured human vascular cells provide us with new alternative experimental models for the assessment of the in vitro actions of existing therapies and, potentially, for the development of novel treatment strategies. Having previously noted that material retrieved from patients receiving angiotensin-converting enzyme inhibitors was less likely to demonstrate successful smooth-muscle cell outgrowth,[29] Bauriedel et al.[30] showed recently by means of cell motion analysis and cell population doubling times that two aspects of smooth-muscle cell growth in culture, migration, and proliferation responded similarly but to different extents to a variety of exogenous pharmacologic agents. The combination of photosensitizing hematoporphyrin derivatives and photoradiation, a potential means of localizing and attacking the atherosclerotic plaque, has been examined by using smooth-muscle cells cultured from tissue retrieved during peripheral arterial atherectomy.[31] These cells were found to be more susceptible to damage than control vascular smooth-muscle cells cultured from healthy arteries biopsied postmortem. Cell-culture models need not be restricted to monolayers of one particular cell type. Coculture systems, as recently reviewed by Betz,[32] can be constructed to mimic the vessel wall and thus cater for important interactions such as those that occur between the endothelium and the media.

"Gene therapy",[33] whereby new genetic material is introduced to the cell by using methods such as lipofection,[34] retroviral vectors,[35] engineered cells,[36,37] and even particle bombardment,[38] is a source of considerable current interest. Cells in culture may be

Table III. Frequency of smooth-muscle cell outgrowth in 98 attempted cultures in relation to presence of organized thrombus in coronary artery plaque tissue excised at directional atherectomy

	Thrombus	*No thrombus*
SMC outgrowth	8/10 (80%)	35/88 (40%)
	$p < 0.025$, X^2 test	

Table IV. Extracellular matrix production of collagen and sulphated-glycosaminoglycans of human coronary cells cultured from plaque tissue excised at directional atherectomy and of smooth muscle cells cultured from media of human umbilical arteries

Cell source	*Collagen*	*Glycosaminoglycans*
Restenosis	0.034 ± 0.006[1]	11.5 ± 1.1[3]
Primary	0.033 ± 0.004[2]	15.4 ± 3.1[4]
Umbilical	0.019 ± 0.004[1, 2]	5.4 ± 1.0[3, 4]

Collagen synthesis was determined by the uptake of tritiated proline and sulphated-glycosaminoglycan synthesis by the incorporation of ^{35}sulphate. Values are nanomols of ligand per microgram of total protein, mean ± SEM; [1-3] $p < 0.05$, [4] $p < 0.005$.

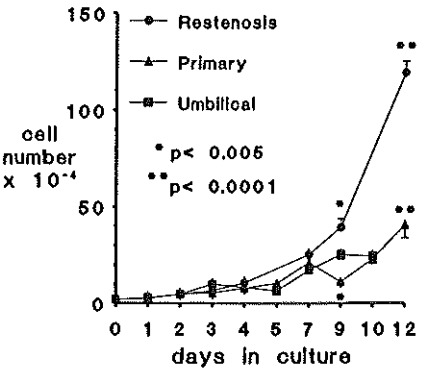

Fig. 11. Growth curves of smooth-muscle cells derived from human coronary restenotic and primary atherosclerotic lesions and from normal human umbilical artery media in secondary culture.

used to evaluate the success and effects of attempts to modify the genome and influence translation and transcription; human vascular cells obtained at atherectomy are a logical preliminary testing ground.

Frozen tissue studies. The recent publication of Leclerc et al.[39] focuses on transcription (Fig. 6) and reports the increased expression of messenger RNA for nonmuscle myosin heavy chain-B (MHC-B) in the intimal smooth-muscle cells of restenosis tissue compared with primary atherosclerotic tissue retrieved at peripheral or coronary atherectomy.[39] This finding is of interest because nonmuscle myosin has been implicated in vascular smooth-muscle cell division and proliferation; the method is a timely reminder of the application of molecular biologic techniques in clinical science. The mRNA for MHC-B was detected by in situ hybridization (Fig. 7) by using an antisense complementary (c)RNA probe prepared from recently cloned complementary deoxynibonucleic acid (DNA) coding for an isoform of the human nonmuscle MHC-B gene. To control for the specificity of the antisense cRNA probe, parallel hybridizations were performed with the sense cRNA probe; to control for cross-hybridization of the nonmuscle myosin probe to smooth-muscle myosin, hybridizations were performed in normal human internal mammary artery media preparations. By using a similar technique, this research group has now investigated the possible role of transforming growth factor-β (TGF-β) and suggests that it may be involved in vascular restenosis.[40] Work of this nature, probing genetic regulation in plaque tissue, has particular relevance in view of the possibilities of gene therapy. However, on a note of caution, as the number of growth factors and other mediators implicated in atherogenesis and restenosis expands the difficulty of interpreting this newfound knowledge of the cell renders the choice of optimal targets less straightforward.

PROSPECTS

The various research techniques we have mentioned are unlikely to excite the cell biologist, who is well acquainted with them. However, with the advent of directional atherectomy, it is now possible to apply such techniques in a systematic manner to the investigation of atherosclerosis, our most common source of mortality, and restenosis, the response to injury that besets vascular intervention, by using human material. The identification of pathophysiologic mechanisms within the cell holds out the prospect of discovering, developing, and testing new pharmacologic or genetic therapies that can then be assessed in human cell culture systems. Work of this nature represents an important advance at a time when, in the field of restenosis, the failure of both empiric drug trials and trials based on apparently sound animal experimental evidence is a cause of concern.[41, 42] Directional atherectomy opens up new

avenues of research, but it falls to the interventionalist to generate the enthusiasm among colleagues in the basic sciences that is the stimulus for fresh collaborative research.

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Chapter 15

SUMMARY AND FUTURE PERSPECTIVES

This thesis summarizes the clinical, angiographic and histologic findings in patients who underwent a directional coronary atherectomy in Rotterdam and Brussels between September 1989 and January 1994. In *part I*, the concept of matching for angiographic and clinical parameters is introduced, validated and subsequently used as a technique to compare the angiographic results of new interventional devices, and atherectomy in particular, with those of conventional balloon angioplasty. In *part II*, the immediate and late clinical outcome of this novel interventional procedure are reviewed. *Part III*, provides an overview of the histologic information obtained from freshly harvested atherosclerotic plaque material.

The purpose of this chapter is to review the results and to present some lessons which have been learned from the Rotterdam atherectomy program and provide a future perspective for directional atherectomy. Because restenosis still remains the Achilles heel of interventional cardiology, the merits of new techniques lay in reducing this phenomenon. Although patient care and clinical outcome remain the central issue, quantitative coronary angiography is the only reliable method to compare interventional techniques with respect to restenosis and remains the golden standard in interventional cardiology. Therefore, this chapter focuses on the values of angiography to summarize the data and provide a future perspective.

How should quantitative coronary angiography data be applied to compare DCA and PTCA?

We have now reached the stage where the safety and favorable immediate results for the various devices have been demonstrated in chapter IX-XII. The next logical step is the comparison of the devices to determine which specific features of a device may favor its use in a particular clinical situation [1,2]. In anticipation of such comparative trials, we have attempted to compare available data according to three methods. First, we extrapolated pathological findings in an animal model to clinical practice, secondly, introduced matching as a surrogate for randomized trials and thirdly we distinguished the angiographic outcome *at* follow-up from the renarrowing process *during* follow-up (i.e. static vs dynamic restenosis criteria).

I) *Relative gain as an 'injury score', relative loss as an index of neo-intimal hyperplasia.* The important observation that a greater gain in lumen (i.e. injury) is associated with a greater loss (ie repair) during follow-up has previously been described by Schwartz et al [3-5]. In a domestic swine stented model, which accurately mimics the proliferative nature of human restenosis, the extent of the

proliferative response was strongly associated with rupture of the internal elastic lamina as induced by oversized and overpressurized balloon inflations, with, or without, coil implantation. In chapter IX this hypothesis is tested in a clinical setting, by substituting the concept of "injury score" and "neo-intimal hyperplasia" as observed in the animal model with the angiographically derived parameters of relative gain and relative loss. Previous balloon angioplasty, stenting and atherectomy angiographic studies revealed a linear relationship between relative gain and relative loss, although the coefficient of correlation is low. More importantly, not only the strength of the correlation varied between devices, the slope of the regression line was steeper in the atherectomy group than in the stent and angioplasty group implying that the reactive response (ie relative loss) was more pronounced after atherectomy than following angioplasty. The slope of the regression line between relative gain and relative loss, which reflects the inherent relationship between the degree of wall injury and the degree of repair represent an index of luminal renarrowing specific for each treatment modality (atherectomy, balloon angioplasty).

II) Matching. In chapters III-VII, we have employed and described the technique of "matching" which is based on three principles: a) the angiographic dimensions of matched lesions are assumed to be "identical", b) the observed difference between the two "identical" lesions must be within the range of the CAAS analysis reproducibility of 0.1 mm (=1 s.d.), and c) the reference diameter of the potentially "matched" vessels are selected within a range of $\pm$ 0.3 mm (=3 s.d.; ie. 99% confidence limits). The appropriate lesions are selected by an independent observer who is unaware of the 6 month angiographic outcome. Subsequent refinement of this technique allowed also the incorporation of clinical variables thereby creating similar patient groups with identical lesion and clinical characteristics. Eventually, matching may be used as a surrogate for randomized trials and may serve as a predictor of the outcome of such trials.

III) *A multivariate analysis of the renarrowing process and late outcome.* While examining the long-term results of intracoronary interventions, two aspects should be considered: (1) the clinical approach in which the determinant of the long-term angiographic *outcome* (minimal luminal diameter at follow-up) is characterized and (2) the biological approach which describes the determinants of the dynamic *process* (late luminal loss) which is initiated by the injury inflicted to the vessel wall during intervention. Initially, these two viewpoints appear contradictory but on deeper examination it may be possible to reconcile the assessment of *outcome* and *process* and find that each view, in its way, may be correct, although not addressing the entire picture. In chapter XI, we sought to reconcile the clinical and biological views (i.e. long-term angiographic *outcome* as well as the dynamic *process* of renarrowing which occurs during follow-up) in a consecutive series of patients treated by

atherectomy. We concluded that while analyzing the long-term results of interventional techniques, the biological *process* (luminal loss during follow-up) - which characterizes the traumatizing nature of the intervention - should be *dissociated* from the clinical *outcome* (minimal luminal diameter at follow-up). It is clear that while improved clinical outcome is associated with larger vessel size and post-procedural luminal diameter, greater relative gain at intervention is strongly predictive of more extensive luminal renarrowing.
The observations made by Kuntz et al [6-9] that achieving greater luminal gain with newer devices may reduce angiographic restenosis *seem* not completely in parallel with the finding that a greater luminal gain results in greater luminal loss. While our group are focusing in clinical studies mainly on the degree of renarrowing as a measure of the extent of the biological process i.e. the development of intimal hyperplasia, others have focused on the angiographic outcome i.e. final minimal luminal diameter. This is the difference, as has been expressed by Schwartz et al [5] between the "doughnut and the doughnut hole". There is little doubt that a larger lumen at follow-up may be clinically "better" for the patient and this parameter is of great importance in assessing the long-term outcome of therapy. However, in large clinical trials directed at the prevention of renarrowing, the effect of therapy must be measured by its restricting effect on the thickness of the "doughnut", which we believe is best encapsulated angiographically by the relative luminal loss during follow-up. As recently described, we believe that application of both approaches (clinical outcome and biological process) to the same population yield similar findings and the apparently diverse conclusions arise not from differences in therapeutic results but from differences in focus and approach [5].

Matching to predict the outcome of randomized device trials:

With the introduction of various new intracoronary devices, it is critical to assess the relative merits of each system. Matching a study population with a reference patient group of similar characteristics can be used to compensate for some of the limitations of nonrandomized studies [10]. Furthermore, it may serve as a surrogate for randomized trials [11] or at least provide a more accurate calculation of power for upcoming randomized trials. In fact this form of comparative analysis has been validated demonstrating its value in predicting the outcome of randomized trials comparing angioplasty with atherectomy [12,13] and angioplasty with stenting [11]. In the matching study described in chapter VI, matching for clinical and angiographic variables resulted in two comparable groups with quite similar baseline stenosis characteristics. Atherectomy resulted in a more pronounced increase in minimal

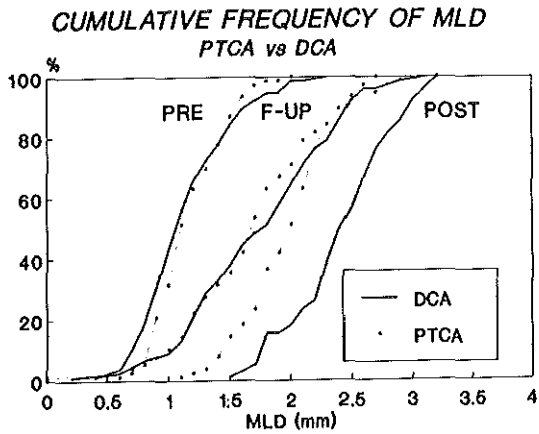

Figure 1: Cumulative frequency curves to illustrate the immediate and follow-up effects in minimal luminal diameter (MLD) of directional atherectomy and balloon angioplasty in matched lesions (modified with permission from reference 12).

luminal diameter than balloon angioplasty (mean ± SD: 1.17 ± 0.29 mm to 2.44 ± 0.42 mm versus 1.21 ± 0.38 mm to 2.00 ± 0.36 mm;$p<0.001$), this favorable immediate result was subsequently lost during late angiographic follow-up so that the minimal luminal diameter at follow-up and the net gain index did not differ significantly between the two groups (1.76 ± 0.62 mm versus 1.77 ± 0.59 mm; $p=0.93$ and 0.18 ± 0.19 versus 0.17 ± 0.17;$p=0.70$) (Figure I). Consequently, the relative gain and relative loss were higher in the atherectomy group. For both techniques, the relative gain is linearly related to the relative loss but, the slope of the regression line is steeper for atherectomy suggesting that the relative loss is proportionally even larger for a given relative gain when compared to the balloon angioplasty group. This study confirmed that the long-term beneficial effect of directional atherectomy were less than expected, and indeed that important information could be derived by the evaluation of matched lesions which might be useful for the design of future randomized trials. For example, it can be calculated from this study that in order to demonstrate that a difference in minimal luminal diameter of 0.07 mm at follow-up between atherectomy and balloon angioplasty groups is statistically different (with a 90% confidence interval and an error of 5%) 1295 patients in each arm would be required in a randomized trial. However this calculation should not preclude attempting a randomized trial which includes less patients (such as the CAVEAT trial) since subgroup analysis might nevertheless unravel a subset of patients (or lesions) who may especially benefit from the new intervention.

Outcome of randomized trials:

The CAVEAT and CCAT trials were the first completed randomized device trials [1,2]. In both trials, the potential long-term benefit of atherectomy was evaluated and compared with conventional balloon angioplasty in primary native coronary arteries (CAVEAT) and primary lesions in the left anterior descending artery (CCAT). The primary endpoint encompassed quantitative angiographic measurements of luminal changes after intervention. Quantitative coronary angiography was performed in core-laboratories with different quantitative analysis systems (CAVEAT: ImageCom and CCAT: CMS). By protocol, the administration of intracoronary nitrates before and after intervention and at follow-up was obligatory. The quantitative coronary analysis was performed for multiple view but reported only for the view in which the lesion was judged to be most severe. At the outset of the trials, restenosis was defined as a diameter stenosis at follow-up $\geq 50\%$ at follow-up.Secondary analysis included the assessment of the minimal luminal diameter at follow-up and its cumulative distribution for the two groups. The cumulative frequency distributions of the

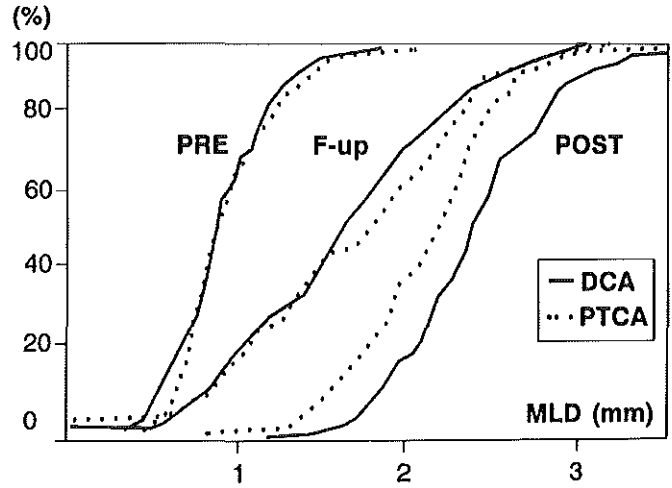

Figure II: Cumulative frequency curves to illustrate the immediate and follow-up effects in minimal luminal diameter (MLD) of directional atherectomy and balloon angioplasty as observed in the CAVEAT randomized trial (modified with permission from reference 1).

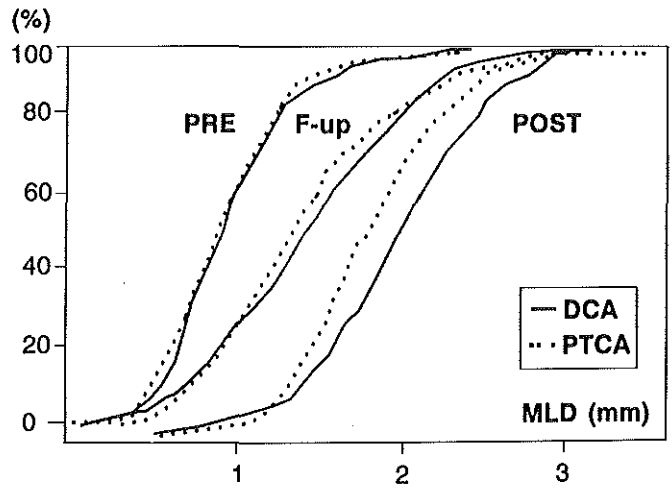

Figure III: Cumulative frequency curves to illustrate the immediate and follow-up effects in minimal luminal diameter (MLD) of directional atherectomy and balloon angioplasty as observed in the CCAT randomized trial (modified with permission from reference 2).

minimal luminal diameter at the three time intervals are provided in figures II (CAVEAT) and III (CCAT). As can be appreciated in both figures, atherectomy induced a larger acute gain and late loss than balloon angioplasty. As a consequence, the minimal luminal diameter at follow-up were comparable in both groups although a trend favoring atherectomy was shown in the CAVEAT study. Consequently, the distribution curves of the minimal luminal diameter at follow-up run closely together. Opposed to the CCAT findings, CAVEAT patients who underwent atherectomy for lesion in the proximal segment of the left anterior descending coronary artery had a significant higher minimal luminal diameter at follow-up compared to those who were treated with balloon angioplasty. Figures I-III summarize the findings of the outcome of the matching study and the outcome of the two randomized trials. It may be concluded that our matching technique is a reliable method to predict the angiographic outcome of randomized trials comparing new interventional devices.

Future Directions:

Although atherectomy did not lead to an improved late clinical or angiographic outcome in the abovementioned trials, further analysis is needed to identify subgroups of patients who may benefit from this procedure (e.g. unstable angina patients). Some investigators stated that the conservative atherectomy strategy in the CAVEAT trial, which represents today's atherectomy practise, is potentially responsible for the disappointing clinical and angiographic atherectomy results. The majority of the clinical events were related to the phenomenon of subacute occlusion which has been shown to be related with a high residual diameter stenosis [14] (post-DCA diameter stenosis of 29% in CAVEAT) and a low anticoagulation status of the patient. Another group of investigators stated that this atherectomy strategy is also responsible for the high restenosis rate in this group since they have identified that a residual post-atherectomy lumen of $\leq 20\%$ diameter stenosis yielded the best results after atherectomy although there series has not been evaluated by quantitative angiography. These findings may urge for new angiographic endpoint definitions for (i) defining atherectomy to be successful and (ii) for defining the angiographic outcome of interventions using a continuous approach (minimal luminal diameter at follow-up) rather than a categorical approach (restenosis rates).
In a preliminary analysis from the Thoraxcenter patient cohort, we identified that atherectomy induced more luminal loss when the acute gain was comparable with a matched PTCA population. This indicates that the operator should strive for a large

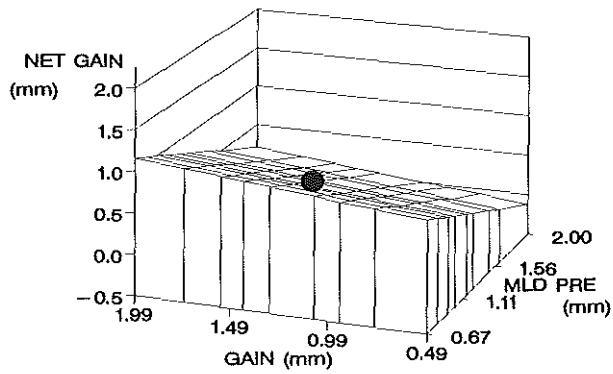

Figure IV: Three dimensional representation of the linear regression model of net gain (MLD fup - MLD pre) after directional atherectomy. Net gain is represented on the Y-axis, gain at atherectomy on the X-axis and MLD pre on the Z-axis. The contribution of gain and MLD pre are represented by dividing the population in 9 equal subgroups (noniles). The lines within the rectangular area represents the median values of these noniles. Positive relationships are found between gain and net gain while a negative relationship exists between MLD pre and net gain, which do not vary with vessel size. The regression plane shift progressively upward with increasing vessel size. The dot in the center of the regression plane represents the median value for the luminal gain and MLD pre. Thus optimal atherectomy (i.e. large net gain) can be achieved in large vessels and the operator should strive for a large luminal gain.

acute gain to ensure a long-term angiographic benefit after atherectomy. Recently, Kuntz et al [15] found that a luminal gain after atherectomy of less than 0.7 mm was associated with a lower minimal luminal diameter at follow-up compared to the optimally treated group. Similarly, by dichotomizing our atherectomy population by the post-DCA minimal luminal diameter it appeared that patients with a large post-atherectomy minimal luminal diameter had the best late outcome. Subsequent analysis showed that optimal atherectomy as defined by a large net gain (mld at follow-up - mld pre) in our population was associated with large vessels and a large luminal gain (Figure IV). These results may call for a new definition of atherectomy success which should then be considered as successful when a post-atherectomy diameter stenosis is less than 20%. Early analysis of the acute results of the Angiopeptin trial have indicated that such an optimal atherectomy (post-DCA diameter stenosis 18%) can be performed with a low acute complication rate [16]. Whether such an optimal atherectomy indeed yields a better long-term result should be tested in a new randomized trial. These new findings should be considered when interpreting the outcome of the CAVEAT and CCAT trials since in these trials only a modest atherectomy was performed.

A second technical wind in the post-CAVEAT and post-CCAT era can be expected when atherectomy can be performed under real-time ultrasound guidance which will enable the operator to selectively remove the plaque. Such ultrasound guidance should also be able to identify subcategories of lesions ideally suited to atherectomy and will permit the achievement of maximal luminal gain with safety. The possibility to measure luminal area and the area inside the external elastic lamina before and after coronary intervention allows one to study the mechanisms of such intervention. Intracoronary ultrasound imaging has shown that gain in luminal area is primarily achieved by plaque removal with directional coronary atherectomy [17].

Ultimately the restenosis process may only be controlled by the combination of a large luminal gain which will provide a large lumen at follow-up and pharmacologic intervention to reduce the increased luminal loss associated with such a large gain. Indeed one such trial (EUROCARE) is soon to be undertaken and will specifically address this issue. This trial is designed from the perspective "the more you gain, the more you lose" and combines a large acute gain in combination with an anti-oxidant and anti-proliferative pharmacological agent to reduce subsequent luminal loss. On the other hand, the BOAT trial will evaluate the effect of optimal atherectomy versus balloon angioplasty and is designed from the perspective "bigger is better" with emphasis on optimal performance. In other words, the BOAT trial will increase the "doughnut's hole" while EUROCARE will also try to reduce the "doughnut".

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SAMENVATTING

Sedert de introductie van de percutane transluminale coronaire angioplastiek als behandeling van coronair lijden hebben voortschrijdende verbeteringen in de cathetertechnieken en in dilatatiestrategieën geleid tot een hoog initieel succespercentage (±90%). Ondanks deze verbeteringen treden in 3% tot 5% acute complicaties op als gevolg van een beschadiging van de vaatwand waardoor een adequate myocardperfusie niet meer mogelijk is. Mede door deze factoren bestaat er behoefte aan nieuwe percutane technieken als alternatief voor de conventionele ballonangioplastiek. Directionele coronaire atherectomie is een van deze nieuwe behandelingstechnieken waarbij op een gecontroleerde wijze de atheromateuze plaque wordt verwijderd. Met het verwijderde materiaal krijgt men op deze wijze levend menselijk (re)stenose materiaal ter beschikking.

Het doel van de in deze dissertatie beschreven studies was het evalueren van de klinische, angiografische en histologische aspecten van directionele atherectomie en de angiografische bevindingen te vergelijken met het resultaat van conventionele ballondilatatie.

In hoofdstuk 1 wordt de toepassing van quantitatieve coronaire angiografie in de interventie cardiologie besproken. Daarnaast wordt de klinische toepasbaarheid hiervan bij directionele coronaire atherectomie samengevat. De resultaten laten zien dat niet alleen de directe en lange-termijns resulaten maar ook het werkingsmechanisme van atherectomie met behulp van quantitative coronaire angiografie ge-evalueerd kunnen worden.

Hoofdstuk 2 is een studie die de resultaten van contourdetectie en videodensitometrie voor en na atherectomie vergelijkt. Het blijkt dat na atherectomie vergelijkbare verschillen bestaan tussen contourdetectie en videodensitometrie. Op grond van deze gegevens kan geconcludeerd worden dat beide analysetechnieken geschikt zijn om de angiografische resultaten van atherectomie te quantificeren.

In hoofdstuk 3 wordt het werkingsmechanisme van atherectomie bestudeerd aan de hand van angiografische en histologische bevindingen. Met atherectomie werd

een significant groter lumen verkregen in vergelijking met ballonangioplastiek. Verder blijkt dat 63% van de luminale verbetering toe te schrijven valt aan een 'Dotter' effect ten gevolge van het inbrengen de grote atherotoom. Quantitatieve coronaire angiografie en een histologische observatie tonen aan dat atherectomie resulteert in een bijna circulair lumen.

In hoofdstuk 4 worden de resultaten van atherectomie vergeleken met die van andere interventietechnieken zoals ballonangioplastiek, stentimplantatie en rotablator. Hiertoe werden 51 atherectomie patienten gepaard aan 51 stent en 51 ballonangioplastiek patienten. In een dergelijke gepaarde analyse blijken atherectomie en stentimplantatie een beter initieel resultaat te geven dan ballonangioplastiek.

Hoofdstuk 5 beschrijft de lange-termijns resultaten van een gepaarde atherectomie en ballonangioplastiek populatie. Opnieuw blijkt dat atherectomie tot een beter acuut resultaat leidt dan ballonangioplastiek maar dat het ook tot een verhoogde activiteit van het restenose proces leidt waardoor bij nacontrole dit gunstige acute effect verdwenen is zodat de minimale luminale diameter bij nacontrole in beide groepen vergelijkbaar is.

In hoofdstuk 6 wordt het angiografische resultaat van atherectomie en ballonangioplastiek in een gepaarde patientenpopulatie beschreven. Drie nieuwe criteria om deze resultaten te kunnen vergelijken werden gedefinieerd. Met atherectomie wordt een grotere initieële winst van de minimale lumen diameter behaald dan met ballonangioplastiek. Enkele maanden later is deze winst echter verloren gegaan. Voor beide technieken werd een lineaire relatie tussen "relatieve winst" en "relatief verlies" gevonden. De helling van de regressielijn is steiler in de atherectomie populatie daarmee aangevend dat het "relatief verlies" in deze groep groter is voor dezelfde "relatieve winst" dan in de angioplastiek groep.

Hoofdstuk 7 geeft de uitkomst weer van een analyse van patienten waarbij met atherectomie of angioplastiek eenzelfde eind-resultaat bereikt werd. Deze studie laat zien dat bij nacontrole de angioplastiek groep een groter lumen had dan de atherectomie groep zodat bij atherectomie meer weggesneden moet worden om een gunstig eindresulaat te behalen. Dit is de eerste studie die aantoond dat restenose afhankelijk is van de wijze van behandeling (snijden versus dilateren). Multivariate analyse laat inderdaad zien dat winst in lumen diameter een onafhankelijke voorspeller is voor het optreden van restenose. Die patienten waarbij het de post-atherectomie diameter stenose minder dan 20% bedroeg hadden een significant beter lange-termijns resulaat.

In hoofdstuk 8 wordt het werkingsmechanisme van atherectomie bestudeerd door middel van kwantitatieve coronaire angiografie, intravasculaire echografie en intracoronaire angioscopie. De informatie verkregen door het gecombineerde gebruik van deze 3 beeldtechnieken geeft aan dat het angiografische resultaat na atherectomie (gladde vaatwand en bijna circulaire lumen configuratie) niet bevestigd wordt door echografie en angioscopie. De lumen toename tijdens

directionele coronaire atherectomie wordt grotendeels veroorzaakt door afname van de plaque area als gevolg van het wegsnijden van de vernauwing.
In hoofdstuk 9 wordt de gezamenlijke klinische en angiografische ervaringen van twee europese atherectomie centra beschreven. In totaal werd in 113 patienten een poging tot atherectomie verricht. Het procedurele succespercentage en primaire angioplastiek succespercentage bedroeg respectievelijk 85.7% en 95.2%. Ernstige complicaties zoals overlijden, myocard infarct of coronaire bypass operatie kwamen in 5.7% van de patienten voor.
In hoofdstuk 10 wordt een overzicht gegeven van de klinische en angiografische lange-termijn resultaten van directionele coronaire atherectomie. Om inzicht te verkrijgen of het klinische syndroom ten tijde van de ingreep van invloed is op de resultaten werd de patientenpopulatie in twee groepen verdeeld: onstabiele versus stabiele angina pectoris. Onze ervaring is dat atherectomie een veilige behandelingsmethode is voor stabiele en onstabiele angina pectoris maar dat de lange-termijns resultaten in patienten met onstabiele angina pectoris slechter zijn. Deze hogere incidentie van complicaties ontstond ondanks het wegsnijden van de onstabiele plaque en lijkt veroorzaakt te worden door de instabiliteit van dit syndroom en niet zozeer door het feit dat met atherectomie geen adequaat lange-termijns resultaat bereikt kan worden.
In hoofdstuk 11 wordt de multivariate analyse gepresenteerd waarin de klinische, angiografische en histologische voorspellers van de 6-maands minimale luminale diameter en van het luminale verlies geïdentificeerd worden. In dit hoofdstuk worden de twee geldende restenose concepten ("bigger is better" versus "the more you gain, the more you lose") verenigd. Wanneer de lange-termijns resultaten na een interventie worden bestudeerd moeten zowel het luminale verlies (restenoseproces) - hetgeen gekarakteriseerd wordt door het genezingsproces van de vaatwand na een interventie - als de 6-maands minimale luminale diameter (klinische uitkomst) tegelijkertijd gekarakteriseerd worden. Het is duidelijk dat een betere klinische uitkomst verkregen wordt bij patienten met grote bloedvaten, een grote post-atherectomie minimale luminale diameter en in niet-LAD lesies terwijl een grote relatieve luminale winst voorspellend is voor een versterkte luminale vernauwing.
In hoofdstuk 12 worden de vroege en late resultaten beschreven van atherectomie van vernauwde coronaire stents bij 9 patienten. De celidentificatie, proliferatie en celdichtheid van het verwijderde restenosemateriaal werd bestudeerd met behulp van conventionele en electronen miscroscopie en immunohistochemische technieken. De resultaten werden vergeleken met een controlegroep van patienten die een PTCA ondergaan hadden. De angiografische resultaten toonden aan dat atherectomie een effectieve behandelingsmethode is maar dat het lange-termijns resulaat bepaald werd door het optreden van restenose. De weefsel studies toonden aan dat de gladde spiercel het belangrijkste celtype is dat aangetroffen werd in restenoseweefsel, onafhankelijk van het type voorgaande interventie en

dat proliferatie van de myocyten een vroegtijdig fenomeen is en 2 maanden na de ingreep nauwelijks meer aantoonbaar is.
In hoofdstuk 13 worden de histologische kenmerken van het verwijderde atherectomie materiaal van 93 procedures bij patienten met stabiele en onstabiele angina pectoris vergeleken. De aanwezigheid van neo-intimale hyperplasie, fibreus weefsel, cholesterol kristalspleten, necrotische weefsel, kalk, macrofagen, trombus, media of adventitia werden beschreven. De resultaten van deze studie laten zien dat trombusvorming en verkalkingen vaker bij onstabiele dan stabiele angina pectoris gevonden werden. Verder bleek dat er geen relatie bestond tussen de duur van onstabiele angina pectoris en de mate van trombusorganisatie. Verder was de aanwezigheid van intimale hyperplasie sterk gecorreleerd met het ondergaan van een eerdere interventie. De restenose lesies hadden een identieke histologische kenmerken onafhankelijk van de aard van de voorafgaande interventie.
In hoofdstuk 14 worden de toepassingen van histologie, celkweektechnieken en immunologie beschreven. De kweek resultaten van gladde spiercellen uit coronaire arterie fragmenten laten zien dat slechts uit de minderheid van de lesies seriële passage mogelijk was en dat gladde spiercellen van restenose lesies een versnelde groei vertoonde dan cellen van primaire lesies of cellen van de navelstrengarterie. Hoewel er werden geen klinische parameters gevonden die uitgroei konden voorspellen, was de aanwezigheid van trombus in het atherectomieweefsel gerelateerd aan uitgroei van gladde spiercellen. Verder vertoonde de cellen uit het atherectomieweefsel een hogere graad van extracellulaire matrixcomponenten cholesterol en glycosaminoglycanen dan navelstreng gladde spiercellen. De celkweektechniek lijkt een nuttig model te zijn bij de bestudering van atherosclerose en in het bijzonder restenose.
In hoofdstuk 15 wordt een samenvatting gegeven van de in dit proefschrift beschreven studies. In het bijzonder worden de bevindingen van de gepaarde vergelijkingen (ballon angioplastiek versus atherectomie) gerelateerd aan de uitkomst van de twee gerandomiseerde studies. Het blijkt dat onze gepaarde analyse zoals beschreven in hoofdstuk 9, de uitkomst van de gerandomiseerde studies nauwkeurig voorspelde. Hoewel atherectomie op dit moment niet aantoonbaar beter is dan ballonangioplastiek zullen toekomstige inzichten en ontwikkelingen zoals i) een betere definitie van een geslaagde atherectomieprocedure, ii) de ontwikkeling van een gecombineerd atherectomie/echo apparaat en iii) de combinatie atherectomie/medicamenteuze therapie de lange-termijns resultaten van atherectomie nog verder verbeteren.

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