INTRACORONARY ULTRASOUND, ANGIOSCOPY AND ANGIOGRAPHY IN THE STUDY OF PLAQUE MORPHOLOGY AND THE MECHANISMS OF ACTION OF CORONARY INTERVENTIONS

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INTRA-CORONAIRE ECHO, ANGIOSCOPIE EN ANGIOGRAFIE ALS METHODES OM PLAQUE MORFOLOGIE VAN CORONAIRVATEN EN WERKINGS-MECHANISMEN VAN CORONAIRE INTERVENTIES TE BESTUDEREN

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CONTENTS

Part III. Intracoronary Imaging in Coronary Interventions.

Nature is built on large principles. Nature does not built distinct principles for a tree, a bush, a flower, a man. All are built on a common, large basic principle - therefore it does not really matter what is the topic that we study, if we are inteligent enough to understand the basic principle, the structure of life.

Albert Szent Györgyi (1893-1986)

à Marina
Bernardo, Pedro e
Francisco
aos meus Pais e
Irmãos

General Overview

Investigation of the characteristics of the atheromatous plaque has gained new interest since the advent of pharmacological and mechanical intervention in the coronary arteries. Most of the information available on plaque substrate and its modification by such interventions was based in pathological or angiographic studies. However, major bias occurs when these sources of knowledge are used. Post-mortem studies are performed only in those patients with the extreme of the clinical manifestations of a syndrome and a fatal outcome, or in cases where death occurred as a consequence of failed intervention. On the other hand, angiography constitutes a "shadowgram" or luminogram which provides limited insights on the nature of coronary obstruction, and no information as to the characteristics of the arterial wall and .

Catheter based intracoronary imaging techniques provide a major opportunity to solve the above discussed limitations. Intracoronary ultrasound and angioscopic imaging provide complementary information as to the structure and composition of the arterial wall and the modifications in the luminal surface of the coronary arteries.

The research collected in this thesis was performed at the time when application of these technologies on living humans was in its early stages. We have divided the thesis into three parts. In the first part of this thesis, some of the potentials and limitations of quantitative angiography are discussed and compared with intracoronary ultrasound. Chapter one, focuses on the potential of quantitative angiography as used in clinical practice, for the identification of a significant coronary lesion. For that purpose, dobutamine stress test was used as a gold standard to detect significant myocardial ischemia. In chapter 2, the value of quantitative angiography for the quantification of the plaque burden and identification of the reference (disease-free) segment was compared with intracoronary ultrasound. Chapter 3, focuses the advantages of intracoronary ultrasound for the assessment of vascular dimensions.

In the second part of this thesis, intracoronary ultrasound and angioscopy were compared with angiography in the study of plaque morphology at different stages of coronary heart disease. In chapter 4, the combined use of intracoronary ultrasound and angioscopy was used to provide insights in the pathogenesis of stable and unstable angina. In chapter 5, angioscopy was used for the study of patients presenting refractory unstable angina, and the histological analysis of the atherectomized specimen was used to validate the angioscopic analysis. In chapter 6, angioscopy was used to investigate in-vivo characteristics of the stenotic lesions in stable and unstable coronary syndromes, with particular attention to the prevalence and extent of coronary thrombosis.

In the third part of this thesis, the value of intracoronary imaging techniques in the study of the action mechanisms of current coronary interventions is discussed.

In chapter 7, the use of intracoronary ultrasound in the assessment of plaque morphology and on the action mechanisms of catheter-based coronary revascularization is briefly reviewed along with our own experience. In chapter 8, the potentials of angioscopy in the setting of percutaneous coronary interventions is reviewed with focus on possible strategies based on angioscopic observations. In chapter 9, ultrasound was used to evaluate the impact of plaque morphology on the mechanisms of lumen enlargement following balloon angioplasty. In addition, the value of the angiographic unrecognized lesions with a disease-free wall on the results of balloon angioplasty were underlined. In chapter 10, the combined used of quantitative angiography, ultrasound and angioscopy were used to derive several injury scores following balloon dilation and directional atherectomy. These scores were used in an attempt to quantify vascular trauma following these interventions and to give further insights into the restenotic process following coronary angioplasty. Chapter 11, reviews the mechanisms of action of directional atherectomy using data derived from these new imaging modalities with particular emphasis to lumen configuration.

Part I

QCA
Potentials and Limitations

Chapter I

Quantitative Coronary Angiography in the Estimation of the Functional Significance of a Coronary Stenosis: Correlations with Dobutamine-Atropine Stress Test

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Abstract

Objectives

The purpose of this study was to determine the predictive value of quantitative coronary angiography in the assessment of the functional significance of coronary stenosis as judged from the development of left ventricular wall motion abnormalities during dobutamine-atropine stress echocardiography.

Background

Coronary angiography is the reference method for assessment of the accuracy of noninvasive diagnostic imaging techniques to detect the presence of significant coronary stenosis. However, use of arbitrary cutoff criteria for the interpretation of angiographic data may considerably influence the true diagnostic accuracy of the technique investigated.

Methods

Thirty four patients without previous myocardial infarction and with single vessel coronary stenosis were studied with both quantitative angiography and dobutamine-atropine stress echocardiography. Two different techniques of quantitative angiographic analysis - edge detection and videodensitometry - were used for measurement of minimal lumen diameter, percent diameter stenosis and percent area stenosis. Two-dimensional echocardiographic images were collected during incremental doses of intravenous dobutamine and later analyzed using a 16-segment left ventricular model. Angiographic cutoff criteria were derived from receiver-operating curves to define the functional significance of coronary stenosis on the basis of dobutamine-atropine stress echocardiopgraphy.

Results

The angiographic cutoff values with the best predictive value for the development of left ventricular wall motion abnormalities during dobutamine-atropine stress echocardiography were minimal lumen diameter of 1.07 mm, percent diameter stenosis of 52%, and percent area stenosis of 75%. Minimal lumen diameter was found to have the best predictive value for a positive dobutamine stress test (odds ratio 51, sensitivity 94%, specificity 75%).

Conclusions

Automated quantitative angiographic measurements of minimal lumen diameter is a practical and useful index for determining both the anatomic and functional significance of coronary stenosis, and a value of 1.07 mm is the best predictor for a positive dobutamine stress test.

Introduction

Establishing the functional significance of coronary stenosis detected by contrast angiography is a clinical challenge, especially in the case of intermediate stenotic lesions. The traditional criteria for determining the presence of functionally significant disease, a 50% reduction in lumen diameter by visual estimation, suffers from considerable interobserver and intraobserver variability [1-3], making this criterion unreliable in the estimation of the functional impact of lumen obstructions [3]. It is in the range of mild to moderate stenoses (30% to 60% diameter stenosis) that the discrepancy between visual estimates and objective measurements of lumen dimensions is most marked [4-5]. Computerized quantitative coronary angiography reduces the latter source of error and provides objective measurements of lumen dimensions, but the physiologic significance of a given coronary stenosis remains unclear. Because of the use of arbitrary cutoff criteria in previous studies addressing this problem, and in which coronary angiographic estimates of severity were compared with other imaging, objective index are lacking.

Recently, dobutamine stress echocardiography has been introduced as a safe and reproducible technique for the diagnosis of coronary artery disease [6-13]. Several studies have indicated good correlation between the development of wall motion abnormalities during stress echocardiography and the severity of coronary stenosis [6-15]. However, these studies have limitations because either visual interpretation of the angiogram was performed [6,7,14] or arbitrary cutoff points [13] for quantitative angiographic data were used.

The goal of this study was to investigate which quantitative angiographic variables of stenosis severity best correlate with the development of ischemia-induced wall motion abnormalities during dobutamine-atropine stress echocardiography. Angiographic cutoff criteria were derived from receiver-operating curves to obtain objective criteria for assessment of functional significance of stenosis severity.

Methods

Study patients

The study patients included 34 consecutive patients referred from the catheterization laboratory, with a single vessel coronary stenosis judged to have ≥30% diameter stenosis by visual assessment. The coronary angiogram was performed within 2 weeks before the performance of dobutamine-atropine stress echocardiography. The stenosis was located in the left anterior descending coronary artery in 26 patients, left circumflex coronary artery in 3 patients and right coronary artery in 5 patients. Mean age was 61.3 ±12.6 years (range 32 to 79). There were 21 (62%) men and 13 (38%) women. Patients with unstable angina, previous myocardial infarction and left bundle branch block were excluded. Patients receiving antianginal medication, consisting of beta-adrenergic blocking agents (24 patients), either alone or in combination with nitrates or

calcium-channel blocking agents, or both, that was not discontinued before the study.

Dobutamine-atropine stress test

The protocol used at the Thoraxcenter in the performance of dobutamine-atropine stress echocardiography has been described in detail elsewhere [16]. Briefly, two dimensional precordial echocardiography was performed at rest and during incremental doses of dobutamine. After a baseline 12-lead electrocardiogram (ECG), dobutamine was infused through an antecubital vein starting at a dose of 10 μg/kg body weight per min for 3 min and increasing by 10 μg/kg per min every 3 min to a maximum of 40 μg/kg per min (stage 4). This was continued for 6 min in the absence of an ischemic response. In patients not achieving 85% of maximal predicted heart rate, atropine (0.25 mg) was given intravenously at the end of stage 4 and repeated to a maximum of 1 mg with the continuation of dobutamine for a further 5 min if necessary to achieve the previously mentioned target heart rate. The infusion of dobutamine was stopped if the patient developed marked new wall motion abnormalities, ST segment depression >0.2 mV 80 ms after the J point, ST segment elevation, typical angina, significant arrhythmias, a decrease in systolic blood pressure >40 mm Hg from rest level or any complication considered to be related to the stress test.

Standard apical and parasternal views were recorded in a closed cine loop quad-screen format on super-VHS videotape, facilitating the comparison of rest and stress images. During the analysis of the images, the left ventricle was divided into 16 segments [17], and each segment was scored using a four point scale: 1 = normal wall motion and thickening; 2 = hypokinesia; 3 = akinesia (absence of systolic wall motion and thickening); 4 = dyskinesia (systolic outward wall motion with thinning).

Images were reviewed by two experienced investigators who were unaware of the clinical and angiographic data. Agreement between the two observers was required for the classification of wall motion abnormalities. In cases of disagreement the opinion of a third investigator was considered. An ischemic response was defined as a stress-induced new wall motion abnormality or a worsening of wall motion abnormality at rest.

The location of wall motion abnormalities was correlated with coronary arterial distribution by the same methodology as previously described by Segar et al. [13] after a modification of the scheme of Bourdillon et al. [17]. The apical lateral and apical inferior segments were considered to be areas of overlap. The apical lateral segment was considered to be part of the left anterior descending coronary artery territories in association with additional septal or anterior wall motion abnormalities. The same segment was considered to be part of the left circumflex coronary artery distribution in association with posterior or posterolateral wall motion abnormalities. The apical inferior segment was related to the right coronary artery system if there were additional inferior wall motion abnormalities and to the left anterior descending coronary artery region in the presence of anterior or anteroseptal wall motion abnormalities.

Quantitative coronary angiography

All 35 mm films were analyzed using the Cardiovascular Angiography Analysis System II (CAAS II, Pie Medical). The automated edge detection and videodensitometric techniques of this system have been validated and described in detail elsewhere [18-22]. All measurements were performed from end-diastolic frames with optimal vessel opacification.

Edge detection. A region of interest of 512 X 512 pixels was selected and digitized using a high fidelity charge-coupled device video camera. The lumen edges were detected on the basis of the weighted sum of the first and second derivative function of the brightness profile of each scan line perpendicular to the vessel centerline. The vessel diameter function was determined by computing the shortest distance between the right and left contours. Calibration of these measurements to absolute values was achieved by using the catheter tip as a scaling device. A computer-derived estimation of the original arterial dimension at the site of obstruction was used to calculate the interpolated reference diameter. This technique is based on a computer-derived estimation of the original values over the analyzed region. The calculation is based on a first degree polynomial computed through the diameter values of the proximal and distal portions of the arterial segment followed by a translation to the 80th percentile level.

Videodensitometry. Densitometry is based on the approximate linear regression that exists between the optical density of a contrast enhanced lumen and its absolute dimensions. To follow this approach, the brightness of each scan line perpendicular to the vessel centerline was transformed into an absorption profile using a simple logarithmic transfer function to correct for the Lambert-Beer law. The background contribution was estimated by computing the linear regression line through the background pixels located left and right of the detected lumen contours. By subtracting this background portion from the absorption profile of the vessel, a net cross-sectional absorption profile was calculated. A cross-sectional area function of the analyzed segment was obtained by repeating this process with all scan lines. An interpolated reference area was calculated from the reference diameter assuming a circular cross section. The cross-sectional area at the narrowest point was identified and expressed in mm2.

Data analysis

All continuous variables are expressed as mean value ± SD. The two-tailed Student t test was used for analysis of continuous data. The chi-square test and Fisher exact test were used to compare differences between proportions. The independent correlation of the angiographic variables to the percent of the maximal age-predicted heart rate was determined by logistic regression analysis. Angiographic variables were entered as categoric variables by use of their respective cutoff values. These values were achieved by determining for each variable the point of the maximal sum of sensitivity and specificity, when the sensitivity is equal to or greater than the specificity. Furthermore, receiver-operator characteristics curve analysis as an objective method for determining the value of the various angiographic variables in the prediction of an abnormal dobutamine

stress test was applied. This technique is independent of definitions of cutoff values. The sensitivity (true positive) is plotted against 1-Specificity (true negative) during the whole range of measurements of a specific variable. Odds ratio and 95% confidence intervals were calculated for comparison of the relative predictive power of the best cutoff value for each angiographically determined variable. A p value < 0.05 was considered statistically significant. The statistical package used was SAS, release 6.04 (SAS Institute).

Results

Results of dobutamine-atropine stress test

Dobutamine-atropine stress echocardiography was positive in 18 patients. There were no significant differences in age, gender or affected coronary artery between patients with a positive (group 1) or negative (group 2) test. Beta-blockers were part of the antianginal therapy in 24 patients (70%). Of these, 10 patients (4%) developed a positive dobutamine stress test compared with 14 (58%) with a negative test (p = NS).

Table 1 summarizes the results of the dobutamine-atropine stress test. The percent of the maximal age-predicted heart rate achieved was noted to be significantly higher (82 ± 14) in group 1 than in group 2 (69 ± 17) (p < 0.05) and in patients without beta-blocker therapy (87 ± 9 vs. 72 ± 17, p < 0.05). Atropine was added in 15 patients (12 were receiving beta-blocker therapy). However, because the presence and severity of the disease is the main determinant of a positive test, the achievement of the target heart rate was not found by logistic regression analysis to be an independent predictor of a positive stress test. In Figure 1, the evolution of the heart rate during the test is shown. Although the maximal heart rate when atropine was added was higher, it did not change the sensitivity of the test. It was also evident that patients taking beta-blockers frequently need atropine at the end of the test to achieve the target heart rate. During the test, angina occurred in 11 patients (32%), with equal distribution in the two groups (6 patients in group 1, 5 patients in group 2, p = NS). An ischemic ECG response during stress testing

Table 1. Results of dobutamine stress test in study groups 1 and 2.

	Group 1 (n=18)	Group 2 (n=16)
% Maximal heart rate	82 ± 14	69 ±17 *
Stress angina	6 (18%)	5 (15%)
Ischemic ST segment deviation	5 (15%)	3 (9%)
Atropine	8 (53%)	7 (47%)

* p < 0.05. Data presented are mean value ± SD or number (%) of patients.

occurred in eight patients (24%), and again there were no significant differences between the two groups (five patients in group 1, three patients in group 2, p = ns).

Results of quantitative angiography

For the entire group, quantitative coronary angiography revealed a mean percent

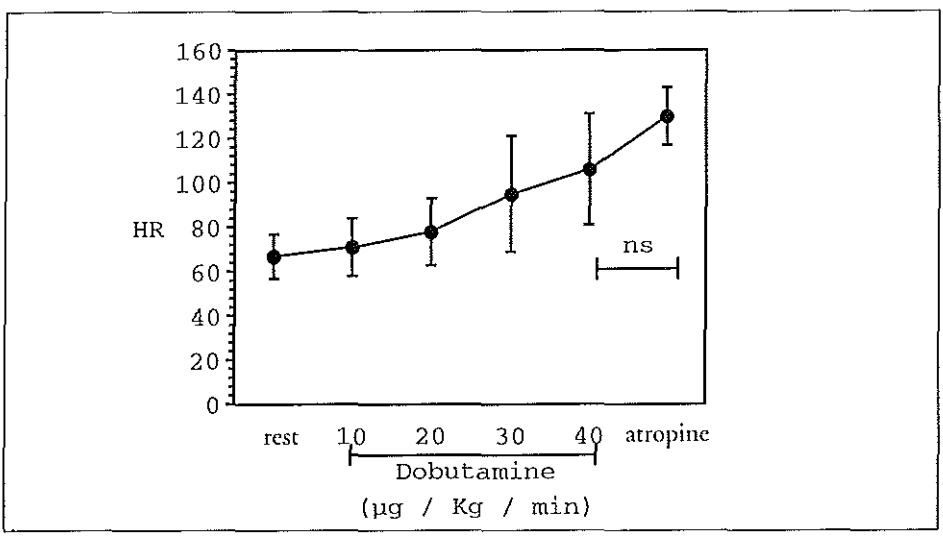

Figure 1.

Evolution of heart rate (HR) during dobutamine infusion and atropine administration. Clearly seen is the steep increase in heart rate with the addition of atropine, although the difference in maximal heart rate between patients who did and did not receive atropine was not statistically significant.

diameter stenosis of 56 ± 20% (range 11% to 100% [four patients with total occlusion]), a mean percent area stenosis of 74 ± 20% (range 24% to 100%), mean minimal lumen diameter of 1.01 ± 0.59 mm (range 0 to 2.84 mm) and mean reference diameter of 2.41 ± 0.52 mm (range 1.64 to 4.07 mm).

Figure 2 shows the relation between the sensitivity and specificity of the dobutamine-atropine stress test and their receiver-operator characteristics curves for each of the angiographic index, as a function of stenosis severity. For clinical purposes, a cut point is often selected to permit computation of sensitivity and specificity, variables that are widely used and understood in the published reports [23]. There are two commonly used schemes for selecting cut points in this setting. The first involves the choice of a convenient but arbitrary point, such as 50% diameter stenosis. The second uses the intersect of the sensitivity and specificity curves as the cut point [24]. In the present study an alternative approach was used on the basis of receiver-operator characteristics curves. We selected the point at which the sum of the sensitivity and specificity, when the sensitivity is equal to or greater than the specificity, reaches a maximum. Because this point takes into account the shape of the two curves near the point of interception (Fig. 2) it was hoped that

this technique would provide better diagnostic accuracy. As an example. in Figure 2 if we select the interception of the sensitivity and specificity curves, the sum will be 159 points (sensitivity 78 + specificity 81). Using our approach, the sum of the sensitivity and specificity will be 169 (sensitivity 94 + specificity 75).
All the quantitative angiographic variables revealed a high sensitivity (range 82% to 94 %) for the identification of ischemia-induced wall motion abnormalities. Although all the angiographic variables had the same specificity (75%), minimal lumen diameter had the highest sensitivity (94%). Because patients with normal coronary arteries were not included in the study, the specificity value is probably underestimated.
Table 2 summarizes the relation of different cutoff points to the outcome of the stress test. Minimal lumen diameter has a predictive value that is considerably larger (odds ratio 51), than the commonly used varibles of relative obstruction (odds ratio of 15 and 23 for percent diameter and percent area stenosis, respectively).

Discussion

Dobutamine stress echocardiography
The use of dobutamine stress echocardiography in the assessment of myocardial ischemia offers advantages over the traditional nuclear techniques, including lower cost, less time, no radiation exposure and greater availability, that justify its growing application in clinical practice [6-10,12,13]. Because wall motion abnormalities are an early and specific indicator of myocardial ischemia, dobutamine stress echocardiography is potentially superior to stress scintigraphy, particularly in patients with mild to moderate stenoses, where transient perfusion defects result from a maldistribution of coronary flow, and do not necessarily reflect "true" myocardial ischemia. In addition, single-photon emission computed tomographic (SPECT) myocardial scintigraphy is associated with a lower specificity compared with dobutamine stress echocardiography in patients with a single vessel coronary stenosis [25-26].
In the study patients the incidence of chest pain and ischemic ECG response during dobutamine echocardiography was low (32% and 24%, respectively) without relation to the outcome of the echocardiographic stress test. This is not surprising, because in previous studies the sensitivity and specificity of stress-induced ECG changes in single-vessel disease were also relatively low [27-30]. The finding of a significant higher heart rate in patients who developed wall motion abnormalities during dobutamine stress echocardiography underlines the importance of chronotropism as an additional mechanism to increase inotropism to induce ischemia. This is in agreement with previous experimental and clinical data [16,31,32].

Table 2. Quantitative angiographic results according to cutoff values.

Angiographic cutoff values	Sensit.	Specif.	P (+)	(P(-)	Odds ratio
MLD ≤ 1.07 mm	94 (84-100)	75 (54-96)	81	92	51 (4-1929)
A Ste ≥ 75%	88 (73-100)	75 (54-96)	79	86	23 (2-242)
D Ste ≥ 52%	83 (66-100)	75 (54-96)	79	80	15 (2-123)

Number in parenthesis are 95% confidence intervals. A Sten. = area stenosis; D Sten. = diameter stenosis; MLD = minimal lumen diameter; P (+) = positive predictive value; P (-) = negative predictive value; Sensit. = sensitivity; Specif. = specificity.

Previous studies

In previous studies, quantitative angiographic measurements of stenosis severity correlated well with the outcome of stress echocardiography [13-15]. In a group of 25 patients with single-vessel disease, Ryan et al. [14], using the criterion of > 50% visually determined percent diameter stenosis, found a sensitivity of 76% for exercise echocardiography. Sheikh et al. [15] studied 34 patients with single-vessel obstruction and reported that all patients with > 75% diameter stenosis by visual assessment developed wall motion abnormalities during exercise echocardiography. However, only 50% of the same patients had an abnormal test if the angiographic cutoff criterion was lowered to 50% diameter stenosis. In a subgroup of 30 patients with normal left ventricular function at rest and single or multivessel disease, Segar et al. [13] described high sensitivity (90%) of the dobutamine stress test to detect significant coronary disease using a diameter stenosis of > 50% by quantitative angiography. Several investigators [8,10,12,16] using the same approach reported a wide variation in the sensitivity values for the detection of significant lumen reduction. All these studies, however, relied on arbitrary cutoff points for the determination of significant stenosis, and few evaluated [13-15] absolute variables of lumen obstruction. The high sensitivity and specificity noted for minimal lumen diameter in our study (94% and 75% respectively), although using a different approach, are in accordance with Segar et al. [13], who reported a high sensitivity of the dobutamine stress test in the identification of coronary stenoses using a cutoff criterion of 1.0 mm for minimal lumen diameter; however in their study an attempt to determine the best cutoff point was not reported.

Relative versus absolute measurements of coronary stenosis

It is known that in the setting of diffuse coronary artery disease, relative variables of lumen narrowing may underestimate the functional impact of stenosis severity [33-35]. In this study, only patients with a single discrete stenosis were included therefore it is of greater significance that minimal lumen diameter was found to be

the best predictor of an abnormal stress test. However, even in the presence of focal disease, angiographically normal segments used in the determination of the relative measures of lumen obstruction are frequently involved in the atherosclerotic process, as reported in several intracoronary echocardiographic studies [36,37]. Therefore, absolute dimensions may be a better indicator of the physiologic importance of coronary stenoses in medium to large arteries. Our finding that a minimal lumen diameter of ≤ 1.07 mm is the best variable for the prediction of ischemia-induced wall motion abnormalities supports this

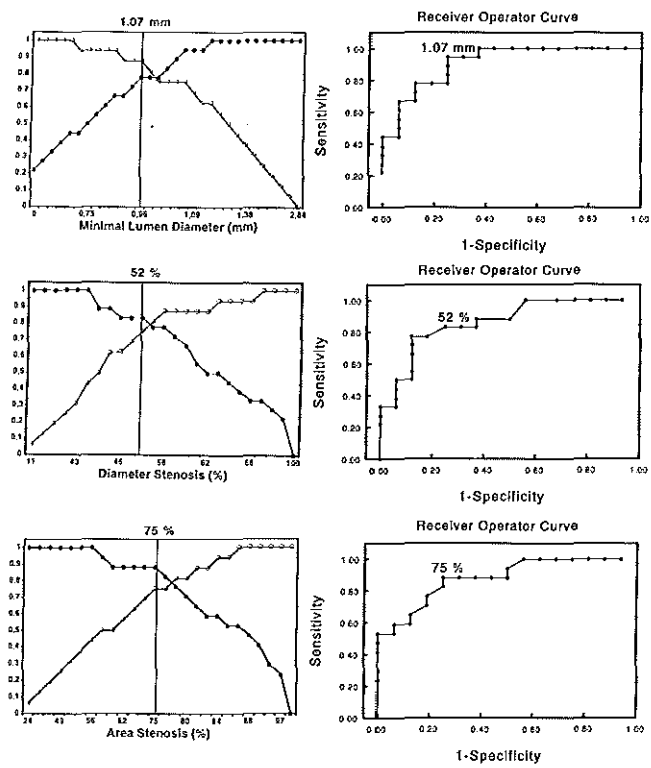

Figure 2.

Relation between the sensitivity and specificity of the dobutamine-atropine stress test and the receiver-operator curves for each of the angiographic indexes as a function of the stenosis severity. Left, variation in sensitivity (solid circles) and specificity (open circles) are presented as a function of cutoff points for the different quantitative angiographic variables. Right, corresponding receiver-operator curves for the angiographic variables.

hypothesis. In this regard, data derived from the MERCATOR study [38] revealed that patients with a minimal lumen diameter < 1.1 mm at the follow-up had a higher occurrence of subsequent clinical events. Although it has been reported that the sensitivity of a visually determined diameter stenosis > 50% and < 70% is low for the occurrence of new wall motion abnormalities during stress

echocardiography [15], the finding in our study of a cutoff point of 52% for the diameter stenosis is in agreement with previous experimental work showing a decline in coronary flow reserve at this level [39] and confirms that for this range of obstructions, visual assessment overestimates quantitative measurements [4,5].

Edge detection versus videodensitometry in angiographic analysis

Serruys et al. [40] and Wijns et al. [41] reported that a videodensitometrically determined area of obstruction > 80% constituted a physiologically significant obstruction as assessed by exercise-redistribution thallium scintigraphy, and these data agree with our criterion of a 75% reduction in cross-sectional area for the prediction of ischemia-induced wall motion abnormalities. Videodensitometric determination of percent area obstruction is theoretically independent of the geometric shape of the lumen obstruction, having the potential to overcome limitations related to edge detection techniques when using a single projection. In our study an average of two projections was used to determine the different angiographic variables, and because situations where the occurrence of a complex lumen shape were not included in the analysis (e.g., postangioplasty, unstable angina); therefore was no clear advantage of the densitometrically determined percent area stenosis over percent diameter stenosis.

Conclusions

Quantitative angiography provides an objective assessment of the functional significance of coronary stenoses as determined by dobutamine stress echocardiography. Although relative measurements of lumen obstruction are predictive of an abnormal stress echocardiogram, minimal lumen diameter appears to be the optimal variable in the determination of the physiologic significance of coronary stenoses in medium to large arteries

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Chapter II

The Significance of Automated Stenosis Detection During Quantitative Angiography: Insights Gained from Intracoronary Ultrasound Imaging

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Abstract

Background

Automated stenosis analysis is a common feature of commercially available quantitative angiography systems (QCA), allowing automatic detection of the proximal and distal boundaries of the stenosis, interpolation of the expected dimensions of the coronary vessel at the point of obstruction, and angiographically-derived estimation of atheromatous plaque size. However, the ultimate meaning of this type of analysis as to the degree of underlying atherosclerotic disease (AD) remains unclear.

Aim of the study

We investigated the relationship between stenosis analysis performed with the CAAS system and the underlying degree of atherosclerotic disease as judged from intracoronary ultrasound (ICUS) imaging.

Methods

In 40 coronary stenoses QCA was used for automated identification of the sites of maximal luminal obstruction and start of the stenosis using curvature analysis of the diameter function. Plaque size was measured using ICUS at both locations, with an additional ICUS measurement immediately proximal to the start of the stenosis. Crescent-like distribution of plaque, indicating an AD-free arc of the arterial wall, was recorded.

Results

At the site of the obstruction total vessel area measured with ICUS was 16.65±4.04 mm², while an equivalent measurement obtained from interpolated reference dimensions was 7.48±3.30 mm², (p=0.0001). Plaque area derived from angiographic data was significantly lower than that calculated from intravascular ultrasound data, (6.32±3.21 and 13.29±4.22 mm², respectively, mean difference 6.92±4.43 mm², p=0.0001). At the site identified as the start of the stenosis by automated analysis, ICUS luminal cross-sectional area was 9.38±3.17 mm², and total vessel area was 18.77±5.19 mm², (50±11% total vessel area stenosis). The arterial wall presented a disease-free segment in 28 (70%) of proximal locations, but only in 5 (12%) sites corresponding to the start of the stenosis and no at the obstruction (p=0.0001). At the site of obstruction all vessels showed a complete absence of a disease free segment, and the atheroma presented a cuff-like or all-around distribution with a variable degree of eccentricity.

Conclusions

1/ AD was consistently present at the start of the stenosis used as a reference site by automated stenosis analysis. 2/ The mean degree of AD involvement at the start of the stenosis was 50% total area stenosis. 3/ A significant change from crescent to all-around distribution of AD was found at the start of the stenosis. These findings suggest that the start of the stenosis identified by automated stenosis analysis represents the point where compensatory vessel enlargement fails to preserve luminal dimensions, and provide insights on the mechanisms involved in this phenomenon.

Introduction

During its relatively short history, the role of coronary angiography as a standard in the assessment of coronary artery disease has been challenged by two types of limitations. First, visual assessment of stenosis severity from the cineangiogram is associated with a high intra- and interobserver variability.[1-4] Second, major discrepancies between the appearance of the opacified vascular lumen and the actual degree of underlying atherosclerosis have been reported.[5-9] These can be due to the presence of extensive diffuse disease which affects the whole length of the opacified coronary tree, without a remnant "healthy" reference segment. More importantly, underestimation of the extent of atherosclerotic disease may occur due to the fact that during the development of both diffuse and focal atherosclerotic lesions coronary arteries undergo compensatory enlargement.[10,11]

The advent of quantitative angiography has reduced significantly the first limitation. Several quantitative angiography systems, including the Cardiovascular Angiography Analysis System (CAAS) which was developed at our Institution, are capable of performing automated stenosis detection in a given coronary segment.[12,13] Using information obtained from computerised analysis of the entire segment, automated analysis detects not only the proximal and distal boundaries of the stenosis, but also an interpolation of the expected dimensions of the coronary vessel at the point of obstruction (a so-called interpolated reference). The angiographic estimation of the amount of atheromatous plaque derived from this data is also a common feature of commercially available quantitative angiography packages, which are likely to become more widely used since they are now built-in features of many modern digital angiographic systems. In spite of this, it remains unknown whether the data calculated from automated stenosis analysis can provide reliable information on the degree or presence of underlying atherosclerotic disease. The use of automatic stenosis detection techniques may reduce the variability associated with the arbitrary selection of a reference segment, being useful in longitudinal angiographic studies. However, its basic premise, that is, that computerised analysis of a large coronary segment encompassing the stenosis can identify the actual boundaries of the stenosis, has never been tested.

Intracoronary ultrasound can provide information on the characteristics of the arterial wall.[14,15] This characteristic justifies its growing application in the study of atherosclerotic coronary artery disease,[15-22] and its proposal as an alternative gold standard to coronary angiography.[14] However, comparisons between intracoronary ultrasound and quantitative angiography have been confined only to its ability to measure luminal dimensions, and never used to investigate the significance of other findings obtained during automated stenosis analysis.[14]

The objective of this study was twofold. First, we wanted to investigate with intracoronary ultrasound the characteristics of the arterial wall at the site

identified by automated stenosis analysis as the proximal boundary of the stenosis, since previous studies with quantitative angiography have assumed the absence of atherosclerotic disease at this location for the calculation of interpolated reference dimensions.[23] Secondly, we were interested in assessing whether, at the site of maximal luminal obstruction, the amount of atheroma derived from automated stenosis analysis reflects the degree of atherosclerotic involvement as judged by intracoronary ultrasound.

Methods

Patient population
The study population consisted of forty patients (31 male and 9 female) with de novo coronary stenosis undergoing cardiac catheterisation immediately prior to percutaneous revascularisation. Mean age was 61±10 years. All investigations were approved by the Institutional Review Board of the Thoraxcenter, and patients were studied after giving informed consent.

Quantitative angiography
In this study both on line and off-line quantitative coronary angiography was performed. On line measurements were performed immediately prior to intravascular ultrasound examination using a Philips DCI angiography system in conjunction with a commercially available quantitative angiography package (ACA, Philips, Eindhoven, The Netherlands). The results of the analysis, including the location of the beginning and end of the stenosis, as well as the point of maximal luminal obstruction identified by the computerized analysis, were permanently displayed in a video monitor, serving as a guide for the operator during the ultrasound study. Coronary cineangiograms were also obtained and later analysed off-line in a 3rd generation edge detection quantitative angiography system (CAAS 2, Pie Data, Maastricht, the Netherlands),[24,25] which uses a similar algorithm as the ACA for the purpose of stenosis identification and reference diameter interpolation.[26] A description of the consecutive steps followed during the analysis of the cineangiogram is given below:

1/ *Image acquisition*: End-diastolic angiographic frames showing the stenosed vessel were selected. Using a CCD camera, a region of interest of 512x512 pixels encompassing a wide vascular segment proximal to the stenosis was selected in the cineframe and digitized for subsequent analysis (Fig. 1A).

2/ *Identification of luminal edges*: Following the identification of the vessel centerline by the computer algorithm, a number of scanlines perpendicular to it were obtained. Luminal edges were detected on the basis of a weighted sum of the first and second derivative function of the brightness profile of each of these scanlines (Fig. 1B).

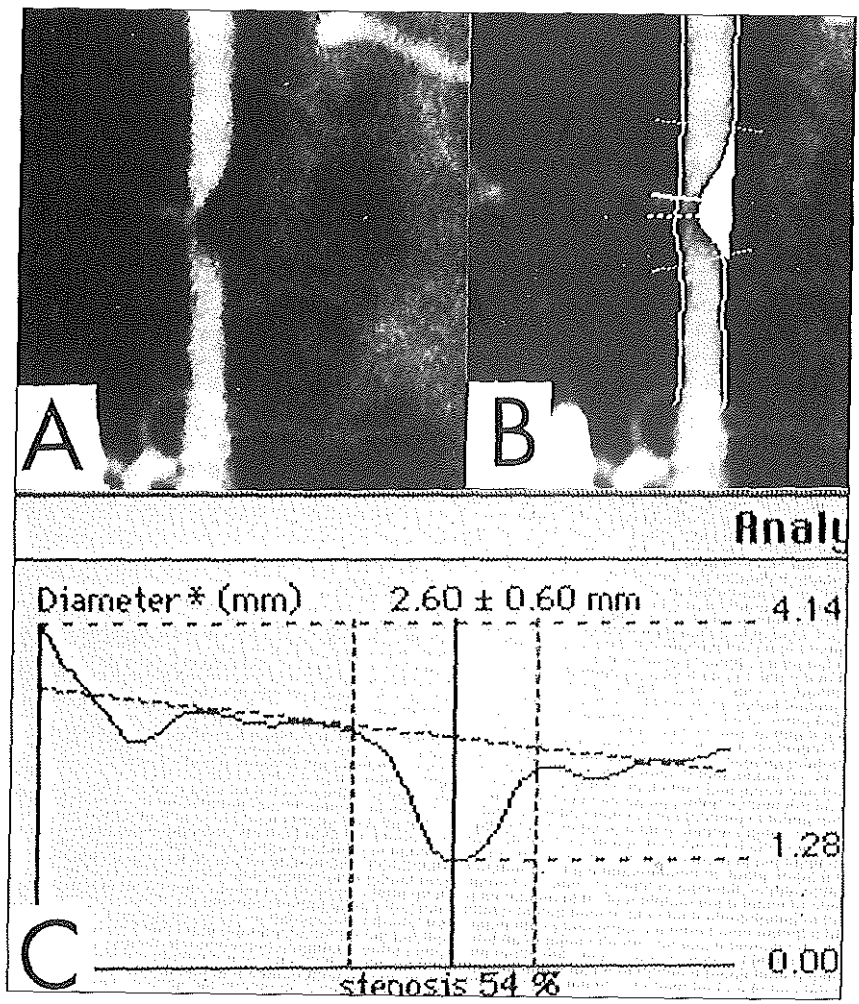

Figure 1

Quantitative angiographic analysis as performed in the present study. After a region of interest in the coronary angiogram showing a wide vascular segment encompassing the stenosis was digitised (A), luminal edges were identified using a contour detection algorithm (B). After calibration using the coronary actehter as a scaling device was performed plotting, the consecutive vessel diameters were plotted to create a so-caled vessel diameter function (C). Application of specific algorithms to this function made possible the identification of the poitn with minimal luminal diameter (solid bar) as well as the proximal and distal boundaries of the stenosis (dotted bars). Based in the diameter function, the expected dimensions of the vessel at the site of the obstruction (interpolated reference diameter) were calculated. (See text for details)

3/ *Diameter function.* Vessel diameters were determined by computing the shortest distance between the left and right edge positions. These measurements were converted to absolute values using the coronary guiding catheter as a scaling device. By plotting all consecutive diameter values obtained at approximately 0.2 mm intervals over the analysed vessel length, a so-called diameter function was created (Fig. 1C).

4/ *Identification of the start of the stenosis.* Application of specific algorithms to the diameter function made possible the identification of vessel location where critical change in the diameter values occurred. In any coronary segment subject of analysis it is possible to observe dips in the diameter function resulting from changes in luminal diameter or image noise. To discriminate between these artifactual changes and the actual change in luminal diameter associated with the start of a stenosis, the diameter function is analysed in the CAAS II system using a curvature detection algorithm which identifies maxima in curvature using variable degrees of smoothing. The algorithm is nearly identical to that described by Rosenfeld and Johnston.[27] The proximal and distal boundaries of the obstruction are defined by the positions featuring the first local maximum in curvature in proximal and distal directions respectively with respect to the minimal diameter position. The extent of the stenosis is indicated in the diameter function by two dotted lines as is represented as a shaded area superimposed on the artery (Fig. 1C)

5/ *Identification of the site of obstruction.* From the diameter function, the site of obstruction is identified as that corresponding to the lowest diameter value in the segment encompassed between the start and end of the stenosis.

6/ *Interpolated reference diameter.* The third parameter derived from the analysis of the diameter curve is the interpolated reference diameter. After the creation of a first degree polynomial computed through the diameter values of the proximal and distal portions of the arterial segment, a translation to the 80th percentile level was performed. Combining this information with the location of the obstruction, the expected diameter of the vessel at the site of minimal luminal diameter was calculated. In this way, a correction for the expected changes in vessel diameter between the start and end of the stenosis, such as those resulting from the origin of side branches. is introduced.

7/ *Angiographically-derived plaque area.* Based in the above discussed premises, plaque area was defined as the difference between the interpolated and luminal dimensions at the obstruction site (Fig. 2A). This is a variation of the calculation of plaque area performed in the CAAS and other commercially available systems[12,13] in the longitudinal axis (Fig. 1 B), and was chosen to facilitate its comparison with cross-sectional areas measured during intravascular ultrasound (Fig. 2B).

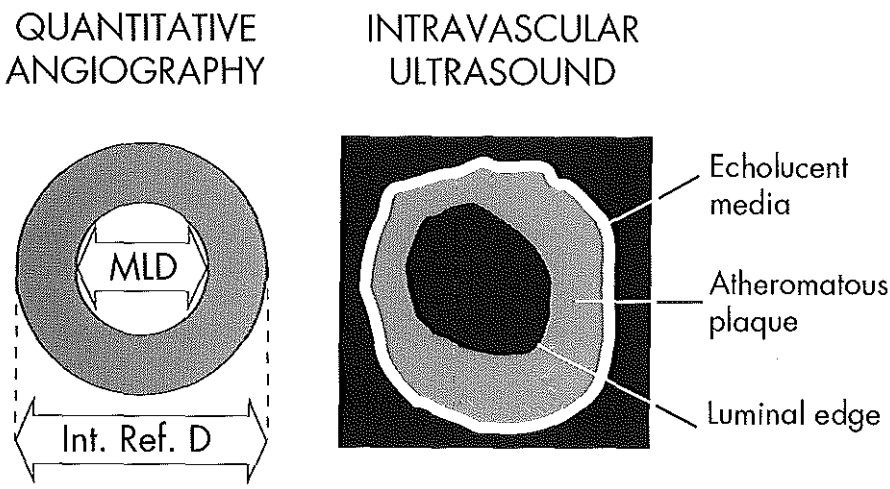

Figure 2

Method used for the calculation of atherosclerotic plaque area using quantitative angiography and intravascular ultrasound. Assuming a circular cross section, plaque area was calculated from quantitative angiography as the difference between the areas derived from the interpolated reference (Int.Ref.D) and minimal luminal (MLD) diameters. Plaque area was defined with intravascular ultrasound imaging as the difference between the areas comprised within the medial and luminal boundaries, obtained directly from planimetric measurements.

Intravascular ultrasound

Intravascular ultrasound was performed using a 30 MHz intravascular ultrasound system (Cardiovascular Imaging Systems, Inc., California). Collection of data was restricted to the pre angioplasty stage. The observer was free to adjust gain, magnification and other settings of the ultrasound system to obtain optimal visualization of the plaque and luminal borders. Particular attention was paid to ensure that the collection of echocardiographic data matched the sites identified by QCA as the beginning of the lesion and the obstruction site. In order to do this, on-line quantitative analysis was performed and displayed in one of the monitors to be used as a reference during the procedure. Once the stenosis was crossed with the guidewire, the operator was free to perform any contrast injection, maneuver with the guiding catheter that were required in order to advance safely the ultrasound catheter until a location distal to or wedged in the stenosis. This location was documented by contrast injection. A slow pull back of the ultrasound catheter was then performed, documenting its location with new contrast injections at the points identified by quantitative angiography as the obstruction site, beginning of the lesion and its adjacent proximal site. During the whole procedure, simultaneous recording of fluroscopy and echocardiographic images was performed using a digital videomixer. This facilitated later the correlation between ultrasound images and the location of the echo probe in the opacified vessel. Furthermore, the location of the echo probe was documented in

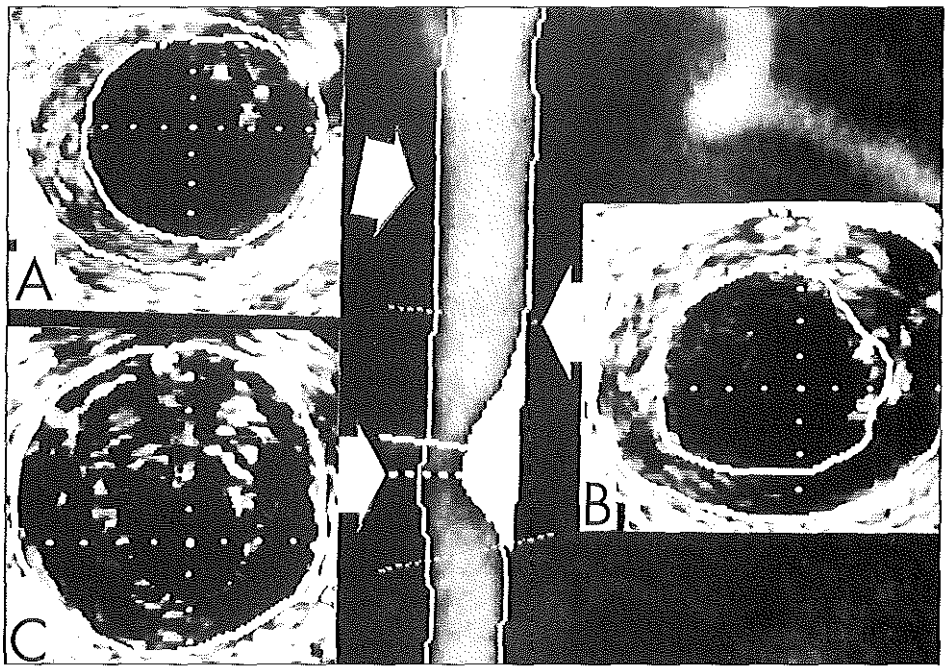

Figure 3

Intravascular ultrasound findings at the site proximal to the stenosis (A), at the start of the stenosis as defined by automated stenosis analysis (B) and at the site of maximal luminal obstruction (C), defined also by automated stenosis analysis. Note the marked change in distribution of atheroma around the lumen (centre of the cross-hair) at the three levels.

pre-designed printed forms during the procedure, using the time counter of the echo machine (which was recorded along the images) as a temporal landmark. After the procedure, off-line area measurements in the locations of interest were performed using digital planimetry which is a build-in feature of the described ultrasound system. Total vessel area was defined as that comprised within the echolucent medial layer, while luminal area as that comprised within the luminal edges. Plaque area was defines as the difference between total vessel and luminal areas. All measurements were performed independently in two separate sessions by two observers with expertise in intravascular ultrasound.

Exclusion criteria

Vessels with anatomical features that interfere with computerized stenosis analysis, including ostial lesions where a proximal segment of the vessel was not present, and total or functional occlusions with incomplete opacification of the coronary segment distal to the stenosis,were excluded from the study.

Statistical analysis

Mean ± standard deviation were calculated for all continuous variables. Least

squares linear regression analysis was performed and correlation coefficients calculated. Continuous variables were compared using two-tailed paired and unpaired Student's t test as required. Bonferroni correction was applied when comparison between more than 2 groups were done. A p value less than 0.05 was considered statistically significant.

Results

Findings at the site of obstruction.
In the 40 patients studied, quantitative angiography revealed a minimal luminal cross-sectional area of 1.24±1.12 mm^2. At the site of obstruction, intravascular ultrasound yielded a luminal area of 2.80±1.64 mm^2. Wedging of the catheter was observed in 24 cases (60%). In the 16 cases where the ultrasound catheter was not wedged a good correlation between angiographic and intravascular ultrasound luminal measurements was observed (r=0.78, p=0.0002).

At the site of the obstruction intravascular ultrasound revealed a total vessel area of 16.65±4.04 mm^2 (83±10% total vessel area stenosis). This was significantly larger than that calculated from the interpolated reference dimensions obtained with quantitative angiography (7.48±3.30 mm^2, p=0.0001). Thus, quantitative angiography underestimated the dimensions of the original vessel as assessed with intravascular ultrasound. As a result of this differences, plaque area derived from angiographic data was significantly lower than that calculated from intravascular ultrasound data, (6.32±3.21 and 13.29±4.22 mm^2 respectively, mean difference 6.92±4.43 mm^2, p=0.0001). Regression analysis yielded a correlation coefficient between both estimates of plaque size of 0.23 (R-squared =0.05, p=NS).

Findings at the start of the stenosis and in the proximal vessel.
At the site identified as the start of the stenosis by automated analysis, intravascular ultrasound cross-sectional area was 9.38±3.17 mm^2, and total vessel area was 18.77±5.19 mm^2 (50±11% total vessel area stenosis). Significant differences were found in the distribution of the atheromatous plaque around the lumen in the proximal vessel, start of the stenosis and site of the obstruction. Thus, the arterial wall presented a disease-free segment in 28 (70%) of proximal locations, but only in 5 (12%) sites corresponding to the start of the stenosis and no at the obstruction (p=0.0001)(Fig. 2). At the site of obstruction all vessels showed a complete absence of a disease free segment, and the atheroma presented a cuff-like or all-around distribution with a variable degree of eccentricity

Discussion

From a historical point of view, the reason for the development of computerized analysis of the stenosis was to reduce the variability associated with arbitrary

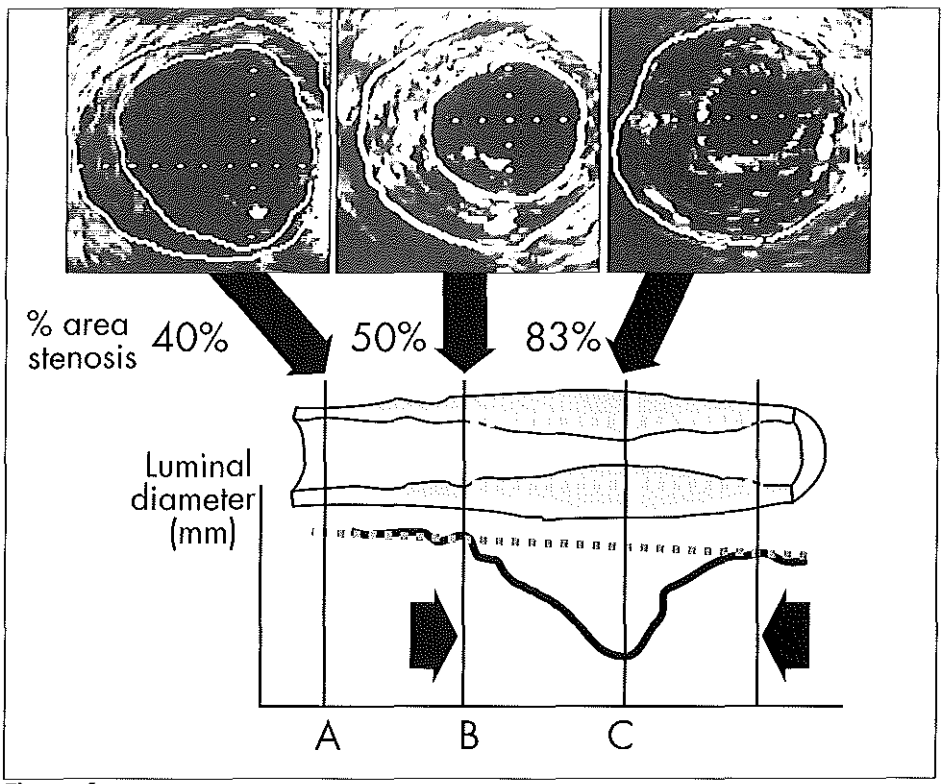

Figure 4

Schematic representation of the findings in the present study. Proximal to the stenosis (A), as defined by automated stenosis analysis (solid arrows in the diameter function), atheroma caused a mean vessel stenosis of 40%. At the site identified as the proximal boundary of the stenosis mean vessel (B) stenosis was 50%, progressing to 83% at the site of maximal obstruction (C). The discrepancy with plaque size calculated from the interpolated reference diameter (dotted line) may be related either to the incorrect assumption that at the start of the stenosis no disease was present, or to outward expansion of the plaque due to compensatory enlargement.

selection for the user of a reference segment, since atherosclerotic involvement could be demonstrated at that location.[28,29] Coronary angiography represents a "luminogram" or "shadowgram" of the vessel, and its visual interpretation conveys little or no information as to the extent of atherosclerotic disease in the arterial wall. Studies comparing angiographic and pathological data have demonstrated that visual interpretation of the angiogram underscores the degree of underlying disease both at the site of the obstruction and in segments which are apparently free of disease.[5-9] Thus, although the advent of early quantitative angiographic systems had facilitated a more accurate assessment of luminal obstruction, choosing a reference coronary segment for clinical purposes such as the calculation of relative measurements of stenotic severity remained associated with high variability and inaccuracy.

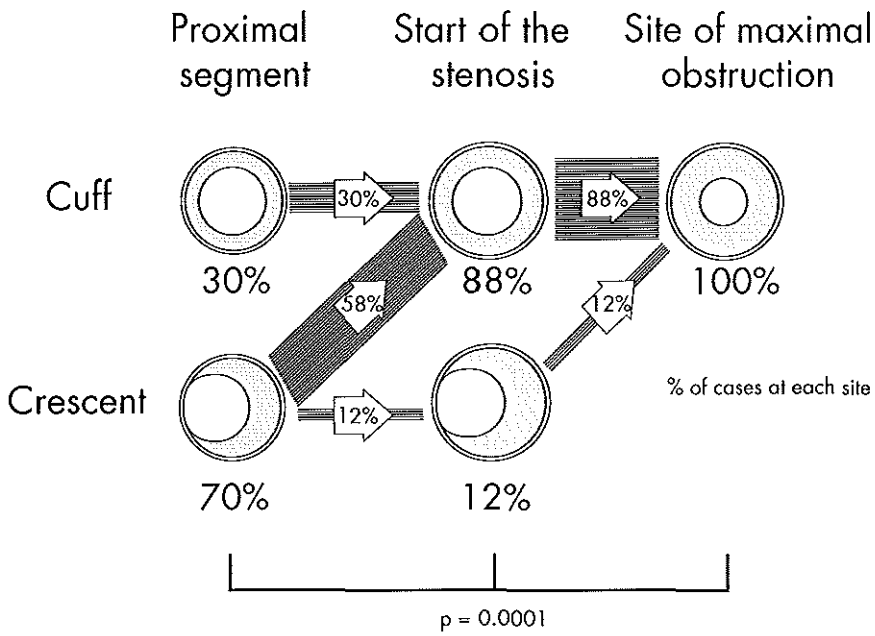

Figure 5

Change in the distribution pattern of atheroma in the analysed vessel. Proximal to the start of the stenosis (as defined by automated analysis) most vessels presented a characteristic crescent-like distribution of atheroma, with an apparently disease-free arc of the vessel wall. A significance change from this pattern to a cuff-like or all-around distribution of atheroma at the sites defined as the start of the stenosis and maximal obstruction was noted. The dissapearence of the disease-free arc in the vascular wall may constitute the landmark for the failure of compensatory mechanisms of vessel enlargement that preserve tha vascular lumen during the early stages of atherosclerosis progression.

In an attempt to find a solution to these problems, several automated methods of analysis of the luminal dimensions have been developed[12,13] with the aims of providing objective identification of the boundaries and length of the stenosis and identifying a segment apparently free of atherosclerotic disease to be used as a reference during the calculation of relative measurements, and for the application of interpolated reference techniques. As we have described above, the approach followed by the CAAS system consists in applying specific algorithms to a so-called diameter function, obtained by plotting all consecutive luminal diameters in the vascular segment encompassing the stenosis. However, the relationship between computerized analysis of the luminal dimensions in a segment that encompasses a stenosis and the underlying degree of atherosclerosis has not been previously studied.

The possibility of inferring information on the degree of underlying atherosclerotic disease from such computerized analysis of luminal dimensions would be supported by the concept that atherosclerosis is a focal[30] and not diffuse[31,32] process. In this regard, Baroldi et al.[33] found in a pathological study of 565 atherosclerotic coronary vessels that the length of coronary lesions was less than 5 mm in 13%, between 5 and 20 mm in 38%, and more than 20 mm in 49% of cases . Thus, a substantial number of coronary lesions have a length covered by conventional computerized angiographic analysis of a vascular segment.

Our observations with intravascular ultrasound indicate that atherosclerotic involvement at the site identified by QCA as the start of the lesion is common. Therefore, the site identified by the curvature detection algorithm in the diameter function does not correspond, as first thought, to a coronary location free of atherosclerotic disease. Interestingly, we found that at this level total vessel area stenosis is quite similar to that found by Glagov et al.[10] to be related with the failure of compensatory mechanisms of vessel enlargement, which is observed during the early phases of atherosclerosis progression.[10] The observations reported by other authors in coronary segments with minimal or no luminal narrowing as assessed by angiography support our findings. In such segments total vessel area was occupied by atheroma in 35±23% and 45±15% in the work of Tobis[17] and Hodgson[18] respectively. Although these observations were performed with a different aim, and therefore the collection of data was not matched with computer analysis of the stenosis, it is fair to conclude that protrusion of atheroma into the lumen probably does not occur below a atherosclerotic involvement causing 50% reduction in total vessel area, which is located at the start of the angiographic stenosis. Based on these observations, we can formulate the first conclusion of our study by saying that the proximal boundary of the stenosis identified during automated stenosis analysis with the CAAS system does not correspond to a location free of atherosclerotic disease but, presumably, where the compensatory mechanisms of vessel enlargement fail in preserving luminal dimensions.

Some qualitative observations with intracoronary ultrasound in performed in the present study may provide new insights on the mechanisms underlying compensatory vessel enlargement. We found that at the level of the proximal boundary of the stenosis there was a significant change in the distribution of the atheroma around the coronary lumen when compared with more proximal locations. This consisted of a change from a crescent-like pattern of atheroma, which

was the dominant pattern in a proximal location , to a cuff-like pattern at the start of the stenosis. At the point of maximal luminal obstruction, only this latter pattern of atheroma distribution was observed, an observation that fits with the findings of Hangartner et al.[34] in a pathological study. The loss of an arc of disease-free wall, characteristic of the crescent-like distribution of atheroma, may, as first proposed by Glagov,[10] be critical in the loss of compensatory vessel enlargement, a phenomenon that, as the present study suggests, can be observed at the start of the stenosis as defined from computerized analysis of the angiogram. Previous work has demonstrated that in the presence of a normal arterial wall, vessel enlargement occurs in circumstances of increased shear rate, a phenomenon that appears to be endothelium-mediated.[35] During the progression of coronary artery disease, reactive expansion to the increased shear stress may constitute the basis of compensatory vessel enlargement, but it would be expected that would disappear when a complete loss of normal reactive wall occurs.[36] The abolishment of such compensatory response might be due to complete encroachment of the lumen by atheroma, leading to a rapid decrease in luminal dimensions caused by inward growth of the atheromatous plaque. This phenomenon might explain the disproportionately larger degree of progression in the reference diameter found in a major study on atherosclerosis regression,[37] since a relatively small progression in the disease process propitiated by disturbances in flow caused by the neighbor narrowing[16] may have led to the critical loss of a remnant arc of reactive vessel wall. These findings complement previous intravascular ultrasound [16] and pathological observations[34] on the presence of multiple crescents of atheroma in "angiographically normal" coronary segments, representing foci of atheroma progression that have not caused luminal obliteration due to ongoing compensatory enlargement.

Finally, we also observed that interpolated techniques are of no use in obtaining a reliable estimate of the underlying plaque area. The basic premise of this principle could be stated by saying that at the point of minimal luminal narrowing the interpolated reference area should be representative of that comprised within the internal elastic lamina. However, we found that the interpolated reference area calculated by quantitative angiography was significantly smaller than total vessel area observed with intravascular ultrasound. This may be partly due to the initial failure of the curvature detection algorithm to identify a segment where no disease was present on which the interpolation could be based. A second source of error could be due to compensatory vessel enlargement may have occurred.

We believe that the observations performed during this study introduce a change in the concepts that are routinely used in quantitative coronary angiography with regard to automated stenosis analysis.

Study limitations

Since wedging of the ultrasound catheter was required in a number of cases in order to visualize vessel wall at the site of maximal obstruction, distortion of the vessel at that site may have occurred. However, since atheroma is not compressible, we believe that this would not influence substantially the measurement of plaque size nor the distribution of

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Chapter III

Advantages and Limitations of Intracoronary Ultrasound for the Assessment of Vascular Dimensions. A Comparison with Quantitative Coronary Angiography

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Introduction

Quantitative angiography has been used to validate the accuracy of the measurement obtained with the early intravascular ultrasound catheters[1,2,3]. In more recent reports[4-12] it was suggested that intravascular ultrasound can be superior to quantitative angiography in the assessment of complex lesions (eccentric stenosis, asymmetric lesions, vascular dissections). In this article, advantages and limitations of the two techniques in the assessment of vascular dimensions are discussed based on the results reported in the literature and of our experience in 94 patients with coronary artery disease.

Previous studies comparing intravascular ultrasound and angiography for the assessment of vascular dimensions

The results of 11 clinical studies in which quantitative angiography and intravascular ultrasound were compared are summarized in Table 1. Differences in equipment and methods of analysis limit the comparison and interpretation of data. Linear regression analysis is most commonly used as a statistical test in these studies. However, a regression coefficient close to 1 is not sufficient to conclude that the two techniques provide similar quantitative measurements[13]. The mean difference of the paired measurements and indexes of dispersion along the line of identity are more meaningful parameters but are not always reported. With the exception of the study by Tobis et al.[6] the results indicate that there is a good correlation between intravascular ultrasound and angiographic measurements in normal or moderatey diseased segments. In general, larger cross-sectional areas were measured with intravascular ultrasound than with angiography[6,8,9,11,12]. A major limitation for a precise comparison is that the measurement of the same arterial cross-section is difficult, particularly when a major change of vascular cross-sectional area occurs in a very short segment. An angiogram of sufficient quality to be quantitatively analyzed can not be obtained during the echographic measurements since the catheter positioned in the stenosis causes a severe arterial occlusion, limiting the distal opacification. In eccentric lesions or lesions treated with balloon angioplasty a poor correlation and a large scatter of the paired measurements was found immediately after balloon dilatation. After angioplasty, Tobis et al.[6] observed that the cross-sectional areas measured with intracoronary ultrasound were up to 50% larger than the corresponding angiographic cross-sectional areas calculated assuming a circular model.

Table 1. Quantitative angiography vs. intravascular ultrasound: Clinical comparative Studies.

Investigators	Pts.	Vessel	"r"	SEE	M.Dif.	% Dif.
Davidson el al. [2]	21	Femoroiliac arteries	0.97	1.83	—	—
Sheikh et al. [3]	15	Femoral arteries	0.95	0.91	—	—
The et al. [4]	8	Femoroiliac arteries	0.96	0.47	—	—
Bartorelli et al. [5]	8	Femoral arteries	0.96	—	0.3 mm	4%
Tobis et al. [6]	27	Normal segments	0.26	—	2.1 mm	30%
		Stenosis post-PTCA	0.18	—	1.7mm	51%
Nissen et al. [7]	8	Normal coronaries	0.92	0.21	-0.05 mm	1%
	43	CAD patients	0.86	0.43	0.06 mm	2%
Werner et al. [8]	14	Normal segments	0.86	—	—	—
		Stenosis post-PTCA	0.48	—	—	—
St.Goar et al. [9]	20	Normal coronaries	0.86	0.07	0.04 mm	12%
		Transpanted patients				
Jain et al. [10]	6	SVG pre/post-PTCA	0.96	—	—	—
Hodgson et al. [11]	34	Reference segment	0.77	—	—	—
		Stenosis post-PTCA	0.63	—	—	—
Haase et al. [12]	20	Stenosis post-PTCA	0.53	—	2.3 mm	—

CAD, coronary artery disease; Dif., difference; M.Dif.,mean differences; Pts., patients; PTCA, percutaneous transluminal coronary angioplasty; SEE, standard error of the estimate; SVG, saphenous vein bypass graft.

Percent diameter and cross sectional area stenosis: which technique provides the correct measurements?

The use of different reference measurements for the calculation of relative vascular dimensions with quantitative angiography and intravascular ultrasound may explain the large discordance between the results obtained with the two techniques (Figure 1). Reference diameter and cross-sectional area are measured in an angiographically normal segment of the vessel with quantitative angiography. In muscular arteries intravascular ultrasound allows a direct measurement of the area inside the internal elastic lamina, the so called original lumen area which equals to the sum of lumen and plaque area. This area is used as a reference in intravascular ultrasound. Intimal thickening is often present in angiographically normal reference segments (Figure 2). Furthermore, a compensatory enlargement of the vessel is almost invariably present at the stenotic site, as confirmed also in recent studies with intracoronary ultrasound[14]. These reasons explain why the angiographic reference lumen cross-sectional area is smaller than the ultrasonic

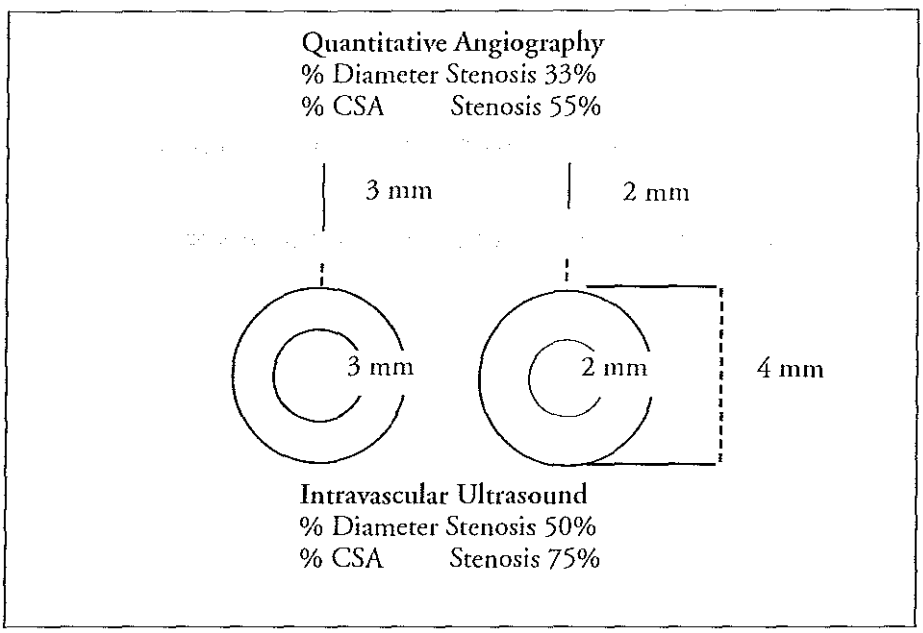

Figure 1.

Calculation of percent diameter and cross sectional area stenosis based on intravascular ultrasound and angiographic quantitative measurements. The reference lumen diameter is measured with quantitative angiography in the normal segments of the vessel while intravascular ultrasound directly measures the thickness of the atherosclerotic plaque at the stenosis site. In the presence of compensatory enlargement of the stenotic site or, as in this example, of a diffuse cocentric intimal thickening involving also the angiographic reference segment, the intravascular ultrasound reference diameter traced within the black band representing the muscular media, is larger than the angiographic reference diameter. As a result the angiographic moderate percent stenosis is considered more severe "significant" according to the normally used criteria (≥ 50% diameter stenosis and ≥ 75% cross-sectional area stenosis) with intravascular ultrasound.

reference area[15] so that less severe percent diameter and cross-sectional area stenosis will be calculated with quantitative angiography than with intravascular ultrasound (Figure 3). In Figure 1, in the presence of a 1/2 mm thick intimal lesion in the reference segment, a major difference is observed in percent diameter and cross-sectional area stenosis between quantitative angiography and intravascular ultrasound.

Percent diameter and cross-sectional area stenosis are physiologically important parameters and are major determinants of the pressure drop across a stenosis[16]. However, the results obtained from animal models of acute external constriction of normal vessels[17] cannot be simply applied to the percent lumen reduction measured with quantitative angiography. Harrison et al[18] showed that the stenosis-related impairment of post-occlusion reactive hyperemia can not be predicted based on the coronary angiographic assessment of percent diameter and cross-sectional area stenosis. Awareness of these drawbacks has already contributed to focus the interest in the measurement of absolute rather than relative lumen

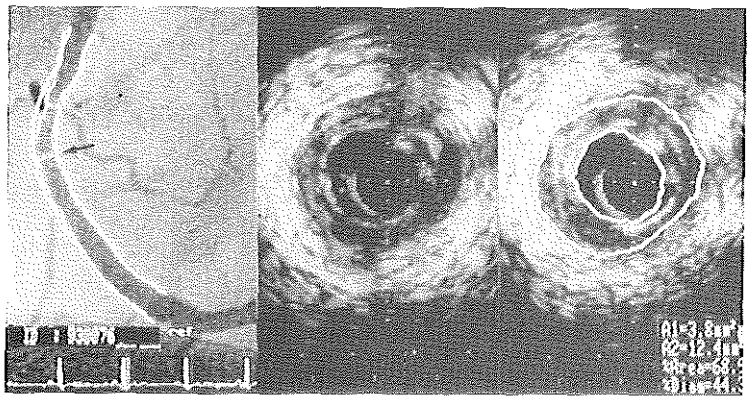

Figure 2.
Digital angiogram of a right coronary artery with the reference diameter positioned at the site examined with intracoronary ultrasound. Note that in this angiographically normal reference segment intracoronary ultrasound shows the presence of a concentric plaque inducing a 44% diameter stenosis. Calibration 0.5 mm.

stenosis in quantitative angiography[19]. Intravascular ultrasound can directly measure plaque area and avoid the use of a reference measurement in a potentially diseased segment of the vessel. However, such reference area does not necessarily reflect the physiologically ideal vascular dimension because of the already mentioned compensatory enlargement. In particular the presence of a crescentic plaque with an outward remodelling of the vessel is likely not to influence the

Table 2. Advantages and limitations of intravascular ultrasound for quantitative assessment of vascular dimensions.

Advantages of Intravascular Ultrasound	Limitations of Intravascular Ultrasound
1) No calibration required	1) Introduction of the catheter is necessary
2) Instantaneous and continuous measurements available	2) Potential erros due to catheter malaligment
3) No contrast medium required	3) Artifacts from non-uniform or rotation* near-field artifacts ** low sampling rate **
4) Independent of lumen eccentricity complex lumen geometry (dissections)	4) Automatic edge detection difficult
5) Simultaneous morphometric analysis of wall components	5) Reproducibility of the measurements not yet tested

* single element mechanically rotating systems; ** multielement synthetic aperture array systems.

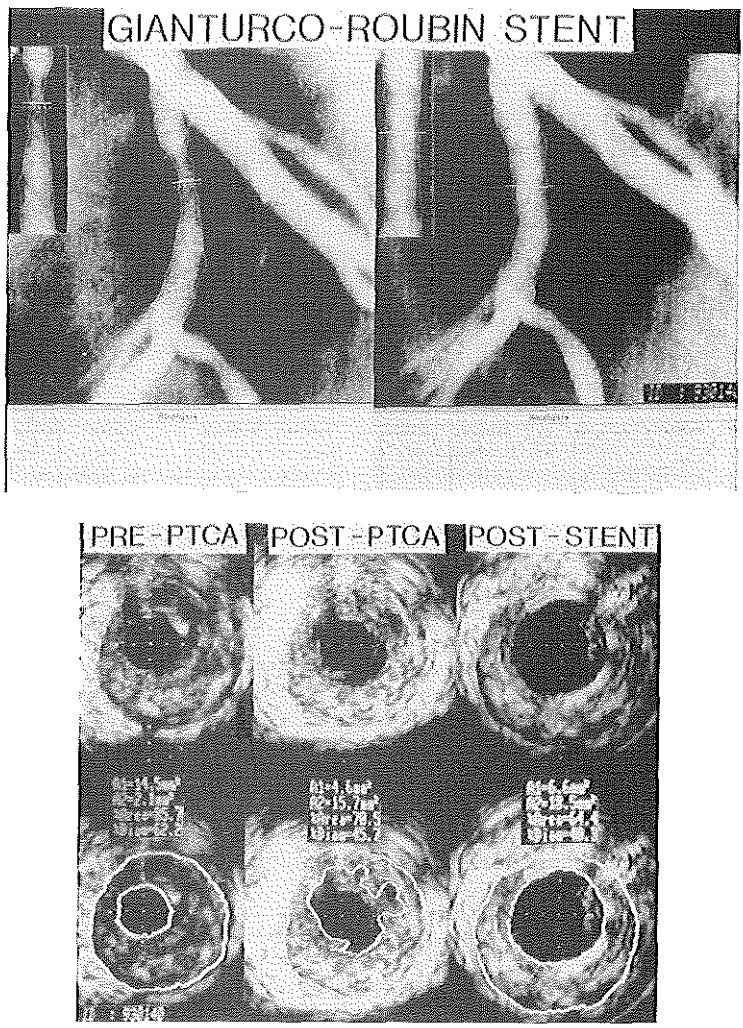

Figure 3.

Top, cineangiogram after automatic contour detection showing a severe proximal stenosis of the left anterior descending coronary artery (left panel) and a regular lumen (ca 10% residual diameter stenosis) after implantation of a Gianturco-Roubin stent (right panel). Bottom. Ultrasonic cross-sectional area in the most severe stenotic segment before angioplasty (left panel) , after a predilation with a 3.0-mm angioplasty balloon (mid-panel), and after implatation of a 3.0 mm Gianturco-Roubin stent (right panel). The lower panels show the same ultrasonic cross-sections after on-line manual tracings of the lumen and plaque contours. Note that a similar plaque area is present before dilation and after balloon dilation and stent implantation (12.2 mm2 and 11.1-11.9 mm2, respectively) despite the large increase in lumen area (from 2.1 mm2 before treatment to 4.6 mm2 and 6.6 mm2 after balloon dilation and stent implantation, respectively) The increase in lume area after ballloon angioplasty is the consequence of multiple irregular fractures of the plaque while a regular luminal cross-sectional area is present after stent implantation. Calibration 0.5mm.

dimension of the vascular lumen. The presence of a reduction of the "ideal" dimension of lumen cross-sectional area is more difficult to be judged in the presence of a diffuse circular ring of intimal thickening (Figure 2)[20]. Therefore the assessment of the physiologic significance of a vascular stenosis requires different approaches such as the measurement of trans-stenotic velocity increase or of the pressure drop at maximal hyperemia across the stenosis, the calculation of coronary flow reserve based on angiographic or Doppler measurements.

Advantages of intravascular ultrasound

Advantages and disadvantages of intravascular ultrsound vs angiography are summarized in Table 2.

No calibration is required
For angiography the measurement of a radiopaque structure of known dimension is required for calibration. When the tip of the catheter is used as a scaling device, possible sources of error are off-plane position of the catheter and the examined vessel, tapering of the catheter at the distal end and discordance between true catheter diameter and diameter reported by the manufacturer[19,21]. Furthermore, calibration must be repeated for every angiographic view. A potentially more precise but even more cumbersome approach is the geometric correction for beam divergence, based on the measurement of the distances between x-ray source, imaged object and image amplifier (isocenter technique)[22].
The measurement of a distance with ultrasound is based on the wavelength of the ultrasound beam and the velocity of sound in the medium. When the instrument is calibrated for the ultrasound speed in blood (1,560 m/s) a negligible overestimation occurs when saline is injected to replace the more echogenic blood and delineate the intimal contour.

Instantaneous measurements are available
Recently introduced digital angiographic equipment allows the performance of on-line measurements of vascular dimensions. As a consequence, quantitative angiography can be used for guidance and immediate evaluation of interventional procedures. The time required for the analysis, however, is still considerable when compared to the really instantaneous measurement available with ultrasound.

No contrast medium required: a continuous monitoring is possible
Angiography requires the injection of contrast material to delineate the vascular lumen. As a consequence, angiography can not be used for a continuous monitoring of vascular dimension. Other disadvantages of the use of contrast medium are the modification of the intraluminal pressure during the forceful contrast injection and the vasoactive properties of these agents.
Intravascular ultrasound allows a continuous real-time measurement of vascular dimensions, a great potential advantage for monitoring interventions and

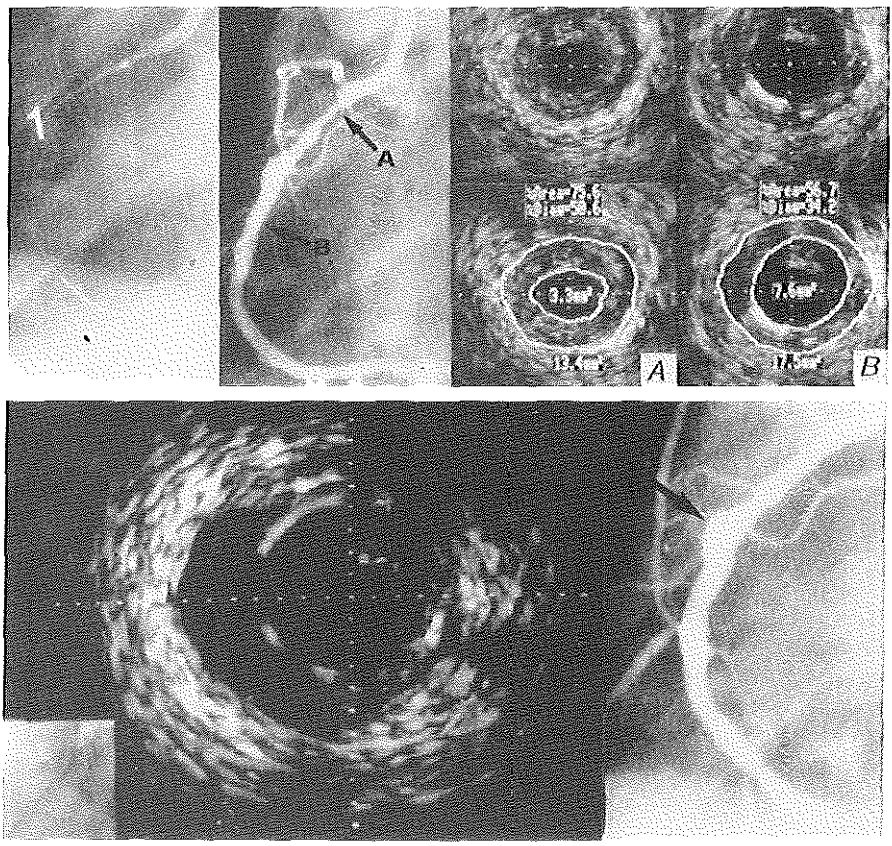

Figure 4.

Top, angiographic and intracoronary ultrasonic examination 4 months after stenting (Gianturco-Roubin) of the mid segment of the right coronary artery. The ultrasonic cross-sections on the right (B) show the segment where the stent was implanted (note the highly echogenic wire, close to the arterial lumen , in the lower left corner). A. de novo lesion was present in the proximal segment (A), with the presence of a large concentric plaque with low echoreflectivity and without calcification. Note that the plaque area in A (10.1 mm2) is similar to the plaque area in B (9.9 mm2) despite the large difference in luminal cross-sectional area and percent cross-sectional area stenosis (76% in position A vs. 57%, position B). Bottom, in the same artery after balloon dilation of the proximal segment, a large echo-free area behind the stent wires and communicating with the arterial lumen (right panel) indicates malapposition of the stent to the arterial wall in a segment with aneurysmatic dilation (arrow in the cineangiogram of the right panel).

assessment of the effects of vasoactive agents on vascular dimensions and dynamics[23].

Morphometric analysis of the vessel wall

Angiography provides only a shadowgram of the vascular lumen, so that the presence of vascular lesions is derived indirectly from irregularities of the luminal contour. The only information on the composition of atherosclerotic plaques concerns the presence of fluoroscopically visible vessel wall calcification. Pathology

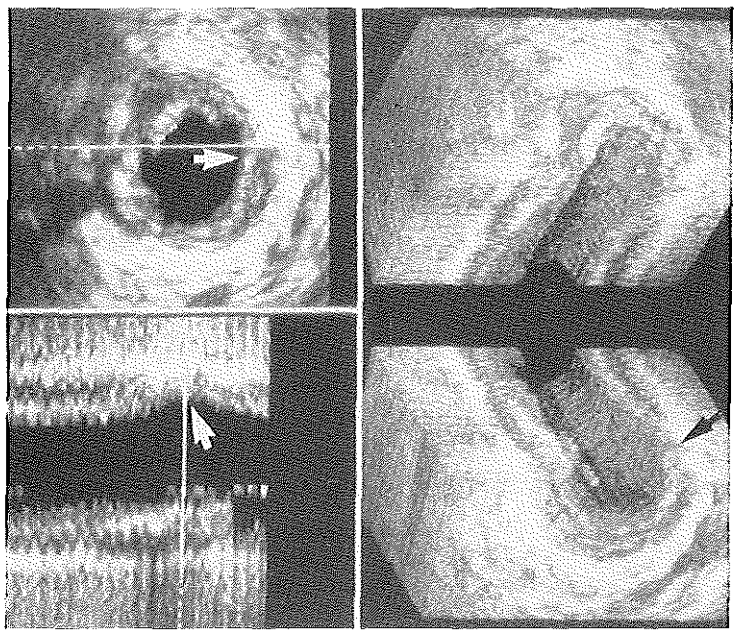

Figure 5.

Proximal segment of the left circumflex artery examined immediately after directional coronary atherectomy. The position of the cut is clearly visible after three-dimensional reconstruction of the intravascular images in the longitudinal format (arrowhead in the left lower corner) than in the image on the right, showing the arterial segment as two open hemicylinders (arrow). The position of the cut is not evident if only a single two-dimensional cross-section is considered (arrow in the area of plaque removal).

studies and, more recently, the application of intraoperative and intravascular high-frequency ultrasound have shown that coronary arteries undergo a progressive enlargement in relation with increases in plaque area, so that a reduction of lumen area is delayed until the atherosclerotic lesion occupies more than 40% of the area circumscribed by the internal elastic lamina[14,24,25] (Figure 4). These findings explain why angiographically normal arterial segments may show an extensive atherosclerotic involvement at autopsy and upon direct surgical inspection . Several reports have confirmed that intravascular ultrasound can detect atherosclerotic changes in angiographically normal segments[4,9] (Figure 2). Furthermore, intravascular ultrasound displays the components of the atherosclerotic plaque with a different intensity proportional to their backscatter power[26-28], allowing their qualitative differentiation. In vitro studies have shown that intravascular ultrasound has a high sensitivity and specificity in the detection of intimal lesions and in the differentiation between fibrous, calcific and lipid-containing plaques[29]. Plaque thickness can be measured, especially if the presence of an echographically hypoechoic medial layer facilitates the delineation of plaque contours and if no shadowing or attenuation from plaque components is present[29]. The possibility to provide information on plaque morphology and dimension at the same time makes intravascular ultrasound an ideal technique for the

assessment of the mechanism of the different coronary interventions and the modalities of progression/regression of the atherosclerotic plaque. Wall stretching and wall dissection have been reported as the main operative mechanism of balloon angioplasty in both coronary[30] and peripheral arteries[31]. A significant

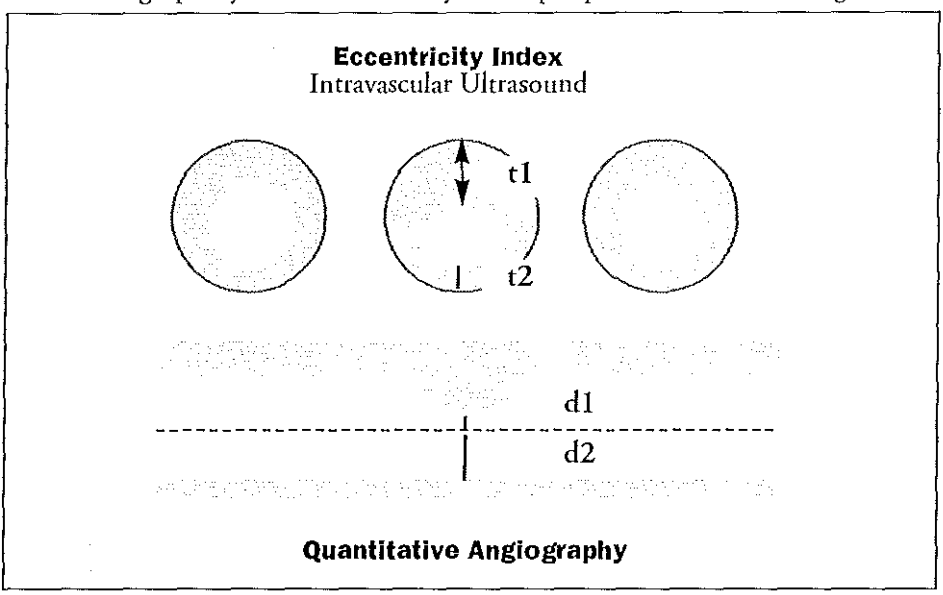

Figure 6.

Eccentricity index calculated with quantitative angiography and intravascular ultrasound. Intravascular ultrasound allows the direct assessment of the wall thickness so that the eccentricity index is based upon the ratio between plaque thikness and the thickness of the opposite wall. Quantitative angiography estimates the eccentricity of a plaque from the distance between the center of the lumen and the luminal contours at the site of the stenosis. In this example, however, the presence of a different thickness of the wall also in the angiographically normal segment induces an underestimation of the plaque eccentricity.

plaque compression (absolute reduction of plaque area) has been more recently reported[32]. In 18 coronary stenoses treated with balloon angioplasty and examined with three-dimensional intracoronary ultrasound, Mintz et al.[33] observed that an axial redistribution of the plaque away from the narrowest cross-sectional area, without significant changes in the total plaque volume. An example of the usefulness of three-dimensional reconstruction of intracoronary ultrasound in the assessment of the results of coronary interventions is shown in Figure 5.

Standard methods used in quantitative angiography for the assessment of regression of atherosclerosis are the measurement of mean luminal area and severity of edge irregularities[34] (roughness profile). A long-term follow-up of large cohorts of patients is necessary to show a statistically significant trend towards regression or delayed progression of plaques in peripheral[35] and coronary[36,37] atherosclerotic disease.

Intravascular ultrasound has the potential of detecting atherosclerotic wall disease in the prestenotic phase and allows the measurement of both lumen and plaque

area[38]. Dietary and pharmacologic interventions may cause a more rapid and complete regression of the vascular changes in the early "prestenotic" phase of atherosclerosis rather than in the more advanced phases[39]. Animal studies have shown that intravascular ultrasound can detect plaque progression earlier and more accurately than quantitative angiography[40,41,42]. The possibility to differentiate lipid plaques, potentially amenable to regression after interventions, from fibro-calcific plaques, less likely to respond to such an intervention[43] is of particular interest.

Plaque eccentricity

In most cases, with the use of multiple projections, an angiogram perpendicular to the maximal thickness of the plaque can be obtained. In less than 50% of the cases, however, appropriate orthogonal projections, amenable to quantitative analysis, can be obtained to measure lumen area from its long- and short-axis when an elliptical area is present[44]. Furthermore, angiography determines the eccentricity of a stenosis comparing the proximal and distal segments of the vessel, assumed as "normal" reference segments so that a misinterpretation is possible if the eccentric plaque involves also the reference segments (Figure 6).
Intravascular ultrasound detects the eccentricity of the lesion from a direct measurement of the maximal and minimal thickness of the plaque. The eccentricity index calculated with intravascular ultrasound is independent from the characteristics of the contiguous segments[45]. The advantage of the direct visualization of eccentric plaques is obvious in the guidance of percutaneous recaqnalization techniques that allow selective removal of atheromatous plaque, avoiding a potentially dangerous treatment in areas of thin, normal wall[46].

Complex lumen geometry (wall dissection)

Pathology studies have shown that splitting of the vessel wall is extremely frequent after balloon angioplasty and is one of the major mechanisms of effective lumen enlargement[47,48]. Only large dissections are angiographically evident after balloon angioplasty. Several reports[6,30,31,32,49,50,51] have confirmed that intravascular ultrasound is more sensitive than angiography in the detection of plaque rupture. The absence of echographically evident plaque rupture has been recently reported to increase the risk of restenosis[52]. The quantitative measurement of residual stenosis early after balloon angioplasty is a poor indicator of the functional result of the procedure as assessed by coronary flow reserve[53] and persistence of scintigraphic and electrocardiographic signs of reversible myocardial ischemia. Several reasons may explain these findings. In some cases, the comparison between echographic and quantitative angiographic measurements suggests that an overestimation of the lumen really available for blood passage may occur when a geometric technique (edge-detection) is used (Figure 7). Densitometric measurements have been suggested in order to overcome the limitations of edge-detection in lesions of complex geometry (including stenosis post-angioplasty and eccentric lesions)[54]. Densitometry, however, requires a homogeneous filling of the

lumen with contrast and a perfect orthogonality of the x-ray beam to the vessel lumen, is highly dependent on the radiographic setting and modalities of film processing and cannot directly provide absolute measurements[55].

Limitations of intravascular ultrasound (Table 2)

Necessity of catheter insertion

Intravascular ultrasound requires the examination with the echo-catheter of the entire vascular segments to be studied. Instrumentation of a coronary vessel is the current practice for all the interventional techniques. However, especially in the examination of the coronary arteries, the insertion of the echo-catheter increases the complexity and duration of the procedure and carries out a potential risk of complications. Recent improvements in catheter flexibility and miniaturization allow the examination of the proximal and middle coronary arteries in most patients. A possible limitation, however, concerns the examination of severe coronary stenosis before interventions, one of the most interesting potential applications of intravascular ultrasound. A quantitative angiographic study of large cohorts of candidates to balloon angioplasty[56] has shown that the measured minimal luminal diameter before balloon dilatation (1.02±0.37 mm) is similar to the diameter of the recently introduced second generation of catheters (from 3.5 to 4.3 French, equal to 1.15-1.4 mm).

The intravascular ultrasound examination is facilitated after successful therapeutic interventions by the increased lumen diameter. However, recrossing large, unstable dissection flaps carries a potential risk of acute occlusion. Furthermore, a correct assessment of the real morphology of a complex spiral dissection and the consequent impairment to blood passage is difficult because it would require a three-dimensional reconstruction of the ultrasonic cross-sections[57,58,59,60,61] and because the communication between true and false lumen are modified by the physical presence of the catheter. Proximal injection of saline or agitated contrast can help in delineating vessel lumen and in detecting the presence of stagnant blood flow. However, an effective injection through the proximal guiding catheter is not always possible while the relatively large ultrasound catheters is still in place. Drop-outs may occur in segments of dissected wall which are explored with an unfavourable angle of incidence of the ultrasound beam[62]. In our experience, such complex artifacts are more frequent in peripheral than in coronary arteries, because in these latter small vessels the physical presence of the ultrasound catheter modifies the orientation of the dissected flap.

The combination of intravascular ultrasound imaging and balloon angioplasty or alternative debulking techniques in the same catheter can facilitate the use of intravascular ultrasound before and after interventions easier and more practical and can allow continuous monitoring and guidance during the procedure. At present, however, only prototypes of catheters for directional atherectomy mounting ultrasound crystals are in the phase of preliminary clinical evaluation

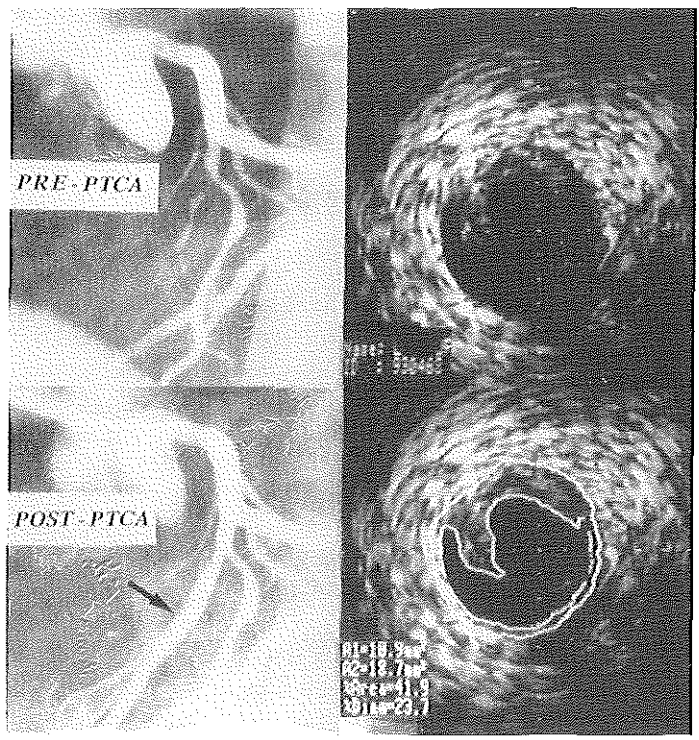

Figure 7.
The upper right panel shows a subocclusive stenosis of the mid segment of the left anterior descending artery with minimal anterograde flow. The lumen enlargement and the normalization of the flow after dilation with a 3.0 mm balloon is evident in the lower right panel, where the arrow indicates a Type B dissection involving also the post-stenotic segment. Note, in the panels of the left, the complex luminal cross-section after balloon dilation. Note that the eccentric plaque has been dissected at the site of its insertion on the normal wall. The complex lumen morphology after angioplasty cannot be correctly measured with angiography, even using multiple angiographic projections. Calibration 0.5 mm.

and in the already available echo-balloon catheters the transducer is mounted proximal to the balloon[63,64]. This configuration maintains a low profile of the balloon and avoids the artifacts induced by the balloon membrane but precludes the possibility of continuous assessment before, during and immediately after balloon dilatation.

Catheter malalignment

A central position of the catheter in the vessel lumen is not frequent in intravascular ultrasound. With a simple eccentricity of the catheter position, the echographic cross-section is still perpendicular to the long-axis of the vessel so that no change in the measured area is expected. When the catheter is not only eccentric but also non-parallel to the long-axis of the vessel the vascular lumen is distorted, with an angle-dependent overestimation of the vascular lumen. In a

tortuous artery the ultrasound catheter can assume an orientation non-parallel to the long-axis of the vessel. Fortunately, the small size of the coronary arteries in comparison the catheter diameter limits the practical relevance of this problem[9].

Non-uniform rotation, near field artifact, inadequate sampling rate
With mechanically rotating catheters, a 1:1 rotation of the ultrasound element (or mirror) can be impossible if the catheter is inserted in very tortuous vessels, resulting in a variable distortion of the ultrasound image. In the multielement systems these artifacts are not present. A limitation of these systems, however, is that the near-field artifact is partially obscuring the structures close to the catheter. Artifacts can also result from the systo-diastolic changes of vascular dimensions or of the position of the catheter inside the vessel throughout the cardiac cycle if a sufficiently high sampling rate is not obtained.

Application of automatic measurements
Sophisticated techniques of edge-detection or videodensitometry have been developed for quantitative angiography[65]. The difference in brightness between the radiographic contrast filling the vascular lumen and the background facilitates the application of the proposed algorithms for computer-assisted automatic contour detection. In intravascular ultrasound, on the contrary, the relatively similar echoreflectivity of blood and of the underlying vessel wall is a potential obstacle to fully automatic measurements of lumen area. Manual redrawing of part of the lumen contours is frequently necessary, resulting in an increase variability of the results of the analysis[66]. A fully automatic technique, based on the measurement of the vessel wall displacement from a semiautomatic defined template image, has been developed at our Institution and is currently used to measure the systo-diastolic changes of vascular dimensions[67] .

Reproducibility of the measurements
Changes in vascular tone, variability of repeated measurements, modifications of radiographic projections and setting, cardiac and respiratory movements influence short- and long-term reproducibility of angiographic measurements, limiting the reliability of angiography in assessing the development of changes in vascular dimensions. Although intravascular ultrasound is less limited by these factors, accurate serial measurements are possible only when the echo-catheter is positioned exactly at the same site in the vessel, a trivial requirement which is practically very difficult to satisfy.

No assessment of blood flow
Various angiographic techniques have been described which use the contrast medium as a marker of flow and calculate relative changes of blood flow based on contrast appearance time and/or on changes in the density of the myocardium[68,69,70]. This principle is not applicable with the current intravascular ultrasound imaging catheters. An alternative ultrasound-based technique is the measurement of the Doppler shift induced by the motion of the red blood cells to

directly calculate blood flow velocity. Prototypes of combined imaging-Doppler catheters have been described[71,72] and Doppler guidewires which can integrate the ultrasound imaging catheters are in current clinical use[73,74,75] (Figure 8).

Conclusions

Intravascular ultrasound can accurately assess luminal dimensions and has potential advantages on quantitative arteriography in the presence of eccentric lesions and lumens of complex geometry. The application of this technique, however, increases duration, risk, complexity and cost of a conventional diagnostic or interventional procedure based on a purely angiographic quantitative assessment. In clinical practice, therefore, it seems unlikely that quantitative arteriography can be replaced by intravascular ultrasound as a routine technique of measurement of luminal dimensions.
Intravascular ultrasound has a potential role as a research tool for the assessment of vessel dynamics and effects of pharmacologic interventions. The information concerning characteristics and composition of the atherosclerotic plaque is not available with angiography and makes intravascular ultrasound potentially more suitable than angiography for the follow-up of interventions aimed at the regression of atherosclerotic lesions. Improvements in catheter technology can make quantitative intravascular ultrasound a valuable tool for the correct planning and guidance of interventional procedures.

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Part II

Intravascular Imaging in the Study of Plaque Morphology

Chapter IV

Ischemia-related Lesion Characteristics in Patients with Stable and Unstable angina: A Study with Intracoronary Angioscopy and Ultrasound

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Abstract

Background

Predominantly post-mortem derived findings support the common belief that 1) lipid-rich coronary plaques with a thin fibrous cap are prone to rupture and 2) rupture and superimposed thrombosis are the major mechanisms causing acute coronary syndromes. In vivo imaging with intracoronary techniques may disclose differences in the characterization of atherosclerotic plaques in patients with stable and unstable angina and thus may provide clues to which plaques may rupture and whether rupture and thrombosis are active.

Methods

We assessed the characteristics of the ischemia-related lesions with coronary angiography and intracoronary angioscopy and determined their composition with intracoronary ultrasound in 44 patients with unstable and 23 with stable angina before angioplasty. The angiographic images were classified as non-complex (smooth borders) and complex (irregular borders, multiple lesions, thrombus). Angioscopic images were classified as either stable (smooth surface), or thrombotic (ulcerated surface with red thrombus). The ultrasound characteristics of the lesion were classified as poorly echo-reflective (representing loose fibrous tissue, necrotic material or lipid), highly echo-reflective with shadowing (representing calcific tissue), and highly echo-reflective without shadowing (representing dense fibrous tissue). Plaque composition was defined as mixed when none of these components occupied more than 75% of the vessel surface.

Results

There was a poor correlation between clinical status and angiographic findings. An angiographic complex lesion (n=33) was concordant with unstable angina in 55% (24/44); a non-complex lesion (n=34) was concordant with stable angina in 61% (14/23). There was a good correlation between clinical status and angioscopic findings. An angioscopic thrombotic lesion (n=34) was concordant with unstable angina in 68% (30/44); a stable lesion (n=33) was concordant with stable angina in 83% (19/23). The ultrasound obtained composition of the plaque was almost similar in unstable and stable patients. Overall there was a poor correlation between the lesion characteristics obtained by angiography, angioscopy and ultrasound. Ultrasound could neither discern plaque rupture or intracoronary thrombosis nor provide information about the thickness of the fibrous cap and presence and size of the lipid pool.

Conclusions

Angiography discriminates poorly between lesions in stable and unstable angina. Angioscopy demonstrates significant differences between lesions in stable and unstable angina. Plaque rupture and thrombosis was present in 17% of stable and 68% unstable angina patients suggesting that this process is a continuum from stable to unstable angina. Possibly in the other one-third of the unstable patients other mechanisms are operative. Currently available ultrasound technology do not discriminate a stable from an unstable plaque.

Introduction

The morphology of coronary atherosclerotic lesions is heterogeneous between and within individuals [1-6]. It is now common belief that acute ischemic syndromes result from a disruption of a lipid rich atheromatous plaque, setting into action a cascade of pathogenic mechanisms such as platelet activation, adhesion and aggregation, increased vasoconstriction and thrombus formation [7-12]. Plaques prone to rupture are lipid-rich and have a thin fibrous capsule [10-12].
In vivo characterization of atherosclerotic lesions in patients with stable and unstable angina is of importance, to better understand the pathogenetic mechanisms operative in an individual patient, and may allow the identification of plaques that have undergone rupture.
Two recently developed intracoronary imaging tools have the potential to provide these insights. Intracoronary ultrasound imaging provides information about size and composition of the plaque [13-15] and intracoronary angioscopy accurately detects the presence of plaque rupture and intracoronary thrombus [16-19].
The purpose of this study was to determine the composition and characteristics of the ischemia-related lesion with the sequential use of intracoronary angioscopy and ultrasound imaging in patients with stable and unstable angina before intracoronary intervention. These findings were correlated with coronary angiographic characteristics.

Patients and methods

Between September 1992 and March 1993 a non-consecutive series of 75 patients who were scheduled for coronary intervention were studied. In one patient the procedure was discontinued because of severe ischemic chest pain after the introduction of the angioscope into the ischemia-related artery. Immediate PTCA was successful without adverse sequelae. In seven patients the angioscope was introduced but the obtained images were of insufficient quality. Thus, the study population comprised 44 patients with unstable angina and 23 patients with stable angina.
The clinical and angiographic data of these patients are presented in Table 1.
The investigations were approved by the Institutional Review Board of the Cardiology Department of the Dijkzigt Ziekenhuis. The patients were studied after informed consent was obtained.

Procedures

Selective coronary angiography in multiple projections was performed before and after angioplasty. All patients received aspirin (250 mg) and intracoronary nitroglycerin before the procedure. They received anticoagulation with heparin, such that activated clotting time was over 300 s.
After passage of a 0.014 in. guide wire across the lesion intracoronary angioscopy was always performed first, and there after intracoronary ultrasound imaging. In all instances an attempt was made to cross the lesion with both devices to obtain

information about the entire lesion.
Coronary angioplasty or other interventional techniques were used according to standard practise.

Table 1. Baseline patient and angiographic characteristics

	Unstable angina (n=44)	Stable angina (=23)
Male/female (N)	40/4	19/4
Age, mean (yrs)(range)	60 (49-71)	51 (39-69)
Previous MI (<14 days) (N)	17	0
Multivessel disease (N)	15	5
Premedication (N):		
Heparin/Aspirin	44/23	0/6
Systemic thrombolysis	7 (all post-MI)	none
Nitroglycerin i.v./oral	39/0	0/21
Calcium channel antagonists	34	21
Beta-blockers	34	21
Time from onset instability (days)	14 ± 14	---
Ischemia-related lesion		
LAD/RCA/CX/SVG	19/16/6/3	15/3/4/1
Minimum luminal diameter (mm) *	1.05 ± 0.42	1.13 ± 0.57
Reference diameter (mm) *	3.2 ± 0.72	3.12 ± 0.49
Complex lesion (N)	24	9

* mean ± 1 SD, determined with quantitative angiography
MI, myocardial infarction; i.v. intravenous; LAD, left anterior descending artery; RCA, right coronary artery, CX, circumflex artery; SVG, saphenous vein graft.

Selection of ischemia-related lesion
In patients wit single vessel disease the most severe lesion within that vessel was considered the ischemia-related lesion. In patients with multivessel disease and unstable angina the selection was determined by the combination of electrocardiographic localization indicated by transient ST-T segment changes occurring during ischemia, at rest and the closest corresponding coronary vessel containing the most severe lesion.

Angiography
A modified classification of angiographic morphology proposed by Ambrose et al. [20] was used to categorize each target lesion as non complex (concentric or eccentric with smooth borders) and complex (eccentric with irregular borders or

overhanging edges; multiple irregularities or intraluminal filling defects).
Quantitative coronary angiography was performed with the CAAS-2 system (PIE Data, Maastricht, The Netherlands) using the non contrast-filled catheter as calibration [21].

Imaging Devices
The percutaneous coronary angioscopic device used is a monorail type polyethylene catheter device, which has a size of 4.5 F and which is accommodated by a 8 F guiding catheter (Baxter Edwards; Irvine California).
Ultrasound imaging was performed with a commercially available intracoronary 4.3 F, 30-MHz ultrasound catheter (Cardiovascular Imaging Systems Inc., Sunnyvale, Calif).
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. This provided a better orientation of where the angioscopic and the ultrasound images were derived from within the coronary tree.

Table 2: Angioscopic characteristics of ischemia-related lesions

	Unstable angina (n=44)	Stable angina (n=23)	p value
Thrombus (N)	30 (68%)	4 (17%)	$p < 0.001$
Occlusive	2	0	
Protruding	8	1	
Mural	20	3	
Surfce lesion (N)			
Ulcerated	20	3	$p < 0.05$
Rough	11	6	
Smooth	13	14	
Yellow plaque (N)	29 (66 %)	16 (69%)	
Thrombotic Lesion (N)	30 (68%)	4 (17%)	$p < 0.01$

Analysis of angioscopic and ultrasound images
Qualitative analysis of both angioscopic an ultrasound images was performed by consensus of three observers with no access to clinical records or cinefilm during assessment. *Thrombi* were defined as a red, intraluminal mass adherent to the intima. Thrombi were categorized as *non-mural* (closely adherent to the vessel wall), *mobile-protruding* into the lumen or totally *occlusive. Yellow plaques* were defined as areas of homogeneous yellow colour clearly identifiable from the normal wall. Wall surface was classified as *ulcerated* when major disruption of the plaque was found. When ulceration was absent but wall irregularities were noted, the surface was classified as irregular. Finally, when none of these alterations was

present and the wall presented the characteristic pattern noted in normal non-stenotic segments the surface was classified as smooth.
Angioscopic images of lesions were classified as *thrombotic lesion* if they have an irregular ulcerated raised surface with presence of thrombus or as *stable lesion* if the raised surface was regular and smooth, without thrombus. The composition of the ischemia-related lesion was classified as poorly echo-reflective or highly echo-reflective intimal thickening (Figure 1). The last was further sub-dived according to the presence or absence of acoustic shadowing. An intimal thickening was considered poorly echo-reflective if the echodensity was less than that seen for the adventitia and highly echo-reflective if the echodensity was equal or greater than that of the adventitia.

Table 3. Intracoronary ultrasound characteristics of ischemia-related lesions

	Unsable angina (n=44)	Stable angina (n=23)
Echo-reflectivity of plaque		
Homogeneous type * (N)	24 (55%)	15 (65%)
Poor	22	14
High without shadowing	1	0
High with shadowing	1	1
Mixed type (N)		
Poor / High without shadowing	2	2
Poor / High with shadowing	18	6
Calcium present ** (N)		
Focal (30-90°)	5	1
Moderate (90-180°)	14	5
Diffuse (>180°)	1	1
Eccentric plaque (index <0.5)	27 (61%)	13 (56%)
Extent plaque (mm2)	15.2 ± 5	17.0 ± 5

* Homogeneous if the plaques induces > 75% of one type of echo-reflectivity.
** Distribution of calcium was classified according to number of degrees of vessel circumference.

The results of previous comparisons between histology and ultrasound have shown that poorly echo-reflective intimal thickening correspond to loose fibrous tissue, lipid and thrombus while highly echo-reflective intimal thickening without shadowing represents dense fibrous tissue and highly echo-reflective intimal thickening with acoustic shadowing indicate calcium deposition [14,22,23]. The concentricity versus the eccentricity of the plaque was determined by the ratio between thinnest and thickest part of the intimal thickening. Eccentricity was defined by a ratio less than 0.5

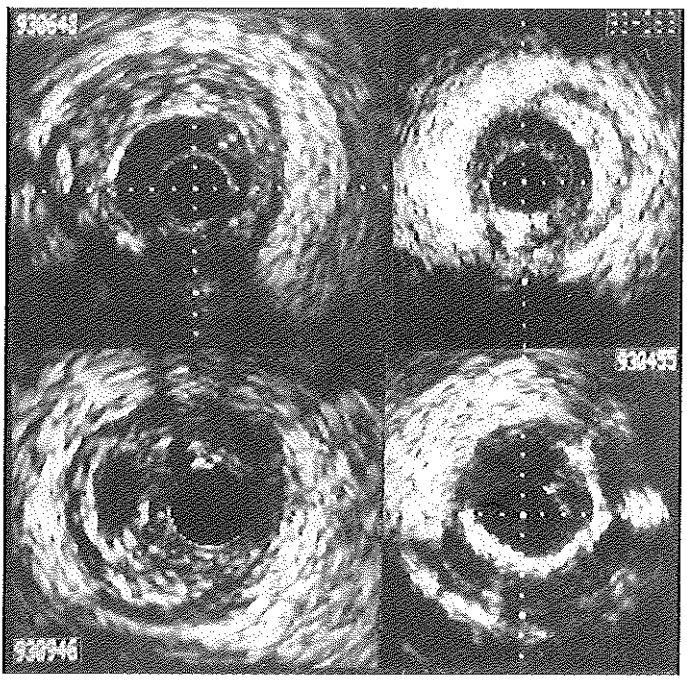

Figure 1.
Examples of plaque composition with ultrasound. Top left, example of a soft plaque, Top right, a fibrous (hard) plaque, Bottom left, a soft plaque. Note at nine o'clock the presence of a lipid pool. Bottom right, a calcific plaque. Note the superficial location of the calcium .

A lesion was considered *homogeneous* if the plaque consisted of > 75% of one type of echoreflectivity induced by the lesion determined from an integrated pull-back image of the entire lesion. A lesion was considered predominantly *calcific* if calcium occupied >180 degrees of the vessel circumference. A lesion was defined *mixed* if the lesion contained both highly and poorly echo-reflective areas, occupying > 25 % of the plaque surface or, if calcium deposits occupying more than 30 degrees and less than 180 degrees of the vessel circumference were present. The intergroup observer variability performed in a random sample of 30 patients for angioscopic image classification yielded Kappa values for presence of thrombus 1.0, protruding or mural 0.78, surface of lesion 0.80, yellow plaque 0.93 and thrombotic lesion 0.94. The Kappa-values for ultrasound classification of echo-reflectivity of lesions ranged from 0.85 (calcium present) to 1.0 (homogeneous vs. mixed type).
Quantitative measurements were obtained from a cross-sectional image taken at the narrowest part of a lesion. *Total vessel area* was defined the area central to the ultrasound-defined boundary between adventitia and media-intima thickening. *Lumen area* was defined as the area central to lumen-intimal boundary. *Plaque area* was calculated as the difference between total vessel area and lumen area. The mean difference of the measurements of 30 lesion lumen areas and 30 plaque areas and interobserver variability obtained by two independent investigators was

0.02 ± 0.37 mm2 (R=0.97) and 0.03 ± 0.0.62 mm2 (R=0.99) respectively.

Statistical analysis
All measurements are represented as mean ± standard deviation. The unpaired T-test, the chi-square test with Yates correction, and the Fischer-exact test were used when appropriate. A p value < 0.05 was considered statistically significant. The interobserver variations were assessed with the use of unweighed kappa coefficients (24).

Table 4. Correlation between angiographic, angioscopic and ultrasound findings of lesions in patients with stable and unstable angina.

	Unstable angina (n=44) Angiographic lesion		Stable angina (n=23) Angiographic lesion	
	non-complex (n=20)	complex (n=24)	non-complex (n=14)	complex (n=9)
Angioscopic lesion (N)				
Thrombotic	13	17	2	2
Stable	7	7	12	7
Ultrasound lesion				
Poorly echo-reflective	7	15	10	5
Highly echo-reflective	1	0	0	0
Highly echo-reflective with shadowing	1	0	1	0
Mixed composition	11	9	3	4

Results

Procedures
Passage of the imaging catheters through the ischemia-related lesion was obstructive to blood flow and associated with chest pain and electrocardiographic ST-T segment changes in almost all patients. These changes were quickly reversible after withdraw of the catheter, except in two patients in whom abrupt occlusion occurred at the site of the ischemia related lesion. This was effectively treated with balloon angioplasty. The angioscope caused a small non-occlusive dissection in one patient. Subsequent balloon angioplasty resulted in an occlusive dissection which was effectively managed by stent implantation.
In four patients the culprit lesion was too tight to allow crossing of the angioscope and the observations were restricted to the proximal aspect of the stenosis. In the two patients in whom the lesion could not be crossed with the ultrasound probe,

the plaque composition was taken from post angioplasty examination.

Lesion characteristics

The angiographic and intracoronary angioscopy findings and ultrasound characteristics of the ischemia-related lesions are shown in Tables 1, 2, and 3. An

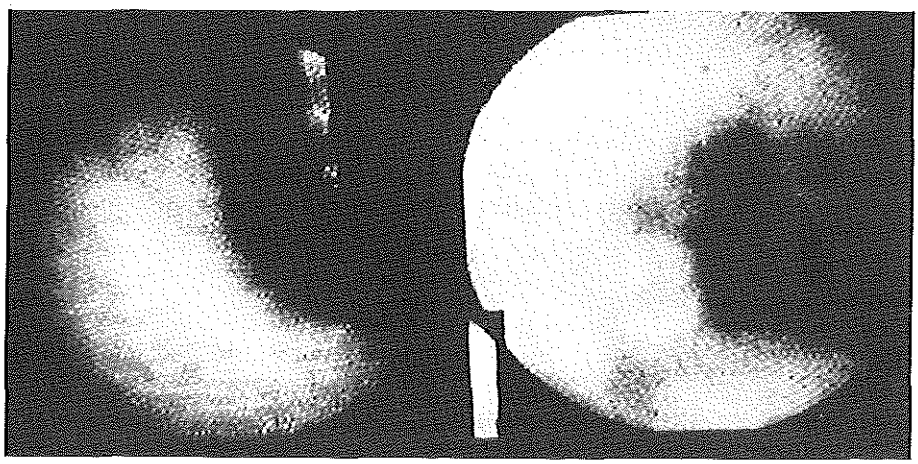

Figure 2.

Stable lesion (left) with smooth, white surface. Thrombotic lesion (right) with disrupted surface and red thrombus.

angiographically complex lesion was present in 39% of the stable patients and in 55% of the unstable patients. An angioscopically thrombotic lesion (Figure 2) was present more often in unstable angina, than in stable angina (68% vs. 17%, $p < 0.01$). The presence of a yellow plaque (containing lipids) was similar in both groups. The presence of wall disruption or ulceration of complex lesions was not detectable with ultrasound. The composition, the presence and distribution of calcium, the eccentricity and extent of the plaque were almost similar in unstable and stable angina patients.

Correlations between clinical, angiographic, angioscopic and ultrasonic lesion characteristics

In Tables 4 and 5 the correlation between the findings of angiography, angioscopy and ultrasound of the ischemia-related lesions in patients with stable and unstable angina are presented. It appears that the clinical syndrome and angiographic findings were poorly correlated. An angiographic complex lesion (n=33) or non-complex lesion (n=34) was concordant with unstable angina (n=44) or stable angina (n=23) in 55% (24/44) and 61% (14/23) respectively (Table 4). An angioscopic thrombotic lesion (n=34) or stable lesion (n=33) was concordant with unstable or stable angina in 68% (30/44) and 83% (19/23) respectively (Table 4). There was no significant correlation between the lesion characteristics obtained with angiography, angioscopy and ultrasound (Table 4 and 5). An angiographic complex lesion (n=33) or non-complex lesion (n=34) was concordant with an

angioscopic thrombotic lesion (n=34) or smooth lesion (n=33) in 58% (19/33) and 56% (19/34) respectively (Table 4).
Ultrasonic defined lesion characteristics were almost equally represented between angiographically complex and non-complex lesion (Table 4) and also between angioscopic thrombotic and stable lesions (Table 5).

Discussion

Individual atherosclerotic lesions have a striking heterogeneity in both their composition and appearance. Predominantly based on postmortem studies much evidence has been accumulated showing that acute ischemic syndromes are associated with plaque fissuring and superimposed thrombosis [7-12]. Clinical angioscopic studies have confirmed the presence of an intracoronary thrombus [16-19]. Recently, Davies et al. [12], performed an elegant postmortem study of aortic plaques from men who died suddenly. They emphasized the importance of the volume of a central lipid pool in plaques that had undergone thrombosis. The size of the extracellular lipid pool exceeded 40% of the cross sectional area of 91% thrombosed plaques, whereas this occurred in only 3.2% of non-thrombosed plaques. Ample evidence has emerged indicating that lipid-rich atheromatous plaques which have a thin, fibrous capsule are prone to plaque fissuring [1,12]. Clearly, it would be of great importance if we were able to identify, in vivo, plaques prone to fissuring. In-vitro pathological studies have shown that intravascular ultrasound imaging has the potential to visualize the fibrous cap and allows acoustic characterization of the composition of a coronary plaque, including calcium, dense fibrous tissue, loose fibrous tissue, intimal hyperplasia and extracellular lipid [14,22,23].
Currently, the experience with intracoronary ultrasound to characterize the composition of coronary lesions in patient studies is limited. Hodgson et al. [15] performed a morphometric analysis of the ultrasound images obtained from ischemia-related lesions in patients with unstable and stable angina. They found that patients with unstable angina had more often poorly echo-reflective lesions and less severe calcific lesions or intraluminal calcium deposits. We could not confirm these findings and we found that the composition of stable and unstable plaques was nearly identical. The discrepancy between the findings in both studies may be explained by differences in image quality. The mechanical system used in this study has a higher dynamic range and resolution. However, the ultrasonic findings should be interpreted with caution because, although poorly echo-reflective lesions are thought to represent lipid-containing lesions, ultrasound imaging systems at present cannot distinguish between loose fibrous tissue, lipid-rich lesions and thrombus.

Our angioscopic findings are in agreement with previous angioscopic studies [16-19] and demonstrate that thrombus and ulcerated plaques are present in two-thirds of the cases. An interesting question arise to why we did not observe the presence of

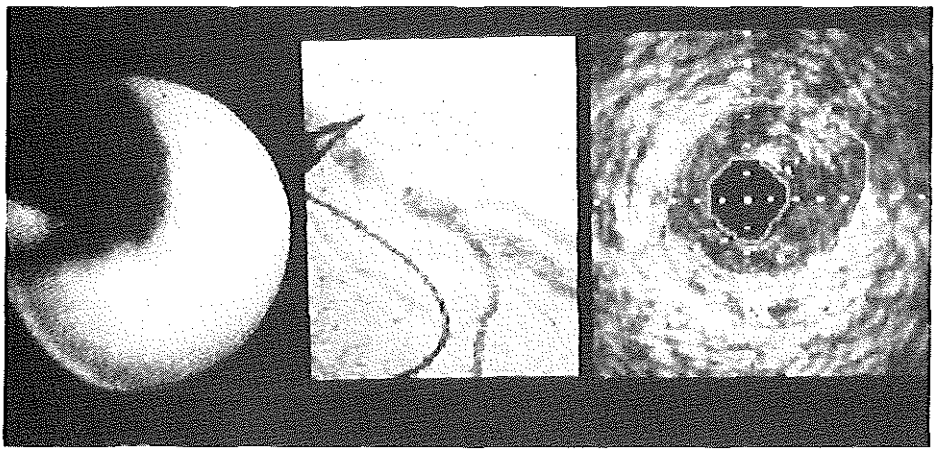

Figure 3.
An example of a good concordance between the three imaging techniques in a patient with stable angina. With angioscopy (left) we may observe a smooth, round yellow lesion; with angiography (center) a concentric lesion with regular borders and with ultrasound (right) a soft plaque.

thrombus in the other one-third of the unstable patients. Several reasons may explain this. The intensive premedication with heparin and aspirin and the time interval between last symptoms and examination may have induced dissolution of thrombus and wall repair. The plaque disruption may have been small and associated with only a small thrombus, difficult to be seen with angioscopy or located in a segment not completely explored with angioscopy. The thrombus may have been dislodged by the catheter, or may have been flushed away into the distal part of the vessel. Another interesting possibility is that our angioscopic observations were correct and that alternative mechanisms other than plaque rupture and thrombosis, such as vasospasm or the recently suggested possibility of smooth muscle cell proliferation with plaque expansion causing luminal narrowing [25]. Of note is also that rupture and thrombosis were observed in 17% of the patients with stable angina. This observation has not been made by other investigators in their patients with stable angina [16-18]. These findings suggest that rupture and thrombosis does not always lead to the clinical manifestation of an acute coronary syndrome. Unfortunately, the resolution of ultrasound imaging is insufficient to reliably visualize a rupture of the plaque; possibly because plaque ruptures are much less smaller than larger dissections after coronary angioplasty which are reliably detected with ultrasound.

We found that approximately two-third of the lesions in patients with stable and unstable angina were yellow. The yellow colour of a plaque is caused by lipid that contains carotene. It should be appreciated that a white plaque may also contain lipid, because cholesterol is white and does not always contain carotene.

Limitations of this study

The study group consists of non-consecutive series of patients, which may have introduced a bias. This study was performed in a subset of patients having angina at rest, or early post-infarction angina, selected for balloon angioplasty, and thus precludes generalization of these findings to all patients with unstable angina.
Unstable angina pectoris is a dynamic process with different pathophysiologic mechanisms waxing and waning over time. Any study therefore represent a snapshot and certain processes may have been missed. Only monitoring during a longer period would resolve this problem.
Currently available imaging devices are yet still bulky and stiff. In few cases the ischemia-related lesions could not be crossed, or could not be completely imaged due to the curvature of the vessels so that entire interrogation of the lesions was not possible and certain lesion characteristics may have been missed.
Even, after crossing the lesion, certain aspects may escape detection because current angioscopic design does not include a flexible, steerable tip so that the entire surface area cannot always be inspected. Structures lying behind calcific lesions cannot be detected with ultrasound because the plaque prevents penetration of the ultrasonic beam. Also, the wire and strut artefact which is present with 4.3 F ultrasound catheter may introduce incomplete visualization of the plaque.

Conclusions

Sequential imaging of the ischemia-related lesion with intracoronary angioscopy and ultrasound is feasible, and safe in patients undergoing coronary intervention. The obtained information is complementary to coronary angiography. Integration of the three imaging modalities provides clinically valuable information about the major mechanism responsible for myocardial ischemia and thus may improve patient management. Both intracoronary imaging techniques do not allow identification of a lipid-rich plaque with a thin fibrous cap known to be prone to rupture.
Thirty megahertz ultrasonic imaging does not yield enough resolution to accurately detect plaque composition. Improvement of the quality of intracoronary ultrasound images is necessary to accurately provide the desirable information on the size of the volume of the extra-cellular lipid pool, the thickness of the fibrous cap or the location and depth of a fissure of the cap [26].

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Chapter V

The Cause of Coronary Luminal Obstruction in Unstable Angina Refractory to Medical Treatment: Insights from Angioscopy and Directional Atherectomy

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Abstract

Background

Coronary angioscopy constitutes a potential tool in determining which is the predominant cause of coronary obstruction in unstable patients refractory to medical treatment.

Aim of the study

To investigate with intracoronary angicoscopy the characteristics of the culprit lesion of primary or post-infarction unstable angina pectoris refractory to medical treatment, and to establish the relationship between the obtained visual findings with coronary angiography and histopathological characteristics of retrieved atherectomy specimens.

Methods

Angioscopy was performed in 41 patients at the time of percutaneous recanalisation. In all cases visual findings were classified objectively, without making a translation to histological terms. In 9 (22%) examination of tissue samples obtained during directional atherectomy possible the correlation between histopathological and angioscopic features. Quantitative angiography and classification of angiographic morphology was performed in all cases and correlated with angioscopic findings.

Results

Red material was seen in 25 (60%) cases, more frequently in patient with post-infarction angina (13/17, 76%) than in primary unstable angina (12/ 24, 50%), and protruded significantly in the lumen in 7 (41%) patients with postinfarction and in 3 (12%) with primary unstable angina. Atherectomy specimens revealed the presence of red thrombus. The protrusion of red material correlated significantly with a lower minimal luminal diameter (0.55±0.56 mm versus 1.11±0.42 mm in stenoses with and without protruding red material, p=0.009) and greater percent diameter stenosis (79±19 % versus 64±15% in stenoses with and without protruding red material, p=0.04). Conversely, the angiographic morphology correlated poorly with the presence of red material during angioscopy (15/21, 71%, with and 10/20, 50%, without complex angiographic morphology (p=NS). Xanthomatous plaques presented more frequently in patients with postinfarction (10/17, 58%) than in unstable patients (5/24, 21%) (p = 0.02), frequently in association with red material (13/15, 87%, versus 2/15, 13%, in stenosis with and without red material respectively, p=0.02), and were associated with deposits of cholesterol crystal clefts in 2 atherectomy specimens. Pink areas were identified in 12 (50%) and 2 (12%) patients with unstable and post infarction angina respectively (p = 0.03). White-gray protruding masses were observed more frequently in unstable (8/24, 33%) than postinfarction patients (3/17, 19%), with 2 atherectomy specimens revealing fibrin-rich and organising thrombus. Finally, an stenotic vessel wall with normal coloration was found in 4 (10%) cases, 3 of which showing an smooth surface and 1 evidence of wall disruption.

Conclusions

These observations provide information as to the cause of luminal obstruction in unstable patients refractory to medical treatment that may be relevant for the formulation of therapeutic strategies.

Introduction

The understanding of the pathological substrate of acute coronary syndromes has been based largely on post-mortem studies of coronary arteries.[1-4] These studies have suggested that sudden disruption of the atheromatous plaque is the common initiating factor of myocardial infarction, primary unstable angina and sudden death, through the onset of several pathogenic mechanisms such as platelet activation, adhesion and aggregation, vasoconstriction and thrombus formation.[5,6]

In spite of the considerable knowledge accumulated on these pathophysiological mechanisms, the management of primary unstable and post-infarction angina pectoris still presents a major therapeutic problem.[7,8] Conventional diagnostic tools provide no direct insight on which pathogenic mechanism is operative or prevails in an individual patient presenting with unstable symptoms. This may partly explain the refractoriness to conventional treatment. Furthermore, it is possible to speculate that some of the pitfalls in the pharmacological treatment of unstable angina are due to incomplete understanding of a continuously evolving pathological substrate.

Percutaneous angioscopy constitutes a unique tool in the study of the coronary syndromes, by facilitating direct visualization of changes taking place in the luminal environment of the culprit stenosis.[9-13] Previous angioscopic studies[11,12] have identified marked differences in the characteristics of the culprit lesion in stable and unstable patients. However, these studies have been focused on changes at the time of the initial clinical presentation, which may be substantially different from those found in patients in whom medical treatment has proved ineffective. Furthermore, a common bias of these studies has been the direct translation of visual findings to pathological terms by the investigating cardiologist.

In the present study we investigated the angioscopic substrate of patients presenting with refractory unstable angina with or without a history of recent myocardial infarction. Visual findings were objectively classified according to chromatic and morphological characteristics, and conclusions on the corresponding pathological substrate were drawn from histological study of atherectomy specimens obtained in a representative sample of the study population.

Patients and methods

During the period between September 1992 and May 1993 percutaneous coronary angioscopy was performed in 41 patients presenting initially with primary unstable angina (class IIB and IIIB in the classification proposed by Braunwald[14]) or postinfarction angina (class IIIC in the same classification).[14] In all cases the patients were receiving intravenous heparin and nitrates since the date

of admission. In 6 cases (15%) systemic thrombolysis had been performed. In addition, all patients were receiving oral antianginal medication, consisting of beta blockers, calcium antagonists or a combination of both. Catheterization was performed with a view to coronary intervention due to persistent clinical evidence of myocardial ischaemia. The investigations were approved by the Institutional Review Board of the Cardiology Department of the Dijkzigt Ziekenhuis and the

Table I. Baseline characteristics of 41 patients

n= 41	
Age (years)	59±10
Male sex	33 (80%)
Time from onset of syndrome (days):	
-Unstable angina	18±16
-Post-infarction angina	15±15
Ischemia-related vessel :	
-RCA	17 (41%)
-LAD	15 (36%)
-LCX	9 (23%)
Reference diameter (mm)	3.15±0.71
Minimal luminal diameter (mm)	0.98±0.51
% diameter stenosis (%)	67±16
Complex angiographic morphology	21 (51%)
Multivessel disease	9 (23%)
Prior coronary intervention	3 PTCA, 2 DCA
Thrombolysis	6 (35 % of all post MI)

RCA: right coronary artery; LAD: left anterior descending coronary artery; LCX: left circumflex coronary artery; MI: myocardial infarction.

patients were studied only after giving informed consent.

Procedures

Selective coronary angiography in multiple projections was performed before and after intervention. All patients received aspirin (250 mg) and i.c. nitroglycerin before the procedure and were on optimal anticoagulation with heparin, with an activated clotting time was over 300 seconds. During the procedure patients received intravenous diazepam. After passage of a 0.014 in. guide wire across the culprit lesion, coronary angioscopy was performed. In all cases an attempt was made to cross the lesion with the angioscope to obtain information from both the proximal and distal aspect of the lesion. Following angioscopy, balloon angioplasty (n=32) or

directional coronary atherectomy (n=9) were performed according to standard practice.

Selection of ischemia-related lesion

Culprit lesion was selected as follows: in cases with single vessel disease the most severe lesion within that vessel was selected; in cases with multivessel disease the selection was determined using angiographic and electrocardiographic criteria, including the location of transient ST-T segment changes in the electrocardiographic leads occurring during ischaemia at rest.

Angiography

Luminal dimensions at the stenotic and reference segment were obtained with quantitative coronary angiographic analysis, which was performed using the CAAS Mark II system,[15,16] which constitutes the latest generation of a previously validated system.[17] Qualitative information was also recorded according to a modification of the angiographic classification of lesion morphology proposed by Ambrose et al.[18] Complex lesion morphology was recorded when eccentric lesions with ragged or overhanging edges were present, or when intraluminal filling defects were noted.

Angioscopic device

The angioscope used was a 4.5 Fr polyethylene monorail catheter (Baxter-Edwards, Irvine, California). The catheter features a compliant occlusive cuff, a flush port, guidewire compatibility and a movable optical bundle with a depth of field > 1 mm and an excursion capability of 5 cm. In order to keep a uniform color temperature in the light source, light intensity is modified by the use of a diaphragm. Thus, artificial variations in the observed colors were minimized. To facilitate the review process of the obtained images, real-time fluoroscopy or cineangiography was recorded simultaneously with angioscopic images using a digital videomixer. This provides a better estimation of the location of the angioscope within the coronary tree.

Analysis of angioscopic images

All images were analysed off-line by three independent interventional cardiologists familiar with coronary angioscopy. In addition, the films were reviewed by an independent cardiovascular pathologist blinded to clinical, angiographic and pathological data. At the site of the stenosis the arterial wall was classified as disrupted (loss of continuity in the arterial wall), irregular (rough surface with wall integrity preserved), or predominantly smooth surface. The presence of red material was recorded, and classified as mural (lining the arterial wall but without significant protrusion in the lumen) or occlusive (accounting for a significant obliteration of the arterial lumen during angioscopy). White protruding masses were recorded independently. The presence of pink areas in the arterial wall or on the surface of a white protruding mass was also recorded. Yellow plaques were defined as areas of homogeneous yellow color clearly identifiable from a

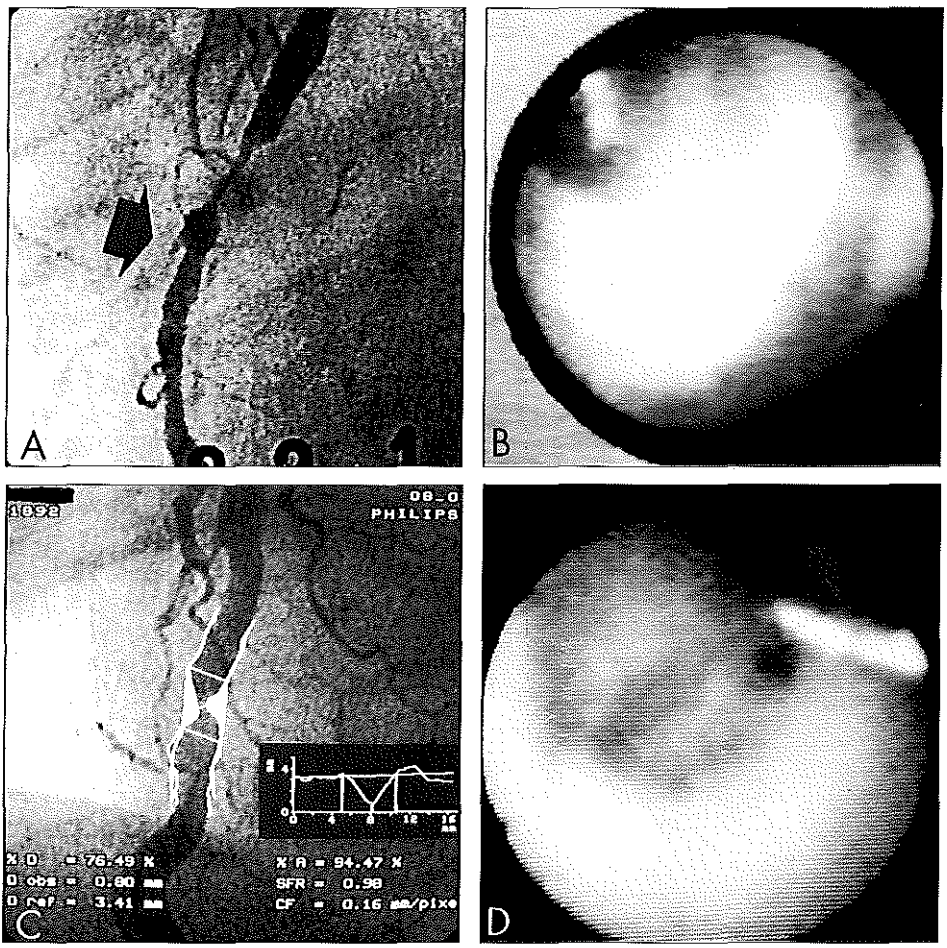


Figure 1

Red material in as visualised by angioscopy in 2 patients with primary unstable angina and a culprit stenosis located in the mid right coronary artery. A: Coronary arteriogram showing an eccentric lesion with an overhanging edge in its distal aspect (arrow). B: Angioscopy revealed that the latter was due to vessel wal disruption, with underlying mural red material. C: On-line quantitative angographic analysis of a concentric stenosis. D: A protruding reddish mass, clearly distinguishable from the vessel wall, became evident during angioscopy.

neighboring area of normal white wall.

Histopathological studies of atherectomy specimens

In the 9 cases undergoing directional coronary atherectomy the obtained specimens were removed from the atherocatheter, flushed with saline, examined macroscopically and then fixed in 10% formalin. Routine processing for light microscopy and haematoxylin-azophloxin and Verhoeff-van Giesson staining was performed. All specimens were reviewed by two independent observers who were

blinded to clinical data. The recommendations layed out in the American Heart Association Medical/Scientific Statement on the Definition of the Intima of Human Arteries and of its Atherosclerosis-Prone Regions[19] were followed in collecting information regarding intimal constituents. 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. Calcifications and lipid deposits such as cholesterol crystal clefts or foam cells were separately recorded independently. No special staining was used to identified calcium. Thrombus and / or intraplaque hemorrhage were identified as amorphous material, in close apposition with atheromatous material, frequently showing collections of leucocytes between layers of fibrin. Large masses of fibrin that might correspond to platelet-rich thrombus and were unlikely to be solely related to the atherectomy procedure were recorded. The Verhoeff-van Giesson staining was used to discriminate between fibrin and dense collagen. Organisation was judged when infiltration by cellular elements, e.g. smooth muscle cells, fibroblasts, capillary sprouts, was observed.

Statistical analysis

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

Results

The baseline characteristics of the 41 patients included in the study are shown in Table I. In 35 (85%) cases the entire target stenosis was satisfactorily visualised by angioscopy, while in the remaining 6 (15%) the stenosis was not crossed with the angioscope and only the proximal aspect of the stenosis was visualised. The introduction of the angioscope at the ischemia-related lesion was associated with chest pain and electrocardiographic ST-T segment changes in 33 cases (80%). These changes were quickly reversible after cuff deflation and withdrawal of the catheter, with the exception of two patients (4%) in whom abrupt coronary occlusion developed. This was effectively treated by balloon angioplasty, without adverse sequelae. In a third patient a small non-occlusive dissection was noted immediately after angioscopy. Subsequent balloon angioplasty resulted in occlusive dissection, which was effectively managed by stent implantation. Finally, in a fourth patient with post-infarction angina, an occlusive dissection in the right coronary ostium, unrelated to angioscopy, was caused during the removal of the

atherectomy guiding catheter, following a technically successful procedure in a mid right coronary artery stenosis. This was complicated by re-infarction (max. CK 600 U/l) which was treated conservatively.

Angioscopic characteristics of the culprit lesion.

In all cases visualization of ≥2/3 of the circumference of the inner vascular wall was achieved. Vessel wall disruption, suggesting ulceration, was identified in 27 (66%) patients. The stenosis presented an irregular surface in a further 8 (19%) patients. In the remaining 6 (15%) patients the stenotic wall was smooth, without disruption or marked irregularities.

Red material (Fig. 1) was seen in 25 (60%) of all cases, more frequently in postinfarction (13/17, 76%) than in primary unstable angina (12/ 24, 50%), although this difference did not reach statistical significance. The presence of red material was not influenced by the time elapsed from the beginning of the syndrome to angioscopy: 15±17 days versus 18±13 days in stenosis with and without red material, respectively. Red material was occlusive in 7 (41%) patients with postinfarction and in 3 (12%) with primary unstable angina (p=NS). The protrusion of red material correlated significantly with a lower minimal luminal diameter (0.55±0.56 mm versus 1.11±0.42 mm in stenoses with and without protruding red material, p=0.009) and greater percent diameter stenosis (79±19 % versus 64 ±15% in stenoses with and without protruding red material, p=0.04) measured with quantitative angiography. The prevalence of red material was significantly related to the angioscopic characteristics of the vessel wall, being present in 19 (70%) of the cases with disrupted, 5 (62%) of the lesions with irregular , and 1 (17%) of the lesions with smooth vessel wall (p=0.05). Conversely, there was no statistical relationship between the existence of a complex angiographic morphology and the presence of red material during angioscopy, the latter observed in 15/21 (71%) lesions with and 10/20 (50%) without complex angiographic morphology (p=NS).

Xanthomatous plaques presented typically as discrete raised plaques with a marked homogeneous yellow color, suggesting the existence of a very thin fibrous cap (Fig. 2A). They were identified in 15 (37%) of all patients, and presented more frequently in patients with postinfarction (10/17, 58%) than in unstable patients (5/24, 21%) (p = 0.02). Yellow plaques were found more frequently in stenoses containing red material (13/15, 87%, versus 2/15, 13%, in stenosis with and without red material respectively, p=0.02).

Pink areas were identified in 12 (50%) and 2 (12%) patients with unstable and post infarction angina respectively (p = 0.03). White-gray protruding masses (Fig. 1B) were observed more frequently in unstable (8/24, 33%) than postinfarction patients (3/17, 19%), although the difference was not statistically significant. In 4 cases (10%) a white protruding mass was seen in a stenosis containing also red material (3 unstable and 1 post-infarction patients). Finally, stenotic vessel wall

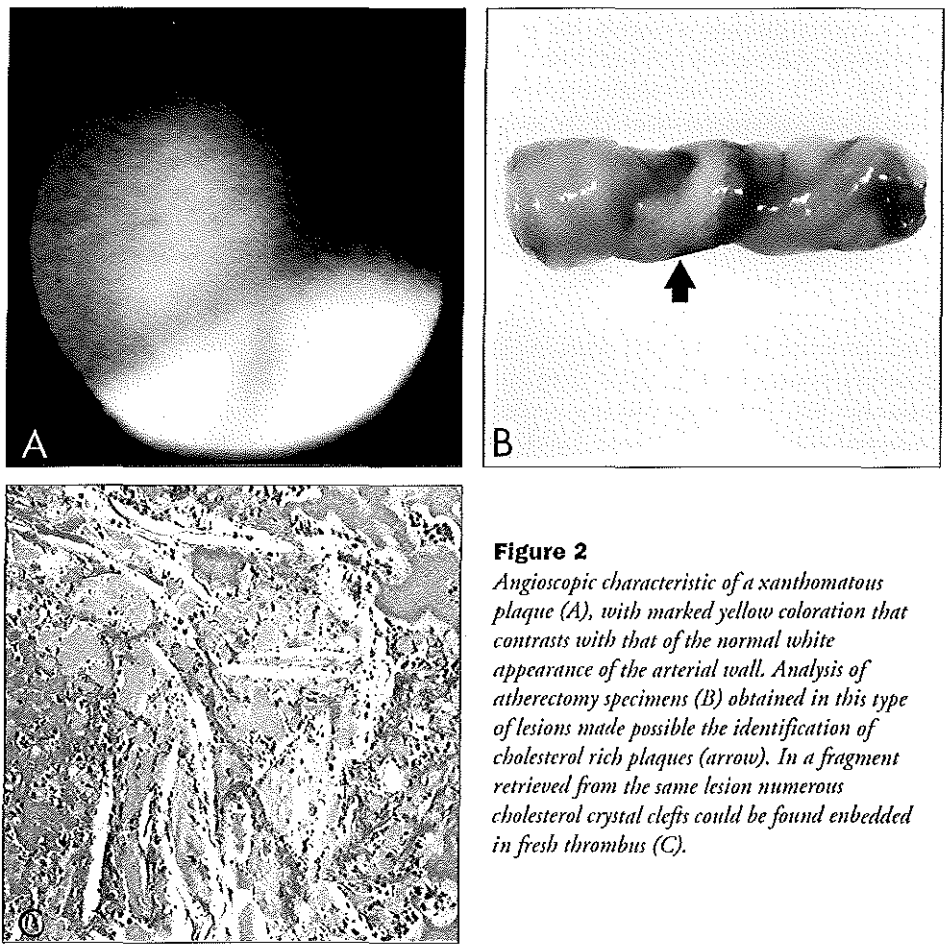


Figure 2
Angioscopic characteristic of a xanthomatous plaque (A), with marked yellow coloration that contrasts with that of the normal white appearance of the arterial wall. Analysis of atherectomy specimens (B) obtained in this type of lesions made possible the identification of cholesterol rich plaques (arrow). In a fragment retrieved from the same lesion numerous cholesterol crystal clefts could be found enbedded in fresh thrombus (C).

with normal coloration was found in 4 (10%) cases, of which 3 showed smooth surface and 1 showed evidence of wall disruption.

Prevalence of red material after thrombolysis
In the postinfarction angina group, 6 patients had received systemic thrombolysis 9±7 days before angioscopy. No significant differences with regard to the presence of red material were noted when this group was compared to the other 11 patients with postinfarction angina who did not receive thrombolysis, showing a prevalence of 4/6 (66%) in patients with and in 9/11 (82%) without prior thrombolysis. Likewise, thrombolysis did not influence the degree of luminal occlusion caused by red material, which was occlusive in 2/4 (33%) and 5/11 (45%) cases with and without previous thrombolysis respectively (p=NS). In one additional patient intracoronary thrombolysis was performed after coronary angioscopy demonstrated total luminal obstruction by red material. Using the

distal lumen of the angioscope, the thrombolytic agent (rTPA) was introduced to the space existing between the occlusion and inflated proximal cuff, in an attempt to increase the concentration of lytic agent in contact with the thrombus (Fig. 4A). After 20 minutes, coronary angiography revealed incomplete coronary recanalisation, while angioscopy showed a substantial change in the color of the previously red material, which now presented several mobile structures of pinkish color which had been covered by the red occlusive mass and which remained unlysed during further observations (Fig. 4B). Subsequent balloon angioplasty yielded an optimal result, with complete restoration of antegrade blood flow through the stenosis.

Analysis of atherectomy specimens

Directional atherectomy was performed in 9 cases (22%), each yielding pathological specimens. Macroscopic examination of the specimens allowed identification of several features visualized during angioscopy. The correlation between histopathological and angioscopic findings in these 9 patients is summarized in Table II. Histopathological analysis of the material retrieved in all 5 stenosis containing red material showed fresh red thrombus (Fig. 2). In three of these patients the presence of a xantomatous plaque had been reported by angioscopy (Fig. 2A). The retrieved material demonstrated the presence of numerous cholesterol crystal clefts with inflammatory cells, associated with fresh red thrombus (Fig. 2C) in two cases, suggesting that extrusion and exposure of lipid material to the bloodstream was the precipitant cause for coronary thrombosis. Directional atherectomy was not performed in any of the cases where pink areas had been visualized. Coronary samples were obtained from two lesions with white-gray protruding masses. Microscopic examination revealed the presence of a large fibrinous mass in one case, and organizing thrombus in the other (Fig. 3B). Finally, atherectomy was performed in one case with a normal-coloured stenotic wall, with the specimen showing the presence of dense fibrous tissue and neointimal hyperplasia.

Discussion

The information accumulated during the last decade on the pathophysiological mechanisms involved in the genesis of acute coronary syndromes[5,6] has enabled the development of specific therapeutic strategies targeted against particular pathophysiological processes.[20-22] Some of these approaches have been shown to reduce significantly the mortality and morbidity associated with the syndrome. However, the management of unstable patients is still far from being straightforward. Although a thrombotic origin in primary unstable angina seems well established,[1-5,23] the syndrome is frequently refractory to thrombolysis, platelet antiaggregants and systemic anticoagulation.[8,24] Likewise, the advent of the thrombolytic era has not diminished the number of patients presenting with unstable angina in the weeks following acute myocardial infarction.[25]

Table II. Correlation between angioscopic and histological findings in patients treated with directional coronary atherectomy.

Pat. no.	Angioscopic findings	Histological findings
1	Red (protruding) material, xanthomatous plaque	Dense fibrous tissue, fresh thrombus, cholesterol crystals
2	Red (mural) material, xanthomatous plaque	Dense fibrous tissue, fresh red thrombus, cholesterol crystals
3	Red (occlusive) material	Dense fibrous tissue, fresh red thrombus, neointimal hyperplasia
4	Red (mural) material	Dense fibrous tissue, fresh thrombus, media + advent.
5	Red (mural) material	Dense + loose fibrous tissue, fresh red thrombus
6	Red (mural) material, xanthomatous mass	Dense fibrous tissue, fresh thrombus.
7	White mass	Dense fibrous tissue, fibrin rich thrombus.
8	White mass	Dense fibrous tissue, organizing thrombus
9	Normal vessel wall	Dense fibrous tissue, neointimal hyperplasia

Part of this therapeutic problem may be related to the lack of knowledge on the evolution of the pathological substrate from the initial stages of the acute coronary syndrome. While post-mortem studies have contributed substantially to the understanding of the underlying pathology, it is obvious that this source of knowledge is biased by case selection, presumably reflecting more acute and extensive changes than those existing in the majority of patients.

Coronary angioscopy may serve as a useful tool in visualizing the ischemia-related vessel in unstable patients, providing insight not only on the genesis but on

further evolution of the changes taking place in the environment of the atheromatous plaque. Previous studies using angioscopy have suggested a high frequency of coronary thrombosis in patients with unstable angina and myocardial infarction.[10-13] Grayish, non-occlusive, presumably platelet rich thrombus has been described as a common substrate of patients presenting with unstable angina, while red, occlusive thrombus was found mainly in patients with myocardial infarction.[12] In the latter group, a higher prevalence of xanthomatous plaques was also found.[12] Although these studies have contributed significantly to the in-vivo study of acute coronary syndromes, they share the common limitation that translation of the visual findings to pathological terms was performed automatically. This is particularly relevant since pathological validation of angioscopic studies has never been performed in-vivo, and in-vitro studies are scarce. These include the work of Tomaru et al.[26] and Mizuno et al.,[27] reporting on the formation of thrombus and subsequent action of thrombolysis in two different experimental models, and that of Siegel et al.[28] validating angioscopic and intravascular ultrasound observations obtained in-vitro in peripheral human arteries. Although in these studies pathological examination of the imaged vascular substrate was performed, it is likely that the models used may be quite far from being representative of those changes found in the culprit lesion of of patients with unstable angina.

Our work differs from all these previous studies in several aspects. First, an objective approach to evaluation of the visual findings was followed to classify the chromatic and morphological characteristics of the culprit stenosis as visualized during angioscopy. To reduce the potential interobserver variability associated with angioscopy we performed panel review of the images, a method which has previously proved useful for this purpose in studies using coronary angiography.[29] A translation to pathological findings was attempted only after concomitant directional atherectomy was performed, yielding histological specimens that were compared with visual findings. The independent contribution of a cardiovascular pathologist was also sought in an attempt to get an expert opinion on the changes seen during angioscopy. Second, the study population was a representative sample of unstable patients with or without previous myocardial infarction, with the common denominator of being refractory to medical treatment and referred for percutaneous recanalisation. This implied a longer time interval (16±15 days) between the onset of the syndrome and the time of angioscopy. Finally, patients with prior thrombolysis were also included in the study.

We found that the chromatic characteristics of the stenotic wall found in the study population were similar to those reported by Mizuno et al.[12] in the very early stages of the syndrome. Red intraluminal material was a frequent finding in unstable and postinfarction patients, and the study of atherectomy specimens revealed that its histological substrate was in fact red thrombus. Thrombus was frequently present in spite of relatively prolonged treatment with therapeutic doses of intravenous heparin, in agreement with the work of Badimon et al

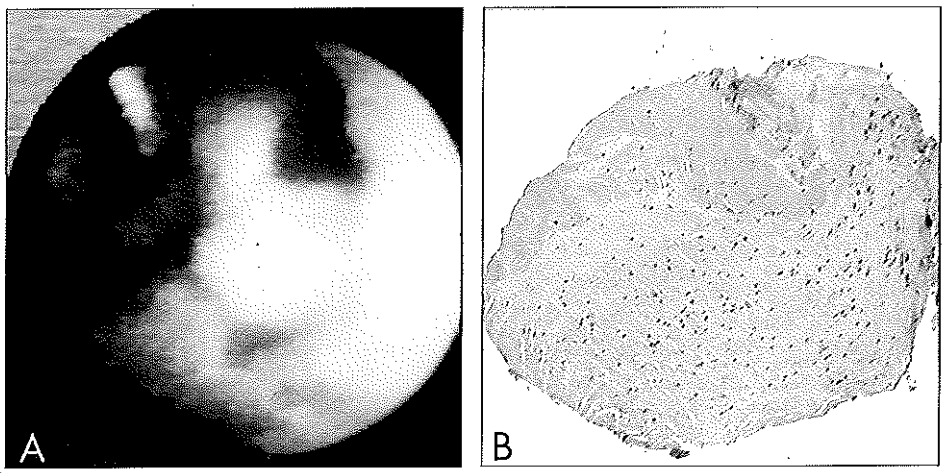


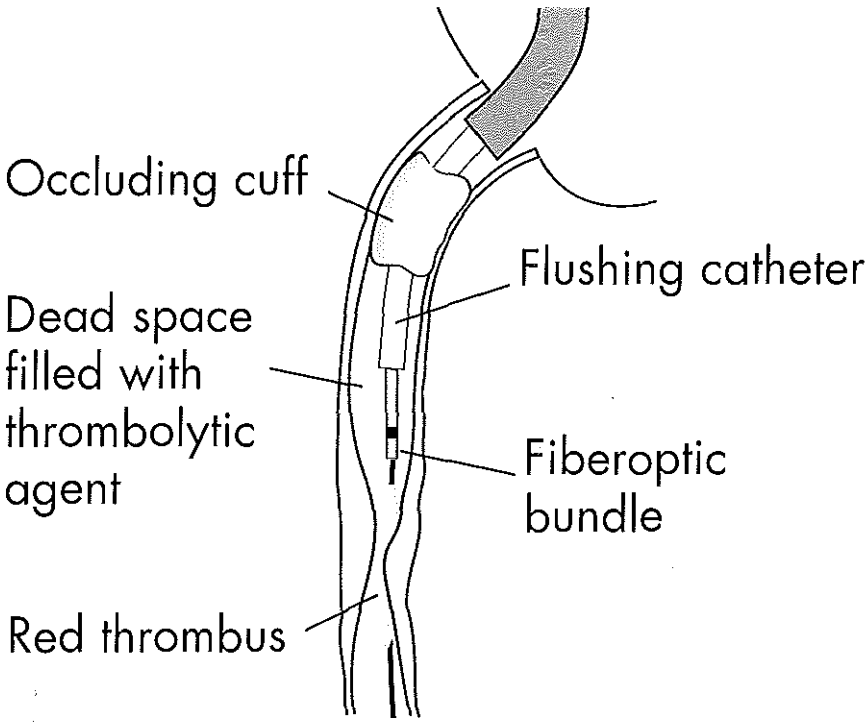
Figure 3

A: Intracoronary angioscopy in a patient with unstable angina pectoris showing a globular white mass that protrudes in the lumen. B: Histological examination of a similar mass observed in a patient undergoing atherectomy revealed moderately cellular fibrous tissue with evidence of thrombotic organisation.

demonstrating that anticoagulation with heparin does not abolish thrombus growth.[30] In the post-infarction group previous treatment with thrombolytic agents did not appear to reduce the prevalence of red thrombus.

Likewise, we found that white protruding masses are relatively common in unstable patients, and occur mainly in patients with primary unstable angina. Insight to the pathological nature of this observation was obtained in two cases. A fibrin-rich thrombus was found in an atherectomy specimen obtained from a lesion with a white-grayish protruding mass. In the second specimen, the underlying substrate was identified as fibrous tissue in association with organising thrombus. In previous studies, we and others found that thrombus organisation is common in atherectomy specimens obtained in patients with primary unstable angina pectoris, even in the early stages of the clinical syndrome.[31,32] It is likely that modification of the color of thrombus which occurs during the process of organisation,[33] with a shift from red to a pinkish, color, can make it undistinguishable from platelet rich thrombus. We also observed a statistically significant preponderance of pink areas in the vessel wall in patients with unstable angina, although its pathological nature remains unclear since no atherectomy was performed in any of these cases. It is possible, however, to speculate that these may correspond to mural thrombus being organised and integrated in the arterial wall, or to the presence of haematic material in the subintima.

Several observations relevant to the vascular substrate underlying thrombus formation were drawn from the angioscopic images. We found a significant



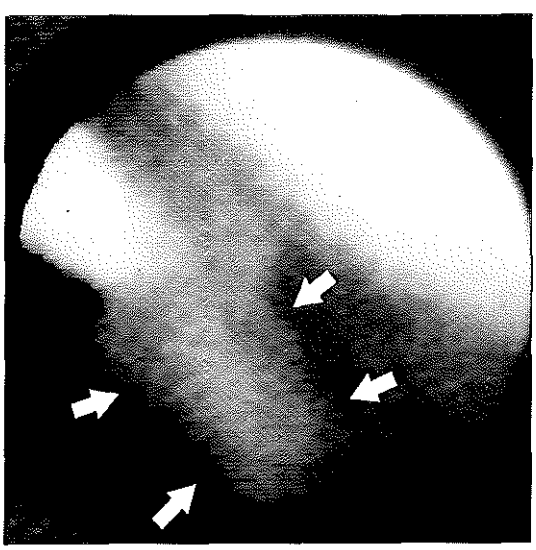


Figure 4

A: Coronary angioscopy can be used as an effective method for thrombolytic drug delivery in selected patients. By inflating the proximal occluding cuff of the angioscope, which is normally used to interrupt antegrade blood flow and facilitate visualisation, thrombolytic agents can be delivered at the site of occlusion, reaching high local concentrations that may facilitate thrombolysis.

B: This technique was successfully applied in a mid righ coronary occlusion by red material, suggestive of fresh thrombus.

During thrombolysis, angioscopy demonstrated marked remodelling of the occluding red material. A mobile, whitish core (arrows) which was underlying the original occluding mass became evident and remained unchanged during the rest of the examination.

gradation in the presence of red material in stenoses with disrupted, irregular and smooth vessel wall. It is likely that these stenosis characteristics imply a variable thrombogenic potential of the stenotic wall. Exposure of deep components of the plaque (type III vascular injury in the classification suggested by Ip et al.)[34] may cause thrombosis more frequently than in areas with merely absent or dysfunctional endothelium (vascular injury type II in the same classification), promoted by shear stress in segments presenting an irregular lumen.[35] Our study supports a previous report on a higher prevalence of xanthomatous plaques in patients who developed myocardial infarction. The presence of red material and xantomatous plaques were strongly correlated. Concomitant study of atherectomy specimens obtained from xanthomatous lesions revealed the presence of cholesterol crystal clefts, sometimes in close association with inflammatory cells and embedded in red thrombus, suggesting that, in accordance with previous postmortem studies, extrusion and dispersion of plaque material secondary to plaque rupture had preceded the episode of thrombosis[1,3,4,36] (Fig. 2). Xanthomatous plaques appeared as discrete, raised plaques where a thin, transparent fibrous cap is assumed since the underlying yellow lipid material can be seen. These observations support current views on the genesis of myocardial infarction, precipitated by rupture of lipid-rich plaques[5,37] that promote thrombus formation.[38,39]

Which is the main cause of persistent luminal obstruction in unstable patients refractory to medical treatment? As judged from angioscopy in the present study, red material protruded significantly in the coronary lumen only in 24% of the cases. Even if patients with a protruding white mass are added to this figure (9 patients, since 1 concomitantly presented a red mass), obstruction by an intraluminal mass occurred in only 46% of all cases. Since the primary aim of thrombolysis is to tackle coronary thrombus as the main cause of intraluminal obstruction, this observation provides clear evidence as to why thrombolytic treatment has previously not been helpful in the treatment of unstable patients. Interestingly, in this study the only angiographic characteristic of lesions showing a significant obliteration of the lumen by red material was the presence of significantly greater stenosis severity by quantitative angiographic analysis. This finding may provide an unexpected explanation of the findings reported by De Zwaan et al.[40] in the sense that only unstable patients with total or subtotal coronary occlusion demonstrated benefit from thrombolytic treatment. In the light of the observations of the present study, such benefit would be derived from selecting cases for treatment where occluding red thrombus plays a considerable aetiological role. As in the present study, less severe stenoses probably present a lower contribution of thrombus to luminal obstruction. These findings suggest that angioscopy may be more useful than angiograhy in reliably and specifically identifying the presence of intraluminal thrombus in order to perform a more selective use of thrombolytic agents.

This applies also to patients with unstable postinfarction angina, as suggested by a

pilot study from the John Hopkins Hospital.[4] In that work, intracoronary streptokinase was given in postinfarction patients with a persistently occluded vessel. Coronary reperfusion was achieved in 9/15 (60%) of patients, who had a better clinical outcome than patients not receiving thrombolysis, or in whom coronary reperfusion was not achieved. We could document the modification of the angioscopic characteristics of occlusive red material in a postinfarction patient following exposure to a highly concentrated dose of thrombolytic agent. An underlying whitish, mobile core which remained unlysed (Fig. 4B) became evident. This observation fits nicely with that of Uchida et al.[10] in their in-vitro angioscopic study on the effect of thrombolysis, where pale material was later identified histologically as a fibrin-rich thrombotic core. It remains unknown whether a similar effect of thrombolysis is to be expected in cases where an intraluminal white protruding mass rich in fibrin predominates. Likewise, the presence of some of the other characteristics of thrombus found in our study, such as the presence of extruded cholesterol crystal clefts and cellular infiltration within a formed thrombus, may interfere with the action of thrombolytic agents.[42]

It has been emphasized that in the acute coronary syndromes thrombosis is a dynamic process[2,3,5,43] with waxing and waning of the cause of coronary occlusion (either red or platelet-rich thrombus). The presence of protruding thrombus may also stimulate thrombus progression due to a combination of rheological factors and the high thrombogenic activity of the actual surface of the thrombus itself.[44] Likewise,the resulting increase in shear stress may lead to new episodes of thrombosis if intermittent fissuring or exposure of its core to the bloodstream occurs later during thrombus organisation, where thrombin remains protected from circulating antithrombin.[34]

It is important to keep in mind that the information provided by angioscopy is limited to the luminal aspect of the vessel, and that therefore changes in plaque geometry as a consequence of the development of intraintimal hemorrhage or haematoma formation can be missed, or underscored by visualization of a mural thrombus at the site of a fissure in the fibrous cap (a "tip of the iceberg" phenomenon) (Fig. 1 A and B). It would be expected that the presence of hemorrhage or haematoma within the intima would constitute a major barrier to the action of thrombolytic agents.[42] Alternatively, and since resolution and organisation of a thrombotic episode seems to be associated with enhanced smooth muscle cell proliferation[45] and development of neointimal hyperplasia,[46-48] changes in plaque geometry may also result from accelerated formation of fibrous tissue which had been initially triggered from a clinically silent episode of thrombosis.

The results of this study reinforce the concept that coronary angioscopy constitute an useful research tool in the study of different coronary syndromes, and that such application is enhanced through concomitant use of directional atherectomy. The technique of angioscopy may additionally allow a more selective application of

thrombolytic treatment in those patients with occluding thrombus. Likewise, it may play a important role in the context of clinical trials aimed at reducing coronary thrombosis, such as in the control of restenosis post intervention, or in testing new pharmacological or mechanical thrombolytic approaches.

Our experience shows that the performance of angioscopy in unstable patients can cause abrupt occlusion, which is probably due to the manipulation of the guidewire and a intracoronary device in an already disrupted vascular segment. In this respect, it must be noted that, in contrast with previous studies, we attempted a complete angioscopic examination of the proximal and distal aspects of the stenosis. Despite the occasional local complications, our study shows that angioscopy with the system described remains a safe technique in unstable patients during percutaneous intervention.

Limitations

Although the capability of angioscopy for providing chromatic information on the vascular lumen constitutes one of its main advantages in the study of acute coronary syndromes, this aspect remains also its main limitation. No studies on the intraobserver and interobserver variability of colorimetric observations are available. However, in a normal population the ability to distinguish between colors varies significantly from one individual to another. We attempted to reduce such variability by panel review of the images, a method which has previously been validated in coronary angiography.[29] Our population was biased by the fact that the patients studied were suitable for percutaneous recanalisation. Thus, information of patients presenting triple vessel disease may have been lost.

Our patients were somewhat selected, since they were refractory to medical therapy and the findings may not be representative of the luminal environment early after the onset of the syndrome. In addition all our patients were suitable for percutaneous recanalisation and clearly had already survived the early acute phase of the syndrome and thus may not be representative of patients who suffer a precipitous clinical deterioration resulting in death. Nevertheless, we believe the combination of angioscopic, quantitative angiographic and histological findings in this study at least demonstrates the exciting possibility that comprehensive study of the elusive cause of unstable angina is clearly feasible. Thus, it is clear that we can anticipate further and rapid progress in this resistant and difficult area.

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Chapter VI

Stable Angina, Unstable Angina and Post-Infarction Angina: A Continuum Spectrum of Disease. Insights gained from Intracoronary Angioscopy

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Abstract

Background

Angiography has limited value in the identification of endoluminal changes such as plaque fissuring and coronary thrombosis. By providing direct visualization and allowing detailed chromatic discrimination between the constituents of the atheromatous plaque, angioscopy may provide new insights on the characteristics and substrate of acute and stable coronary syndromes.

Objectives

The aim of our study was to investigate in-vivo the luminal characteristics of stenotic lesions in stable angina and acute coronary syndromes settings using coronary angioscopy.

Methods

Patient population consisted of 78 consecutive patients undergoing successful angioscopic inspection prior to percutaneous coronary revascularization. Twenty five patients presented stable angina (group A), 36 patients unstable angina (group B), and 17 post-infarction angina (group C). Angioscopic variables recorded included lumen shape (round or elliptical, slit-like or complex shape); vessel intimal surface (smooth / irregular or ulcerated); and the presence of xanthomatous plaques or thrombi (mural / protruding and red / white). An estimation of the thrombotic burden present at each lesion was obtained using an angioscopic thrombotic score which takes in consideration the type and extent of thrombus and the number of subsegment involved.

Results

There was no correlation between angiographically and angioscopically defined complex lesion (kappa=0.10). With angioscopy, a complex lumen shape was more frequent in unstable syndromes (20%, 39% and 65 %, respectively groups A, B or C). Ulcerated vessel surface was also more frequent in unstable syndromes as compared with stable angina (12%, 47% and 53%, respectively groups A, B or C, $p<0.05$ between groups A and B and A and C). Xanthomatous plaques were present in two-thirds of patients and equally distributed among the clinical syndromes. The prevalence of red thrombi was significantly different in the 3 clinical syndromes (16%, 69%, 82 %, in groups A, B or C respectively). The thrombotic burden was higher in plaques with yellow material present (thrombotic score 3.08 ± 2.07 points, no yellow plaque vs. 5.87 ± 3.93 points, yellow plaque, $p<0.05$).

Conclusions

Coronary angioscopy appears as a more sensitive technique for detection of intraluminal changes than angiography. Coronary thrombus was detected in both stable and acute coronary syndromes, although with a higher prevalence and greater extent in the latter. Xanthomatous plaques were found in a similar proportion in stable and acute syndromes, and were associated with more larger thrombus when serving as the plaque substrate for coronary thrombosis. These observations provide insights obtained in-vivo on the role of thrombus in the natural history of coronary atherosclerosis, and support the potential application of coronary angioscopy as a research tool in this area.

Introduction

The progress made during the last 15 years in the study of coronary syndromes has established significant differences in the pathophysiological substrate of those with acute onset and chronic evolution [1]. Plaque fissuring and subsequent coronary thrombosis which results in acute flow reduction and ischemia at rest constitutes the accepted mechanism underlying the majority of the cases of acute myocardial infarction and a significant proportion of those presenting with unstable angina [1-3]. Conversely to the sudden onset of myocardial ischemia in acute coronary syndromes, stable angina results from hemodynamic modification introduced by coronary stenoses progressing at a slower pace. It is a matter of controversy wether subclinical episodes of coronary thrombosis play a role in the progression of this latter type of stenosis, and in that case which are the characteristics and the factors contributing on the development of such subclinical thrombosis [4].

These considerations have been mainly based in pathological studies and in information with diagnostic tools, particularly coronary angiography [5,6]. Angiography correlates of plaque ulceration and thrombosis, such as the presence of eccentric stenosis with narrow neck, overhanging edges or irregular borders, or intraluminal defects, have been noted more frequently in acute coronary syndromes than in stable angina [6]. However, the persistence of such angiographic patterns during months and even years of follow-up, well beyond the expected time of resolution of thrombus or vessel wall disruption [7], and the frequent lack of modification under the effect of thrombolytic agents [8] cast doubts as to the sensitivity of angiography to detect coronary thrombus.
In this regard coronary angioscopy may constitute an optimal instrument for in-vivo documentation of changes in the culprit stenosis of coronary syndromes [9-13] since it is superior to angiography in the detection of coronary thrombosis and vessel wall disruption [14-16].
The aim of our study was to investigate with coronary angioscopy the endoluminal characteristics of the ischemia-related lesion in acute (unstable angina and post-myocardial infarction angina) and chronic (stable angina) coronary syndromes, with particular attention to the prevalence and extent of coronary thrombosis.

Methods

Study patients
Out of 83 consecutive patients undergoing percutaneous catheter revascularization with vessel anatomy suitable for angioscopic inspection, 5 patients were excluded because of inadequate images (n=2) or lesion not crossed (n=3). The remaining 78 patients constitute the study population. Twenty five patients (32%) presented stable angina (group A), 36 (46%) patients unstable

angina (group B)(class II B, III B, in the Braunwald classification) [17], and 17 (22%) post-infarction angina (group C) (class III C of the same classification). None of the patients was studied within the first 48 hours of myocardial infarction. All patients with unstable angina or post-infarction angina were receiving intravenous nitrates and heparin with or without aspirin. The investigations were approved by the Institutional Board of the Cardiology Department of the Dijkzigt Ziekenhuis and the patients were studied only after giving informed consent.

Selection of ischemia-related lesion
Identification of the culprit lesion was based in angiographic data (stenosis morphology and severity) and its correlation with the location of ischemia in ECG leads.

Procedure technique
During the procedures all patients received aspirin (250 mg) and were fully anticoagulated with heparin, providing an activated clotting time in excess of 300 seconds. After the passage of a 0.014 inch guide wire across the target lesion, coronary angioscopy was performed. During the procedure real-time fluoroscopy or cineangiography along with angioscopic images were viewed on a high resolution monitor (PANASONIC BT-M 1420 PY) using a digital videomixer and simultaneously recorded on a S-VHS tape for off-line review by two observers. This technique facilitates the comparison between angioscopic and angiographic images, and provides information as the location of the angioscope tip in the vessel during imaging.

Coronary angiography
Prior to the performance of angiography, control of coronary vasomotion was achieved by intracoronary injection of isosorbide dinitrate (1-3mg). Multiple angiographic views of the target lesion were then acquired. Quantitative angiographic analysis was performed in the obtained 35 mm films using the latest version of the Cardiovascular Angiography Analysis System II (CAAS II, Pie Medical, The Netherlands) which has been described in detail elsewhere [18]. The angiographic morphology of the target lesions was also recorded after revision of the films by two independent observers, according to a modification of the classification proposed by Ambrose et al [6]. Lesions were considered to have a complex angiographic morphology when at least in one angiographic projection they presented either ragged or overhanging edges, an intraluminal filling defect with convex borders of persisting staining.

Fiberoptic intracoronary angioscopy
Before and after coronary interventions an intracoronary angioscope (ImageCath, Baxter Laboratories, Irvine, California) was introduced and the lesion crossed along its length. The catheter is of the monorail type with a diameter of 4.5 Fr (1.43 mm) and features a compliant cuff which can be inflated at low pressure

proximal to the stenosis to a diameter of up to 5 mm, a flush port distal to this catheter and a movable optical bundle with an extension range of 5 cm. The imaging bundle is composed of 3.000 individual optical fibres of 2 μm diameter and terminates at a grin lens constructed with a gradient index of refraction so that all the images tend to appear on the focus regardless of the distance from the lens. The central imaging bundle is surrounded by 12 light fibres of 120 μm of diameter, coupled to a light source located at the base of the catheter and with an illuminating power of 100.000 lux, although only an effective illumination power of 45 lux is delivered at the tip of the catheter. After positioning of the angioscope over the wire in the segment to be examined, the balloon is inflated and a continuous flushing with the Ringer's lactate is performed at infusion rates variable from 30 to 50 ml/min. Once the crystalloid solution has cleared the image field from blood, the tip of the catheter is advanced to explore the lesion under study.

Analysis of angioscopic images

Target lesion was classified using the previously validated classification designed by the European working group of angioscopy [9]. Lumen shape was classified in: *round or elliptical*, *slit-like or complex shape* (disruption of the plaque or the presence of thrombus). Vessel intimal surface was classified as *smooth / irregular* (rough surface with wall integrity preserved) or *ulcerated* (loss of continuity of arterial wall). Additionally, the presence of yellow plaques was recorded (areas of homogeneous yellow colour clearly identifiable from a neighbouring area of normal white wall). Red mural thrombus was defined as a red, predominantly mural, non-mobile, superficial mass adhered to the vessel surface. Protruding thrombus as a red, intraluminal protruding, mobile or non-mobile mass adhered to the vessel surface. Occlusive thrombus when a red intraluminal mass occluded completely the lumen. White thrombus was defined for red thrombus but with white colour.

Interobserver variability of angioscopic data

In a random sample of 30 patients the interobserver variability of the angioscopic images yielded a kappa value of 1.0 for the presence of thrombus, 0.78 for protruding or mural thrombus, 0.80 for the surface of lesion, 0.93 for yellow plaque and 0.94 for thrombotic lesion.

Angioscopic thrombus score

In order to establish a semi-quantitative evaluation of the extent of coronary thrombosis present in each angioscopic inspection, an original score was used. First, point values were assigned to the increasing degrees of luminal thrombosis as follows:1 point for a single lining thrombus, 2 points for multiple lining thrombus, 3 points for protruding thrombus and 4 points for occlusive thrombus. the final score was obtained by adding the point values obtained in the proximal, middle and distal subsegments of the stenosis, as identified by combined angioscopy and angiography (Figure 1)

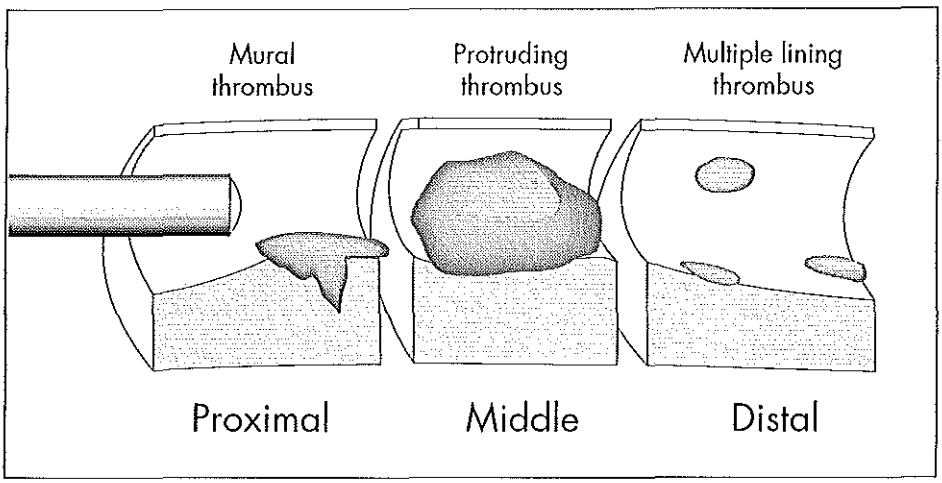

Figure 1.

Squematic representation of the angioscopic thrombus score. By adding the point values derived from the morphology and extent of thrombus present at each stenosis subsegment a final semi-quantitative estimation of the thrombotic burden present at the ischemia-related lesion was obtained. In this example a final score of 6 points was obtained (1 point for the proximal mural thrombus, 3 points for the mid protruding thrombus and 2 points for the distal multiple mural thrombi).

Statistical analysis

All continuous variables were expressed as mean ± SD. The two-tailed Student's t test was used for analysis of continuous data. A chi-square test and Fisher's exact test were used to compare differences between proportions. The Mann-Whitney and the Kruskal-Wallis test were used to compare ordinal data (scores). Agreement between 2 classifications was assessed using the Cohen Kappa value. A p value of < 0.05 was considered statistically significant.

Results

Angioscopic inspection was associated with transitory chest pain and electrocardiographic ST-T changes in almost all patients. These changes disappeared with deflation of the compliant cuff of the system and restoration of anterograde coronary blood flow. In two patients abrupt occlusion occurred following angioscopic imaging and was effectively treated with balloon angioplasty. Small dissections noted after the passage of the imaging catheter along the stenosed segment, occurred in 5 patients. This was angiographically unnoticed and did not influence the outcome of the subsequent coronary intervention.

Table 1 shows the clinical and angiographic characteristics of the 78 patients included in the study, grouped according to the syndrome. Complex angiographic morphology was noted in less than half of the patients, with an similar prevalence in the three groups (44%, 39% and 41 % respectively groups A, B and C). There

Table 1. Patient and vessel characteristics demographics.

Demographics	SAP (n=25)	UAP (n=36)	Post-MI (n=17)	p value
Age (mean ± SD)	56±8	59±10	59±9	ns
Sex				
Male	20 (80%)	32 (89%)	14 (82%)	ns
Ischemia-related lesion				
LAD	6 .(24%)	9 (25%)	10 (59%)	ns
LCX	15 (56%)	18 (50%)	4 (23%)	ns
RCA	4 (16%)	7 (19%)	2 (12%)	ns
SVG	1 (4%)	2 (6%)	1 (6%)	ns
Multivessel disease	7	12	10	
Premedication				
Heparin/Aspirin	0/8	36/22	17/11	
Systemic thrombolysis	none	none	7	
Onset instability (days)	---	15±11	12±8	
Complex lesion	11 (44%)	14 (39%)	7 (41%)	ns
MLD (mm)	1.14±0.55	1.08±0.43	1.04±0.41	
Reference diameter	3.2±065	3.12±.58	3.13±0.64	

LAD = left anterior descending, LCX = left circunflex, RCA = right coronary artery, SVG = saphenous vein graft.

was no correlation between an angiographically-derived complex lesion and a complex lesion by angioscopy (kappa=0.10). The positive predictive value for an angiographic complex lesion to predicted an ulcerated plaque with or without thrombus was 63% and the negative predictive value was 48%. The angioscopic characteristics of the culprit lesion is shown in Table 2. Figure 2 shows examples of various vessel surfaces. Complex lumen shape was increasingly more prevalent in patients with stable, unstable and post-myocardial angina (20%, 39% and 65 %, respectively groups A, B or C). Likewise, stenosis presented an ulcerated vessel surface more frequently in unstable syndromes than in stable angina (12%, 47% and 53%, respectively groups A, B or C, $p<0.05$ between groups A and B and A and C). Yellow plaques were present in the majority of patients, with a similar prevalence in the three clinical groups.

Thrombus evaluation

Although red thrombi could be documented in patients belonging to the three clinical syndromes, a significant difference in its prevalence in the three groups was noted (16%, 69%, 82 %, respectively groups A, B or C, $p<0.05$ between groups A and B and A and C). There was also a trend towards a larger thrombotic

Table 2. Angioscopic lesion characteristics.

	SAP(n=25)	UAP (n=36)	Post-MI (n=17)	p value
Lumen shape				
round	19 (76%)	20 (56%)	5 (29%)	<0.05
slit-like	1 (4%)	2 (6%)	1 (6%)	ns
complex	5 (20%)	14 (39%)	11 (65%)	<0.05
Vessel surface				
ulcerated	3*.¥ (12%)	17 * (47%)	9 ¥ (53%)	*¥ < 0.05
Red thrombus	4*¥ (16%)	25* (69%)	14 ¥ (82%)	*¥ < 0.05
protuding/mural	1/3 (25%)	10/15 (40%)	7/7 (50%)	
White thrombus	2 (8%)	14 (39%)	6 (35%)	<0.05
Yellow plaque	18 (72%)	22 (61%)	12 (71%)	ns

burden from patients with stable angina to post-myocardial infarction patients as expressed by a higher percentage of protruding thrombus and thrombus score. A similar incidence of xanthomatous plaques in the three groups was noted (Figure 3). In those lesions with evidence of thrombosis, the presence of a xanthomatous plaque as substrate was associated with more thrombotic burden: mean thrombotic score was 3.08 ± 2.07 points when the substrate was a lesion with white coloration, versus 5.87 ± 3.93 points in case of xanthomatous plaques ($p<0.05$). White thrombus were present in all clinical syndromes at places with red thrombus, and with a higher incidence in unstable syndromes but with similar proportions between them (8%, 39% and 35%, respectively groups A, B and C, $p<0.05$ between groups A and B). Figure 4 shows different types of thrombi occurring in acute ischemic syndromes

Discussion

The introduction of intracoronary imaging devices creates new possibilities of studying changes in the coronary arteries in the living man. The superiority of angioscopy over angiography in the detection of coronary thrombosis and intimal disruption, reported previously [14-16] and supported from the results of the present work, suggests that angioscopy may become an alternative standard to angiography for the identification of such changes in prospective studies. At a difference with prior works with angioscopy in the field of acute coronary syndromes [9-11], we extended our observations to patients with stable angina to cover a wider spectrum of the manifestations of coronary atherosclerosis.

As discussed above, a lack of correlation between angioscopic findings and angiographic morphology was noted in the present study. Vessel wall disruption may be masked by the very nature of coronary angiography, which represents a "shadowgram" of vessel. We found that the presence of wall disruption during angioscopy was associated with a larger thrombotic burden. The angioscopic

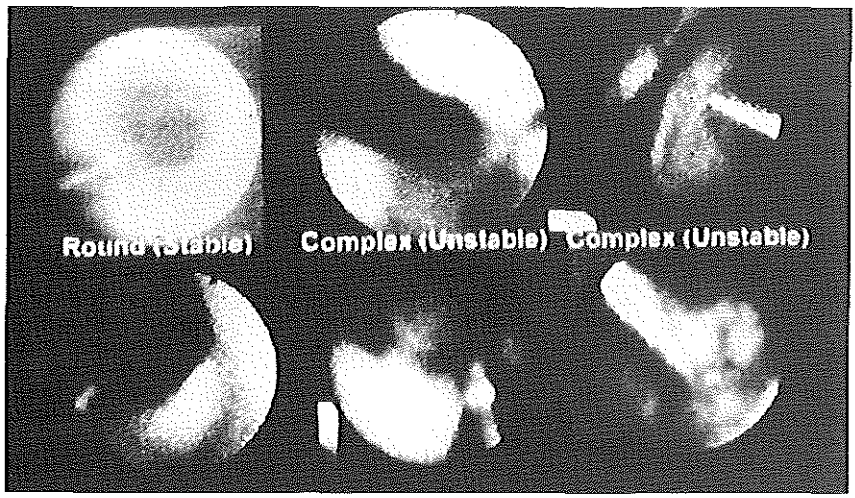

Figure 2.

Examples of different lumen morphologies with angioscopy. Top left, normal aapearance; Bottom left, round shape with smooth surface typical of stable angina. Top middle, slit-like shape with a red thombus at the entrance of the lesion; Bottom middle and right, complex shapes characteristic of unstable syndromes.

thrombotic score increased from 3.25±2.22 points in stable to 5.86±4.66 points in post-myocardial patients. This can be explained on the grounds of previous research demonstrating that the development of coronary thrombosis is closely associated with the degree of vessel wall disruption [20]. Moreover, additional insights on the influence of plaque substrate in the degree of the associated thrombosis were obtained. A strong association between the extent of the thrombotic burden and the prevalence of xanthomatous plaques was noted in the present study. Xanthomatous plaques visualized by angioscopy are likely to represent cholesterol-rich lesions (with yellow coloration secondary to its contents of carotenoids) Furthermore, its visualization by angioscopy suggest that lipid deposits separated from the arterial lumen by a thin, transparent fibrous cap.

We believe that these observations are relevant to the growing evidence suggesting that subintimal lipid deposits and necrotic core play a role not only on the destabilization and fracture of the atheromatous plaque, but also in the subsequent degree of thrombus formation. Plaques with lipidic core have more macrophages and less smooth muscle cells in the fibrous cap [21] favouring plaque fissuring under the effect of tensile stress [22-23], which is unevenly distributed in these lesions due to the different mechanical properties of lipid and fibrous tissue [24]. If rupture of the fibrous cap ensues and exposure of the lipid core to the bloodstream happens, an intense thrombotic response may follow, since the lipid-rich necrotic core is far more thrombogenic than other plaque constituents, such as collagen matrix [25]. Macrophages located in lipid-containing lesions express more tissue factor than those in other locations [26]. In addition, the occurrence of an intense thrombotic response causes significant protrusion of thrombus in the

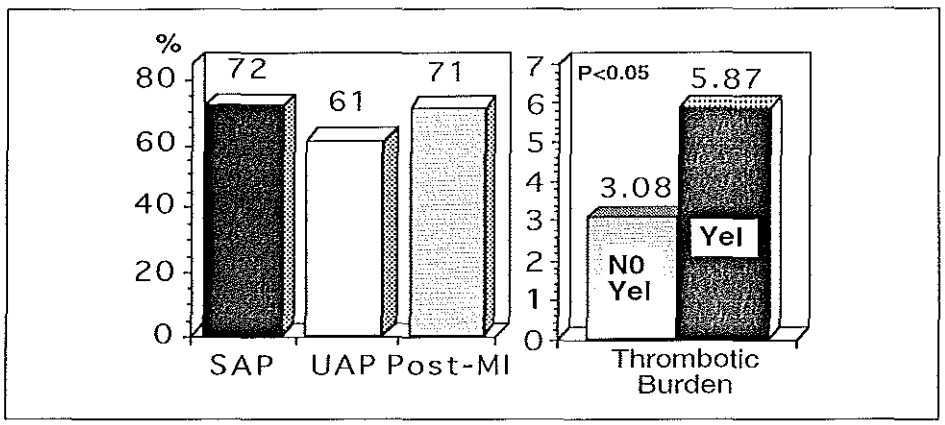

Figure 3.

Prevalence of xanthomatous plaques in the three groups of patients (left panel). In the presence of an yellow plaque, the amount of thrombus formation as assessed by the thrombotic score was about the double as compared to lesions without identifiable yellow material (right panel).

arterial lumen, introducing significant modifications in the haemorrheological conditions of the stenosis. This combination of factors has recently been shown to be a potent stimulus of thrombus growth, which may explain why thrombosis in this context becomes rapidly occlusive [27] (Figure 5). We did not disclose significant variations in the prevalence of xanthomatous plaques in the three clinical syndromes studied. Since myocardial infarction is the first manifestation of atherosclerotic coronary artery disease in a significant number of cases, the observations performed in stable patients may represent the baseline conditions prior to the development of plaque fissuring and occlusive thrombosis. Furthermore, the high prevalence of xanthomatous plaques in stable patients may partially explain the potential of antilipidic therapy [28] in reducing future cardiac events by reducing the potential of extensive thrombus formation in case of plaque fissuring.

Our observations in stable and unstable coronary syndromes revealed that the presence of intimal disruption and coronary thrombus is not exclusive of the latter, and can also be documented in patients with stable angina (12% and 16% of the patients with stable angina showed evidence of intimal disruption and thrombus formation respectively). Conversely to acute ischemic syndromes, in patients with stable angina coronary thrombus was less frequent, often lining or mural, and rarely protruding in the lumen. this supports the concept that silent thrombosis occurs during the evolution of atherosclerotic coronary artery disease, following the documentations by Davies et al of plaque fissuring and non-occlusive thrombosis in asymptomatic patients with coronary artery disease [29]. Even the development of acute coronary syndromes may be preceded by silent episodes of thrombosis, as suggested by the presence of well organized thrombi in the culprit lesion of patients with acute myocardial ischemia [30].

Coronary thrombosis may be an important factor for plaque progression. The

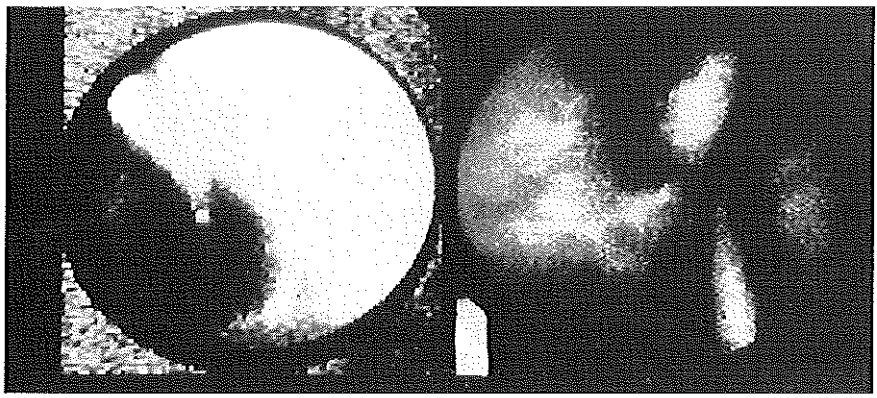

Figure 4.
Left, occlusive red thrombus occuring in the subacute phase of myocardial infarction. Right, mixed thrombus (red and white) occuring near a yellow plaque in a patient presenting with unstable angina.

increase in plaque size may be larger than that of the thrombotic bulk, since even small amounts of thrombus may trigger biological modifications in the plaque, which may cause significant remodeling. Resolution and organization of a thrombotic episode is associated with enhanced smooth muscle cell proliferation and the development of neointimal hyperplasia [31], a fact that may explain why patients with unstable angina often present an important component of fibrous neointimal hyperplasia [32]. According to these views, plaque progression would not follow a slowly progressive "step by step" course, but rather a 'jumping" evolution with brisk transitions in lumen diameter as a result of episodes of increased biological activity.

White thrombi , which have been attributed to platelet rich masses, were present in 39% of the patients with unstable angina and 35% of patients with post-myocardial angina. Differences with the study of Mizuno et al. [11], who noted a higher prevalence of thrombus in unstable angina than in acute myocardial infarction, may be partly due to the inclusion in the present work of patients in the post-infarction period. In this patients coronary thrombus presented an heterogeneous composition which may be different with that observed during the acute phase of myocardial infarction. Alternatively, such heterogeneity may be related with the refractoriness of the syndrome to conventional treatment which eventually lead to the performance of percutaneous revascularization.

Several limitations have to be kept in mind with the regard to the present study. Angioscopic observations were only performed in patients with anatomy suitable for angioscopic imaging and percutaneous coronary intervention, precluding generalization of our findings to all coronary patients. For this reason, early stages of coronary atherosclerosis may have been missed. Difficulties in the manipulation of the angioscopic catheter precludes sometimes inspection of the complete vessel circumference. Because thrombus formation is a dynamic process, restriction of our observations to a single occasion may give a false impression o the temporal changes occurring during the disease process. Differences in the total amount of

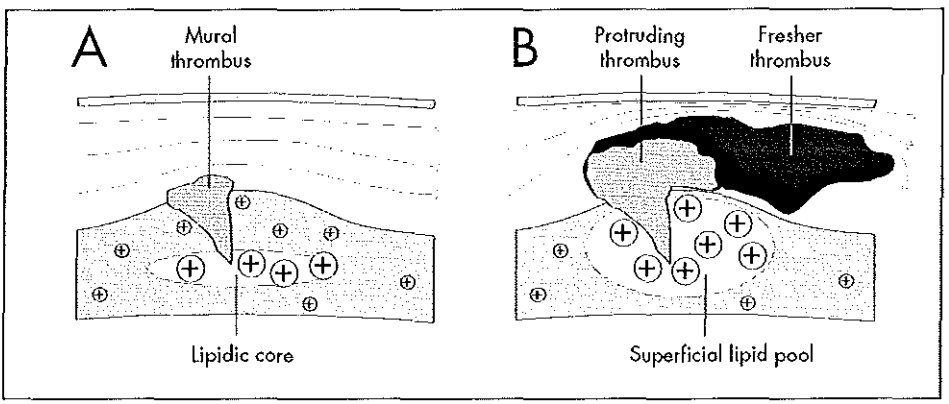

Figure 5.
Influence of plaque substrate on the extent of the thrombotic response. A, exposure of substrates with moderate thrombogenicity (small+), such as collagen, as a result of plaque fissuring, triggers the development of mural thrombosis, which causes slight modification in the hemorrheology of the stenosis. B, on the contrary, rupture of plaques with superficial lipid deposits and thin caps, which is highly thrombogenic (large +), promote the development of protruding thrombus. The concomitant modification of hemorrheological conditions by protruding thrombotic mass constitutes an intense stimulus for further thrombotic development, leading to complete occlusion or downstream progression.

lipid deposits between the study groups cannot be excluded, since angioscopy only allows visualization of the endoluminal surface of the vessel and provides no information on the structure of deeper vascular layers. Even the prevalence of xanthomatous areas representing superficial lipid deposits may be underestimated by angioscopy when covered by extensive thrombosis.

Conclusions

Coronary angioscopy appears as a more sensitive technique for detection of intraluminal changes than angiography. Coronary thrombus was detected in both stable and acute coronary syndromes, although with a higher prevalence and greater extent in the latter. Xanthomatous plaques were found in a similar proportion in stable and acute syndromes, and were associated with more larger thrombus when serving as the plaque substracte for coronary thrombosis. These observations provide insights obtained in-vivo on the role of thrombus in the natural history of coronary atherosclerosis, and support the potential application of coronary angioscopy as a research tool in this area.

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Part III

Intracoronary Imaging in Coronary Interventions.

Chapter VII

Intracoronary Two-dimensional Ultrasound Imaging in the Assessment of Plaque Morphology and Planning of Coronary Interventions.

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Introduction

Until recently, contrast angiography remained the gold standard in the evaluation of atherosclerotic heart disease. Because angiography represents a shadowgram of the lumen, it does not provide information concerning the disease process occurring in the arterial wall. Therefore, information obtained with this technique is virtually restricted to assessment of stenosis severity. Investigations indicate that stenosis assessment can not accurately predict future cardiac events. Whereas severe stenoses frequently progress to total occlusions without causing myocardial necrosis, coronary lesions with mild or unnoticed angiographic irregularities are often associated with future cardiac events such as myocardial infarction or unstable angina [1-5]. Plaque rupture and associated thrombus formation may occur in small angiographic lesions resulting in acute changes in lumen dimensions and morphologic features. It has been shown that these plaques prone to rupture have a high lipid content and a thin fibrous cap infiltrated by macrophages [6]. Richardson, et al. [7] identified ruptured soft plaques beneath 83% of 85 coronary thrombi examined. Besides plaque composition, certain plaque morphologic characteristics associated with high shear stresses, such as plaque thickness, plaque stiffness and the strength of the fibrous cap [7-8] makes these lesions prone to rupture. Most of the plaque volume responsible for lumen encroachment, on the contrary, is constituted by dense collagenous tissue (hard), that is biologically stable [9-10].

The existence of extensive atherosclerotic disease in vessel segments with a normal angiographic appearance has been noted by several authors [11-13] (Figure 1). This phenomenon is the result of compensatory vessel wall enlargement which is part of the natural history of coronary artery disease [14], yielding an underestimation of the atherosclerotic process when angiography is used as the investigational technique [13]. Therefore, it is questionable whether angiography should continue to be used as the gold standard for studying the natural history of coronary heart disease or in assessing regression or progression of atherosclerosis under the effect of specific pharmacologic interventions.

Since the pathologic processes that results in acute ischemic syndromes take place in the arterial wall, plaque characterization may provide diagnostic and prognostic markers useful for patient care. Therefore, it is understandable that intracoronary ultrasound (ICUS), a technique with the potential to quantify plaque size as well as to investigate its composition [15-18] has been accepted as a new gold standard for the study of coronary artery disease [19]. In this article we review the contributions and potential possibilities of intravascular ultrasound along with our own findings.

Technique

There are two basic types of intravascular ultrasound in clinical use. One type is based on the mechanical rotation of a transducer or mirror (mechanical system).

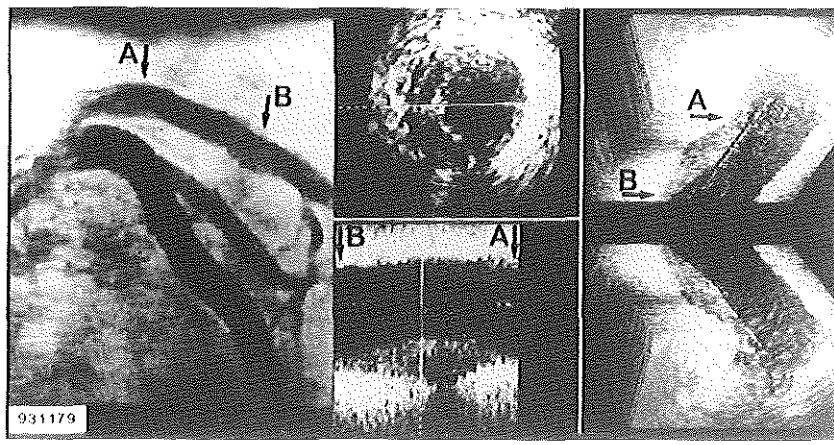

Figure 1.

Three-dimensional reconstruction of an angiographic normal coronary segment between points A and B. Ultrasound imaging identifies an eccentric plaque in the tomographic view. Note that in the longitudinal and three-dimensional reconstruction a localized Glagov phenomena is identified (external bulging of the arterial wall) to preserve lumen dimensions.

The other approach consists of several electronically interconnected crystals mounted around the tip of a catheter (phased array). Both systems permit a circumferential scanning perpendicular to the catheter's longitudinal axis. Advantages and disadvantages of the two systems are summarized as follows:

Mechanical systems

The main advantage is that this type utilizes a single piezoelectric crystal, thus facilitating catheter miniaturization. This results in a superior quality image than the phased arrays systems, without near field artifact. However, because the motor unit is external, building a driving mechanism while maintaining a flexible and steerable catheter is difficult. As a result, uneven rotation of the element/mirror at the catheter tip can occur causing image distortion.

Phased array

This system has multiple elements at the catheter tip and the signal is processed by ultraminiaturized integrated circuits. These elements can be connected in a such way that they are activated in sequence. Alternately, each element transmits and receives independently. Because there is no need for a driving mechanism, the catheter shaft remains flexible, and there is no image distortion. Disadvantages are a near-field artifact around the catheter tip, precluding imaging of the structures close to the tip of the catheter, and limited resolution and dynamic range of the system.

Coronary Wall Morphology

Normal wall structure

Two basic types of arteries can be differentiated by ICUS. In the study of Gussenhoven et al [15], ultrasonic appearance of human arteries was related to their histological composition. It was found that muscular arteries such as adult coronary arteries, typically have a three layer appearance. This feature results from the hypoechoic smooth muscle component of the media, which is situated between the bright internal and external elastic laminae. This arrangement most likely reflects the absence of concentric arranged elastin fibers in the media. In contrast, the media of elastic arteries has a more homogeneous wall appearance, as the result of the increased backscatter from the densely packed elastin fibbers.

Table 1. Intravascular ultrasound vs Quantitative angiography.

Investigators	Pts.	Vessel	"r"	SEE	M.Dif.	% Dif.
Davidson el al.[23]	21	Femoroiliac arteries	0.97	1.83	—	—
Sheikh et al.[24]	15	Femoral arteries	0.95	0.91	—	—
The et al.[25]	8	Femoroiliac arteries	0.96	0.47	—	—
Bartorelli et al.[26]	8	Femoral arteries	0.96	—	0.3 mm	4%
Tobis et al.[27]	27	Normal segments	0.26	—	2.1 mm	30%
		Stenosis post-PTCA	0.18	—	1.7mm	51%
Nissen et al.[28]	8	Normal coronaries	0.92	0.21	-0.05 mm	1%
	43	CAD patients	0.86	0.43	0.06 mm	2%
Werner et al.[29]	14	Normal segments	0.86	—	—	—
		Stenosis post-PTCA	0.48	—	—	—
St.Goar et al.[30]	20	Normal coronaries	0.86	0.07	0.04 mm	12%
		Transpanted patients				
Jain et al.[31]	6	SVG pre/post-PTCA	0.96	—	—	—
Hodgson et al.[21]	34	Reference segment	0.77	—	—	—
		Stenosis post-PTCA	0.63	—	—	—
De Scheerder et al.[32]	48	46 normal seg.	0.92	—	—	—
		80 coronary stenosis	0.47	—	—	—
		48 seg. post-PTCA	0.28	—	—	—
Haase et al.[33]	20	Stenosis post-PTCA	0.53	—	2.3 mm	—

CAD, coronary artery disease;Dif., difference; M.Dif., mean difference; Pts, patients; PTCA, percutaneous transluminal coronary angioplasty; SEE, standard error of the estimate; SVG, saphenous vein bypass graft.

Fortunately, most intervented vessels are either muscular (coronary, femoral) or transitional arteries (iliac), facilitating plaque area delineation.

Diseased wall

In vitro studies have shown that soft plaques containing lipids, intimal hyperplasia, thrombi or loose connective tissue produce echolucent echoes (less dense than the adventitia) [16,18]. Dense fibrous tissue produces bright echoes, whereas calcific plaques produce bright echoes with acoustic shadowing [16]. There are several similar classifications in clinical use. Based on our own previous work and work from others [15,20-22], we classify plaque composition according to their ultrasonic appearance as illustrated in Figure 2. *Soft plaques*: more than 75% of plaque area is composed of tissue with an echodensity less than that of the reference adventitia. *Fibrous plaques*: more than 75% of plaque area is composed of tissue producing 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 >180 degrees of vessel wall circumference. *Mixed*: This plaque consits of a combination of types of plaque tissue.

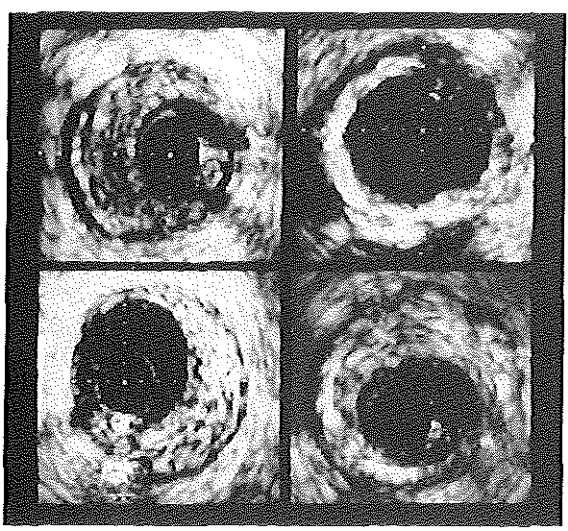

Figure 2.
Examples of plaque composition with ultrasound. Top left, a soft plaque. Top right, a calcific plaque. Bottom left a hard plaque. Bottom right a mixed plaque.

Ultrasound dimensions

From ultrasound images it is possible to derive the following dimensions [21]: *Luminal area*, integrated area central to the leading edge of the intimal echo; *external elastic membrane area*, integrated area central to media-adventitia interface; *plaque plus media area*, difference between external elastic membrane area and luminal area; and *stretching*, difference between external elastic membrane area before and after intervention.

Several validation studies of ICUS measurements have been performed. Table 1 summarizes the results of 10 clinical studies [21,23-32] and our own experience [33] in

which quantitative angiography and intravascular ultrasound were compared. Results of initial studies have demonstrated that intravascular ultrasound provides accurate lumen [21,23-26,28-30] and plaque measurements both in vitro and in vivo (15,17). Studies in vitro have compared the ultrasound determined cross sectional area and plaque dimensions with histologic measurements. Studies in vivo have correlated intravascular ultrasound measurements with those obtained by quantitative angiography. The correlation coefficients found differ according to the type of vessel and the presence of disease, with the best correlation for large vessels of regular cross sectional area. Figure 3 shows a comparison between lumen quantification by ICUS and quantitative angiography. In this case, the presence of a dissection post-balloon angioplasty clearly influences the measurements made by both techniques.

Effect of lumen size and shape

Quantitative angiography has reduced some of the limitations of visual interpretation of the angiograms in several clinical situations. However, computerized analysis of the stenotic segment still provide inaccurate results. This is the case of arterial segments that contain complex plaques [34] or that have undergone percutaneous interventions [35-36].

Nissen et al [28,37] reported a good correlation between quantitative angiography and intravascular ultrasound measurements in normal vessels (r = 0.98 for cross sectional area) and also in atherosclerotic vessels with circular lumen contour (r = 0.92 for lumen diameter). However, moderate correlation [21,33,38] or poor correlation [27,32] has been found after balloon angioplasty. These studies suggest that ICUS may be superior to contrast angiography because of the possibility of a direct visualization of the irregular lumen borders. In this regard, the work of Escaned et al [39] provides further insight. In this study there was a good correlation (r = 0.99) between ultrasound measurements and the actual luminal dimensions and also a good interobserver variability (r = 0.99) in circular phantoms. In irregular negative casts of human coronary arteries both the correlation coefficient (r = 0.90) and interobserver variability were lower (r = 0.77). This may be due to greater interobserver variability during the luminal measurements as the lumen looses its circular shape, and also to a possible overestimation of lumen area induced by non-coaxial positions of the catheter, as the lumen eccentricity increases [40,41]. In the same study there was no clear advantage of ICUS measurements as compared to quantitative angiography using edge detection techniques in two orthogonal views. However, complex lesions with tears or dissections like those frequently found after coronary interventions, were not evaluated.

Plaque morphology and the correlation with the clinical syndrome

Although plaque rupture has been reported as the major pathophysiological mechanism underlying acute ischemic syndromes, most fissures are clinically silent. Angiographic [42-44] and angioscopic studies [45-46] have shown that the amount of thrombus present at sites of plaque fissure is related to the severity of the clinical syndrome. What is still unclear is why some lesions progress to acute

Table 2. Ultrasonic determined plaque composition in unstable vs stable angina (%).

Investigators	Patients	Soft	Fibrous	Calcific	Mixed	Ca^{++}present
Hodgson et al [21]	22/43	74/41*	0/0	9/23	16/36	16/45*
Baptista et al.[§]	72/69	41/51	7/2	12/6	41/40	28/36

* $p<0.01$
[§] unpublished data

occlusions, whereas others do not. It appears that the depth of the vessel injury is determinant in the amount of thrombus formation [47]. In addition, plaque composition may determine the degree of activation of the coagulation cascade. In fact, ruptured plaques generally have a core of extracellular lipid underneath their fibrous cap [5]. Although angiography and angioscopy may identify plaque rupture, they are unable to identify these sites before rupture occurs. Because ICUS is able to identify different plaque compositions, this technique may be used in an effort to identify plaques prone to rupture.

Table 2 summarizes the only study published to date and our own experience (unpublished data) with ultrasonic determined plaque composition in patients with unstable angina. In a recent work, Hodgson et al. [21] found that in patients with unstable angina, soft plaques were significantly more frequent (74% vs. 41%) than in patients with stable angina. Conversely, the later patients had more calcific and mixed plaques than did patients with unstable angina (59% vs. 25%). In our own experience, we did not find differences in plaque composition between patients with unstable and stable angina (unpublished data) although the majority of patients with stable angina had soft components in their plaque composition.

Evaluation of Mechanisms of Lumen Enlargement after Balloon Angioplasty

Since the introduction of PTCA in 1977, this technique has gained a wide acceptance as an alternative to surgery in selected patients. However, despite its widespread use, the mechanisms of lumen enlargement have still not been fully elucidated. In general three main mechanisms are considered to contribute to an increased luminal area after PTCA. (1) *Plaque compression*: Dotter and Judkins [48] initially attributed lumen enlargement after balloon angioplasty to a compression of the atherosclerotic plaque. Although this mechanism may operate in vitro [49-51], the magnitude of this phenomenon in vivo is uncertain [52-53]. Pure, soft, young plaques present in animal models of atherosclerosis are seldom seen in advanced disease in humans. These plaques are generally composed of dense fibrous tissue and they are often calcified, thereby making plaque compression an unlikely mechanism [52-53]. Recently, it has been suggested from three-dimensional

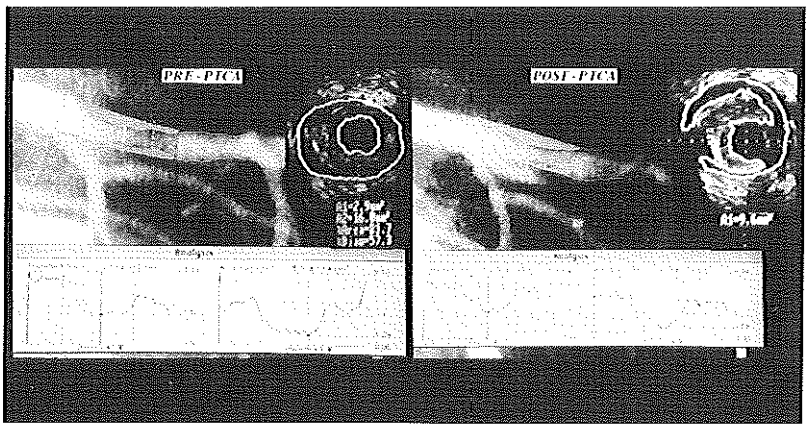

Figure 3.

Lumen quantification by quantitative angiography and intracoronary ultrasound following balloon dilation. Angiography underestimates lumen area, since it did not identify the contribution of the dissected lumen, as opposed to ultrasound.

Table 3. Mechanisms of lumen enlargement following balloon angioplasty.

Investigators	Pts.	Vessel	LA Gain	Plaq Red	Stretc.	Diss	% Diss
Losordo et al.[64]	40	iliac	13.9 (112%)	11.3 (81%)	2.5 (18%)	10.0	100%
The et al[65]	16	femoral	8.6 (85%)	1.98 (23%)	6.6 (77%)	----	43%
Suneja et al.[66]	25	coron	3.07 (126%)	2.90 (94%)	0.18 (6%)	----	---
Braden et al.[67])	30	coron	2.80 (108%)	0.54 (19%)	2.26 (81%)	---	---
Baptista et al.	63	corons	3.0 (166%)	1.52 (51%	1.48 (49%)	---	28%

Diss = Dissections, LA Gain = Lumen area gain, Plaque Red = plaque reduction, Pts = Patients, Stret. = Stretching (total area pre-intervention minus total area post-intervention).

ultrasound reconstruction [54] that axial plaque redistribution may occur during balloon dilation. Mintz et al., analyzed 18 segments from 11 patients after angioplasty. A volumetric analysis based on the three-dimensional reconstruction of the target segments showed that rather than plaque compression there is axial plaque redistribution along the stenotic segment. (2) *Plaque fracture and medial dissection*: Necropsy studies after angioplasty suggest that the major mechanism of lumen enlargement is due to plaque rupture and medial dissection [52,55]. Plaque composition and morphology are important predictors of the localization of the plaque fracture [56] which typically occurs at the thinnest portion of atheroma or at the transition of atheroma with the normal arterial wall [53]. Failure to achieve a permanent wall deformation by plaque dissection may result in a higher elastic recoil and consequent early restenosis after a initially successful dilation [52,57,58].

Nobuyoshi et al [58], evaluated 229 patients using prospective angiographic follow-up at day 1 and then at 1, 3, 6, and 12 months after successful angioplasty. They found that at 24 hours, coronary restenosis defined as a loss >50% of the initial gain was already present in 27 (14.6%) of the 185 patients evaluated. This study established that some cases of early restenosis are the result of elastic recoil, and do not involve an intimal hyperplastic response. (3) *Wall stretching*: Because coronary atherosclerosis is frequently eccentric, the plaque segments containing a disease free wall may distend during balloon inflation without the development of plaque fracture [59-62]. However, this temporary wall stretching may be subsequently followed by elastic recoil, resulting in a final lower luminal gain after balloon dilation [63].

Table 3 shows the relative contribution of the different mechanisms of lumen enlargement after PTCA in our own experience, and in published studies [64-67] where ICUS was performed before and after intervention. Discrepancies are clearly seen with regard to the relative contribution of the different mechanisms among the studies. At one extreme, Braden et al [67] suggest that wall stretch accounted for 81% of the gain in luminal area as compared to 6 % in the study of Suneja et al [66]. Arterial wall dissections are a frequent finding after PTCA [53,64]. However, because IVUS catheter can "stent" dissections to the arterial wall, the contribution of this mechanism for increased luminal patency was quantified only in the study of Losordo et al. in peripheral arteries [64]. In their study, plaque rupture was responsible for 10.0 mm2 of the 13.9 mm2 increase in luminal area after intervention. In another study, Potkin et al [53] examined 29 patients using ICUS before or after successfully balloon dilation. After dilation, dissections were seen in 27% of the cases with contrast angiography versus 83% with intravascular ultrasound. Arterial expansion, defined as an area within external elastic membrane greater at the angioplasty site than at the proximal reference segment, occurred in 29% of the calcified plaques as compared with 86% of noncalcified plaques.

Selection of Devices and Guidance

Plaque composition may influence the acute success of coronary interventions [68-69]. Soft lesions may be more prone to elastic recoil, whereas large calcific lesions may predispose to more severe dissections after balloon dilation, or result in a lower luminal gain after directional atherectomy. Therefore, ultrasound imaging may assist in the selection of a specific device for a particular lesion and may guide the operator during coronary procedures.

PTCA

Despite the high success rate of PTCA, acute complications, such as abrupt closure, still persist in about 5.6% of patients 70. In general, these complications are the consequence of artery spasm, localized thrombi or coronary dissections in the majority of the patients [60] and are difficult to predict by contrast angiography.

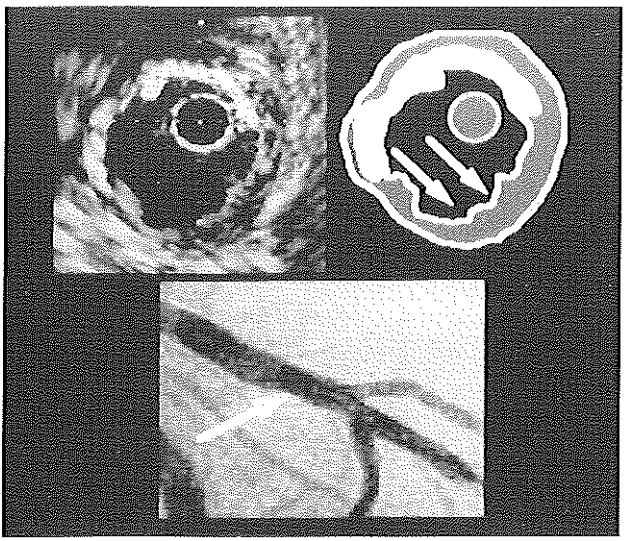

Figure 4.
After a sucessful atherectomy, ICUS identifies a significant residual plaque burden. Note the presence of a cut (arrows) at the end of a calcific deposit.

Arterial spasm occurs more frequently in eccentric plaques due to the abrupt relaxation of an overstretched disease free wall, and large dissections occur more often after dilation of calcific plaques [52]. Because contrast angiography only detects extreme cases of eccentricity [71] or calcification, the use of intravascular ultrasound may help in predicting and avoiding these complications. In cases of very eccentric lesions, directional atherectomy or stenting may be a rational alternative. Heavily calcified plaques may be more efficiently treated using a rotablator catheter. The use of combined balloon-echo catheters may detect during balloon inflation the moment when a dissection may begin, avoiding the use of high pressures in lesions of presumed high risk morphology [72]. After dilation, quantification of residual plaque burden may help in the choice of alternative strategies for improved final results.

Atherectomy

Restenosis after atherectomy seems to increase when there remains a significant residual plaque accumulation, and is a function of the depth of the cut, although these observations are controversial [73]. Furthermore, it is recognized that even after an angiographically successful atherectomy, the residual plaque burden is still about 50%-60% of the vessel area as exemplified in Figure 4. These data suggest a place for a more aggressive plaque debulking with this technique. In this regard, ultrasound guidance with or without combined echo-atherectomy devices have shown promising results [74-75], increasing the extent of plaque removal and minimizing deep vessel wall injury.

Among the angiographic predictors of failed atherectomy, the presence of calcium,

mainly in a superficial location, is one of the most important. In our experience, ICUS is more sensitive in detecting plaque calcification than angiography. Similar results have been reported by other groups [62,71]. Leso et al [69] reported the use of intracoronary ultrasound in 66 patients for guiding and assessing the atherectomy results. They divided the target lesions into two groups, according to the plaques' morphologic features (echolucent and echogenic plaques). Mean ultrasound estimation of plaque reduction was higher in the echolucent group (72 ± 21%) as compared with the echogenic plaque group. However, during follow-up these echolucent plaques had a higher restenosis rate (seven of seven echolucent lesions vs. four of 12 echogenic lesions; $p < 0.05$) most likely because of a higher lipid and cellular content. Also, in selecting patients for rotablator therapy, additional information about plaque composition (calcium) and lumen size may be useful. Because subendothelium calcium prevents an effective plaque removal with directional atherectomy [76], calcific plaques may be a good indicator for the use of rotablator therapy. A recent ultrasound study has confirmed that calcific plaques are more efficiently treated (larger lumen and fewer dissections) with rotablator catheter as opposed to soft plaques [77].

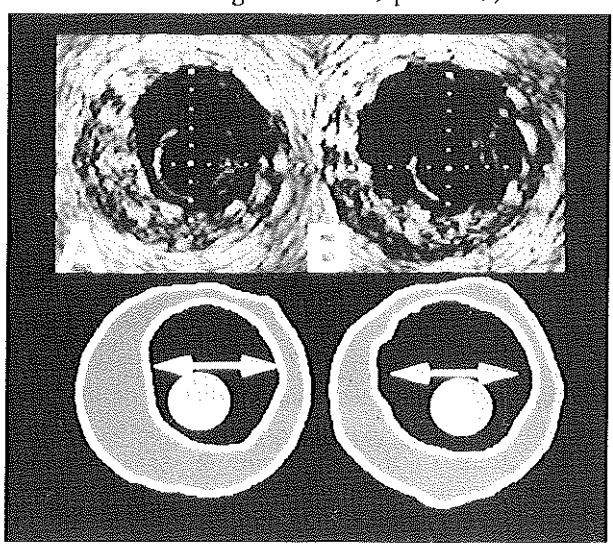

Figure 5.
Ultrasound imaging immediatly after stent deployment (A) and after an adjunctive balloon dilation (B). Immediatly after stent deployment there is an inadequate stent expansion, identified also by the oval lumen shape. After additional balloon dilation there is an increased lumen area and a nearly circular lumen configuration.

Stent

Because of the circular cross sectional area of these devices and their echogenicity, these low radiopaque devices are easily visualised during ultrasonic imaging. This feature can be helpful in sizing the vessel and also in determining the degree of expansion and apposition of the stent with respect to vessel wall [78]. ICUS guidance during stent deployment [79] has been shown to improve the immediate final results of this procedure, eventually resulting in a lower restenosis rate at the 6 months follow-up [80]. It was demonstrated that even after a final good angiographic result, ICUS is able to identify inappropriate stent expansion, defined as a stent area <80% of the expected balloon cross-sectional area (Figure 5). This finding prompted additional balloon dilation, resulting in an increased final luminal gain

in about 70% of the cases [79]. Based on intravascular ultrasound guided stent deployment the same group of investigators [81] have optimized stent expansion achieving a negative diameter stenosis. With this approach, patients were discharged without anticoagulation, and did well in the immediate follow-up. In our experience, the presence of an eccentric plaque with a disease free wall is associated with a smaller luminal gain after balloon dilation [63]. Because this plaque morphology is associated with higher elastic recoil of the vessel wall, the alternative use of a stent may decrease the associated elastic recoil.
During phase I of the GUIDE trial (guidance by Ultrasound Imaging for Decision Endpoints), angiography and intravascular ultrasound assessment of lesion characteristics were performed on-line during coronary interventions. Operators reclassified lesion characteristics after ultrasound was performed in 68% of the cases, and modification in the therapeutic approach occurred in 48% of these patients. This modification was based on the presence of unsuspected dissections, heavy calcification prior to directional atherectomy and large residual plaque burden after atherectomy leading to an upsizing of the atherectomy device[82].

Restenosis

Despite the improvement in catheter technology resulting in a high success rate of PTCA, restenosis still affects 30-50% of treated patients. The pathogenesis of this long term limitation is not yet fully understood, but factors such as plaque composition, the amount of endothelial and medial damage [83], elastic recoil [58], and residual stenosis after balloon dilation [84] may have a role in the development of clinical restenosis.
Although angiography can quantify elastic recoil and indirectly derive vessel wall damage from the acute gain after intervention [80,84,85], the influence of plaque composition or the mechanism of lumen enlargement in the restenotic process can not be accurately determined. Several studies [62,86] suggest that ICUS can identify patients with increased risk of subsequent cardiac adverse events after balloon dilation. In the pioneer studyof ICUS byf Tenaglia et al [86] using ultrasound, major dissections were the only predictable variable of future adverse events. Ultrasound imaging disclosed dissections in 55% of patientsafter PTCA, and this morphologic marker was more frequent in patients who subsequently had an adverse event (63% vs. 35%, $p < 0.005$). Honye et al [62] classified cases into 6 groups according to the extent of plaque fracture after PTCA. It was observed that 37 (77%) of the 48 eccentric plaques developed fracture in response to balloon inflation. The exceptions occurred with plaques within a disease free wall, where instead of plaque fracture there was stretching of the wall. At the other extreme, in 78% of the patients with concentric plaques did not developed dissections during balloon inflation. In addition, plaques with major calcium deposits incurred a higher dissection rate after PTCA as opposed to noncalcific lesions. These studies suggest that ultrasound imaging may predict the likelihood of restenosis more

accurately than angiography, based on the morphological plaque patterns after balloon angioplasty. Recent data [87] indicates that the most important parameter associated with restenosis is the geometric remodeling of the vessel wall, accounting for about 60% of the loss of luminal area during the 6 months follow-up period. No restenotic lesions are associated with a smaller residual plaque burden after coronary interventions and some vessels developed arterial dilation during the follow-up (increase in external elastic membrane area from the acute phase to follow-up) [88].
Based on these preliminary data, a prospective multicenter trial, the Post Intracoronary Treatment Ultrasonic Result Evaluation has been started in Netherlands with the purpose of relating ICUS imaging after successful PTCA to the development of future restenosis.

Limitations

At present, miniaturization of the currently available ultrasound catheters is still desirable in order to allow a morphologic assessment of more severe stenoses. Limited steering capabilities of the intravascular ultrasound catheters precludes the correction of non-coaxial or eccentric intravascular positions (41), yielding potential partial dropouts in the delineation of vessel lumen. The current quality of the images precludes an accurate measurement of vessel dimension as well as a good discrimination between the different plaque components in all patients.

Future Developments

Future improvements in image quality should provide a more widespread use of ICUS measurements to guide interventional techniques and the development of automatic contour detection will decrease interobserver variability of quantitative measurements, making this tool the new gold standard for assessing progression and regression of the atherosclerotic process.
Improvements in backscatter analysis will provide a more accurate tissue characterization, eventually identifying plaques in risk of future cardiac events. High risk plaques could be treated by local drug delivery systems under ultrasonic guidance. A reliable three dimensional reconstruction will improve the observation of changes in plaque volume during interventional procedures clarifying the mechanisms of enlargement induced by different devices [54,89,90,91]. This may assist in improved device selection for a particular lesion [54]. Combined echo-atherectomy catheters will better guide the operators towards an optimal plaque debulking, improving the results of this technique.

Conclusions

Intracoronary ultrasound is a new technique that has already contributed to a better understanding of vessel morphology and plaque composition. Possible future technological developments will incorporate ICUS images in clinical practice for a better understanding of coronary artery disease.

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Chapter VIII

The Use of Angioscopy in Percutaneous Coronary Interventions

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Introduction

Although coronary angiography is still the gold standard coronary imaging modality for the interventional cardiologist, more information is emerging on the specific limitations that percutaneous recanalisation poses to the interpretation of angiographic images. Coronary angioscopy, which can be used during percutaneous coronary interventions and provides a more accurate picture of the luminal aspect of the vessel, has been shown to be complementary to angiography.[1] We review some of the contributions that coronary angioscopy has made to interventional cardiology during its short existence, as well as the current trends for its application in a wider spectrum of clinical situations.

Contributions of angioscopy to the study of acute coronary syndromes

One of the strengths of coronary angioscopy over other imaging techniques such as angiography and intravascular ultrasound is its high sensitivity for the detection of coronary thrombosis[2,3] which stems from the marked differences in colour between thrombus and the normal arterial wall or atheroma. Using intra-operative angioscopy during bypass grafting, Sherman et al.[4] found that coronary thrombus is common in patients with unstable angina, and that frequently are not identifiable by coronary angiography. Although this work was limited by patient selection and the performance of retrograde visualization of the lesion from the arteriotomy site, it set a landmark in the in-vivo study of the substrate of unstable syndromes. The development of more flexible angioscopes that can be used percutaneously and allow antegrade visualization of the culprit lesion has facilitated further progress in this field.[5-7] Differences in the visual characteristics of thrombus have been reported in unstable angina and myocardial infarction. Mizuno et al.[6] reported that thrombus in unstable angina is predominantly grayish and non-occlusive, while thrombus associated with myocardial infarction is predominately red and causes complete occlusion. The former was though to correspond to platelet rich thrombus, while the latter was identified as rich in red blood cells and poorer in fibrin. Conclusions on the pathological substrate giving origin to thrombosis have also been drawn from angioscopic examination. Xantomatous plaques have been identified particularly in patients with myocardial infarction,[5] providing additional support to the hypothesis that plaque rupture leading to myocardial infarction often happens in weakened lipid-rich plaques.[8]

Although coronary angioscopy has played a significant role in facilitating the study of acute coronary syndromes in-vivo, most studies have been biased by translation of visual findings to pathological terms by the cardiologist, without the assistance of a cardiovascular pathologist. As discussed above, the sensitivity of angioscopy in detecting thrombus probably relies on the existence of substantial chromatic differences between red thrombus and the arterial wall (Fig. 1).

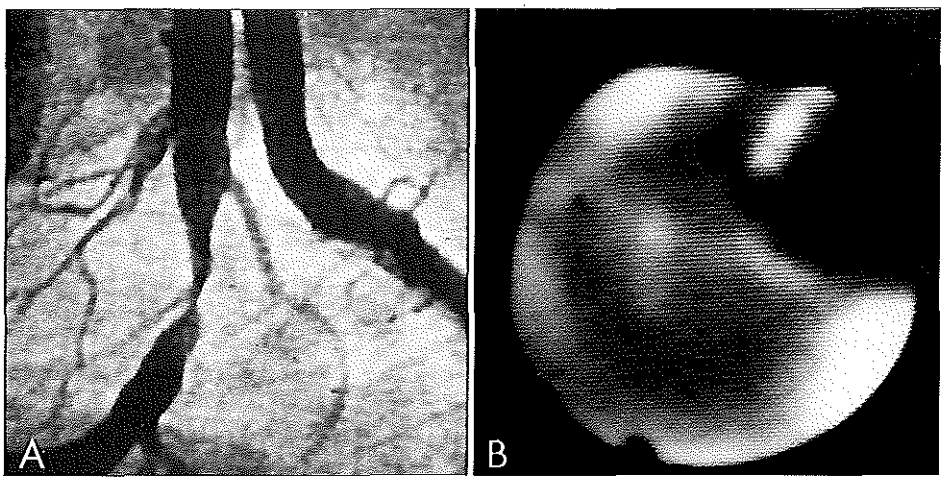

Figure 1

Angioscopy of a stenosis in the mid left anterior descending coronary artery in a patient with post-infarction angina pectoris. Although the angiographic morphology of the lesion (A) does not suggest the presence of coronary thrombus, angioscopy (B) reveals a large area of ulceration and thrombus which can be clearly differentiated from the white vascular wall. Note the heterogeneity of the thrombus, with white areas that may correspond to fragments of the fibrous cap, deposits of platelet-rich thrombus or areas of thrombotic organisation.

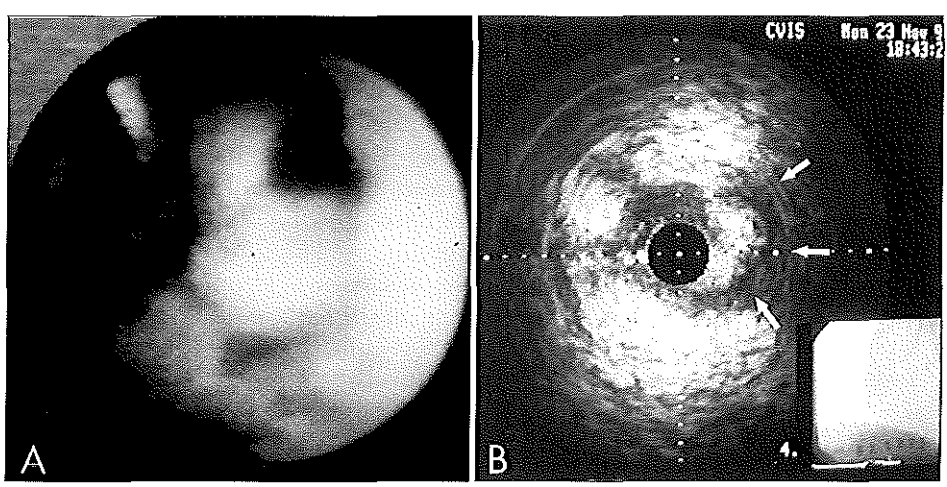

Figure 2

Intracoronary imaging in a patient with unstable angina pectoris. A globular mass that resembles a platelet rich thrombus was evident during angioscopic examination (A). However, concommitant examination with intravascular ultrasound suggests that this structure had a moderately high echogenicity, suggesting that visualised structure was more likely to have a fibrocalcific substrate (B).

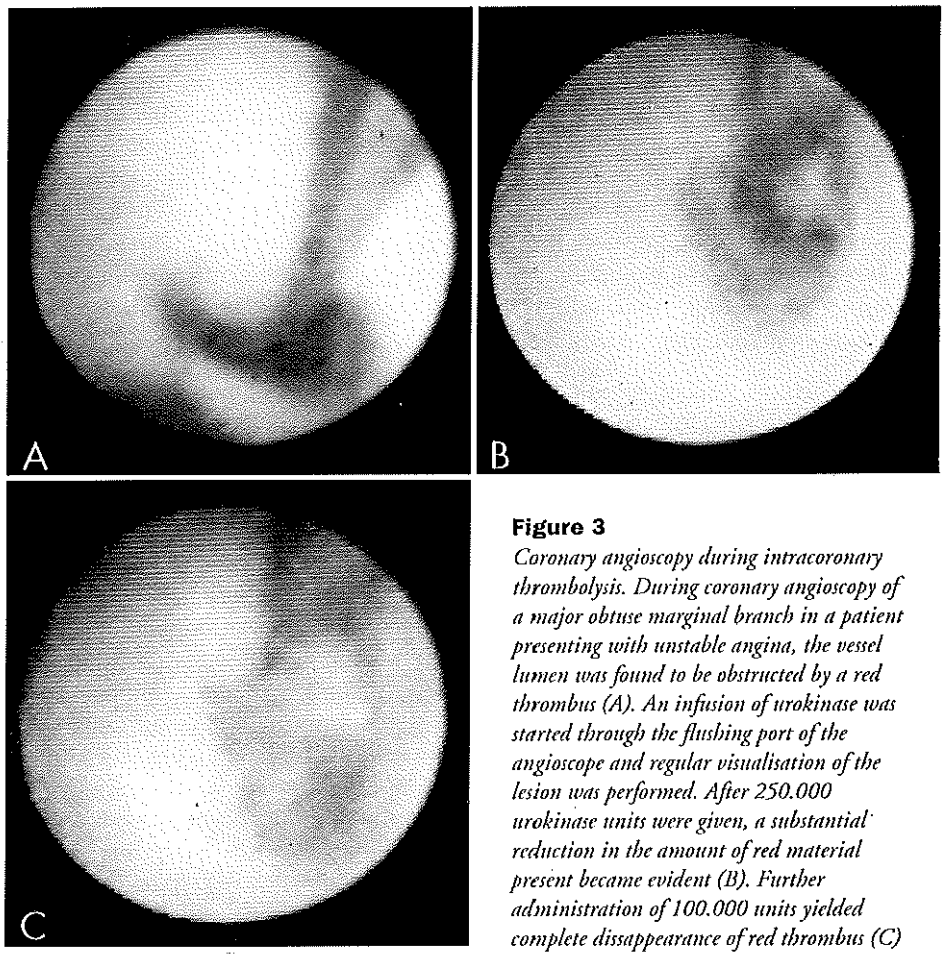

Figure 3

Coronary angioscopy during intracoronary thrombolysis. During coronary angioscopy of a major obtuse marginal branch in a patient presenting with unstable angina, the vessel lumen was found to be obstructed by a red thrombus (A). An infusion of urokinase was started through the flushing port of the angioscope and regular visualisation of the lesion was performed. After 250.000 urokinase units were given, a substantial reduction in the amount of red material present became evident (B). Further administration of 100.000 units yielded complete dissappearance of red thrombus (C) and marked angiographic improvement. The underlying lesion was a grayish lesion with irregular borders suggesting plaque ulceration (Courtesy of Dr Antoni Serra, Hospital Clinic, Barcelona, Spain).

However, it is a matter of concern that structures that are not "red" are identified as "white" or platelet thrombus. The various steps leading to the development of red occlusive thrombus in the injured vessel have been documented by angioscopy in animal models.[3,9] The first step of this process consists of adhesion of fibrinous network-like material and white components of thrombus (platelet aggregates), followed by the apposition of mixed red and white components that finally occlude the vessel lumen. Analysis of the white components of the observed thrombus has demonstrated that it was composed of platelet aggregates and strands of fibrin, while the red thrombus was rich in red blood cells trapped in a fibrin network.[3] It has not been established that in clinical practice angioscopy may be equally sensitive to the detection of white components of thrombus, since

the latter may not differ significantly in colour from other structures. In addition to this, it is well known that thrombus organisation modifies red thrombus to a wide range of hues, ranging from opaque red or pink (after endothelialization of the thrombotic surface) to gold (as macrophages are transformed into foam cells by digesting cholesterol from red blood cell membranes) and white (infiltration by myofibroblasts).[10-12] The use of directional atherectomy as a sampling tool in acute coronary syndromes has led to the suggestion that a higher prevalence of these changes are to be expected in-vivo than in post-mortem studies.[13,14] In this regard, it is foreseeable that the validation of in-vivo angioscopic observations will emerge from the concomitant use of other imaging devices and the study of atherectomy samples obtained during the same study (Fig. 2).

Angioscopy in stratification and assessment of patients with unstable angina

The contribution of angioscopy to the study of acute coronary syndromes goes well beyond the pure study of natural history and may contribute to unveil several management dilemmas posed by patients with unstable angina. The first of these has been precipitated by the failure of thrombolytic agents in reducing mortality or morbidity in that syndrome. Although the current paradigm of the syndrome postulates that mural thrombosis is the key cause of myocardial ischaemia in unstable angina through several mechanisms (thrombotic occlusion, enhanced vasoreactivity),[15,16] multiple randomized trials have failed in showing any clinical benefit of thrombolytic treatment.[17] The reasons for this failure are unknown. A lower prevalence of thrombus than expected from coronary angiography and post-mortem studies, or an enhanced resistance of thrombus to lytic therapy, secondary to organisation or protection from circulating lytic agents by mechanical barriers, have been proposed as possible explanations. It is clear that angioscopy could provide further insights on whether these hypothesis have a real basis. Furthermore, it is foreseeable that the combination of angioscopy and thrombolysis, which has been reported in experimental models,[9,18] will be more frequently used in the catheterisation laboratory in the near future. This might facilitate not only the selection of candidates for thrombolysis based on a more specific detection of thrombus, but also a more objective assessment of the success or failure of thrombolytic therapy. In a recent work, Inoue et al.[19] have reported on the success of systemic thrombolysis based on angiographic and angioscopic criteria. Residual thrombus was disclosed by angioscopy in 50% and 100% cases with TIMI reperfusion grades III and II respectively. In addition to the assessment of its efficacy, angioscopy may play a more participative role in coronary thrombolysis, facilitating the delivery of high concentrations of thrombolytic agents through the flushing port of the angioscope while assessing lysis (Fig. 3). Likewise, the effect of novel non-pharmacological thrombolysis such as that performed with ultrasonic devices,[20] which can that theoretically overcome some of the limitations of the pharmacological agents outlined above, could be also

tested.
Angioscopy may also be useful in investigating the pathological substrate for the high complication rate of percutaneous coronary interventions in unstable patients. Again, the presence of intraluminal thrombus has been proposed as a key factor, since its disturbance may potentiate further episodes of thrombosis.[21,22] However, the use of thrombolytic agents prior to intervention in vessels with angiographically suspected thrombus has failed to reduce procedural complications, even showing a trend toward increase.[23] As discussed above, the use of angioscopy may contribute to a more selective stratification of patients based on the presence or extent of coronary thrombosis than can be achieved by applying angiographic criteria.[24] On the contrary, the detection of other mechanisms leading to sudden change in plaque morphology, such as plaque disruption, aggressive atherosclerosis or intramural hemorrhage may favor the selection of specific recanalisation techniques, such as balloon angioplasty, coronary stenting or atherectomy .

Optimizing and assessing the results of coronary intervention with angioscopy.

Angioscopy has been used to document the changes undergone by the vessel wall immediately after balloon angioplasty[18,25-27] and new interventional devices.[18,28-30] These studies have similar findings than those reported in post-mortem examination of vessels that had undergone percutaneous recanalisation and that frequently are undetected by angiography, such as intimal flaps, major vessel wall disruption, thrombus and subintimal hemorrhages.[31] In many of these instances, the information obtained with angioscopy can be comparable to that obtained with intravascular ultrasound. Figure 4A shows a major plaque dehiscence originating after balloon dilatation. The concomitant use of intravascular ultrasound imaging makes possible to document a deep extension of the dissection to medial layers (Fig. 4B) , similar to that found in a post-mortem examination of a dilated arterial segment (Fig. 4C).

The consequences of vessel wall laceration are twofold. Firstly, vessel wall dissection can lead to the development of acute vessel closure, as demonstrated in angiographic studies.[32] Several reports based on experimental[18,33] and clinical[34,35] work suggest that the use of angioscopy can be superior to angiography in detecting intimal flaps and filling defects originating from wall injury (Fig. 5). Using percutaneous angioscopy, Jain et al.[36] identified the primary cause of acute occlusion during PTCA in 10 patients as occlusive thrombus in 2 cases and vessel dissection in 8.

A second aspect of the consequences of vessel wall laceration during intervention is its impact on the long-term procedural outcome. Although reports on the use of angioscopy to study the substrate of restenosis are scarce,[29,37] it is likely that this

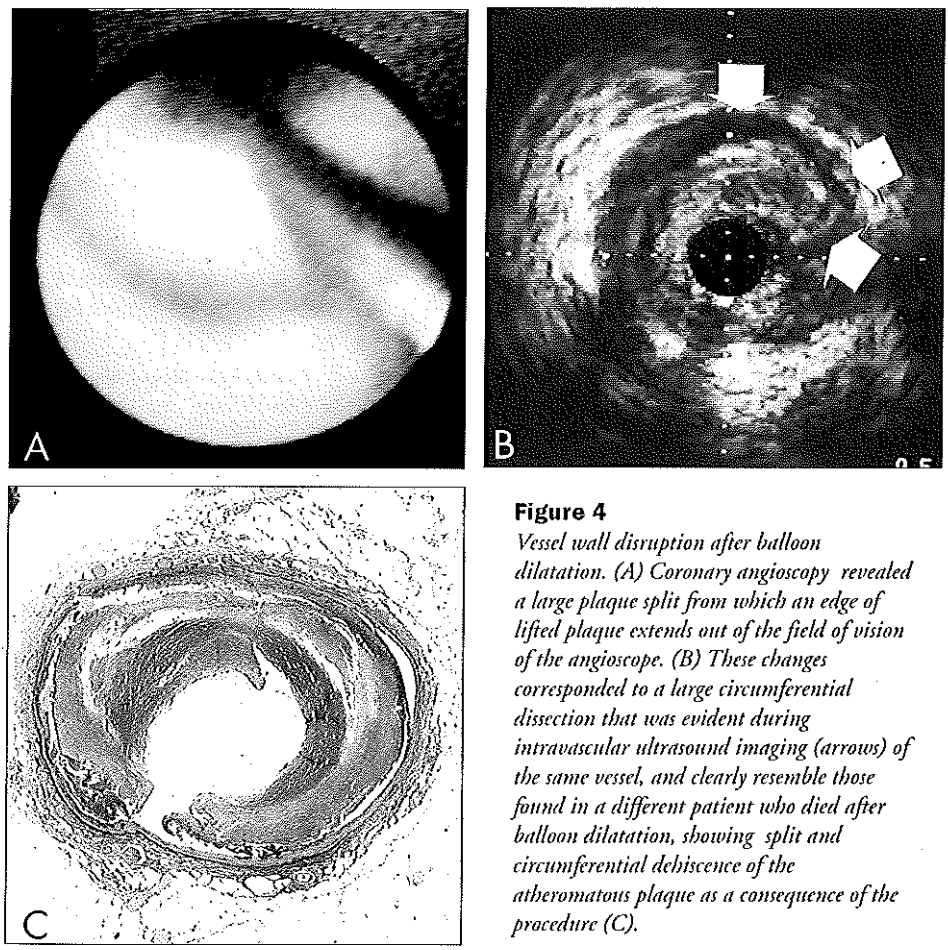

Figure 4
Vessel wall disruption after balloon dilatation. (A) Coronary angioscopy revealed a large plaque split from which an edge of lifted plaque extends out of the field of vision of the angioscope. (B) These changes corresponded to a large circumferential dissection that was evident during intravascular ultrasound imaging (arrows) of the same vessel, and clearly resemble those found in a different patient who died after balloon dilatation, showing split and circumferential dehiscence of the atheromatous plaque as a consequence of the procedure (C).

application of angioscopy will be implemented in the design of future clinical studies for the prevention of restenosis. The first and perhaps more unexplored area of restenosis consist in the identification of suboptimal procedural results that escape angiographic detection and that can lead to a phenomenon of "pseudorestenosis". This is particularly important since although coronary angiography has been the only method used in assessing restenosis post intervention, the complex vessel morphology associated with several recanalisation techniques makes difficult the interpretation of the angiographic image as to the gain in true luminal dimensions achieved, a fact that may explain why the reliability of quantitative coronary angiography decreases significantly after percutaneous interventions.[38,39]

A proportional relation between the extent of vessel wall injury and the

subsequent loss of luminal dimensions has been suggested.[40-42] Angioscopic quantification of vessel damage may found a better predictive value than angiography, allowing a more direct assessment of the results obtained with different recanalisation techniques.[20,26-30] The relation between wall injury and lining coronary thrombosis has also been proposed as a key factor in the development of neointimal proliferation,[43] and has been suggested as the cause for the high restenosis restenosis rate associated to percutaneous interventions performed in unstable patients.[44] As shown by den Heijer et al.,[29] angioscopy demonstrates coronary thrombus progression during the first hour after balloon angioplasty that is otherwise undetected by angiography. A wider application of this concept might provide information on the relationship between mural thrombosis and restenosis, as well as constitute a tool in assessing the efficacy of pharmacological strategies directed towards the avoidance of this phenomenon.

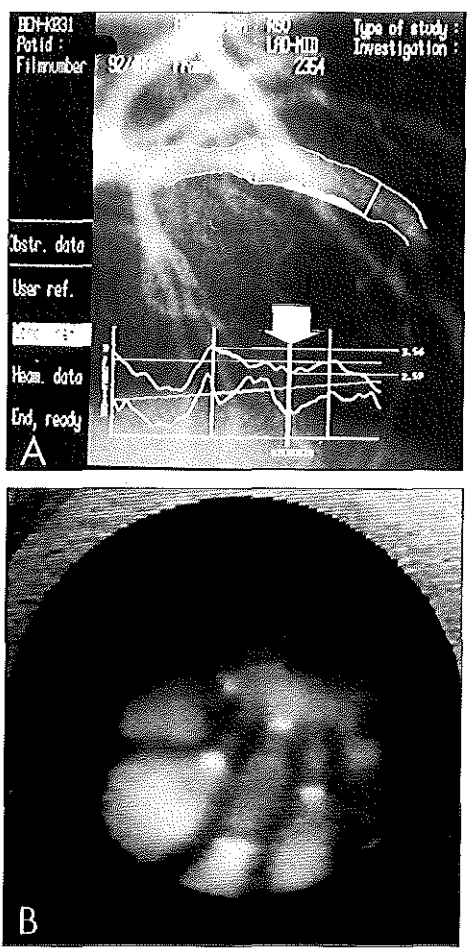

Figure 5

Quantitative angiographic analysis (A) after deployement of a Palmar-Schatz stent in the mid left anterior descending lesion, showing a large discrepancy (arrow) between luminal area obtained with edge detection (upper curve) and videodensitometric analysis (lower curve). During angioscopy a good result was noted in the distal subunit of the stent (B). However, a large area of disrupted vessel wall (C, arrows) was evident at the point where the two subunits of the stent are articulated by a single strut, failing to provide adequate scaffolding.

Although the use of angioscopy as a quantitative technique has been neglected, new methods are currently being applied to obtain an angioscopic estimation of luminal size. Preliminary results with the use of a light wire have recently been reported by Spears et al.[44] Other authors have proposed a semi-quantitative approach, using the width of the guidewire as a scaling device. Several outstanding issues that may affect the reliability of the measurements obtained have yet to be solved. The distending coronary pressure during imaging may differ significantly from normal. Furthermore, a coaxial placement of the angioscope is not always possible to ensure complete visualization of the coronary lumen.

State-of-the-art and future developments in coronary angioscopy

From the first coronary angioscopy performed with a 1.8 mm thick fiber optic angioscope and reported by Spears et al. in 1983, the technique has undergone major changes. Today's angioscopes are highly sophisticated system that can be used without difficulty in most routine cases performed in the interventional catheterisation laboratory. In the following paragraphs we review some of the advantages and limitations of the state-of-the-art angioscopy, as well as some of the research trends in new applications.

Current angioscopy systems are built using bundles with a high number of independent fibers, tipped with highly regular epoxy lenses of less than 0.3 mm in diameter, have a high flexibility and provide excellent image quality. Charge couple device (CCD) cameras which are small and can be easily handled are used. Full compatibility with conventional over-the-wire equipment is now the rule. Better visualization is facilitated by a new generation of delivery catheters with low-pressure inflatable cuffs to temporarily interrupt antegrade blood flow. These systems are difficult to use in very proximal arterial segments or when cuff inflation compromises blood supply to more than one large epicardial vessel. A variety of dedicated irrigation pumps is used to flush transparent medium during angioscopy. The use of Ringer's lactate is preferred over saline by some operators since it has been suggested to have less arrhythmogenic potential. Oxygen-carrying solutions may facilitate longer visualization times during angioscopy, and its performance in patients with moderately impaired left ventricular function, or a large area of dependent myocardium, but their use has been limited thus far by high viscosity. Establishing the spatial location of the angioscope in the vessel during on-line and off-line image analysis can be facilitated by simultaneous recording of angioscopic and fluoroscopic images with a videomixer during the procedure. As progressive refinements and improvements are made, steerability of the catheter tip is now the main limitation to collecting adequate information, particularly in tortuous vessels. Several systems to correct for misalignment of the angioscope and to facilitate more selective visualization are under development.

Many of the strengths of coronary angioscopy discussed in previous sections of

this article are related to the capability for retrieving chromatic information of the structures present in the luminal aspect of the vessels. Most available systems have automatic white balance systems aimed to ensure a faithful reproduction of luminal colours. However, the angle of incidence of the light beam on the visualized surface and manual adjustment of light intensity, which is frequently needed to optimize visualization, may significantly alter colours in the obtained images. Although no studies are yet available on the interobserver variability associated with this type of observations, the fact that in a normal population the ability to distinguish between colours varies significantly from one individual to other makes probable that it is significantly high. Automated colour analysis can possible contribute to the solution of this limitation, as suggested by preliminary results obtained by our group. Other factors may interfere with colour characterization, including the chromatic aberration resulting from the absorption of particular wave-lengths by optic fibers and the modifications due to magnetic storage in videotapes and their subsequent off-line analysis.

Further technological developments in image processing may allow interpretation of angioscopically obtained images to provide objective information on the constitution of the atherosclerotic vessel wall, which does not rely on subjective evaluation. Based on the characteristic absorption patterns of the constituents of the atheromatous plaque, several groups have reported in the possibility of applying laser-induced fluorescence to the diagnosis of atherosclerosis.[45-47] Although still in its developmental stages, this "spectroscopic angioscopy"[46] might provide insights to the structure of the vascular wall which have so far been confined to the realm of intravascular ultrasound imaging.

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Chapter IX

Impact of Plaque Morphology and Composition on the Mechanisms of Luminal Enlargement Following Balloon Angioplasty. A Study Using Intracoronary Ultrasound and Quantitative Angiography

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Abstract

Objectives

To investigate the influence of plaque morphology and composition on the results and mechanisms of balloon angioplasty, using quantitative angiography and intracoronary ultrasound.

Background

Limited information is provided by angiography concerning the plaque morphology and composition before balloon angioplasty. Identification of plaques associated with reduced luminal gain or high complication rate may provide the rational for using alternative revascularization devices.

Methods

Sixty-three patients were studied with quantitative angiography and intracoronary ultrasound before and after balloon dilation. Angiography was used to measure transient wall stretch and elastic recoil. Intracoronary ultrasound was used to investigate the mechanisms of lumen enlargement among different plaque compositions and in the presence of a disease-free wall (minimal thickness ≤ 0.6 mm)

.

Results

Angiography underestimated the presence of vessel calcification, (17% vs. 76%) lumen eccentricity (38% vs. 65%) and wall dissection (37% vs. 56%) as compared with ultrasound. Balloon angioplasty increased lumen area from 1.81 ± 0.49 mm2 to 4.81 ± 1.39 mm2. Lumen enlargement was the result of the combined effect of an increase in the total cross-sectional area of the vessel (wall stretching, 43%) and of a reduction of the area occupied by the plaque (plaque compression or redistribution, 57%). Vessels with a disease free wall had smaller lumen gain as compared with other types of plaques (2.16 ± 1.23 mm2 vs. 3.57 ± 1.50 mm2 respectively, p < 0.01). Wall stretching was the most important mechanism of lumen enlargement in vessels with a disease-free wall (65% vs. 39% in the other cases). Angiography revealed a direct correlation between temporary stretch and elastic recoil that was responsible for 25% of the loss of the potential lumen gain.

Conclusions

Lumen enlargement after balloon angioplasty is the combined result of wall stretch and plaque compression or redistribution. Intracoronary ultrasound indicates that plaques with a remnant arc of disease-free wall are dilated mainly by wall stretching as compared with other types of plaques and are associated with a smaller luminal gain. Consequently, identification of this particular plaque morphology may provide the rational for the use of alternative devices such as directional atherectomy or stents.

Introduction

Contrast angiography the gold standard for the evaluation of coronary artery disease, provides limited information regarding plaque dimensions and composition[1-2]. Therefore, despite the wide use of balloon angioplasty the impact of plaque morphology and composition, in vivo, on the outcomes of this technique remains to be fully elucidated. Restenosis, the major limitation of balloon angioplasty is the result of several factors such as the hyperplastic reaction in response to the trauma inflicted to the vessel wall[3-4], the magnitude of the elastic recoil[5] and chronic vessel wall remodeling[6] and can not be accurately predicted by angiography[7]. Because it has been suggested that ultrasound derived plaque morphology[8] after balloon dilation correlates with the likelihood of developing restenosis and that the bigger the lumen gain after intervention the bigger the lumen dimensions at the follow-up[9-10], interventions aimed to increase the acute minimal lumen diameter, may result in a larger long-term vessel dimensions[10-12]. Balloon angioplasty is a non-directional technique, thereby, during balloon inflation factors like difference in plaque thickness and composition may cause an unequal transmission of the balloon circunferencial stress to the vessel wall, resulting in different responses of the vessel wall to balloon angioplasty. Identification of particular plaques types associated with a suboptimal result, may provide the rational for the use of alternative devices for a particular lesion. Intracoronary ultrasound provides a unique opportunity not only to identify different plaques composition[13-14], but also different mechanisms of lumen enlargement during balloon angioplasty[2].
The aim of our study was to evaluate the influence of plaque morphology and composition on the mechanisms of lumen enlargement following balloon angioplasty, using quantitative angiography and intracoronary ultrasound.

Methods

Study patients

Sixty three consecutive patients (fifty-three men and 10 women, with a mean age of 59 ± 9 years) undergoing balloon angioplasty were studied with intracoronary ultrasound (ICUS) before and after intervention. Thirty-six patients presented with unstable angina (class II B, III B and II C and III C in the Braunwald classification)[15], and 27 presented with stable angina pectoris. The investigations were approved by the Institutional Board of the Cardiology Department of the Dijkzigt Ziekenhuis and the patients were studied only after giving informed consent.

Quantitative coronary angiography

All 35 mm films were analyzed using the Cardiovascular Angiography Analysis System II (CAAS II, Pie Medical, The Netherlands). The automated edge detection of this system have been validated and described in detail elsewhere[16-18].

Lesion symmetry was defined as the coefficient of the left hand distance and the right hand distance between the reconstructed interpolated reference diameter and actual vessels contours, at the site of obstruction. In this equation, the largest distance between actual and reconstructed contours becomes the denominator, so that a perfectly symmetrical lesion has a value of 1 and a severely eccentric lesion has a value of zero[19].

Dissections, wall stretch and elastic recoil

Dissections were evaluated according to the modified classification of the Blood, Lung and Heart Institutes[19-20]. A dissection was classified as type A in the presence of a small radiolucent area within the lumen of the vessel and as type B or C when there was an extravasion of non persisting or persisting contrast medium respectively. A dissection was classified as type D in the presence of spiral-shaped filling defect with delayed distal flow and as type E if a persistent lumen defect with delayed antegrade flow was seen on the final angiogram. A filling defect accompanied by a total coronary occlusion was classified as type F dissection .
Temporary wall stretch[21] was defined as the difference between the mean balloon diameter (of the largest balloon used) and minimal lumen diameter after balloon dilation, normalized for vessel size. Elastic recoil[21] was defined as the difference in minimal balloon diameter and the minimal lumen diameter following coronary angioplasty, normalized for vessel size.

Ultrasound study

Before and after coronary interventions a 4.3 Fr mechanical 30-MHz intravascular ultrasound catheter (INSIGHT "3" ultrasound system, CVIS, Sunnyvale, Calif.) was introduced along a 0.014 inch high torque floppy guide wire. The catheter was advanced distal to the stenosis and a slow manual pullback or (last 22 patients) motorized mechanical pullback at 1mm/s was performed from distal to proximal to the lesion. The segment comprising the stenotic lesion was examined along the entire length using side branches as landmarks and the images were recorded on S-VHS videotape. To improve the delineation of the lumen-vessel wall interface, intracoronary injection of contrast or saline was applied when necessary. The measurement system was digitally calibrated, and after a careful review of each videotape, one image at the site of the minimal luminal cross sectional area before and after intervention was selected for quantitative analysis.
The integrated information acquired during the pullback manoeuvre along the stenotic segment was used to classify plaque composition according to their ultrasonic appearance[13, 22-23] as follows:
Plaques with low echogenicity ("Soft plaques"): More than 75% of the plaque area is composed of tissue with echodensity less than the reference adventitia.
Plaques with high echogenecity ("Hard 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 degrees of vessel wall circumference.

Plaques with a mixed echogenicity. When there occurs a combination of different types of plaque composition.
Additionally, vessel dimensions were measured as follows[23]: *Luminal area (LA),* integrated area central to the leading edge of the intimal echo; *External elastic membrane area (EEM-A),* integrated area central to media-adventitia interface; *Plaque plus media area (P+M-A),* difference between EEM-A and LA. From the comparison of these measurements at the site of the minimal luminal cross-sectional area before and after angioplasty, several indices were calculated, including: *Wall stretch* or *Acute vessel dilation (Δ EEM-A),* difference in external elastic membrane area before and after intervention; *Plaque reduction (Δ P+M-A),* difference in plaque plus media area before and after intervention. IVUS eccentricity index was obtained dividing the minimal plaque thickness for the maximal plaque thickness. A plaque was considered eccentric when the eccentricity index calculated as the minor diameter divided by the major diameter was ≤ 0.5. A plaque was classified as having a disease-free wall when the plaque minimal thickness was ≤ 0.6 mm, irrespectively of its eccentricity (Figure 1)

Variability of the ultrasound determined lumen dimensions

We have previously reported[24] the correlation of ultrasound luminal dimensions

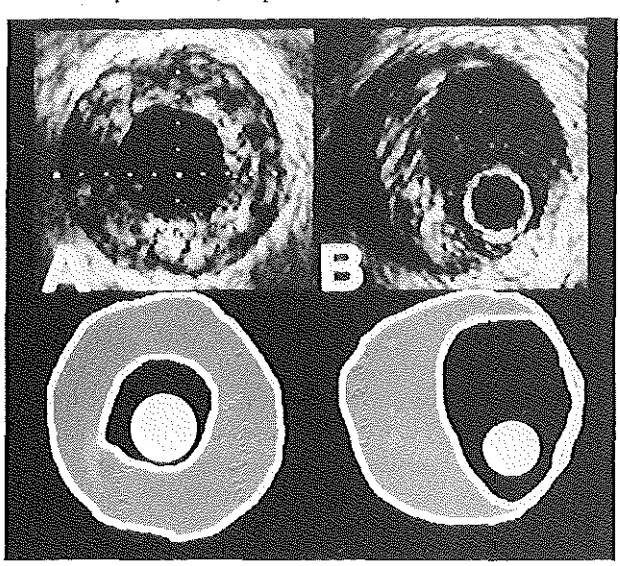

Figure 1.
Left panel, an example of a very concentric plaque; Right panel, a very eccentric plaque with a remnant arc of disease-free wall.

with circular phantoms and human coronary casts. The correlations coefficient and mean differences ± SD between ultrasound measurements and coronary luminal areas of the casts were 0.90 and 0.63±0.71 mm2 and for circular phantoms 0.99 and -0.08 ± 0.39 mm2, p = 0.012. In 40 patients studied before and after balloon angioplasty, we found a good correlation (r = 0.86, Y = 0.37 + 0.95x, SEE = 1.06) between observers for the minimal cross sectional area measurements at the stenotic site[25]. The mean difference of the measurements of all lesion cross sectional areas by both observers was 0.61±1.05 mm2 and was statistically significant (p < 0.0001) .

Tears and dissections

Tears or fractures were defined as an demarcated, focal, superficial break in the

linear continuity of the plaque that extended only in a radial direction [28]. Dissections were defined as demarcated ruptures of the plaque with circumferential or longitudinal involvement of the internal elastic membrane [28].

Procedure technique

During the procedures all patients received aspirin (250 mg) and i.c. isorsobide dinitrate (1-3 mg) before and after the procedure and were fully anticoagulated with heparin, so that the activated clotting time was over 300 seconds. Selective coronary arteriography was performed in multiple matched views before and after the coronary interventions. After the passage of a 0.014 inches guide wire across the target lesion, intravascular echocardiography was performed with the guidance of a fluoroscopic window and multiple contrast injections. This assured proper comparison between ultrasound, and angiographic images. Coronary angioplasty was performed according to standard practice.

Table 1. Patient and target lesion characteristics prior to balloon dilation.

Demographics	n= (%)
Age (mean ± SD)	59±9 years
Sex	
Male	53 (84%)
Female	10 (16%)
Angina type	
Stable	27 (43%)
Unstable	36 (57%)
Vessel treated	
LAD	27 (43%)
LCX	14 (22%)
RCA	19 (30%)
SVG	3 (5%)
IVUS characteristics	
Soft plaques	29 (46%)
Hard plaques	1 (2%)
Diffuse calcific	4 (6%)
Mixed plaques	29 (46%)
No calcium	15 (24%)
Calcium	48 (76%)

Statistical analysis

All continuous variables were expressed as mean ± SD. The two-tailed Student t test was used for analysis of continuous data. The chi-square test and Fisher exact test were used to compare differences between proportions. Agreement between 2 techniques was determined using the Cohen Kappa coefficient. A $p<0.05$ was considered statistically significant.

Results

Table 1, shows the patient and target lesion characteristics before balloon angioplasty. The majority of patients (56%) presented with unstable angina, and the vessel most frequently treated was the left anterior descending artery (46%). Most of the treated lesions were classified as soft (46%) or mixed plaques (46%) by intracoronary ultrasound. Fluoroscopy underestimated the presence of calcium

Table 2. Concordance between intracoronary ultrasound and contrast angiography for the determination of lesion eccentricity.

	Angio concentric	Angio eccentric	Total
ICUS concentric	18	6	24
ICUS eccentric	23	16	39
Total	41	22	63

Angio = contrast angiography; ICUS = intracoronary ultrasound.

at the target lesion as compared with ultrasound (11 patients,17% vs. 48 patients 76% respectively, $p < 0.0001$). A eccentric plaque was more often judged to be eccentric with ultrasound (41, 65%) as compared with angiography (24, 38%, ns). Table 2 shows the agreement of the eccentricity index between intracoronary ultrasound and angiography.

Angiographic measurements

Table 3 shows angiographic measurements before and after angioplasty. Minimal lumen diameter increased significantly following balloon angioplasty, from 1.10 ± 0.43 mm to 2.01 ± 0.47 mm ($p < 0.0001$). Balloon artery ratio using the measured mean balloon diameter balloon was 1.12 ± 0.25. Transient wall stretch during balloon inflation was 0.67 ± 0.25 of reference vessel size. Following balloon dilation 0.25 ± 0.17 of the target reference size was lost due to elastic recoil. Transient wall stretch and elastic recoil were not significantly influenced by the determined angiographic eccentricity. Relative wall stretch was directly correlated with relative elastic recoil ($Y = 0.281x + 0.064$, $r2 = 0.172$, $p < 0.005$).

Ultrasound measurements

Table 4 shows ultrasound measurements before and after angioplasty. After balloon dilation there was a significantly increase in lumen area from 1.81 ± 0.49 mm2 to 4.81 ± 1.39 mm2 ($p < 0.0001$). This was achieved by a combination of plaque reduction (1.72 ± 2.48 mm2, 57% of lumen gain) and permanent wall stretch (1.28 ± 2.29 mm2, 43% of lumen gain). Plaque composition did not seem to influence the magnitude of lumen gain after balloon dilation (2.73 ± 1.36 mm2 soft plaques vs. 3.24 ± 1.64 mm2 other types of plaques, $p = 0.21$). Figure 2 and 3 shows the influence of a disease free wall or an eccentric plaque as compared with more concentric plaques on the final luminal gain and the mechanisms of lumen enlargement following balloon dilation. The presence of a disease-free wall was associated with lower lumen gain following intervention (2.16 ± 1.23 mm2, disease-free wall vs. 3.57 ± 1.50 mm2, no disease-free wall, $p < 0.001$). Also, lumen enlargement after balloon angioplasty was obtained by different mechanisms according to the presence or absence of a disease-free wall. In patients with a disease-free wall, lumen enlargement was achieved mainly by wall stretch (1.40 ± 1.42 mm2, 65% of luminal gain) and additionally by plaque compression or redistribution (0.78 ±1.33 mm2, 35% of lumen gain). This

Table 3. Angiographic dimensional measurements.

Measurements	Pre-PTCA	Post-PTCA	Δ	p value
Reference MLD (mm)	2.86±0.65	2.89±0.61	0.06	ns
Reference CSA (mm2)	6.75±3.13	6.84±3.32	0.09	ns
Stenosis MLD (mm)	1.10±0.43	2.01±0.47	0.91	<0.0001
Stenosis CSA (mmm2)	1.09±0.92	3.34±1.60	2.25	<0.0001
% Diameter stenosis	61±15	30±13	31	<0.0001
% CSA stenosis	82±15	49±19	33	<0.0001
Eccentricity index	0.59±0.25			

CSA, cross-sectional area; MLD, minimal lumen diameter; PTCA, percutaneous transluminal coronary angioplasty.

Table 4. Ultrasound dimensional measurements.

Measurements (mm2)	Pre-PTCA	Post-PTCA	Δ	p value
Reference LA	8.71±3.46	8.84±3.24	0.13	ns
Stenosis LA	1.81±0.49	4.81±1.39	3.00	<0.0001
Stenosis EEM area	16.18±4.92	17.46±4.86	1.28	<0.0001
Stenosis P+M area	14.36±4.95	12.64±4.55	1.72	<0.0001
% Plaque area	87.71±5.06	71.43±8.63	16.28	<0.0001
Eccentricity index	0.43±0.21			

EEE, external elastic membrane; LA, lumen area; PTCA, percutaneous transluminal coronary angioplasty.

contrasted with the mechanisms of lumen enlargement when there was not a preserved arc of normal wall (wall stretch 1.41±1.80, 39% of luminal gain, plaque compression or redistribution 2.16 ± 1.94, 61% of luminal gain). These differences in the mechanisms and magnitude of balloon dilation were due to the presence of a disease free segment and not the result of plaque eccentricity, since eccentric plaques with or without a disease-free wall had a similar lumen gain after balloon angioplasty as compared with concentric plaques (3.00 ± 1.65 mm2, eccentric plaques vs. 3.02 ± 1.33 mm2, concentric plaques, ns) and comparable mechanisms of lumen enlargement (wall stretch 1.36 ± 1.70 mm2, 45% of the luminal gain, eccentric plaques vs. wall stretch 1.42 ± 1.69 mm2, 47% of the luminal gain, concentric plaques).

Lumen morphology after balloon dilation

Table 5 shows the concordance between intracoronary ultrasound and angiography for the detection of dissections (Table 5) after balloon dilation. Intracoronary ultrasound detected dissections more frequently than angiography (35 patients, 56% vs. 20 patients, 37% respectively, p=0.01). Additionally an

irregular lumen contour was identified in 22 (35%) more patients with ultrasound. The degree of agreement between the 2 techniques for the detection of dissections was low (kappa 0.30). Figure 4 shows an example of dissection starting at the transition of the normal wall with the atheroma. After balloon

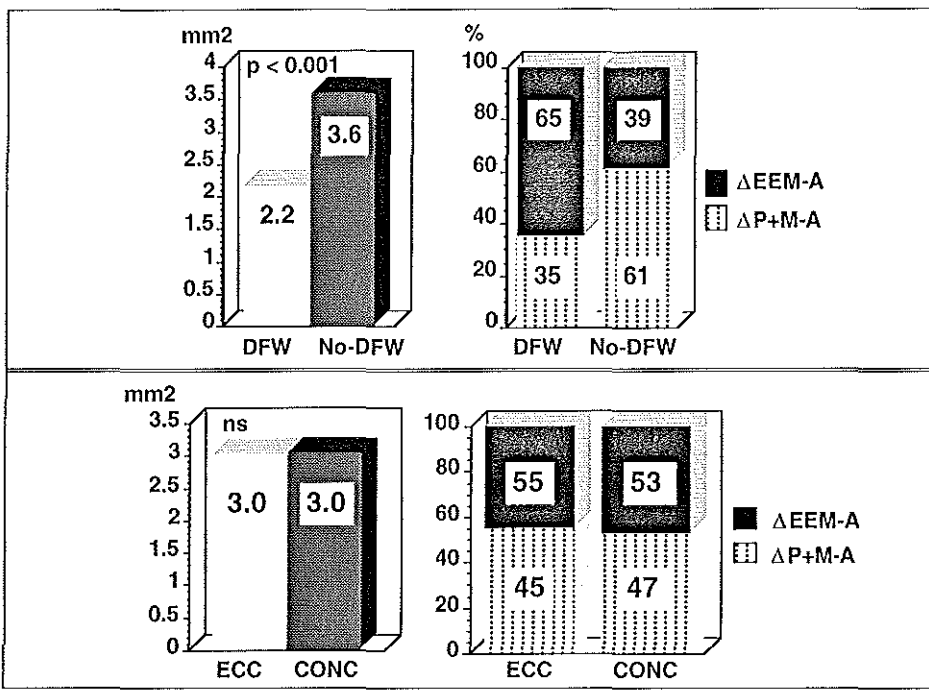

Figure 2 (top) and 3 (bottom).

Top, influence of a disease-free wall (DFW) on the luminal gain (top left) and on the mechanisms of lumen enlargement (top right) after balloon angioplasty. Bottom, influence of plaque eccentricity on the gain and on the mechanisms of luminal gain following angioplasty. Note that its the presence of a disease-free wall and not plaque eccentricity that determines the magnitude of the luminal gain following balloon dilation.

(ECC, eccentric plaque, CONC, concentric plaque).

dilation soft plaques as compared with other morphologic plaque compositions were associated with a lower dissection rate (soft plaques 13/29, 37% vs. 22/34, 63% in other types of plaques, p=0.006). The presence of calcium in the plaque was not a predictor of vessel dissection after angioplasty (calcific plaques 28/48, 58% vs. 7/15, 47% no calcium, ns). Ultrasound determined plaque eccentricity was not associated with a higher likelihood of developing dissection after balloon dilation (eccentric plaques 24/41, 59% vs. 11/22, 50% concentric plaques, ns). There was a trend towards a larger luminal gain as evaluated by ultrasound when dissections were present after angioplasty (3.27 ± 1.68 mm2, dissection vs. 2.72 ± 1.35 mm2 no dissection, ns).

Table 5 - Concordance between intracoronary ultrasound and contrast angiography for the detection of dissections.

	Angio smooth	Angio dissection	Total
ICUS smooth	24	4	28
ICUS dissection	19	16	35
Total	43	20	63

Angio = contrast angiography; ICUS = intracoronary ultrasound, Angio dissection = dissection class type B or higher; ICUS dissection = tear or dissection.

Discussion

Until recently, the mechanisms of lumen enlargement following balloon angioplasty were mainly derived from necropsy, animal models or in-vitro studies [27-31]. Extrapolation of these data to a clinical setting may be misleading since several bias may occur. For instances, patients dying after balloon angioplasty, may have a higher rate of extensive dissections when compared with survivors. Animal studies of induced atherosclerosis, have a preponderance of soft young plaques, different from the more heterogeneous plaque composition found in in-vivo patients and therefore different mechanisms of lumen enlargement may operate [32]. Additionally, when angiography is used as the investigational technique, because it only represents a shadowgram of the vessel lumen, the mechanisms of balloon dilation might be inappropriately assessed[1,2].

Despite the high success rate of balloon angioplasty, this technique as opposed to surgical techniques is performed in "semi-blinded" way, since a direct visualization of the target lesion is not routinely performed. Furthermore, the same treatment (balloon inflation) is applied to the majority of plaques irrespective of their histological composition and morphology. It is appealing to think, that new devices may have a higher impact if used on those plaque types associated with a lower success rate or high complication rate following balloon dilation.

The first conclusions of our study, is that they are important discrepancies between ultrasound and angiography, for the correct identification of plaque calcification, plaque eccentricity and residual plaque burden. All these parameters were underevaluated by angiography, and our results are in agreement with others[33]. Because of the potential impact of undetected vessel calcification and eccentricity on the outcome of some revascularization techniques such as laser and atherectomy[34-35] ultrasound guidance may be of considerable help in the selection of the most appropriate revascularization device. Also importantly the angiographic unsuspected residual plaque burden[36], may bear important impact on the renarrowing process[7]. A recent interim analysis of the GUIDE trial[7] identified residual plaque burden by ultrasound as one of the most important

predictive factors for restenosis among several angiographic and ultrasound parameters.

Comparison with previous studies

Although the first described mechanisms of lumen enlargement was plaque compression[37-39], necropsy studies identified plaque dissection as the most significant mechanism[32,40]. Only recently, intravascular ultrasound was used to elucidate the mechanisms of lumen enlargement following balloon dilation in vivo[41-43]. In peripheral arteries, dissections were reported in a high percentage and were selected as the most important mechanism of vessel enlargement secondary to neo-lumen formation[41]. However, the relative contribution of this mechanism is more difficult to assess in coronaries arteries, because the relatively bulky ultrasound catheters can "tack-up" dissections against the vessel wall rendering the detection of dissections more elusive. In our study ultrasound clearly identified wall dissection in 56% of the patients and an irregular lumen contour compatible with small intimal tears in more 35% of the patients. Therefore, the true incidence of plaque fractures is underevaluated even with ultrasound, as shown by angioscopy that identifies flaps and dissections in 94% of the cases following balloon dilation[44]. It is possible that plaque fracture is an prerequisite to achieve acute wall dilation, as it has been suggested by necropsy[32] and ultrasound studies[8]. Our data also indicate that "limited" plaque fracture is important to achieve a larger lumen dimension, as there was a trend towards a larger luminal gain in dissected plaques vs. plaques without discernable dissection, respectively 3.27 ± 1.68 mm2 vs. 2.72 ± 1.35 mm2. In addition, Honye et al.[8] observed a higher restenosis rate in concentric plaques without dissection suggesting that limited wall dissection can be beneficial for a long term lumen patency. In our study wall stretch and plaque compression or redistribution contributed in similar proportions to the final lumen dimensions following angioplasty (43% vs. 57%, respectively). Our results are a compromise between those reported by The et al.[45] who identified wall stretch as the major responsible (77% of the lumen gain) for the lumen gain or those of Suneja et al.[42] who reported plaque reduction as major mechanism of angioplasty (94% of the lumen gain). These discrepancies in the mechanisms of balloon dilation may be in part the result of different plaque morphologies. Although permanent wall stretch is an important mechanism of lumen enlargement, angiography identified that 25% of the potential lumen gain was immediately lost after balloon deflation as a result of the elastic recoil. The only variable related to the magnitude of the elastic recoil was temporary stretch as already described by others[46]. The poor correlation between angiographic and ultrasound lumen dimension after angioplasty[47] may explain the lack of correlation between plaque composition or morphology and the magnitude of the elastic recoil. Although Isner et al.[48] reported the combined use of balloon-ultrasound catheter for the measurements of recoil that could achieve 61% of inflated balloon cross sectional area, the small number of patients in this study precluded further analysis of recoil as a function of plaque composition.

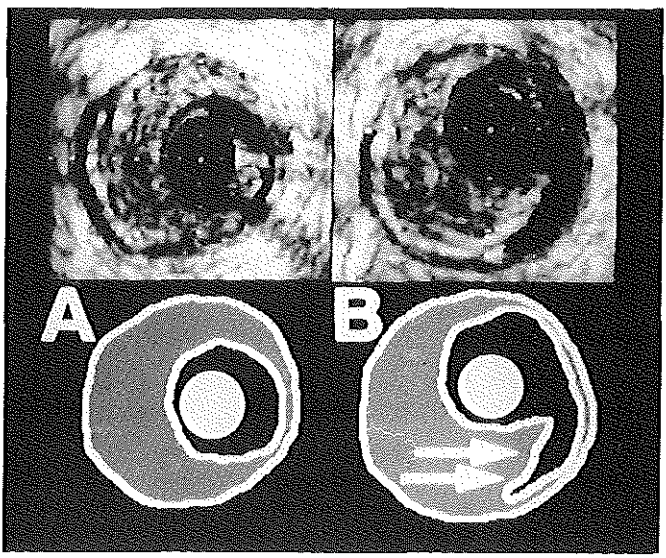

Figure 4.
An example of a wall dissection occurring at the transition of the normal wall with the atheroma.

Influence of plaque composition and thickness on the results of balloon dilation

Necropsy studies have indicated that eccentric lesionswith a disease-free wall are mainly dilated by localized wall stretching[32]. Our study confirms in vivo that the presence of a relatively disease-free wall has considerable impact on the mechanisms of lumen enlargement following balloon angioplasty. Stenotic lesions with a disease-free wall were associated with lower lumen gains after balloon dilation (2.16 ± 1.23 mm2, disease-free wall vs. 3.57 ± 1.50 mm2, no disease-free wall, $p < 0.001$) and this lumen enlargement was mainly obtained by wall stretch (65% of luminal gain) as opposed to plaques without a disease-free wall (35% of lumen gain). Moreover, this phenomena was specifically related to the presence of a disease free wall, because eccentric plaques as opposed to concentric plaques did not respond in a different manner after balloon angioplasty. These findings are supported by other studies that demonstrate that lesions with a disease-free wall because they have a preserved segment of media, may be more prone to vasospastic phenomena[49] and higher elastic recoil[50]. However, recoil is most likely the explanation for the lower luminal gain obtained by these plaques, since intracoronary dinitrate isorsobide was given routinely prior to each ultrasound examination to relieve any abnormal vasomotor tone. These data are in disagreement with necropsy data showing larger lumen gains after angioplasty were observed in eccentric plaques[40]. It should be pointed out in postmortem analysis that balloon dilation has taken place prior to the morphometric analysis so that plaque remodeling and redistribution[51] induced by the barotrauma may have interfered and thereby invalidated the conclusions of these necropsy studies. In our study plaque thickness and the eccentricity index were measured prior to

balloon dilation.
Dissections after angioplasty generally occur at areas of local high shear stress[52] at transitions between normal wall and atheroma[53] or near deposits of calcium[54]. Our date did not clearly identify a particular plaque type with a higher likelihood of developing dissection. However, in the majority of patients calcium was present in less than 25% of the vessel circumference and the true incidence of plaque fractures is underestimated by ultrasound in the coronary arteries[44].

Conclusions

Intracoronary ultrasound provides a more detailed information concerning plaque composition and morphology as compared with contrast angiography that may bear important significance for a better planning of coronary interventions. The presence of a stenotic lesion with a remnant arc of disease-free wall as judged by ultrasound is associated with a lower lumen gain probably due to higher elastic recoil. Alternative devices, such as stents or directional atherectomy may be selected on these lesions to improve the immediate and eventually the long term results of coronary interventions.

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Chapter X

Mechanisms of Luminal Enlargement and Quantification of Vessel Wall Trauma Following Balloon Coronary Angioplasty and Directional Atherectomy. A Study using Intracoronary Ultrasound, Angioscopy and Angiography.

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Abstract

Objectives

The purpose of this study was to assess the dual action of enlargement of the lumen and damage of the vessel wall following either balloon angioplasty or directional atherectomy, using intracoronary ultrasound, and angioscopy.

Background

Differences in mechanisms of action of balloon angioplasty and directional atherectomy may have a significant bearing on either the immediate outcome and the 6 months restenosis.

Methods

A total of 36 patients were studied before and after either balloon angioplasty (n=18) or directional atherectomy (n=18). Ultrasound measurements included changes in lumen area, external elastic membrane area and plaque burden. In addition, the presence and extent of dissections were assessed to derive a damage score. Angioscopic assessment of the dilated or atherectomized stenotic lesions was translated into semi-quantitative dissection, thrombus and hemorrhage scores.

Results

Atherectomy patients had a larger angiographic vessel size compared with the angioplasty group (3.55±0.46 mm vs. 3.00±0.64 mm, p<0.05), however minimal lumen diameter (1.18±0.96 mm vs. 0.85±0.49 mm) and plaque burden (17.04±3.69 vs. 15.23±4.92 mm2) measurements did not differ significantly. As a result of plaque reduction, atherectomy produced a larger increase in luminal area compared to the angioplasty group (5.80±1.78 mm2 vs. 2.44±1.36 mm2, p<0.0001). Lumen increase after angioplasty was the result of "plaque compression" (50%) and wall stretching (50%). Additionally, in both groups there was indirect angioscopic evidence of thrombus "microembolization" as an adjunctive mechanism of lumen enlargement. Angioscopy identified big flaps in 6 and small intimal flaps in 11 of the atherectomized patients as compared with 5 and 12 patients in the angioplasty group. Changes in thrombus score following both coronary interventions were identical (0.72±3.42 points atherectomy vs. -0.38±3.27 points balloon angioplasty, ns).

Conclusions

Lumen enlargement after directional atherectomy is mainly achieved by plaque removal (87%), whereas balloon dilation is the result of vessel wall stretching (50%) and plaque reduction (50%). Despite the fact that the luminal gain achieved by directional atherectomy is twice as large as with balloon angioplasty, the extent of trauma induced by both techniques seems to be similar.

Introduction

Most of the studies addressing the mechanisms of enlargement of the lumen and damage of the vessel wall following either balloon angioplasty (PTCA) or directional atherectomy (DCA) are derived from necropsy studies [1-9] and just a few use ultrasound for an in vivo estimation of these mechanisms [10-19]. Therefore, the mechanisms underlying the dual action of enlargement of the lumen and damage to the vessel wall in vivo are yet not fully elucidated. Their understanding may have important implications for the immediate and long term outcome and may facilitate selection of a specific device for a specific lesion.
In the animal model the restenotic process is proportional to the amount of trauma inflicted to the vessel wall [20-24] therefore it is appealing to identify new prognostic markers of restenosis using the combined information provided by new diagnostic tools, such as intracoronary ultrasound and angioscopy. These techniques provide a unique opportunity to assess the changes induced by balloon angioplasty or DCA, on plaque volume and coronary lumen (10-19), as well as changes of the intimal surface [25-32]. This previously irretrievable information in vivo may facilitate insights into the mechanisms of DCA and balloon angioplasty.
The purpose of this study is to assess the mechanisms of balloon angioplasty as compared to directional atherectomy and to characterize semi-quantitatively the nature and extent of wall trauma, using intracoronary angioscopy and intravascular imaging.

Methods

Study patients
The study population consisted of 36 patients (31 men and 5 women with a mean age of 59±9 years) who underwent elective coronary balloon angioplasty (n=18) or directional atherectomy (n=18). Fourteen patients presented with unstable angina (class II B, III B, II C and III C, in the Braunwald classification) [33], and 22 presented with stable angina pectoris. The investigations were approved by the Institutional Board of the Cardiology Department of the Dijkzigt Ziekenhuis and the patients were studied only after giving informed consent.

Quantitative coronary angiography
All 35 mm films were analyzed using the Cardiovascular Angiography Analysis System II (CAAS II, Pie Medical, The Netherlands). The automated edge detection of this system have been validated and is described in detail elsewhere[34-38]. Lesion eccentricity was defined as the coefficient of the left hand distance and the right hand distance between the reconstructed interpolated reference diameter and actual vessels contours, at the site of obstruction. In this equation, the largest distance between actual and reconstructed contours becomes the denominator, so that a perfectly symmetrical lesion has a value of 1 and a severely eccentric lesion has a value of zero

Angiographic determined damage
Since it has been shown that the relative loss in minimal luminal diameter at follow-up is proportional to the acute relative gain [39-43], we used this index as a measure of angiographic determined trauma. Dissections were evaluated according to the modified classification of the Blood, Lung and Heart Institutes [44-45]. A dissection was classified as type A in the presence of a small radiolucent area within the lumen of the vessel and as type B or C when there was an extravasion of non persisting or persisting contrast medium respectively. A dissection was classified as type D in the presence of spiral-shaped filling defect with delayed distal flow and as type E if a persistent lumen defect with delayed antegrade flow was seen on the final angiogram. A filling defect accompanied by a total coronary occlusion was classified as type F dissection .
Temporary wall stretch [46] was defined as: (device cross sectional area minus minimal lumen cross sectional area pre-intervention) divided by reference cross sectional area before intervention. Elastic recoil [46] was defined as: (device cross sectional area minus minimal lumen cross sectional area after intervention) divided by reference cross sectional area before intervention. Atherectomy device cross sectional area was calculated taking into account the elliptical shape of the device and using as short axis the diameter of the housing chamber, and as long axis the inflated balloon diameter.

Ultrasound device
Before and after coronary interventions a mechanical 4.3 Fr intravascular ultrasound catheter (INSIGHT "3" ultrasound system, CVIS, Sunnyvale, CA) was introduced through a 0.014 inch high torque floppy guide wire. The segment comprising the stenotic lesion was examined over its entire length using side branches as landmarks and the images were recorded on S-VHS videotape. To improve the delineation of the leading edge echo, intracoronary injection of saline was applied when necessary. The measurement system was digitally calibrated, and after a careful review of each videotape, one image at the site of the minimal luminal cross sectional area before and after intervention was selected for quantitative analysis.
The integrated information acquired during the pullback manoeuvre along the stenotic segment was used to classify plaque composition according to their ultrasonic appearance [47-50] as follows:
Soft plaques : More than 75% of the plaque area is composed of tissue 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 degrees of vessel wall circumference.
Mixed plaques: :When there occurs a combination of different types of plaque composition.

Additionally, ultrasound dimensional calculations were calculated as follows [49]: *Luminal area*: integrated area central to the leading edge of the intimal echo; *External elastic membrane area*: integrated area central to media-adventitia interface; *Plaque plus media area* (P+M): difference between external elastic membrane area and luminal area; *Acute vessel dilation* difference in external elastic membrane area before and after intervention. In the presence of calcific plaques, the contour of the external elastic membrane was drawn assuming a circular vessel shape in the shadowed segment or drawing the contour of the continuous vessel segment without calcium.

Variability of the ultrasound determined lumen dimensions

We have previously reported [51] the correlation of ultrasound luminal dimensions with circular phantoms and human coronary casts. The correlations coefficient and mean differences ± SD between ultrasound measurements and coronary luminal areas of the casts were 0.90 and 0.63±0.71 mm2 and for circular phantoms 0.99 and -0.08±0.39 mm2, p=0.012. In 40 patients studied before and after balloon angioplasty, we found a good correlation (r=0.86, Y=0.37+0.95x, SEE=1.06) between observers for the minimal cross sectional area measurements at the stenotic lesion [52]. The mean difference of the measurements of all lesion cross sectional areas by both observers was 0.61±1.05 mm2 and was statistically significant (p<0.0001).

Ultrasonic damage score

Tears were defined as demarcated, focally superficial breaks in the linear continuity of the plaque that extended solely in a radial direction and dissections were defined as demarcated breaks in the linear continuity of the plaque with circumferential or longitudinal involvement of the internal elastic membrane [11]. For the purpose of quantifying the amount of damage to the internal elastic lamina, a ultrasonic damage score was derived: Tears (1 point); Dissections involving less than 25% of the vessel circumference (2 points); Dissections involving more than 25% but less than 50% of the vessel circumference (3 points); Dissections involving more than 50% of the vessel circumference (4 points).

Fiberoptic intracoronary angioscopy

Before and after coronary interventions and prior to the echo examination a 4.5 F coronary angioscope (ImageCath, Baxter Laboratories, Irvine, California) was used to visualize the lesion along its length. After positioning the angioscope over the wire (0.014 inch) in the segment to be examined, the balloon is inflated and a continuous flushing with the Ringer's lactate at body temperature is performed at infusion rates between 30 to 50 ml/min. Once the crystalloid solution has cleared the image field, the tip of the catheter is advanced to explore the lesion under study with an extension range of 5 cm. During this procedure all the images were viewed using a high resolution monitor (PANASONIC BT-M 1420 PY) and simultaneously recorded on a S-VHS tape for off-line review to achieve the

consensus of 2 observers.

Angioscopic classification of vessel trauma

For a qualitative assessment of the intimal vessel trauma, the following parameters were evaluated using a previously validated classification designed by the European working group of angioscopy [53]: Mural thrombus was defined as a red, predominantly mural, non-mobile, superficial mass adhered to the vessel surface.

Table 1. Patient and target lesion characteristics prior to coronary interventions.

Demographics	PTCA (n=18)	DCA (n=18)	p value
Age (mean ± SD)	60±11	58±7	NS
Sex			
Male gender	16 (89%)	15 (83%)	NS
Angina type			
Unstable	14 (78%)	8 (45%)	0.08
Vessel treated			
LAD	7 (39%)	13 (72%)	0.09
LCX	4 (22%)	2 (11%)	NS
RCA	7 (39%)	3 (17%)	NS
ICUS characteristics			
Soft plaques	10 (56%)	10 (56%)	NS
Fibrous plaques	0	0	NS
Diffuse calcific	1 (6%)	0	NS
Mixed plaques	7 (39%)	8 (44%)	NS
No or focal calcium	11 (61%)	11 (61%)	NS
Calcium > 25% P+M	7 (39%)	7 (39%)	NS
Angioscopic characteristics.			
Presence of Thrombus	12 (67%)	5 (28%)	0.05
Mural Thrombus	10 (56%)	1 (6%)	0.004
Protruding thrombus	2 (11%)	4 (22%)	NS

DCA = directional atherectomy, ICUS = intracoronary ultrasound, LAD = left anterior descending artery, LCX = left circumflex artery, PTCA = percutaneous balloon coronary angioplasty, RCA = right coronary artery.

Protruding thrombus as a red, intraluminal protruding , mobile or non-mobile mass adhered to the vessel surface. Occlusive thrombus when a red intraluminal mass occluded completely the lumen. Wall hemorrhage was defined as a distinct, demarcated, red, non-elevated discoloration of the vessel wall. Small surface disruptions were defined as small, very mobile structures which are contiguous

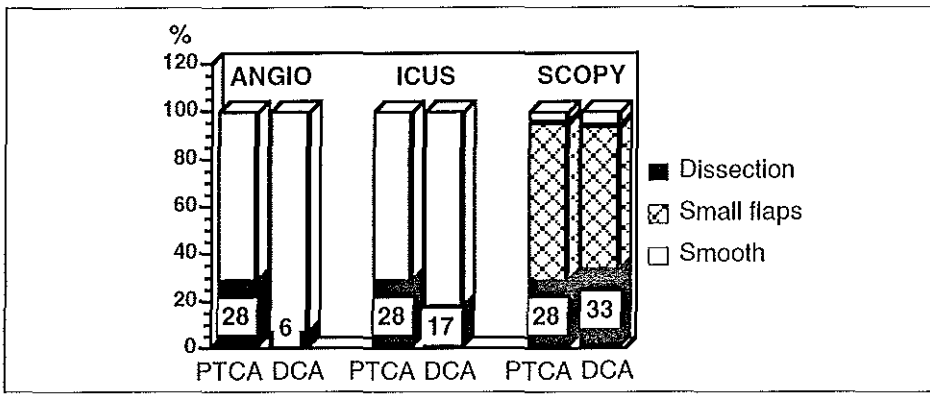

Figure 1.
Percent frequency of dissections detected by each technique.

with the vessel wall. They do not impede the visualization of the lumen. Large dissections were defined as visible cracks or fissures on the luminal surface and/or large mobile or non-mobile protruding structures, which are contiguous and have homogeneous appearance with the vessel wall. They partially impede visualization of the lumen.

Interobserver variability of angioscopic data
The angioscopic diagnosis of thrombus and dissection was associated with the higher intra- and inter-observer agreements using the Ermenonville classification (53). Intra-observer agreement for dissections and red thrombus were 77% (kappa 0.57), and 82 % (kappa 0.57) respectively, while the inter-observer variability was 53% (kappa 0.27) and 71 % (kappa 0.29) respectively.
Angioscopic damage scores. In order to establish a semi-quantitative evaluation of the amount of trauma/disruption present in each angioscopic inspection three scores were derived by computing the type of trauma (hemorrhage, thrombus, dissection) present in each stenotic subsegment by the number of subsegments involved (proximal, middle, and distal stenotic segments). The hemorrhagic score consisted of 0.5 point for single hemorrhage and 1 point for multiple hemorrhage. The thrombus score consisted of 1 point for a single lining thrombus, 2 points for multiple lining thrombus, 3 points for protruding thrombus and 4 points for occlusive thrombus. The dissection score consisted in 1 point for a single small flap, 2 points for multiple small flaps and 3 points for big flap(s) or disruption. Additionally, a delta score was computed by subtracting from the post-intervention scores the pre interventions scores.

Procedure Technique
During the procedures all patients received aspirin (250 mg) and i.c. isorsobide dinitrate (1-3 mg) before and after the procedure and were fully anticoagulated with heparin, providing an activated clotting time in excess of 300 seconds. Selective coronary arteriography was performed in multiple matched views before

and after the coronary interventions. After the passage of a 0.014 inch guide wire across the target lesion, sequential coronary angioscopy and intravascular ultrasound were performed with the guidance of a fluoroscopic window and multiple contrast injections. This technique assured proper comparison between angioscopic, echocardiographic, and angiographic images. Coronary angioplasty and directional atherectomy were performed according to standard practice, using the post intervention ultrasonic and angioscopic images to achieve an optimal final result. In this cohort all patients selected for atherectomy were solely treated with atherectomy.

Histology

After atherectomy, histological examination of the retrieved specimens was used to determine the depth of the wall cut according to the histological identification of fragments of the intima, media or adventitia [54-55].

Statistical analysis

All continuous variables were expressed as mean ± SD. The two-tailed Student's t test was used for analysis of continuous data. A chi-square test and Fisher's exact test were used to compare differences between proportions. The Mann-Whitney rank sum test was used to compare ordinal data (scores). A p value of < 0.05 was considered statistically significant .

Table 2. Quantitative angiographic measurements in the two treatment groups

Measurements	PTCA (n=18)	DCA (n=18)	p value
Reference MLD- Pre (mm)	3.00±0.64	3.55±0.46	0.007
Reference CSA Pre (mm2)	7.40±3.2	10.06±2.88	<0.05
Eccentricity index	0.60±0.20	0.66±0.20	NS
Stenosis MLD Pre (mm)	0.85±0.49	1.18±0.96	0.05
Stenosis MLD Post (mm)	1.90±0.58	2.75±0.63	0.0002
Stenosis CSA Pre (mm2)	0.75±0.59	1.25±0.96	0.07
Stenosis CSA Post (mm2)	3.09±1.89	6.27±2.70	<0.0001
% Diameter stenosis Pre	70±18	67±12	NS
% Diameter stenosis Post	33±17	25±15	NS

DCA = directional atherectomy, CSA = cross sectional area, MLD = minimal lumen diameter, PTCA = percutaneous balloon coronary angioplasty.

Results

The demographic characteristics of the patients, the baseline ultrasound and the angioscopic characteristics of the target lesions prior to intervention are shown in Table 1. There was a higher percentage of patients with unstable angina in the balloon angioplasty group, whereas a higher percentage of left anterior descending target stenosis was seen in the atherectomy group. The prevalence of unstable angina (14 vs. 8 patients, p=0.08) and red thrombus (12 vs. 5 patients, p=0.05) was higher in the conventional angioplasty group as compared with atherectomy group, although no significant difference in the echocardiographic determined type of plaque was observed. After intervention, the incidence of thrombus in both groups was similar (11 patients, balloon angioplasty vs. 12 patients, atherectomy, ns).

Table 3. Ultrasound quantitative measurements in the two treatment groups.

Measurements (mm2)	PTCA (n=18)	DCA) (n=18	p value
Reference LA Pre	8.64±2.78	10.31±2.63	0.09
Stenosis LA Pre	1.73±0.59	1.96±0.77	NS
Stenosis LA Post	4.38±1.53	7.57±2.02	<0.0001
Δ Stenosis LA	2.44±1.36	5.80±1.78	<0.0001
Stenosis EEM area Pre	16.96±4.90	19.00±3.78	NS
Stenosis EEM Post	18.10±4.79	20.28±4.25	NS
Δ stenosis EEM area	1.22±2.67	0.73±1.38	NS
Stenosis P+M area Pre	15.23±4.92	17.04±3.69	NS
Stenosis P+M area Post	13.72±4.60	12.70±4.17	NS
Δ P+M area	1.22±1.78	5.07±2.27	<0.0001
% Plaque area Pre	89±5	89±4	NS
% Plaque area Post	74±10	62±9	<0.0001
Delta % Plaque area	15±8	29±7	<0.0001

DCA = directional atherectomy, EEM = external elastic membrane, LA = lumen area, MLD = minimal lumen diameter, P+M = plaque plus media, PTCA = percutaneous balloon coronary angioplasty.

Angiographic data

Quantitative angiographic measurements in both treatment groups are shown in Table 2. Patients treated with directional atherectomy had larger reference diameters (3.55 ± 0.46 mm atherectomy vs. 3.00 ± 0.64 mm balloon angioplasty, p<0.01,), and larger minimal lumen diameters at the stenotic sites prior to the procedure (1.18 ± 0.46 mm atherectomy vs. 0.85 ± 0.49 mm balloon angioplasty,

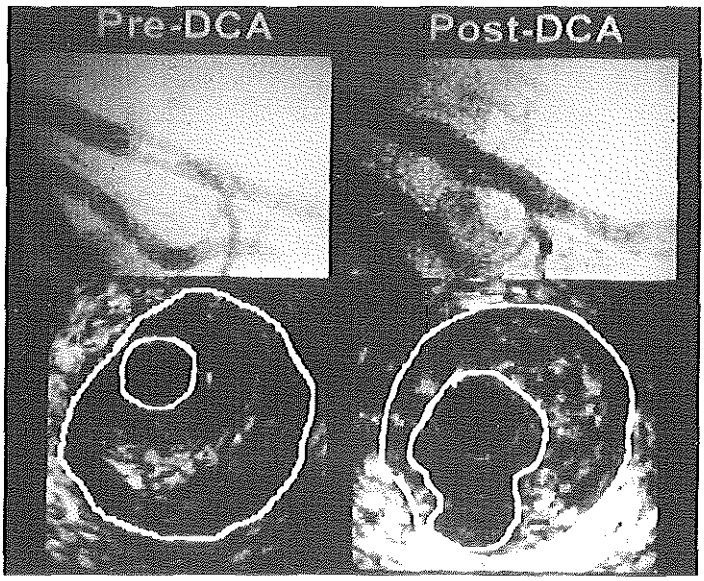

Figure 2.
A very eccentric soft plaque before and after atherectomy. Despite the good angiographic result after intervention, ultrasound identified an important residual plaque burden and an atherectomy "bite" in the normal wall. Histology identified components of adventitia.

p=0.07), as expected. After intervention, patients in the atherectomy group showed a significantly larger increase in lumen dimensions as compared to the balloon angioplasty patients, resulting in a final larger minimal lumen diameter (2.75 ± 0.63 mm atherectomy vs. 1.90 ± 0.58 mm balloon angioplasty, p < 0.001), a larger relative gain (0.52 ± 0.26 atherectomy vs. 0.31 ± 0.20 balloon angioplasty, p=0.01) but a similar residual percent diameter stenosis (25 ± 15% vs. 33 ± 17%, ns).

Ultrasound data

Ultrasound derived quantitative measurements in the two groups of patients are given in Table 3. Reference luminal area was also larger with intravascular ultrasound in the atherectomy group (10.31 ± 2.63 mm2 atherectomy vs. 8.64 ± 2.78 mm2 balloon angioplasty, p = 0.09). Despite a normal angiographic appearance of the reference segment, the plaque area occupied roughly 50% of the external elastic membrane area in both groups of patients. After intervention, patients treated with directional atherectomy showed a significantly larger increase in lumen dimensions than in those patients treated with the balloon dilation, which resulted in a final larger luminal area (7.57 ± 2.02 mm2 atherectomy vs. 4.38 ± 1.53 mm2 balloon angioplasty, p<0.0001) and in a smaller percent plaque area (62 ± 9%, atherectomy vs. 74 ± 10%, balloon angioplasty, p=0.0005). The larger lumen gain achieved in the atherectomy group (5.80 ± 1.78 mm2 atherectomy vs. 2.44 ± 1.36 mm2, balloon angioplasty, p<0.0001) was obtained

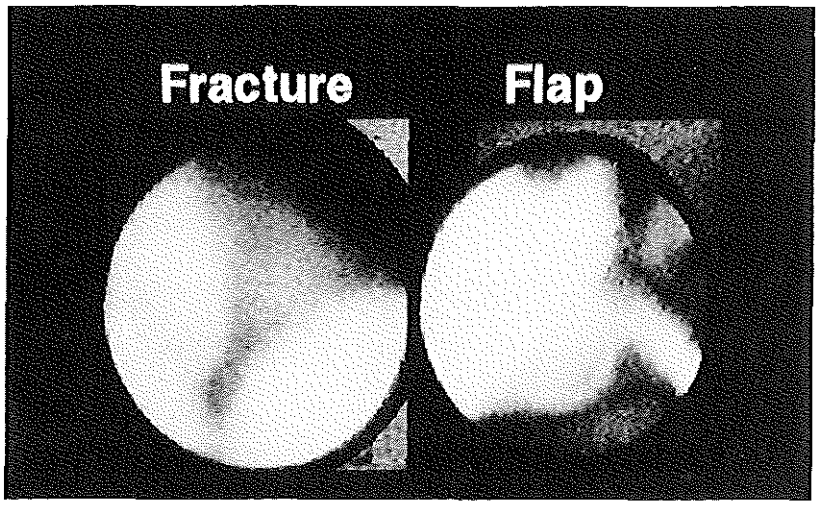

Figure 3.
Angioscopic appearance of a plaque fracture and flap, typically occurring after balloon angioplasty.

by a significantly reduction of plaque (5.07 ± 2.27 mm2 atherectomy vs. 1.22 ± 2.67 mm2 balloon angioplasty, p<0.0001). Thus plaque reduction accounted for 87% of the lumen gain obtained with atherectomy whereas with conventional angioplasty lumen gain was achieved in similar proportions (50%) by wall stretch (Δ EEM) and plaque reduction or redistribution (Δ P+M).
There was a trend towards augmented luminal enlargement and large plaque reduction following atherectomy, when the procedure was performed on soft plaques rather than on other types of plaques (6.19 ± 1.71 mm2 vs. 5.30 ± 1.87 mm2, respectively, p=0.34). Plaque composition did not seem to influence the outcome of balloon angioplasty.

Semi-quantitative assessment of vessel wall injury
The computed damage scores observed after each type of intervention are given in Table 4. All of these damage scores showed a remarkable similarity after each coronary procedure with the exception of relative gain, plaque reduction and angiographic recoil. Figure 1 shows the frequency of dissections detected by each technique. It is evident that angiography as compared to intracoronary ultrasound and angioscopy underestimates the number of dissections. In the atherectomized vessels, angioscopy identified 6 (33%) big flaps and 11 (61%) small intimal flaps compared with 5 (28%) and 12 (67%) in the angioplasty group.
The ultrasound damage score was larger after balloon angioplasty than after atherectomy (Table 4). In this group, intracoronary ultrasound detected atherectomy "bite" in the obstructing plaque in 15 (83%) patients. Of these specimens, histologic examination identified the presence of media in 5 patients and adventitia in 3 additional patients. Figure 2 shows the ultrasound appearance of a cut in the normal wall. Similar to the ultrasonic scores, the semi-quantitative

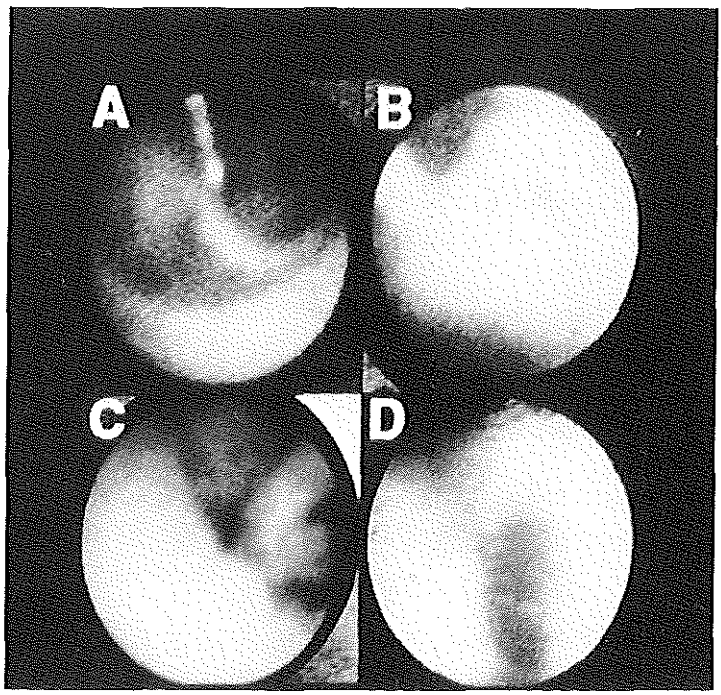

Figure 4.
Four different patterns of damage following either balloon angioplasty or directional atherectomy. A = hemorrhage; B = a flap with an attached red thrombi to its tip; C and D = disruption of the fibrous cap with extrusion of yellow material (lipid) and thrombus formation.

angioscopic damage score did not disclose any difference in the intimal damage (hemorrhage, thrombus and dissection) between the two groups. Figures 3,4 and 5 exemplify different types of trauma and thrombi seen after intervention. A graphic representation of the procedural change of the "thrombotic burden" is shown in Figure 6. It is important to note that thrombi decreased or disappeared in 7 (39%) patients in the conventional angioplasty group and in 4 (22%) patients in the atherectomy group. Only 3 patients in the balloon group and 6 patients in the atherectomy group were without thrombus before and after the coronary procedures. Plaque composition was not specifically associated with development of thrombus or dissections after coronary interventions.

Discussion

Mechanisms of action of balloon angioplasty and directional atherectomy

Necropsy studies after balloon angioplasty suggest that the major mechanism of lumen enlargement is plaque rupture and localized medial dissection [1-8]. This

Table 4. Delta damage scores after coronary interventions.

Scores	PTCA	DCA	p value
Angiography			
Relative gain (%)	0.31±0.20 (2)	0.52±0.26 (1)	0.01
Temporary wall stretch (%)	57.3±24.6 (1)	53.5±13.7 (2)	NS
Recoil (%)	21.0±22.3 (1)	3.5±29.3 (2)	0.05
ICUS			
Stretch (mm2)	1.22±2.67 (1)	0.73±1.38 (2)	NS
Plaque reduction (mm2)	1.22±2.67 (2)	5.07±2.27 (1)	<0.0001
ICUS damage score	2.40±1.51(1)	1.30±0.57(2)	NS
Angioscopy			
Dissection score	3.38±2.17 (1)	3.38±1.19 (1)	NS
Thrombus score	-0.38±3.27 (2)	0.72±3.42 (1)	NS
Hemorrhage score	1.47±1.85 (2)	1.77±1.90 (1)	NS
TOTAL	13 points	13 points	

DCA = directional atherectomy, ICUS = intracoronary ultrasound, PTCA = percutaneous balloon coronary angioplasty. In brackets are given 1 or 2 points for the comparison of the different damages scores between the two interventions (1 point = higher damage, 2 points = lower damage)

generally occurs at regions of higher shear stress at the thinnest portion of atheroma, or at the junction of atheroma with the normal arterial wall [10-11]. Although plaque compression may also play a role in vitro [56-58], the magnitude of this phenomenon in vivo is uncertain [11,6]. Nevertheless, three-dimensional ultrasound reconstruction [59] of human coronary arteries has indicated that axial plaque redistribution may occur during balloon dilatation.

In a effort to overcome some of the limitations of conventional angioplasty, directional atherectomy was introduced as a debulking device with the potential of minimizing vessel wall damage, as documented by the smooth appearance of the post procedure angiogram. Studies using contrast angiography indicated that the so called "Dotter-effect" results in 50- 60 % of the final luminal gain [60-61]. However, recent ultrasound studies clearly identified plaque reduction as the major determinant of lumen increase after this procedure [15,16,62].

Comparison with previous studies

Our data shows that two major mechanisms account for lumen enlargement after balloon angioplasty. Acute vessel expansion (Δ EEM) and plaque reduction (Δ P+M) contributed in equivalent proportions (50%) to the final luminal gain achieved in these patients. However, it is not possible from our data to know whether plaque reduction was the result of plaque compression or redistribution.

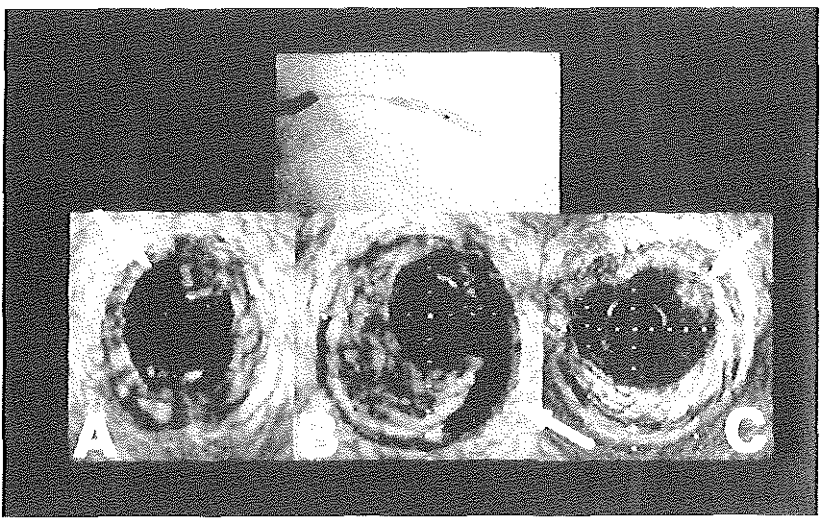

Figure 5

Different ultrasound patterns of trauma to the vessel wall following balloon angioplasty. A= tear (arrow) ; B = wall dissection C = thrombi (arrow)

There are a few published studies addressing the mechanisms of balloon angioplasty with quantitative measurements performed before and after intervention [13,16,63]. The relative contribution of the different mechanisms yielding increased lumen area vary among the different studies. At one extreme, The et al [63] suggest that wall stretch account for 77% of the luminal gain following balloon dilation compared with only 6% in the study of Suneja et al [16]. In a previous study [17] with 48 patients studied with ultrasound before and after balloon angioplasty we found that plaque reduction accounted for 55% of the lumen gain. Different types of arteries and methodologies used in the studies may account for a part of these discrepancies.

Plaque reduction was the major mechanism of atherectomy, accounting for 87% of the luminal gain. Whether this plaque reduction represents tissue removal or plaque redistribution, has not been clarified in this study, since a three dimensional reconstruction of the stenotic segment was not routinely performed. Nevertheless, other authors [64] using three-dimensional reconstruction have shown that plaque redistribution may occur after atherectomy, although the magnitude of this effect could not be quantitatively assessed.

Unique to this study is the angioscopic evidence that the thrombotic burden prior to both procedures, may decrease or even disappear after coronary interventions. Although we can not exclude multiple instrumentation of the coronaries as a source of microemboli, this is unlikely because angioscopy that is a forward looking imaging device would probably be able to detect it. During conventional angioplasty the inflated balloon can induce dispersion or microembolization of the thrombotic material, a finding supported by necropsy studies [65]. However, because thrombus is represented by soft echoes, ultrasound will misinterpret this

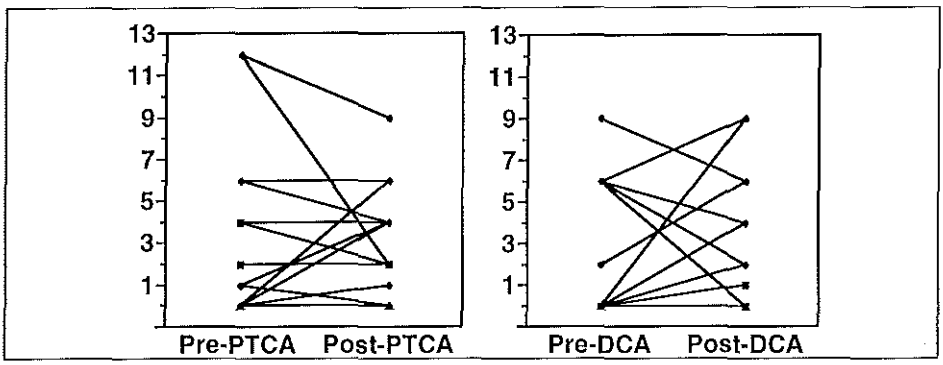

Figure 6.

Changes in the thrombus score with both interventions. While some patients have an increase in the score after interventions, others have a smaller thrombotic burden (see text for discussion).

soft plaque reduction as plaque compression. With atherectomy, thrombus removal and/or microembolization by dispersion or dislodgment can explain thrombus reduction [54]. Despite the angioscopic presumption of microembolization, there were in our patients no clinical symptoms or electrocardiograhic signs suggesting this phenomenon, which has been until now rarely reported in the literature [44,66]. However, an unexpectedly high rate of non Q-wave myocardial infarction after atherectomy in the CAVEAT study [67] could be interpreted as an indirect evidence of microembolization, as suggested by others [68-69].

Plaque composition seems to have a predominant impact on the procedure outcome of atherectomy. Similar to other authors [15] our data shows a trend towards larger plaque reduction and greater luminal gain for soft plaques as compared to other types of plaques. It is a common clinical experience that calcific material can not be easily retrieved by atherectomy [70-71].

Is directional debulking less traumatic than dilation?

Since the restenotic process is presumably proportional to the amount of damage imparted to the vessel wall [22,72-73], we attempted to quantify vessel wall injury using the complementary information derived from different diagnostic techniques. We took advantage of quantitative angiography to determine the relative gain which has been established as an unspecific injury index [39-43,74]. Additionally, temporary wall stretch and elastic recoil were used as a measure of the distention of smooth muscle cells in the media.

Intravascular ultrasound was used to assess three complementary indices. These indices are acute vessel distention as an index of the distention of the external elastic membrane and media, the intravascular damage score as a measure of the trauma inflicted to the internal elastic lamina, and plaque reduction (Δ P+M) as an index of damage to the intima. In addition, various types of endoluminal injury were evaluated by angioscopic scores. Despite the only fair values of inter

and intra-observer variability for the angioscopic assessment of thrombi and dissections this should not be considered a major drawback since this diagnosis is associated with a high sensitivity and specificity [32] Furthermore, quantitative angiography the present gold standard for evaluation of coronary artery disease has also reasonable variability between different commercial systems in the estimation of lumen diameters, and also in the same system if the operator is let free to select the optimal cineframe for analysis.

The first conclusion of our study is that both coronary interventions induce a similar degree of vessel wall injury. Secondly, angiography underestimates the incidence of dissections and thrombus compared to intravascular ultrasound and angioscopy. Despite a larger (relative) luminal gain in the atherectomy group, the angioscopic indices of intimal injury were similar in both treatment groups. This finding might at first appear paradoxical, since a cutting device could expose deep vessel wall components to the bloodstream and trigger large thrombus formation [72,73]. However, it should be recalled that thrombus formation is a dynamic process evolving over time [75] and our study only analyzed the immediate outcome of the procedures. Dissections were also detected in equivalent proportions in the two treatment populations. After balloon angioplasty, dissections are the result of barotraumatic distension and disruption of the atherosclerotic plaque. Whereas, after atherectomy the dissections are the result of the cutting mechanism of this procedure, evidenced by the fact that dissections were present near identified cuts.

Mechanical stretching of the media has been associated with smooth muscle cell proliferation and change in phenotype [73]. In this respect, both interventions induced similar amounts of temporary stretch, but a significantly higher elastic recoil was measured after balloon angioplasty. The mean small elastic recoil observed after atherectomy reflects the ablative tissue nature of this technique.

An in vivo assessment of damage to the internal elastic lamina induced by these devices is problematic. Animal experiments have demonstrated a good correlation between the extent of damage to the internal elastic lamina and the magnitude of the hyperplastic response ([4,21]). Ultrasound damage score was higher after balloon dilation and consequently an increased hyperplastic response could be expected after balloon angioplasty. However, atherectomy histology disclosed evidence of deep cuts in 8 (44%) patients, which in itself can induce a strong local proliferative response [20,76]. When directional atherectomy is not properly guided, non-directional cuts from the device can generate unwanted damage, comparable to that generated by the non-directional barotrauma of angioplasty.

Despite the overall similarity in the wall injury scores, it is not possible from our study to determine which is the most powerful determinant of late lumen loss. It is possible that for each intervention a specific type of wall injury may be responsible for a different mechanism of restenosis. For instances, restenosis following balloon angioplasty may be the result of deep dissections involving the media and adventitia inducing vessel remodeling or vessel shrinkage [77-78], whereas after atherectomy cutting into the media with exposition of deep collagen may induce a more aggressive neointimal formation [78]

Nevertheless, the acute and long term outcome of the atherectomy procedure will

be dramatically improved once the directional nature can be properly applied by ultrasonic guidance incorporated in a single device.

Limitations

In this study, the contribution of neo-lumen (intraparietal) formation to the final lumen dimensions could not be correctly assessed by ultrasound imaging. Because ultrasound catheters are still relatively bulky as compared to vessel size, their presence may "tack up" dissections precluding the quantification of this mechanism. However, the high prevalence of dissections identified by angioscopy are consistent with the concept that plaque disruption is an important adjunctive mechanism of action of theses devices [13,14]. Due to the small number of patients studied so far with both techniques, it was not possible to perform a comparison based on matched and comparable populations. Ultimately, the physical presence of the imaging catheters and the flushing procedure required for an adequate angioscopic visualization can artifactually alter some morphological lesion characteristics

Conclusions

Intravascular ultrasound and angioscopy provide valuable complementary information concerning the mechanisms of lumen enlargement after conventional angioplasty and directional atherectomy. While balloon angioplasty induces lumen enlargement by a combination of wall stretch and plaque compression or redistribution, directional atherectomy mainly debulks the stenotic segment. It appears that the degree and nature of injury imparted to the wall by the two devices is similar, albeit the luminal enlargement observed after atherectomy is almost twice as large as the dilation effect obtained with balloon angioplasty. This observation indicates that long term outcome after atherectomy may be more favourable than after balloon angioplasty if this debulking technique is fully and optimally exploited.

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Chapter XI

Angiographic, Ultrasonic and Angioscopic Assessment of the Coronary Artery Wall and Lumen Configuration after Directional Atherectomy: The Mechanism Revisited

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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 ± 0.70 mm2 to 7.86 + 2.16 mm2 at atherectomy. The achieved gain mainly resulted from plaque removal since plaque + media area decreased from 18.16 ± 4.47 mm2 to 13.13 ± 3.10 mm2. Vessel wall stretching (i.e. change in external elastic lamina area) accounted for only 15% of lumen area gain. Luminal gain was higher in noncalcified (6.52 ± 2.12 mm2) than in lesions containing deeply located calcium (5.19 ± 0.99 mm2) and lowest in superficially calcified lesions (5.41 + 2.41 mm2).

Ultrasound imaging identified an atherectomy byte in 85% of the cases, while angioscopy revealed such a crevice in 74%. The complementary use of the 3 techniques 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 so far 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 1). There were 22 men and 4 women with a mean age of 57 ± 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 one 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

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)

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	17
RCA	6
LCX	3
AHA/ACC classification	
type a	3 (12%)
type B	21 (88%)
type C	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.

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].

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

	Pre-atherectomy	Post-atherectomy	p value
Angiography			
Reference dia (mm)	3.52 ± 0.52	3.70 ± 0.59	NS
Minimal lumen dia (mm)	1.16 ± 0.43	2.85 ± 0.62	< 0.0001
Diameter stenosis (%)	67 ± 11	23 ± 13	< 0.001
Minimal CSA (mm2)	1.20 ± 0.87	6.67 ± 2.70	< 0.0001
Area stenosis (%)	88 ± 8	39 ± 20	< 0.001
Ultrasound (mm2)			
EEM-A	20.11 ± 4.43	21.00 ± 3.91	0.02
Plaque + media area	18.16 ± 4.47	13.13 ± 3.10	< 0.0001
Lumen area	1.95 ± 0.70	7.86 ± 2.16	< 0.0001

CSA, cross sectional area;Dia, diameter; EEM-A, external elastic membrane area

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 dissection (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 as a scaling device. The computer-estimation of the original dimension of the artery at the site of the obstruction allows to define the interpolate 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). 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.

After balloon deflation, these abnormalities subsided and the chest pain disappeared.

Quantitative angiography (Table 2)

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

Table 3. Ultrasonic assessment of plaque reduction and lumen area gain achieved at atherectomy according to calcium location and histological confirmation.

Plaque area Reduction (mm2)

Ultrasound	Histology		
	Calcium	No Calcium	Total
Subendothelium Ca^{++}	4.13 ± 2.11 (n=5)	none (n=0)	4.13 ± 2.11 (n=5)
Base of the plaque Ca^{++}	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)
Total	5.16 ± 3.16 (n=15)	4.88 ±2.10 (n=11)	

Lumen area gain (mm2)

	Calcium	No Calcium	Total
Subendothelium Ca^{++}	5.41 ± 2.41 (n=5)	none (n=0)	5.41 ± 2.41 (n=5)
Base of the plaque Ca^{++}	5.19 ± 2.41 (n=5)	5.83 ± 1.57 (n=5)	5.51 ± 1.28 (n=10)
No calcium	6.34. ± 2.725 (n=5)	6.68 ± 1.66 (n=6)	6.52 ± 2.12 (n=11)
Total	5.69 ± 2.13 (n=15)	6.33 ±1.61 (n=11)	

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 mm2 to 6.67 ± 2.70 mm2 ($p<0.001$)

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.

No difference in external elastic membrane area between the reference and stenotic segment (20.94 ± 5.39 mm2 vs. 20.11 ± 4.43 mm2; 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 mm2 to 7.86 ± 2.16 mm2 ($p<0.0001$) and a decrease in plaque plus media area from 18.16 ± 4.47 mm2 to 13.13 ± 3.10 mm2 ($p<0.0001$). The

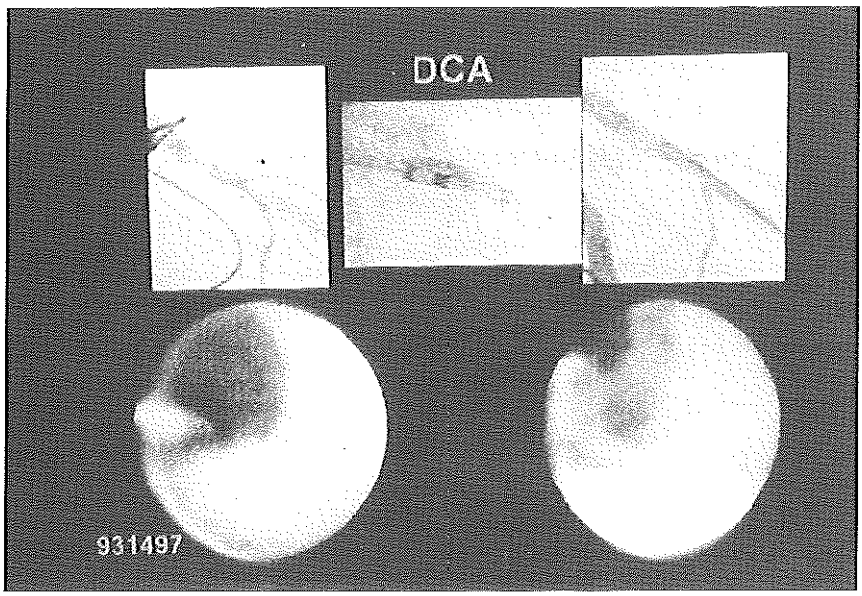

Figure 1.
Left panel shows lumen morphology prior to atherectomy. Note the regular lumen contour both with angiography (top) and angioscopy (bottom). After intervention (right) its is clearly seen with angioscopy, several cuts resulting in lumen irregularity and wall hemorrhage.

external elastic membrane area changed from 20.11± 4.43 mm2 to 21.00 ± 3.91 mm2 (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 mm2 vs 5.51± 2.41 mm2). Plaque reduction in cross-sectional lumen area was greatest in ultrasonic non-calcified lesions when compared with calcified lesions (5.89 ± 3.47 mm2 vs 4.13 ± 2.11 mm2). 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 confined the presence of calcium in all plaques containing ultrasound evidence of superficial calcium (n=5) whereas it confined 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 3).

The post-atherectomy lumen area configuration.
Angiography after atherectomy revealed a smooth luminal lining in 19 patients, persistent haziness in four, a dissection in two and thrombus in one. Ultrasound imaging showed a regular lumen configuration in four of the 26 patients, an irregular configuration in 15, a subintimal tear in four (15%) and a dissection in three 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 mm2 vs 5.95 ± 1.68 mm2; 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 one 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 four of these patients (21%) this was a new thrombus while in the remaining seven 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 1).

Complementary information of the three imaging techniques
Figure 2 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

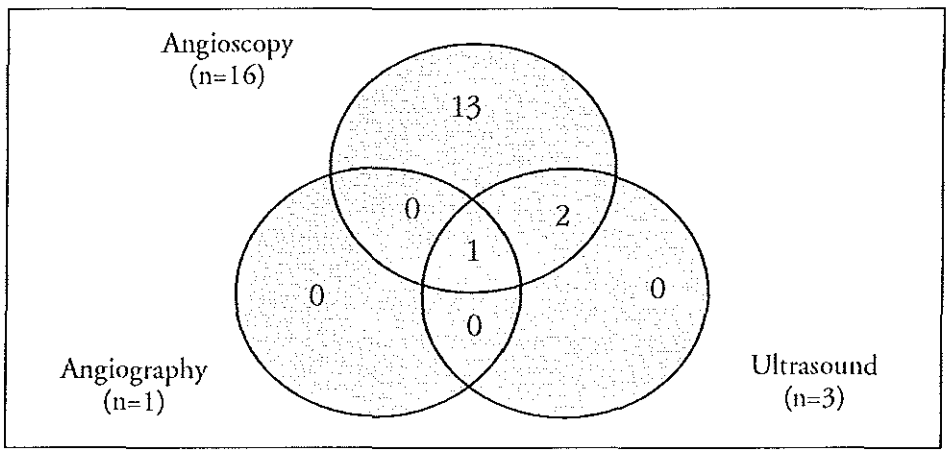

Figure 2

Venn diagram to illustrate the complementary 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.

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 to be 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 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 are 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 remodeling
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.

Dissection
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].

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 angioscopic information it was not our intention to examine the impact of these imaging techniques on procedural outcome.

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.

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Conclusion

Although coronary angiography is still considered the gold standard in the assessment of epicardial coronary arteries, a growing awareness of its limitations for the study of plaque morphology and for the assessment of the mechanisms of lumen enlargement has enhanced the interest in other coronary imaging techniques. The rapid growth of percutaneous coronary recanalization, with the development of atherectomy systems, endoluminal protheses, excimer lasers, etc. has created new demands which cannot be fulfilled solely by contrast angiography. Appraisal of the nature of the atheromatous plaque (such as the presence of calcium deposits), its size and morphology, as well as on-line assessment of the changes introduced by the intervention in the vessel, constitute new requirements for ideal imaging techniques in the field of intervention cardiology. In the present thesis observations on the action mechanism of various percutaneous recanalization techniques were obtained using intracoronary imaging.

Advantages and disadvantages of quantitative angiography

Contrast angiography provides an extensive and rapid overview of the coronary circulation. In addition, it may be used to assess the physiological significance of single coronary obstructions. These advantages justify "per se" its continued use in the near future despite some limitations when compared with new diagnostic imaging techniques. For instance, lesion characteristics such as vessel calcification and lumen eccentricity are often misinterpreted by angiography. Because of the potential impact of these features on the results of coronary interventions, these plaque characteristics are important to bear in mind when planning coronary interventions. Eccentric plaques with a disease-free wall are associated with suboptimal results of balloon angioplasty. Should elastic recoil be the mechanism implicated in these lesions, prompt identification might lead to the selection of an alternative technique, such as coronary stenting or directional atherectomy. Vessel calcification particularly in subendothelium localization has been associated with a smaller luminal gain after directional atherectomy, justifying the alternative use of rotablators. Despite the rational of these strategies corroborated in the GUIDE trial and in the experience of the Washington group, the clinical benefit of such strategies remains to be settled in large multicentric trials.

Angiography has inherent limitations in identifying changes in the progression and regression of atherosclerotic disease, particularly at a time when there is overwhelming evidence that during the natural history of the disease changes in the arterial wall happen well before luminal narrowing. As illustrated in chapter 2 even computerized analysis of the angiogram fails to identify disease-free wall or

reference coronary segments, and causes underestimation of the degree of underlying involvement. Therefore, parameters of lumen obstruction that just take into account the changes occurring at the inner circumference of the vessel without looking at the adventitia, will not detect the volumetric changes in the plaque burden occurring over time. Future developments in the 3-dimensional reconstruction of the coronary arteries using ultrasound imaging could provide enormous potential for its use in longitudinal studies.

Use of intracoronary imaging for the study of plaque composition and morphology

Intracoronary imaging may be useful as a research tool on other aspects of the evolution of coronary atherosclerosis. Chapters 4,5 and 6 deal with the investigation of the culprit lesions of patients with acute and chronic coronary syndromes. Angioscopy, which proved to be superior to angiography and intravascular ultrasound in the detection of coronary thrombosis, was successfully used to obtain information on the cause of luminal obstruction, the extent of coronary thrombosis and the characteristics of plaque substrate influencing its extent. It is foreseeable that improvements in tissue characterization from backscatter analysis with intravascular ultrasound will expand the observations outlined in these chapters. Furthermore, concomitant extraction of tissue during percutaneous recanalization may, as illustrated by chapter 5, constitute an opportunity for the in-vivo validation of the observations performed during intracoronary imaging.
Angioscopy identified vessel ulceration and thrombus formation in all stages of coronary artery disease although their incidence increased significantly with the severity of the syndrome. This suggests that different coronary syndromes are the expression of a continuous disease, where certain plaque characteristics may suddenly modify the course of the disease. Factors like the thickness of fibrous cap that are still not evaluated by ultrasound may bear considerable prognostic value. When lipid plaques were visualized with angioscopy in ulcerated lesions suggesting the existence of a thin fibrous cap or a superficial lipid pool, the amount of thrombus formation was significantly larger as compared with the smaller thrombotic burden when no lipidic material was detected. This may partially explain the benefit of antilipidic therapy in decreasing the number of future cardiac events by reducing the plaque substrate for the process of thrombus formation.

Intracoronary imaging in planning current coronary interventions

Intracoronary ultrasound and angioscopy may be used for several purposes during coronary interventions. First, it may be used to characterize lesion morphology prior to coronary intervention assisting the physician in planning coronary intervention. Soft eccentric plaques may be selected to directional atherectomy whereas calcific plaques may be treated with rotablator or laser. The presence of a

fresh thrombus in a vessel suitable for stent implantation may be used as an indicator for the use of thrombolytic agents or to the use of a more aggressive anticoagulant regimen prior to stent deployment. Lesions of uncertain significance may be checked with ultrasound in order to have a second assessment of lumen dimensions. Second, during coronary intervention intracoronary ultrasound may be used to select the proper device size by measuring directly lumen dimensions at the target and reference site. Third, after intervention intracoronary ultrasound may be used to evaluate residual plaque burden and the estimation of lumen dimensions. Unsuspected large plaque burden after atherectomy may guide the interventionist towards a more aggressive plaque debulking with probable impact in the restenotic process. On the contrary, the presence of a cut in a normal wall in a patient with suboptimal result may change the operator strategy towards the use of adjunctive balloon dilation or stenting. After stent deployment, ultrasound may be used to assess the degree of apposition of the stent to the vessel wall, reducing the risk of stent thrombosis. Likewise, angioscopy may detect unsuspected thrombus or uncovered dissections.

Mechanisms of lumen enlargement and their implications in the restenotic process

Mechanisms of lumen enlargement are different among different devices. Lumen gain after balloon dilation is the combined result of vessel compression or redistribution and wall stretching whereas after atherectomy lumen enlargement is mainly the result of plaque reduction. Immediately after intervention, wall disruption and thrombus formation was similar in both intervention groups suggesting that similar restenosis rates can be expected with these two interventions. However, the relative importance of each injury parameter could not be clarified in the present work. For instances cutting deep into the plaque, destroying the fibrous cap of lipid pools could induce a larger thrombus formation than after balloon dilation. Its reasonable to think that since there are different mechanisms operating in vessel enlargement, there would be different mechanisms in the restenotic process. After balloon dilation restenosis is mainly due to chronic vessel remodelling or vessel shrinkage, whereas after atherectomy lumen loss may occur mainly as a result of intimal hyperplasia. Recent randomized trials provide indirect evidence that acting at these two levels may lead to a reduction in the restenotic rate. The STRESS and BENESTENT trials proved that it is possible to reduce the restenotic rate by the use of stents. It is probable that these devices are preventing chronic vessel remodelling that occurs after other intervention modalities. The EPIC trial showed that it is also possible to reduce restenosis by acting in the other mechanism of the restenotic process: intimal hyperplasia. By reducing the first stages of thrombus formation through the action of an antiplatelet agent directed against the platelets receptors IIIa/IIb, it was possible to decrease the amount of subsequent intimal hyperplasia. Therefore it is appealing to think that the combined use of such strategies may even result in a larger reduction in the restenotic process.

Future developments

Improvements in catheter technology with further miniaturization of current imaging modalities will permit a more widespread utilization of these devices on a routine basis, namely prior to coronary intervention. 3-D reconstruction of the ultrasound images will give a more detailed information of the dynamic changes in atheroma formation occurring at the vessel wall, mainly when this information will be combined by flow parameters derived from doppler probes in the same catheter. Intervention devices will incorporate imaging modalities for a better efficacy such as ultrasound in stents, balloons or atherotomes and angioscopy with lasers wires. Along with the three-dimensional reconstruction, computerized analysis of the vessel morphology may identify areas of high shear stress associated with a high risk of wall dissection. In the diagnostic field, angioscopy combined with coulored monoclonal agents directed against particular plaque components could be used as a guide for local pharmacological therapy. Ultimately, new imaging modalities like forward looking echo catheterswith the possibility of using ultrasound energy to ablate or modify plaque components, may make these fascinating imaging modalities even more appealing.

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Curriculum Vitae

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1986, October. National theoretical examination for admission to Cardiology, with the second best grade and 8 th position from more than 2500 concurrents (90%).

1987-1991. Fellow of Cardiology, department of Cardiology, Hospital de Santa Cruz, Lisboa. (Director:Prof Dr. Ricardo Seabra Gomes).

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