Clinical Application of Intracoronary Ultrasound (IVUS) and Quantitative Coronary Angiography (QCA) to Assess Coronary Intervention and Atherosclerosis

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Clinical Application of Intracoronary Ultrasound (IVUS) and Quantitative Coronary Angiography (QCA) to Assess Coronary Intervention and Atherosclerosis

Klinische toepassing van intracoronair ultrageluid (IVUS) en kwantitatieve coronair angiografie (QCA) om coronair ingrijpen en atherosclerose te evalueren

Thesis

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by

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born in Osaka, Japan

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	Prof.dr. J.J. Piek

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Chapter 1

Introduction and General Overview

Introduction and General Overview

Ischemic heart disease remains a major cause of mortality and morbidity in Europe, the United States and Japan. It has been proposed that coronary atherosclerosis is the consequence of the vascular response to injurious effects of exposure to the classical cardiovascular risk factors including smoking, diabetes, hypertension and hyperlipidemia. However, the relationship between such coronary risk factors and atherosclerotic coronary plaque burden has not yet been fully elucidated. The epidemic of cardiovascular disease demands further efforts to elucidate the mechanisms of atherosclerosis and further research to develop and guide treatments. Since Andreas R. Grűntzig performed the first percutaneous transluminal coronary angioplasty on September 16th 1977, coronary intervention has become accepted as an effective therapy for patients with coronary artery disease all over the world. The initial success achieved with percutaneous coronary intervention continues to be limited by restenosis. Intracoronary ultrasound (IVUS) studies reveal that late vessel remodeling and plaque growth plays an important role in the restenosis process. Coronary stenting, by supporting the vessel wall, limits early and late vessel remodeling and subsequently decreases restenosis. More recently short- to medium-term restenosis appears to have been further ameliorated by the advent of drug-eluting stent (DES) technologies. However, several limitations still restrict the widespread application of this technique including concerns about subacute or late stent thrombosis, the limited success rates of PCI for complex lesion morphology (e.g. chronic total occlusion (CTO)) and interventional cost. The ultimate goal of interventional cardiology is to disclose the mechanism of progression and regression of coronary atherosclerosis, and to provide less invasive and more effective treatments for the patients suffering from ischemic heart disease. Each interventional device should be carefully sized and deployed using reliable techniques such as intracoronary ultrasound (IVUS) and quantitative coronary angiography (QCA).

Part I of this thesis (Chapters 2 to 4) addresses the reliability of three methodologies including quantitative coronary angiography (QCA), intracoronary ultrasound (IVUS) and coronary angioscopy. ***In Chapter 2***, we validate intracoronary ultrasound (IVUS) measurements and quantitative coronary angiography (QCA) by using geometric and densitometric techniques. ***In Chapter 3***, we report the results of experimental and clinical QCA comparison between cinefilm and digital video recording with and without edge enhancement.

Pathological studies support the common beliefs that lipid-rich coronary plaques with

a thin, fibrous cap are prone to rupture, and that the rupture and superimposed thrombosis are the primary mechanisms causing acute coronary syndromes such as unstable angina. ***In Chapter 4***, to examine the mechanism of the plaque rupture, we compared unstable and stable lesions using three imaging modalities: IVUS, QCA and coronary angioscopy.

Having validated our primary methodological techniques, ***Part II of this thesis (Chapters 5 to 8)*** proceeds with the sequential evaluation of progression and regression of coronary atherosclerosis in relation to abnormal vasomotor tone and smoking status. The primary role of coronary spasm in vasospastic angina and certain categories of myocardial infarction are established. While it has been known for decades that coronary spasm frequently occurs at sites of significant atherosclerosis, it has not yet been determined whether vasospasm may play a role in the progression or regression of atherosclerosis. ***In Chapter 5***, we examine the impact of vasospastic activity on the progression and regression of coronary atherosclerosis by QCA. ***In Chapter 6***, we examine the influence of long-term vasospastic activity on clinical presentations. ***In Chapter 7***, we compared basal coronary tone and vasospastic activity by measuring changes in the mean luminal diameter of each entire spastic segment, segments adjacent to the spastic segment, and segments in non-spastic vessels at baseline, after administration of ergonovine and after administration of isosorbide dinitrate using QCA.

Although cigarette smoking is a strong risk factor for coronary artery disease, the exact effects of the smoking habit on coronary plaque burden and restenosis after PCI remain uncertain. ***In Chapter 8***, using the QCA and IVUS techniques and knowledge obtained in the Thoraxcenter Erasmus University Rotterdam, we examined the relationship between smoking status and plaque burden, vascular remodeling and restenosis in 1039 patients undergoing PCI. We performed stenting or balloon angioplasty with either IVUS guidance (450 patients) or angiography-guidance alone (589 patients) in both European and Japanese patients.

Using our primarily validated methodologies and techniques, ***in Part III of this thesis (Chapter 9 to 13)*** we examine the short- and long-term efficacy of coronary stent implantation as well as cutting balloon angioplasty. ***In Chapter 9***, we hypothesized that oversized Wallstent implantation with a policy of "*restitutio ad integrum*" (resetting the vessel size into undiseased condition) would produce enforced mechanical remodelling of the coronary vessel with subsequent reduction in restenosis rates. To test this hypothesis we performed Wallstent implantations in native coronary arteries with acute or threatened closure post balloon angioplasty and assessed long-term outcome by the serial QCA. Since restenosis after successful dilatation of chronic total occlusions (CTO) is significantly higher than after

successful dilatation of non-occluded stenoses, ***in Chapter 10*** we examined this strategy of oversized Wallstent deployment after successful laser or balloon angioplasty. QCA was performed pre-intervention, post-balloon angioplasty, post-high pressure balloon angioplasty after oversized Wallstent deployment, and at 6 months follow-up. ***In Chapter 11***, we report our initial experience with the AVE stent primarily in the domain of multiple stenting of long and complex coronary dissections. ***In Chapter 12***, the problem of restenosis assessment within the radiopaque tantalum Cordis stent is assessed by IVUS and QCA using both geometric and densitometric techniques in both an experimental restenosis model and in the clinical follow-up of patients.

Applying the QCA and IVUS techniques and knowledge obtained in the Thoraxcenter Erasmus University Rotterdam ***in Chapter 13*** we report the results of a Japanese multicenter study to determine the long-term efficacy of cutting balloon angioplasty (CBA) prior to stenting strategy. We investigated whether IVUS-guided Cutting Balloon Angioplasty (CBA) before stenting could achieve restenosis rates comparable to those achieved with drug-eluting stents (DES). We randomized 521 patients to CBA before stenting (260 pts) or plain old balloon angioplasty (POBA) before stenting. IVUS-guided procedures were performed in 279 (54%) patients and angiography guidance was used in the remainder.

In the final part of this thesis (***Chapter 14***) we examine the role and usefulness of IVUS and QCA as techniques for investigating the mechanisms of coronary atherosclerosis and the potential scope for their use in evaluating the short and long-term success of coronary interventions.

Part 1 - Methodology

Chapter 2

Comparison of coronary luminal quantification obtained from intracoronary ultrasound and both geometric and videodensitometric quantitative angiography before and after balloon angioplasty and directional atherectomy.

Ozaki Y, Violaris AG, Kobayashi T, Keane D, Camenzind E, Di Mario C, de Feyter PJ, Roelandt JRTC, Serruys PW.

Circulation 1997;96:491-499

Comparison of Coronary Luminal Quantification Obtained From Intracoronary Ultrasound and Both Geometric and Videodensitometric Quantitative Angiography Before and After Balloon Angioplasty and Directional Atherectomy

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Background Debate exists regarding the relationship between angiographic and intracoronary ultrasound (ICUS) measurements of minimal luminal cross-sectional area after coronary intervention. We investigated this and the factors that may influence it by using ICUS and quantitative angiography.

Methods and Results Patients who underwent successful balloon angioplasty (n=100) or directional atherectomy (n=50) were examined by using ICUS and quantitative angiography (edge-detection [ED] and videodensitometry [VID]) before and after intervention. Luminal damage postintervention was qualitatively graded into three categories based on angiographic results (smooth lumen, haziness, or dissection). Correlation of minimal luminal cross-sectional area measurements by ICUS and ED was .59 before and .47 after balloon angioplasty. Correlation between ICUS and VID was .50 before and .63 after balloon angioplasty. Postintervention, the difference between ICUS and VID was less than the difference between ICUS and ED ($P<.01$). Additionally, the correlation was .74 between ICUS and ED measurements and .78 between ICUS and VID measurements in the smooth lumen group, .46 and .63, respectively, in the presence of haziness, and .26 and .46, respectively, in lesions with dissection. Similar results were obtained after directional atherectomy: the agreement between ICUS and quantitative angiography deteriorated according to the degree of vessel damage, but less so with VID than ED.

Conclusions Complex morphological changes induced by intervention may contribute to discordance between the two quantitative imaging techniques. In the absence of ICUS, VID may be a complementary technique to ED in lesions with complex morphology after balloon angioplasty and directional atherectomy. (***Circulation.* 1997;96:491-499.**)

Key Words • angiography • angioplasty • imaging • coronary disease • ultrasonics

Although QCA is the gold standard in interventional cardiology, pathology studies indicate that angiography may underestimate the extent and severity of atherosclerotic disease.[1,2] While ICUS provides unique information regarding vessel wall morphology compared with angiography,[3-8] precise quantitative analysis of luminal CSA by ICUS would offer a significant advantage in the guidance of coronary intervention procedures.[9-11] A recent multicenter ICUS study in patients with coronary angioplasty indicated that postinterventional luminal dimensions obtained by ICUS but not QCA may be a significant predictor of restenosis at follow-up.[12] Additionally, another multicenter study suggests that a large residual plaque burden remains on ICUS imaging, despite optimal angiographic results.[13] Nakamura et al[9] and Colombo et al[10] also suggest that luminal measurements provided by ICUS may be helpful for optimal stent deployment. Previous studies, however, have provided conflicting evidence on the agreement between quantitative measurements derived from ICUS and those derived from QCA.[3,4,7,14-17] The aim of our study was to clarify whether ICUS measurements agree with QCA measurements and to determine which factors, if any, may play a role in any discordance between the techniques. To do this, we compared MCSA obtained from ICUS and both ED and VID computer-based QCA before and after BA and DCA.

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Methods

Patients

Patients who had an ICUS examination before and after single-vessel BA (n=100) or DCA (n=50) with adequate

Selected Abbreviations and Acronyms

BA = balloon angioplasty
CSA = cross-sectional area
DCA = directional coronary atherectomy
ED = edge detection
ED-QCA = edge-detection quantitative coronary angiography
ICUS = intracoronary ultrasound
MCSA = minimal luminal cross-sectional area
MLD = minimal luminal diameter
QCA = quantitative coronary angiography
RD = reference diameter
VID = videodensitometry
VID-QCA = videodensitometric quantitative coronary angiography

quality of ICUS and angiographic images for quantitative analysis were enrolled in this study. Preintervention, the US catheter did not cross the target lesions in 20 lesions because of proximal vessel tortuosity, the severity of the target stenosis, or transient serious arrhythmia during the ICUS examination. Additionally, the ultrasound catheter completely occluded the coronary lesion in 89 lesions. Thus, preintervention MCSA of the stenotic segment was measured in the remaining 41 lesions. Postintervention ICUS measurements were obtained in all 150 lesions in the 150 patients.

BA or DCA Procedures

All patients received full anticoagulant therapy including intravenous aspirin and heparin before ICUS examination and intervention. Coronary angiograms were recorded on cinefilm after the intracoronary administration of isosorbide dinitrate (1 to 2 mg). The size of the balloon or atherectomy device was determined to match the vessel RD obtained from the online QCA measurement. Luminal damage postintervention was qualitatively graded into three categories by angiographic assessment as none (smooth lumen), generalized haziness, or dissection. Dissection was defined according to the dissection classification types B, C, D, E, and F of the classification of the National Heart, Lung, and Blood Institute.[18]

ED-QCA

The new version of the computer-based Coronary Angiography Analysis System (CAAS II)[19,20] was used to perform the ED and VID quantitative analyses. In the CAAS analysis,[19-24] the entire 18×24-mm cineframe is digitized at a resolution of 1329×1772 pixels, and the boundaries of a selected coronary segment are detected automatically. The absolute diameters of the stenosis (MLD and RD) are determined by using the contrast-free guiding catheter as a scaling device. To standardize the method of analysis before and after intervention, all study frames selected for analysis were end-diastolic to minimize motion artifact, and arterial segments were measured between the same identifiable branch points in multiple views after the administration of isosorbide dinitrate.[20-24] MCSA was calculated as $\pi\times(\text{MLD1})\times(\text{MLD2})\div 4$ from measurements obtained from the ED analysis in orthogonal views (MLD1 and MLD2) before and after intervention.

VID-QCA

VID measurement is based on the relationship between the attenuating power of the lumen filled with contrast medium and the x-ray image intensity.[25] Using this relationship, a VID profile that was proportional to the CSA of the lumen was obtained. Subtraction of patient structure noise was applied after computing the linear regression line through the background pixels located on both sides of the detected luminal contours. Consecutive densitometric profiles of the analyzed segment were acquired in all scan lines perpendicular to the vessel including lesion, reference, and nondiseased areas. Conversion of the individual VID profiles to absolute values was performed after a transformation of the VID profile found in a CSA of a nondiseased segment, assuming a CSA at any point is proportional to the densitometric profiles at that point. MCSA was calculated from the average value obtained from the VID system in multiple views. The basic principles of the technique are illustrated in Fig 1.

ICUS Image Acquisition

Following angiography, an ICUS catheter (30 MHz; 2.9F, 3.2F, or 4.3F; Cardiovascular Imaging Systems) was introduced over a 0.014-in. guide wire and positioned distal to the lesion. Lesion geometry was then imaged by using a slow, continuous catheter pull-back procedure. Catheter position was documented by simultaneous fluoroscopy superimposed on the ICUS display screen. ICUS images were stored on super VHS tape for offline analysis.

Quantitative and Qualitative Assessment of ICUS

Luminal CSA was defined as the integrated area central to the intimal leading-edge echo. Images with MCSA were selected from the pull-back sequence by reviewing the position of the ICUS catheter on the angiographic image that was recorded on the same ICUS image and by reviewing the time log and audio recording of the procedure to analyze the same coronary segment as the quantitative angiogram. Total vessel CSA was defined as the area inside the interface between the plaque-media complex and adventitia (ie, the area inside the external elastic membrane). When the dissected lumen communicated constantly with the true lumen, the dissected lumen was included in the luminal area, as exemplified in Fig 2. Echo reflectivity was categorized as either low or high (plaque reflectivity lower or higher, respectively, than the bright adventitial layer).[26] Calcium deposits were defined as highly echoreflective tissue with acoustic shadowing. A lesion was considered homogeneous if the plaque consisted of >75% of one type of echo reflectivity. A lesion was defined as mixed if it contained both high and low echo-reflective areas occupying >25% of the plaque area.[26] A lesion was considered predominantly calcific if calcium occupied >180° of the vessel circumference.[26]

Luminal damage postintervention was qualitatively graded into three categories: regular lumen, irregular lumen including a small tear not extending to the media, and dissected lumen with circumferential tear behind the plaque or tear extending to the media.[5,6,27] The eccentricity ratio was calculated as the ratio between minimal and maximal wall thickness (1 indicates concentric plaque, <1 indicates increasing eccentricity).[27] To determine the interobserver variability of ICUS measurements, 30 videotapes of the complete original recording were used by two independent observers to select and measure the minimal CSA. The mean signed difference and correlation of the measurements of minimal CSA were -0.12 ± 0.79 mm^2 and 0.94, respectively.

Statistical Analysis

In the absence of the known true values, Bland and Altman[28] recommend the use of the mean and SD of the signed differences between two measurement systems as an index of agreement between the two systems. Thus, we took the mean and SD of the signed differences between ICUS and QCA measurements as an index of agreement between ICUS and QCA measurements instead of linear regression analysis. The individual measurements obtained from ICUS and QCA were compared by using the paired Student t test and correlation coefficient. A probability value of <.05 was considered significant.

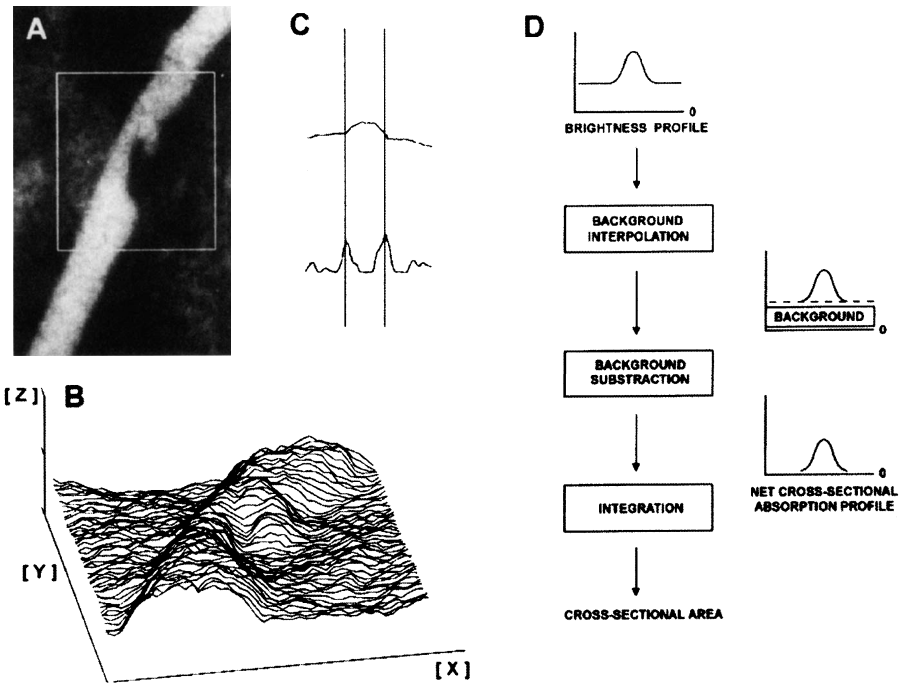

FIG 1. A, In the VID technique, a matrix is placed over the area selected for analysis from the right coronary angiogram encompassing a complex coronary obstruction. B, Pseudo–three-dimensional representation of the brightness information within the matrix and the coronary artery can be recognized as a mountain ridge with a deep pass at the site of the obstruction; the brightness profile along one particular scan line is plotted. C, Positions with maximal values of the sum of the first- and second-derivative functions left and right of the center positions of the artery correspond to the edge positions of the artery. D, Flow chart of the analysis indicates the main procedures followed for the computation of the VID area function.

Results

Baseline Clinical and Angiographic Characteristics

No difference was found in gender, age, anginal symptoms, or distribution of diseased vessels between the BA and DCA groups (Table 1). QCA measurements were obtained in 100 lesions before and after BA and in 50 lesions before and after DCA. ED-QCA indicated that the RD before and after intervention and MLD postintervention were significantly larger in the DCA than the BA patients. MCSA was measured by using ICUS in 26 lesions before BA and 15 lesions before DCA without wedge of the ICUS catheter. One hundred lesions after BA and 50 lesions after DCA were esti-

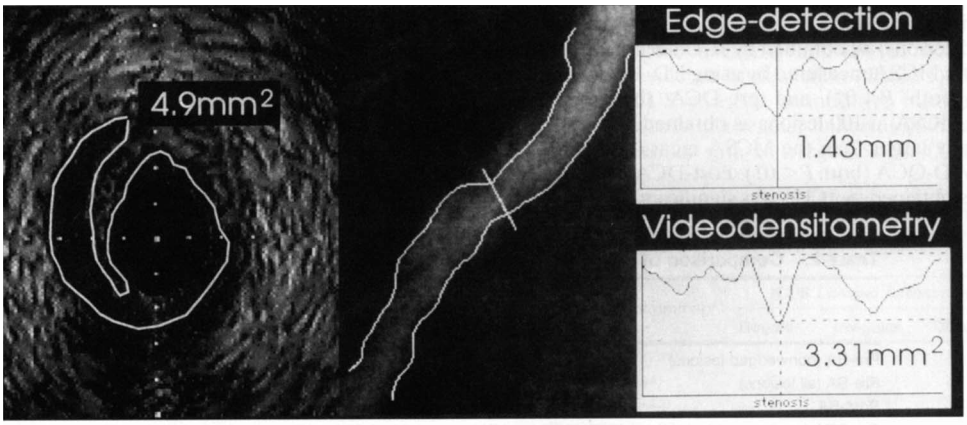

FIG 2. ED-QCA, VID-QCA, and ICUS analyses after BA in the middle segment of the left anterior descending coronary artery. Left, Dissection is clearly seen in the ICUS image. Middle, ED algorithm partially traces between the true and the dissected lumen. Right, Complex morphological changes caused by BA may explain the discordance between MCSA measurements obtained from ICUS (4.9 mm^2) and ED-QCA (2.96 mm^2; MLD, 1.43 mm) and VID-QCA (3.31 mm^2). The VID-QCA value is nearer to the ICUS measurement than the ED-QCA value; see "Discussion."

TABLE 1. Baseline Clinical and Angiographic Characteristics of 150 Patients

	BA (n=100)	DCA (n=50)	P
No. of patients (M/F)	100 (81/19)	50 (43/7)	
Age, y	59±10	58±9	NS
Stable/unstable angina, n	53/47	24/26	NS
RCA/LAD/LCX/SVG, n	31/47/18/4	8/34/8/0	NS
Luminal diameter by ED-QCA, mm			
MLD before	1.05±0.50	1.20±0.43	NS
RD before	2.85±0.64	3.51±0.61	<.001
MLD after	2.04±0.55	2.81±0.59	<.001
RD after	2.98±0.70	3.69±0.59	<.001
Plaque composition estimated by ICUS, n			
Homogeneous plaque (echo reflectivity: poor/high with shadow/high without shadow)	64 (54/8/2)	31 (26/5/0)	NS
Mixed plaque	36	19	NS
None/<90°/≥90° calcium deposits	26/42/32	15/19/16	NS
Luminal measurement by ICUS			
Total vessel area before, mm^2	17.00±5.35	19.66±4.84	<.05
Plaque and media area before, mm^2	13.65±4.97	16.97±4.99	<.05
Plaque and media area before, %	79±7%	86±5%	<.05
Eccentricity index	0.43±0.24	0.38±0.22	NS

RCA indicates right coronary artery; LAD, left anterior descending coronary artery; LCX, left circumflex coronary artery; and SVG, saphenous vein graft. All 150 lesions were analyzed by QCA before and by QCA and ICUS after intervention. Preintervention, 26 and 15 lesions that were to be treated by BA and DCA, respectively, were analyzed by ICUS; lesions with wedge of ICUS catheter (BA=74 and DCA=35) were excluded from ICUS analysis.

mated by using ICUS, which revealed that 64 lesions in BA and 31 lesions in DCA consisted of homogeneous plaque; all remaining lesions were classified as mixed. Most of the homogeneous plaque was low echo reflective. Focal calcium deposits were observed in 42 lesions in BA and 19 lesions in DCA, while moderate-to-diffuse calcification was seen in 32 lesions in BA and 16 lesions in DCA (P=NS). Total vessel CSA, plaque and medial CSA, and percent plaque and medial CSA preintervention were larger in the DCA than the BA group. Lesion eccentricity was not significantly different between the two groups.

MCSA Measured by ICUS, ED-QCA, and VID-QCA Before and After Interventions

Table 2 shows the MCSA measured by ICUS, ED-QCA, and VID-QCA before and after BA and DCA. MCSA in nonwedged lesions (BA=26 lesions and DCA=15 lesions) as obtained by ICUS was significantly larger than MCSA measured by using ED- or VID-QCA pre-BA (both $P<.01$) and pre-DCA (both $P<.01$). Post-BA MCSA in 100 lesions as obtained by ICUS was significantly larger than the MCSA measured by either ED- or VID-QCA (both $P<.01$). Post-DCA MCSA in 50 lesions as obtained by ICUS was significantly larger than MCSA as measured by ED-QCA ($P<.01$) but not VID-QCA.

Agreement Between ICUS, ED, and VID Before and After BA and DCA

Table 3 compares the agreement between the three measurement techniques, and Figs 3 and 4 display the postintervention agreement between measurements obtained from ICUS and ED-QCA (Fig 3) and from ICUS and VID-QCA (Fig 4). The correlation coefficient between the ICUS and ED measurements decreased from .59 pre-BA to .47 post-BA and from .57 pre-DCA to .44 post-DCA. The absolute difference between ICUS and ED was significantly greater post-BA and post-DCA than pre-BA and pre-DCA (both $P<.05$). The agreement between ICUS and ED deteriorated post-BA and DCA compared with the pre-BA and DCA agreement. The correlation coefficient between ICUS and VID measurements increased from .50 pre-BA to .63 post-BA and from .50 pre-DCA to .72 post-DCA (Table 3). The difference between ICUS and VID was not significantly different from pre-BA and DCA to post-BA and DCA. Postintervention, the difference between ICUS and VID was significantly less than the difference between ICUS and ED post-BA and post-DCA (both

TABLE 2. Comparison of MCSA Measurements Between BA and DCA

	MCSA, mm^2		
	ICUS	ED-QCA	VID-QCA
Pre-BA (nonwedged lesions)	3.36±0.99 (n=26)*†	1.93±1.36 (n=26)	2.21±1.22 (n=26)
Pre-BA (all lesions)	. . .	1.12±0.96 (n=100)†	1.32±1.02 (n=100)
Post-BA	5.19±1.90 (n=100)*†	3.48±1.76 (n=100)†	3.92±1.82 (n=100)
Pre-DCA (nonwedged lesions)	2.69±0.89 (n=15)*†	1.61±1.08 (n=15)	1.64±1.02 (n=15)
Pre-DCA (all lesions)	. . .	1.29±0.79 (n=50)	1.26±0.77 (n=50)
Post-DCA	7.57±1.85 (n=50)*	6.58±2.43 (n=50)†	7.25±2.20 (n=50)

*$P<.05$ vs ED-QCA.
†$P<.05$ vs VID-QCA.

TABLE 3. Comparison of Agreement Between Measurements of MCSA by ICUS, ED, and VID Before and After BA and DCA

	Correlation Coefficient	Mean±SD, mm^2
ICUS vs ED		
Pre-BA (nonwedged lesions)	.59	1.43±1.12
Post-BA	.47	1.71±1.87
Pre-DCA (nonwedged lesions)	.57	1.08±1.00
Post-DCA	.44	0.95±2.30
ICUS vs VID		
Pre-BA (nonwedged lesions)	.50	1.15±1.12
Post-BA	.63	1.27±1.61
Pre-DCA (nonwedged lesions)	.50	1.05±0.96
Post-DCA	.72	0.28±1.54
VID vs ED		
Pre-BA (all lesions)	.78	0.20±0.65
Post-BA	.82	0.43±1.08
Pre-DCA (all lesions)	.74	−0.04±0.56
Post-DCA	.73	0.67±1.71

$P<.01$). The discordance between ICUS and VID was smaller than the discordance between ICUS and ED both post-BA and post-DCA. While in both pre-BA and DCA no significant difference was observed between ED and VID, in post-BA and DCA there was a significant difference between the two (BA, $P<.001$; DCA, $P<.01$).

Luminal Damage Postintervention as Assessed by Angiography and ICUS

The degree of luminal damage postintervention as assessed by using angiography and ICUS is given in Table 4. Concordance between the two qualitative imaging techniques was found in 23 (70%) of the 33 patients with angiographically detected dissected lesions and 23 (66%) of the 35 patients with dissection as detected by ICUS post-BA and in 10 (83%) of the 12 patients with angiographically detected dissected lesions and 10 (59%) of the 17 patients with dissection as detected by ICUS post-DCA.

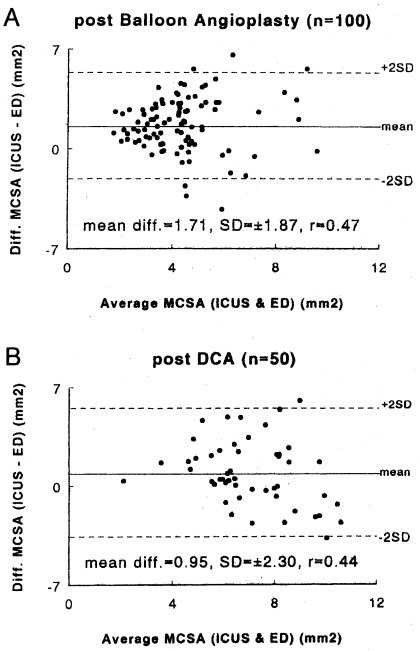

FIG 3. Plots show agreement of measurements of MCSA between ICUS and ED-QCA after (A) BA and (B) DCA according to the statistical approach proposed by Bland and Altman.[28] Diff. indicates difference.

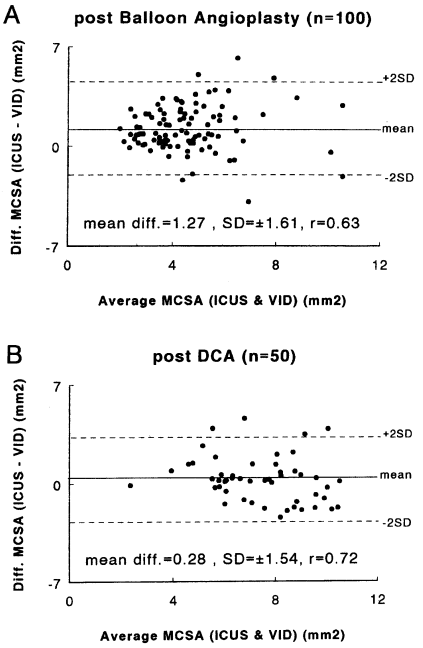

FIG 4. Plots show agreement of measurements of MCSA between ICUS and VID-QCA after (A) BA and (B) DCA according to the statistical approach proposed by Bland and Altman.[28] Diff. indicates difference.

Influence of Vessel Damage Induced by BA and DCA in the Agreement Between ICUS and QCA

The correlation coefficient of ICUS and ED quantitative measurements was .74 in lesions with an angiographically determined smooth lumen, .46 in lesions with angiographic haziness, and .26 in lesions with angiographic evidence of dissection (Table 5). The correlation of ICUS and ED quantitative measurements was .70 in lesions with a regular lumen as determined by ICUS, .52 in lesions with an irregular lumen, and .10 in

TABLE 4. Luminal Damage As Assessed by Using ICUS and Angiography in 150 Patients After Coronary Intervention

Angiographic Luminal Assessment	ICUS Luminal Assessment		
	Regular	Irregular	Dissected
BA			
Smooth (n=44)	26	13	5
Haziness (n=23)	2	14	7
Dissection (n=33)	4	6	23
DCA			
Smooth (n=24)	13	9	2
Haziness (n=14)	1	8	5
Dissection (n=12)	0	2	10

TABLE 5. Comparison of Agreement Between Measurements of MCSA by ICUS, ED, and VID According to Degree of Vessel Damage Induced by BA

	Correlation Coefficient	Mean±SD, mm²
ICUS vs ED		
Angiography		
Smooth lumen (n=44)	.74	1.21±1.27
Haziness (n=23)	.46	2.01±1.69
Dissection (n=33)	.26	2.16±2.47
ICUS		
Regular lumen (n=32)	.70	1.36±1.66
Irregular lumen (n=33)	.52	1.45±1.71
Presence of dissection (n=35)	.10	2.27±2.11
ICUS vs VID		
Angiography		
Smooth lumen (n=44)	.78	1.02±1.29
Haziness (n=23)	.63	1.46±1.34
Dissection (n=33)	.46	1.48±2.09
ICUS		
Regular lumen (n=32)	.80	1.03±1.48
Irregular lumen (n=33)	.54	1.02±1.70
Presence of dissection (n=35)	.37	1.73±1.57
VID vs ED		
Angiography		
Smooth lumen (n=44)	.93	0.19±0.75
Haziness (n=23)	.86	0.55±0.89
Dissection (n=33)	.64	0.68±1.48
ICUS		
Regular lumen (n=32)	.93	0.32±0.92
Irregular lumen (n=33)	.79	0.43±1.09
Presence of dissection (n=35)	.60	0.54±1.22

TABLE 6. Comparison of Agreement Between Measurements of MCSA by ICUS, ED, and VID According to Degree of Vessel Damage Induced by DCA

	Correlation Coefficient	Mean±SD, mm²
ICUS vs ED		
Angiography		
Smooth lumen (n=24)	.70	0.58±1.72
Haziness (n=14)	.34	1.43±2.62
Dissection (n=12)	.04	1.46±2.83
ICUS		
Regular lumen (n=14)	.72	0.30±1.58
Irregular lumen (n=19)	.49	0.77±2.39
Presence of dissection (n=17)	.28	1.68±2.61
ICUS vs VID		
Angiography		
Smooth lumen (n=24)	.79	−0.01±1.40
Haziness (n=14)	.71	0.64±1.61
Dissection (n=12)	.55	0.46±1.84
ICUS		
Regular lumen (n=14)	.83	−0.23±1.28
Irregular lumen (n=19)	.69	0.29±1.53
Presence of dissection (n=17)	.70	0.69±1.71
VID vs ED		
Angiography		
Smooth lumen (n=24)	.76	0.59±1.68
Haziness (n=14)	.74	0.80±1.68
Dissection (n=12)	.63	0.99±1.69
ICUS		
Regular lumen (n=14)	.87	0.53±1.15
Irregular lumen (n=19)	.72	0.48±1.54
Presence of dissection (n=17)	.67	1.00±2.19

lesions with ICUS evidence of dissection. Thus, the presence of vessel damage induced by BA was associated with a deterioration of agreement between ICUS and ED measurements. While agreement between ICUS and VID-QCA also deteriorated in the presence of morphological changes induced by BA, the difference of the measurements between ICUS and VID was significantly less than the difference between ICUS and ED in the presence of both angiographic ($P<.05$) and ICUS ($P<.05$) evidence of dissection. While high agreement was obtained between ED-QCA and VID-QCA, agreement between these two techniques also decreased post-BA according to the increase of vessel damage.

A similar pattern was seen when lesions treated by DCA were categorized according to their morphological characteristics (Table 6). Poor agreement was obtained in lesions with angiographic or ICUS evidence of vessel damage compared with lesions with an angiographically smooth lumen or ICUS appearance of a regular lumen. The absolute difference of the measurement between ICUS and VID was significantly less than the difference between ICUS and ED in the presence of both angiographic ($P<.01$) and ICUS ($P<.01$) evidence of dissection.

Correlation Between QCA Analyses of the Same Lesion From Multiple Views

To ensure that the better relationship between VID and ICUS was a true phenomenon and not due to a greater variation in values obtained from different views, we looked at the correlation and differences between orthogonal measurements for both VID and ED before and after intervention.[29-31] The correlation and differences between orthogonal measurements obtained by ED were 0.69 (0.21±0.62 mm²) preintervention and 0.49 (0.39±2.33 mm²) postintervention. The values obtained for VID were 0.69 (0.14±0.71 mm²) preintervention and 0.67 (−0.33±1.79 mm²) postintervention.

Discussion

The principle findings of our study were (1) that MCSA obtained by ICUS was significantly larger than MCSA as measured by either ED- or VID-QCA both before and after BA and DCA, (2) that the agreement between ICUS and ED deteriorated considerably after both BA and DCA, (3) that the complex morphological changes induced by BA and DCA contributed to the discordance of the agreement between ICUS and ED, and (4) that VID measurements were found to provide a better agreement with ICUS than ED measurements, particularly in lesions with complex morphological changes post-BA and DCA.

Agreement Between ICUS and ED-QCA in Previous Studies

Previous studies have provided conflicting evidence on whether luminal measurements obtained from ICUS agree with ED-QCA measurements in human coronary arteries. In general, studies that examined ICUS and ED measurements in normal coronary segments report a favorable correlation between the two quantitative imaging modalities,[3,7] while those that examined lesions postangioplasty report a poor correlation.[4,15,16] Naka-

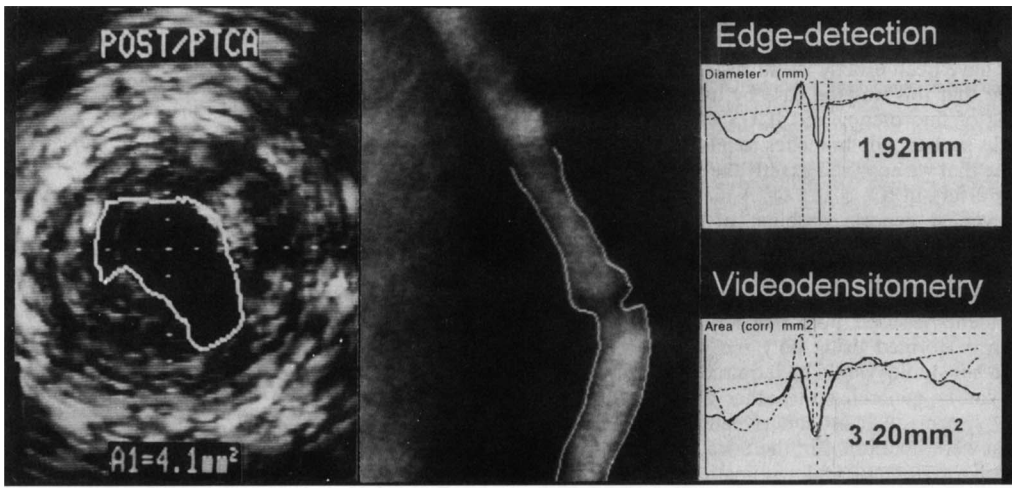

FIG 5. ED-QCA, VID-QCA, and ICUS analysis after BA in the middle segment of the left circumflex coronary artery. Left, ICUS image shows an irregular lumen with partial rupture of a soft eccentric plaque post-BA. The elliptical and irregular shape of the lumen may explain the discordance between measurements of the MCSA obtained from ICUS (4.1 mm^2) and ED-QCA (2.99 mm^2; MLD, 1.92 mm) and VID-QCA (3.20 mm^2). The VID-QCA value is closer to the ICUS measurement than the ED-QCA value; see "Discussion."

mura and colleagues[17] report that dissection induced by BA plays a role in the discordance between ICUS and ED-QCA measurements, but there are several methodological differences between their study and ours. First, they did not examine VID measurements. Second, they showed only the correlation coefficient in groups with and without dissection, and no statistical difference was found in the difference of the individual ICUS and angiographic measurements between two groups. Finally, they did not use a computer-based QCA system but rather caliper measurements, which have a poor reproducibility and result in frequent underestimation or overestimation of stenosis severity.[32] Our study is the first to compare both ED- and VID-QCA measurements with ICUS measurements.

Factors Contributing to the Discordance of ICUS and QCA Measurements

Agreement of luminal area measurements as obtained by using ICUS and ED deteriorated considerably after BA and DCA. A progressive deterioration in the relationship between the ICUS and QCA measurements was seen in accordance with the presence of increasing vessel damage and increasing luminal complexity postintervention. Thus, the cross-sectional shape of the vessel lumen postintervention may be a significant factor in the discrepancy between ICUS and ED-QCA measurements. MLD obtained from ED-QCA depends on the angiographic projection. Although we calculated luminal area from two orthogonal views, the chances of obtaining the exact minimal and maximal diameters of the lesion CSA using ED-QCA would be small, particularly in the complex elliptical shape of the lumen postintervention (Fig 5). ICUS and VID are not projection dependent, and both would provide a measure of the "depth" as well as the "width" of the lumen cross section. ED, however, provides only a measure of one diameter (the "width") of the lumen. Consistent with this is the fact that VID-QCA provided a better agreement and less relative underestimation in relation to ICUS measurements than ED-QCA.

The underestimation by ED relative to ICUS measurements may reflect the propensity of the contour-detection algorithm to trace the change in the brightness profile in the contrast-weak channel between the true and false lumens[33] (Fig 2), while ICUS measurements and VID measurements in multiple views may include the contribution of the false lumen. Such a phenomenon, however, would not account for the relative underestimation by ED in the preintervention phase. Another possibility is that the interventional cardiologist tends to select angiographic projections that best demonstrate both the stenosis preintervention and the residual stenosis postintervention, ie, "worst view" angiography. Even using multiple orthogonal views, as we did in our study, the assumed elliptical cross section may have been based on multiple "worst views," which although they were, per protocol, >45° apart, were not necessarily a combination of truly "worst view" and "best view." Such a limitation to ED-QCA has been an inherent problem in all coronary interventional trials, and attempts to address this by three-dimensional imaging in truly orthogonal views are currently under evaluation.[34,35]

Two additional ICUS-related factors may also have contributed to the observed discordance between ICUS and quantitative angiographic measurements. Elliptical angulation of the ultrasound catheter within the longitudinal axis of the vessel may have led to overestimation of luminal dimensions by ICUS. Additionally, introduction of the ultrasound catheter may have itself resulted in tacking back of dissection flaps, with a resultant larger lumen during ICUS examinations postintervention compared with the less invasive technique of contrast angiography. Our data also suggest that quantitative angiography may yield larger luminal measurements than ICUS in a significant number of patients (Figs 3 and 4). This increase in the apparent angiographic diameter may be caused by extraluminal contrast within fissures, cracks, and dissection as seen around the true lumen.

Study Limitations

First, the coronary sites compared by ICUS and QCA may not have been exactly identical. Although we tried to ensure that this was the case by using simultaneous recording of fluoroscopy and ICUS imaging as well as landmarks such as side branches to guide us, there is no guarantee that we analyzed exactly the same point of the coronary artery in ICUS and QCA measurements. This is, however, a generic problem of any ICUS-QCA study[3,4] that would be very difficult to overcome, as the presence of the ICUS catheter at the lesion site during coronary arteriography would interfere with the QCA measurements. Second, both ED- and VID-QCA analysis were performed using only the CAAS II system. Thus, further studies would be required to confirm if our findings can be generalized to other QCA hardware or software systems.[21] It is conceivable that if an ED algorithm were inaccurate in the normal reference segment, then a systematic underestimation or overestimation of vessel diameters could be translated to subsequent VID measurements. Third, it is also possible that ultrasound image analysis fails to see the true leading intimal edge, especially if the plaque has a low fibrous component and appears relatively hypoechoic, thus overestimating luminal dimensions. Additionally, a poor dynamic range can also induce technical intimal dropout, leading to lumen overestimation.

Clinical Implications

Although ICUS provides unique information regarding the vessel wall morphology, the clinical utility of this technique remains unproven to date. ICUS luminal measurements, however, do provide important additional information to that obtained by visual assessment for optimal stent implantation.[9,10] Whether ICUS provides more accurate information than QCA, however, has not yet been determined. Additionally, whether luminal measurements obtained from ICUS are a superior index for the short- and long-term success of interventional procedures awaits the results of recent multicenter trials.[12,13,36] While ICUS is not universally available and involves additional time and expense,[11] QCA is more widely available and less time-consuming. Our data suggest that in the absence of the known true value and assuming that ICUS gives the most accurate estimate of luminal dimensions, QCA measurements, particularly ED, may be compromised, especially in assessing the complex luminal morphology following BA or DCA. Our study suggests that VID may offer a better correlation with the true luminal dimensions, as reflected by ICUS, than ED-QCA. VID may thus be the "poor man's" ICUS, especially in lesions with complex morphology.

Conclusions

MCSA measurements obtained by ICUS are significantly larger than measurements provided by either geometric or VID-QCA both before and after intervention. Agreement between ICUS and geometric QCA measurements deteriorate considerably after intervention. Complex morphological changes induced by intervention may play a role in such a discordance between the two quantitative imaging techniques. In the absence of ICUS, VID, which is currently available in an online QCA system, may provide a better alternative than ED-QCA in lesions with complex morphology.

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Chapter 3

Coronary arteriography for quantitative analysis: experimental and clinical comparison of cinefilm and video recordings

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Coronary arteriography for quantitative analysis: Experimental and clinical comparison of cinefilm and video recordings

Although use of videotape for the recording of coronary angiograms continues to grow, the validity of quantitative coronary angiographic analysis of video images remains unknown. To estimate the reliability of angiographic images recorded on videotape, experimental and clinical angiograms were recorded simultaneously on both 35 mm cinefilm and super-VHS videotape with normal images and with spatial filtering of the images (edge enhancement) on a digital cardiac imaging system. The experimental angiographic studies were performed with plexiglass blocks and stenosis phantom of 0.5 to 3.0 mm in diameter. The clinical angiograms were recorded in 20 patients undergoing percutaneous transluminal coronary angioplasty (31 frames before and 20 frames after percutaneous transluminal coronary angioplasty). The cinefilm and corresponding videotapes were analyzed off-line with the new version of the coronary angiography analysis system. For the experimental study, measurements of minimal luminal diameter obtained from cinefilm, normal-image videotape, and edge-enhanced videotape were compared with the true phantom diameter. In the clinical study the agreement between measurements obtained from cinefilm and measurements from normal-image videotape and edge-enhanced videotape was examined. In the phantom series the accuracy and precision of quantitative coronary angiography measurement for cinefilm were −0.10 ± 0.08 mm, for normal-image videotape −0.11 ± 0.18 mm, and for edge-enhanced videotape −0.10 ± 0.11 mm (mean ± SD). In the clinical series, the differences between measurements from cinefilm and normal-image videotape were 0.14 ± 0.20 mm and from cinefilm and edge-enhanced videotape 0.04 ± 0.13 mm. In the experimental phantom study, the use of cinefilm resulted in the most precise measurements. In the clinical study, edge-enhanced videotape provided the highest agreement with measurements obtained from cinefilm. These findings suggest that cinefilm is more reliable than video as a recording medium for quantitative coronary analysis in scientific studies; however, for routine practice, videotape with edge-enhanced images may provide an acceptable alternative. (AM HEART J 1995;129:471-5.)

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Coronary angiography continues to be the gold standard for coronary artery imaging in clinical practice. With the increasing demand for quantitative coronary angiography (QCA) and the development of digital acquisition systems, there has been a substantial growth in the deployment of videotape as a recording medium because of its easy handling, instant replay capability, and low cost.[1-4] In some institutions videotape has replaced 35 mm cinefilm as the original imaging medium. However, despite proposals for the replacement of cinefilm by videotape, the suitability of video recordings for QCA analysis has not been established. To evaluate the potential application and reliability of videotape recording for QCA for clinical studies, recordings of experimental phantom stenoses[5-8] and clinical coronary artery stenoses before or after balloon angioplasty were as-

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sessed with the new version of a computer-based coronary angiography analysis system.[5]

METHODS

Experimental image acquisition of phantom stenoses. For the in vitro validation we used radiolucent plexiglass cylinders (50 mm length, 20 mm in outer diameter) with precision-drilled concentric circular lumens (tolerance 0.01 mm) of 0.5, 0.75, 1.0, 1.5, 2.0, 2.5, and 3.0 mm in diameter. The length of each phantom stenosis channel was 20 mm, and the adjacent "normal" channel length of the proximal and distal segments was 30 mm. The plexiglass channel (including the artificial stenosis) was filled with contrast medium (iopamidol 370; 370 mg iodine/ml [Bracco, Milano, Italy]). Digital and cinefilm acquisition was performed with additional plexiglass blocks (12.5 cm anteriorly and 5 cm posteriorly). These plexiglass blocks provide a more appropriate (kilovolt level and a scatter medium that more closely approximates the radiologic scatter of the human thorax during angiography. Angiograms were performed with the 5-inch field of an image intensifier, with separate recordings and two different focal spots (0.5 mm, which was used for most of the experimental and clinical series, and 0.8 mm) and at an image acquisition rate of 25 frames/sec. The radiographic system settings were kept constant (kilovolt, milliampere, x-ray pulse width) in each projection. All phantoms were imaged at the radiographic isocenter of the x-ray gantry[9] and acquired simultaneously on 35 mm cinefilm (Kodak CFE type 2711, Paris, France) and digitally (Philips Digital Cardiac Imaging [DCI] system Philips, Best, The Netherlands).

Coronary arteriographic procedure before and after percutaneous transluminal coronary angioplasty (PTCA). Coronary angiography was performed in multiple projections with 8F polyurethane catheters (Cordis, Miami, Fla.), in 20 patients before and after PTCA at the Thoraxcenter, Rotterdam. To control vasomotion, intracoronary isosorbide dinitrate (1 to 3 mg)[10] was administered before manual injection of contrast medium (iopamidol 370; 370 mg iodine/ml) at 37° C. The 5-inch field of the image intensifier was selected and the radiographic settings were kept constant (kilovolt, milliampere, x-ray pulse width) in each projection. All clinical images were simultaneously acquired digitally by DCI and on 35-mm cinefilm with frame rates of 25 images/sec.

Image processing and spatial filtering (edge-enhancement) in the DCI. Both experimental and clinical angiographic images were stored on a 474 MB Winchester disk. The DCI system uses a matrix size of 512 × 512 pixels (average horizontal pixel size 200 μm; density resolution 8 bits = 256 gray levels). The images were processed with the automated coronary analysis software package of the DCI system.[8, 11, 12] Edge-enhanced images were produced by spatial filtering on the DCI system. The algorithm of spatial filtering operates by substituting new pixel values for the original pixel values on the coronary angiogram.[13] A visible horizontal edge of the coronary artery is formed when a string of horizontally connecting pixels displays values that are different from those immediately above or below. Similarly, a vertical edge of the coronary artery is formed when a string of vertically connecting pixels have values different from those immediately to the right or to the left. Oblique edges are generated through combinations of horizontal and vertical components. The default edge-enhancement mode of the DCI system was used. Spatial filtering amplifies the pixel differences between the opacified vessel and its background, thereby providing a more distinct border to the coronary artery. Images with and without edge-enhancement were then directly relayed to the video recorder (Panasonic 7330, Osaka, Japan) and recorded on super-VHS tape (Fuji-film double coating SE-60, Sizuoka, Japan).

Stenosis characteristics. Twenty-one experimental frames and the 51 pre-PTCA and post-PTCA clinical frames were selected for quantitative analysis, and their minimal luminal diameter was measured. Of the clinical angiograms, the 31 pre-PTCA frames consisted of 16 left anterior descending, 10 left circumflex, and 5 right coronary artery lesions. Of the 20 post-PTCA frames evaluated, 10 showed left anterior descending, 8 left circumflex, and 2 right coronary artery lesions. All pre-PTCA lesions had >50% diameter stenosis.

Correction of pincushion distortion. Before the performance of the calibration and analyses of the stenoses, computerized correction for pincushion distortion was applied by the recording and subsequent off-line digitization of a centimeter grid placed in front of the image intensifier.

Calibration of images. For the experimental in vitro series, the measurements of the phantom stenoses were calibrated with a contrast-filled 3.0 mm–diameter circular channel in a plexiglass cylinder as a scaling device. This calibration frame was digitized and traced by the automated contour detection algorithm before the series of analyses of the in vitro phantoms was begun. In the clinical study, cinefilm and videotapes were calibrated by the use of the recorded contrast-free catheter tip as a scaling device. The nontapering catheter tip was measured with a precision micrometer (Mitutoyo no. 293-501, Tokyo, Japan; accuracy 0.001 mm).

Quantitative analysis in CAAS II. Cinefilms and corresponding frames of videotapes with and without spatial filtering (edge enhancement) were quantitatively analyzed off-line by using the computer-based Cardiovascular Angiographic Analysis System (CAAS II; Pie Medical, Maastricht, The Netherlands).[5, 14-19] In the experimental study a sufficiently long segment of the plexiglass cylinders including the stenosis phantom was selected for analysis. In the clinical study frames without foreshortening or overlapping side branches were selected. Arterial dimensions of clinical frames were measured at specific distances from identifiable branch points in end-diastolic frames. The entire cineframe of size 18 × 24 mm is digitized at a resolution of 1329 × 1772 pixels in the CAAS II system. During image acquisition of videotape a time-base corrector was implemented to ensure high-quality stand-still images.[1] The video signal from tapes with and without spatial filtering (edge-enhancement) were digitized at a resolution of 512 × 512 pixels by the CAAS II system. In the CAAS II

Table I. Comparison of phantom diameter and minimal luminal diameter obtained from cinefilm, normal-image videotape, and edge-enhanced videotape in experimental in vitro phantom study

Recording medium	*Accuracy*	*Precision*	*Difference*	*Correlation*	*Linear regression analysis*	*SEM*
Cinefilm	−0.10	±0.08	$p < 0.01$	0.997	$y = 0.01 + 0.93x$	0.05
Normal-image videotape	−0.11	±0.18	$p < 0.05$	0.987	$y = 0.13 + 0.85x$	0.12
Edge-enhanced videotape	−0.10	±0.11	$p < 0.01$	0.992	$y = -0.06 + 0.98x$	0.11

system, the edge-detection algorithm is based on the first and second derivative functions applied to the digitized brightness profile along scan lines perpendicular to a model that uses minimal cost criteria.[20, 21] The contour definition is carried out in two iterations. First, the user defines a number of center-line points within the arterial segment that are interconnected by a straight line and serve as the first model. Subsequently, the program recomputes the center line, determined automatically as the midline of the contour positions that were detected in the first iterations. A computer-derived estimation of the original dimensions of the artery at the site of the obstruction was used to determine interpolated reference values for arterial diameter and area. Manual correction of the automatically detected contours was neither necessary nor performed in either the experimental phantom nor the clinical studies (in routine practice at angiographic core laboratories, subjective manual correction of the detected contours at the minimal luminal diameter is only occasionally performed in the case of complex dissections with parallel luminal extravasation, which was not present in our clinical angiograms).

Statistics. In the experimental study, the individual measurements of minimal luminal diameter were compared with the true phantom diameter by using the paired Student *t* test and linear regression analysis. The mean of the signed differences between the true phantom diameters and the individual minimal luminal diameter values derived from measurements of cinefilm and of videotape were considered an index of accuracy and the SD of the differences an index of precision. In the clinical study, the mean ± SD of the signed differences between measurements of minimal luminal diameter derived from cinefilm and measurements of minimal luminal diameter derived from videotape were used as an index of agreement between measurements from the different recording media. This statistical approach to the comparison of two measurement systems has been previously recommended by Bland and Altman.[22]

RESULTS

In vitro results. The results of QCA measurements obtained from cinefilm, videotape with normal image, and videotape with spatial filtering (edge enhancement) and their comparisons with the true phantom diameters are summarized in Table I and displayed graphically in Fig. 1. Of the three recording modes, cinefilm was found to provide the most precise measurement results.

Clinical results. The results of measurements from normal-image videotape are plotted against those from cinefilm in Fig. 2, *A*.[22] The agreement between the two sets of measurements was poor (0.14 ± 0.20 mm ($p < 0.01$)). The results of measurements from edge-enhanced video are plotted against those from cinefilm in Fig. 2, *B*.[22] Although the agreement between the two sets of measurements was better with edge-enhanced video than with normal-image videotape, the difference between the edge-enhanced videotape and cinefilm measurements still achieved statistical significance (0.04 ± 0.13 mm ($p < 0.05$)).

DISCUSSION

We have demonstrated that of the three image recording modes studied, cinefilm produces the most precise QCA measurements. The reasons for this finding may relate to the high resolution afforded by cinefilm frame analysis (1329 × 1772 pixels) compared to the limited resolution provided by the analysis of a single video field (312 lines per field; each video frame consists of two interlaced fields). The noise introduced by the video recording process and by the videotape itself may contribute to the lower precision of the QCA measurements. This video-induced noise was not overcome by our compensatory steps of recording on super-VHS videotape to reduce the signal/noise ratio[3] and deploying a time-base corrector during image acquisition to overcome jitter.[1] As was expected, the introduction of a systematic noise such as that associated with video recording did not exert a significant effect on the accuracy of our QCA measurements.

Our studies of both experimental and clinical images indicate that video recording with on-line spatial filtering results in more reliable QCA measurements than videotape without enhancement. These findings support the view that on-line spatial filtering (edge enhancement) before the introduction of video noise provides a more distinct border to the coronary vessel (or phantom stenosis), which is more

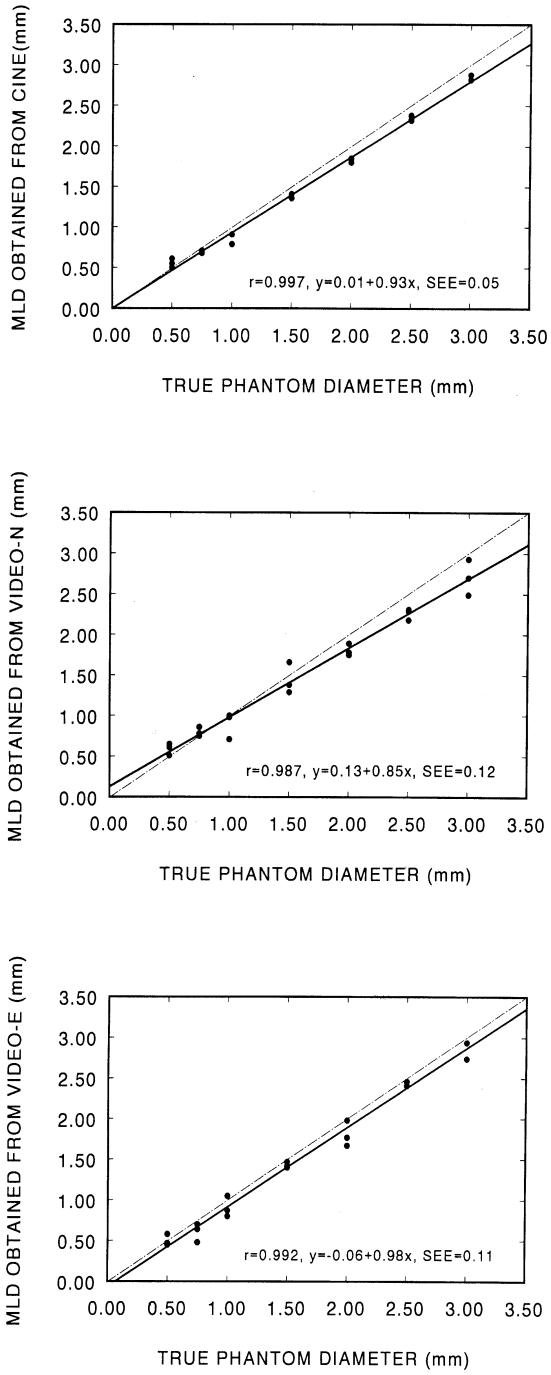

Fig. 1. Linear regression analysis of QCA measurements obtained from cinefilm *(CINE)*, normal-image videotape *(VIDEO-N)* and edge-enhanced videotape *(VIDEO-E)*, against true phantom diameter. *Top*, Cinefilm vs phantom; *Middle*, normal-image videotape phantom; *Bottom*, edge-enhanced videotape vs phantom. *MLD*, Minimal luminal diameter.

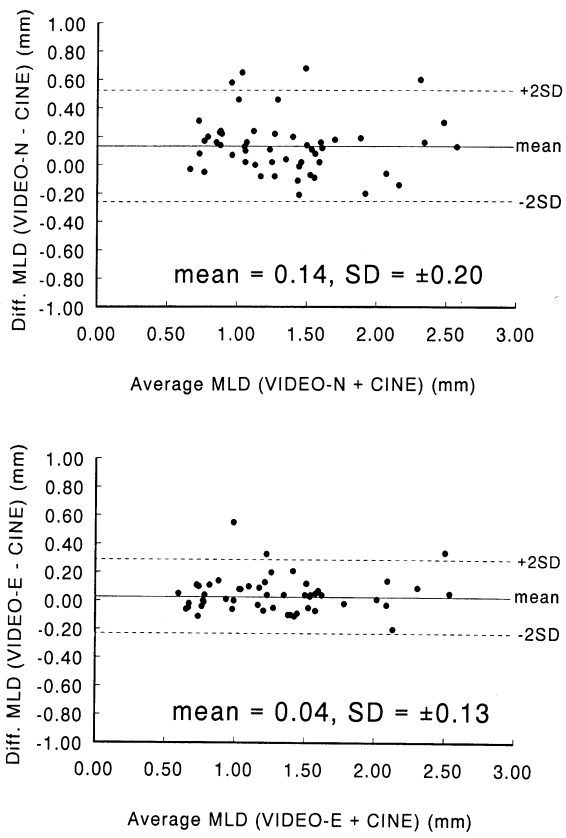

Fig. 2. Agreement between measurements obtained from cinefilm and video recordings according to statistical approach proposed by Bland and Altman.[22] *Top*, Difference between normal-image videotape and cinefilm measurements has been plotted against their mean. *Bottom*, Difference between edge-enhanced videotape and cinefilm measurements has been plotted against their mean. Abbreviations as in Fig. 1.

faithfully tracked by the off-line QCA edge-detection algorithm than the vessel border of an unenhanced image.

Study implications. Financial considerations have now become an important factor in the administrative and technical decision-making process of most cardiac catheterization laboratories. A single videotape can store the complete angiographic records of approximately 40 patients at a cost of less than $1 per patient; cinefilm increases the cost per patient to $40. Our findings suggest that the adoption of videotape with edge-enhanced images may present an acceptable alternative to cinefilm for routine purposes and possibly for QCA purposes under certain circumstances. It should be recognized, however, that the

addition of any noise or imprecision to the system of off-line QCA will increase the SD of the angiographic results of the study. In turn, this might increase the number of patients needed for detection of a statistically significant difference among two study populations under comparison.[23] Thus the inclusion of videotape in the design of a restenosis prevention or progression-regression trial may present a false economy by virtue of a concomitant increase in the number of patients required and subsequent greater total study costs.

Study limitation. The edge enhancement of images and subsequent QCA analysis in our study was performed by the Philips DCI system and CAAS II system. Further studies will be required to confirm whether our findings can be generalized to other hardware or software systems. It is conceivable that if an on-line edge-enhancement algorithm was inaccurate, a systematic underestimation or overestimation of vessel diameters could be translated to subsequent off-line QCA measurements.

Conclusion. Despite the application of on-line edge enhancement, the selection of super-VHS videotape and the deployment of a time-base corrector in the processing of video images for off-line QCA, cinefilm continues to present a more reliable image recording medium of coronary angiograms for scientific studies. For routine practice, however, videotape with edge-enhanced images may provide an acceptable alternative.

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Chapter 4

Ischemia-related lesion characteristics in patients with stable or unstable angina: a study with intracoronary angioscopy and ultrasound

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Ischemia-Related Lesion Characteristics in Patients With Stable or Unstable Angina

A Study With Intracoronary Angioscopy and Ultrasound

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Background Postmortem-derived findings support the common beliefs that lipid-rich coronary plaques with a thin, fibrous cap are prone to rupture and that rupture and superimposed thrombosis are the primary mechanisms causing acute coronary syndromes. In vivo imaging with intracoronary techniques may disclose differences in the characterization of atherosclerotic plaques in patients with stable or unstable angina and thus may provide clues to which plaques may rupture and whether rupture and thrombosis are active.

Methods and Results We assessed the characteristics of the ischemia-related lesions with coronary angiography and intracoronary angioscopy and determined their compositions with intracoronary ultrasound in 44 patients with unstable and 23 patients with stable angina. The angiographic images were classified as noncomplex (smooth borders) or complex (irregular borders, multiple lesions, thrombus). Angioscopic images were classified as either stable (smooth surface) or thrombotic (red thrombus). The ultrasound characteristics of the lesion were classified as poorly echo-reflective, highly echo-reflective with shadowing, or highly echo-reflective without shadowing. 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 of 44); a noncomplex lesion (n=34) was concordant with stable angina in 61% (14 of 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 of 44); a stable lesion (n=33) was concordant with stable angina in 83% (19 of 23). The ultrasound-obtained composition of the plaque was similar in patients with unstable and stable angina.

Conclusions Angiography discriminates poorly between lesions in stable and unstable angina. Angioscopy demonstrated that plaque rupture and thrombosis were present in 17% of stable angina and 68% of unstable angina patients. Currently available ultrasound technology does not discriminate stable from unstable plaques. (***Circulation.* 1995;92:1408-1413.**)

Key Words • angina • ultrasonics • angiography

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 or unstable angina is of importance to better understand the pathogenic 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 plaque size and composition,[13-15] and intracoronary angioscopy accurately detects the presence of plaque rupture and intracoronary thrombus.[16-19]

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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.

Methods

Between September 1992 and March 1993, a nonconsecutive series of 75 patients who were scheduled for coronary intervention were studied. In 1 patient, the procedure was discontinued because of severe ischemic chest pain after introduction of the angioscope into the ischemia-related coronary artery. Immediate percutaneous transluminal coronary angioplasty was successful without adverse sequelae. The angioscope was introduced in 7 patients, but the obtained images were of insufficient quality. Thus, the study population comprised 44 patients with unstable angina and 23 patients with stable angina. Table 1 lists the clinical and angiographic data of these patients.

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

TABLE 1. Baseline Patient and Angiographic Characteristics

	Unstable Angina (n=44)	Stable Angina (n=23)
Sex, M/F	40/4	19/4
Age, y		
Mean	60	51
Range	49-71	39-69
Previous MI (<14 days), n	17	0
Multivessel disease, n	15	5
Premedication		
Heparin/aspirin, n	44/33	0/6
Systemic thrombolysis, n	7 (all post-MI)	None
Nitroglycerin IV/oral	39/0	0/21
Calcium channel antagonists, n	34	9
β-Blockers, n	34	21
Time from onset instability, d	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

MI indicates myocardial infarction; LAD, left anterior descending coronary artery; RCA, right coronary artery; CX, circumflex artery; and SVG, saphenous vein graft.
*Mean±SD, determined with quantitative coronary angiography.

procedure. They received anticoagulation with heparin, so activated clotting time was >300 seconds.

After passage of a 0.014-in guide wire across the lesion, intracoronary angioscopy was always performed first, followed by 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 practice.

Selection of Ischemia-Related Lesion

In patients with 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 ECG localization indicated by transient ST-T segment changes 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 noncomplex (concentric or eccentric with smooth borders) or 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) with the non–contrast-filled catheter as calibration.[21]

Imaging Devices

The percutaneous coronary angioscopic device was a 4.5F monorail-type polyethylene catheter device accommodated by an 8F guiding catheter (Baxter-Edwards).

Ultrasound imaging was performed with a commercially available intracoronary 4.3F, 30-MHz ultrasound catheter (Cardiovascular Imaging Systems Inc).

To facilitate the review process, a real-time fluoroscopy or cineangiography was combined with real-time angioscopy and ultrasound imaging by use of split-screen videotaping. This provided a better orientation of the place from which the angioscopic and ultrasound images were derived within the coronary tree.

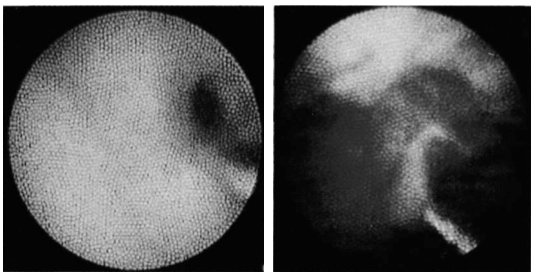

FIG 1. Angioscopic images of a stable lesion (left) with smooth, white surface and thrombotic lesion (right) with disrupted surface and red thrombus.

Analysis of Angioscopic and Ultrasound Images

Qualitative analyses of both angioscopic and ultrasound images were performed by the 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 nonmobile and mural (closely adherent to the vessel wall), mobile (protruding into the lumen), or totally occlusive. Yellow plaques were defined as areas of homogeneous yellow clearly identifiable from the normal white wall.

Wall surface was classified as ulcerated when a 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 nonstenotic segments, the surface was classified as smooth.

Angioscopic images of lesions were classified as thrombotic lesions if they had an irregular, ulcerated raised surface with the presence of thrombus or as stable lesions if the raised surface was regular and smooth without thrombus (Fig 1).

The composition of the ischemia-related lesion was classified as poorly echo-reflective or highly echo-reflective intimal thickening (Fig 2). The last group was further subdivided according to the presence or absence of acoustic shadowing. An intimal thickening was considered poorly echo-reflective if the echo density was less than that seen for the adventitia and highly echo-reflective if the echo density was equal to or greater than that of the adventitia.

The results of previous comparisons between histology and ultrasound showed that poorly echo-reflective intimal thickening corresponds to loose fibrous tissue, lipid, and thrombus; highly echo-reflective intimal thickening without shadowing represents dense fibrous tissue; and highly echo-reflective intimal thickening with acoustic shadowing indicates calcium deposition.[14,22,23] The concentricity versus the eccentricity of the plaque was determined by the ratio between the thinnest and thickest parts of the intimal thickening. Eccentricity was defined by a ratio <0.7.

A lesion was considered homogeneous if the plaque consisted of >75% of one type of echo-reflectivity induced by the lesion determined from an integrated pullback image of the entire lesion. A lesion was considered predominantly calcific if calcium occupied >180° of the vessel circumference. A lesion was defined as mixed if it contained both highly and poorly echo-reflective areas occupying >25% of the plaque surface or if calcium deposits occupying >30° and <180° of the vessel circumference were present. The intergroup observer variability performed in a random sample of 30 patients for angioscopic image classification yielded κ values of 1.0 for the presence of thrombus, 0.78 for a protruding or mural throm-

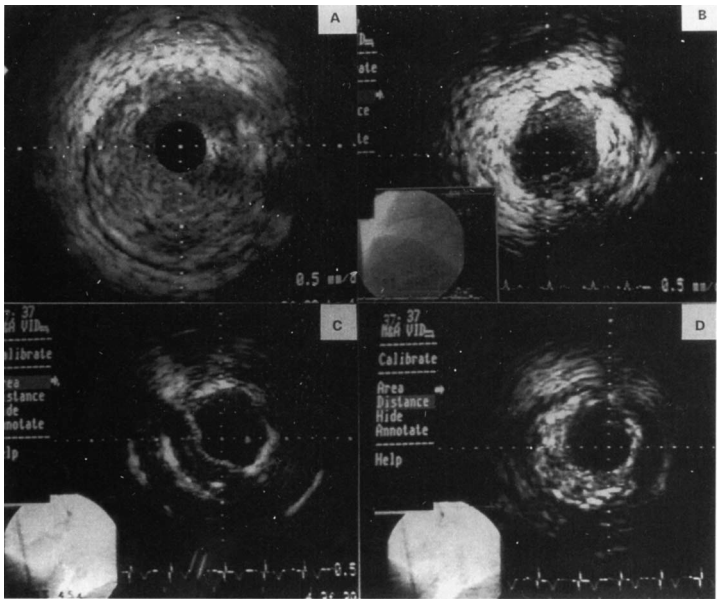

FIG 2. Angioscopic images of the types of ultrasound-derived lesions: (A) plaque with poorly echo-reflective tissue between 4 and 9 o'clock, (B) plaque with highly echo-reflective tissue with eccentric location between 1 and 4 o'clock, (C) plaque with highly echo-reflective tissue with shadowing, and (D) mixed plaque composed of poorly echo-reflective tissue at 6 to 11 o'clock and highly echo-reflective with shadowing at 1 to 5 o'clock.

bus, 0.8 for the surface of a lesion, 0.93 for yellow plaque, and 0.94 for a thrombotic lesion. The κ values for ultrasound classification of echo-reflectivity of lesions ranged from 0.85 (calcium present) to 1.0 (homogeneous versus mixed type).

Quantitative measurements were obtained from a cross-sectional image taken at the narrowest part of the lesion. Total vessel area was defined as 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 and 0.03 ± 0.62 mm^2 (r=.97 and r=.99), respectively.

Statistical Analysis

All measured values are presented as mean±SD. The unpaired t test, the χ^2 test with Yates' correction, and Fisher's exact test were used when appropriate. A value of $P<.05$ was considered statistically significant. The interobserver variations were assessed with the use of unweighted κ coefficients.[24]

Results

Procedures

Passage of the imaging catheters through the ischemia-related lesion was obstructive to blood flow and associated with chest pain and ECG ST-T segment changes in almost all patients. These changes were quickly reversible after withdrawal of the catheter except in 2 patients in whom abrupt occlusion occurred at the site of the ischemia-related lesion. This was treated effectively with balloon angioplasty. The angioscope caused a small, nonocclusive dissection in 1 patient. Subsequent balloon angioplasty resulted in an occlusive dissection that was managed effectively by stent implantation.

In 4 patients, the culprit lesion was too tight to allow crossing with the angioscope, and the observations were restricted to the proximal aspect of the stenosis. In the 2 patients in whom the lesion could not be crossed with the ultrasound probe, the plaque composition was taken from postangioplasty examination.

Lesion Characteristics

Tables 1 through 3 give the angiographic and intracoronary angioscopy findings and ultrasound characteristics of the ischemia-related lesions. An angiographically complex lesion was present in 39% of the stable angina patients and in 55% of the unstable angina patients. An angioscopically thrombotic lesion was present more often in patients with unstable angina than in patients with stable angina (68% versus 17%, $P<.01$). 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, presence and distribution

TABLE 2. Angioscopic Characteristics of Ischemia-Related Lesions

	Unstable Angina (n=44)	Stable Angina (n=23)	*P*
Thrombus, n (%)	30 (68)	4 (17)	<.001
Occlusive	2	0	
Protruding	8	1	
Mural	20	3	
Surface lesion, n			
Ulcerated	20	3	<.05
Rough	11	6	
Smooth	13	14	
Yellow plaque, n (%)	29 (66)	16 (69)	

TABLE 3. Intracoronary Ultrasound Characteristics of Ischemia-Related Lesions

	Unstable 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 (%)	20 (45)	8 (35)
Poor/high without shadowing	2	2
Poor/high with shadowing	18	6
Calcium present,† n (%)	20 (46)	7 (31)
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, mm^2	15.2±5	17.0±5

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

of calcium, and eccentricity and extent of the plaque were similar in unstable and stable angina patients.

Correlations Among Clinical, Angiographic, Angioscopic, and Ultrasonic Lesion Characteristics

Tables 4 and 5 list the correlations among the findings of angiography, angioscopy, and ultrasound of the ischemia-related lesions in patients with stable and unstable angina. It appears that the clinical syndrome and angiographic findings were poorly correlated. An angiographic complex lesion (n=33) or noncomplex lesion (n=34) was concordant with unstable angina (n=44) or stable angina (n=23) in 55% (24 of 44) and 61% (14 of 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 of 44) and 83% (19 of 23), respectively (Table 4).

There were no significant correlations among the lesion characteristics obtained with angiography, angioscopy, and ultrasound (Tables 4 and 5). An angiographic complex lesion (n=33) or noncomplex lesion (n=34) was concordant with an angioscopic thrombotic lesion (n=34) or stable lesion (n=33) in 58% (19 of 33) and 56% (19 of 34), respectively (Table 4).

TABLE 4. Correlation Between Angiographic, Angioscopic, and Ultrasound Findings of Lesions in Patients With Stable and Unstable Angina

	Angiographic Lesion			
	Unstable Angina (n=44)		Stable Angina (n=23)	
	Non-complex (n=20)	Complex (n=24)	Non-complex (n=14)	Complex (n=9)
Angioscopic lesion				
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	11	9	3	4

TABLE 5. Correlation Between Angioscopic and Ultrasound Lesion Characteristics in Patients With Stable or Unstable Angina

	Angioscopic Lesion			
	Unstable Angina (n=44)		Stable Angina (n=23)	
	Thrombotic (n=30)	Smooth (n=14)	Thrombotic (n=4)	Smooth (n=19)
Ultrasound lesion				
Poorly echo-reflective	15	7	1	13
Highly echo-reflective	0	1	0	0
Highly echo-reflective with shadowing	1	0	0	1
Mixed	14	6	3	5

Ultrasonic-defined lesion characteristics were almost equally represented between angiographically complex and noncomplex lesions (Table 4) and between angioscopic thrombotic and stable lesions (Table 5).

Discussion

Individual atherosclerotic lesions have a striking heterogeneity in both their composition and appearance. Much evidence has accumulated, primarily from postmortem studies, to show that acute ischemic syndromes are associated with plaque fissuring and superimposed thrombosis.[7-12] Clinical angioscopic studies 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 had 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 in 91% of thrombosed plaques but in only 3.2% of nonthrombosed plaques. Ample evidence indicates that lipid-rich atheromatous plaques that have a thin, fibrous capsule are prone to plaque fissuring.[1-12] Clearly, it would be of great importance if we could identify, in vivo, plaques prone to fissuring. In vitro pathological studies showed that intravascular ultrasound imaging can allow us to visualize the fibrous cap and provides 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, experience with using intracoronary ultrasound to characterize the composition of coronary lesions in patient studies is limited. Hodgson et al[15] performed a morphological analysis of the ultrasound images obtained from ischemia-related lesions in patients with unstable or stable angina. They found that patients with unstable angina had more poorly echoreflective lesions and fewer severe calcific lesions or intraluminal calcium deposits than patients with stable angina. We could not confirm these findings, and we found that the compositions of stable and unstable plaques were nearly identical. The discrepancy between the findings of these two studies may be explained by differences in image quality. The mechanical system used in this study has a higher dynamic range and resolution than that used by Hodgson et al. However, the ultrasonic findings should be interpreted with cau-

tion 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 arises as to why we did not observe the presence of a thrombus in the other one third of the unstable patients. This question has several possible answers. The intensive premedication with heparin and aspirin and the time interval between the last symptoms and examination may have induced dissolution of thrombus and wall repair. Plaque disruption may have been small and associated with only a small thrombus that was difficult to see with angioscopy or was 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 rupture and thrombosis, such as vasospasm or the recently suggested possibility of smooth muscle cell proliferation with plaque expansion, cause luminal narrowing.[25] It is also of note that rupture and thrombosis were observed in 17% of the patients with stable angina. This observation has not been made by other investigators in patients with stable angina.[16-18] These findings suggest that rupture and thrombosis do 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 smaller than larger dissections after coronary angioplasty that are reliably detected with ultrasound.

We found that approximately two thirds of the lesions in patients with stable and unstable angina were yellow. This yellow color of a plaque is caused by lipid that contains carotene. A white plaque may also contain lipid because cholesterol is white and does not always contain carotene.

Study Limitations

The study group consists of a nonconsecutive series of patients, which may have introduced a bias. This study was performed in a subset of unstable patients having angina at rest or early postinfarction angina selected for balloon angioplasty and thus precludes generalization of the findings to all patients with unstable angina.

Unstable angina pectoris is a dynamic process with different pathophysiological mechanisms that wax and wane over time. Therefore, any study will 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 still bulky and stiff. In a few cases, the ischemia-related lesions could not be crossed or could not be completely imaged because of the curvature of the vessels, so interrogation of the entire lesion was not possible and certain lesion characteristics may have been missed.

Even after the lesions were crossed, certain aspects may have escaped detection because the current angioscopic design does not include a flexible, steerable tip, so 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 artifact present with the 4.3F 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 relatively safe in patients undergoing coronary intervention. Additional imaging can be associated with ischemic complications, which could be successfully managed with subsequent coronary interventions. The information obtained with angioscopy is complementary to coronary angiography with regard to the distinction between stable and unstable features of the coronary lesion. Ultrasound does not discriminate between stable and unstable plaques.

Both intracoronary imaging techniques do not allow identification of a lipid-rich plaque with a thin fibrous cap known to be prone at rupture.

Ultrasonic imaging (30-MHz) does not yield enough resolution to accurately detect plaque composition. Improvement of the quality of intracoronary ultrasound images is necessary to provide accurate information on the size of the volume of the extracellular lipid pool, thickness of the fibrous cap, or location and depth of a fissure of the cap.[26]

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Part 2 - Assessment of Coronary Atherosclerosis

Chapter 5

Progression and regression of coronary stenosis in the long-term follow-up of vasospastic angina

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Progression and Regression of Coronary Stenosis in the Long-term Follow-up of Vasospastic Angina

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Background Whether focal vasospasticity plays a pathogenic role in the progression or regression of coronary atherosclerosis is unknown. To determine whether evidence for such a role exists, we studied long-term changes in coronary luminal measurements in patients with vasospastic angina.

Methods and Results Quantitative coronary angiography and repeated ergonovine provocation tests were performed 45±16 months apart in 30 patients. All patients had vasospastic anginal symptoms and coronary spasm on the initial provocation test. Of the 30 patients, 16 had persistent symptoms of vasospastic angina and showed coronary spasm at the same site on the follow-up angiogram (group 1), while the remaining 14 whose vasospastic anginal symptoms disappeared at follow-up demonstrated a negative response to ergonovine on the follow-up tests (group 2). There was no significant difference in patients' baseline characteristics between the two groups. Long-term changes in minimal (MLD) and mean (MEAN) luminal diameter were measured (in millimeters) after administration of isosorbide dinitrate in 19 spastic and 93 nonspastic segments in group 1 and in 17 previously spastic and 81 nonspastic segments in group 2. Both MLD and MEAN were measured in 210 coronary segments of the 30 patients at baseline and after administration of ergonovine and isosorbide dinitrate by use of a computer-based quantitative coronary angiography system. Stenosis progression and regression of individual lesions were defined as a change in MLD of ≥0.40 mm. In group 1, both the MLD and MEAN of 19 spastic segments were significantly smaller (progression) at follow-up compared with the initial angiogram (MLD, 2.21±0.54 initially versus 1.95±0.65 at follow-up, $P<.01$; MEAN, 2.80±0.56 initially versus 2.56±0.58 at follow-up, $P<.01$), whereas the MLD and MEAN of 93 nonspastic segments in group 1 were not significantly different between the initial and follow-up angiograms (MLD, 2.47±0.67 initially versus 2.44±0.69 at follow-up, P=NS; MEAN, 2.96±0.69 initially versus 2.91±0.68 at follow-up, P=NS). In group 2, the MLD of the 17 previously spastic segments significantly improved (regression) at follow-up (MLD, 1.99±0.68 initially versus 2.24±0.54 at follow-up, $P<.05$); the MLD and MEAN of the 81 nonspastic segments were not significantly different (MLD, 2.36±0.59 initially versus 2.39±0.60 at follow-up, P=NS; MEAN, 2.81±0.58 initially versus 2.81±0.61 at follow-up, P=NS). In group 1, significant stenosis progression of individual lesions was observed more frequently at spastic than nonspastic segments (6 of 19 versus 10 of 93, $P<.05$), whereas stenosis regression was observed in no spastic and 3 nonspastic segments (P=NS). In group 2, stenosis progression was observed at 1 previously spastic segment and 4 nonspastic segments (P=NS), while significant stenosis regression of individual lesions was seen more commonly in previously spastic than nonspastic segments (6 of 17 versus 7 of 81, $P<.01$).

Conclusions These results have demonstrated in patients an association between persistent vasospastic activity and progression of atherosclerosis and an association between cessation of vasospastic activity and regression of atherosclerosis. (***Circulation.* 1995;92:2446-2456.**)

Key Words • atherosclerosis • vasospasm • angina • coronary spasm • tests • angiography

Progression or regression of coronary atherosclerosis is of prognostic importance in patients with angina pectoris in the determination of risk of MI and sudden cardiac death.[1-10] The primary role of coronary spasm in vasospastic angina[11-19] and certain categories of MI[20-23] is established. Although it has been known for decades that coronary spasm frequently occurs at sites of significant atherosclerosis,[11,14-16,20,21,24] it has not yet been determined whether vasospasm plays a role in the progression or regression of atherosclerosis.

Attempts in previous experimental and clinical studies to indirectly detect a possible link between spasm and acceleration of atherosclerosis have provided conflicting circumstantial evidence. In an animal model, severe coronary spasm was found by Nagasawa et al[25] and Kuga et al[26] to induce intimal hemorrhage and intimal thickening and eventual rapid progression of fixed stenosis; however, no such results have been found in humans. In a single patient, Marzilli et al[27] reported rapid progression of coronary atherosclerosis at a site of previous spasm, while in a study of 10 patients with variant angina, Kaski et al[28] found that stenosis progression at the spastic site was rare (only 1 patient) despite the persistence of vasospastic activity in all patients.

To determine whether focal vasospastic activity over several years in human coronary arteries is linked with the progression or regression of local atherosclerosis, we compared the chronological changes in MLD and MEAN of the AHA coronary segment in patients with persistent symptoms of vasospastic angina with those of patients with vasospastic angina whose symptoms resolved over a follow-up period of 45 months. We used a

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Selected Abbreviations and Acronyms

AHA = American Heart Association
CAAS = Coronary Angiography Analysis System
LAD = left anterior descending coronary artery
LCx = left circumflex artery
MEAN = mean luminal diameter
MI = myocardial infarction
MLD = minimal luminal diameter
QCA = quantitative coronary angiography
RCA = right coronary artery

computer-based coronary angiographic analysis system (CAAS II) to make this comparison.

Methods

Criteria of Vasospastic Angina

The following criteria of vasospastic angina were used: (1) chest pain at rest associated with ST-segment changes of >0.2 mV on ECG, (2) pain relief immediately after the administration of nitroglycerin, (3) no subsequent evidence of MI, and (4) ergonovine-provoked coronary spasm associated with chest pain and ischemic ECG changes. Coronary spasm was defined as a transient total or near-total occlusion reversible with isosorbide dinitrate or as a transient significant (>50%) narrowing reversible with isosorbide dinitrate in normal or nearly normal segments.[29-31] We used the ergonovine provocation test because it has been found to have high sensitivity and specificity and short-term reproducibility of spontaneous angina attacks in patients with vasospastic angina.[32-34]

Study Population

To determine the relation between long-term focal vasospasticity and the progression of atherosclerosis, we compared the progression of atherosclerosis in 16 patients with persistent vasospasm at a constant coronary location with that in 14 patients in whom vasospastic angina completely resolved. The study population was selected from a total of 44 patients with variant angina who had undergone long-term angiographic and ergonovine provocation follow-up.

Of the 44 patients who had chest pain at rest with ischemic ST-segment changes at the time of the initial angiographic study, vasospastic anginal symptoms were persistent during the follow-up period in 29, while in the remaining 15 patients, symptoms of vasospastic angina resolved during follow-up. Of the 29 patients, 13 did not demonstrate vasospasticity at the same site on the initial and the follow-up angiograms. In these 13 patients with a change in location in vasospasticity, it was not possible to determine exactly when vasoconstriction started at the new site or when vasospasm ceased at the previous spastic location; therefore, they were excluded from the study. Of the 29 patients, 16 had persistent symptoms of vasospastic angina with ischemic ST-segment changes during the follow-up period, and vasospasm was reproduced at the identical coronary site at the follow-up angiogram (group 1). Of the 15 patients, 1 showed vasoconstriction at the follow-up angiogram despite a complete absence of clinical symptoms. Because this patient did not have anginal pain during follow-up, which had been observed previously at the initial test, it was not possible to determine whether long-term vasospastic activity had persisted throughout the follow-up period or whether the patient had simply retained hypersensitivity to ergonovine; therefore, this patient was excluded from the study. In the remaining 14 patients, symptoms of vasospastic angina disappeared completely, and neither ischemic evidence on ECG monitoring nor positive response to ergonovine was demonstrated during the follow-up period (group 2).

Basal Clinical Characteristics

Tables 1 and 2 give the clinical characteristics of groups 1 and 2, respectively. Specifically, no significant differences were found between groups 1 and 2 in age (55±8 versus 55±7 years), sex (women, 1 of 16 versus 1 of 14), follow-up period (45±15 versus 45±18 months), or coronary risk factors such as smoking, diabetes, hypertension, total cholesterol level, or HDL cholesterol level at the time of the initial angiogram or at follow-up (total cholesterol: group 1, 190±35 and 196±37 mg/dL; group 2, 193±33 and 198±36 mg/dL; HDL cholesterol: group 1, 51±15 and 50±15 mg/dL; group 2, 53±21 and 50±15 mg/dL, initially and at follow-up, respectively). Blood pressure was well controlled throughout the follow-up period in those patients with a history of hypertension. No patient had insulin-dependent diabetes mellitus, and 2 patients (1 from each group) had diet-controlled adult-onset diabetes.

Medication

Medication (Tables 1 and 2) consisted of sustained-release isosorbide dinitrate and a calcium antagonist (diltiazem). Two patients were maintained on an additional calcium antagonist (nicorandil). Four patients took an additional calcium antagonist (nifedipine) for a short period only. The average doses of calcium antagonist (diltiazem 218±30 mg/d) and sustained-release isosorbide dinitrate (59±5 mg/d) in group 1 were significantly higher than in group 2 (diltiazem 189±18 mg/d, isosorbide dinitrate 53±10 mg/d) because of persistent symptoms of vasospastic angina in group 1. The medication was effective in both groups. In group 1, the medication reduced the frequency of ischemic attacks; however, vasospastic angina persisted throughout the follow-up period. Waters et al[35] and Previtali et al[36] reported that the response to the ergonovine provocation test is of value in the prediction of spontaneous activity of vasospastic angina. Thus, we performed follow-up angiography and ergonovine provocation testing to detect the progression and regression of coronary atherosclerosis, to estimate vasospastic activity, and to provide information on the necessity for long-term medication. In patients whose symptoms disappeared (group 2), the dose was tapered or discontinued after the follow-up angiogram.

Anginal Symptoms During Follow-up

The disease activity of vasospastic angina was assessed by anginal symptoms, 12-lead ECG during attacks, and ambulatory in-hospital ECG monitoring or out-of-hospital Holter monitoring in all patients. Of the 30 patients studied, 29 had intermittent chest pain with ST-segment elevation and 1 had intermittent chest pain with ST-segment depression at the time of the initial angiographic study (Tables 1 and 2). These attacks were observed over a period of a few days to several weeks (the so-called "hot phases" of the disease[28]). In group 1, over the follow-up period, 10 of the 16 patients had a second hot phase, 4 had a second and third hot phase, and the remaining 2 did not require readmission for management of a hot phase but complained of regular anginal symptoms throughout the follow-up period (Table 1). During the second and third hot phases, all 14 patients required readmission and had ischemic episodes of ST-segment changes recorded on ambulatory ECG monitoring and/or resting 12-lead ECG in hospital. Of the remaining 2 patients who did not experience a second hot phase but had regular variant anginal attacks, 1 showed ST-segment elevation during an exercise test in the morning, and 1 had ST-segment elevation during out-of-hospital Holter monitoring. Patients 3 and 10 developed a non–Q-wave MI (maximal creatinine phosphokinase was more than double but less than triple the upper limit of the normal range), and patient 13 experienced transient complete AV block during an anginal attack during the follow-up period. While all group

TABLE 1. Clinical and Angiographic Characteristics in Group 1

Patient	Age, Sex y	FU, mo	Risk Factors of Coronary Artery Disease	Total Cholesterol, mg/dL		HDL Cholesterol, mg/dL		Hot Phase, d		Cardiac Events During FU	Medication During FU, mg/d
				Initial	FU	Initial	FU	Initial	FU		
1	57 M	24	Smoking, diabetes	137	150	43	51	14	7	None	Dil 180 Iso 60
2	54 M	33	Smoking	170	145	57	44	5	11	None	Dil 180 Iso 60
3	41 M	30	Smoking	227	193	46	34	3	9 and 3*	Non–Q wave MI**	Dil 240 Iso 60 Nico 15
4	48 F	54	. . .	235	198	66	40	12	2	None	Dil 180 Iso 60
5	54 M	40	Smoking	236	242	79	61	7	10	None	Dil 240 Iso 40
6	55 M	69	Smoking	189	242	70	66	8	13	None	Dil 240 Iso 60
7	35 M	61	Smoking	236	231	36	38	15	No hot phase†	None	Dil 240 Iso 60
8	64 M	22	Smoking	135	165	44	83	12	7 and 9‡	None	Dil 240 Iso 60
9	67 M	44	Smoking	202	187	37	46	4	18	None	Dil 180 Iso 60 Nif 40
10	60 M	38	Smoking	181	178	49	39	5	3	Non–Q wave MI**	Dil 240 Iso 60
11	56 M	66	Smoking, HT	162	152	38	40	21	3 and 2 #1	None	Dil 180 Iso 60 Nif 40
12	57 M	53	Smoking	219	279	50	55	7	7	None	Dil 240 Iso 60
13	61 M	50	Smoking, HT	189	189	82	75	14	5 and 8 #2	AV block††	Dil 240 Iso 60
14	63 M	28	Smoking	180	204	39	31	8	17	None	Dil 180 Iso 60
15	49 M	67	Smoking	142	183	37	43	9	No hot phase†	None	Dil 240 Iso 60
16	63 M	36	Smoking	193	203	44	47	5	9	None	Dil 240 Iso 40

FU indicates follow-up; HT, hypertension; Dil, diltiazem; Iso, isosorbide dinitrate; Nif, nifedipine; and Nico, nicorandil (nifedipine and nicorandil were used in addition to diltiazem and isosorbide dinitrate). The hot phase is a period of extremely high disease activity (see text).[28] Coronary segments were defined according to the AHA classification.[50]

§Regression was expressed as a plus value of MLD and progression was expressed as a minus value of MLD.

*Interval of two hot phases was 12 months.

**Maximal creatinine phosphokinase was more than double but less than triple the upper normal range.

†Patient did not have the second hot phase but regular variant anginal attacks.

‡Interval of two hot phases was 6 months. #1 Interval of two hot phases was 7 months. #2 Interval of two hot phases was 35 months.

††Transient complete AV block was observed during a variant anginal attack.

2 patients underwent 12-lead ECG recording at follow-up, ambulatory in-hospital ECG monitoring, and out-of-hospital Holter monitoring, none experienced either chest pain or a cardiac event during follow-up (Table 2).

Study Protocol

The study was approved by the hospital's ethics committee, and written informed consent was obtained from each patient before examination. All 30 patients studied were admitted to the coronary care unit before the study. Sublingual nitroglycerin was administered as required, but calcium antagonists and oral nitrate were gradually tapered, and calcium antagonists were discontinued for 36 hours and oral nitrate was discontinued for 24 hours before the study. Coronary angiography was performed in the morning (from 8:30 to 11 AM) by the Sones' technique at Anjo Kosei Hospital, Anjo, Japan. After baseline angiograms suitable for quantitative analysis of the right and left coronary arteries had been obtained, 0.2 mg IV ergonovine maleate was administered by a rapid bolus injection during the initial and follow-up angiograms. Radiographic projections were identical during the sequential angiographic studies. Heart rate and aortic pressure were monitored continuously, and 12-lead ECGs were recorded at 30-second intervals. Whenever chest pain or significant ST-segment changes were observed, selective coronary angiograms were immediately performed. When coronary spasm was not seen, a further rapid bolus of up to 0.4 mg ergonovine was given.[16,29,30,35,37] Coronary vasospasm was relieved by isosorbide dinitrate[38-42] given as one or two intracoronary boluses to a total of 5 mg. To exclude the possibility of pseudoprogression, we gave a dose (5 mg IC) of isosorbide dinitrate, which was greater

TABLE 1. Continued

Location of ST-Segment Changes (Leads)	MLD (mm) and Percent Diameter Stenosis at Spastic Site After Administration of Isosorbide Dinitrate		
	Initial Angiogram	FU Angiogram	Difference of MLD §
II, III, aVf, V_6	2.81 (31%) segment 13	2.80 (22%) segment 13	−0.01
II, III, aVf	2.50 (22%) segment 2	2.65 (27%) segment 2	0.15
V_2-V_4	2.44 (24%) segment 7	2.00 (28%) segment 7	−0.44
III, aVf, F_6	1.07 (49%) segment 13	1.22 (39%) segment 13	0.15
II, III, aVf	1.83 (3%) segment 1	1.42 (25%) segment 1	−0.41
II, III, aVf	2.73 (18%) segment 1	2.77 (15%) segment 1	0.04
III, aVf	2.28 (8%) segment 11	1.25 (55%) segment 11	−1.03
V_2-V_4	1.98 (38%) segment 7	1.14 (65%) segment 7	−0.84
II, III, aVf	3.23 (22%) segment 2	2.99 (16%) segment 2	−0.24
	1.95 (27%) segment 13	1.70 (31%) segment 13	−0.25
II, III, aVf	1.87 (42%) segment 1	0.82 (62%) segment 1	−1.05
III, aVf	2.68 (21%) segment 1	2.62 (15%) segment 1	−0.06
II, III, aVf	2.23 (28%) segment 2	2.31 (24%) segment 2	0.08
II, III, aVf, V_6	2.17 (42%) segment 1	2.19 (28%) segment 1	0.02
	2.48 (29%) segment 13	2.28 (15%) segment 13	−0.20
V_2-V_4	1.19 (45%) segment 7	1.23 (41%) segment 7	0.04
III, aVf, V_3-V_5	2.62 (19%) segment 2	1.92 (31%) segment 2	−0.70
	1.99 (34%) segment 6	1.93 (27%) segment 6	−0.06
II, III, aVf	1.86 (35%) segment 11	1.76 (38%) segment 11	−0.10

than the dose (3 mg) previously demonstrated to achieve maximal coronary vasodilatation in patients with vasospastic angina.[38,39] The follow-up angiogram was performed in the same angiographic projection as the initial angiogram after the initial angiographic records and cinefilm were viewed. Then, the severity of fixed stenoses was quantified in matched views between the initial and follow-up angiograms by use of the quantitative angiographic analysis system.

QCA Analysis

The new version of CAAS II[43,44] was used to perform the quantitative analysis in a core angiographic laboratory (Cardialysis, Rotterdam, the Netherlands). In the CAAS analysis, which is described elsewhere,[44-47] the entire 18×24-mm cineframe is digitized at a resolution of 1329×1772 pixels. Correction for pincushion distortion is performed before analysis. Boundaries of a selected coronary segment are detected automatically. The absolute diameter of the stenosis (in millimeters) is determined with the guiding catheter as a scaling device. To standardize the method of analysis of the initial and follow-up angiograms, the following measures were taken.[48,49] All study frames selected for analysis were end-diastolic to minimize motion artifact. Arterial segments were measured between the same identifiable branch points at baseline and after the administration of ergonovine and isosorbide dinitrate.

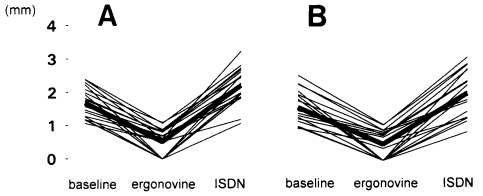

FIG 1. Plots showing changes in MLD in the spastic segments in group 1 at baseline, after administration of ergonovine, and after administration of isosorbide dinitrate (ISDN) on the initial (A) and follow-up (B) angiograms. No significant change in responsiveness to ergonovine is seen between the two tests (spastic response during the initial study, 1.17±0.47 mm; at follow-up, 1.07±0.46 mm, P=NS).

Coronary Segments Analyzed

The coronary segments were coded according to the AHA system.[50] The entire lengths of the major AHA segments of the RCA, LAD, and LCx were analyzed after administration of isosorbide dinitrate (AHA segments 1, 2, 3, 6, 7, 11, and 13). Tables 1 and 2 show the sites of coronary spasm in both groups. The locations of coronary spasm on the initial and follow-up angiograms in group 1 were 9 RCA, 4 LAD, and 6 LCx segments; the locations on the initial angiogram in group 2 were 7 RCA, 8 LAD, and 2 LCx segments.

Criteria of Progression or Regression

Only the absolute luminal diameter obtained after administration of isosorbide dinitrate was used to assess progression or regression of atherosclerosis.[51,52] We measured the MLD and MEAN of AHA coronary segments.[50] A difference greater than twice the SD for repeated measurements of the CAAS system may represent a true change with >95% confidence. Because both Waters et al[53] and our group[54] recently reported that the SD of repeated quantitative measurements with the CAAS system of serial clinical coronary angiograms is 0.20 mm, we therefore accepted a change in MLD of ≥0.40 mm as a reliable indicator of the presence of progression or regression of coronary atherosclerosis.

Statistical Analysis

A paired Student's t test was used to compare chronological changes at the same segment in the same patients. Unpaired Student's t tests were used to compare the two study groups. Differences between proportions were analyzed by the χ^2 test with correction. A value of $P<.05$ was considered significant.

Results

Patient Groups

Of the 30 patients studied, 16 had persistent symptoms of vasospastic angina with ischemic ST-segment changes during the follow-up period, and vasospasm was reproduced at the same coronary site at the follow-up angiogram (group 1), while vasospastic angina disappeared completely during follow-up in the remaining 14 patients in whom vasospasm was provoked by ergonovine at the initial angiogram and was not provoked at the follow-up angiogram (group 2).

Response to Ergonovine at Spastic Segments

Fig 1 gives the changes in MLD in the spastic segments in group 1 at baseline and after the administration of ergonovine and isosorbide dinitrate on the initial and

TABLE 2. Clinical and Angiographic Characteristics in Group 2

Patient	Age, y	Sex	FU, mo	Risk Factors of Coronary Artery Disease	Total Cholesterol, mg/dL		HDL Cholesterol, mg/dL		Hot Phase, d		Cardiac Events During FU	Medication During FU, mg/d
					Initial	FU	Initial	FU	Initial	FU		
17	43	M	25	Smoking	219	225	78	52	16	None	None	Dil 210 Iso 60 Nico 15
18	50	M	37	Smoking	168	189	33	45	5	None	None	Dil 180 Iso 60
19	55	M	38	Smoking	125	157	39	50	13	None	None	Dil 180 Iso 60 Nif 20
20	56	M	35	Smoking	220	237	58	62	6	None	None	Dil 180 Iso 60
21	60	M	88	Smoking	141	144	38	37	12	None	None	Dil 180 Iso 40
22	58	M	31	Smoking, HT	239	246	96	75	21	None	None	Dil 180 Iso 40 Nif 40
23	52	M	54	Smoking, HT	224	228	37	34	9	None	None	Dil 180 Iso 40
24	61	M	45	Smoking, diabetes	228	205	53	52	14	None	None	Dil 180 Iso 60
25	57	M	35	Smoking	182	173	58	43	7	None	None	Dil 180 Iso 60
26	58	F	61	. . .	172	159	41	43	4	None	None	Dil 180 Iso 60
27	68	M	73	. . .	190	194	44	48	7	None	None	Dil 180 Iso 40
28	40	M	28	Smoking	204	172	22	23	3	None	None	Dil 210 Iso 40
29	51	M	30	Smoking	204	256	82	76	12	None	None	Dil 180 Iso 60
30	58	M	49	Smoking, HT	206	187	58	57	10	None	None	Dil 240 Iso 60

Abbreviations and explanations as in Table 1.

follow-up angiograms. At follow-up, no significant change in responsiveness to ergonovine was seen (spastic response, 1.17±0.47 and 1.07±0.46 mm initially and at follow-up, respectively; P=NS). Fig 2 gives the changes in MLD in the spastic segments in group 2 at baseline and after the administration of ergonovine and isosorbide dinitrate on the initial and follow-up angiograms. At follow-up, the vasospastic responsiveness to ergonovine was lost in group 2 (1.00±0.39 and 0.32±0.38 mm initially and at follow-up, respectively; P<.001).

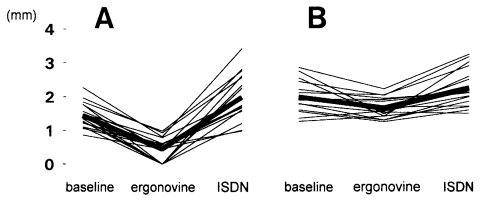

FIG 2. Plots showing changes in MLD in the spastic segments in group 2 at baseline, after administration of ergonovine, and after administration of isosorbide dinitrate (ISDN) on the initial (A) and follow-up (B) angiograms. At follow-up, the vasospastic responsiveness to ergonovine was lost compared with the initial test in group 2 (response during the initial study, 1.00±0.39 mm; at follow-up, 0.32±0.38 mm, P<.001).

Stenosis Progression or Regression: Assessment of Absolute Values

Both the MLD and MEAN of AHA coronary segments after the administration of isosorbide dinitrate were compared (Table 3) between the initial and follow-up angiograms in group 1 (19 spastic segments and 93 nonspastic segments) and group 2 (17 previously spastic and 81 nonspastic segments). At the initial angiogram, no significant differences were observed between groups 1 and 2 in MLD and MEAN values in both spastic and nonspastic segments. In group 1, both the MLD and MEAN of the 19 spastic segments significantly decreased (progression) (P<.01 for both) at the follow-up angiogram, whereas the MLD and MEAN of the 93 nonspastic segments in group 1 were not significantly different between the initial and follow-up angiograms. In group 2, the MLD of the 17 previously spastic segments significantly increased (regression) at follow-up (P<.05), whereas the MEAN of the 17 previously spastic segments and both the MLD and MEAN of 81 nonspastic segments in group 2 were not significantly different between the two angiograms.

TABLE 2. Continued

Location of ST-Segment Changes (Leads)	MLD (mm) and Percent Diameter Stenosis at Spastic Site After Administration of Isosorbide Dinitrate		
	Initial Angiogram	FU Angiogram	Difference of MLD §
V_2-V_4	0.99 (62%) segment 7	1.71 (44%) segment 7	0.72
II, III, aVf	2.26 (22%) segment 2	1.85 (27%) segment 2	−0.41
V_3-V_5	1.70 (17%) segment 7	1.69 (12%) segment 7	−0.01
I, aVL, V_2-V_4	1.21 (59%) segment 6	2.11 (23%) segment 6	0.90
III, aVf	3.42 (17%) segment 2	3.19 (11%) segment 2	−0.23
II, III, aVf, V_5	1.69 (26%) segment 1 2.57 (29%) segment 6	2.12 (18%) segment 1 3.12 (13%) segment 6	0.43 0.55
II, III, aVf	2.34 (23%) segment 3	2.48 (21%) segment 3	0.14
I, aVL, V_2-V_4	1.58 (42%) segment 6	1.60 (37%) segment 6	0.02
V_2-V_5	1.01 (51%) segment 6	2.00 (35%) segment 6	0.99
V_2-V_5	1.91 (20%) segment 7	2.09 (8%) segment 7	0.18
II, III, aVf	1.74 (20%) segment 11	2.16 (11%) segment 11	0.42
III, aVf, V_2-V_4	2.81 (19%) segment 1 1.67 (22%) segment 7	2.98 (12%) segment 1 1.98 (22%) segment 7	0.17 0.31
II, III, aVf, V_6	2.77 (24%) segment 1 1.61 (43%) segment 11	2.86 (31%) segment 1 1.50 (43%) segment 11	0.09 −0.11
II, III, aVf	2.62 (39%) segment 2	2.57 (35%) segment 2	−0.05

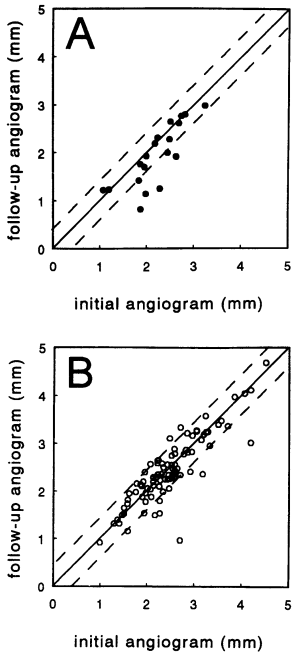

FIG 3. Scatterplots showing a comparison of MLD for group 1 of 19 spastic (A) and 93 nonspastic (B) segments between the initial and follow-up angiograms. Data points below the line of identity indicate that luminal diameters at follow-up were smaller than at the time of the initial angiogram; data points above the line of identity indicate larger luminal diameters at follow-up than during the initial angiogram. Whereas data points below the dotted line (0.40 mm decrease in MLD at follow-up) indicate significant stenosis progression (≥0.40 mm reduction in MLD), data points above the dotted line (0.40 mm increase in MLD at follow-up) indicate significant stenosis regression (≥0.40 mm increase in MLD).

The changes in luminal diameter at spastic and nonspastic segments between the initial and follow-up angiograms are displayed graphically for group 1 in Fig 3 and for group 2 in Fig 4. In both figures, data points below the line of identity (dashed line) indicate that the luminal diameters at follow-up were smaller than at the initial angiogram, while data points above the line of identity indicate that the luminal diameters at follow-up were larger than at the initial angiogram. Whereas data points below the dotted line (0.40-mm decrease in MLD) indicate significant stenosis progression (≥0.40-mm reduction in MLD) in Figs 3 and 4, data points above the dotted line (0.40-mm increase in MLD) indicate significant stenosis regression (≥0.40-mm increase in MLD) in both figures. In group 1 (Table 1), significant stenosis progression (≥0.40-mm reduction in MLD) of individual stenoses was observed in 6 (32%) of the 19 spastic segments and 10 (11%) of the 93 nonspastic segments ($P<.05$), while significant regression (≥0.40-mm increase in MLD) occurred in no spastic segments and 3 (3%) of the 93 nonspastic segments (P=NS). In group 2 (Table 2), progression was observed in only 1 previously spastic and 4 nonspastic segments (P=NS), and regression of individual stenoses was observed in 6 (35%) of the 17 previously spastic segments and 7 (9%) of the 81 nonspastic segments ($P<.01$). The remaining segments without significant progression or regression (13 spastic segments and 80 nonspastic segments in group 1 and 10 spastic segments and 70 nonspastic segments in group 2) were

TABLE 3. Comparison of MLD and MEAN Between the Initial and Follow-up Angiograms in Groups 1 and 2

	Initial Angiogram, mm	Follow-up Angiogram, mm	*P*
Group 1			
Spastic segment			
MLD	2.21±0.54	1.95±0.65	<.01
MEAN	2.80±0.56	2.56±0.58	<.01
Nonspastic segment			
MLD	2.47±0.67	2.44±0.69	NS
MEAN	2.96±0.69	2.91±0.68	NS
Group 2			
Spastic segment			
MLD	1.99±0.68	2.24±0.54	<.05
MEAN	2.71±0.66	2.74±0.52	NS
Nonspastic segment			
MLD	2.36±0.59	2.39±0.60	NS
MEAN	2.81±0.58	2.81±0.61	NS

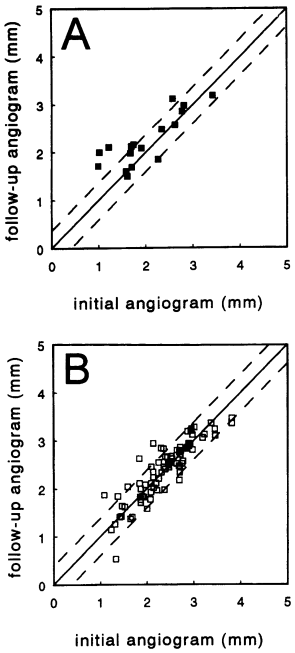

FIG 4. Scatterplots showing a comparison of MLD for group 2 of the 17 spastic (A) and 81 nonspastic (B) segments after administration of isosorbide dinitrate between the initial and follow-up angiograms. Data points below the line of identity indicate that luminal diameters at follow-up were smaller than during the initial angiogram; data points above the line of identity indicate larger luminal diameters at follow-up than during the initial angiogram. Whereas data points below the dotted line (0.40 mm decrease in MLD at follow-up) indicate significant stenosis progression (≥0.40 mm reduction in MLD), data points above the dotted line (0.40 mm increase in MLD at follow-up) indicate significant stenosis regression (≥0.40 mm increase in MLD).

regarded as stabilized. Fig 5 gives an example of angiographic evidence of regression of a patient in group 2.

Assessment of Relative Values: Percent Diameter Stenosis

Tables 1 and 2 give the fixed percent diameter stenosis of individual spastic segments at the initial and follow-up angiograms after administration of isosorbide dinitrate. In patients with significant fixed stenosis (>50% luminal narrowing), the location of coronary spasm coincided with the site of significant fixed stenosis (Tables 1 and 2). In group 1, at the initial angiogram none of the spastic segments had significant fixed stenosis, whereas at follow-up 3 spastic segments had significant fixed stenosis. In group 2, at the initial angiogram 3 spastic segments had significant fixed stenosis, whereas at follow-up no segment had significant fixed stenosis. Table 4 shows the average percent diameter stenosis of the spastic and nonspastic segments in both groups. Although percent diameter stenosis of spastic segments tended to be more severe at follow-up in group 1 (P=NS), percent diameter stenosis of spastic segments was less severe at follow-up in group 2 ($P<.01$). No difference was observed in nonspastic segments in either group.

Caution should be applied, however, in the use of percent diameter stenosis in the study of progression and regression of coronary artery disease in view of the risk of "pseudoregression" as described below in the "Discussion."[51,52]

Discussion

The novel findings of this study were as follows. First, angiographic follow-up of the average MLD of the patients with persistent vasospastic angina (group 1) revealed significant progression of coronary artery stenoses in the segments, demonstrating persistent vasospasticity, whereas angiographic follow-up of the patients in whom symptoms of vasospastic angina resolved (group 2) showed significant regression of coronary artery disease in the previously spastic segments. Second, MLD and MEAN of nonspastic segments did not change at follow-up in both groups. Third, significant individual stenosis progression was observed more frequently in spastic than nonspastic segments in group 1. Fourth, significant individual stenosis regression was seen more commonly in previously spastic than nonspastic segments in group 2. These results indicate an association between long-term focal vasospastic activity and local progression and regression of fixed coronary stenoses.

Previous Experimental Studies

In 1981, Gertz et al[55] studied the endothelial response to partial arterial constriction (by external ligation to achieve 40% to 60% reduction in transluminal diameter) in a canine coronary model and a rabbit carotid model. Scanning electron microscopy revealed endothelial damage as evidenced by endothelial craters, fragmentation, desquamation, and platelet attachment to exposed subendothelial tissues and microthrombi. Endothelial injury and platelet activation may be an initiating process of the development of atherosclerosis, which was again proposed by Ross[56,57] in a revision of the "response-to-injury hypothesis" in 1986. These findings may suggest a potential pathophysiological role for coronary spasm in the development of coronary atherosclerosis.

Recent studies by Nagasawa et al[25] and Kuga et al[26] in swine models provide further experimental evidence suggesting that vasoconstriction may be causally related to coronary atherosclerosis. They observed that strong coronary spasm caused histological intramural hemorrhage and intimal thickening, which frequently resulted in rapid progression of coronary atherosclerosis. Conversely, in a study of vasospastic responsiveness to serotonin in hypercholesterolemic primates over time, Heistrad and colleagues[58] observed that regression of atherosclerotic plaques was associated with a reduction in vasospastic responsiveness.

Although the results of the above[25,26] and other[58-63] experimental studies have almost consistently provided indirect evidence to suggest a causal link between repeated coronary spasm and atherogenesis in a variety of animal models, the results of most clinical studies to date have been conflicting and have not provided hard evidence of an association between vasospastic activity and progression or regression of atherosclerosis in humans.

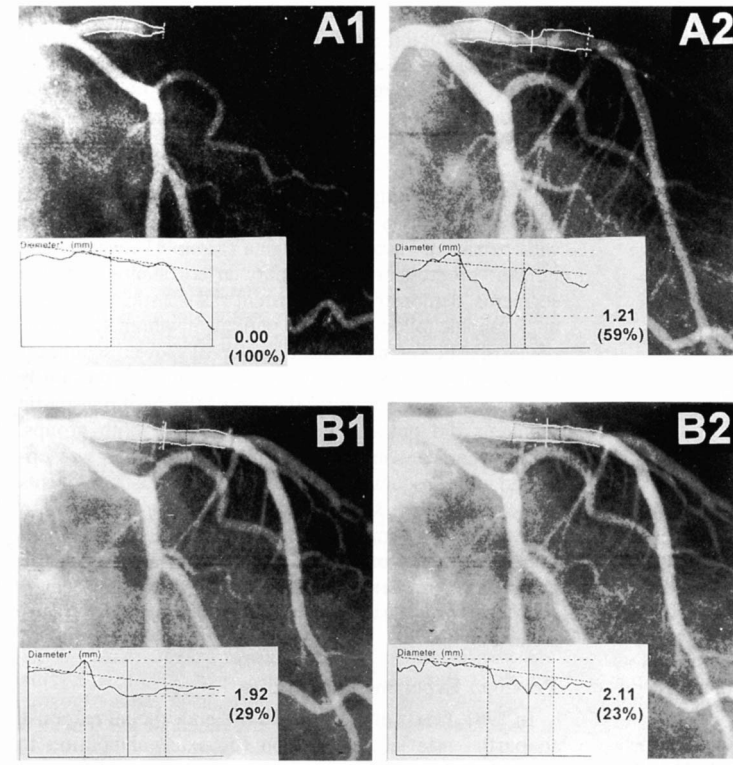

FIG 5. Coronary angiograms of the left coronary artery in patient 20 in group 2. During the initial angiogram, transient total occlusion (100% coronary spasm) was observed after administration of 0.2 mg IV ergonovine (A1) at the proximal segment of the LAD, and significant fixed stenosis was observed after administration of 5 mg IC isosorbide dinitrate (A2). At follow-up at the same site of the LAD, coronary spasm was not observed after administration of 0.4 mg ergonovine (B1), and the MLD had increased (regression) from 1.21 mm (59% stenosis) at the initial angiogram to 2.11 mm (23% stenosis) after the administration of 2.5 mg isosorbide dinitrate (B2) at follow-up.

Previous Clinical Studies

Kaski et al[28] recently reported a lack of stenosis progression in vasospastic segments in 10 patients with vasospastic angina despite chronic disease activity over years. Several differences in methodology may explain the discordance between the results of the study of Kaski et al and our results. First, the average follow-up period of their study was 25 months, while in our study it was 45 months. A longer observation period in their study might have revealed more frequent occurrence of progression.[3,8] Second, their study included 10 patients with vasospastic angina, whereas ours is the largest study ever undertaken on the relation between coronary vasospasticity and progression of atherosclerosis and is the largest study in the field of vasospastic angina to perform quantitative angiographic analysis. Third, their criterion of stenosis progression was different from ours. They determined progression by the difference in percent diameter stenosis between the baseline and follow-up angiograms. We insisted on using absolute changes in MLD (≥0.40 mm) as criteria of progression or regression. The advantages of using an absolute rather than a relative measure of stenosis progression include the following. If diffuse segmental progression has occurred and the reference diameter itself decreases at follow-up, then comparison of percent diameter stenosis may fail to detect true progression or regression at the site of the stenosis.[51] In our study, both the MEAN and MLD of AHA coronary segments of group 1 were significantly smaller at follow-up; thus, percent diameter stenosis at follow-up failed to detect a significant progression (increase in percent diameter stenosis) because of the concomitant diffuse progression in the reference vessel diameter. Moreover, Stone et al[52] recently suggested that changes in percent diameter stenosis can be misleading in progression or regression trials because the MLD and adjacent reference segments may progress independently at different rates at follow-up (pseudoregression[51]).

TABLE 4. Comparison of Percent Fixed Stenosis of Spastic and Nonspastic Segments Between Initial and Follow-up Angiograms in Groups 1 and 2

	Initial Angiogram, %	Follow-up Angiogram, %	*P*
Group 1			
Spastic segment	28±12	32±15	NS
Nonspastic segment	19±9	20±11	NS
Group 2			
Spastic segment	31±15	24±12	<.01
Nonspastic segment	20±11	19±11	NS

In conflict with the above findings, indirect evidence in support of an association between vasospasticity and development of atherosclerosis from other clinical studies has been reported. Nobuyoshi et al[64] recently found that a positive response to an ergonovine provocation test was a predictor of subsequent MI and progression of coronary atherosclerosis at angiographic follow-up, although they did not perform repeated ergonovine tests and thus did not examine the relation between focal spastic site and site of progression or perform QCA analysis. Marzilli et al[27] reported that a patient with coronary spasm developed a rapid progression of coronary atherosclerosis at the site of coronary spasm and

suggested that coronary spasm might be an antecedent to atherosclerosis. Little et al[65] observed in a recipient of an orthotopic heart transplant that coronary spasm preceded the development of coronary atherosclerosis. Further indirect evidence of the interaction of coronary spasm and coronary artery disease has been derived from several studies reporting that patients who demonstrate coronary vasospastic activity before or after balloon angioplasty are predisposed to the subsequent development of restenosis.[31,66-68]

Study Limitations

Whereas patients in whom anginal symptoms resolved (group 2) underwent 12-lead ECG at follow-up, ambulatory in-hospital ECG monitoring, and out-of-hospital Holter monitoring, no patient experienced either chest pain or a cardiac event during follow-up. Although it was practically impossible to perform Holter monitoring every day for several years, these patients had symptoms of variant angina, ischemic ECG changes, and a positive ergonovine test at the initial angiogram; then these symptoms and ECG changes disappeared during follow-up. Thus, it is clinically assumed that vasospastic activity ceased during follow-up.

Bertrand et al[15] and Bott-Silverman and Heupler[69] reported that coronary spasm involves the RCA more commonly than the LAD or LCx. A similar tendency was shown in our total patient population (16 spastic segments were RCA, 8 were LCx, and 12 were LAD). In group 1 (the progression group), 4 spastic segments were in the LAD of a total of 19 spastic segments; in group 2 (the regression group), 8 spastic segments were in the LAD of a total of 17 spastic segments (not statistically significant). It remains undetermined from the data obtained whether the distribution of the coronary artery location directly relates to the propensity to progression or regression.

We examined changes of absolute luminal diameter over time at the vasospastic site after the administration of intracoronary isosorbide dinitrate using QCA. While recent progress in intracoronary ultrasound techniques may provide us with additional tomographic information on mural morphology, we feel that a number of limitations remain to be resolved in applying intracoronary ultrasound to long-term progression and regression studies. First, in our study the average follow-up period was 4 years, and intracoronary ultrasound itself was not available when our study began. Second, the reported correlation of luminal measurements between intracoronary ultrasound and QCA has ranged from 0.12 to 0.92,[70-72] and a satisfactory agreement between ultrasound measurement and angiographic measurements has not yet been established. Third, although it is easy with QCA to compare the same coronary sites at the initial and follow-up angiograms to estimate progression and regression,[51,73,74] it can be rather difficult during ultrasound examination to ensure that the exact same position of the coronary artery is quantified at follow-up. Finally, many previous and ongoing progression and regression studies have been and still are performed using QCA only, and we think that angiographic information is still the gold standard in this field.[2,4,5,7,9] Thus, we feel that widespread adoption of intracoronary ultrasound as an integral or essential component of progression and regression studies with an interval of several years may have to wait until the current rapid development phase of intracoronary ultrasound technology reaches a plateau (as occurred with QCA) and ECG-gaited three-dimensional reconstructed images become more widely available.[75]

Conclusions

We have demonstrated in patients an association between persistent vasospastic activity and progression of atherosclerosis and between cessation of vasospastic activity and regression of atherosclerosis. These results indicate that persistent vasospastic angina is not a benign disease and that patients with persistent symptoms of vasospastic angina require long-term follow-up. Further studies will be required to determine the mechanism of the association between vasospasticity and atherosclerosis in humans and to determine effective medical therapy for the prevention of progression of atherosclerosis in these patients.

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Chapter 6

Fluctuation of spastic location in patients with vasospastic angina: a quantitative angiographic (QCA) study

Ozaki Y, Keane D, Serruys PW

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Fluctuation of Spastic Location in Patients With Vasospastic Angina: A Quantitative Angiographic Study

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Objectives. **This study sought to determine whether the location of coronary spastic activity may change over time in patients with persistent variant angina.**

Background. **Although electrocardiographic studies have provided indirect evidence to indicate that the location of ischemia may change in patients with variant angina, it has not been tested by quantitative angiography whether the location of vasospastic activity may change over time.**

Methods. **Paired ergonovine provocation tests and coronary angiography were performed at a mean (±SD) interval of 43 ± 13 months apart in patients with persistent symptoms of vasospastic angina in the absence of significant atherosclerosis. A total of 87 spastic and nonspastic segments of 87 major vessels in 29 patients were analyzed by quantitative angiography at baseline, after the administration of ergonovine and after isosorbide dinitrate at the initial and follow-up tests.**

Results. **In 13 patients (group 1), coronary spasm was observed in the same 16 coronary segments at both the initial and follow-up ergonovine provocation tests. In 16 patients (group 2), the following angiographic changes occurred between the initial and follow-up tests in 48 major vessels: Of the 23 segments that developed spasm at the initial test, 10 did not have spasm at the follow-up test; of the 25 vessels that did not demonstrate spasm on the initial test, 12 demonstrated spasm on the follow-up test (a new site of spasm). Thus, in 22 (46%) of 48 vessels, fluctuation of spastic location was observed at follow-up.**

Conclusions. **Quantitative coronary angiography and repeated ergonovine tests revealed that some patients with persistent vasospastic angina demonstrate fluctuation of vasospastic location, whereas others exhibit a fixed location of vasospasm. Vasospastic angina may not only be a transient disease restricted in location, but may also be a persistent and variable condition involving multiple vessels over many years.**

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Coronary spasm plays a role in a wide spectrum of ischemic coronary events, including variant angina and some cases of unstable angina and acute myocardial infarction (1–13). Although vasospastic anginal symptoms have undergone spontaneous remission in some patients with variant angina (14–17), persistent symptoms have been observed over many years in other patients without significant atherosclerosis (17–20). Although Kaski et al. (21) observed that coronary spasm may remain active over years in the same coronary segments despite medical therapy, other investigators (14,22,23) demonstrated variability of electrocardiographic (ECG) changes during repeated ergonovine tests and recurrent spontaneous attacks. However, whether the location and degree of vasospasm may change over a period of several years has not yet been established quantitatively.

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Although many clinical studies (4,6,8,9,15,21) have shown that coronary spasm frequently occurs at sites of advanced atherosclerosis, Conti et al. (7) suggested that the presence of significant atherosclerosis may reduce the role of vasospasm in ischemic attacks. To determine the long-term role of vasospastic activity and its variation in location, we repeated ergonovine provocation tests in patients without advanced atherosclerosis but with persistent symptoms of variant angina at an average interval of 43 months apart, using a computer-based quantitative coronary angiographic analysis system (CAAS II).

Methods

Criteria of vasospastic angina. The following criteria of *vasospastic angina* were used: 1) chest pain at rest associated with ST segment changes >0.2 mV on the ECG; 2) pain relief immediately after administration of nitroglycerin; 3) no subsequent evidence of myocardial infarction; 4) ergonovine-provoked coronary spasm associated with chest pain and ischemic ECG changes. *Coronary spasm* was defined as 1) a transient total or nearly total occlusion reversible with isosorbide dinitrate, or 2) a transient, significant (>50%) narrowing reversible with isosorbide dinitrate in normal or nearly normal segments (24–26). We used the ergonovine provocation test because it has been found (27–29) to have a high sensitivity and

Table 1. Clinical and Angiographic Characteristics of 29 Patients With Vasospastic Angina

Pt No.	Age (yr)/ Gender	ST Segment Changes During Spasm		Percent Fixed Stenosis at Spastic Site After ISDN	
		Initial ECG	Follow-Up ECG	Initial Angiogram	Follow-Up Angiogram
Group 1					
1	56/M	III, aVF	III, aVF	21% seg 1	15% seg 1
2	63/M	V_2–V_4	V_2–V_4	45% seg 7	41% seg 7
3	63/M	II, III, aVF	II, III, aVF	35% seg 11	38% seg 11
4	67/M	II, III, aVF	II, III, aVF	22% seg 2, 27% seg 13	16% seg 2, 31% seg 13
5	49/M	III, aVF, V_3–V_5	III, aVF, V_3–V_5	19% seg 2, 34% seg 6	31% seg 2, 27% seg 6
6	57/M	II, III, aVF	II, III, aVF	28% seg 2	24% seg 2
7	61/M	II, III, aVF, V_6	II, III, aVF, V_6	42% seg 1, 29% seg 13	28% seg 1, 15% seg 13
8	54/M	II, III, aVF	II, III, aVF	22% seg 2	27% seg 2
9	55/M	II, III, aVF	II, III, aVF	18% seg 1	15% seg 1
10	41/M	V_2–V_4	V_2–V_4	24% seg 7	28% seg 7
11	57/M	II, III, aVF, V_6	II, III, aVF, V_6	31% seg 13	22% seg 13
12	48/F	III, aVF, V_6	III, aVF, V_6	49% seg 13	39% seg 13
13	54/M	II, III, aVF	II, III, aVF	3% seg 1	25% seg 1
Group 2					
14	62/M	V_2–V_4	II, III, aVF	42% seg 7, 18% seg 13	13% seg 13
15	57/F	II, III, aVF	II, III, V_2–V_5	17% seg 3	13% seg 2, 29% seg 7, 25% seg 13
16	54/M	II, III, aVF, V_3–V_4	II, III, aVF	29% seg 1, 19% seg 7, 23% seg 11	39% seg 1
17	42/M	V_2–V_5	II, III, aVF	25% seg 7	16% seg 3
18	52/M	III, aVF, V_2–V_5	II, III, aVF	7% seg 4, 14% seg 7	20% seg 4, 21% seg 11
19	56/M	V_3–V_5	II, III, V_3–V_4	17% seg 7	14% seg 1, 47% seg 7
20	68/M	III, aVF	III, aVF, V_2–V_4	30% seg 11	20% seg 6, 36% seg 11
21	58/F	II, III, aVF	II, III, aVF, V_2–V_5	20% seg 4	25% seg 4, 25% seg 7
22	62/M	II, III, aVF	II, III, aVF, V_6	9% seg 2, 29% seg 13	42% seg 13
23	66/M	III, aVF, V_4–V_5	II, III, aVF	13% seg 3, 17% seg 13	36% seg 13
24	44/M	V_2–V_4	II, III, aVF	2% seg 2, 29% seg 6	19% seg 2
25	50/M	V_1–V_4	II, III, aVF	7% seg 6	24% seg 2
26	61/M	II, III, aVF	II, III, aVF, V_2–V_4	16% seg 2	19% seg 1, 29% seg 7
27	37/M	II, III, aVF	II, III, aVF, V_6	17% seg 1	31% seg 1, 6% seg 13
28	46/M	V_2–V_5, I, aVI	II, III, aVF	48% seg 6	45% seg 2
29	43/M	AVI, V_5–V_6	II, III, aVF, V_6	18% seg 11	6% seg 3, 26% seg 11

ECG = electrocardiogram; F = female; ISDN = isosorbide dinitrate; M = male; Pt = patient; seg = coronary segment as defined by the American Heart Association classification (43).

specificity for, and short-term reproducibility of, spontaneous anginal attacks in patients with vasospastic angina. Follow-up angiography and provocation testing were performed to estimate the progression of atherosclerosis as well as to determine the location of vasospastic activity and to provide information on the necessity to continue long-term medication.

Study patients. Because the purpose of the present study was to examine the role of pure vasospasm in ischemic attacks during long-term follow-up, we excluded patients with significant atherosclerosis (>50% diameter stenosis after administration of isosorbide dinitrate). The study group was selected from a total of 50 patients with variant angina who had undergone long-term angiographic and ergonovine provocation follow-up. Of the 50 patients who had chest pain at rest with ischemic ST segment changes at the time of the initial angiographic study, vasospastic anginal symptoms were persistent during the follow-up period in 34. In the remaining 16 patients, symptoms of vasospastic angina resolved during follow-up, and these 16 patients were excluded from the study. Of the former 34 patients, 5 who developed significant, fixed stenosis (>50% diameter stenosis after administration of isosorbide dinitrate) during follow-up were excluded from the study. Of the remaining 29 patients, 13 had persistent symptoms of vasospastic angina with ischemic ST segment changes during the follow-up period, and vasospasm was reproduced at the same coronary segment at the follow-up angiogram (group 1); 16 patients had persistent symptoms of vasospastic angina with ischemic ST segment changes during the follow-up period, and vasospasm occurred in different vessels at follow-up (group 2).

Ischemic episode during follow-up. Vasospastic anginal activity was assessed by anginal symptoms, 12-lead ECG monitoring during anginal attacks and ambulatory in-hospital ECG monitoring or Holter monitoring out of hospital in all patients. All 29 patients had intermittent chest pain with ST segment changes at the time of the initial angiographic study (Table 1). These attacks were frequently observed over a period of a few days to several weeks (so-called hot phases of the disease [21]). The medication, combined with a calcium antagonist (diltiazem) and sustained-release isosorbide dinitrate (Table 2), was effective and reduced the frequency of ischemic attacks in both groups; however, vasospastic angina

Table 2. Clinical Characteristics of Groups 1 and 2

	Group 1 (n = 13)	Group 2 (n = 16)	p Value
Age (yr)	56 ± 7	54 ± 9	0.50
M/F	12/1	14/2	0.85
Coronary risk factors			
Hypertension	2	3	0.80
Diabetes	1	1	0.56
Smoking	12	14	0.85
Hypercholesterolemia	1	1	0.55
Serum cholesterol (mg/day)			
Initial test	191 ± 33	188 ± 28	0.82
Follow-up test	197 ± 39	194 ± 29	0.81
Interval of tests (mo)			
20–29	2	2	0.85
30–39	3	5	0.94
40–49	2	6	0.36
50–59	3	2	0.80
60–69	3	1	0.44
Mean	46 ± 15	41 ± 11	0.39
Calcium antagonist (diltiazem) (mg/day)	212 ± 31	203 ± 35	0.44
Sustained-release ISDN (mg/day)	57 ± 8	58 ± 7	0.83

Data presented are mean value ± SD or number of patients, unless otherwise indicated. Abbreviations as in Table 1.

persisted throughout the follow-up period. Over the follow-up period, 22 of the 29 patients had a second or a third hot phase. During the repeated hot phases, all 22 patients required readmission and showed frequent ischemic episodes of ST segment changes recorded on ambulatory ECG monitoring or rest 12-lead ECG monitoring in hospital. Of the remaining seven patients who did not experience a repeated hot phase but had regular vasospastic anginal attacks, three showed ST segment elevation during an exercise test early in the morning, and four had ST segment elevation on Holter monitoring out of hospital during follow-up.

Angiographic procedure. The present study was approved by the hospital ethics committee, and written informed consent was obtained from each patient. All patients were admitted to the coronary care unit before the study. Sublingual nitroglycerin was administered as required, but calcium antagonists and oral nitrates were gradually tapered, and calcium antagonists were discontinued for 36 h and oral nitrates for 24 h before the study. Coronary angiography was performed in the morning (from 8:30 AM to 11 AM) by the Sones technique at Anjo Kosei Hospital in Japan. After baseline angiograms suitable for quantitative analysis of the right and left coronary arteries had been obtained, 0.2 mg of ergonovine maleate was administered intravenously by a rapid bolus injection. Radiographic projections were identical during the sequential angiographic studies. Heart rate and aortic pressure were monitored continuously, and 12-lead ECGs were recorded at 30-s intervals. Whenever chest pain or significant ST segment changes were observed, selective coronary angiograms were immediately obtained. Coronary vasospasm was relieved by isosorbide dinitrate, given as one or two intracoronary boluses to a total of 5 mg. To exclude the possibility of persistent spasm, we gave a dose (5 mg) of intracoronary isosorbide dinitrate that was greater than the dose previously demonstrated (30,31) to achieve maximal coronary vasodilation in patients with vasospastic angina (3 mg). The follow-up angiogram was obtained in the same angiographic projection as the initial angiogram after viewing the initial angiographic records and cine film. Then, the response to ergonovine and the severity of fixed stenoses were quantified in the matched views of the initial and follow-up angiograms using the quantitative angiographic analysis system. No complications occurred during the repeated ergonovine provocation tests and the angiographic procedures.

Quantitative coronary angiographic analysis. The new version of the computer-based coronary angiography analysis system (CAAS II) (32,33) was used to perform the quantitative analysis in a core angiographic laboratory (Cardialysis, Rotterdam, The Netherlands). The CAAS analysis has been described in detail elsewhere (33–39). Briefly, the entire cine frame of 18 × 24 mm is digitized at a resolution of 1,329 × 1,772 pixels. Correction for pin-cushion distortion is performed before analysis. Boundaries of a selected coronary segment are detected automatically. The absolute diameter of the stenosis in millimeters is determined using the guiding catheter as a scaling device (40). To standardize the method of analysis of the initial and follow-up angiograms, all study frames selected for analysis were end-diastolic to minimize motion artifact, and arterial segments were measured between the same identifiable branch points at baseline, after administration of ergonovine and after administration of isosorbide dinitrate (41,42).

In the CAAS II system (32–42), minimal lumen diameter was determined by computer-based edge-detection contour using minimal cost criteria. The CAAS II system determines the size at the target coronary segment using a computer-derived interpolated reference diameter rather than an operator-selected reference point. The interpolated reference diameter is derived from the edge-detection diameter function of the nonstenotic/nonspastic proximal and distal subsegments. The reference vessel diameter values are estimated by fitting a straight line to the diameter function proximal and distal to the obstruction followed by a shift such that 80% of the diameter values are below the adjusted straight line. This line then represents the reconstructed reference diameter function and gives an estimate of the arterial size at each point along the analyzed coronary segment. The interpolated reference vessel diameter is taken as the value of the reconstructed diameter function at the position of the minimal lumen diameter. The advantages of this approach are that it is essentially user independent, and thus highly reproducible, and that every measurement is based on multiple measurements (every scan line) proximal and distal to the lesion.

Segments analyzed. The coronary segments were coded according to the recommendations of the American Heart Association (AHA) (43). One AHA segment from each of the three major epicardial vessels was analyzed. For vessels that demonstrated vasospasticity, the segment in which vasospasm occurred was analyzed. For vessels in which no vasospasm

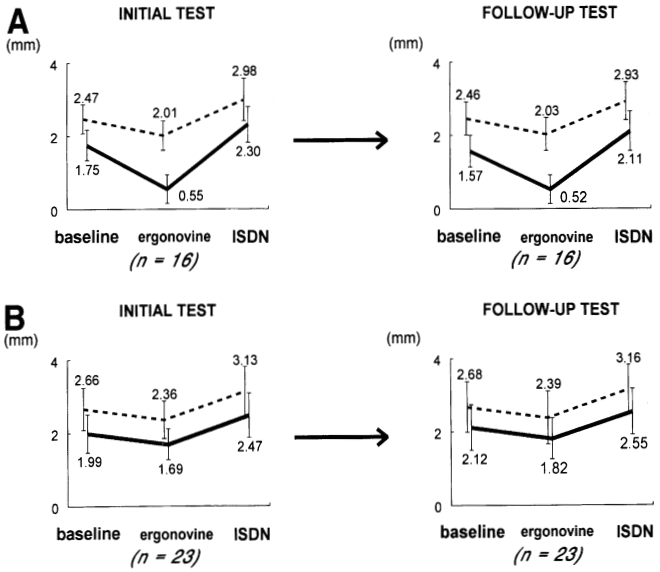

Figure 1. Reference (**dotted line**) and minimal lumen diameter (**solid line**) changes at baseline and after administration of ergonovine and isosorbide dinitrate (ISDN) at both initial and follow-up angiography in group 1. **A,** After administration of ergonovine, minimal lumen diameter constricted significantly in 16 spastic segments of 16 vessels at both the initial and follow-up tests. **B,** Reference and minimal lumen diameter responses to ergonovine were equivalent in 23 nonspastic segments of 23 vessels at both the initial and follow-up tests.

occurred, the AHA segment analyzed was that which had the most diseased appearance. Quantitative angiographic analysis provided the minimal lumen and reference vessel diameters for all AHA segments analyzed.

Statistical analysis. The unpaired Student *t* test was used to compare the two groups of patients. Differences between proportions were analyzed by the chi-square test with correction; $p < 0.05$ was considered significant.

Results

Clinical characteristics. All patients demonstrated persistent symptoms of vasospastic angina with ischemic ST segment changes during follow-up that were detected by in-hospital 12-lead or ambulatory ECG monitoring, or both, or Holter monitoring out of hospital. Medication was a combination of a calcium antagonist (diltiazem) and sustained-release isosorbide dinitrate. Although the medication reduced the frequency of ischemic attacks, symptoms of variant angina persisted throughout the follow-up period.

The ECG and angiographic results for all 29 patients are presented in Table 1. The location of myocardial ischemia indicated by ECG changes and the spastic coronary segment shown by angiography were similar at the initial and follow-up tests in 13 patients (group 1, Patients 1 to 13) but were different at follow-up in 16 (group 2, Patients 14 to 29). With regard to clinical characteristics, no significant differences were found between groups 1 and 2 for age (56 ± 7 vs. 54 ± 9 years); gender (1 of 13 vs. 2 of 16 female patients); coronary risk factors, such as hypertension, diabetes, smoking and hypercholesterolemia; and average serum cholesterol level (Table 2). The mean interval to angiographic follow-up (46 ± 15 vs. 41 ± 11 months) was similar in the two groups, and there was no significant difference in medication.

Location of coronary spasm. In group 1, no fluctuation in location of vasospasticity was observed at follow-up. In group 2, fluctuation of spastic location was observed at follow-up in 22 (46%) of 48 vessels.

Group 1. The average minimal lumen and reference diameters of 16 spastic segments in 13 patients at baseline, after administration of ergonovine and after administration of isosorbide dinitrate at the initial and follow-up tests are shown in Figure 1A. Coronary spasm was observed in 16 segments of 16 vessels in group 1: Minimal lumen diameter decreased after administration of ergonovine from 1.75 ± 0.43 to 0.55 ± 0.40 mm during initial angiographic study and decreased from 1.57 ± 0.44 to 0.52 ± 0.39 mm at follow-up. The minimal lumen and reference diameters of the remaining 23 nonspastic segments of 23 nonspastic vessels in group 1 are shown in Figure 1B. The response to ergonovine (minimal lumen diameter reduction) between the two tests was similar in these 23 nonspastic segments.

Group 2. Coronary spasm was observed in 23 segments at initial angiography (Fig. 2A). At follow-up, 13 of the 23 segments showed persistent vasospastic activity, but the remaining 10 segments showed no vasospasm. The minimal lumen and reference diameter changes for the remaining 25 segments of 25 vessels in group 2 are shown in Figure 2B. No spasm was observed at the initial test in these 25 segments, but at follow-up, 12 of the 25 exhibited vasospasm after ergonovine, and 13 had no vasospasm. An example of angiographic evidence of fluctuation in vasospastic location between initial and follow-up angiography in a patient in group 2 is shown in Figure 3.

Discussion

Quantitative coronary angiography and repeated ergonovine provocation tests demonstrated that in some patients with

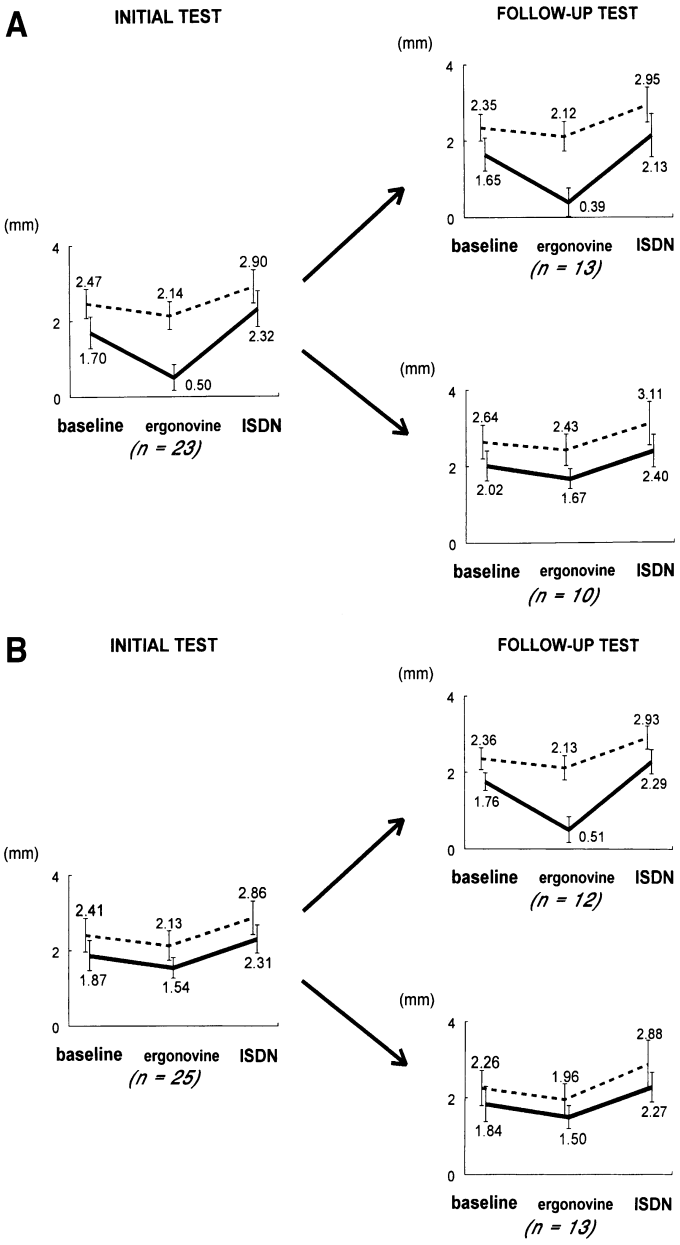

Figure 2. Reference (**dotted line**) and minimal lumen diameter (**solid line**) changes at baseline and after administration of ergonovine and isosorbide dinitrate (ISDN) at initial and follow-up angiography in group 2. **A,** In 13 of the 23 initially spastic segments, minimal lumen diameter reduced from 1.65 ± 0.44 to 0.39 ± 0.44 mm and vasospasm was again demonstrated at follow-up, whereas in the remaining 10 segments, vasospasm was not observed at follow-up. **B,** In 12 of the 25 initially nonspastic segments, minimal lumen diameter decreased from 1.76 ± 0.23 to 0.51 ± 0.34 mm and vasospasm was demonstrated at follow-up, whereas in the remaining 13 segments, vasospasm was not observed at follow-up.

persistent variant angina, spasm may fluctuate from one vessel to another over a period of several years, whereas in others the location of coronary spasm is fixed over time.

Previous studies. Although several studies have reported the spontaneous remission of vasospastic angina (14–17), persistence of symptoms of variant angina has been reported in other studies with long-term follow-up of up to 10 years (17–20). Although Kaski et al. (21) recently reported the consistency of angiographic location of vasospasm in 10 patients with variant angina despite medical therapy, conflicting and indirect evidence from previous ECG studies (14,22,23) suggests that the location and degree of coronary spasm may not be fixed. In a nonquantitative coronary angiographic study (18), we previously showed that percent diameter stenosis as assessed visually may fluctuate over time, although the relation of such relative measures to atherosclerosis was not explored. Waters et al. (14) reported that the location of myocardial ischemia indicated by ST segment changes at follow-up was similar to that at the initial ergonovine test. However, the direction of ST segment shifts (elevation or depression) changed in 3 of 10 patients who had repeated vasospastic attacks at follow-up. Previtali et al. (23) reported that difference of location of myocardial ischemia as determined by ST segment changes was observed in a single patient, yet the dose

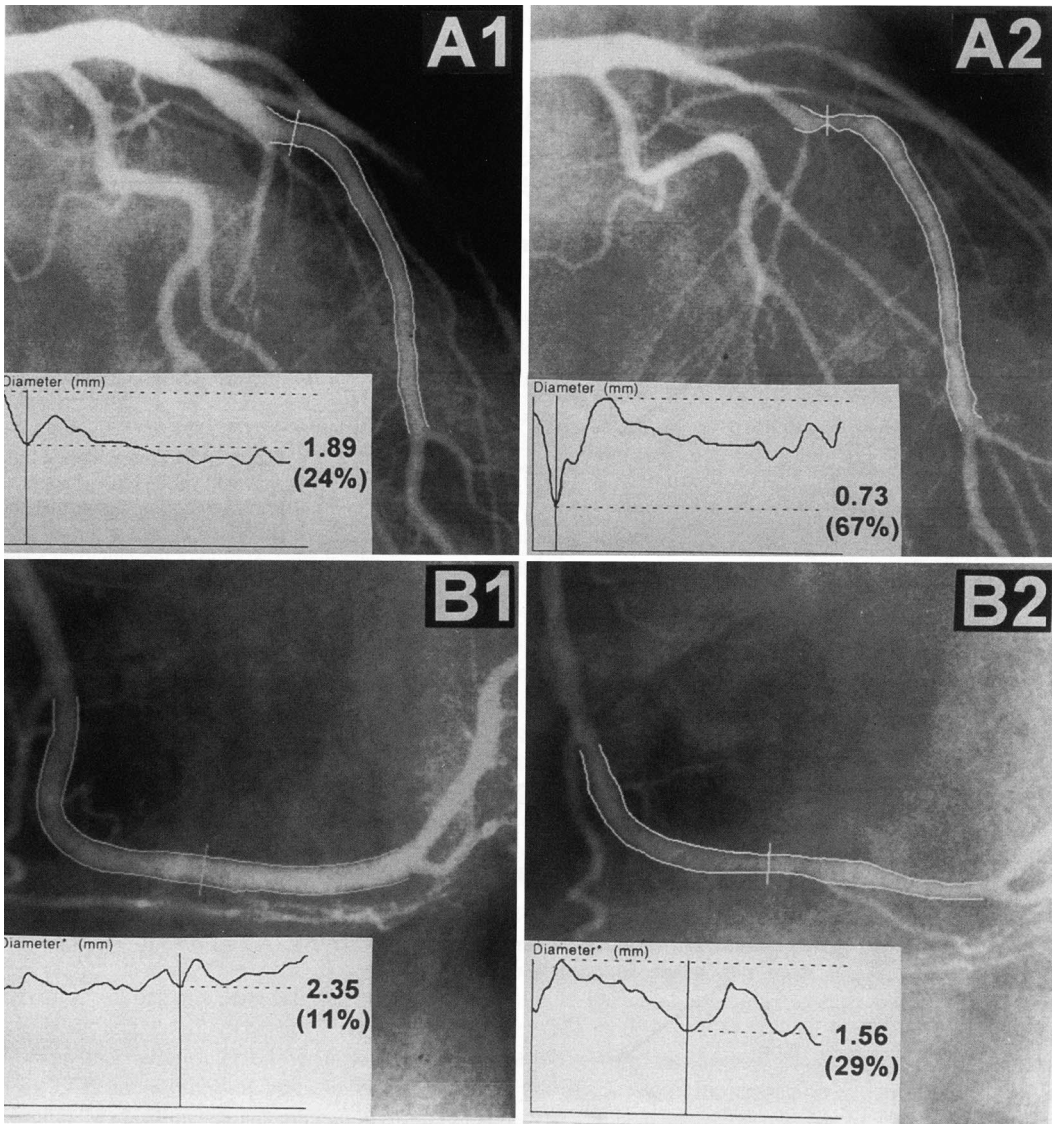

Figure 3. Initial and follow-up coronary angiograms and quantitative angiographic analysis from Patient 17, group 2. Angiograms **A1, A2, C1** and **C2** of the left anterior descending coronary artery were obtained in the right anterior oblique projection; angiograms **B1, B2, D1** and **D2** of the right coronary artery were obtained in the left anterior oblique projection. Initial angiograms were obtained at baseline (**A1** and **B1**) and after administration of 0.2 mg of intravenous ergonovine (**A2** and **B2**). After administration of ergonovine, minimal luminal diameter decreased from 1.89 to 0.73 mm, and a transient 67% lumen narrowing (coronary spasm) was observed in American Heart Association (AHA) segment 7 of the left anterior descending coronary artery **(A2),** and minimal lumen diameter decreased from 2.35 to 1.56 mm, with no coronary spasm observed, in AHA segment 3 of the right coronary artery **(B2)**. Follow-up angiograms **C1** and **D1** were obtained before (control) and angiograms **C2** and **D2** after 0.2 mg of intravenous ergonovine. After administration of ergonovine, minimal luminal diameter decreased from 2.09 to 1.54 mm, and no vasospasm was observed in AHA segment 7 of the left anterior descending coronary artery **(C2),** the site of previously observed spasm. However, in AHA segment 3 of the right coronary artery **(D2),** minimal lumen diameter decreased from 2.11 to 0.61 mm, and a new, transient 75% lumen narrowing (vasospasm) was observed. *(Figure 3 continued on page 1612.)*

of ergonovine required to induce vasospasm was different at follow-up in the majority of patients. Whittle et al. (22) reported that variable and unpredictable ECG responses to repeated ergonovine tests were observed in 6 of 10 patients, whereas the remaining 4 exhibited reproducible ECG responses to ergonovine. Our quantitative coronary angiographic study clearly demonstrated that the location of coronary spasm was variable in some patients with persistent symptoms of angina. The variability of ECG changes seen during recurrent vasospastic angina attacks may be due to these phenomena.

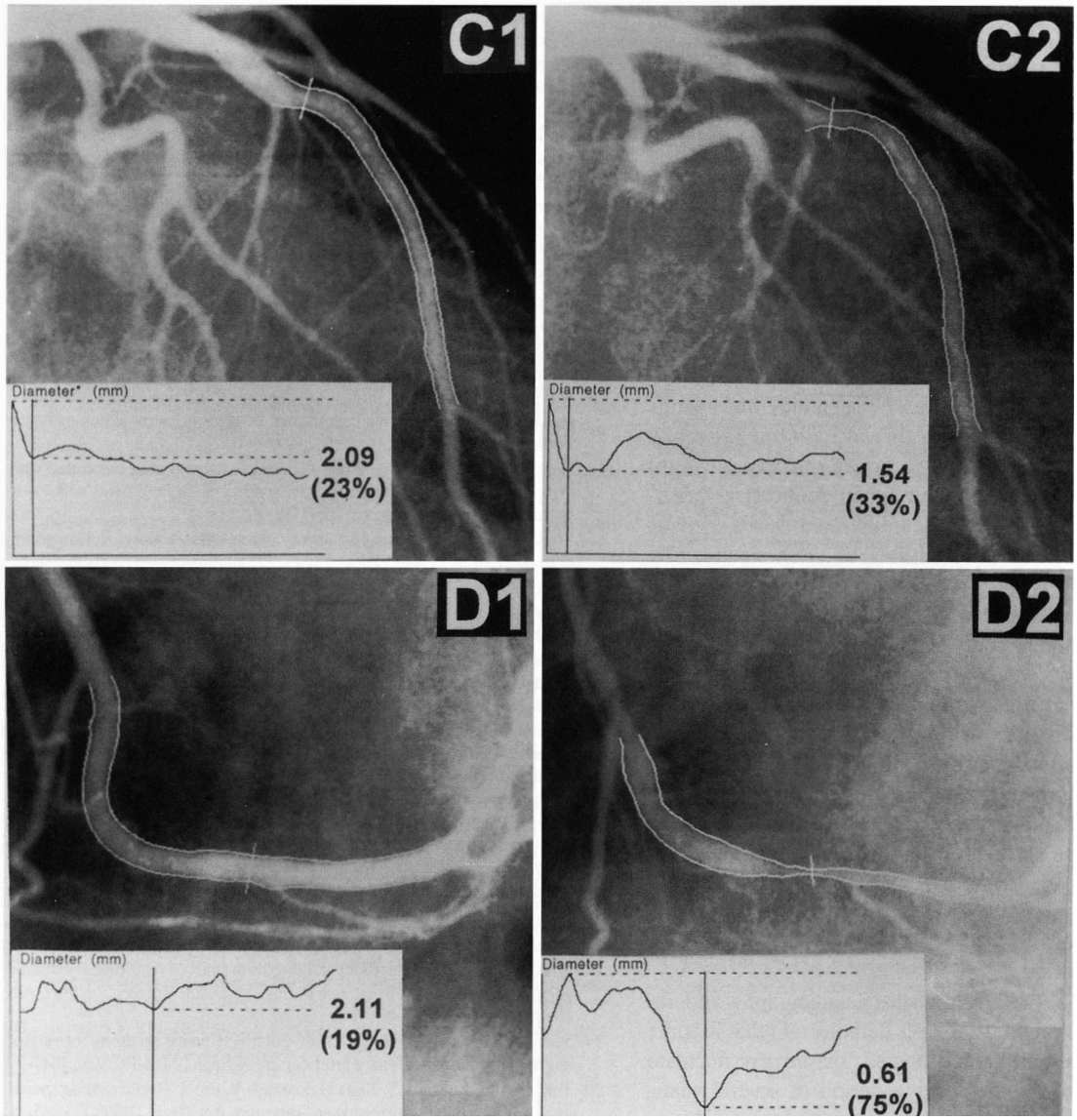

Figure 3. *Continued*

Proposed mechanism of spatial fluctuation of coronary spasm. The mechanism of fluctuation of vasospasm is still unknown. It has been proposed that the parasympathetic nervous system may play a role in the pathogenesis of variant angina (44), and variation in autonomic tone may therefore contribute to fluctuations in vasospastic behavior. Recent experimental studies (45–50) demonstrate that several endothelium-derived factors mediate vascular smooth muscle tone and that damaged endothelium may play a major role in the pathogenesis of vasospasm. Endothelial damage may occur even in the early stages of atherosclerosis (48–50). Zeiher et al. (51) indicated that abnormal vasoconstriction was observed in early atherosclerotic sites in patients without variant angina, using intracoronary ultrasound. Yamagishi et al. (52) reported that early stages of atherosclerosis were observed by intracoronary ultrasound at the site of spasm in patients with variant angina.

In our study, although the minimal lumen diameter of fixed stenosis tended to be smaller at follow-up than at the initial angiogram in 9 of 12 new spastic segments, in 8 of 10 previous spastic segments the minimal lumen diameter of fixed stenosis tended to be larger at follow-up. Both Waters et al. (53) and our group (54) recently reported that the standard deviation of repeated quantitative measurements with the CAAS system of serial clinical coronary angiograms is ±0.20 mm, and a difference greater than twice the standard deviation for repeated measurements of the CAAS system may represent a true change with >95% confidence. If we adopt a per-lesion categoric approach to the definition of progression or regres-

sion of atherosclerosis, we would include only lesions with a change >0.40 mm at follow-up. If such a categoric approach were applied, then a significant progression occurred in group 2 with 95% confidence in 2 of 12 new spastic segments, and significant regression was not seen in any new spastic segments (0 of 12). Significant progression of fixed atherosclerosis was not observed in any previously spastic segments in which spastic activity was no longer provoked (0 of 10), and significant regression was seen in 2 of 10 previous spastic segments. If a continuous statistical approach is adopted in which the mean change in minimal lumen diameter is analyzed for the study group, we find that in Group 2 the minimal lumen diameter after administration of isosorbide dinitrate at new spastic segments was significantly smaller at follow-up than that at initial angiography (2.44 ± 0.32 mm initially vs. 2.29 ± 0.30 mm at follow-up, $p < 0.05$). However, the minimal lumen diameter in previous spastic segments, which demonstrated vasospasm at initial angiography but not at follow-up, was significantly larger at follow-up than at initial angiography (2.24 ± 0.51 mm initially vs. 2.40 ± 0.42 mm at follow-up, $p < 0.05$). Thus, if a continuous statistical approach is adopted for each study cohort, we observe that the development of spasm at a new site is associated with a reduction, and the disappearance of spasm with an improvement, in minimal lumen diameter after isosorbide dinitrate.

The present data lend support to the concept that fluctuation of spastic locations might relate to the pathologic process of local progression and regression of early atherosclerosis in coronary arteries. Clearly, a large prospective (and probably multicenter) trial with long-term angiographic follow-up and repeated ergonovine testing would be required to definitively establish this point.

Conclusions. Quantitative coronary angiography and repeated ergonovine provocation tests demonstrate that in some patients with persistent variant angina, spasm may fluctuate from one vessel to another over a period of several years, whereas in others the location of coronary spasm is fixed over time. Vasospastic angina may not only be a transient disease restricted in location, but may also be a persistent and variable condition involving multiple vessels over many years.

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Chapter 7

Relationship of basal coronary tone and vasospastic activity in patients with variant angina

Ozaki Y, Keane D, Serruys PW

Heart 1996;75:267-273

Relation of basal coronary tone and vasospastic activity in patients with variant angina

Yukio Ozaki, David Keane, Patrick W Serruys

Abstract

***Objective*—To examine the vasoconstrictor response to ergonovine and the vasodilator response to isosorbide dinitrate in spastic and non-spastic coronary segments from 31 patients undergoing serial angiographic follow up of variant angina.**

***Methods*—Coronary angiograms and ergonovine provocation tests were repeated at an interval of 45 (SD 15) months apart. While all 31 patients showed a positive response to ergonovine initially, vasospastic responsiveness persisted in only 16 patients at follow up (group 1) and not in the other 15 patients in whom symptoms of variant angina had resolved (group 2). Mean luminal diameter of 170 normal or near normal entire coronary segments (American Heart Association classification) were measured (a) at baseline, (b) after the administration of ergonovine, and (c) after the administration of isosorbide dinitrate, during both the initial and follow up angiograms using a computer based quantitative angiography analysis system (CAAS II).**

***Results*—In vasospastic patients (initial and follow up angiograms in group 1, and initial angiogram in group 2), basal tone was significantly higher in spastic segments compared to adjacent segments or segments in non-spastic vessels. The diagnostic sensitivity and specificity at 20% increase in basal coronary tone for the prediction of vasospasm were 77% and 73%, respectively.**

***Conclusions*—Coronary artery tone may change in proportion to the activity of variant angina over several years. Contrary to some previous reports, the estimation of basal coronary tone may be useful in the assessment of vasospastic activity in patients with variant angina.**

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Coronary vasospasticity plays an integral role in the genesis of variant angina, some types of acute myocardial infarction, and restenosis after balloon angioplasty.[1–9] The proposed mechanism of vasospasm includes hypersensitivity to endothelium derived factors, platelet derived vasoactive substances, and autonomic nervous tone.[10–13] Basal coronary tone is felt to be related to the regulation of vascular smooth muscle tension by local endothelium derived factors, humoral factors, and parasympathetic nervous tone.[14–16] Thus similar factors may play a role in both vasospasm and the mediation of basal coronary tone. Despite the common mediators, previous clinical studies attempting to determine whether basal coronary tone is increased in patients with vasospastic angina have yielded conflicting evidence[17–22] and the chronological interaction of basal coronary tone and vasospastic activity over several years is unknown.

To examine the role of coronary tone, its chronological changes, and its relation to vasospastic anginal attacks, we compared basal coronary tone and vasospastic activity during both initial and follow up angiographic studies in 31 patients. We measured changes in mean luminal diameter of each entire spastic segment, segments adjacent to the spastic segment, and segments in non-spastic vessels at baseline, after administration of ergonovine and after administration of isosorbide dinitrate, using computer based quantitative coronary angiography.

Methods

PATIENT SELECTION

Thirty one patients who met the following criteria of variant angina were included in the study: (1) chest pain at rest associated with ST segment changes of more than 0·2 mV on ECG; (2) pain relief immediately following the administration of glyceryl trinitrate; (3) no subsequent evidence of myocardial infarction; and (4) ergonovine provoked coronary spasm associated with chest pain and ischaemic ECG changes. Coronary spasm was defined as a transient total or nearly total occlusion reversible with isosorbide dinitrate, or as a transient but significant (> 50%) narrowing reversible with isosorbide dinitrate in normal or nearly normal segments.[8 23 24]

The disease activity of vasospastic angina was assessed by anginal symptoms, 12-lead ECG during symptoms, and ambulatory in-hospital electrocardiographic monitoring, or Holter monitoring out of hospital. Of the 31 patients who had symptoms of variant angina at the time of the initial angiographic study, 16

had persistent symptoms of vasospastic angina with ischaemic electrocardiographic changes during the follow up period, and vasospasm was reproduced at the same coronary site at the follow up angiogram (group 1), while in 15 patients symptoms of variant angina had resolved completely and neither ischaemic ST segment changes nor positive response to ergonovine was demonstrated during follow up (group 2).

Table 1 shows the clinical and electrocardiographic characteristics of the two groups. There were no significant differences in age, gender, duration of follow up, coronary risk factors, or location of ischaemic ST segment changes on ECG. One patient of each group with ST elevation in both anterior and inferior leads had spasm in the right coronary and left anterior descending coronary arteries.

It has been reported that the response to an ergonovine provocation test is of value in the prediction of spontaneous activity of vasospastic angina.[25 26] We therefore performed follow up angiography and ergonovine provocation testing when progression of coronary atherosclerosis was suspected, frequency of anginal attacks increased, or vasospastic activity was thought to have resolved, and it may no longer have been necessary to continue long term drug treatment. In patients who had a negative response to ergonovine at the follow up test (group 2) the treatment dose was tapered or discontinued after the follow up angiogram. At angiographic follow up, coronary spasm was observed at the same coronary arterial site in group 1, while no spasm was reproduced at follow up in group 2.

STUDY PROTOCOL

The study was approved by the hospital's ethics committee and informed written consent was obtained from each patient before examination. All patients were admitted to the coronary care unit before the study. Sublingual glyceryl trinitrate was given as required, but calcium antagonists and oral nitrates were gradually tapered, and calcium antagonists were discontinued for 36 h and oral nitrate was discontinued for 24 h before the study. Coronary angiography was performed in the morning (from 8:30 to 11:00 am) by the Sones technique at Anjo Kosei Hospital in Japan.

After baseline angiograms suitable for quantitative analysis of the right and left coronary arteries had been obtained, 0·2 mg ergonovine maleate was given intravenously by a rapid bolus injection. Radiographic projections were identical during the sequential angiographic studies. Heart rate and aortic pressure were monitored continuously, and 12-lead ECGs were recorded at 30 s intervals. Whenever chest pain or significant ST segment changes were observed, selective coronary angiograms were immediately performed. In patients of group 2 at follow up, unresponsiveness to ergonovine was confirmed by the administration of a further rapid bolus of up to 0·4 mg ergonovine. In group 1 at both tests and group 2 at the initial test, all coronary spasms were observed after the first administrated dose of ergonovine (0·2 mg).

Coronary vasospasm was relieved by isosorbide dinitrate, given as one or two intracoronary boluses to a total of 5 mg. To exclude the possibility of persistent spasm, we gave a dose (5 mg) of intracoronary isosorbide dinitrate which was greater than the dose previously shown to achieve maximum coronary vasodilatation in patients with vasospastic angina (3 mg).[27 28]

The follow up angiography and provocation tests were performed in the same angiographic projection as the initial angiogram after viewing the initial angiographic records and cinefilm. The response to ergonovine and isosorbide dinitrate and the severity of fixed stenosis after the administration of isosorbide dinitrate were quantified in matched views between the initial and follow up angiograms using a quantitative angiographic analysis system.

QUANTITATIVE CORONARY ANGIOGRAPHIC ANALYSIS

The new version of the computer based Coronary Angiography Analysis System (CAAS II)[29] was used to perform the quantitative analysis in a core angiographic laboratory (Cardialysis, Rotterdam, The Netherlands). In the CAAS analysis, which has been described elsewhere previously,[29–33] the entire cineframe of size 18 × 24 mm is digitised at a resolution of 1329 × 1772 pixels. Correction for pincushion distortion is performed before analysis. Boundaries of a selected coronary segment are detected automatically. The absolute diameter of the stenosis (in mm) is determined using the guiding catheter as a scaling device. To standardise the method of analysis of the initial and follow up angiograms, the following measures were taken[34]: all study frames selected for analysis were end diastolic to minimise motion artefact; and arterial segments were measured between the same identifiable branch points at baseline, after the administration of ergonovine, and after the administration of isosorbide dinitrate. Changes in the mean luminal diameter of each entire coronary segment as well as the minimum luminal diameter of each analysed coronary segment were studied.

ANALYSED SEGMENTS

In group 1, the 16 spastic segments studied were located in the right coronary artery

Table 1 Baseline characteristics of 31 patients with vasospastic angina in groups 1 and 2

	Group 1	*Group 2*	*p value*
Number of patients	16	15	
Age, years (SD)	55 (8)	55 (12)	NS
Male/female	15/1	14/1	NS
Follow up period, months (SD)	45 (15)	45 (18)	NS
Coronary risk factors (No of patients)			
Hypertension	2	3	NS
Hypercholesterolaemia	1	1	NS
Diabetes	1	1	NS
Smoking	15	13	NS
Site of ST elevation			
Anterior	3	6	NS
Inferior	12	8	NS
Both	1	1	NS

(RCA) in eight patients, left anterior descending coronary artery (LAD) in two patients, and left circumflex coronary artery (LCX) in six patients. In group 2, the 16 spastic segments were located in the RCA in eight patients, the LAD in six patients, and the LCX in two patients. The three major coronary arteries were divided according to the classification of the American Heart Association (AHA) committee report.[35] The proximal and distal segments of each coronary artery were analysed. The proximal segment of the RCA was taken as AHA segments 1 and 2, the distal segment of the RCA was AHA segment 3, the proximal segment of the LAD was AHA segment 6, the distal segment was AHA segment 7, the proximal segment of the LCX was AHA segment 11, and the distal segment was AHA segment 13.

For the purpose of this study only angiographically normal or nearly normal segments were selected. Of a total of 93 major coronary arteries in both groups, four vessels in each group with a significant stenosis (> 50% diameter stenosis) were excluded from analysis.[21] Sixteen spastic AHA segments, 16 AHA segments adjacent to spastic segments (adjacent segment), and 56 segments in non-spastic vessels were estimated in group 1; 16 spastic AHA segments, 16 segments adjacent to spastic segments, and 50 segments in non-spastic vessels were assessed in group 2.

ESTIMATION OF BASAL CORONARY TONE AND VASOCONSTRICTION

Basal coronary tone and vasoconstriction were determined from the change in the mean luminal diameter of each entire AHA coronary segment at baseline, after the administration of ergonovine, and after the administration of isosorbide dinitrate. To express the degree of basal coronary artery tone and the degree of vasoconstriction,[17 19 21] the per cent dilatation after administration of isosorbide dinitrate and per cent vasoconstriction after administration of ergonovine were used as follows:

Basal coronary tone (dilatation after isosorbide dinitrate) (%) =

$$\frac{(\text{Mean luminal diameter after isosorbide dinitrate} - \text{baseline mean luminal diameter}) \times 100}{\text{Baseline mean luminal diameter}}$$

Constriction after ergonovine (%) =

$$\frac{(\text{Baseline mean luminal diameter} - \text{mean luminal diameter after ergonovine}) \times 100}{\text{Baseline mean luminal diameter}}$$

DIAGNOSTIC PREDICTIVE VALUES OF BASAL TONE FOR VASOSPASM IN CORONARY ARTERY

The diagnostic sensitivity and specificity were defined as follows[22]:

$$\text{Diagnostic sensitivity (\%)} = \frac{\text{True positive} \times 100}{\text{True positive} + \text{false negative}}$$

$$\text{Diagnostic specificity (\%)} = \frac{\text{True negative} \times 100}{\text{True negative} + \text{false positive}}$$

While the true positive value indicates the number of spastic segments in spastic vessel which show basal coronary tone above a value of coronary tone, the false negative value indicates the number of spastic segments in spastic vessel which show basal coronary tone below the same value. While the true negative value indicates the number of non-spastic segments in non-spastic vessel which show basal coronary tone below a value of coronary tone, the false positive value indicates the number of non-spastic segments in non-spastic vessel which show basal coronary tone above the same value.

STATISTICAL ANALYSIS

All values are expressed as mean (SEM). The paired Student t test was used to compare the chronological changes at the same segment in the same patients. The unpaired Student t test was used to compare different segments or different patient groups. Differences between proportions were analysed by the χ^2 test with correction. A P value of less than 0·05 was considered significant.

Results

RESPONSE TO ERGONOVINE AT THE SPASTIC SITE

Coronary spasm was observed at the same site in group 1, while no spasm was reproduced at follow up in group 2. In group 1, the absolute reduction in the minimum luminal diameter in the spastic segment was 1·21 (SEM 0·09) mm with a reduction in minimum diameter of 70 (5)% during the initial angiogram and 1·05 (0·09) mm [68 (5)% reduction] at follow up; in group 2, the reduction in minimum luminal diameter was 1·04 (0·09) mm [69 (5)% reduction] during the initial angiogram and 0·32 (0·07) mm [15 (3)% reduction] at follow up.

Table 2 Mean diameter of coronary artery segment and response to ergonovine during initial and follow up angiograms in groups 1 and 2. Values are means (SEM)

	Initial angiogram			*Follow up angiogram*		
	Baseline (mm)	*After ergonovine (mm)*	*Reduction (%)*	*Baseline (mm)*	*After ergonovine (mm)*	*Reduction (%)*
Group 1						
Spastic segment	2·14 (0·10)	1·56 (0·08)	27 (3)	2·00 (0·12)	1·48 (0·10)	26 (2)
Adjacent to spastic segment	2·28 (0·09)	1·90 (0·09)	17 (2)	2·21 (0·10)	1·93 (0·11)	17 (2)
Segment of non-spastic vessel	2·61 (0·07)	2·20 (0·07)	15 (1)	2·58 (0·08)	2·22 (0·08)	14 (1)
Group 2						
Spastic segment	2·07 (0·12)	1·46 (0·09)	29 (3)	2·45 (0·11)	2·09 (0·08)	13 (3)
Adjacent to spastic segment	2·22 (0·10)	1·84 (0·10)	16 (1)	2·49 (0·12)	2·11 (0·10)	14 (3)
Segment of non-spastic vessel	2·52 (0·07)	2·18 (0·07)	14 (1)	2·54 (0·06)	2·22 (0·06)	13 (1)

Adjacent to spastic segment, segments either proximal or distal to the spastic segment.

Table 3 Mean diameter of coronary artery segment and response to isosorbide dinitrate during initial and follow up angiograms in groups 1 and 2. Values are means (SEM)

	Initial angiogram			*Follow up angiogram*		
	Baseline (mm)	*After isosorbide dinitrate (mm)*	*Dilatation (%)*	*Baseline (mm)*	*After isosorbide dinitrate (mm)*	*Dilatation (%)*
Group 1						
Spastic segment	2·14 (0·10)	2·84 (0·14)	33 (4)	2·00 (0·12)	2·65 (0·13)	35 (4)
Adjacent to spastic segment	2·28 (0·09)	2·78 (0·10)	23 (2)	2·21 (0·10)	2·74 (0·12)	24 (2)
Segment of non-spastic vessel	2·61 (0·07)	3·02 (0·07)	16 (1)	2·58 (0·08)	2·98 (0·08)	16 (1)
Group 2						
Spastic segment	2·07 (0·12)	2·80 (0·18)	35 (4)	2·45 (0·11)	2·81 (0·15)	15 (3)
Adjacent to spastic segment	2·22 (0·10)	2·73 (0·16)	23 (4)	2·49 (0·12)	2·83 (0·16)	14 (3)
Segment of non-spastic vessel	2·52 (0·07)	2·87 (0·08)	15 (1)	2·54 (0·06)	2·90 (0·07)	15 (1)

Adjacent to spastic segment, segments either proximal or distal to the spastic segment.

VASOMOTOR BEHAVIOUR OF THE SEGMENTS AT THE INITIAL AND FOLLOW UP TESTS

Table 2 shows the average values of mean luminal diameter of each spastic segment, of the adjacent segments, and of segments of non-spastic vessels at baseline and after administration of ergonovine, and the per cent vasoconstriction, in groups 1 and 2. Table 3 gives the average value of the mean luminal diameter at baseline and after administration of isosorbide dinitrate, and the per cent dilatation (basal coronary tone) in groups 1 and 2.

Group 1

Figure 1 shows the vasoconstriction and basal coronary tone in group 1. Vasoconstriction of the spastic segment was greater than that of the adjacent segment or of segments in non-spastic vessels during the initial and follow up tests. Basal coronary tone in the spastic segments was also greater than in the adjacent segments or in segments of non-spastic vessels during the initial and follow up tests. No significant difference between the initial and follow up tests was found in either vasoconstriction or basal tone in any of the spastic or adjacent segments or the segments in non-

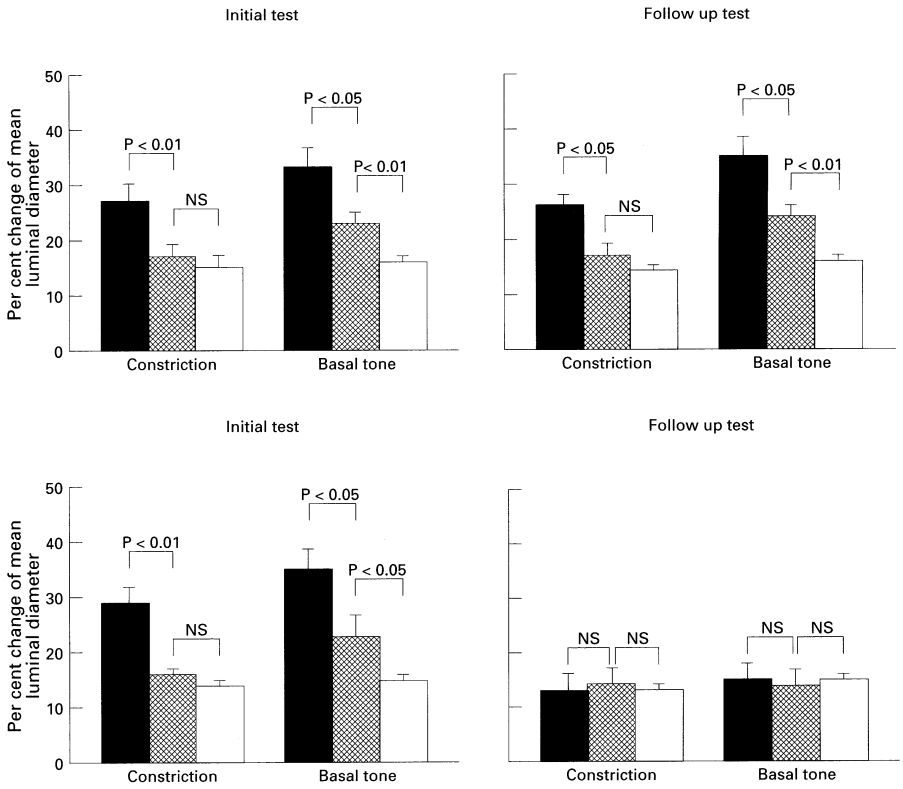

Figure 1 Group 1: Vasomotor responses to ergonovine (constriction) and isosorbide dinitrate (basal tone) in spastic segments (black bar), adjacent segments (hatched bar), and segments in non-spastic vessels (white bar) of patients in group 1 at the initial and follow up angiograms. Vasoconstriction and basal coronary tone in the three segments were similar between the initial and follow up tests. Error bar indicates 1 SEM.

Figure 2 Group 2: Vasomotor responses to ergonovine (constriction) and isosorbide dinitrate (basal tone) in spastic segments (black bar), adjacent segments (hatched bar), and segments in non-spastic vessels (white bar) of patients in group 2 at the initial and follow up angiograms. Vasoconstriction and basal coronary tone in the spastic segments decreased significantly from the initial to the follow up tests. Basal tone of the adjacent segments also decreased from the initial to the follow up test, while vasoconstriction of the adjacent segments was unchanged (NS). Segments in non-spastic vessels showed similar vasoconstriction and basal coronary tone at both tests (NS). Error bar indicates 1 SEM.

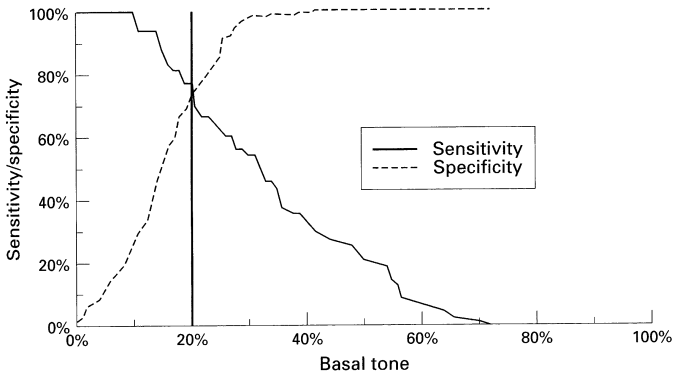

Figure 3 Distribution curves of sensitivity and specificity of increased basal coronary tone for the prediction of vasospasm in a coronary artery. At a 20% increase in basal coronary tone (thick vertical line), which is the nearest rounded number to the crossing point of the two distribution curves, the sensitivity was 77% and the specificity 73%.

spastic vessels. Although vasoconstriction in the adjacent segments was not significantly different from the vasoconstriction in segments of non-spastic vessels, basal tone in the adjacent segment was greater than that of segments in non-spastic vessels during both the initial and follow up tests.

Group 2

Figure 2 shows the vasoconstriction and basal coronary tone in group 2. During the initial test, vasoconstriction of the spastic segments was greater than in the adjacent segments or in segments in non-spastic vessels. During the initial test, vasoconstriction was comparable in adjacent segment and non-spastic segments, while basal coronary tone in the spastic segment was greater than in the adjacent segments and in the segments of non-spastic vessels. Furthermore, during the initial test, basal tone in the adjacent segments was greater than in the segments of non-spastic vessels. At follow up, no difference was observed in either vasoconstriction or basal tone among previously spastic and adjacent segments and segments in non-spastic vessels. Both vasoconstriction and basal coronary tone of the spastic segments decreased significantly from the initial to the follow up angiograms. Basal tone of the adjacent segments also decreased significantly from the initial to the follow up angiograms. Vasoconstriction of the adjacent segment was similar during the initial and follow up angiograms. We found no difference in vasoconstriction and basal tone of segments in non-spastic vessels between the initial and follow up angiograms

PREDICTIVE VALUE OF BASAL TONE FOR THE PRESENCE OF VASOSPASM

Figure 3 shows distribution curves of the sensitivity and specificity of basal coronary tone for the prediction of vasospasm in coronary artery. The sensitivity and specificity were calculated from all 48 spastic segments in spastic vessels and all 162 non-spastic segments in non-spastic vessels in the initial and follow up angiograms of group 1 and the initial angiogram of group 2. At 20% increase in basal tone, which is the nearest rounded number to the crossing point of two distribution curves, the sensitivity was 77% and specificity 73%.

Discussion

The specific findings of this study are as follows: (1) neither basal coronary tone nor vasoconstriction changed over time in patients with persistent variant angina, while in patients in whom symptoms of variant angina resolved, both vasoconstriction and basal coronary tone of previously spastic segments were restored to normal; (2) vasoconstriction in adjacent segments and segments in non-spastic vessels was equivalent both in patients with active disease and in patients with inactive disease; (3) in patients with active disease, basal tone in spastic segments was greater than in adjacent segments or segments in non-spastic vessels; (4) adjacent segments only showed increased basal coronary tone compared to segments in non-spastic vessels during the period of disease activity.

DISCORDANT FINDINGS OF PREVIOUS STUDIES

Previous studies have provided conflicting evidence on whether basal coronary tone is increased in spastic segments.[17-22] Hill *et al* reported that basal coronary tone in the spastic site, estimated after the administration of 0·4 mg of sublingual glyceryl trinitrate, was greater than in non-spastic sites in 17 patients with variant angina.[17] Hoshino *et al* reported that coronary artery tone assessed after the administration of 5 mg intraaortic isosorbide dinitrate was greater in the entire coronary tree in 30 patients with variant angina than in 35 patients without coronary spasm.[19] Hackett *et al*, however, found that basal coronary tone, analysed after the administration of 2 mg intracoronary isosorbide dinitrate, was not different at spastic sites than at non-spastic sites in six patients with variant angina.[18] Kaski *et al* also found that basal coronary tone of segments in non-spastic vessels, estimated after the administration of 1 to 2 mg intracoronary isosorbide dinitrate, was not different between 13 patients with variant angina and 41 patients without coronary spasm.[21] Kuga *et al* found that basal coronary tone was increased in 15 patients with variant angina but not in five others after the administration of 0·26 mg intravenous glyceryl trinitrate.[22]

The conflicting results of previous studies may relate to differences in patient selection and the methods employed, including (1) use of nitrates, (2) selection of angiographic segments, and (3) disease activity:

Use of nitrates

Although in all previous studies basal coronary tone was determined by the magnitude of vasodilator response to organic nitrates, there are differences in the dose and route of administration of nitrates (intracoronary or sublingual) in previous studies. In 1982, Lablanche *et al* found that maximum vasodilatation was achieved in patients with variant angina by 3 mg of intracoronary isosorbide dinitrate.[27,28]

However, we have found that further vasodilatation may be achieved in some patients by doubling the dose of isosorbide dinitrate from 2·5 mg to 5·0 mg. With the aim of achieving maximal vasodilatation in all our study population we estimated coronary artery diameter after the intracoronary administration of 5 mg isosorbide dinitrate. While Feldman *et al*[36] reported that 0·4 mg of sublingual glyceryl trinitrate evoked maximum coronary vasodilatation, Jost *et al*[37] recently found that 0·8 mg was necessary to achieve maximum vasodilatation. Varying dosages and routes of administration of isosorbide dinitrate or glyceryl trinitrate as detailed above may have contributed to the different degree of vasomotor reposes observed in previous studies.

Selection of angiographic segments

The degree of vasodilatation following the administration of nitrates will not necessarily be identical at all points within a coronary segment (as evidenced by the difference in our results between changes at the spastic point and changes in the entire AHA segment with spasm). In some studies the vasomotor responses were measured at specific points of bifurcation,[19] while we feel that change in the mean luminal diameter of each entire AHA coronary segment is of greater relevance for the assessment of coronary tone. Such differences in the selection of quantitative angiographic sites may add to the discrepancies of the results of previous studies.

Disease activity

The results of our study indicate that basal coronary tone changes in relation to changes in activity of vasospastic disease. Kuga *et al*[22] recently reported that basal coronary artery tone was increased at the spastic site when spasm was provoked by a low dose of ergonovine, whereas basal tone was not increased at those spastic sites that required a higher dose of ergonovine to induce spasm. Previtali *et al*[26] indicated that a low dose of ergonovine was required in patients with a high degree of vasospastic angina, while in patients with low level of disease activity a high dose of ergonovine was necessary to provoke spasm. Thus the inverse relation between the dose of ergonovine required to provoke spasm and the degree of basal coronary tone may indirectly support our findings. Given the close relation between disease activity and vasomotor response, it is conceivable that differences in the state of disease activity in the patients of previous studies may have contributed to the discrepancies of their results.

PATHOPHYSIOLOGICAL ROLE OF BASAL CORONARY TONE IN VASOSPASM

Experimental studies have indicated that various endothelium dependent vasoactive factors which modulate vascular smooth muscle contraction may play an important role.[10–12] Waters *et al*[38] and Kaski *et al*[39] have shown that coronary spasm may be induced by several stimuli such as ergonovine, histamine, hyperventilation, and exercise in the same patient with variant angina and have suggested that vasospasm is caused by a variety of nonspecific stimuli. Basal coronary artery tone is thought to be mediated by a balance of various stimuli such as the parasympathetic nervous system, humoral factors, and local endothelium dependent vasoactive factors.[14–16] Given the above similarities in mediation of coronary spasm and mediation of coronary tone, the demonstration of a close relation between coronary vasospastic disease and basal coronary vessel tone is not surprising. It could be hypothesised that basal coronary tone may express a "threshold" for vasospastic activity. Increased tone not in only spastic segments but also in adjacent segments may reflect a low "threshold" for vasospasm during high activity of the disease

CONCLUSIONS

Coronary artery tone may change in proportion to the activity of vasospastic disease over time. While vasoconstrictor response to ergonovine is increased in spastic segments only, basal tone of both spastic and adjacent segments is augmented during periods of active disease and is restored to normal during disease inactivity. The high diagnostic sensitivity and specificity of basal tone for prediction of spasm in coronary arteries indicates that the estimation of basal coronary tone may be useful in the assessment of vasospastic activity in patients with variant angina.

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Chapter 8

Impact of Smoking Status on Coronary Plaque Burden, Remodeling Mode and Restenosis Assessed by Intracoronary Ultrasound (IVUS) and Quantitative Coronary Angiography (QCA)

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ABSTRACT:

Background: Although smoking is an established risk factor for coronary atherosclerosis, its influence on vascular remodeling and plaque burden is uncertain. Similarly, the impact of smoking status on restenosis after percutaneous coronary intervention (PCI) is unclear.
Methods and Results: We examined the relationship between smoking status and plaque burden, vascular remodeling and restenosis in 1039 patients undergoing PCI. Intravascular ultrasound examination was performed in 450 patients to determine vessel area (VA), lumen area (LA) and plaque area. Remodeling index was defined as the ratio between lesion and average reference VA. Restenosis was defined as ≥50% diameter stenosis at follow-up. Of the 1039 patients, 248 were current smokers, 468 ex-smokers and 323 non-smokers. Current smokers were more likely to be younger than ex-smokers or non-smokers (56.8±9.9 *v* 60.3±9.8 *v* 64.5±9.5 years, *P*=0.001), and to suffer from unstable angina (25.0% *v* 13.5% *v* 13.6%, *P*=0.001). Current smokers had a significantly greater plaque burden in the lesion (13.6±4.6mm^2 *v* 11.1±4.1mm^2 *v* 10.6±3.8mm^2, *P*=0.001) as well as in the reference segments (7.7±3.7 mm^2 *v* 6.3±2.5mm^2 *v* 6.0±2.7mm^2, *P*=0.001) and were more likely to have a positive remodeling index (1.04±0.23 *v* 0.96±0.20 *v* 0.94±0.17, *P*=0.001). Restenosis rates were similar between the three groups (25.4% *v* 24.6% *v* 24.3%, *P*=0.955).
Conclusions: Although restenosis was not affected by smoking, current smoking appears to result in an earlier and unstable presentation of coronary disease, reinforcing the importance of smoking cessation.

INTRODUCTION:

Current models describe atherosclerosis as the consequence of the vascular response to the injurious effects of the classical cardiovascular risk factors [1]. It has become clear that as part of this vascular inflammatory response, in the early stages of atherosclerosis, affected vessels may undergo outward expansive remodeling to mitigate against incipient stenosis [2,3]. Epidemiological studies have established that smoking is a major risk factor for atherosclerotic ischemic heart disease [4-6]. The pleiotropic deleterious effects of smoking on atherosclerosis and thrombosis are beginning to be better delineated [7], however, the influence and impact of smoking on vascular remodeling remains poorly understood. Weissman and colleagues have reported that smoking is associated with focal contraction or negative remodeling of the atherosclerotic plaque [8]. Other groups however have reported that smoking does not influence remodeling mode or local plaque burden [9]. Evidence is emerging to suggest that as well as having a significant influence on the development of flow-limiting coronary stenoses, the

vascular remodeling mode may significantly impact on plaque stability, with plaques undergoing positive remodeling being more vulnerable to subsequent rupture and thrombosis [10-12]. The few studies examining the effect of smoking on plaque burden and the mode of vascular remodeling have been hampered by small numbers, and a lack of follow-up [8,9].

The last three decades has seen a growth in the use of percutaneous coronary interventions to manage symptomatic coronary atherosclerosis, however, despite the advent of drug-eluting stent technologies, the success of these techniques continues to be limited by restenosis [13]. The response to injury paradigm can also be employed to investigate this process and the vascular remodeling associated with it [14]. To date however, other major atherosclerotic risk factors have not emerged as risk factors for restenosis [15,16]. The influence of smoking on restenosis has been previously investigated with some studies suggesting a deleterious effect [17, 18] and other studies suggesting no direct effect [19-22]. These studies have been limited by small numbers [17], low follow-up rates [18,19], or a reliance on contrast angiography alone [21,22]. The latter invariably underestimates the extent of atherosclerosis, whereas intravascular ultrasound (IVUS) allows the vessel wall to be interrogated in exquisite detail and reveals the true burden of atheroma [23].

We investigated the effect of smoking on plaque burden, remodeling mode and on the process of restenosis in 1039 patients undergoing percutaneous coronary intervention. Of these, 450 patients underwent intravascular ultrasound study providing unique insights into the *in vivo* impact of smoking on the progression of atherosclerosis and restenosis.

METHODS:

Study Design and End-points

To determine the impact of smoking on coronary atherosclerosis and restenosis, we performed percutaneous coronary intervention in 1039 patients at the Fujita Health University Hospital, Toyoake, Japan, Aichi Medical University Hospital, Nagakute, Japan, and Thoraxcenter, Erasmus Medical Center, Rotterdam, The Netherlands. Of these patients, 450 underwent intravascular ultrasound examination and the remainder contrast-angiography alone. The primary angiographic end-point was restenosis (defined as ≥50 percent diameter stenosis at follow-up by quantitative coronary angiography) and the primary clinical end-point was major adverse cardiac events (MACE: defined as sub-acute or late stent thrombosis, death, myocardial infarction, and target lesion revascularization) at six months follow-up.

Patient Selection

The inclusion criteria were: (1) unstable or stable angina; (2) a single target lesion in a native

coronary artery with vessel diameter less than 4 mm; (3) either stenting or plain old balloon angioplasty (POBA); (4) agreement with angiographic follow-up. Patients were excluded from the study if they had: (1) contraindications to anticoagulation and antiplatelet therapy; (2) an acute myocardial infarction within the previous 7 days; (3) graft disease, left main coronary artery disease, or severe triple vessel disease; (4) an ostial lesion where the reference segment could not be identified in the IVUS group; (5) severe heavy calcification rendering it impossible to determine the true external elastic membrane (vessel) area in IVUS group; and (6) life expectancy less than a year. The study was approved by local ethics committees and was carried out according to the guidelines of the Declaration of Helsinki. Written informed consent was obtained from all patients.

Smoking history

A history of smoking was requested as part of the routine work up. Patients were asked if they had never or ever smoked and whether they were continuing to smoke and their answers recorded on the data sheet.

Percutaneous Coronary Intervention Procedures

Percutaneous coronary intervention was performed according to standard clinical practice using the trans-radial or trans-femoral approaches. Guide catheters 6F or greater in size were used to facilitate subsequent quantitative coronary angiographic (QCA) analysis [24]. A bolus of 8,000 to 10,000 IU of heparin (repeated if necessary) was administrated during the procedure, followed by a combination of antiplatelet therapy [24]. According to standard patient care, treatment with aspirin at a dose of 81 to 300mg daily was started before the procedure and continued indefinitely and treatment with ticlopidine at 200 mg daily was begun before or immediately after the procedure and continued for at least 2 weeks.

Optimal Percutaneous Coronary Intervention Criteria

Device sizes were determined by angiographic reference vessel diameter (angiography-guided group) and vessel size and plaque distribution detected by IVUS (IVUS-guided group). The angiographic criteria for optimal stenting were (1) no flow limiting dissection; and (2) residual stenosis less than 30%. The IVUS criteria for optimal stenting were (1) good stent apposition; (2) full stent expansion with sufficient lumen area (lumen area 80% or greater of the average reference lumen area pre-intervention; and (3) the absence of major dissection [25,26].

Quantitative Coronary Angiography (QCA)

Coronary angiograms were obtained in multiple views after the intracoronary injection of nitrates.

QCA analyses were performed using the computer-based edge-detection Coronary Angiography Analysis System (CAAS II, Pie Medical, Maastricht, the Netherlands) at the Coronary Imaging Core Laboratory in Aichi Medical and Fujita Health University [25-27]. The absolute diameter of the stenosis (in mm) was determined using the guiding catheter as a scaling device [27-29]. To standardize the method of analysis for pre-, post- and follow-up angiograms, the study frames selected for analysis were end-diastolic to minimize motion artefact, and arterial segments were measured between the same identifiable branch points after the administration of nitrates [24, 27, 29]. Acute gain and late loss were calculated as the improvement in minimal luminal diameter (MLD) achieved at intervention (MLD post-intervention minus MLD pre) and the changes at follow-up (MLD post-intervention minus MLD at follow-up) respectively. Loss index (late loss divided by acute gain) was also studied.

Intravascular Ultrasound Image Acquisition Protocol

Following selective coronary angiography after the intracoronary injection of nitrates, a mechanical intracoronary ultrasound imaging catheter (40-MHz, 2.6Fr or 2.5Fr, Boston Scientific Corporation, Freemont, California, USA) was introduced over a 0.014-inch guide wire before, immediately after coronary intervention and at follow-up [29]. After the imaging catheter was passed into and beyond the lesion, a motorized pullback was started to obtain an assessment of the target lesion. IVUS images were stored on Super-VHS videotape for off-line analysis [29,30].

Quantitative IVUS Assessment

Serial IVUS analysis pre-procedure, immediately post-procedure and at six-month follow-up was performed at an independent core laboratory in Aichi Medical and Fujita Health University. Cross-sectional luminal area was defined as the integrated area central to the intimal leading edge echo [29-31]. The total vessel cross sectional area was defined as the area inside the interface between the plaque-media complex and adventitia (area inside the external elastic membrane) [3,29-31]. Vessel area, lumen area and plaque area were measured with a commercially available planimetry software package (TapeMeasure, Index Systems, Mountain View, California, USA) [31]. The lesion segment was determined from pre-intervention images including the frame with the smallest lumen area, while the proximal and distal reference segments were defined as the location of the least amount of disease within 10 mm proximal or distal to the lesion but before the emergence of a major side branch. Remodeling index was defined as the ratio of the vessel area at the target lesion divided by the average of proximal and distal reference segment vessel area. The corresponding frames at post-intervention and follow-up were determined by using peri- and intra-coronary landmarks such as calcium deposits, side branches and venous structures [29-31]. With quantitative intravascular ultrasound, late lumen

loss was defined as lesion lumen area post-intervention minus lesion lumen area at follow-up; late intimal hyperplasia was defined as lesion plaque area at follow-up minus lesion plaque area post-procedure; and late vessel recoil was defined as the lesion vessel area post-procedure minus lesion vessel area at follow-up.

Statistical Analysis

Data was analyzed using the SAS statistical software package. All continuous values are expressed as mean±SD. Differences in categorical variables were assessed using the Chi-squared test and Fisher's exact test. The ANOVA test was used to assess differences in continuous variables between three groups. Where multiple comparisons between sub-groups were necessary, Tukey's method was used to assess the significance of differences observed by ANOVA. To study the relationship between continuous outcome parameters and multiple categorical and continuous determinants, multiple linear regression analysis was used. For all statistical tests, a two-tailed value of $P<0.05$ was considered significant.

RESULTS:

Baseline Clinical and Angiographic Characteristics

A total of 1039 patients entered the study. Of these 323 had never smoked, 468 were ex-smokers and 248 were still smoking at the time of the coronary intervention. Current smokers were significantly younger than non-smokers or ex-smokers (Table 1).

TABLE 1. Baseline Clinical and Demographic Characteristics.

	Never Smoker (n=323)	Ex-Smoker (n=468)	Current Smoker (n=248)	P (ANOVA)
Age (years, mean±SD)	64.5±9.5	60.3±9.8	56.8±9.9	*0.001*
Male (%)	61.3	89.7	91.5	*0.001*
Diabetes Mellitus (%)	26.6	22.2	23.4	0.353
Hypertension (%)	53.6	43.4	38.3	*0.001*
Hypercholesterolemia (%)	39.6	45.7	44.8	0.215
Previous MI (%)	22.9	31.8	27.8	*0.023*
Unstable Angina (%)	13.6	13.5	25.0	*0.001*

Coronary intervention was required on average 8 years earlier in smokers than non-smokers and nearly 4 years earlier in ex-smokers when compared with non-smokers (P=0.001). There was

a significantly higher proportion of men in the current as well as ex-smokers groups (*P*=0.001). While hypertension was more common in non-smokers (*P*=0.001), there was no significant difference in the other coronary risk factors including diabetes and hypercholesterolemia. In spite of having a younger mean age, previous myocardial infraction was more common in current and ex-smokers (*P*=0.023) and current smokers were more likely to have unstable angina (*P*=0.001) relative to non-smokers. There were no significant differences in the baseline qualitative and quantitative angiographic characteristics between the three groups (Table 2).

TABLE 2. Angiographic Characteristics before and after Percutaneous Coronary Intervention.

	Never Smoker (n=323)	Ex-Smoker (n=468)	Current Smoker (n=248)	P (ANOVA)
Target Coronary Artery (%)				
RCA	26.0	26.9	32.7	0.234
LAD	55.1	56.6	48.4	-
LCX	18.8	16.4	18.9	-
AHA/ACC Lesion Class (%)				
A	24.8	26.9	27.8	0.958
B1	28.8	29.1	29.0	-
B2	38.7	35.5	34.7	-
C	7.7	8.5	8.5	-
Overall (Stent & POBA) pre				
RD Pre (mm)	2.81±0.46	2.83±0.53	2.88±0.52	0.340
MLD Pre (mm)	1.00±0.31	1.01±0.33	1.02±0.37	0.751
MLD Post (mm)	2.19±0.44	2.23±0.44	2.27±0.47	0.121
MLD Follow-up (mm)	1.65±0.58	1.74±0.56	1.72±0.61	0.099
Lesion Length (mm)	11.6±6.1	11.2±5.8	11.1±5.6	0.583
Stent				
Acute Gain	1.38±0.39	1.43±0.45	1.44±0.46	0.336
Late Loss	0.73±0.57	0.63±0.52	0.69±0.56	0.183
Loss Index	0.53±0.47	0.45±0.41	0.52±0.51	0.152
POBA				
Acute Gain	0.95±0.39	0.97±0.39	0.99±0.45	0.667
Late Loss	0.31±0.46	0.35±0.48	0.38±0.49	0.567
Loss Index	0.37±0.58	0.35±0.80	0.41±0.79	0.775
Overall Restenosis rate (%)				

	24.3	24.6	25.4	0.955
RR with Stent	24.1	16.6	20.9	0.173
RR with POBA	24.6	33.8	31.3	0.200

RCA=Right Coronary Artery, LAD=Left Anterior Descending coronary artery; LCX=Left Circumflex coronary artery; RD=Reference Vessel Diameter; MLD=Minimal Lumen Diameter; POBA=Plain Old Balloon Angioplasty.

Comparison of Angiographic Restenosis Rates between Three Groups

Follow-up angiography was performed in 963 (92.7%) of the 1039 study patients and follow-up intravascular examination in 422 (93.7%) of the 450 who underwent pre-intervention intravascular ultrasound. There were no significant differences between the three groups with respect to follow-up rates (*P*=0.451). Similarly, no significant difference was found between non-smokers, ex-smokers, and current smokers with respect to the overall angiographic acute gain, late loss and loss index. Furthermore, no significant difference was observed between the three groups when the data were analyzed according to whether patients underwent stenting or POBA (Table 2). The restenosis rates experienced by the three groups at 6 months follow-up were also similar. Once again, the lack of a significant difference was consistent regardless of whether patients underwent stenting or POBA.

TABLE 3. Intracoronary Ultrasound Assessments in 450 patients.

	Never Smoker (n=146)	Ex-Smoker (n=200)	Current Smoker (n=104)	P (ANOVA)
Lesion morphology (stent and POBA)				
Soft/Fibrotic/Mixed/Calcified (%)				
	61/2/30/7	51/3/32/14	55/2/31/12	0.343
Calcium angle (degree)	76.1±67.1	71.1±82.6	66.1±86.5	0.609
Reference (Ref) segment (stent and POBA)				
Proximal Ref VA pre (mm^2)	14.5±4.3	15.4±4.5	16.6±4.8	*0.002*
Distal Ref VA pre (mm^2)	11.9±4.6	12.1±4.6	13.7±4.6	*0.005*
Average Ref VA pre (mm^2)	13.2±4.0	13.7±4.1	15.2±4.2	*0.001*
Average Ref PLA pre (mm^2)	6.0±2.7	6.3±2.5	7.7±3.7	*0.001*
Lesion segment (stent and POBA)				
Lesion VA Pre (mm^2)	12.4±4.0	13.0±4.3	15.5±4.7	*0.001*
Lesion PLA Pre (mm^2)	10.6±3.8	11.1±4.1	13.6±4.6	*0.001*
Remodeling Index	0.94±0.17	0.96±0.20	1.04±0.23	*0.001*

Stent				
Late Loss	2.1±2.3	2.4±2.2	2.5±2.5	0.664
Vessel Recoil	-0.5±3.4	-0.7±3.2	-0.7±3.8	0.903
Plaque Growth	2.6±3.8	3.1±3.6	3.4±4.2	0.475
POBA				
Late Loss	1.0±2.2	1.6±1.9	1.7±2.2	0.178
Vessel Recoil	0.3±2.5	0.2±5.2	0.6±4.2	0.881
Plaque Growth	0.6±3.0	1.3±5.2	1.1±3.8	0.604

IVUS=Intravascular Ultrasound; VA=Vessel Area; PLA=Plaque Area; POBA=Plain Old Balloon Angioplasty

Quantitative Intravascular Ultrasound Assessments and Restenosis

Although qualitative IVUS lesion morphology was similar between the three groups, quantitative IVUS evaluation revealed marked differences (Table 3). Reference vessel size either proximal or distal was significantly greater in smokers than non-smokers (proximal; *P*=0.002, distal; *P*= 0.005) and plaque burden in the reference segment was significantly greater in current smokers than non-smokers (*P*=0.001). In the lesion segment, vessel area and plaque area were consistently greater in current smokers than non-smokers (vessel area, *P*=0.001; plaque area, *P*=0.001). Current smokers also had a significantly greater plaque burden than the other groups in both reference (*P*=0.001) and lesion segments (*P*=0.001). Despite having a greater plaque burden in the reference segment, current smokers had a significantly greater positive remodeling index in the lesion segment relative to the other groups (*P*=0.001). Although there was a significant difference in plaque burden among the three groups, no difference was observed in late loss, vessel recoil and plaque growth in both stent and POBA groups (Table 3), individually and overall.

Clinical Outcomes at Six Months follow-up

Eighty-nine (27.6%) of the non-smokers, 116 (24.8%) of the ex-smokers and 63 (25.4%) of the current smokers met clinical end-points (MACE; *P*=0.673). Reflecting a similar restenosis rate, target lesion revascularization rates were similar between three groups (*P*=0.852). No significant difference was observed between the three groups with respect to the occurrence of any MACE (Table 4).

TABLE 4. Comparison of Major Adverse Cardiac Events and Target Lesion Revascularization rates between the three groups.

	Never Smoker (n=323)	Ex-Smoker (n=468)	Current Smoker (n=248)	P
Death (n, %)	3 (0.9)	2 (0.4)	3 (1.2)	0.483
Cardiac death (n, %)	3 (0.9)	1 (0.2)	2 (0.8)	0.367
Non-cardiac death (n, %)	0 (0.0)	1 (0.2)	1 (0.4)	0.546
Myocardial Infraction (n, %)	12 (3.7)	12 (2.6)	8 (3.2)	0.646
TLR				
PCI (n, %)	59 (18.3)	91 (19.4)	45 (18.1)	0.879
CABG (n, %)	15 (4.6)	11 (2.4)	7 (2.8)	0.182
Overall TLR (n, %)	74 (22.9)	102 (21.8)	52 (21.0)	0.852
Overall MACE (n, %)	89 (27.6)	116 (24.8)	63 (25.4)	0.673

TLR: Target Lesion Revascularization; PCI: Percutaneous Coronary Intervention; CABG: Coronary Artery Bypass Graft Surgery; MACE: Major Adverse Cardiac Events.

Multivariate Analysis Results

Multiple linear regression analyses to evaluate the respective contributions of clinical, angiographic and IVUS variables to plaque burden in the lesion segment indicated that smoking habit, male gender and unstable anginal symptoms were significant independent predictors for greater plaque burden (Table 5).

TABLE 5. Summary Findings of Multiple Linear Regression Analysis of the Contributions of Clinical, Angiographic and Intravascular Ultrasound variables to Coronary Plaque Burden

	Regression Coefficient	Standard Error of Regression Coefficient	P
Smoking Habit	1.123	0.283	*0.001*
Male Gender	1.855	0.536	*0.006*
Unstable Angina Pectoris	0.885	0.416	*0.034*
Hypertension	0.744	0.396	0.061
Hypercholesterolemia	0.585	0.389	0.133

DISCUSSION:

Our data indicate that there are marked differences in baseline clinical and IVUS characteristics between smokers and non-smokers, which cannot be detected by conventional contrast angiography alone. Smokers required coronary interventions on average eight years earlier than non-smokers and four years earlier than ex-smokers. This is similar to the findings of Hasdai and colleagues who found that smokers required percutaneous coronary intervention on average ten years before non-smokers [32]. However, our data have also shown that once coronary intervention had been successfully done, six-month clinical and angiographic outcomes were similar between the three groups.

The incidence of unstable angina was nearly double in current smokers in comparison to ex-smokers or non-smokers (current *v* ex- *v* non-smokers, 25.0% *v* 13.5% *v* 13.6%, *P*=0.001). The greater plaque burden seen in the lesion and reference segments of current smokers and the positive remodeling mode observed could have played a role in fostering the development of unstable lesions (Table 3). Our findings are in line with previous studies which have suggested that a positive or expansive remodeling mode is associated with plaque instability and an unstable clinical presentation [11,12]. An alternative explanation for this finding is that smoking directly enhances plaque instability and results in an earlier clinical presentation with unstable disease whereas the older plaques seen in non-smokers have had more time to attain stability and undergo negative or constrictive remodeling. This could therefore perhaps result in a greater likelihood of presentation with stable disease in the older non-smokers. However, these scenarios are not mutually exclusive. Smoking results in endothelial dysfunction through decreasing nitric oxide production and enhancing oxidant injury [7, 33,34]. This provides a potent stimulus for the recruitment of macrophages to the plaque and their expression of matrix metalloproteinases, the gelatinase enzymes that are thought to play a key role in both vascular remodeling and the development of plaque instability [1,35].

Contrary to the findings of our study, a previous study by Weissman and colleagues found that smoking was associated with constrictive or negative remodeling [8]. However, only 61 of the 169 patients entered into that study had adequate reference segments for study, and remodeling was only detected in 43 lesions, of which only 16 underwent negative remodeling. This provided only a limited sample size from which to draw definitive conclusions.

Multivariate analysis demonstrated that smoking status is significantly related to plaque burden independent of age. Current smokers had significantly greater plaque burden not only in the

lesion segment but also reference segments, associated with positive vessel remodeling in the lesion segment. In spite of having a younger age, current smokers could therefore potentially have a greater longitudinal expansion of plaque deposits, that is, more diffuse disease. This serves to highlight the deleterious effects of smoking on atherosclerosis. A previous IVUS study by Kornowski had suggested that smokers had similar arterial size and plaque burden in both reference and lesion segments [9]. However, in that study, smokers were not divided into current and ex-smokers, and smokers tended to have a greater plaque area and vessel size in comparison to non-smokers, albeit without a significant difference [9]. Their different classification of smoking status and sample size factors could have accounted for the differences between their findings and ours.

Influence of Smoking on Restenosis

Numerous studies have explored the impact of smoking on restenosis [17-22]. Two previous studies using QCA have suggested that restenosis rates were similar between smokers and non-smokers [21,22]. Our study represents the first large-scale use of IVUS with QCA to evaluate the impact of smoking status on restenosis. It was characterized by high follow-up rates (92.7%) and revealed that there was no significant difference in restenosis rates between smokers, ex-smokers and non-smokers. In particular, smoking had no effect on vessel recoil and plaque growth over the six months following PCI. These findings emphasize that although there are superficial similarities between the pathophysiological processes of atherosclerosis and restenosis, the vascular response to injury and remodeling which takes place in restenosis cannot be assumed to be subject to the same influences. This is exemplified by the finding in other studies that other classical risk factors such as hypercholesterolemia do not affect restenosis [15].

Clinical Implications

While those who continue to smoke after successful coronary intervention are at greater risk of Q-wave infarction and death than nonsmokers [32], the Framingham study reported that men under the age of 65 who were cigarette smokers at entry and subsequently stopped had myocardial ischemic attack rates which were half those experienced by those who continued to smoke [36]. In general, it has been observed that stopping smoking delays the onset of atherosclerotic disease by about a decade [6, 32]. Our smokers experienced PCI on average eight years earlier than nonsmokers, and four years earlier than ex-smokers. IVUS indicated that ex-smokers had less plaque burden and negative remodeling as compared to current smokers. Thus, smoking cessation, by removing a potent stimulus for endothelial injury and dysfunction, could favor changes in plaque structure that enhance plaque stability, thereby

reducing cardiovascular events during long-term follow-up. The finding that smoking status has no impact on restenosis should not therefore detract from the wealth of evidence from this and other studies reinforcing the importance of smoking cessation in retarding the development of atherosclerosis and reducing the risk of unstable disease [4-6,36].

Study Limitations

Our study has a number of limitations. Firstly, we do not have objective verification of the patient's self-reported smoking status, as we did not specifically assess whether supposed ex-smokers had truly stopped or whether they were still continuing to smoke. Second, our data only apply to successful procedures and to the immediate 6-month follow-up period. We therefore do not know if smoking reduces the chances of acute success or increases the immediate acute complications of the procedure. Furthermore, our study does not take into account any changes in smoking behavior that may have occurred following percutaneous coronary intervention.

CONCLUSIONS

Smoking status did not significantly influence restenosis rates. However, current smokers required PCI nearly 8 years earlier than non-smokers and 4 years earlier than ex-smokers. In spite of having a younger mean age, current smokers had a greater plaque burden in the lesion and reference segments, associated with a positive or expansive remodeling mode. This was associated with an increased likelihood of unstable presentation. Thus, the time of percutaneous coronary intervention should be regarded as a golden opportunity to extol the health benefits of smoking cessation.

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Part 3 - Assessment of

Percutaneous Coronary Intervention (PCI)

Chapter 9

Short- and long-term clinical and quantitative angiographic results with the new less shortening Wallstent for vessel reconstruction in chronic total occlusion (CTO): a quantitative angiographic study

Ozaki Y, Violaris AG, Hamburger JN, Melkert R, Foley D, Keane D, de Feyter PJ, Serruys PW

J Am Coll Cardiol 1996;28:354-360

Short- and Long-Term Clinical and Quantitative Angiographic Results With the New, Less Shortening Wallstent for Vessel Reconstruction in Chronic Total Occlusion: A Quantitative Angiographic Study

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Objectives. **This study was designed to examine whether oversized implantation of the new, less shortening Wallstent provides a more favorable long-term clinical and angiographic outcome in chronic total occlusions than does conventional coronary balloon angioplasty.**

Background. **Restenosis and reocclusion remain major limitations of balloon angioplasty for chronic total occlusions. Enforced mechanical remodeling by implantation of the oversized Wallstent may prevent elastic recoil and improve accommodation of intimal hyperplasia.**

Methods. **Lumen dimension was measured by a computer-based quantitative coronary angiography system (CAAS II). These measurements (before and after intervention and at 6-month follow-up) were compared between the groups with Wallstent implantation (20 lesions, 20 patients) and conventional balloon angioplasty (266 lesions, 249 patients) for treatment of chronic total occlusion. Acute gain (minimal lumen diameter after intervention minus that before intervention), late loss (minimal lumen diameter after intervention minus that at follow-up) and net gain (acute gain minus late loss) were examined.**

Results. **Wallstent deployment was successful in all patients. High pressure intra-Wallstent balloon inflation (mean ± SD 14 ± 3 atm) was performed in all lesions. Although vessel size did not differ between the Wallstent and balloon angioplasty groups, acute gain was significantly greater in the Wallstent group (2.96 ± 0.55 vs. 1.61 ± 0.34 mm, $p < 0.0001$). Although late loss was also significantly larger in the Wallstent group (0.81 ± 0.95 vs. 0.43 ± 0.68 mm, $p < 0.05$), net gain was still significantly greater in this group (2.27 ± 1.00 vs. 1.18 ± 0.69 mm, $p < 0.0001$). Angiographic restenosis (≥50% diameter stenosis) occurred at 6 months in 29% of lesions in the Wallstent group and in 45% of those in the balloon angioplasty group ($p = 0.5150$).**

Conclusions. **Implantation of the oversized Wallstent, with full coverage of the lesion length, ensures resetting of the vessel size to its original caliber before disease and allows greater accommodation of intimal hyperplasia and chronic vessel recoil. Wallstent implantation provides a more favorable short- and long-term clinical and angiographic outcome than does conventional balloon angioplasty for chronic total occlusions.**

(J Am Coll Cardiol 1996;28:354–60)

The rate of restenosis is significantly higher after successful dilation of total coronary occlusions than after successful dilation of nonoccluded stenoses (1–3). We (3) recently demonstrated, using both a categoric and a continuous approach, that this higher restenosis rate is mainly due to an increased rate of occlusion at follow-up angiography. Multivariate analysis suggested that this increased rate is specifically related to total inflation time and vessel reference diameter after intervention. For several reasons the acute lumen diameter obtained after successful balloon angioplasty is significantly smaller for chronic total occlusions than for nonoccluded stenoses (3). The new less shortening self-expanding Wallstent is characterized by longitudinal flexibility, a protective membrane, a low profile and a customized range of diameters and lengths (4–6). The recent modification in braiding angle and stent strut have resulted in a new device with less shortening on expansion and a concomitant reduction in radial force and improvement in radiopacity (4–6). These modifications may convey a lower restenosis rate because of lower metallic surface per segment and increased feasibility of stent delivery because of higher visibility and less shortening when the stent expands.

We hypothesized that enforced mechanical remodeling by oversized stent implantation after coronary angioplasty may lead to improved local flow dynamics, with a resulting low incidence of acute and subacute occlusion as well as prevention of chronic elastic recoil and improved accommodation of reactive intimal hyperplasia. The new, less shortening Wall-

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stent is ideal for this situation because it is self-expanding, comes in a customized range of long lengths (up to 42 mm) and large diameters (up to 6.0 mm). We examined this strategy of oversized Wallstent deployment in 20 patients after successful laser or balloon angioplasty. Quantitative coronary angiographic analysis was performed before intervention, after balloon angioplasty, after high pressure balloon angioplasty after oversized Wallstent deployment ("Swiss kiss") and at 6-month follow-up. The results were compared with those in patients with total occlusions undergoing successful balloon angioplasty and quantitative angiographic follow-up at 6 months in the same angiographic core laboratory.

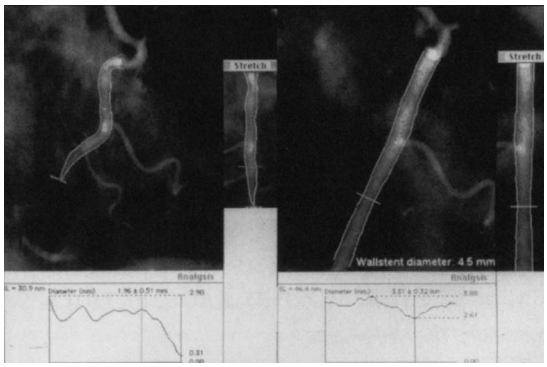

Figure 1. Left panel, Angiogram showing total occlusion of a mid-right coronary artery and a maximal vessel diameter of 2.90 mm in the proximal segment. A Wallstent (diameter 4.5 mm, length 35 mm) 1.60 mm larger than the maximal vessel diameter was deployed (**right panel**). Minimal lumen diameter increased from 0 to 2.61 mm, and Thrombolysis in Myocardial Infarction (TIMI) grade 3 flow was restored.

Methods

Study patients. *Wallstent implantation group.* To determine the feasibility and efficacy of deployment of the new, less shortening Wallstent in patients with chronic total occlusion, we deployed 25 Wallstents in 20 native coronary artery lesions in 20 patients who had coronary balloon or laser angioplasty of chronic total occlusion >3 months old.

Balloon angioplasty group. To provide further insight into the potential short- and long-term mechanisms involved in implantations of the grossly oversized Wallstent, we compared our serial angiographic measurements with those of 266 arteries with total occlusion in 249 patients undergoing successful balloon angioplasty. This study group was selected from 3,582 patients with significant native coronary artery stenosis who were prospectively enrolled in four major restenosis studies and underwent successful coronary angioplasty (7–10). Quantitative angiographic assessment before and after balloon angioplasty and at 6-month follow up was performed with use of the same methodology and at the same angiographic core laboratory (3) for all 266 lesions in 249 patients.

Laser and balloon angioplasty. Coronary angioplasty was performed according to standard clinical practice by the femoral approach at the Thoraxcenter (Rotterdam, The Netherlands). Laser angioplasty was applied in patients who had had previously unsuccessful balloon angioplasty. Primary laser angioplasty using a laser wire and catheter was carried out in six patients. Laser wire (0.018-in. [0.046-cm] diameter, Spectranetics) was used to pass into and beyond a lesion with chronic total occlusion when a flexible guide wire (0.014 in. [0.036 cm]) failed to cross the lesion (11,12). Excimer laser system (Spectranetics CVX 300) produced laser fluency with an energy level of 60 mJ/mm^2 and a pulse repetition frequency of 25 Hz. The laser wire was advanced ~1 mm/s. After the wire successfully crossed the lesion, a laser catheter (1.4- or 1.7-mm diameter, Spectranetics) was passed over the wire to enlarge the coronary lumen (11,12). After the successful laser procedure, adjunctive balloon angioplasty was carried out. In the remaining 14 patients balloon angioplasty was performed after successful crossing with 0.014-in. guide wire. During the primary balloon angioplasty the balloon diameter was 2.67 ± 0.66 mm and the maximal inflation pressure was 10.3 ± 3.0 atm.

Wallstent implantation. Intracoronary ultrasound studies (13–16) have reported that atherosclerotic plaque is commonly observed in angiographically normal proximal reference segments in patients with significant coronary stenosis. We therefore used the maximal vessel diameter, which may be closer to the original vessel diameter in the nondiseased condition than is the interpolated reference diameter traditionally used for stent sizing. After determination of the maximal vessel diameter on the diameter function of the on-line quantitative Coronary Angiographic Analysis System (CAAS II), a Wallstent with a nominal diameter 1.5 mm greater than the maximal vessel diameter and nominal length 5 to 10 mm longer than the lesion length was selected (Fig. 1). Of the 25 stents used in 20 lesions, 1 had a diameter of 4 mm, 2 of 4.5 mm, 6 of 5 mm, 9 of 5.5 mm and 7 of 6 mm. Eleven of the 25 stents had a length of 23 to 28 mm, 8 of 35 mm and 6 of 42 mm. Fifteen patients received one Wallstent and the remaining five patients received two Wallstents. After delivery of the stent, high pressure inflations ("Swiss kiss", 14.0 ± 3.3 atm) using balloon diameters of 3.9 ± 0.7 mm to optimize stent expansion were performed in all 20 patients.

Anticoagulant therapy. Patients were given an intravenous bolus dose of 10,000 IU of heparin, and subsequently 5,000 IU at the beginning of the intervention, as required to maintain the activated clotting time >300 s throughout the procedure. In this early experience a standardized postintervention anticoagulant regimen was used (17,18): One hour after removal of the femoral sheath, a heparin intravenous infusion was begun to maintain activated partial thromboplastin time between 70 and 90 s until oral anticoagulant therapy (warfarin sodium [Coumadin]) had achieved a prothrombin time international normalized ratio of 2.5 to 3.5. Coumadin was prescribed for 3 months after stent

implantation and aspirin indefinitely (17,18). Ticlopidine was not used.

Study end points and definitions. Procedural success was defined as technically successful deployment of the stent in the absence of any adverse cardiac events, defined as acute or subacute stent thrombosis, repeat intervention, coronary artery bypass surgery, myocardial infarction or death. Angiographic success was defined as a <30% residual diameter stenosis after final deployment of the stent. The primary clinical end point of the study was the occurrence of any adverse cardiac event. Subacute thrombosis was defined as a clinical event leading to cardiac catheterization that identified stent thrombosis within 14 days of stent deployment. Angiographic restenosis was defined as lumen narrowing ≥50% diameter stenosis at follow-up. Long-term clinical outcome included all cardiovascular events occurring within 6 months of stent deployment.

Quantitative coronary angiographic analysis. The new version of the computer-based CAAS II system (19) was used to perform on-line quantitative analysis (for immediate guidance of stent sizing in the catheterization laboratory) and the subsequent off-line cine film analysis. In the CAAS analysis, which has previously been described elsewhere (20–25), the entire 18- × 24-mm cine frame is digitized at a resolution of 1,329 × 1,772 pixels. Correction for pincushion distortion is performed before analysis. Boundaries of a selected coronary segment are detected automatically. The absolute diameter of the stenosis (in mm) is determined by using the guiding catheter as a scaling device (26). To standardize the method of analysis of the initial and follow-up angiograms, the following measures were taken: All study frames selected for analysis were end-diastolic to minimize motion artifact; arterial segments were measured between the same identifiable branch points after administration of isosorbide dinitrate (27–30).

Quantitative angiographic variables. Acute gain and late loss represent the improvement in minimal lumen diameter achieved at intervention (minimal lumen diameter after stenting minus that before stenting) and the changes at follow-up (minimal lumen diameter after stenting minus that at follow-up), respectively. Net gain (gain minus loss) was examined. Vessel size was defined as a interpolated reference diameter after balloon angioplasty (31). Because the algorithm cannot measure total occlusions, a value of 0 mm was imputed for the minimal lumen diameter, and the reference diameter after balloon angioplasty was substituted for that before intervention. Net gain index (net gain divided by the reference diameter before angioplasty), relative loss (loss divided by the reference diameter before intervention) and loss index (loss divided by gain) were studied.

Statistical analysis. Data were analyzed by using the SAS statistical software package. Categoric variables are presented as absolute numbers (%). Continuous variables are expressed as mean value ± 1 SD. Differences between groups were evaluated by using adjusted chi-square tests for categoric variables and Student *t* tests for continuous variables. A p value < 0.05 was considered significant.

Table 1. Clinical and Angiographic Characteristics of the Patients

	Wallstent Implantation Group (n = 20 patients)	Balloon Angioplasty Group (n = 249 patients)	p Value
Male	95.0%	85.1%	0.3765
Age (yr)	55.9 ± 9.3	54.4 ± 9.6	0.5011
Prior myocardial infarction	50.0%	54.2%	0.8958
Prior successful balloon angioplasty	5.0%	3.6%	0.5445
Prior coronary bypass surgery	10.0%	1.6%	0.0971
Coronary risk factors			
Hypercholesterolemia	30.0%	33.3%	0.9538
Systemic hypertension	30.0%	30.1%	0.8087
Cigarettes (ever smoked)	65.0%	73.1%	0.6034
Diabetes	10.0%	10.8%	0.7966
CCS angina class			
None	5.0%	6.0%	0.7603
I	10.0%	10.0%	0.7032
II	35.0%	33.7%	0.8961
III	30.0%	28.9%	0.4736
IV	20.0%	21.3%	0.8815
No. of diseased vessels			
1	60.0%	61.0%	0.8838
2	30.0%	34.5%	0.8676
3	10.0%	3.6%	0.4233
Lesion location			
RCA	70.0%	33.7%	0.0026
LAD	30.0%	39.4%	0.5564
LCx	0	26.9%	0.0160
TIMI flow before intervention			
TIMI 0	75.0%	41.0%	0.0063
TIMI 1	25.0%	59.0%	0.0063

Data presented are percent of patients or mean value ± SD. CCS = Canadian Cardiovascular Society; TIMI = Thrombolysis in Myocardial Infarction grade flow (32).

Results

Baseline clinical and angiographic characteristics in the Wallstent and balloon angioplasty groups (Table 1). No difference was found between the Wallstent implantation and balloon angioplasty groups in gender, age, previous myocardial infarction, previous successful balloon angioplasty, previous coronary bypass surgery, coronary risk factors, angina class or number of diseased vessels. The incidence of absolute total occlusions (Thrombolysis in Myocardial Infarction [TIMI] grade 0 [32]) was significantly higher in the Wallstent group than in the balloon angioplasty group. The Wallstent was predominantly deployed in the right coronary artery, which has few significant side branches at risk of occlusion by full coverage of a long lesion using the Wallstent (4).

Clinical outcome. Delivery of all 25 Wallstents was possible, and no cardiac event occurred during the procedure.

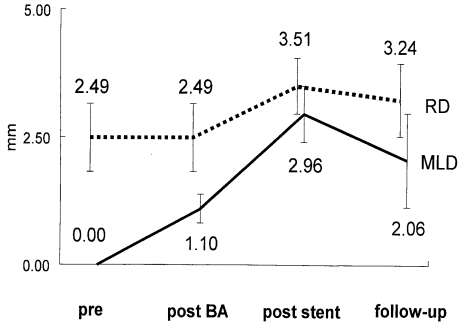

Figure 2. Changes in minimal lumen diameter (MLD) and reference diameter (RD) in 20 lesions from before (pre) intervention through the periods after balloon angioplasty (post BA) and after stent implantation (post stent) to follow-up. Minimal lumen diameter improved markedly after Wallstent implantation and the performance of a Swiss Kiss.

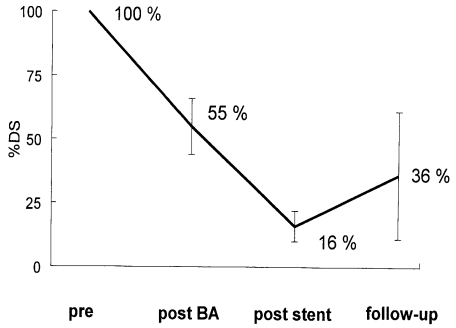

Figure 4. Changes in percent diameter stenosis (% DS) in 20 lesions from before intervention (pre) through after balloon angioplasty (post BA) and after stent implantation (post stent) to follow-up. There was a marked decrease in residual stenosis after Wallstent implantation and the performance of a "Swiss kiss".

Angiographic success (<30% diameter stenosis) was achieved in all patients with Wallstent implantation. One patient sustained a subacute occlusion on day 1 associated with a non-Q wave myocardial infarction (creatine kinase 228 IU/liter) and was immediately treated by balloon angioplasty, which promptly restored TIMI grade 3 flow. Of the 19 patients in the Wallstent group eligible for 6-month angiographic follow-up, 2 asymptomatic patients declined restudy. Thus, the angiographic follow-up rate of the Wallstent group was 89%, a rate comparable to the 86% rate in the control balloon angioplasty group (3). Angiographic restenosis (≥50% diameter stenosis) at 6 months occurred in 5 (29%) of 17 lesions in the Wallstent group and in 119 (45%) of 266 lesions in the balloon angioplasty group. The overall event-free survival rate at 6-month follow-up was 75% (15 of 20 patients) in the Wallstent group and 71% (195 of 249 patients) in the balloon angioplasty group.

Quantitative angiographic analysis in the Wallstent group. The average nominal diameter of the Wallstents used was 1.82 ± 0.83 mm greater than the maximal vessel diameter and 11.0 ± 7.3 mm longer than the lesion length. Minimal lumen diameter increased from 0 mm before intervention to 1.10 ± 0.28 mm after balloon angioplasty (Fig. 2). After stent implantation, high pressure balloon dilation of 14.0 ± 3.3 atm ("Swiss kiss") using balloons of 3.9 ± 0.7-mm diameter was performed in all lesions. Implantation of the Wallstent further increased the minimal lumen diameter to 2.96 ± 0.55 mm (Fig. 2). At 6-month follow-up, minimal lumen diameter decreased to 2.06 ± 0.92 mm. Figure 3 provides an example of the serial angiographic outcome in an individual patient. Figure 4 shows percent diameter changes from the period before intervention through the period after stent implantation to 6-month follow-up.

Quantitative angiographic comparison with the group undergoing balloon angioplasty (Table 2). No difference was found in vessel size (interpolated reference diameter before intervention) between the Wallstent and balloon angioplasty groups. There was a significantly greater reference diameter after intervention in the Wallstent group, and this difference remained at follow-up. The minimal lumen diameter increased substantially more after Wallstent implantation, as reflected in the substantially lower percent residual stenosis. At follow-up, although the absolute loss was significantly higher in the Wallstent group, the greater initial gain allowed improved accommodation of the intimal hyperplasia, and both the minimal lumen diameter and percent diameter stenosis at follow-up were significantly lower in the Wallstent group. Although the restenosis rate using the categoric approach

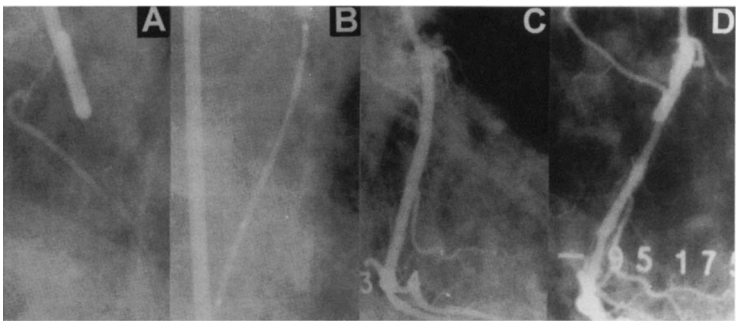

Figure 3. Coronary angiograms of the right coronary artery in a patient with total occlusion before balloon angioplasty (**A**). After balloon angioplasty a Wallstent (nominal diameter 6.0 mm, length 42 mm) was deployed. The radiopaque stent delivery system and the markers can be seen during deployment (**B**). After Wallstent deployment, minimal lumen diameter was 3.06 mm in association with a 15% residual diameter stenosis (**C**). Follow-up angiography at 6 months revealed a minimal lumen diameter of 2.16 mm in association with a 35% diameter stenosis (**D**).

Table 2. Quantitative Angiographic Analysis Results in the Wallstent and Balloon Angioplasty Groups

	Wallstent Implantation Group (n = 20 lesions)	Balloon Angioplasty Group (n = 266 lesions)	p Value
Reference diameter (mm)			
Before stent implantation	2.49 ± 0.67	2.46 ± 0.49	0.7976
After intervention	3.51 ± 0.55	2.46 ± 0.49	< 0.0001
At follow-up	3.24 ± 0.72	2.60 ± 0.55	< 0.0001
Minimal lumen diameter (mm)			
Before intervention	0	0	—
After intervention	2.96 ± 0.55	1.61 ± 0.34	< 0.0001
At follow-up	2.06 ± 0.92	1.18 ± 0.69	< 0.0001
Differences in minimal lumen diameter (mm)			
Absolute gain	2.96 ± 0.55	1.61 ± 0.34	< 0.0001
Relative gain	1.19 ± 0.30	0.66 ± 0.09	< 0.0001
Absolute loss	0.81 ± 0.95	0.43 ± 0.68	0.0201
Relative loss	0.33 ± 0.39	0.17 ± 0.28	0.0175
Absolute net gain	2.27 ± 1.00	1.18 ± 0.69	< 0.0001
Net gain index	0.92 ± 0.40	0.48 ± 0.28	< 0.0001
Loss index	0.27 ± 0.31	0.26 ± 0.43	0.9189
Percent diameter stenosis (% DS)			
Before intervention	100	100	—
After intervention	15.85 ± 6.33	34.16 ± 8.46	< 0.0001
At follow-up	36.38 ± 24.78	54.08 ± 25.67	0.0031
% DS at follow-up ≥50%	29.41%	44.74%	0.5150

Data presented are mean value ± SD or percent of lesions.

tended to be lower in the Wallstent group, this difference did not achieve statistical significance.

Discussion

Our study showed that implantation of the grossly oversized Wallstent can be safely and successfully performed in patients with total coronary occlusion. Furthermore, after successful delivery of the stent, angiographic success, as defined by <30% residual diameter stenosis, can be achieved in all cases. Despite the propensity to reocclusion of lesions in this group, Wallstent deployment resulted in a low risk of acute or subacute stent thrombosis and a low rate of restenosis and reocclusion at 6-month follow-up. Thus, our policy of oversized Wallstent implantation resulted in a resetting of vessel size and a tendency toward a lower restenosis rate than that of occlusions undergoing standard balloon angioplasty.

Reasons for high delivery success rate and safety. The high delivery success rate may be explained by the low profile (1.57 mm) and longitudinal flexibility of the Wallstent, which allow successful negotiation of tortuous vessels. Furthermore, the protective rolling membrane of the Wallstent prevents migration of the stent during negotiation of the target lesion, and the fine mesh structure of the device may prevent distal embolization of friable tissue from the recanalized total occlusion after successful laser or balloon angioplasty. Although a previous study (33) of angioplasty with deliberately oversized balloons in coronary stenoses suggested that that procedure may result in a higher rate of acute complications, the self-expanding nature of the Wallstent and its fine mesh structure are probably also responsible (by providing support and scaffolding for the vessel wall) for the safe deployment of such grossly oversized stents in total occlusions.

Comparison with balloon angioplasty group. By comparing our results with those of a group of total occlusions undergoing coronary balloon angioplasty and 6-month quantitative angiographic follow-up in the same angiographic core laboratory, we were able to demonstrate that our policy of gross oversizing does indeed result in resetting of the vessel size to what is assumed to be its original state before disease. Furthermore, this oversizing results in a minimal lumen diameter after implantation that is significantly larger than the balloon angioplasty group reference diameter. Thus, despite the greater absolute and relative loss during follow-up of the Wallstent, the minimal lumen diameter at follow-up was significantly higher and the percent stenosis lower in this group. Although the resulting reduction in the categoric restenosis rate did not achieve statistical significance, this may have been due to the small number of lesions in our Wallstent group. The loss index was almost identical in both groups, ~0.26 compared to a reported loss index of 0.50 for nonoccluded stenoses (34,35), suggesting that although the vessel reaction is similar after either balloon dilation or grossly oversized stent implantation, the relative fibroproliferative response in total occlusions is only half that seen in nonoccluded stenoses (34). This observation may represent significant differences in the underlying pathologic substrate, with total occlusions having less normal vessel wall and vessel media with which to mount a substantial fibroproliferative response (36,37). Alternatively, differences in elastin content may result in less chronic recoil and vessel remodeling in successfully dilated occlusions (36,37).

Comparison with other stents for the treatment of total occlusions. Previous studies (38–41) have also examined stent implantation for the treatment of total coronary occlusions as elective therapy or as therapy for suboptimal results or for acute or threatened vessel closure. Depending on the indication and type of stent used, follow-up angiographic restenosis rates have varied from 24% to 57%; the highest rate was obtained with the Gianturco-Roubin stent used in bailout situations. Our results compare favorably with these previously published data, and we believe that the Wallstent has some additional advantages over other stent designs in total coronary occlusions. These include the customized length of up to 42 mm, which enables full coverage of the totally occluded lesion and avoids multiple stenting, which is more time-consuming and is also more likely to result in subacute thrombosis (42). The larger expanded diameter of up to 6.0 mm also allows implantation of the grossly oversized Wallstent and resetting of the previously occluded vessel to its original condition before disease. Additionally, the high flexibility of the Wallstent allows more natural bending and tortuosity, factors that may be more favorable to dynamic

coronary flow. The self-expanding characteristics of the stent may play a role in preserving the large initial gain during follow-up by exerting a persisting strong radial force.

Limitations of study. Our study has several limitations: 1) Because our study numbers are small, the data need to be confirmed by larger multicenter studies. 2) We used an unmatched control group of lesions undergoing successful balloon angioplasty and quantitative angiographic follow-up for comparison. Differences in study patients and procedural characteristics between the Wallstent and balloon angioplasty groups may have exerted some influence on clinical and angiographic outcome. For example, there are significant differences between the left anterior descending and right coronary arteries in local flow dynamics, vessel geometry, external compressive forces (43) and propensity to restenosis (44). The predominance of right coronary artery lesions in our stent group may have had a substantial influence on the subsequent risk of occlusion and restenosis. Although there was a greater incidence of TIMI grade 0 lesions in the stent group, there is no evidence to suggest that these lesions are either more or less prone to restenosis than TIMI grade 1 lesions (3). Similarly, although patients in the Wallstent group received anticoagulant therapy for 3 months after intervention, there is no evidence to suggest that this treatment may have led to a reduction in restenosis (45).

Clinical implications. Recanalization of total occlusions remains limited by a higher restenosis rate than that seen after successful dilation of nonocclusive stenoses. Our study suggests not only that implantation of the grossly oversized new Wallstent is feasible and safe but that the resulting mechanical remodeling of the vessel can improve local flow dynamics with a resulting low incidence of subacute occlusion and prevention of late elastic recoil enabling increased accommodation of late lumen loss during follow-up. Our results need to be confirmed in larger, multicenter, randomized studies but suggest that a policy of implantation of the grossly oversized Wallstent in patients with total occlusion will result in a lower angiographic restenosis rate and improved clinical outcome. Adoption of a policy of gross oversizing with more rigid, balloon-expandable stents, such as the Palmaz-Schatz stent, may be entirely inappropriate and unsafe. Thus, the implications of our study should be limited to the new self-expanding, less shortening Wallstent. Finally, because the Wallstent is a fine mesh stent, performing angioplasty to a side branch through it is technically very difficult. Furthermore, even if angioplasty were performed for disease in a side branch before stent deployment in the main vessel, difficulties would be encountered if restenosis occurred. Additionally, a certain amount of intimal hyperplasia is anticipated inside the Wallstent; thus, if a side branch has a significant untreated narrowing at its origin before stent implantation in the main vessel, there is a significant risk of disease progression during follow-up. Because of these considerations the Wallstent was used predominantly in the right coronary artery in this and previous studies (4), and its use will be more limited in the left coronary system.

Conclusions. The safety and feasibility of implantation of the oversized Wallstent for the treatment of chronic total coronary occlusions were demonstrated. Oversized Wallstent implantation, with full coverage of the lesion length, ensures resetting of the vessel size to its original caliber before disease in patients with chronic total occlusion and allows greater accommodation of intimal hyperplasia and chronic vessel recoil. In comparison with conventional balloon angioplasty, oversized Wallstent implantation conveys a more favorable short- and long-term clinical and angiographic outcome.

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Chapter 10

Six-month clinical and angiographic outcome of the new less shortening Wallstent in native coronary arteries

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Six-Month Clinical and Angiographic Outcome of the New, Less Shortening Wallstent in Native Coronary Arteries

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Background The new, less shortening, self-expanding Wallstent is characterized by longitudinal flexibility, a protective membrane, a low profile, and a customized range of diameters (3.5 to 6.0 mm). The recent modification of the braiding angle of the Wallstent has resulted in a new device with less shortening on expansion and a concomitant reduction in radial force. We hypothesized that the enforced mechanical remodeling produced by the selection of an oversized Wallstent might result in improved accommodation of subsequent reactive intimal hyperplasia and prevention of chronic recoil of the vessel.

Methods and Results To prove this hypothesis, we recently implanted 44 new, less shortening Wallstents in 35 native coronary arteries in 35 patients with acute or threatened closure after balloon angioplasty, according to a strategy of oversizing of Wallstent diameter and complete coverage of the lesion length. The initial and 6-month follow-up angiograms were analyzed with a computer-based quantitative coronary angiography (QCA) system. Acute gain (minimal luminal diameter [MLD] post minus MLD pre) and late loss (MLD post minus MLD at follow-up) were examined. Stent deployment was successful in 44 of 44 attempts (100%). Nominal stent diameter used was 1.40 mm larger than the maximal vessel diameter. One patient (3%) with a dilated but unstented lesion proximal to the stented segment sustained a subacute occlusion on day 1 associated with myocardial infarction. Event-free survival at 30 days after stent implantation was 97% (34 of 35 patients). Of the 34 patients eligible for 6-month angiographic follow-up, 3 who were asymptomatic declined repeat angiography. MLD (and percent diameter stenosis [% DS]) changed from 0.83±0.50 mm (72%) pre through 3.06±0.48 mm (15%) post to 2.27±0.74 mm (28%) at follow-up. Acute gain was 2.23±0.63 mm, and late loss was 0.78±0.61 mm. Angiographic restenosis (>50% DS) was observed in 5 of 31 patients (16%) at 6 months, all of whom underwent repeat angioplasty. Thus, the overall event-free survival at 6-month follow-up was 83% (29 of 35 patients).

Conclusions The oversized Wallstent implantation with complete coverage of the lesion length conveyed a favorable 6-month clinical and angiographic outcome. The large acute gain obtained by the Wallstent afforded greater accommodation of the subsequent late loss. The enforced mechanical remodeling by oversized new Wallstents may result in prevention of acute and chronic recoil of the vessel wall and subsequently a lower restenosis rate at follow-up. (***Circulation*. 1996; 93:2114-2120.**)

Key Words • arteries • stents • coronary disease • restenosis • angiography • angioplasty

The new, less shortening, self-expanding Wallstent is characterized by longitudinal flexibility, a protective membrane, a low profile, and a customized range of diameters (3.5 to 6.0 mm) and lengths (12 to 42 mm). The recent modification in braiding angle has resulted in a new device with less shortening on expansion and a concomitant reduction in radial force.[1,2] The fine mesh structure of the Wallstent provides maximal scaffolding to the vessel wall, which has previously encouraged extensive implantation of the original Wallstent prototype for the treatment of friable coronary vein grafts and a limited and less favorable implantation experience in native coronary arteries in the late 1980s.[3-8] However, the safety and efficacy of implantation of the new, less shortening Wallstent in native coronary arteries is unknown. While we have long recognized that the greater the gain, the greater the loss,[9] we also recognize that achieving a greater acute luminal gain allows greater subsequent accommodation of loss (in accordance with simple geometry and percent tax laws), and thus, although the absolute loss is greater, the net gain is also greater. Additionally, a recent multicenter stent study using a Palmaz-Schatz stent matched to vessel size demonstrated that the greater initial luminal gain contributed to a significantly lower restenosis rate in the stented group compared with the balloon angioplasty group.[10] We hypothesized that implantation of the oversized new Wallstents in native coronary arteries (a policy of resetting the vessel size into undiseased condition) would produce enforced mechanical remodeling of the coronary vessel with subsequent reduction in subacute occlusion and improved accommodation of reactive intimal hyperplasia.

To test this hypothesis, we recently implanted 44 Wallstents into 35 native coronary arteries in 35 patients with acute or threatened closure post coronary balloon angioplasty. Wallstents were selected to produce oversizing of the stent diameter and complete coverage of the lesion length. QCA measurements were made pre primary balloon angioplasty and post Wallstent implan-

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Selected Abbreviations and Acronyms

CAAS = coronary angiography analysis system
% DS = percent diameter stenosis
IRD = interpolated reference diameter
MLD = minimal luminal diameter
MVD = maximal vessel diameter
QCA = quantitative coronary angiography

tation and the follow-up angiogram by use of a QCA analysis system (CAAS II).

Methods

Study Patients

To determine the feasibility and safety of deployment of the oversized new, less shortening Wallstent, we deployed 44 Wallstents in 35 native coronary arteries in 35 patients. Patients who had acute or threatened closure post coronary intervention with a dissected lesion length of >18 mm, an MVD of >3.0 mm, absence of significant disease in the major side branches, and absence of clinical contraindication to anticoagulation were included in the study.

Study End Points and Definition

The primary clinical end point of the study was the occurrence of any of the following adverse cardiac events: acute or subacute stent thrombosis, repeat coronary intervention, coronary bypass surgery, myocardial infarction, or death. Procedural success was defined as technically successful deployment of the stent in the absence of an adverse cardiac event. Angiographic success was defined as a <30% residual diameter stenosis after final deployment of the stent. Stent thrombosis was defined as a clinical event leading to catheterization that identified stent thrombosis within 14 days of deployment. Long-term clinical outcome included all cardiovascular events occurring within 6 months of stent deployment. Angiographic restenosis was defined as luminal narrowing ≥50% diameter stenosis at follow-up.

Criteria of Acute and Threatened Vessel Closure

Post balloon angioplasty (primary coronary angioplasty), lesion morphology was categorized according to the dissection criteria proposed by Huber et al,[11] and coronary flow distal to the lesion was classified according to the TIMI criteria.[12] Acute occlusion was defined as TIMI 0 flow. Threatened closure was defined as TIMI 1, 2, or 3 flow with visible dissection type C, D, E, or F or as dissection type A or B and TIMI 1, 2, or 3 flow with a residual diameter stenosis of >50%.[11,12]

Stent Implantation

Balloon angioplasty and stent deployment were performed according to standard clinical practice by the femoral approach at the Thoraxcenter (Rotterdam, Netherlands). Recent intracoronary ultrasound studies reported that atherosclerotic plaque is frequently present even in angiographically normal proximal reference segments in patients with significant coronary stenosis.[13,14] We therefore used the MVD from on-line QCA, which would be expected to be closer to the original vessel diameter in the nondiseased condition compared with the more traditional use of the IRD for stent sizing. After determination of the MVD on the diameter function of the on-line QCA analysis system (in millimeters), a Wallstent with a nominal diameter of 1.0 mm greater than the MVD and nominal length 5 to 10 mm longer than the lesion length was selected (see Fig 1). Of the 44 stents used in 35 lesions, 3 were 4 mm in diameter, 11 were 4.5 mm in diameter, 10 were 5 mm in diameter, 15 were 5.5 mm in diameter, and 5 were 6 mm in diameter. Of the 44 stents, 3 were 18 mm long, 26 were 23 to 28 mm long, 8 were 35 mm long, and 7 were 42 mm long. Twenty-two patients received a single Wallstent, 7 received two Wallstents, and 1 had three Wallstents implanted. During the primary balloon angioplasty, the balloon diameter was 3.0±0.6 mm and the maximum inflation pressure was 10.6±3.1 atm. After delivery of the stent, high-pressure intrastent balloon inflations (14.2±3.3 atm) using balloon diameters of 4.0±0.6 mm to optimize stent expansion were performed in all 35 patients.

Anticoagulant Therapy

At the beginning of the procedure, patients were given an intravenous bolus dose of 10 000 IU heparin and subsequently 5000 IU as required to maintain the activated clotting time >300 seconds throughout the procedure. All patients received 100 mg/d aspirin. The postintervention anticoagulant regimen was conventional[15]: 1 hour after

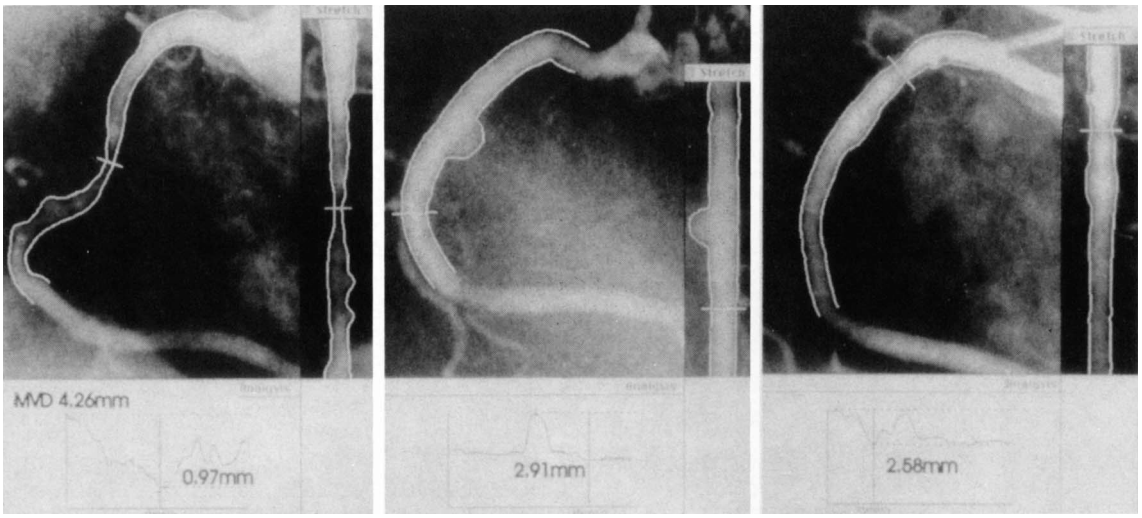

FIG 1. QCA of the right coronary artery revealed that MLD was 0.97 mm, MVD was 4.26 mm, and lesion length was 30.0 mm (left). A Wallstent (5.5 mm in diameter and 35 mm long) that was 1.24 mm greater than the MVD was deployed, and partial contrast extravasation caused by balloon rupture was observed (middle). At 6-month follow-up, MLD decreased to 2.58 mm associated with a 14% residual DS; however, the extravasation was restored and restenosis was not observed (right).

removal of the femoral sheath, an intravenous heparin infusion was commenced to maintain the activated partial thromboplastin time between 70 and 90 seconds until oral anticoagulant therapy (warfarin) had achieved a prothrombin time international normalized ratio of 2.5 to 3.5. Warfarin was prescribed for 3 months post stent implantation, and aspirin indefinitely.[16]

QCA Analysis

The new version of the computer-based CAAS (CAAS II)[16] was used to perform both the on-line QCA analysis (for immediate guidance of stent sizing in the catheterization laboratory) as well as the subsequent off-line cinefilm analysis. In the CAAS analysis, which has previously been described elsewhere,[17-23] the entire cineframe, 18×24 mm, is digitized at a resolution of 1329×1772 pixels. Correction for pincushion distortion is performed before analysis. Boundaries of a selected coronary segment are detected automatically. The absolute diameter of the stenosis (in millimeters) is determined by use of the guiding catheter as a scaling device.[24] To standardize the method of analysis of the initial and follow-up angiograms, the following measures were taken: all study frames selected for analysis were end-diastolic to minimize motion artifact, and arterial segments were measured between the same identifiable branch points after the administration of isosorbide dinitrate.[25,26]

QCA Parameters

Acute gain and late loss represent the improvement in MLD achieved at intervention (MLD post stenting minus MLD pre) and the changes at follow-up (MLD post stenting minus MLD at follow-up), respectively. Net gain (gain minus loss), net gain index (net gain divided by IRD pre), relative loss (loss divided by IRD pre), and loss index (loss divided by gain) were studied. Acute stent recoil (MLD during intrastent balloon inflation minus final MLD post stenting) and percent acute stent recoil (acute recoil divided by MLD during intrastent balloon inflation) were measured.[27]

Results

Clinical Characteristics

The baseline clinical characteristics of the 35 patients are provided in Table 1. Thirty of the patients were men, and the mean age was 60±9 years (range, 40 to 76 years). Twenty-seven patients had stable angina, and 8 had unstable angina.[28] Of the 8 patients with unstable angina, 5 had Braunwald type II and 3 had type III.[28]

Angiographic Characteristics

The angiographic characteristics of the treated lesions are given in Table 2. Of 35 lesions, 22 were in the right coronary artery, 11 were in the left anterior descending coronary artery, and the remaining 2 were in the circumflex coronary artery. Seven of the lesions were ostial, and 16 were at sites of a bifurcation. Pre balloon angioplasty, the lesions were categorized according to the American College of Cardiology/American Heart Association Task Force criteria.[29] Of the 35 lesions, 1 was type A, 22 were type B, and the remaining 12 were type C. Post primary balloon angioplasty and before Wallstent implantation, 1 lesion had a type A dissection, 6 a type B dissection, 24 a type C dissection, 2 a type D dissection, and 2 a type F dissection.[11] TIMI flow[12] was grade 0 in 2 lesions, grade 2 in 1 lesion, and grade 3 in 32 lesions. Intracoronary thrombus (intraluminal filling defect on angiography) was evident in 8 lesions.[30]

TABLE 1. Clinical Characteristics of 35 Patients

	No.
Male sex	30
Ischemic syndrome	
Stable angina pectoris*	27
Unstable angina pectoris*	8
Prior myocardial infarction	13
Prior balloon angioplasty	13
Prior coronary bypass surgery	1
Coronary risk factors	
Hypercholesterolemia	10
Systemic hypertension	10
Cigarette smoking	15
Diabetes	3

*Angina pectoris classification.[28]

Clinical Outcome

Stent deployment was successful in 44 of 44 stents (100%) in 35 patients. Fig 2 shows the clinical outcome of the 35 patients. One patient with a dilated but unstented lesion proximal to the stented segment sustained a subacute occlusion on day 1 associated with a Q-wave myocardial infarction (creatine phosphokinase, 1840 IU/L) and was subsequently treated by proximal implantation of a Palmaz-Schatz stent. The event-free survival at 30-day follow-up was 97% (34 of 35 patients). Of the 34 patients eligible for 6-month angiographic follow-up, 3 who were asymptomatic declined repeat angiography. Angiographic restenosis (>50% DS) was

TABLE 2. Angiographic Lesion Characteristics of 35 Lesions

	No.
Location of lesions, RCA/LAD/LCx	22/11/2
Portion of lesions in artery stented	
Ostial site	7
Bifurcation site	16
Middle segment	12
Modified AHA/ACC classification*	
Type A	1
Type B1	8
Type B2	14
Type C	12
Type of dissection before stent†	
Type A	1
Type B	6
Type C	24
Type D	2
Type E	0
Type F	2
TIMI flow before stent‡	
TIMI 0	2
TIMI 1	0
TIMI 2	1
TIMI 3	32
Thrombus before stent§	8
Reason for stenting	
Threatened closure	33
Acute complete occlusion	2

LAD indicates left anterior coronary artery; RCA, right coronary artery; and LCx, left circumflex coronary artery.
*AHA/ACC task force.[29]
†Dissection classification.[11]
‡TIMI flow.[12]
§Presence of thrombus.[30]

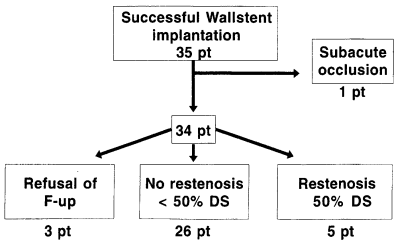

FIG 2. Flow chart of outcome after Wallstent implantation in native coronary arteries. pt indicates patient; F-up, follow-up angiogram.

observed in 5 of 31 patients (16%) at 6 months, all of whom underwent repeat angioplasty. Thus, the overall event-free survival at 6-month follow-up was 83% (29 of 35 patients).

QCA Analysis

Table 3 shows the relationship between the nominal diameter and length of the Wallstents selected and QCA analysis results. The average nominal diameter of the Wallstents used was 1.40 mm greater than the MVD and 9.4 mm longer than the lesion length. Fig 3 provides an example of the serial angiographic outcome in an individual patient; Fig 4 displays the results of serial luminal diameter changes measured by QCA analysis for the study population. MLD was 0.83±0.50 mm pre intervention. Post stent implantation, high-pressure intrastent balloon dilatation of 14.2±3.3 atm with balloons 4.0±0.6 mm in diameter was performed in all lesions. Implantation of the Wallstent increased the MLD to 3.06±0.48 mm.

Acute stent recoil and percent acute stent recoil were 0.52±0.31 mm and 14±8%. Acute gain was 2.23±0.63 mm, late loss 0.78±0.61 mm, net gain 1.47±0.92 mm, net gain index 0.55±0.37, relative loss 0.29±0.23, and loss index 0.38±0.37. Angiographic success (<30% residual diameter stenosis) was achieved in all lesions (100%). Of the 31 patients who underwent follow-up angiography, 5 had angiographic restenosis, yielding an angiographic restenosis rate of 16% (5 of 31 patients). Fig 5 shows the sequential changes in % DS for the study population. Average % DS decreased significantly from 72% pre intervention to a final residual value of 28% at follow-up.

TABLE 3. Quantitative Coronary Angiographic Results of Wallstent Implantation

MVD, mm	3.69±0.67
Nominal Wallstent diameter, mm	5.09±0.59
Nominal stent diameter minus MVD, mm	1.40±0.79
Lesion length, mm	26.2±8.4
Wallstent length, mm	35.6±16.0
Wallstent length minus lesion length, mm	9.4±6.2
MLD pre, mm	0.83±0.50
IRD pre, mm	2.92±0.73
Stent diameter/vessel diameter (IRD) pre ratio	1.84±0.49
MLD post, mm	3.06±0.48
IRD post, mm	3.61±0.46
MLD follow-up, mm	2.27±0.74
IRD follow-up, mm	3.13±0.68
Acute stent recoil, mm	0.52±0.31
% Acute stent recoil	14±8
Acute gain, mm	2.23±0.63
Late loss, mm	0.78±0.61
Net gain, mm	1.47±0.92
Net gain index	0.55±0.37
Relative loss	0.29±0.23
Loss index	0.38±0.37

Values are mean±SD.

Discussion

The novel findings of this study were as follows. (1) Delivery of the new, less shortening Wallstent to the target lesion can be achieved in a high proportion of cases (44 of 44 stents). (2) After delivery of the stent, angiographic success as defined by <30% residual diameter stenosis can be achieved with high-pressure intrastent balloon inflations in a high proportion of cases (35 of 35 lesions). (3) Despite the bailout indication, oversizing of the stent diameter and complete coverage of the lesion length resulted in a low risk of subacute stent thrombosis (3%) and subsequently conveyed a low restenosis rate at 6-month follow-up (16%).

Procedural Outcome

The high successful delivery rate of the Wallstent may be attributed to a number of factors. First, the 1.57-mm profile of the unexpanded Wallstent delivery system compares favorably with that of other stents, and thus, an intraprocedural exchange of the guiding catheter should rarely be necessary.[2] Second, the unconnected junctions of each filament of the Wallstent enhance the longitudinal flexibility of the stent to aid the negotiation of tortuous vessels. Third, the protective rolling membrane of the Wallstent prevents dislodgment of the stent off the delivery system during the delivery process to the target lesion. Fourth, the operators who implanted the stents have extensive previous experience with the Wallstent delivery system, which relative to other stents is user-unfriendly and has a longer learning curve.

Early Outcome

Previous studies of bailout stenting have been reported for the Gianturco-Roubin stent,[31-35] the Palmaz-Schatz stent,[36-40] the original Wallstent prototype,[7,8] and the new AVE Microstent.[41] These have been associated with a deployment success rate of 89% to 100%, a myocardial infarction rate of 4% to 43%, a coronary bypass surgery rate of 0% to 60%, and a subacute thrombosis rate of 7% to 16%. In the present study, 34 of 35 lesions had dissection types B, C, D, E, and F, with a lesion length of >18 mm after primary angioplasty; however, stenting was effective in tacking back the dissection flap and restoring TIMI 3 flow in all 35 lesions. Although 7 of the lesions had angiographic evidence of intracoronary thrombus before stenting, deployment of the Wallstent without the administration of intracoronary thrombolytic therapy resulted in a low subacute thrombosis rate (3%). Complete coverage of the dissection flaps (average stent length, 35.6 mm) and optimal stent expansion by high-pressure intrastent balloon inflation (14.2±3.3 atm) of the oversized new, self-expanding Wallstent are all factors that may have contributed to the low rate of subacute thrombosis and a low risk of early clinical events.[42]

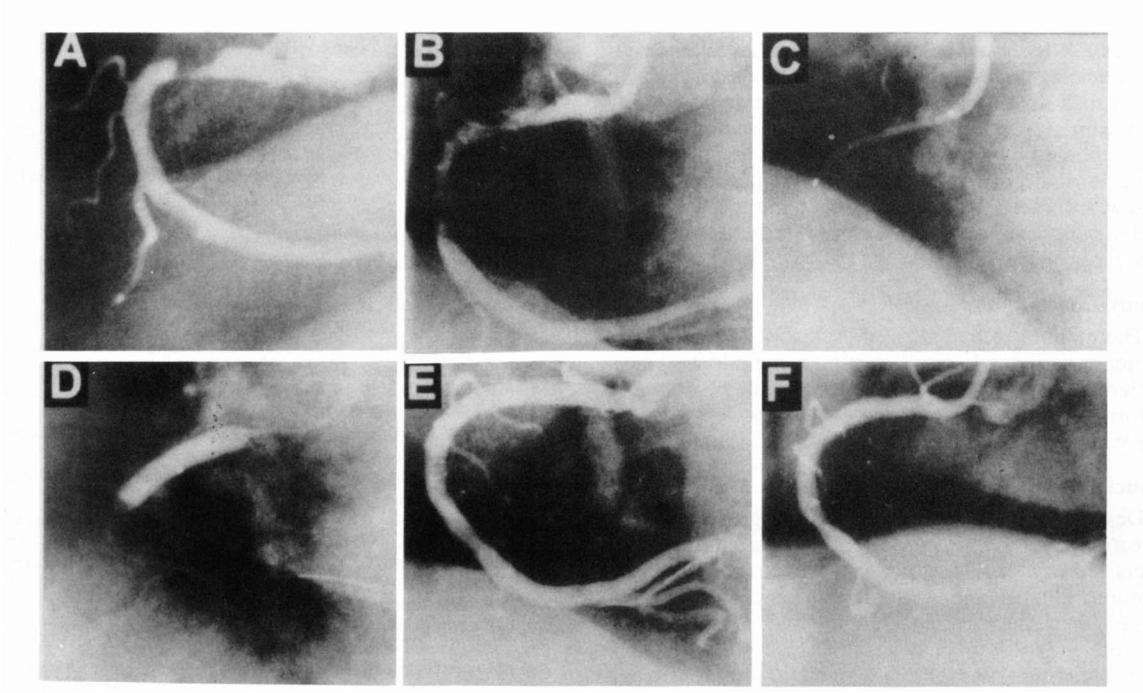

FIG 3. Coronary angiography of the right coronary artery in a patient with dissection after primary balloon angioplasty. Pre balloon angioplasty, the MLD was 0.71 mm, the IRD was 3.61 mm associated with 80% DS, and the MVD was 4.07 mm (A). Post balloon angioplasty, the lumen had enlarged; however, a type C dissection with TIMI 3 flow was present (B). A Wallstent (nominal diameter of 5.0 mm and 23 mm long) that was nearly 1.0 mm greater than the MVD was deployed, and the radiopaque stent markers can be seen during the deployment (C). Post stent balloon dilatation (4.0 mm×20 mm) at 16 atm was performed (D). Post Wallstent deployment, MLD was 3.71 mm, which was greater than IRD pre deployment (3.61 mm) associated with 9% residual diameter stenosis (E). Six-month follow-up angiography revealed no restenosis, with an MLD of 3.43 mm associated with a 19% DS (F).

Late Outcome

While the reported angiographic restenosis rates (≥50% DS at follow-up) have ranged from 21% to 53% for the Gianturco-Roubin stent,[31-35,43] 13% to 38% for the Palmaz-Schatz stent,[10,36-40,44,45] and 14% to 34% for the original Wallstent prototype,[3-5] the angiographic restenosis rate in this study was 16%. In our study, the oversized Wallstent resulted in larger MLD post stenting (3.06 mm) that was even greater than the reference vessel diameter pre intervention (2.92 mm). While in previous stent studies, acute luminal gain at stent implantation has ranged from 1.40 to 1.95 mm and late loss at follow-up from 0.65 mm to 0.92 mm associated with restenosis rates ranging from 22% to 38%,[10,16,39,44] in our study, acute luminal gain at the stent implantation was 2.23 mm and late loss at follow-up was 0.78 mm associated with a restenosis rate of 16%. The low loss index of 0.38 and large net gain index of 0.55 indicate that our policy of oversizing of the new Wallstent results in sufficient mechanical remodeling of the vessel to enable accommodation of the limited luminal loss and resultant low restenosis rate. Although the presence of dissection has not been found to convey a more favorable angiographic outcome after balloon angioplasty,[46] the vessels in which the internal elastic lamina has been disrupted before stent placement may be more predisposed to a greater initial luminal gain post stenting. The increased arterial distensibility resulting from significant dissections might also contribute to an improved long-term angiographic outcome in a stented vessel compared with a stented vessel without significant dissection. This may be one of the elements contributing to our more favorable loss index compared with that recently reported for elective stenting in the BENESTENT and STRESS

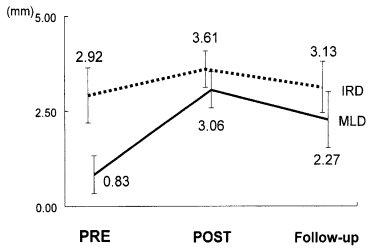

FIG 4. Changes of MLD and IRD in 35 lesions from pre procedure through stent implantation to 6-month follow-up. Post stent delivery, high-pressure intrastent balloon inflation (14.2± 3.3 atm) was performed in all 35 lesions.

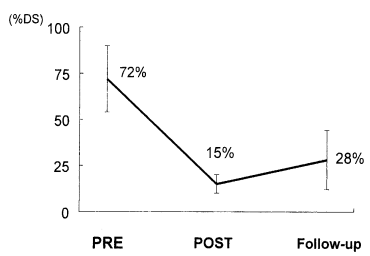

FIG 5. Changes in % DS from pre procedure to post stent implantation in 35 lesions. The % DS was 28% at follow-up.

studies.[10,16] It should be acknowledged that adoption of an oversizing policy with more rigid balloon-expandable stents such as the Palmaz-Schatz stent may be entirely inappropriate and unsafe, and the implications of our study should be limited to the self-expanding new Wallstent. Furthermore, it remains to be seen (a multicenter trial with the new Wallstent has been initiated) whether such a policy can be safely executed at other centers with less experience with the Wallstent.

Study Limitations

The number of patients reported in this early single-center experience is small, and further multicenter experience with this new stent design will be required before our policy of oversizing of the new, less shortening Wallstent can be recommended.

Conclusions

Despite the indication of bailout management and the selection of long, dissected lesions, implantation of the oversized new Wallstent conveys a favorable acute and 6-month clinical and angiographic outcome. The enforced mechanical remodeling by the oversized self-expanding Wallstent may result in prevention of subacute occlusion and chronic recoil of the vessel and subsequently improved restenosis rates at follow-up.

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Chapter 11

Acute clinical and angiographic results with the new AVE micro coronary stent in bailout management

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Am J Cardiol 1995;76:112-116

Acute Clinical and Angiographic Results With the New AVE Micro Coronary Stent in Bailout Management

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To determine the feasibility and safety of deployment of this new stent, we deployed 28 AVE Micro stents in 23 native coronary artery lesions in 20 patients who developed acute or threatened closure after balloon angioplasty (BA). Ten stents were deployed in the left anterior descending artery, 10 in the circumflex, and 8 in the right coronary artery. Luminal dimensions were measured using a computer-based quantitative coronary angiographic analysis system (CAAS II). Stent deployment was successful in 27 of 28 attempts (96%). In 1 patient with a threatened closure of the left anterior descending artery associated with proximal vessel tortuosity, attempted stent deployment was unsuccessful. The clinical course of the other 19 patients in whom stent deployment was successful was free of coronary reintervention, bypass surgery, and death. A myocardial infarction was observed in 2 patients (10%), in 1 of whom the stent was implanted within 24 hours after the onset of acute myocardial infarction, and in the other acute vessel occlusion was present for 58 minutes before stent implantation. No subacute occlusion was observed. Event-free survival at 30 days after stent implantation was 85% (17 of 20 patients). Minimal luminal diameter was 0.85 ± 0.57 mm before and 1.19 ± 0.66 mm after BA, 2.61 ± 0.39 mm during balloon inflation, 3.26 ± 0.46 mm during and 2.74 ± 0.51 mm after stenting, 3.43 ± 0.52 mm during balloon inflation after stenting (Swiss Kiss), and 2.85 ± 0.48 mm after Swiss Kiss. Average percent diameter stenosis was reduced from 69% before through 56% after BA to 17% after stenting. During the initial stent implantation, stent recoil was 0.52 ± 0.30 mm (16 ± 9% of minimal luminal diameter during stent inflation). A Swiss Kiss was performed in 14 stents with an average pressure of 14 ± 4 atm, and residual stenosis was reduced from 2.55 mm (21% diameter stenosis) to 2.85 mm (15% diameter stenosis) in these lesions. Angiographic success (<30% residual diameter stenosis) was achieved in all stented lesions. The results of this early experience would indicate that the new AVE Micro stent may be deployed with a high procedural success rate and a minimal learning curve. Implantation of the stent for the bailout management of failed BA can be achieved with a low incidence of adverse cardiac events and a high angiographic success rate.

(Am J Cardiol 1995;76:112–116)

One of the major risks associated with balloon angioplasty (BA) is acute or threatened closure of the coronary artery. When acute coronary occlusion persists after balloon dilatation, 20% to 40% of patients sustain a myocardial infarction and 4% to 8% of patients die.[1–4] Several nonrandomized studies have suggested that deployment of the Wallstent,[5,6] Gianturco-Roubin stent,[7–11] or Palmaz-Schatz stent[12–14] may be of value in bailout management[15,16] of acute or threatened closure after BA. A number of second generation stents have recently been developed and are currently entering the clinical arena. One of the most recently developed stents is the AVE Micro stent (see Figure 1). This study reports early experience with the AVE Micro stent in the clinical arena. Clinical events up to 30 days (to cover both the period of in-hospital events and period of risk of subacute thrombosis) are reported as well as the acute angiographic results. Quantitative angiographic measurements were obtained at 7 intraprocedural phases: before primary BA, during primary balloon inflation, after BA at the time of acute or threatened vessel closure, during stent inflation, after stent deployment, during high-pressure intrastent balloon inflation (Swiss Kiss), and finally after Swiss Kiss, using a quantitative coronary angiographic analysis system (CAAS II).

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METHODS

Patients: To determine the feasibility and safety of deployment of this new stent, we placed 28 AVE Micro stents in 23 native coronary artery lesions in 20 patients who developed acute or threatened closure after BA. The average age was 56 ± 7 years (range 45 to 68), and 17 patients were men. Thirteen patients had stable angina and the remaining 7 patients had unstable angina.[17] Of the 7 patients with unstable angina, 4 had Braunwald type II and 3 had type III angina.[17]

Criteria of acute and threatened vessel closure: After BA, lesion morphology was categorized according to the dissection criteria proposed by Huber et al,[18] and coronary flow distal to the lesion was classified according to the Thrombolysis in Myocardial Infarction trial (TIMI) criteria.[19] Acute occlusion was defined as TIMI 0 flow. Threatened closure was defined as TIMI 1, 2, or 3 flow,

with visible dissection type C, D, E, or F, or as dissection type A or B and TIMI 1, 2, or 3 flow with a residual diameter stenosis of >50%.[18,19]

Stent design: This short stent is characterized by a simple balloon-expandable deployment technique, and 0.008-inch stainless steel struts with moderate radiopacity and a zigzag structure. The metallic surface area in the expanded state has been found in vitro to be 8.4% for the stent with a 3.5 mm diameter. This stent is composed of 4 mm welded and unconnected segments providing a range of lengths from 4 to 16 mm (Figure 1).

Balloon angioplasty and stent implantation: BA and stent deployment (Figure 1) were performed according to standard clinical practice by the femoral approach at the Thoraxcenter (Rotterdam, The Netherlands). The coronary stents were delivered on a premounted balloon catheter. The size of the balloon is 0.25 mm larger than the stent diameter to allow for stent recoil. Selection of the nominal stent size was determined to match the vessel reference diameter obtained from on-line quantitative angiographic measurement. Of the 28 stents used in 23 lesions, 9 had a 3 mm diameter, and 15 had a 3.5 mm and 4 a 4 mm diameter. Of the 28 stents 7 were 4 mm in length, 17 were 8 mm, 2 were 12 mm, and 2 were 16 mm. During primary BA, the nominal balloon diameter was 2.98 ± 0.41 mm, and the maximal inflation pressure given was 9.3 ± 3.0 atm. After initial deployment of the stent, high-pressure inflations (14.6 ± 3.5 atm) to optimize stent expansion (Swiss Kiss) were obtained with balloons with 3.50 ± 0.55 mm nominal diameter.

Anticoagulant therapy: At the beginning of the procedure, patients were given an intravenous bolus dose of 10,000 IU of heparin, and subsequently 5,000 IU, as required, to maintain the activated clotting time of >300 seconds throughout the procedure. The postintervention anticoagulant regimen was conventional[20]: One hour after removal of the femoral sheath, a heparin intravenous infusion was begun to maintain the activated partial thromboplastin time between 70 and 90 seconds until oral anticoagulant therapy (warfarin) had achieved a prothrombin time international normalized ratio of 2.5 to 3.5. Warfarin was prescribed for 3 months after stent implantation, and aspirin indefinitely.[20]

Quantitative coronary angiographic analysis: The new version of the CAAS II analysis[21,22] was used to perform quantitative analysis. In the CAAS II analysis, which has previously been described elsewhere,[22–24] the entire cineframe of 18 × 24 mm is digitized at a resolution of 1,329 × 1,772 pixels. Correction for pincushion distortion is performed before analysis. Boundaries of a selected coronary segment are detected automatically. The absolute diameter (mm) of the stenosis is determined using the guiding catheter as a scaling device. To standardize the method of angiographic analysis, the following measures were taken: All study frames selected for analysis were end-diastolic to minimize motion artifact, and arterial segments were measured between the same identifiable branch points at each stage of the procedure.

TABLE I Angiographic Lesion Characteristics of 23 Narrowings

	Number
Location of narrowings	
Left anterior coronary artery	8
Right coronary artery	6
Left circumflex coronary artery	9
Portion of artery stented	
Ostial or major bifurcation site	9
Middle segment	14
Modified AHA/ACC classification*	
Type A	2
Type B1	6
Type B2	9
Type C	6
Type of dissection before stent†	
Type A	2
Type B	4
Type C	8
Type D	1
Type E	7
Type F	1
TIMI flow before stent‡	
TIMI 0	1
TIMI 1	0
TIMI 2	8
TIMI 3	14
Thrombus before stent§	7
Reason for stenting	
Threatened closure	22
Acute complete occlusion	1

*American Heart Association/American College of Cardiology Task Force.[25]
†Dissection classification.[18]
‡Thrombolysis in Myocardial Infarction trial flow.[19]
§Presence of thrombus.[26]

Study end points and definitions: The primary clinical end point of the study was the occurrence of any of the following adverse cardiac events: acute or subacute stent thrombosis, repeat intervention, coronary artery bypass surgery, myocardial infarction, or death. Procedural success was defined as technically successful deployment of the stent in the absence of an adverse cardiac event. Angiographic success was defined as a <30% residual diameter stenosis after final deployment of the stent. Subacute thrombosis was defined as a stent thrombosis within 14 days of deployment. Acute clinical outcome included all cardiovascular events occurring within 1 month of stent deployment.

Statistical analysis: A paired Student's *t* test was used to compare sequential changes at the same segment in the same patients. A p value <0.05 was considered significant.

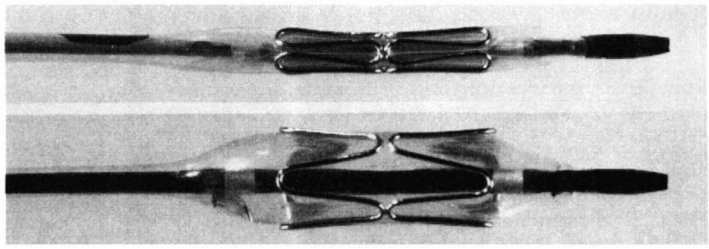

FIGURE 1. An 8 mm AVE Micro stent. The AVE Micro stent is a premounted balloon-expandable stainless steel stent composed of 4 mm welded or unconnected segments.

RESULTS

Lesion characteristics: Angiographic characteristics of the treated lesions are listed in Table I. Of 23 lesions, 8 lesions were in the left anterior descending coronary arteries, 6 were in the right coronary arteries, and the remaining 9 were in the circumflex coronary arteries. Four of the lesions were ostial and 5 were at sites of major bifurcation. Before BA, the lesions were categorized according to the American Heart Association/American College of Cardiology Task Force criteria.[25] Of the 23 lesions, 2 were type A, 15 were type B, and the remaining 6 were type C. After primary BA, at the time of acute or threatened vessel closure, 2 lesions had a type A dissection (with >50% diameter stenosis), 4 a type B dissection (with >50% diameter stenosis), 8 a type C, 1 a type D, 7 a type E, and 1 a type F dissection.[18] At this present phase, TIMI flow[19] was grade 0 in 1 lesion, grade 2 in 8, and grade 3 in 14 lesions, and the angiographic appearance of intracoronary thrombus (intraluminal filling defect) was present in 7 lesions.[26]

Procedural outcome: Stent delivery was possible in 27 of 28 stents (96%). In 1 patient, the stent could not be advanced beyond an oblique curved branch point to the target stenosis in the midleft anterior descending artery. The unexpanded stent was withdrawn through the guiding catheter without difficulty and the patient was managed by emergency bypass surgery, after which the patient had no further event. In a second patient, a 12 mm stent was deployed at the origin of the left anterior descending artery. During the process of stent inflation, the proximal 4 mm unit of the 12 mm stent migrated proximally into the mainstem of the left coronary artery. This 4 mm unit was then expanded fully in the left mainstem and the patient had an uneventful clinical course.

In-hospital events: One patient in whom stent delivery was unsuccessful underwent emergency bypass surgery and had a normal postoperative recovery. The clinical course of the other 19 patients in whom stent deployment was successful was free of coronary reintervention, bypass surgery, and death. A myocardial infarction was observed in 2 patients (10%), in 1 of whom the stent was implanted within 24 hours after the onset of acute myocardial infarction, and in the other patient acute vessel occlusion was present for 58 minutes before stent implantation. A femoral hemorrhage and hematuria requiring blood transfusion were observed in 1 patient (5%). All patients remained event free after hospital discharge, and thus the event-free survival at 30 days follow-up was 85% (17 of 20 patients).

Quantitative angiographic analysis: Quantitative angiographic analysis provided measurements of luminal diameter at each procedural phase. Minimal luminal diameter (MLD) was seen to change from 0.85 ± 0.57 mm before primary BA to 1.19 ± 0.66 mm after BA at the time of dissection. Implantation of the AVE Micro stent increased the MLD to 2.74 ± 0.51 mm ($p < 0.001$). The changes in MLD from before primary BA through stent implantation to after Swiss Kiss are shown in Figure 2. In 14 lesions requiring poststent balloon dilatation (Swiss Kiss), the MLD increased significantly from 2.55 ± 0.52 mm (before Swiss Kiss) to 2.85 ± 0.48 mm (after Swiss Kiss, $p < 0.01$). The absolute value of the acute stent recoil in the initial implantation (MLD during stent inflation, MLD after stent) was 0.52 ± 0.30 mm, and the acute recoil ratio of this stent (MLD during stent inflation, MLD after/during stent inflation) was 16 ± 9%. An example of the stent implantation in the dissection after BA can be seen in Figure 3. Angiographic success was achieved in all lesions with successful deployment of the stent. Thus, the angiographic success rate of all lesions attempted was 96% (22 of 23 lesions). Average percent diameter stenosis decreased significantly from 69% before intervention to a final residual value of 17% after stent deployment. Figure 4 shows the sequential changes in percent diameter stenosis. Performance of a Swiss Kiss in 14 lesions achieved a further reduction in residual percent diameter stenosis from 21% after AVE to 15% after Swiss Kiss ($p < 0.05$).

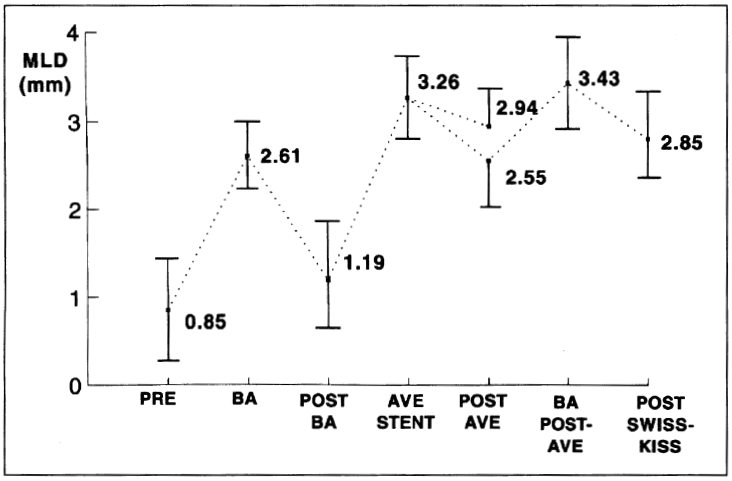

FIGURE 2. Changes in minimal luminal diameter (MLD) in 23 lesions from before (PRE) the procedure through stent implantation to the performance. Swiss Kiss (see text) was performed in 14 lesions. Minimal luminal diameter improved significantly after (POST) AVE stent implantation and after the performance of a Swiss Kiss (14.6 ± 3.5 atm). BA = balloon angioplasty.

DISCUSSION

The key findings of this early experience were as follows: (1) Delivery of the AVE Micro stent to the target lesion can be achieved in a high proportion of cases (22 of 23 lesions). (2) After delivery of the stent (22 lesions), angiographic success as defined by <30% residual diameter stenosis can be achieved in a high proportion of cases (22 of 22). (3) Acute recoil after dilatation of the Micro stent in vivo compares favorably with other stents.[27,28] (4) Despite the bailout indication for stenting, deployment of the Micro stent resulted in a low risk of acute or subacute stent thrombosis (0 of 22 stented lesions).

Successful delivery of the Micro stent may be attributed to 2 characteristics of the stent design. First, the 1.65 mm profile of the Micro stent in its

unexpanded balloon-mounted state compares favorably with that of previous stents, and thus an intraprocedural exchange of the guiding catheter or guidewire should rarely be necessary. Second, the unconnected junctions of the modules and the 4 and 8 mm length of the individual modules provide the stent with hinge joints and very limited rigid segments to aid the negotiation of tortuous vessels. Furthermore, these 2 features, in conjunction with the primarily longitudinal orientation of the stent struts, should permit passage of an additional Micro stent through a proximally placed stent when necessary. The proximal migration during inflation of a 4 mm segment of an unconnected 12 mm stent into the left mainstem in 1 of our patients, indicates that only connected (welded) units of the AVE Micro stent should be placed in ostial lesions to prevent such an occurrence.

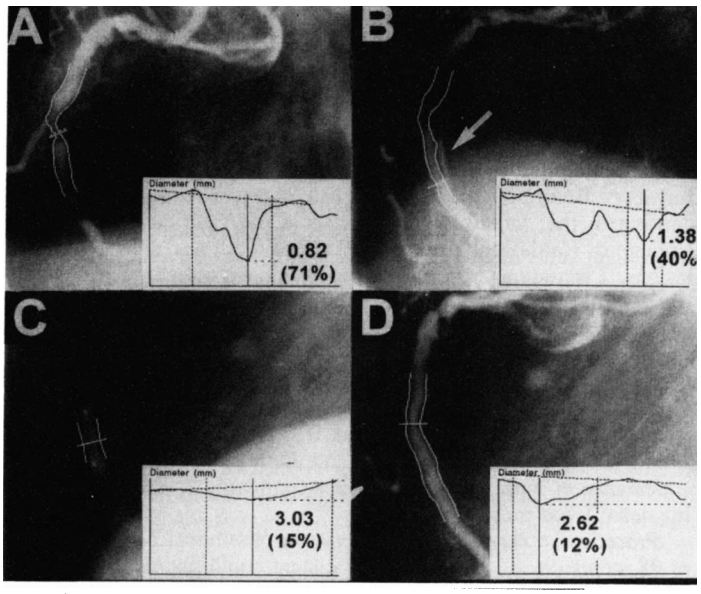

FIGURE 3. Coronary angiography of the right coronary artery in a patient with dissection after primary balloon angioplasty. Before balloon angioplasty, the minimal luminal diameter (MLD) was 0.82 mm *(A)*. After balloon angioplasty, the MLD increased to 1.38 mm; however, a type C dissection with Thrombolysis in Myocardial Infarction trial III flow was present *(B)*. Two AVE Micro stents (each 3 mm in diameter and 8 mm in length) were deployed and the moderately radiopaque stent struts can be seen during inflation of the stent *(C)*. After stent deployment, the MLD improved to 2.62 mm with resolution of the dissection *(D)*.

Although 21 of 23 lesions had dissection type B, C, D, E, and F after primary BA, stenting was effective in tacking back the dissection flap and restoring TIMI 3 flow in all lesions stented. Although 7 of the lesions with threatened closure had angiographic evidence of intracoronary thrombus before stenting, deployment of the Micro stent without the administration of intracoronary thrombolytic therapy resulted in neither acute nor subacute thrombosis during follow-up. The absence of stent thrombosis may relate to the low metallic surface area of the Micro stent (8.4% for the 3.5 mm stent in the expanded state) and the optimal expansion of the stent (<30% residual diameter stenosis in all stented lesions), with the additional performance, when necessary, of a Swiss Kiss.[29]

Two of our patients (10%) had significantly elevated creatine phosphokinase levels and electrocardiographic changes in myocardial infarction. In 1 of these 2 patients, stent implantation was performed within 24 hours of the onset of an acute Q-wave myocardial infarction, and the patient became asymptomatic after stenting and creatine phosphokinase levels continued to decline after stenting without a further increase. In the other patient, acute vessel closure had been present for 58 minutes before stent deployment. This patient had no further chest pain after stent implantation and the peak creatine phosphokinase level in this patient was 720 IU/L. Lincoff et al[9] indicated that peak creatine phosphokinase levels directly related to the time of stent placement after the onset of vessel closure and significant creatine phosphokinase elevation was frequently observed when vessel closure persisted for >49 minutes. Thus, the elevated creatine phosphokinase levels in our 2 patients were believed to reflect their clinical events before stent deployment rather than the occurrence of an acute or subacute thrombosis after stenting.

Both single center and multicenter observational series of bailout stenting have been reported for the Wallstent,[6] Palmaz-Schatz stent,[7–11] and Gianturco Roubin stent.[12–14] These have been associated with a deployment success

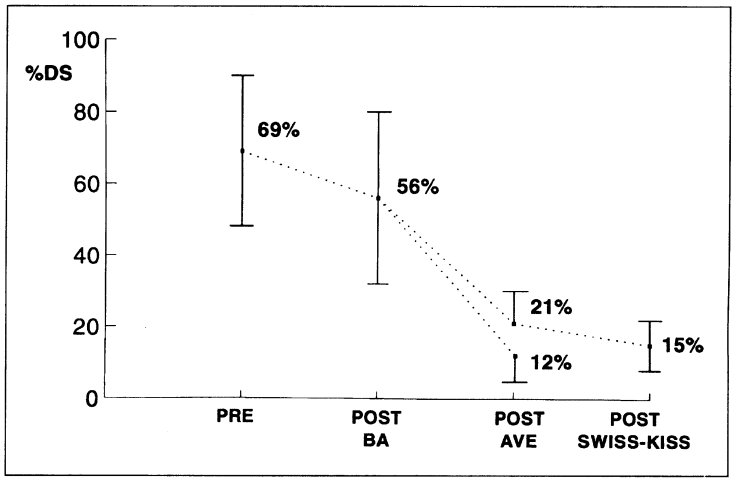

FIGURE 4. Changes in percent diameter (%DS) stenosis from before (PRE) the procedure to after (POST) stent implantation in 23 lesions. A Swiss Kiss with high pressure (14.6 ± 3.5 atm) was performed in 14 lesions and the percent diameter stenosis improved from 21% to 15%. BA = balloon angioplasty.

rate of 89% to 98%, a myocardial infarction rate of 4% to 43%, a bypass surgery rate 1% to 60%, a subacute thrombosis rate 7% to 16%, and a mortality rate of 1% to 7%. More recently, a number of new stents have become available for clinical evaluation; these include the Cordis and Advanced Cardiovascular Systems stents. Whereas the structural design of these stents can be grouped into 2 categories of mesh stents and coil stents, the AVE Micro stent represents a new design concept. Given their fundamental differences in structural design (profile in the unexpanded state, longitudinal flexibility, mechanism of deployment, metallic surface area in the expanded state, interstrut distance, strut orientation, and radial strength), each stent will have to prove its own safety and efficacy for each clinical indication in prospective trials. It is likely that stents with a low metallic surface may be more suited to the more thrombogenic substrate of bailout stenting, while the more rigid mesh stents with higher metallic surface area may be more suited to the elective treatment of primary or recurrent stenoses with strong elastic recoil in nontortuous vessels.

This study revealed sequential changes in luminal diameter from before primary intervention, through stent implantation, to the performance of a Swiss Kiss. Percent diameter stenosis decreased from 69% (before BA) through 56% (after BA) to 15% (after Swiss Kiss). Whereas previous in vitro testing of this stent has found recoil to be 8.7% for the 3.5 mm diameter stent, in this quantitative angiographic study of the stent in diseased coronary arteries in vivo, we found recoil to be 16 ± 9% (0.52 mm), with an average stent diameter of 3.41 mm. Furthermore, the poststent MLD achieved matched or was greater than the nominal stent size in only 3 of 22 stented lesions. The performance of a high-pressure (14 atm) Swiss Kiss may result in an increase in MLD by 0.31 mm, and may be a useful complementary technique when on-line quantitative angiographic analysis is available to guide the optimization of stent deployment.

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Chapter 12

Coronary lumen at 6 month follow-up of the new radiopaque Cordis tantalum stent using quantitative angiography (QCA) and intracoronary ultrasound (IVUS)

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Am J Cardiol 1995;76:1135-1142

Coronary Lumen at Six-Month Follow-Up of a New Radiopaque Cordis Tantalum Stent Using Quantitative Angiography and Intracoronary Ultrasound

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To determine the reliability of geometric (edge-detection) quantitative coronary angiographic analysis (QCA) of restenosis within a new Cordis tantalum stent, QCA and intracoronary ultrasound (ICUS) measurements were compared in both an experimental restenosis model and in the clinical follow-up of patients. In the experimental series, Plexiglas™ phantom vessels with concentric stenosis channels ranging from 0.75 to 3.0 mm in diameter and with a reference diameter of 3.0 mm were imaged both before and after their insertion in tantalum stents. In the clinical series, the agreement of QCA and ICUS measurements were studied in 23 patients who had undergone coronary implantation of the new tantalum stent and in 23 patients who had undergone balloon angioplasty 6 months previously. The reliability of QCA declined in the presence of the radiopaque stent (accuracy of QCA decreased from −0.07 to −0.12 mm), whereas the reliability of lumen measurements by ICUS was independent of the presence of the radiopaque stent (−0.12 and −0.13 mm). Without the stent, the average minimal luminal diameter (MLD) obtained by QCA of the 1.00 mm Plexiglas vessel was 1.00 ± 0.01 mm, and the 3.00 mm reference vessel diameter was 2.81 ± 0.05 mm, providing a 64 ± 1% diameter stenosis. After introduction of the stent, the average MLD and reference vessel diameter were 0.99 ± 0.06 and 3.36 ± 0.17 mm, respectively, providing a diameter stenosis of 71 ± 2%. ICUS measurements (2.77 mm) of the reference vessel diameter (3.00 mm) were unaffected by the presence of the stent. Agreement of ICUS and QCA measurements (ICUS − QCA) was poorer in patients who had undergone balloon angioplasty (0.68 ± 0.42 mm) than in patients who had stent implantation (−0.05 ± 0.42 mm). In the 6-month follow-up of patients who had undergone implantation of a highly radiopaque Cordis tantalum stent, assessment of restenosis was reliably quantified by QCA with the use of the MLD rather than the percent diameter stenosis. Although ICUS measurements are unaffected by the radiopaque stent, the mechanical problem of ICUS catheter wedging in stenoses of <1.00 mm and the substantial cost of ICUS catheters will restrict the widespread application of ICUS for the assessment of intrastent restenosis.

(Am J Cardiol 1995;76:1135–1143)

Whereas most of the available coronary stents are of low or moderate radiopacity,[1–4] a new helical coil stent composed of crenulated 0.005-inch tantalum wire (Cordis, Miami, Florida) is highly radiopaque. Although during the interventional procedure itself, the strong radiopacity of tantalum stents facilitates the precise positioning of the stent in the target lesion and the subsequent placement of additional noncompliant balloons for high-pressure intrastent inflations, the radiopaque stent struts may interfere with the quantitative assessment of restenosis within the stent at angiographic follow-up.[5,6] To evaluate the potential application and reliability of computer-based quantitative coronary angiographic analysis (QCA) of restenosis within the new radiopaque stent, we compared automated QCA and intracoronary ultrasound (ICUS) measurements of the vessel lumen with and without the radiopaque stent in both an in vitro Plexiglas (ICI, Rotterdam, The Netherlands) restenosis model as well as in a 6-month follow-up of patients who had undergone implantation of the new tantalum stent and patients who had undergone balloon angioplasty 6 months previously.

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METHODS

Experimental series: EXPERIMENTAL IMAGE ACQUISITION OF PLEXIGLAS RESTENOSIS MODEL WITH AND WITHOUT STENT: The stenosis phantoms were produced at the workshop of Erasmus University, Rotterdam, The Netherlands. For the in vitro assessment of restenosis measurements within a new radiopaque stent, phantom vessels were filmed before and after their insertion in new balloon-expanded tantalum stents of 3.5 mm nominal diameter (see Figure 1). Phantom vessels were composed of radiolucent Plexiglas cylinders (35 mm in length, 3.6 mm in outer diameter) with precision-drilled concentric circular lumens of 0.75, 1.0, 1.25, 1.5, 2.0, 2.5, and 3.0 mm in diameter.[7–9] The length of each phantom stenosis channel was 5 mm and the adjacent "normal refer-

ence" channel length of the proximal and distal segments was 15 mm. The Plexiglas channel, including the artificial stenosis, was filled with contrast medium (Iopamidol 370™; 370 mg iodine/ml [Bracco, Milan, Italy]). Cinefilm acquisition was performed with additional Plexiglas blocks (50 mm anteriorly and 50 mm posteriorly). These Plexiglas blocks provide a more appropriate kV level and a scatter medium that more closely approximates the radiologic scatter of the human thorax during angiography. Angiograms were recorded using a 5-inch field-of-image intensifier, with separate recordings using 2 different focal spots (0.4 and 0.7 mm). All phantoms were imaged at the radiographic isocenter of the x-ray gantry[10] and acquired on 35 mm cinefilm (Kodak CFE type 2711, Paris, France). For each of the 7 phantom vessels, 10 cineframes were selected both before and after their insertion in the new tantalum stents, providing a total of 140 cineframes for quantitative analysis.

Clinical series: CORONARY BALLOON ANGIOPLASTY: Balloon angioplasty was performed in 23 lesions of 23 patients at the Thoraxcenter, Erasmus University, Rotterdam, The Netherlands. The size of the balloon was selected to match the reference vessel diameter obtained from on-line quantitative angiographic analysis after intracoronary administration of isosorbide dinitrate.[11,12] Of the 23 lesions treated, a 2.5 mm diameter balloon was used in 6 lesions, a 3.0 mm in 10 lesions, a 3.5 mm in 6 lesions, and a 4.0 mm balloon in 1 lesion. Of the 23 lesions, 11 were in the left anterior descending coronary artery, 5 in the left circumflex coronary artery, and 7 in the right coronary artery. The follow-up angiogram and ICUS examination were performed at 6 ± 2 months after balloon angioplasty.

CORONARY STENT IMPLANTATION: After predilatation, a new radiopaque coronary Cordis stent was implanted in 23 lesions of 23 patients at Kokura Memorial Hospital, Kitakyushu, Japan. Twenty-one stents were implanted in 21 lesions of 21 patients and 4 stents were deployed in 2 lesions of 2 patients (2 stents in each lesion). Of the 25 stents used in 23 lesions, 14 stents were 3.0 mm and 11 were 3.5 mm in diameter. Of the 23 lesions, 11 were in the left anterior descending coronary artery, 5 in the left circumflex coronary artery, and 7 in the right coronary artery. Follow-up angiographic and ICUS examinations were performed at 6 ± 1 months after stent implantation. The number and location of lesions were identical in the balloon angioplasty and stent implantation groups.

CLINICAL ANGIOGRAPHIC IMAGE ACQUISITION AT 6-MONTH FOLLOW-UP: Six-month follow-up coronary angiography was performed after the administration of intracoronary isosorbide dinitrate[11,12] before manual injection of contrast medium (Iopamidol 370; 370 mg iodine/ml) at 37°C. The 5-inch field-of-image intensifier was selected and the radiographic settings were kept constant (kV, mA, x-ray pulse width) in each projection. All clinical images were acquired on 35 mm cinefilm at a frame rate of 25 images/s. An average of 2.6 cineframes/patient was selected for quantitative angiographic analysis. Minimal luminal diameter (MLD), reference vessel diameter, and luminal dimension at the proximal and distal extremities of the radiopaque stent were measured.

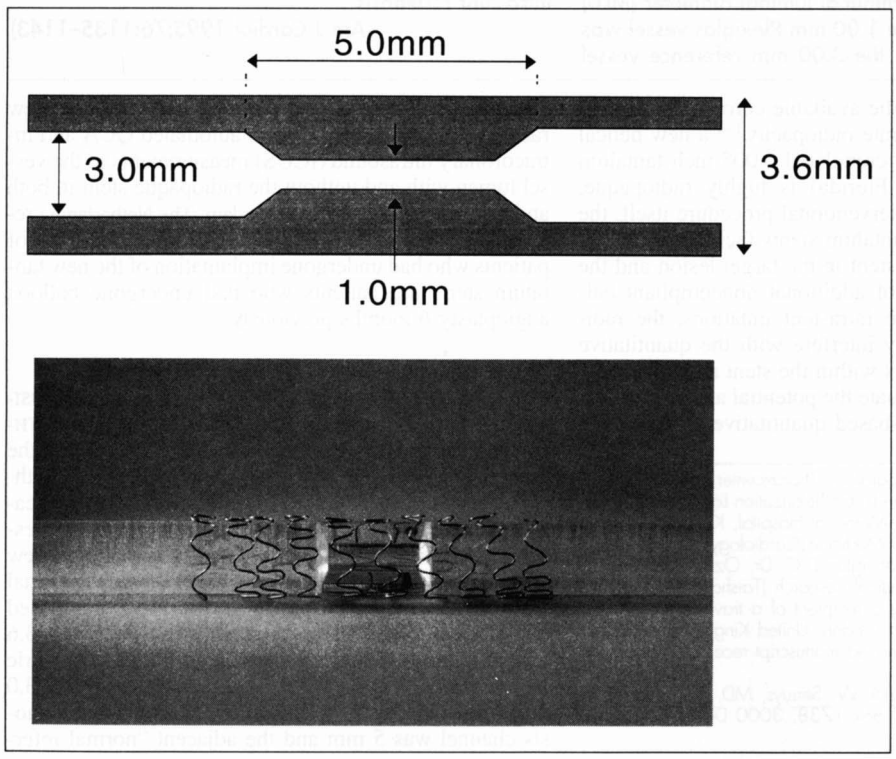

FIGURE 1. The phantom Plexiglas vessel served as an in vitro model for intrastent restenosis by insertion of the model into the expanded stent. Quantitative angiographic measurements were obtained of the contrast-filled lumen without and subsequently with the Cordis stent.

Quantitative angiographic analysis: Cinefilms from both the experimental and clinical series were quantitatively analyzed using a computer-based Cardiovascular Angiographic Analysis System (CAAS II; Pie Medical, Maastricht, The Netherlands).[7–9,12–17] Before performance of the calibration and analyses of the stenoses, computerized correction for pincushion distortion was applied by the recording and subsequent off-line digitization of a centimeter grid placed in front of the image intensifier in each cardiac catheterization laboratory. For both the experimental and clinical angiograms, quantitative measurements were calibrated by the use of the recorded contrast-free catheter tip as a scaling device.[18] The nontapering catheter tip was measured with a precision micrometer (no. 293-501, Mitutoyo, Tokyo, Japan; accuracy 0.001 mm). In the experimental study, a sufficiently long segment of the Plexiglas cylinders, including the phantom stenosis with or without the stent, was selected for analysis. In the clinical study, frames without foreshortening or overlapping side branches were selected.[19] Arterial dimensions of clinical frames were measured at specific distances from identifiable branch points in end-diastolic frames.

In the CAAS II system, the entire cineframe of size 18 × 24 mm is digitized at a resolution of 1,329 × 1,772 pixels. In the CAAS system, the edge-detection algorithm is based on the first and second derivative functions applied to the digitized brightness profile along scanlines perpendicular to a model using minimal cost criteria.[16] A computer-derived estimation of the original dimensions of the vessel at the site of the obstruction was used to determine the interpolated reference vessel diameter. If the automatically detected contour did not faithfully track the border of the lumen, the level of the light-emitting diode, which regulated the image brightness during digitization of the cineframe, was changed. Manual correction of the automatically detected contours was not performed in either the experimental phantom or the clinical studies. MLD and reference diameter were quantified in multiple averaged views.

Image acquisition of intracoronary ultrasound: After selective coronary angiography, a mechanical ICUS imaging catheter (30 MHz, 2.9Fr, Cardiovascular Imaging Systems, Sunnyvale, California) was introduced over a 0.014-inch guidewire. In the experimental series, a slow manual pullback was performed to assess the luminal dimension at the site of stenosis. In the clinical series, after the imaging catheter was passed into and beyond the lesion, a motorized pullback (Cardiovascular Imaging Systems) with a constant speed of 0.5 mm/s was begun to obtain an initial assessment of the target lesion. A simultaneous fluoroscopic image of the position of the ICUS catheter tip was continuously displayed. Side branches and stent struts visible on both the ultrasound and angiographic images served as reference points to ensure that the coronary sites of ultrasound and quantitative angiographic analysis were identical. ICUS images were stored on super VHS videotape for subsequent analysis.

Quantitative assessment of intracoronary ultrasound: The luminal area was defined as the integrated area central to the intimal leading-edge echo. Images with minimal cross-sectional area in the stent were selected from the pullback sequence by reviewing the position of the ICUS catheter on the angiographic image. Contrary to QCA, calculation of the reference vessel diameter by ICUS is based on a point measurement and is not interpolated. MLD and reference vessel diameter were derived from the minimal cross-sectional area (πr^2). To

TABLE I Results of Measurements of the Minimal Luminal Diameter Within the Plexiglas Vessel With and Without Stents*

Comparison	Accuracy	Precision	Correlation
QCA in stenosis without stent versus phantom diameter	−0.07	±0.08	0.997
QCA in stenosis with stent versus phantom diameter	−0.12	±0.10	0.992
ICUS in stenosis without stent versus phantom diameter	−0.12	±0.09	0.989
ICUS in stenosis with stent versus phantom diameter	−0.13	±0.11	0.986

*$p < 0.001$.
ICUS = intracoronary ultrasound; QCA = quantitative coronary angiographic analysis.

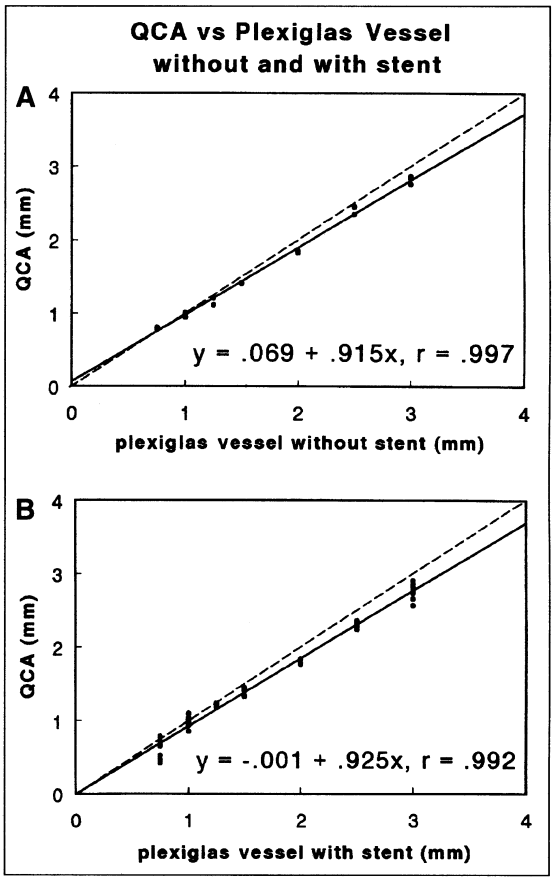

FIGURE 2. Quantitative coronary angiographic analysis (QCA) obtained from 70 cineframes of the Plexiglas restenosis model without *(A)* and subsequently with *(B)* insertion of the vessel in the new tantalum stent. The measurement values have been plotted against the true diameter of the contrast-filled lumen of the Plexiglas vessel (linear regression).

determine the interobserver variability of ICUS measurements, 30 lesions were independently measured by 2 observers. The mean signed difference and correlation of the measurements of cross-sectional area were 0.02 ± 0.37 mm^2 and 0.97, respectively.

Statistical analysis: In the experimental study, the mean of the signed differences between the true phantom diameters and the individual MLD values derived from measurements of QCA and ICUS was considered an index of accuracy, and the SD of the differences was considered an index of precision. In the clinical study, the mean ± SD of the signed differences between measurements of MLD derived from QCA and from ICUS were used as an index of agreement between measurements.[20]

RESULTS

Experimental series: EXPERIMENTAL RESULTS FOR MINIMAL LUMINAL DIAMETER: Results of measurements of the MLD within the Plexiglas vessel with and without the stent are presented in Table I and in Figures 2A and 2B (QCA) and 3A and 3B (ICUS). Before positioning the Plexiglas vessels in the stents, measurements of the phantom vessel lumen by QCA were more accurate than ICUS. The reliability of QCA, however, declined in the presence of the radiopaque stent (accuracy of QCA decreased from –0.07 to –0.12 mm), whereas the reliability of lumen measurements by ICUS was independent of the presence of the radiopaque stent (–0.12 and –0.13 mm before and after introduction of the stent, respectively).

EXPERIMENTAL RESULTS OF REFERENCE VESSEL DIAMETER AND PERCENT DIAMETER STENOSIS: Results of reference vessel measurements by QCA and ICUS are displayed in Figures 4A and 4B. Measurement by QCA of the reference vessel diameter was significantly larger within than without the stent ($p < 0.001$) and the percent diameter stenosis was consequently significantly more severe with than without the stent ($p < 0.001$). Without the stent, the average MLD obtained by QCA of the 1.00 mm Plexiglas vessel was 1.00 ± 0.01 mm, and the reference vessel diameter was 2.81 ± 0.05 mm, providing a 64 ± 1% diameter stenosis. After introduction of the Plexiglas vessel in the stent, the average MLD was 0.99 ± 0.06 mm, and the average reference vessel diameter was 3.44 ± 0.10 mm, providing a diameter stenosis of 71 ± 2%. An example of angiographic measurement of the MLD and reference vessel diameter of a Plexiglas

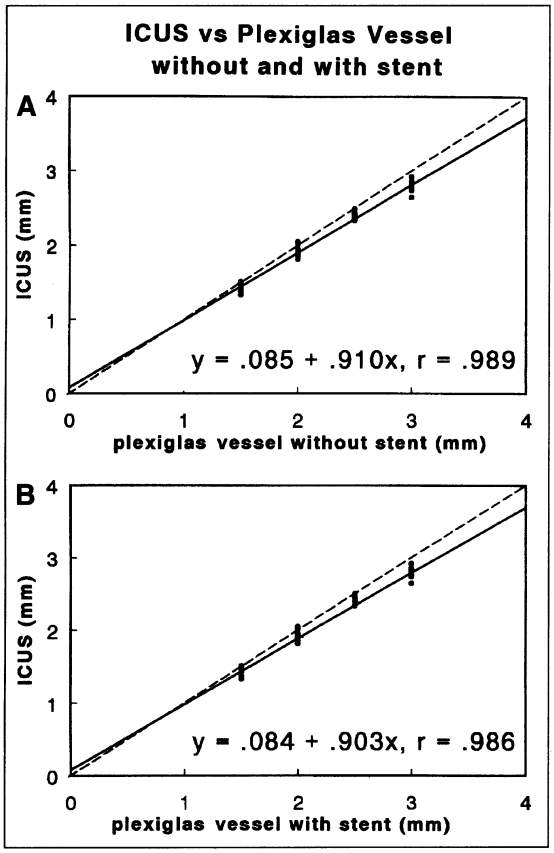

FIGURE 3. Intracoronary ultrasound (ICUS) measurements obtained from 40 frames of the Plexiglas restenosis model without *(A)* and subsequently with *(B)* insertion of the vessel in the new tantalum stent. The measurement values have been plotted against the true diameter of the contrast-filled lumen of the Plexiglas vessel (linear regression).

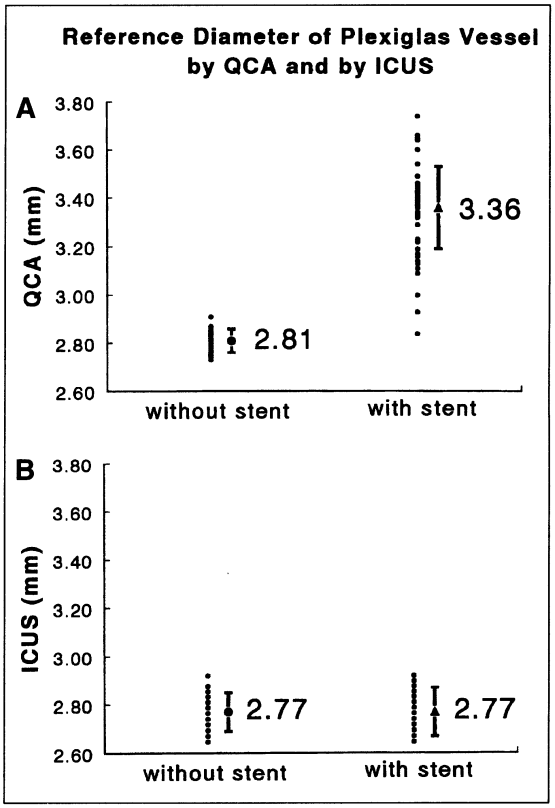

FIGURE 4. Comparison of reference diameter obtained from quantitative coronary angiographic analysis (QCA) *(A)* and by intracoronary ultrasound (ICUS) *(B)* without and with the new radiopaque stent. Although measurement obtained by quantitative coronary angiographic analysis of the reference vessel diameter within the stent was significantly larger than without the stent ($p < 0.001$), intracoronary ultrasound measurements were unaffected by the radiopaque stent (p = NS).

vessel with and without the new radiopaque stent can be seen in Figure 5. ICUS measurements (2.77 mm) of the reference vessel diameter (3.00 mm) were unaffected by the presence of the stent.

Clinical series: The results of measurements of MLD by ICUS are plotted against those by QCA for patients who had balloon angioplasty and those who had coronary stents in Figures 6A and 6B, respectively. Of the 23 stented lesions, 3 showed signs of catheter wedging of the ICUS catheter, and in the remaining 20 lesions the minimal cross-sectional area and MLD were measured. Of the 23 balloon angioplasty lesions, 8 showed signs of catheter wedging. The agreement of ICUS and QCA measurements (ICUS – QCA) was poorer in patients who had undergone balloon angioplasty (0.68 ± 0.42 mm) than in patients who had stent implantations (–0.05 ± 0.42 mm). Similarly, correlation of ICUS and QCA measurements was 0.40 in the balloon angioplasty population and 0.60 in the stented patients.

To ensure that the differences between QCA and ICUS measurements of the minimal lumen diameter were not related to analysis at different locations in the stented coronary segment by ICUS and QCA, measurements were also compared at the proximal and distal extremities of the stent, which were clearly identifiable during both QCA and ICUS analysis. The results of measurements of the luminal dimension at the proximal and distal extremity of each radiopaque stent (46 measurements) by ICUS are plotted against those by QCA in Figure 7. Agreement between the 2 sets of measurements at the extremity of the stent was –0.06 ± 0.42 mm (mean ± SD of the signed differences), and was associated with a correlation coefficient of 0.63. An example of angiographic measurement of the MLD of a patient with a new radiopaque stent at 6-month follow-up can be seen in Figure 8.

DISCUSSION

The principal findings of our study are: (1) In the Plexiglas restenosis model, QCA provided more accurate measurements of MLD than ICUS. (2) After introduction of the Plexiglas vessel in the radiopaque stent, the accuracy of QCA declined, whereas the accuracy of ICUS measurements of both the MLD and the reference vessel diameter was unaffected by the radiopaque stent. (3) Measurements by QCA of the interpolated reference vessel diameter of the Plexiglas vessel were rendered inaccurate by the presence of the radiopaque stent and resulted in overestimation of the severity of the percent diameter stenosis. (4) In the 6-month follow-up of patients after coronary intervention, agreement of ICUS and QCA measurements was higher in patients who underwent stent implantation than in those who underwent balloon angioplasty alone.

Comparison between intravascular ultrasound and edge-detection quantitative coronary angiographic measurement: Previous studies examining the relation of ICUS and QCA measurements in normal coronary segments reported a favorable correlation between the 2 quantitative imaging modalities,[21,22] whereas studies that included lesions after balloon angioplasty reported a poor correlation of the 2 measurement techniques.[23–25] Complex morphologic changes caused by balloon angioplasty may result in a failure of agreement between the 2 measurement systems after balloon angioplasty,[26] whereas the more smooth and circular lumen of a stented coronary segment may improve agreement of ICUS and QCA measurements.

Limitation of quantitative coronary angiographic analysis: During QCA of the MLD within a stented vessel segment, the automated edge-detection algorithm will trace the true diameter of the contrast-filled lumen at the point

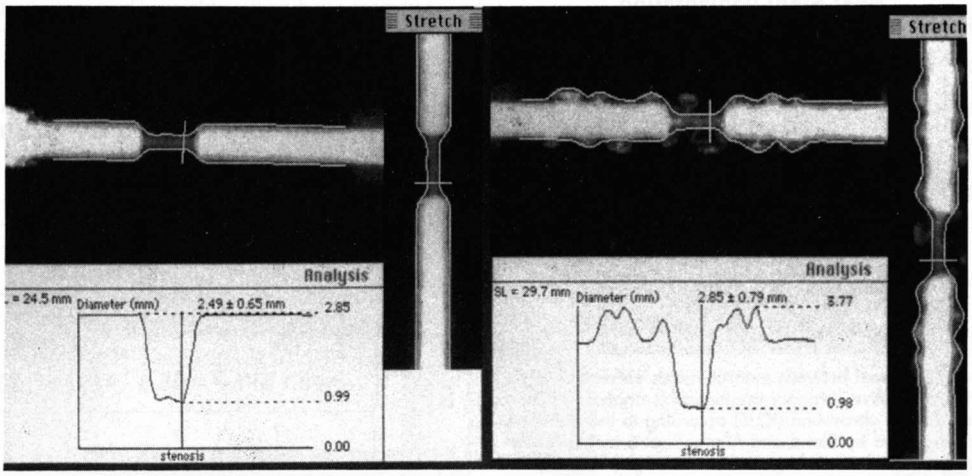

FIGURE 5. The contrast-filled lumen of the Plexiglas vessel is shown without the new Cordis tantalum stent *(left panel)* and after insertion of the vessel within the radiopaque stent *(right panel)*. Automated quantitative angiographic analysis was found to faithfully track the contour of the stenotic segment in both the absence and subsequent presence of the stent. Automated quantitative angiographic analysis of the normal reference vessel diameter, however, was significantly affected by the presence of the radiopaque stent, with undulations and evident tracking out to include the contour of the stent struts rather than tracking the true edge of the contrast filled lumen. The maximal diameter was found to be 3.77 mm after introduction of the stent. Overestimation of the reference vessel diameter in the presence of the stent resulted in an exaggeration of the severity of the percent diameter stenosis.

of most severe stenosis in between the radiopaque stent struts (i.e., in the interstrut intervals). QCA of the MLD will thus remain reliable for 2 reasons: First, at 6-month follow-up in the presence of significant intimal hyperplasia, the outer edge of the radiopaque stent struts will be deeply embedded in the vessel wall at an adequate distance from the border of the contrast-filled true lumen and will thus not interfere with the automated edge-detection process. Second, the measurement is based on a very limited segment of the coronary lumen (according to the degree of smoothing or minimal cost criteria), which is shorter in length than the gap between successive radiopaque stent struts. However, during measurement of the interpolated reference vessel diameter, QCA by automated edge detection may be unreliable for 2 reasons: First, beyond the subsegment of maximal restenosis, the outer contour of the radiopaque stent struts lies in close proximity to the border of the true lumen and may therefore interfere with the automated edge detection, which may be unable to differentiate the outer contours of the lumen and stent struts. Second, the interpolated reference vessel diameter is based on multiple scanlines over a large extent of the analyzed segment, which will incorporate both scanlines that do and do not include the outer contour of the radiopaque stent struts.

Rather than using a subjective operator-selected reference point, the default mode of the CAAS system determines the size at the target coronary segment using an objective computer-derived interpolated reference diameter.[7–9,12–17] The interpolated reference diameter is derived from the edge-detected diameter function of the nonstenotic proximal and distal subsegments. The reference vessel diameter values are estimated by fitting a straight line to the diameter function proximal and distal to the obstruction, followed by a shift so that 80% of the diameter values are below the adjusted straight line. This line then represents the reconstructed reference diameter function and gives an estimate of the arterial size at each point along the analyzed coronary segment. The interpolated reference vessel diameter is taken as the value of the reconstructed diameter function at the position of the MLD. The advantages of this approach are that it is essentially user-independent and thus highly reproducible, and every measurement is based on multiple measurements (every scanline) proximal and distal to the lesion. The limitation of this technique is in ostial lesions where a proximal segment is unavailable and, in the case of this new highly radiopaque tantalum stent, where selection of a reference point either proximal or distal to the new Cordis tantalum stent (or an average of both) may prevent overestimation of vessel size associated with use of the default-interpolated reference vessel diameter mode.

Although not directly addressed by our study, it should be acknowledged that interference with the reliability of

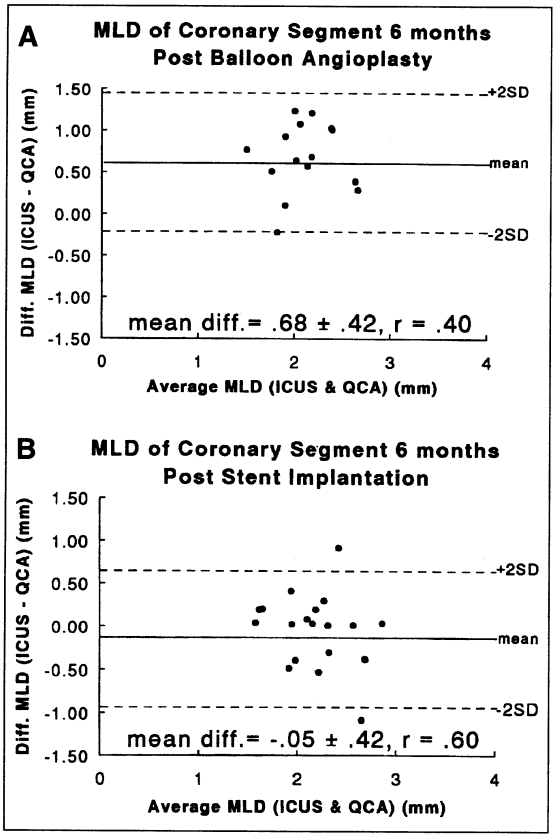

FIGURE 6. Agreement between measurements obtained from geometric quantitative coronary angiographic analysis (QCA) and intracoronary ultrasound (ICUS) according to the statistical approach proposed by Bland and Altman[20] at 6-month follow-up of patients who had undergone balloon angioplasty *(A)* and of patients who had undergone implantation of the radiopaque stent *(B)*. *A*, the difference (diff.) in values between the ICUS and QCA measurements has been plotted against their mean value in 15 lesions without wedging of the ICUS catheter at follow-up in the balloon angioplasty group. *B*, the difference in values between the ICUS and QCA measurements has been plotted against their mean value in 20 lesions without wedging of the ICUS catheter at follow-up of patients who had undergone stent implantation.

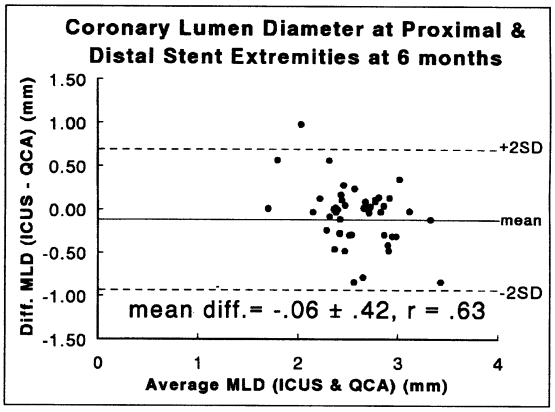

FIGURE 7. Agreement between measurements obtained from quantitative coronary angiographic analysis (QCA) and intracoronary ultrasound (ICUS) at the 46 proximal and distal extremities of the 23 stents at 6-month follow-up according to the statistical approach proposed by Bland and Altman.[20] The differences (diff.) between intracoronary ultrasound and quantitative coronary angiographic analysis values have been plotted against their mean value.

QCA by this new radiopaque stent may also occur immediately after stent implantation, and thus similar precautions in the application of QCA should be applied.

Limitations of intracoronary ultrasound: ICUS can provide clinically useful information on lesion and vessel characterization as well as on guidance of optimal stent deployment.[27–30] However, the 2.9Fr size of the ultrasound catheter restricts application of ICUS for lumen quantification to lesions of >1.0 mm in diameter because of mechanical wedging of the catheter. In our study, 3 of 23 stented lesions and 8 of the 23 lesions previously treated with balloon angioplasty showed signs of catheter wedging, and these measurements were therefore excluded from analysis. Thus, although ICUS may be useful immediately after intervention for assessment of stent deployment, by 6-month follow-up lesions with significant restenosis may be unsuitable for ICUS evaluation. Furthermore, because the price of ultrasound catheters remains expensive (approximately $1,300), it is difficult to justify the use of ICUS for routine follow-up of all stented patients.

Derivation of the MLD by ICUS measurement of the minimal luminal cross-sectional area (πr^2) inherently assumes a circular lumen, which may not be appropriate in the presence of severely eccentric atherosclerotic disease. Our use of a symmetric lumen in our phantom vessel allowed measurement by ICUS of the MLD to be obtained by either direct diameter measurement or by derivation from the minimal luminal cross-sectional area (πr^2). The ratio of the 2 derived diameters in our stent and balloon angioplasty series was 0.89 ± 0.08 and 0.82 ± 0.08, respectively, consistent with a relatively symmetric lumen morphology at 6-month follow-up.

Given the unique inherent limitations of both ICUS and QCA techniques, the observation of a difference in their measurements in the absence of the known true diameter does not permit a conclusion on the absolute accuracy of either technique. We therefore included a phantom restenosis model with known internal dimensions to provide a measure of accuracy of both techniques.

Implications: For patients undergoing 6-month angiographic follow-up of this new radiopaque Cordis stent, measurements by QCA of the MLD may be performed reliably. When a QCA system is used that offers a default-interpolated reference vessel diameter mode, the reference vessel diameter of the stented segment may be overestimated and thus the severity of the percent diameter stenosis may also be overestimated, unless a manually selected reference point(s) proximal and/or distal to the Cordis tantalum stent is used. Alternatively, for determination of relative loss (absolute loss in MLD normalized for vessel size), the interpolated reference vessel diameter measured before intervention may be used.

At the time of stent implantation, and thus before the development of intimal hyperplasia, the stent struts will be in apposition to the vessel wall and thus the outer contour of the radiopaque stent struts should be coincident with the outer contour of the contrast-filled lumen. At this procedural phase, we do not find in clinical practice that the radiopacity of the stent struts interfere with on-line QCA during stent deployment. Thus, determination of the absolute (MLD post – MLD pre) and relative (MLD post – MLD pre normalized for reference vessel diameter pre) gain achieved at stent implantation, the absolute (MLD post – MLD follow-up) and relative (MLD post – MLD follow-up normalized for reference vessel diameter pre) loss in MLD over 6 months, and the loss index (loss/gain) (restenosis process), as well as measurement of the absolute MLD at follow-up (final outcome), should be feasible with QCA in patients undergoing implantation of this tantalum stent.

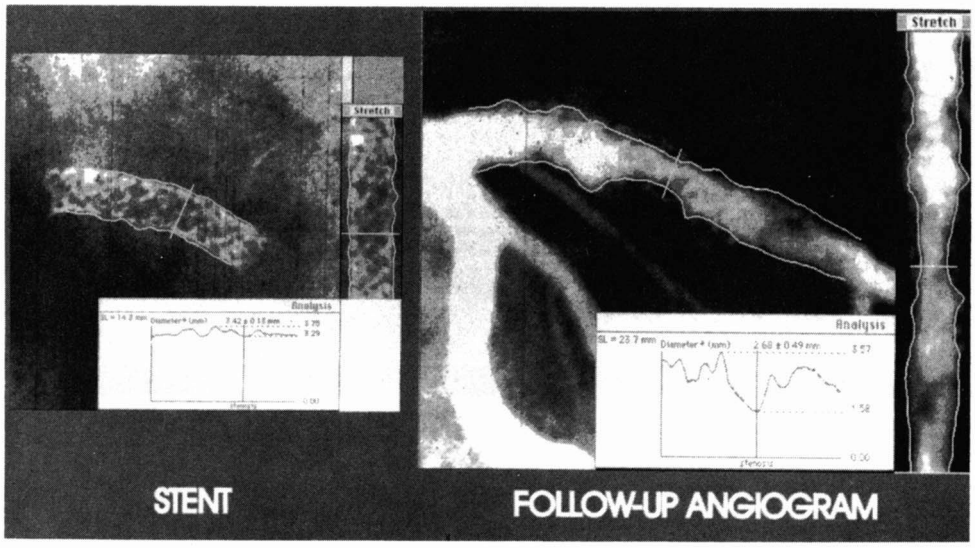

FIGURE 8. At 6-month follow-up angiography, the radiopacity of the new Cordis tantalum stent can be traced by automated edge detection without contrast media *(left panel)*. In this patient, automated edge detection of the minimal luminal diameter appeared to function reliably after contrast injection *(right panel)*.

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IMPLICATIONS FOR COST-EFFECTIVENESS

While the primary role of intracoronary ultrasound (ICUS) may be the imaging of coronary mural pathology, precise quantification of luminal cross-sectional area post stent implantation would offer a significant advantage.[1–6] Two multicenter Palmaz-Schatz stent trials—MUSIC (**M**ulticenter **U**ltrasound **S**tent **i**n **C**oronary Artery Disease) with ICUS examination and MUST (**Mu**lticenter **S**tent **T**iclopidine) without ICUS examination—are now ongoing. While the MUSIC trial involves 160 patients using only aspirin as antiplatelet therapy after stent deployment, the MUST trial consists of 260 patients using aspirin and ticlopidine following stent implantation. The preliminary data from these studies indicate subacute occlusion rates of 0.95% in the MUSIC trial and 1.15% in the MUST trial. Although the pharmacologic protocols between the 2 studies are different, and ICUS examination may convey a difference in the restenosis rate at 6-month follow-up, no statistically significant difference was found in the subacute thrombosis rate between the MUSIC and MUST trials. Compared with the MUST trial, a minimal additional cost (excluding the price of the ultrasound system) for the ICUS catheter in the MUSIC trial is $1,300 (× 160 patients = $208,000).

At our institution (Thoraxcenter, Rotterdam, The Netherlands), an on-line quantitative coronary angiographic system (CAAS II, Pie Medical, Maastricht, The Netherlands) is available during the interventional procedure. The time required for quantitative coronary angiographic analysis using the CAAS II system is 20 seconds per frame × 2 views (or additional multiple projections) = 40 seconds. ICUS catheter insertion time, image acquisition time (using a motorized pullback system), and image analysis time including qualitative assessment of stent apposition and quantitative assessment (minimal lumen diameter and area of the stent, reference diameter and area proximal and distal to the stent) amounts to 20 minutes. Thus the time-effectiveness of the CAAS II system is far superior to the ICUS system for the same interventional procedure (i.e., high-pressure post-stent dilatation; Swiss Kiss).

Although ICUS may provide novel tomographic information on coronary arteries post stent implantation, we at the Thoraxcenter find it difficult to justify ICUS examination of all patients with stent implantation, due to our limited hospital finances and the time constraints for interventional procedures for each patient.

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Chapter 13

Impact of cutting balloon angioplasty prior to stenting on stent restenosis; a prospective randomized multicenter trial comparing cutting balloon angioplasty with balloon angioplasty before stenting (Reduce)

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(submitted to J Am Coll Cardiol)

ABSTRACT:

Objectives: We investigated whether IVUS-guided Cutting Balloon Angioplasty (CBA) before stenting could achieve restenosis rates comparable to those achieved with drug-eluting stents (DES).

Background: Stent restenosis and thrombosis still occur even with DES and their long-term safety is uncertain. There remains a need to explore other strategies for ameliorating restenosis.

Methods: We randomized 521 patients to CBA before stenting (260 pts) or plain old balloon angioplasty (POBA) before stenting. IVUS-guided procedures were performed in 279 (54%) patients and angiography guidance was used in the remainder. Patients were divided into 4 groups based on device used before stenting and the use of IVUS-guidance (IVUS-guided CBA stent: 137; angiography-guided CBA stent: 123; IVUS-guided POBA stent: 142; and angiography-guided POBA stent: 119 patients). The primary end-point was restenosis.

Results: The IVUS-guided CBA-stent strategy achieved a significantly lower restenosis rate of 6.6% (p=0.016) versus rates of 17.9% (angiography-guided CBA-stent), 19.8% (IVUS-guided POBA-stent) and 18.2% (angiography-guided POBA-stent) in the remaining groups. The device size used before stenting was significantly greater with IVUS than with angiography-guidance in CBA (3.37$\pm$0.41mm vs. 3.26$\pm$0.35mm, p=0.039) and with POBA (3.32$\pm$0.38mm vs. 3.19$\pm$0.41mm, p=0.010). Lumen area (LA) after CBA and POBA was significantly greater in IVUS-CBA than IVUS-POBA group (5.3$\pm$1.6mm^2 vs. 4.1$\pm$1.3mm^2, p=0.019) as was LA after stenting (7.4$\pm$2.2mm^2 vs. 6.6$\pm$2.0mm^2, p=0.035) and at follow-up (5.3$\pm$2.8 mm^2 vs. 4.4$\pm$2.0 mm^2, p=0.043).

Conclusions: The IVUS-guided CBA-stent strategy provided restenosis rates (6.6%) similar to those achieved with DES. Such a strategy could therefore be a viable alternative to the use of DES.

INTRODUCTION:

Restenosis has been a major limitation to the success of percutaneous coronary intervention over the last two and a half decades. Whilst with the advent of drug-eluting stents, it would appear that the interventional cardiologist has overcome the nemesis of restenosis, there are significant concerns about the long-term efficacy and safety of such devices [1,2]. Recent major multicenter randomized studies including RAVEL, SIRIUS and TAXUS have suggested that drug-eluting stents (DES) could drastically reduce 6-month restenosis rates to between 0-8.9% [3-5]. However, there is little long-term follow-up and safety data available beyond three years [1,2,6]. A recent FDA public health report has warned that subacute thrombosis (SAT), late stent thrombosis (LST) and hypersensitivity reactions to sirolimus could have contributed to the serious major adverse cardiac events experienced in some patients

treated with DES [7]. Furthermore, a pathological study has suggested that a hypersensitivity reaction to the polymer of the DES could cause LST [8]. The number of DES and the stent length required for each lesion is substantially increasing based on the recent policy of full lesion coverage to avoid any potential injury at the stent edges. With the increasing cost constraints of modern healthcare practice, this could significantly limit the use of DES in clinical practice. Cost and long-term safety concerns highlight the need to continue to explore alternative strategies for reducing the burden of restenosis.

The cutting balloon is a unique device that consists of a balloon catheter with three to four blades that creates longitudinal incisions in the atherosclerotic lesion during the balloon inflation. While a randomized multicenter study of the use of cutting balloon angioplasty (CBA) without stent implantation or IVUS guidance failed to show a long-term advantage of CBA over plain old balloon angioplasty (POBA)[9], another study has indicated some clinical benefit [10]. We postulated that the use of IVUS guidance could be essential to obtaining optimal results with a strategy of cutting balloon angioplasty prior to stenting. IVUS can facilitate optimal device sizing based on vessel size and plaque distribution, and can reveal vascular wall injury after CBA. This may help to significantly reduce the incidence of vascular complications such as coronary perforation. We hypothesized that IVUS-guided CBA prior to stenting would assist in achieving full stent expansion, improve accommodation of reactive intimal hyperplasia, and thereby produce favourable long-term restenosis rates comparable to those achieved with DES.

To test this hypothesis we performed a prospective, randomized, multicenter trial to compare CBA with POBA before stenting in 521 patients with and without IVUS guidance.

METHODS:

Study Design and End-Points

The REDUCE trial was designed as a prospective, multicenter, randomized study to compare cutting balloon angioplasty before the bare metal stent implantation and balloon angioplasty prior to stenting. Five hundred twenty-one patients were randomly assigned to either cutting balloon prior to stenting or balloon angioplasty in an envelope manner at 37 participating centers. To ensure an equal distribution of both treatments per center, the randomization sequence was developed on a site basis. To compare IVUS-guided PCI and angiography-guided PCI, IVUS-guided procedures (pre and post) and follow-up were performed in 20 centers and angiography-guided procedures were done in the remaining 17. While IVUS-guided procedures were performed in 279 (54%) patients, angiography-guided procedures were done in the remaining 242 (46%) patients.

The primary angiographic end-point was restenosis (defined as ≥50 percent diameter

stenosis at follow-up by QCA) and the primary clinical end-point was major adverse cardiac events (subacute or late stent thrombosis, death, MI, and target lesion revascularization [TLR]).

Patient selection

Patients with unstable angina, stable angina or silent myocardial ischemia, a single target lesion in a native coronary artery with a vessel diameter less than 4 mm, and planned stent implantation with up to 2 stents were included. Patients were excluded from the study if they had (1) contraindication to anticoagulation and antiplatelet therapy; (2) an acute myocardial infarction within the past 7 days; (3) graft disease; or (4) left main coronary artery disease. The study was approved by local ethics committees and was carried out according to the guidelines of the Declaration of Helsinki. Written informed consent was obtained from all patients.

PCI procedures

CBA and POBA prior to the stent implantation were performed according to standard clinical practice using the trans-radial or trans-femoral approaches using guide catheters 6F or greater in size for subsequent quantitative coronary angiographic (QCA) analysis [11]. A bolus of 8,000 to 10,000 IU of heparin (repeated if necessary) was administrated during the procedure, followed by a combination of anti-platelet therapy [11]. According to standard patient care, treatment with aspirin at a dose of 81 to 300mg daily was started before the procedure and continued indefinitely and treatment with ticlopidine at 200 mg daily was begun before or immediately after the procedure and continued for at least 2 weeks.

Optimal stenting criteria

CBA, POBA and stent sizes were determined by angiographic reference vessel diameter (angiography-guided group) and vessel size and plaque distribution detected by IVUS (IVUS-guided group). The angiographic criteria for optimal stenting were (1) no flow limiting dissection; and (2) residual stenosis less than 30% [11]. The IVUS criteria for optimal stenting were (1) good stent apposition; (2) full stent expansion with sufficient lumen area (lumen area 80% or greater of the average reference lumen area pre-intervention; and (3) the absence of major dissection [12,13].

Quantitative Coronary Angiography (QCA)

Coronary angiograms were obtained in multiple views after the intracoronary injection of nitrates. QCA analyses were performed using the computer-based edge-detection coronary angiography analysis system (CAAS II, Pie Medical, Maastricht, NL) at the Coronary Imaging Core Laboratory at Aichi Medical University [12-14]. The absolute diameter of the stenosis

(in mm) was determined using the guiding catheter as a scaling device [14-16]. To standardize the method of analysis pre-, post- and follow-up angiograms, study frames selected for analysis were end-diastolic to minimize motion artefact, and arterial segments were measured between the same identifiable branch points after the administration of nitrates [11,14,16].

Image Acquisition of Intracoronary Ultrasound (IVUS)

Following selective coronary angiography after the intracoronary injection of nitrate, a mechanical intracoronary ultrasound imaging catheter (40-MHz, 2.7Fr or 2.5Fr, Boston Scientific Corporation, Freemont, California) was introduced over a 0.014-inch guidewire before, immediately after CBA or POBA, after stenting, and at follow-up [16,17]. After the imaging catheter was passed into and beyond the lesion, a motorized pullback was started to obtain an assessment of the target lesion. IVUS images were stored on super VHS videotape for off-line analysis [16,17].

Quantitative IVUS assessment (QCU)

Serial IVUS analysis pre-procedure, immediately after CBA or POBA, post-stenting and at 6-month follow-up were performed at an independent core laboratory at Aichi Medical University. Cross-sectional luminal area was defined as the integrated area central to the intimal leading edge echo [16-18]. The total vessel cross sectional area (VA) was defined as the area inside the interface between the plaque-media complex and adventitia (area inside the external elastic membrane) [16-18]. Vessel area (VA), lumen area (LA) and plaque area (PLA) were calculated by the imaging computer (Tapemeasure, Index Systems, Mountain View, California) [10,18]. The lesion segment was determined from pre-intervention images including the frame with the smallest LA, while the proximal and distal reference segments were defined as the location of the least amount of disease before the emergence of any major side branches. The corresponding frames at post-intervention and follow-up were determined by using peri- and intra-coronary landmarks such as calcium deposits, side branches and venous structures [16-18].

Statistical analysis

Data was analyzed using the SAS statistical software package. All continuous values are expressed as mean$\pm$SD. Differences in categorical variables were assessed using the chi-squared test and Fisher's exact test. The unpaired *t* test was used to assess difference in continuous variables between two groups and ANOVA for three or more groups. To study the relationship between binary restenosis and multiple categorical and continuous determinants, multiple logistic regression analysis was performed. Univariate variables with a p value <0.2 were entered into the multivariate models. Forward stepping was used to determine the

independent predictors of restenosis. For all statistical tests, a two-tailed value of $p<0.05$ was considered significant. All data were analyzed on an intention-to-treat basis.

RESULTS:

Patient and Lesion Characteristics

Five hundred twenty-one patients entered the study, of which 260 were randomized to CBA before stent implantation and 261 to POBA prior to stenting. One hundred and thirty-seven patients underwent CBA and stenting under IVUS-guidance and 123 under angiography-guidance. One hundred and fourty-two patients underwent POBA under IVUS-guidance and the remaining 119 under angiography-guidance. All four groups were well matched without significant differences in baseline clinical, demographic and angiographic characteristics (Table 1).

Procedure-related events

Of the 260 patients randomized to CBA with stenting, four did not undergo CBA due to failure to cross the lesion but were successfully treated with balloon angioplasty and one did not undergo stent implantation after cutting balloon angioplasty. Two patients had myocardial infarction due to side branch occlusions. Therefore the primary procedure success rate of CBA with stenting was 97% (253 out of 260 patients).

Of the 261 patients randomized to POBA with stenting, all patients underwent successful POBA and stenting (procedural success, 100%). One patient experienced sub-acute stent thrombosis with myocardial infarction 4 days after the procedure but received emergency PCI and TIMI III flow was quickly restored.

Significant differences were observed in the nominal balloon size used prior to stenting among the four groups (Table 2). The nominal device size used before stenting was significantly greater with IVUS-guidance than angiography-guidance in both the CBA group (3.37 ± 0.41mm vs. 3.26 ± 0.35mm, $p=0.039$) and the POBA group (3.32 ± 0.38mm vs. 3.19 ± 0.41mm, $p=0.010$). The use of IVUS-guidance consistently resulted in the selection of greater device sizes prior to stenting than angiography-guidance alone.

There was also a significant difference in the inflated balloon size measured by QCA between the four groups (Table 2). The inflated balloon size was significantly greater in CBA than POBA groups (3.32 ± 0.51mm vs. 3.20 ± 0.42mm, $p=0.035$), although nominal balloon size was similar between IVUS-guided CBA and IVUS-guided POBA (3.37 ± 0.41mm vs. 3.32 ± 0.38mm, $p=0.348$).

Table 1. Baseline clinical and lesion characteristics.

	Cutting Balloon with Stent (n=260)		POBA with Stent (n=261)		p
	IVUS-CBA (n=137)	Angio-CBA (n=123)	IVUS-POBA (n=142)	Angio-POBA (n=119)	(ANOVA)*
Age (yrs)	65±9	64±9	66±9	64±10	0.140
Male (%)	73.7	82.1	79.6	73.1	0.239
DM (%)	27.0	27.6	36.6	28.6	0.264
HT (%)	55.5	56.1	57.0	61.3	0.787
HLP (%)	43.8	48.8	37.3	50.4	0.134
Smokers	38.7	44.7	46.5	42.0	0.585
MI (%)	32.1	31.7	35.2	24.4	0.292
Angina pectoris (%)					
UAP	26.3	24.4	27.5	27.7	0.930
SAP	73.7	75.6	72.5	72.3	-
Target artery (%)					
RCA	38.7	39.0	39.4	31.1	0.770
LAD	43.8	41.5	39.4	46.2	-
LCX	17.5	19.5	21.1	22.7	-
AHA/ ACC lesion class (%)					
A	8.8	12.2	10.6	8.4	0.834
B1	32.1	22.8	26.8	23.5	-
B2	46.7	52.0	51.4	55.5	-
C	12.4	13.0	11.3	12.6	-

QCA results

While no significant difference was found in the baseline reference vessel size and minimal lumen diameter pre-procedure (MLD pre) between the four groups (Table 2), a significant difference was observed in the MLD post-procedure (p=0.034). The greatest MLD-post was achieved with IVUS-guided CBA with stenting and the smallest with angiography-guided POBA prior to stenting (Table 2).

The overall angiographic follow-up rate was 87% (453 of 521 patients), with a mean follow up period of 6.8 months. There was no significant difference between the four groups with regard to follow-up rates and duration. The incidence of restenosis was 6.6% (8 out of 122 patients) in the IVUS-guided CBA with stent group, 17.9% (19 out of 106 patients) in the angiography-guided CBA with stent groups, 19.8% (25 out of 126 patients) in IVUS-guided

POBA with stent group, and 18.2% (18 out of 99 patients) in angiography-guided POBA with stent group (p =0.016) (Table 2).

Table 2. Comparison of procedural characteristics, QCA and IVUS.

	Cutting Balloon with Stent (n=260)		POBA with Stent (n=261)		p
	IVUS-CBA (n=137)	Angio-CBA (n=123)	IVUS-POBA (n=142)	Angio-POBA (n=119)	(ANOVA)*
Procedure characteristics					
Nominal balloon size (mm)					
	3.37±0.41	3.26±0.35	3.32±0.38	3.19±0.41	0.003
Inflated balloon size measured by QCA (mm)					
	3.32±0.51	3.19±0.46	3.20±0.42	3.09±0.43	0.002
QCA (mm)**					
RD pre	2.82±0.48	2.82±0.46	2.83±0.49	2.78±0.45	0.286
MLDpre	1.05±0.32	1.04±0.31	1.03±0.28	1.00±0.34	0.364
MLDpost	2.62±0.42	2.58±0.38	2.59±0.44	2.48±0.36	0.034
MLDfup	1.88±0.54	1.83±0.56	1.81±0.58	1.75±0.50	0.390
Restenosis rate (%)**					
	6.6	17.9	19.8	18.2	0.016
IVUS (mm^2)					
LA pre	1.7±0.8		1.7±0.6		0.262
LA post CB/POBA					
	5.3±1.6		4.1±1.3		0.019
LA post Stent					
	7.4±2.2		6.6±2.0		0.035
LA at follow-up					
	5.3±2.8		4.4±2.0		0.043

*ANOVA was applied only in four-group comparison and unpaired *t*-test was used in two IVUS group comparisons.

IVUS results

While baseline lumen areas (LA) were similar between IVUS-guided CBA-stent and the IVUS-guided POBA-stent group, LA immediately after CBA was significantly greater than LA following POBA (5.3±1.6mm^2 versus 4.1±1.3mm^2, p=0.019) (Table 2). This favorable greater LA achieved by IVUS-guided CBA than by IVUS-guided POBA carried over after

stenting (7.4±2.2mm^2 versus 6.0±2.0mm^2, p = 0.035) and subsequently at follow-up (5.3± 2.8mm^2 versus 4.4±2.0mm^2, p=0.043).

Table 3. Comparison of major adverse cardiac events (MACE) and target lesion revascularization (TLR) rates between four groups

	Cutting Balloon with Stent (n=260)		POBA with Stent (n=261)		p
	IVUS-CBA (n=137)	Angio-CBA (n=123)	IVUS-POBA (n=142)	Angio-POBA (n=119)	(ANOVA)*
Subacute stent thrombosis (SAT, n)					
	0	0	0	1*	0.336
Late stent thrombosis (LST, n)					
	0	0	0	0	-
Death (n)	1	0	2	0	0.364
MI (n)	1	1	0	1*	0.766
TLR (n, %)					
PCI	10 (7.3)	17 (13.8)	23 (16.2)	16* (13.4)	0.145
CABG	0	0	0	1 (0.8)	0.336
Overall TLR (n, %)					
	10 (7.3)	17 (13.8)	23 (16.2)	17 (14.3)	0.138
Overall MACE (n, %)					
	12 (8.7)	18 (14.6)	25 (17.6)	19 (16.0)	0.171

All MACE recorded even if one event led to another, *the same patient

Clinical Outcomes

One patient in the IVUS-guided CBA with stent group was lost to angiographic follow-up and died of a ventricular arrhythmia 12 months after the procedure (Table 3). Late thrombosis or acute myocardial infraction was not observed in the CBA groups during follow-up period after the successful procedure, while two patients (one was IVUS-guided group the other was angiography-guided group) had procedure related myocardial infarction.

In the POBA with stent group, one patient died of heart failure 4 months after the procedure and one patient without follow-up angiography died of lung cancer 12 months after the procedure. In the angiography-guided POBA with stent group, one patient had myocardial infarction due to subacute stent thrombosis (Table 3).

There was a trend towards lower target lesion revascularization rates in the

IVUS-guided CBA group but this did not reach statistical significance (Table 3). Similarly, while the overall MACE was not significantly different between four groups, again the incidence of MACE was lowest in the IVUS-guided CBA group.

Multivariate analyses results

Multivariate analyses to evaluate the respective contributions of clinical, angiographic and IVUS variables to restenosis indicated that use of POBA but not CBA, smaller vessel area by IVUS, DM, LAD lesion location and stent length were independent predictors for stent restenosis at follow-up (Table 4). Minimal lumen area post stenting tended to be a significant (p=0.072) but not an independent predictor.

Table 4. Multiple logistic regression analysis to evaluate the respective contributions of clinical, angiographic and intracoronary ultrasound (IVUS) variables to restenosis (≥50% diameter stenosis at follow-up)

	Regression Coefficient	Standard Error	p	Odds Ratio	Confidence Limits Lower	Upper
POBA use	1.691	0.489	0.001	5.425	2.078	14.160
Vessel size by IVUS	-0.214	0.067	0.002	0.807	0.707	0.922
Diabetes	1.423	0.454	0.002	4.149	1.703	10.109
LAD location	1.356	0.479	0.005	3.883	1.518	9.933
Stent length	0.054	0.026	0.041	1.056	1.002	1.112
Min-CSA* post by IVUS	0.228	0.127	0.072	1.256	0.979	1.611

*CSA: Cross-sectional area

DISCUSSION:

This prospective multicenter randomized study has demonstrated that the use of an IVUS-guided cutting balloon strategy prior to stent implantation can achieve acceptably low restenosis rates (6.6%) that are comparable to those achieved with drug eluting stents. There was a 97% procedural success rate with no sub-acute or late stent thrombosis despite the fact that 30% of patients were diabetics and the lesions tackled were typically long, in small vessels and complex in character (63% AHA/ACC lesion type B2/C). While IVUS guidance consistently provided greater nominal balloon size than angiography guidance alone,

IVUS-guided CBA consistently achieved a greater lumen area than IVUS-guided POBA immediately after balloon pre-dilatation, after stenting and subsequently at follow-up. The greater lumen obtained by an IVUS-guided CBA strategy could have contributed to the favorable long-term outcomes observed. Multivariate analyses indicated that use of POBA but not CBA, small vessels, DM, LAD lesion location and stent length were independent predictors for restenosis at follow-up.

Mechanism of favorable outcome in IVUS guided CB prior to stent

IVUS guidance allowed us to use significantly greater balloon sizes than those by angiography guidance in the CBA and POBA groups (Table 2). Information about true vessel size and plaque distribution provided by IVUS significantly influenced the selected device size prior to the stent implantation and thereby significantly affected angiographic and clinical outcomes.

Although nominal balloon size was similar between IVUS-guided CB and IVUS-guided POBA, the inflated CBA size by QCA was significantly greater than inflated POBA size (3.32±0.51mm vs. 3.20±0.42mm, p=0.035). The greater inflated balloon size by CBA relative to POBA as well as the presence of cutting blades to create longitudinal incisions in the plaque may have contributed to the greater lumen area immediately after CBA relative to POBA (5.3±1.6mm^2 versus 4.1±1.3mm^2, p=0.019). This favorable effect of CBA also contributed to the greater lumen achieved after stenting (7.4±2.2mm^2 versus 6.0±2.0mm^2, p = 0.035) and subsequently, the greater lumen area seen at follow-up (5.3±2.8mm^2 versus 4.4± 2.0mm^2, p=0.043) (Table 2). These findings could explain the significantly lower restenosis rate (6.6%) in the IVUS-guided CBA group when compared with the other strategies (Table 2).

Previous studies investigating the benefit of IVUS guided PCI strategy have yielded conflicting evidence. While Fitzgerald and his coworkers indicated that IVUS guided stenting resulted in more effective stent expansion and subsequently, a lower restenosis rate in comparison with angiographic guidance alone [18], Mudra and his colleagues reported that optimizing stent implantation by IVUS failed to show beneficial effects on long-term outcome [19]. Mudra and his co-workers suggested that extensive experience with IVUS could produce similar final results to those without IVUS guidance. However, our data indicated that selected nominal CB and POBA sizes were significantly greater in IVUS-guided group than angiography-guided group. Recently, Oemrawsingh and Mintz and coworkers revealed that angiographic and clinical outcome after stenting for long lesions guided by IVUS is superior to that by angiography alone [20]. This suggests that IVUS guidance could still confer an advantage in long or complex lesions as well as in the cutting balloon related procedures.

Comparison with Previous Cutting Balloon Studies

While previous non-randomized studies indicated clinical benefit of this device[10], a multicenter study without IVUS and stenting failed to show an advantage of CBA over simple balloon angioplasty [9]. Our study is the first multicenter randomized trial comparing the strategy of using a CBA versus POBA prior to the stent implantation with and without IVUS guidance. Since using cutting balloon blades to create longitudinal incisions within the plaque incurs the potential risk of extravasation or coronary perforation, an understanding of plaque distribution and true vessel size gained by using IVUS is vital to maximizing the effect of the cutting balloon while minimizing the risk of major complications. We actually determined cutting balloon size including balloon length and the position based on the IVUS findings. This process may have some similarity to IVUS guided aggressive directional coronary atherectomy (DCA) rather than simple POBA or direct stenting [21]. Without IVUS guidance, an interventional operator tends to select undersized devices due to fears about the inherent danger of vessel perforation. This may negate the benefits of CBA and result in a sub-optimal smaller lumen similar to that which might be achieved with POBA.

Impact of the CBA-stent Strategy in the Era of Drug Eluting Stent (DES)

While pre-clinical studies revealed modest suppression of intimal hyperplasia, the First experience In Man (FIM) and the RAVEL studies indicated complete inhibition of restenosis [3,22]. The broader application of DES in the SIRIUS study markedly reduced but did not eliminate the problem of restenosis. Substantial growth in the real-life clinical use of DES has revealed some potential significant limitations. A recent FDA public health notification has warned that the occurrence of subacute stent thrombosis (SAT), late stent thrombosis (LST) and hypersensitivity reactions to sirolimus may have significantly contributed to the serious adverse cardiac events experienced in some patients [7]. Both subacute and late stent thrombosis have been associated with non-fatal myocardial infarction or death [8,23-25]. Similar problems have bedeviled the use of intracoronary brachytherapy [26]. Furthermore, long-term safety beyond three to four years is not yet available, while conventional stent use has a history spanning nearly two decades. In our study sub-acute and late stent thrombosis were not observed in the CBA arm and overall event-free survival of CBA with stent was 88.5% at follow-up.

The SIRIUS study obtained restenosis rates of 8.9% and a more recent multicenter paclitaxel eluting stent showed restenosis rate of 7.9% [4,5]. While reference vessel size was similar in the SIRIUS study, TAXUS IV study and our own REDUCE study (SIRIUS: 2.80±0.47mm, TAXUS IV: 2.75±0.47mm, our REDUCE: 2.80±0.47mm) and 64% of our patients had type B2/C, the restenosis rates of SIRIUS (8.9%) and TAXUS VI (7.9%) were similar to those achieved by our IVUS-guided CBA with bare metal stent strategy (6.6%) [4,5]. While it

is commonly believed that IVUS procedures are time consuming, it generally takes a few minutes in a single pullback in experienced IVUS catheterization laboratory. Whilst the list price of a cutting balloon is $950, IVUS $640 and the bare metal stent price has rapidly fallen down in the recent market, the drug-eluting Cypher stent is $3,195 and the Taxus stent $2,950. Furthermore, a recent strategy for DES requires full coverage of the lesion (i.e. increasing stent length and number of stents used), and substantially pushes up the interventional cost. Taking these circumstances into consideration, an IVUS-guided CBA-stent strategy could be an equally efficacious, safe, and cost-effective alternative to drug-eluting stents.

Study Limitations

Firstly, patients with lesions suitable for less than two stents were included in this study therefore it is not known whether the results can be extrapolated to longer lesions spanning three or more stents. Secondly, our data indicated that IVUS guided CBA prior to stenting contributed to reduced restenosis at follow-up. However, it is not confirmed whether IVUS guided direct stenting can obtain a similar outcome to the present study.

Conclusions

Despite tackling complex lesion morphology in small vessel, this prospective multicenter randomized study clearly indicated that the use of CBA prior to a bare metal stent strategy had high procedural success rate (97%) with favorable event-free survival (88.5%) at follow-up. IVUS guided CBA and stenting conveyed low restenosis rates (6.6%) comparable to those achieved in recent DES studies, suggesting that this strategy could be a viable substitute for DES in some clinical settings.

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APPENDIX:

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Chapter 14

Summary and Conclusion

Summary and Conclusion

Percutaneous coronary intervention (PCI) is a well established and effective therapy for patients with coronary artery disease. Several diagnostic tools are available to guide therapeutic interventions, assess coronary lesion morphology and monitor chronological changes in coronary luminal dimensions including quantitative coronary angiography (QCA), intracoronary ultrasound (IVUS) and angioscopy. Part I of this thesis (chapter 2 to 4) we assessed the reliability of these three quantitative and qualitative methodologies at the Thoraxcenter, Erasmus University, Rotterdam. Using our validated primary methodological techniques, in part 2 of this thesis (chapter 5 to 8) we investigated the impact of abnormal vasomotor tone and smoking status on the progression and regression of coronary atherosclerosis. In part 3 of this thesis (chapter 9 to 13) we evaluated the short- and long-term outcome of coronary stent implantation as well as cutting balloon angioplasty.

Chapter 1 provides the introduction and overview of the thesis including the clinical, scientific and methodological background.

Chapter 2 describes the measurements provided by geometric and videodensitometric QCA in comparison to IVUS measurements in 150 patients undergoing PCI. Following PCI the correlation between measurements of minimal lumen area by IVUS and those by edge-detection QCA was 0.74 in smooth contour, 0.46 in lesions with haziness, and 0.26 in lesions with dissection. Post PCI the difference between ICUS and videodensitometric QCA was less than the difference between ICUS and edge-detection QCA ($P<0.01$). We found that the complex morphological changes induced by intervention may contribute to the discordance between IVUS and QCA measurements. QCA with videodensitometry may be a complementary technique to edge-detection in lesions with complex morphology following PCI.

Chapter 3 reports experimental and clinical QCA comparison between cinefilm and digital video recording with and without edge enhancement. The experimental angiographic studies were performed using plexiglass blocks and stenosis phantoms 0.5 to 3.0 mm diameter. The clinical angiograms were recorded in 20 patients undergoing PCI. In the experimental phantom study, the utilization of cinefilm resulted in the most precise QCA measurements. In the clinical series, the differences between measurements from cinefilm and digital video without edge-enhancement were 0.14 ± 0.20 mm and from cinefilm and digital video with edge-enhancement were 0.04 ± 0.13 mm. These findings suggest that cinefilm is a more

reliable recording medium for QCA in scientific studies. However, for routine practice, digital video recording with edge-enhanced images may provide an acceptable alternative.

Chapter 4 compares three imaging modalities including coronary angioscopy, intracoronary ultrasound (IVUS) and quantitative coronary angiography (QCA) in unstable and stable patients. Post-mortem studies suggest that plaque rupture with superimposed thrombosis is the primary mechanism responsible for acute coronary syndromes such as unstable angina, and that in particular, lipid-rich coronary plaques with thin fibrous caps are most prone to rupture. We found that angioscopy demonstrated that plaque rupture and thrombosis were present in 17% of stable angina and 68% of unstable angina patients, although angiography discriminates poorly between lesions in stable and unstable angina. The ultrasound-derived plaque composition does not discriminate stable from unstable angina. While angioscopy is more sensitive in the presence of thrombus than the other modalities, intracoronary ultrasound could not clearly disclose differences in the characterization of atherosclerotic plaques in patients with stable or unstable angina.

Chapter 5 evaluates the long-term changes in coronary luminal dimension in patients with persistent vasospastic angina in comparison with patients transient vasospastic angina symptoms, using QCA and repeated ergonovine provocation tests. While it has been known for decades that coronary spasm frequently occurs at sites of significant atherosclerosis, it has not yet been determined whether vasospasm may play a role in the progression or regression of atherosclerosis. The minimal luminal diameter (MLD) and mean diameter of 19 spastic segments was significantly smaller (progression) at follow-up compared to the initial angiogram (mean follow-up; 45±16 months). The MLD and mean diameter of 93 non-spastic segments were not different between initial and follow-up angiograms. In patients whose symptoms resolved, the MLD and mean diameter of the 17 previously spastic segments significantly improved (regression) at follow-up, whilst the MLD and mean diameter of the 81 non-spastic segments were not significantly different at follow-up. Our results have demonstrated in patients an association between persistent vasospastic activity and progression of atherosclerosis and an association between cessation of vasospastic activity and regression of atherosclerosis.

Chapter 6 shows the relationship of long-term vasospastic activity to clinical presentations. Coronary spasm plays a role in a wide spectrum of ischemic coronary events including variant angina, and some cases of unstable angina and acute myocardial infarction. Quantitative coronary angiography and repeated ergonovine tests revealed that some patients with persistent vasospastic angina demonstrate fluctuation of vasospastic location (22 of 48 spastic vessels),

while others exhibit a fixed location of vasospasm. Vasospastic angina may not only be a transient disease restricted in location but may also be a persistent and variable condition involving multiple vessels over many years.

Chapter 7 addresses the role of coronary tone in the chronological changes of vasospastic anginal attacks. We compared basal coronary tone and vasospastic activity during both initial and follow-up angiographic studies in 190 coronary segments of 31 patients. We measured changes in the mean luminal diameter (Mean LD) of each entire spastic segment, segments adjacent to the spastic segment, and segments in nonspastic vessels at baseline after administration of ergonovine and after administration of isosorbide dinitrate, using QCA. The diagnostic sensitivity and specificity at 20% elevation of basal coronary tone for the prediction of vasospasm were 77% and 73%, respectively. We found that contrary to some previous reports, the estimation of basal coronary tone may be useful in the assessment of vasospastic activity in patients with variant angina.

Chapter 8 demonstrates the relationship between smoking status and plaque burden, vascular remodeling and restenosis in 1039 patients undergoing PCI. IVUS examination was performed in 450 patients to determine vessel area, lumen area, plaque area and remodeling index. Of the 1039 patients, 248 were current smokers, 468 ex-smokers and 323 non-smokers. Current smokers were more likely to be younger than ex-smokers or non-smokers (P=0.001), and to suffer from unstable angina (P=0.001). Current smokers had a significantly greater plaque burden in the lesion (P=0.001) and were more likely to have a positive remodeling index (P=0.001). Restenosis rates were similar between the three groups (P=0.955). Although restenosis was not affected by smoking, current smoking appears to result in an earlier and unstable presentation of coronary disease, reinforcing the importance of smoking cessation.

Chapter 9 represents the impact of Wallstent implantation on bailout management. We hypothesized that implantation of the oversized new Wallstents in native coronary arteries applying a policy of *restitutio ad integrum* (resetting the vessel size into the undiseased condition) would produce enforced mechanical remodelling of the coronary vessel with subsequent reduction in sub-acute occlusion and improved accommodation of reactive intimal hyperplasia. To test this hypothesis, we implanted 44 Wallstents in 35 native coronary arteries in 35 patients with acute or threatened closure following balloon angioplasty. We found that the Wallstent implantation conveyed a favourable six month angiographic outcome with restenosis rates of 16%. The enforced mechanical remodelling induced by the new oversized Wallstent may result in prevention of acute and chronic recoil of the vessel wall and subsequently confer a

lower restenosis rate in patients requiring bailout management.

Chapter 10 indicates the strategy of oversize Wallstent deployment for chronic total occlusion (CTO) in comparison with balloon angioplasty. We hypothesized that enforced mechanical remodelling by oversized stent implantation for CTO would convey a more favourable outcome than balloon angioplasty. The results were compared with a population of total occlusions undergoing successful balloon angioplasty and quantitative angiographic follow-up at 6 months in the same angiographic core laboratory. We found that oversized Wallstent implantation conveys a favourable short and long-term clinical and angiographic outcome (restenosis rate: 29%) in comparison with conventional balloon angioplasty (restenosis rate: 45%) for CTO.

Chapter 11 presents our early experience with the AVE stent primarily in long and complex coronary dissections after balloon angioplasty. To determine the feasibility and safety of deployment of this stent, we deployed 28 AVE micro stents in 23 native coronary artery lesions in 20 patients who developed acute or threatened closure after balloon angioplasty. The results of this early experience indicated that the AVE stent was deployed with a high procedural success rate (96%) and a minimal learning curve. Implantation of the stent as bailout management can be achieved with a low incidence of adverse cardiac events and a high angiographic success rate.

Chapter 12 reveals the problem of restenosis assessment within the radio-opaque tantalum Cordis stent. To determine the reliability of geometric (edge-detection) quantitative angiographic analysis (QCA) of restenosis within a tantalum stent, we compared QCA and intracoronary ultrasound (ICUS) in both an experimental restenosis model (plexiglass phantom vessels with concentric stenosis channels ranging from 0.75 to 3.0 mm in diameter) and in the clinical follow-up of 23 patients. We found that IVUS measurements are unaffected by the radiopaque stent. However, the mechanical problem of IVUS catheter wedging and the substantial cost of IVCUS catheters could limit the widespread application of IVUS for the assessment of intra-stent restenosis.

Chapter 13 discloses the impact of IVUS-guided Cutting Balloon Angioplasty (CBA) prior to stenting on restenosis at follow-up. We randomized 521 patients to CBA before stenting (260 pts) or plain old balloon angioplasty (POBA) before stenting. IVUS-guided procedures were performed in 279 (54%) patients and angiography guidance used in the remainder. The IVUS-guided CBA-stent strategy achieved a significantly lower restenosis rate of 6.6% (P=0.016) versus rates of 17.9% (angiography-guided CBA-stent), 19.8% (IVUS-guided

POBA-stent) and 18.2% (angiography-guided POBA-stent) in the remaining groups. The IVUS-guided CBA-stent strategy could therefore be a viable alternative to the use of drug eluting stents in achieving significant reductions in restenosis rates following percutaneous coronary intervention.

Chapter 14 conveys the conclusions of this project.

In conclusion, while QCA is still the gold standard for the estimation of coronary stenosis in terms of a quick overview of entire coronary tree during the procedures, it is increasingly important to evaluate the tomographic dimensions of the coronary lumen and morphological composition of vessel wall by IVUS. Our studies indicate that both QCA and IVUS are feasible and reliable techniques for estimating serial changes in coronary luminal dimensions. The use of QCA and IVUS has provided unique insights into the progression and regression of coronary atherosclerosis, and in particular the roles of smoking and coronary vasospasm. These techniques are also valuable for both studying and preventing restenosis. They have help to reveal that conventional coronary stenting, by supporting the vessel wall, limits early and late vessel remodeling and decreases restenosis. While short to medium term restenosis seems to have been overcome by the advent of drug eluting stent (DES), several limitations still remain to apply this technique to all the patients. IVUS guided cutting balloon angioplasty with stenting conveyed low restenosis rates (6.6%) comparable to those achieved in recent DES studies, suggesting that this strategy could be a viable substitute for DES in some clinical settings. The ultimate goal of interventional cardiology is to substitute coronary artery bypass grafting (i.e. a more invasive form of treatment) for less invasive percutaneous revascularization and control the progression of coronary atherosclerosis in long-term follow-up. The use of QCA and IVUS in concert with novel interventional strategies and devices heralds a new era in interventional cardiology in which these laudable aspirations may be realized.

Chapter 15

Samenvatting

Samenvatting

Progressie en regressie van coronaire atherosclerose zijn een belangrijke determinant voor het klinisch beloop van patiënten met ischaemisch hartlijden. Evolutie van het coronarialijden kan gemeten worden middels kwantitatieve coronair angiografie (QCA), intravasculaire echo (IVUS) en angioscopie. Hiermee kan afhankelijk van de gebruikte methode het lumen en/of de pathologie in de vaatwand zelf onderzocht worden. Deze technieken werden in het Thoraxcentrum onderzocht en vergeleken met elkaar (hoofdstuk 2-4), evenals het effect van een afwijkend gedrag van de vaatwand (vaattonus) en roken op de evolutie van het coronarialijden (hoofdstuk 5-8). In hoofdstuk 9013 werden de korte en lange termijn effecten van stent implantatie en cutting ballon angioplastiek geëvalueerd.

Hoofdstuk 1 betreft de inleiding en samenvatting van dit proefschrift.

In hoofdstuk 2 werd de geometrische en videodensitometrische QCA gegevens vergeleken met morfologische gegevens van IVUS in 150 patiënten die een PCI ondergingen. De correlatie was afhankelijk van de gebruikte techniek (contour detectie vs IVUS of videodensitometrie vs IVUS) en van de morfologische veranderingen van de plaque na PCI. Een belangrijke discordantie na PCI werd gevonden tussen IVUS en contour detectie. Mogelijk biedt videodensitometrie hiervoor een oplossing.

Hoofdstuk 3 beschrijft experimenteel en klinisch onderzoek waarin de resultaten van QCA worden vergeleken bij analoge (cinefilm) en digitale (met en zonder randversterking) beelden. Voor de experimentele studies werden plexiglas modellen gebruikt met daarin een vernauwing van 0.5 tot 3.0 mm. De klinische experimenten hebben betrekking op 20 patiënten die een PCI ondergingen. QCA meting in analoge beelden leverden de meest precieze resultaten op in het experimenteel onderzoek. Klinisch was het verschil tussen cinefim en digitale beelden het kleinst bij randversterking. (0.04 +/- 0.13 mm). Cinefilm geniet derhalve de voorkeur, zeker in het kader van wetenschappelijk onderzoek. Voor dagelijks gebruik is digitaal beeld met randversterking een goed alternatief.

In hoofdstuk 4 worden QCA, IVUS en angioscopie onderzocht en vergeleken in patiënten met stabiele en onstabiele angina pectoris. Angioscopie toonde aan dat plaque ruptuur en thrombus aanwezig was bij 17% van de patienten met stabiele angina pectoris en bij 68% bij patiënten met onstabiele angina pectoris. Contrast angiografie kan niet of slecht het onderscheid maken

tussen stabiele en onstabiele plaques. Dat is ook het geval voor IVUS.

In hoofdstuk 5 worden de veranderingen van het coronair lumen op lange termijn vergeleken tussen patiënten met persisterende en tijdelijke vasospastische angina pectoris. Hiervoor werd gebruik gemaakt van coronair angiografie (QCA) in combinatie met ergonovine. Van coronair spasme is bekend dat dit fenemeen vooral voorkomt in de coronair boom waar atherosclerose aanwezig is. Het is niet bekend of vasospasme een betrokken is bij progressie of regressie van coronaire atherosclerose. Progressie werd vastgesteld op de plaats van vasospasme bij patiënten met persisterende vasospastische angina. Regressie werd vastgesteld bij patienten bij wie klachten verdwenen. Deze bevindingen suggereren een relatie tussen vasospastische angina pectoris enerzijds, en pro- en regressie anderzijds, afhankelijk van persisteren of verdwijnen van klachten.

In hoofdstuk 6 wordt het effect van vasospasme op symptomen en klinische manifestaties op lange termijn onderzocht. Vasospame komt voor bij verschillende ziektebeelden zoals variant angina, onstabiele angina pectoris en zelfs acuut myocard infarct. QCA en ergonovine tests tonen aan dat de locatie van vasospasme in de coronair boom kan wisselen (22 van de 48 onderzochte bloedvaten). Bij andere patiënten bleef de plaats van vasospasme onveranderd. Zoals eerder beschreven, kan vasospame ook een tijdelijk fenomeen zijn.

In hoofdstuk 7 wordt de rol van coronaire vaattonus onderzocht bij patiënten met angina pectoris op basis van vasospasme. De verandering van minimale lumen diameter (MLD) van 191 segmenten van 31 patiënten werd met QCA (voor en na ergonovine en isosorbide dinitraat) onderzocht. Het betroffen segmenten met vasospasme, nabijgelegen segmenten en segmenten die geen vasospasme vertoonden. De gevoeligheid en specificiteit van QCA, uitgaand van een 20% verandering van basale tonus, bedroeg 77 en 73%, respectievelijk. In tegenstelling tot eerder onderzoek, vonden wij dat de basale vaattonus wel van nut is voor het vaststellen van vasospastische angina pectoris.

In hoofdstuk 8 wordt de relatie tussen, enerzijds, roken en, anderzijds, hoeveelheid plaque, vaatwand remodelleren en restenose bij 1039 patiënten die een PCI ondergingen, onderzocht. IVUS werd bij 450 patiënten uitgevoerd voor het bepalen van de dimensies van de coronair arterie en plaque, evenals voor het bepalen van de index van het remodelleren. Van deze groep, waren er 248 patiënten die nog steeds roken, 468 waren gestopt met roken en 323 hebben nooit gerookt. Patiënten die nog steeds roken waren jonger en leden meer aan onstabiele angina pectoris. Ze hadden een significant grotere hoeveelheid plaque in de onderzochte vernauwing,

maar ook meer een positieve remodelleringsindex. Het optreden van restenose was gelijk in de drie groepen. Dit onderzoek suggereert dat roken leidt tot het eerder optreden van klinische tekenen van coronaire atherosclerose met tekenen van onstabiliteit.

In hoofdstuk 9 wordt de hypothese onderzocht dat implantatie van een Wallstent , waarvan de ontplooide diameter groter is dan deze van het ontvangende vaatbed teneinde de initiële grootte van de coronair arterie te herstellen, gepaard gaat met een versterkte remodellering, minder van effect van eventuele neoinitma hyperplasie op de bloedstroom en minder stentafsluiting. Dit werd onderzocht bij 35 patiënten bij wie 44 stents werden geïmplanteerd wegens dreigende of acute afsluiting van een kransslagader na ballon angioplastiek. Restenose kwam voor bij 16% van de patiënten 6 maanden na implantatie. Het is mogelijk dat implantatie van een te grote stent in relatie tot de vaatdiameter gepaard gaat met een lagere kans op terugveren van de vaatwand en restenose.

In hoofdstuk 10 wordt dezelfde hypothese onderzocht als in hoofdstuk 9 maar in patiënten met een chronische totale afsluiting van de kransslagader en in vergelijking met ballon angioplastiek. Restenose 6 maanden na stent implantatie was 29% en was 45% na ballon angioplastiek.

Onderwerp van onderzoek in hoofdstuk 11 is de evaluatie van de toepasbaarheid en veiligheid van implantatie van de AVE micro stent. Dit werd geëvalueerd in 20 patiënten bij wie 28 AVE stents in 23 kransslagaderen werden geïmplanteerd wegens dreigende of acute vaatafsluiting na ballon angioplastiek. Stent implantatie verliep zonder problemen in 96% van de patiënten Er was een lage incidentie van cardiale gebeurtenissen en een hoog percentage van angiografisch geslaagde ingrepen.

In hoofdstuk 12 wordt het optreden van restenose na implantatie van een tantalum Cordis stent onderzocht. Tantalum laat weinig Röntgenstralen door en kan derhalve QCA analyse met contour detectie verstoren. Daarom werd naast QCA ook IVUS uitgevoerd en met elkaar vergeleken. Dit werd uitgevoerd in een experimenteel model (fantomen uit plexiglas met gekende diameters) en klinisch (stent implantatie bij 23 patiënten). Zoals verwacht werd de IVUS meting niet verstoord door de radio-opake stent. Echter, technische factoren zoals afsluiten van het bloedvat door de IVUS catheter en prijs van de IVUS catheter zijn een beperkende factor voor het algemeen gebruik van deze techniek voor het bepalen van in-stent restenose.

In hoofdstuk 13 wordt het optreden van restenose onderzocht na cutting ballon angioplastiek

onder geleide van IVUS. In totaal werden 521 patiënten gerandomiseerd naar cutting ballon of standaard ballon angioplastiek gevolgd door stent implantatie in beide gevallen. IVUS werd uitgevoerd bij 279 patiënten (54%). Bij de overige patiënten werd enkel contrast angiografie uitgevoerd. Restenose na IVUS geleide cutting ballon angioplastiek was 6.6%, 17.9% na angiografische geleide cutting ballon angioplastiek, 19,8% na IVUS geleide standaard ballon angioplastiek en 18.2% na angiografische geleide standaard ballon angioplastiek.

Besluit:

QCA is nog steeds de gouden standaard voor het bepalen van de ernst van een coronaire stenose. Tomografische dimensie van het lumen en inzicht in plaque compositie middels IVUS zijn in toenemende mate belangrijk voor het bepalen van het beleid van coronaire interventie. Zowel met QCA als IVUS kan op adequate wijze seriële veranderingen van het lumen van een kransslagader onderzocht worden.
Prognose van een patiënt met coronaire atherosclerose is mede afhankelijk van pro- en regressie van het ziekteproces. Wij vonden dat coronaire spasme en cardiovasculaire risicofactoren zoals roken hierin een belangrijke rol spelen.
Stent implantatie voorkomt vroeg en laattijdig remodelleren van de vaatwand en vermindert restenose. Het gebruik van stents die een medicijn afgeven aan de vaatwand (DES) verlagen zo mogelijk nog verder de kans op restenose. Gebruik van deze stents wordt gekenmerkt door een aantal beperkingen. Wij vonden dat restenose het laagst was na IVUS geleide cutting ballon angioplastiek met stent implantatie (6.6%). Dit komt overeen met de kans op restenose na DES implantatie. IVUS geleide ballon angioplastiek met stent implantatie kan derhalve overwogen worden als alternatief voor DES.

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Curriculum Vitae

Curriculum Vitae

The author was born in Osaka, Japan on October 19, 1954 where he received his primary and secondary school education. He graduated from Nagoya University School of Medicine and was subsequently awarded the MD degree associated with the Physician's License authorized by the Ministry of Health, Labour and Welfare in 1981. He did internal medicine residency between 1981 and 1983 at the Anjou Kosei Hospital. In 1983 he became a member of physicians at the Anjou Kosei Hospital and received further clinical experience of internal medicine and cardiology. Between 1983 and 1985 he gained further clinical cardiology experience including cardiac catheterization, cardiac ultrasound and patient managements in the CCU at the Anjou Kosei Hospital. From 1985 to 1992 he worked as a staff cardiologist and performed coronary interventions with Dr. Fumimaro Takatsu, Dr. Junichi Ohosugi (Anjou Kosei Hospital) and occasionally under the guidance of Prof. Tetsu Yamaguchi (Mitsui Memorial Hospital). He also started to receive research training from Prof. Junji Toyama, Prof. Itsuo Kodama, Prof. Kaichiro Kamiya and Dr. Takafumi Anno (Nagoya University). In 1992 he was subsequently awarded the PhD degree from Nagoya University School of Medicine. In 1992 he was awarded an international fellowship to investigate clinical aspects of restenosis, vasospasm and coronary atherosclerosis and moved to the Thoraxcenter Erasmus University Medical Center Rotterdam, the Netherlands. While he was working under the promotion of Prof. Patrick W. Serruys, Prof. Jos RTC Roelandt and Prof. Pim de Feyter at the Thoraxcenter, Erasmus MC from 1992 to 1996, he established the clinical research background especially for this thesis. In 1996 he was invited as a chief of catheterization laboratory and became an assistant professor of cardiology, Aichi Medical University Hospital, Nagakute, Japan. In 1999 he was made a fellow of the American College of Cardiology (FACC) as well as a fellow of the European Society of Cardiology (FESC). In 2001 he was recommended as a senior fellow of Japanese Society of Interventional Cardiology (SFJSIC). In 2004 he was again invited as a chief of catheterization laboratory as well as an associated professor of cardiology, Fujita Health University Hospital, Toyoake, Japan. He continues to be deeply involved in coronary interventions, emergency patient care, medical education and clinical research as a senior interventional cardiologist at the Fujita Health University Hospital.

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