CORONARY STENTING :

A QUANTITATIVE ANGIOGRAPHIC AND CLINICAL EVALUATION

CORONAIR STENTING :

EEN QUANTITATIEVE ANGIOGRAFISCHE EN KLINISCHE EVALUATIE

Proefschrift

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To my wife Sharon

and our children Stephen, Anna, and Michael.

C O N T E N T S

Coronary Stenting : A Quantitative Angiographic and Clinical Evaluation

Introduction

Methodology

Angiographic & Clinical Evaluation

Conclusion

Introduction

Chapter I

Introduction and Overview of Thesis

Introduction and overview of thesis

Following implantation of the first coronary stent in 1986 by Jacques Puel in Toulouse, coronary stenting has, from a sequence of pioneering registries in the late 1980's to an era of randomized trials in the 1990's, come to adopt a prominent role in today's practice of interventional cardiology. In its conventional naked metallic form, coronary stenting represents a mechanical approach to a biological problem. When appropriately deployed, the coronary stent can tack back dissections and restore normal flow in vessels with threatened or acute closure and provides a means to optimize elective angioplasty of primary and recurrent stenoses in both native coronary arteries and aorto-coronary vein grafts by enforced remodelling.

Much of our current understanding and expectations from coronary stenting has been derived from extensive experience with three primary stent prototypes, namely the Palmaz-Schatz (a balloon-expandable mesh stent), the Gianturco-Roubin (an unsheathed balloon-expandable coil stent), and the Wallstent (a sheathed self-expanding mesh stent with coil-like flexibility). The last few years has witnessed in addition to modifications of the above prototypes, the introduction of a new generation of stent designs with variable emphasis on low metallic surface area, low balloon-mounted profile, flexibility, and radiopacity. With such a variety of structural designs and such a spectrum of coronary lesions amenable to stenting, it is likely that each new stent will have to prove its own indications and niche. Instead of comparing the efficacy of each stent design with conventional balloon angioplasty, new stents will soon have to demonstrate their efficacy relative to previously established stents.

Our evaluation of coronary stenting has been primarily through the recording of hard clinical endpoints (reintervention, bypass surgery, myocardial infarction, and death) and through the technique of quantitative coronary angiography (QCA). QCA provides, at the time of the interventional procedure, guidance of optimal stent deployment and allows quantification of acute luminal gain and acute recoil following stent implantation. At angiographic follow-up, QCA provides a measurement of intrastent restenosis in addition to changes in vessel calibre proximal and distal to the stent.

The decision on whether or not to stent during an interventional procedure is frequently based upon the angiographic findings alone in the absence of (and to prevent) any clinical deterioration of the patient. The documentation by QCA of a residual stenosis post intervention (the suboptimal result) or the progressive deterioration in the minimal luminal diameter of a threatened vessel closure may provide an indication to stent. Once committed to stenting, QCA facilitates precise sizing of both the diameter and length of the selected stent. QCA of both the inflated intrastent balloon and the resultant stented lumen allows the sensitive detection of points of residual luminal narrowing and guidance of additional high pressure intrastent balloon inflations.

The recent introduction of on-line QCA to nearly all interventional suites, has contributed significantly to the transformation of the previous art of coronary stenting of the 1980's associated with an unfavourable rate of subacute stent thrombosis and restenosis to the current practice and science of QCA-optimized stenting characterised by a large acute luminal gain often with a negative residual diameter stenosis and consequent low rate of subacute stent thrombosis and ability to accommodate intimal hyperplasia over the ensuing

six month period. In addition to complementing clinical observation, QCA has in multicenter stent trials served as a surrogate for clinical endpoints. Such a surrogacy is of increasing importance as the incidence of hard clinical events post stenting continues to fall and the era of randomized trials for the comparison of stents of different design is dawning. The reliability and validation of QCA thus becomes of fundamental importance for both the optimal practice and scientific evaluation of coronary stenting.

Part I of this thesis addresses the reliability of the methodology we currently use to evaluate coronary stenting, namely QCA. The reliability and validation of quantitative angiographic measurements and the validity of clinical surrogacy by QCA for coronary interventional trials are examined, while Part II of this thesis reports the results of quantitative angiographic and clinical evaluation of the acute and long-term outcome of both elective and bailout stenting of native coronary arteries and the primary stenting of aorto-coronary vein grafts.

In chapter II, we report for the first time our results of three studies ((i) on the discordance and surrogacy of clinical events and QCA, (ii) catheter calibration for QCA measurements, and (iii) the application of the technique of signal-averaging for the analysis of analogue video data) conducted over the last two years to evaluate quantitative coronary angiography. The validity of utilising QCA as a surrogate for clinical endpoints is analyzed with cumulative frequency curves by the comparison of the minimal luminal diameter at angiographic follow-up in patients with and patients without clinical end-points who have participated in multicenter interventional trials of balloon angioplasty and coronary stenting. On the basis of the relationship between clinical and QCA endpoints and the recent insights provided by our matching studies and by intracoronary ultrasound, a strategy for the design of sequential restenosis prevention studies is proposed. In chapter II we also report the results of a study on catheter calibration adding more data to the ongoing controversy on whether catheter calibration of QCA measurements should be performed on the catheter in the contrast-free or contrast-filled state. Furthermore in chapter II, the value of conventional statistical parameters for the reporting of validation studies is critically appraised, the current shortcomings are expounded with the aid of hypothetical validation results, and a new approach for the reporting and interpretation of QCA validation studies is proposed and applied to the results of one of our most recent comparative validation studies. Finally in chapter II, we report the results of our application of the technique of signal averaging in an attempt to increase the signal to noise ratio of analogue angiographic images recorded on videotape for QCA analysis. In-vitro stenoses of known diameter were recorded at reduced speed in edge-enhanced and in unfiltered modes on videotape at four different catheterization laboratories. With the use of a multiple frame grabber and customized digital signal averaging software, the potential applicability of the technique was evaluated.

In chapter III, the results of a comparative study evaluating the performance of 10 QCA systems at major core laboratories in North America and Europe are reported. A standardized set of cineangiograms of intracoronary phantom stenoses were analyzed at each laboratory in an objective and user independent manner. No system was found to be perfect and all systems demonstrated both random as well as systematic errors. A global tendency to underestimate large luminal diameters and to overestimate small luminal diameters by all QCA systems was revealed.

In chapter IV, we report the results of an attempt to overcome the overestimation of small luminal diameters by the introduction of a dynamic edge detection algorithm with variable weighting of the first and second derivative and variable kernel size of the derivative

operator. The experimental algorithm was evaluated on a set of in-vivo phantom stenoses with a range of 0.5mm to 1.9mm. On the basis of the promising results it is conceivable, that the conventional approach of a fixed weighting of the first and second derivatives for all QCA measurements may be inappropriate, and that overestimation of small diameters may be solved by increasing the weighting of the first derivative and reducing the kernel size of the derivative operator and similarly underestimation of large diameters might be addressed in the future by increasing the relative weighting of the second derivative.

With the advent of coronary stents and the "bigger is better policy", larger minimal luminal diameters are now being achieved by coronary interventional procedures compared to the results previously achieved by balloon angioplasty alone. To date no in-vivo model has allowed the evaluation of QCA performance in the range of lumen diameters encountered by stenting. In chapter V, we report a new technique for the delivery of coronary "stent stenoses" for the evaluation of QCA measurements of large luminal diameters in pigs. While our previous technique of intracoronary insertion of phantom stenoses required the permanent attachment of double lumen plexiglass channels to the tip of a Fogarty catheter, we devised a new technique based on the principles of coronary stent delivery. Single channel stenoses were mounted on a compliant balloon catheter. Prior to the introduction of the balloon-mounted plexiglass stenoses through the carotid sheaths of anaesthetized pigs, the balloons were inflated at low pressure within the stenoses to produce a firm dumbell fixture with subsequent secure and effective delivery of the stent stenoses to the coronary arteries. Deflation and subsequent withdrawal of the mounted balloons allowed the acquisition of angiographic stenoses of up to 2.9 mm for the evaluation of QCA performance.

Quantitative coronary angiography can be performed by two basic techniques, geometric (the edges of the vessel are detected in two dimensions) and densitometric (the relative brightness intensity of the vessel is quantified to provide a three-dimensional estimation of cross-sectional area from a single view). In chapter VI, we compare the measurements provided by these two QCA techniques with the measurements provided by intracoronary ultrasound in patients undergoing coronary interventional procedures.

Having validated our primary methodological technique for the evaluation of coronary stenting, Part II of this thesis proceeds with the sequential evaluation of the stents currently available for clinical evaluation. In chapters VII - IX, the Wallstent is evaluated, in chapter X the Palmaz-Schatz stent, in chapter XI and XII the Gianturco Roubin stent, in chapter XIII the bailout stent, in chapter XIV the AVE Micro stent, in chapter XV the Wiktor stent and Wallstent, and in chapter XVI the Cordis stent. In chapter XVII the mechanical, radiographic, and angiographic characteristics of all currently available stents including the ACS Multilink stent are quantitatively compared and finally in the concluding chapter, (chapter XVIII) a potential clinical niche for each stent design is proposed.

The European registry of coronary Wallstent implantation in the 1980's reported a high rate of subacute thrombosis which was felt to relate in part to the high requirement for multiple stents and thus result in the delivery of a higher metallic (and thus potentially thrombogenic) burden. This arose from a major degree of longitudinal shortening upon expansion of the Wallstent. To address this limitation, the design of the Wallstent was changed to produce the new Less Shortening Wallstent (LSS). These changes in structural design and insights gleaned from the previous European multicenter registry data are presented in detail in chapter VII.

Concerns over the potential longterm sequelae of a foreign body in the coronary vessel wall

have been expressed over stenting throughout the last decade and restraint in elective stenting urged until such data becomes available. In collaboration with Jacques Puel and his team in Toulouse, the long-term quantitative angiographic outcome of patients who received a Wallstent in the mid 1980's including the first patient ever stented is presented in Chapter VIII. The quantitative angiographic results are compared with those of the acute procedural and 6 month angiographic follow-up and are found to be most encouraging. The results indicate that, as with balloon angioplasty the restenosis process following stent implantation appears to be a time limited phenomenon, that progression of intrastent atherosclerosis is not accelerated, and that the ostia of side branches "jailed" by the mesh of the Wallstent remain patent. Such reassuring data suggests that the development of biodegradable stents may not offer many long-term mechanical advantages over coated metallic stents beyond the advantage of providing a greater reservoir for prolonged elution of pharmacological agents.

In chapter IX the results of the first evaluation of the new Less Shortening Wallstent are presented from a multicenter safety and feasibility study in coronary vein grafts taking the new Wallstent design off from the bench top and into the clinical arena.

In the BENESTENT trial, elective implantation of the Palmaz-Schatz stent was shown to convey an improvement of both clinical and angiographic outcome compared to conventional balloon angioplasty. In chapter X, the impact of vessel size on clinical outcome is examined for the stent and balloon populations of BENESTENT. Using both a logistic regression (continuous) as well as a categorical approach, it is determined that stenting in vessels below 3.0mm conveys an increased risk of subacute stent thrombosis and an increased number of clinical events in the 12 month follow-up period. Furthermore, the interaction of vessel size and stent : vessel ratio on outcome is analyzed using a multivariate approach. The study provides clinical guidelines on the range of vessels suitable for stenting as well as directions for stent sizing under the guidance of on-line QCA.

The Gianturco-Roubin stent is a flexible coil stent with transversely oriented struts. In chapter XI the expansion and distribution of recoil following Gianturco-Roubin stent deployment are examined in a detailed quantitative angiographic analysis. A policy of stent oversizing and use of an additional high pressure intrastent inflation with a non-compliant balloon are recommended to compensate for recoil and improve the acute angiographic result.

In chapter XII, the GRACE trial (Gianturco-Roubin stent in Acute Closure Evaluation), in which the author of the thesis has been integrally involved over the last two and half years, is reviewed. The substrate of the trial - acute and threatened closure following angioplasty is reviewed and the relative efficacy of bailout stenting versus repeated prolonged balloon inflation are compared by a review of the literature. The concept of the "pre-study" for the screening and learning curve of investigators with the Gianturco-Roubin stent deployment technique and the concept of the "rolling protocol" design with periodic updates in an attempt to ensure that, when reported, the results of the randomized trial have implications for current clinical practice with optimal stent sizing and evolving approaches to anticoagulation and antiplatelet therapy. In chapter XIII, the current concepts and challenges of bailout stenting are addressed and the inherent difficulties of hard and soft criteria are discussed with implications for future clinical trials.

The AVE Micro stent represents a new direction in stent design. Its short size and radiopacity render it ideal for exquisite positioning under radiographic guidance in ostial

lesions as a single device, and for improving the inflow and outflow of longer stents as a complementary device in multiple stenting. In chapter XIV, we report our experience with this new stent primarily in the domain of multiple stenting of long and complex coronary dissections.

In chapter XV, the gain loss relationship and luminal renarrowing process following Wiktor stent and following Wallstent implantation are studied and compared with results obtained with balloon angioplasty and directional coronary atherectomy by the technique of linear regression analysis after normalization for vessel size.

In chapter XVI, the problem of restenosis assessment within the new radiopaque tantalum Cordis stent is assessed by intracoronary ultrasound and by quantitative coronary angiography using both geometric and densitometric techniques.

In chapter XVII the quantitative mechanical, radiographic, and angiographic characteristics of each of the currently available coronary stents are compared. To determine in a standardized and uniform manner the relative compliance and radial force provided by each stent design, we designed a customized bench-top stent compliance measurement device. Pressure-compliance curves were created for each of the stent designs. While the AVE Micro stent was found to provide the greatest radial force, the Wallstent was found to be the most compliant. To determine the relative radiopacity of each stent we performed densitometric analysis on an alignment of all stent designs and found the ACS stent to be the most radiolucent and the Cordis stent to be the most radiopaque. We subsequently compared the influence of each of the stents on the reliability of automated quantitative angiographic measurements. These characteristics are of relevance for QCA as well as for ease of precise positioning of each stent under radiographic guidance.

In the concluding chapter, (chapter XVIII) the characteristics and substrate of each of the current clinical indications and coronary lesions for stent implantation are evaluated with specific reference to their stent requirements. The suitability of each stent design to match these interventional requirements are reviewed on the basis of the findings of this thesis, on the basis of clinical experience, and on the basis of published studies. Finally the advantages and disadvantages of each stent are discussed a potential clinical niche for different stent designs is proposed.

Coronary stenting has in ten years come a long way. As coated and drug delivery stents now undergo clinical evaluation and the era of randomized trials comparing stents of different design for each clinical indication is dawning, it is becoming clear that coronary stenting is here to stay.

Methodology

Chapter II

Quantitative coronary angiography: An integral component of interventional cardiology.

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QUANTITATIVE CORONARY ANGIOGRAPHY

Since the development of semiautomated quantitative ventriculography by the use of the first and second derivatives of the brightness profile by Slager and coworkers [1–3] in the mid 1970s, the application of these principles and the conversion from analogue to digital processing for the development of semiautomated quantitative coronary angiography (QCA) by Reiber and coworkers [4] in the late 1970s, and the clinical application of QCA to interventional cardiology in the early 1980s by Serruys and coworkers [5], QCA has undergone a series of refinements. These include reduction in processing time; more user-friendly hardware and software; more versatile handling capabilities—not only for cineangiograms but also for angiographic images stored on analogue videotape and on a variety of digital storage and media formats; techniques for isocentric calibration [6]; three-dimensional reconstruction of biplane angiograms [7]; and more sophisticated edge detection algorithms [8]. Perhaps the most exciting refinement over the past decade has been the provision of on-line QCA.

The development of QCA has paralleled our advances in interventional cardiology and has contributed significantly to our current understanding of coronary artery disease. The replacement of visual assessment by semiautomated QCA for the conduction of scientific studies was both timely and welcome [9,10,11•]. By providing computerized, objective, and reproducible measurements of coronary luminal dimensions, QCA offered a scientific medium for the study of acute procedural results and serial changes over medium-term (6 months) and long-term follow-up. In particular, changes in the absolute minimal luminal diameter (MLD) have been utilized for the study of acute luminal gain and subsequent restenosis following coronary interventional procedures and changes in the mean luminal diameter have been utilized for the study of progression-regression of coronary artery disease [12]. Following the establishment of off-line QCA as a reliable research tool, on-line QCA was adopted in routine clinical practice to guide coronary interventional procedures. Its virtually ubiquitous availability in modern interventional suites has allowed the application of interventional principles, such as "the bigger, the better," learned from off-line QCA analyses and device sizing using on-line QCA has now become an accurate science rather than subjective art.

With the advent of complementary or competitive imaging modalities (intracoronary ultrasound, angioscopy, intracoronary Doppler, magnetic resonance imaging, ultrafast computerized tomography and three-dimensional echocardiography) for coronary luminal quantification, defense by QCA of its title, the gold standard for scientific research and subsequent growth of its role in clinical practice will become critically dependent upon the demonstration of superior reliability of QCA measurements. Given that QCA

TABLE 12-1. NEGATIVE QUANTITATIVE CORONARY ANGIOGRAPHY RESULTS FOR THREE PHARMACOLOGIC TRIALS ON RESTENOSIS PREVENTION AFTER BALLOON ANGIOPLASTY*

Study	Patients, *n*	MLD follow-up placebo mean± SD (range)	MLD follow-up active Rx mean± SD (range)	Loss placebo mean± SD (range)	Loss active Rx mean± SD (range)
CARPORT	522	1.46±0.59 mm (0.00–2.95)	1.49±0.58 mm (0.00–3.15)	0.31±0.54 mm (-1.09–2.89)	0.31±0.55 mm (-0.71–2.54)
MERCATOR	595	1.48±0.54 mm (0.00–3.15)	1.54±0.54 mm (0.00–3.15)	0.29±0.49 mm (-1.04–2.29)	0.27±0.51 mm (-0.99–2.26)
PARK	592	1.44±0.58 mm (0.00–3.41)	1.43±0.62 mm (0.00–3.57)	0.24±0.52 mm (-0.81–2.29)	0.27±0.49 mm (-1.16–2.21)

*Note the relatively high standard deviation of the measurements which incorporates the variability of quantitative coronary angiography (QCA) measurements (±0.20 mm) as well as the clinical range of outcome following intervention (ranging from total occlusions to an increase in minimal luminal diameter [MLD] at follow-up [>3.5 mm]).

necessitates the performance of repeated invasive procedures, and yet does not provide direct data on the vessel wall, it is unlikely that the current dominant role of QCA will survive into the next decade. Given that 1) 18 years following the introduction of interventional cardiology, its overwhelming limitation continues to be the bane of restenosis, and 2) that angiographic predictors of primary procedural success and complications are primarily derived from the art of qualitative angiography [13–21] rather than the science of semiautomated quantitative angiography, this chapter reviews the insights provided by, the current limitations of, and the challenges ahead, for QCA in interventional research and practice.

QUANTITATIVE CORONARY ANGIOGRAPHY IN CLINICAL RESEARCH

QCA as a Surrogate for Clinical Events in the Study of Restenosis Following Coronary Intervention

STUDIES OF PHARMACOLOGIC AGENTS FOR THE PREVENTION OF RESTENOSIS

Over the past 5 years, a significant number of scientifically conducted trials on the prevention of restenosis following coronary intervention using QCA endpoints as a surrogate for clinical events have been entirely negative [22–28]. The failure of the tested phamacologic agents to exert any detectable effect on luminal loss at follow-up as assessed by QCA (Table 12-1) has been disheartening in view of the promising results of preclinical in vitro and in vivo studies. The disappointing angiographic results of these trials threw into question the ability of QCA to detect minor differences in study populations (because of the random and systematic errors of QCA measurements). Of some restoration of faith in QCA, in addition to being angiographically negative, these trials also failed to detect a difference in clinical outcome between the actively treated and control patients. Although it should be acknowledged that the power calculations of these trials were based on QCA-derived primary endpoints and not clinical event rates.

In support of the tenet that QCA presents a reliable surrogate for coronary events, a subanalysis of the MERCATOR study population demonstrated an association or coupling between the QCA-derived parameter, minimal luminal diameter (MLD) at follow-up and the clinical event rate [23]. MLD at follow-up was divided into quintiles and a pattern of decreasing MLD with increasing coronary events and decreasing exercise test performance was demonstrated (Table 12-2) [23].

To further test the validity of using QCA as a surrogate for clinical events in restenosis prevention studies following coronary intervention, we can compare the QCA results of those patients in whom a major clinical event (reintervention, bypass surgery, myocardial infarction, or death) ocurred with QCA results of those patients in

TABLE 12-2. PROGNOSTIC VALUE OF THE MLD AT FOLLOW-UP IN 595 PATIENTS IN THE MERCATOR TRIAL DIVIDED INTO FIVE EQUAL GROUPS*

MLD follow-up, *mm*	Exercise test, *n (%)*		Clinical events, *n (%)*			
	<1 mm ST change and no chest pain	≥1 mm ST change and chest pain	MI	Reintervention	Angina	None
<1.10	70 (75)	24 (26)	5 (4)	49 (41)	24 (20)	41 (35)
1.10–1.39	88 (88)	12 (12)	1 (1)	18 (15)	25 (21)	74 (63)
1.40–1.63	103 (90)	11 (10)	2 (2)	10 (8)	31 (26)	77 (64)
1.64–1.91	99 (93)	8 (7)	1 (1)	7 (6)	21 (15)	89 (75)
≥1.91	111 (98)	2 (2)	1 (1)	7 (6)	18 (15)	94 (78)
Total patients	471	57	10	91	119	375

*A relationship between the quantitative coronary angiography-derived variable, MLD at follow-up and both functional performance and clinical events is apparant. MI—myocardial infarction; MLD–minimal luminal diameter. *From* [23]; with permission.

whom a clinical event did not occur (Figure 12-1). Despite failure of QCA to detect an effect of the pharmacologic agents on luminal narrowing, it is clear in Figure 12-1 that QCA is effective in the separation of clinical-event-positive and clinical-event-negative patient groups. In three drug studies the difference in mean MLD between the clinical-event-positive and the clinical-event- negative patients was 0.37 mm for CARPORT ($P = 3.E^{13}$); 0.42 mm for MERCATOR ($P = 6.E^{17}$); and 0.51 mm for PARK ($P = 3.E^{27}$). For patients who received a Palmaz-Schatz (Johnson & Johnson, USA) stent in the BENESTENT study, the difference in MLD between the clinical-event-positive and the clinical-event-negative patients was even more striking, 0.86 mm ($P = 2.E^{48}$). These differences offer further support to the validity of including QCA endpoints as either primary or secondary endpoints in the study of medium-term outcome following coronary interventional procedures.

SHOULD QCA BE EXPECTED TO DETECT A PHARMACOLOGIC REDUCTION OF RESTENOSIS FOLLOWING BALLOON ANGIOPLASTY?

To address this important question the following points should be considered.

1. The reproducibility of analyses of serial angiographic studies in a given static patient population for a QCA system (which is currently in use at a core laboratory for the analysis of multicenter restenosis trials) has been assessed in two recent studies [11,29]. In both studies this clinical reproducibility has been shown to be ± 0.20 mm. This figure would be

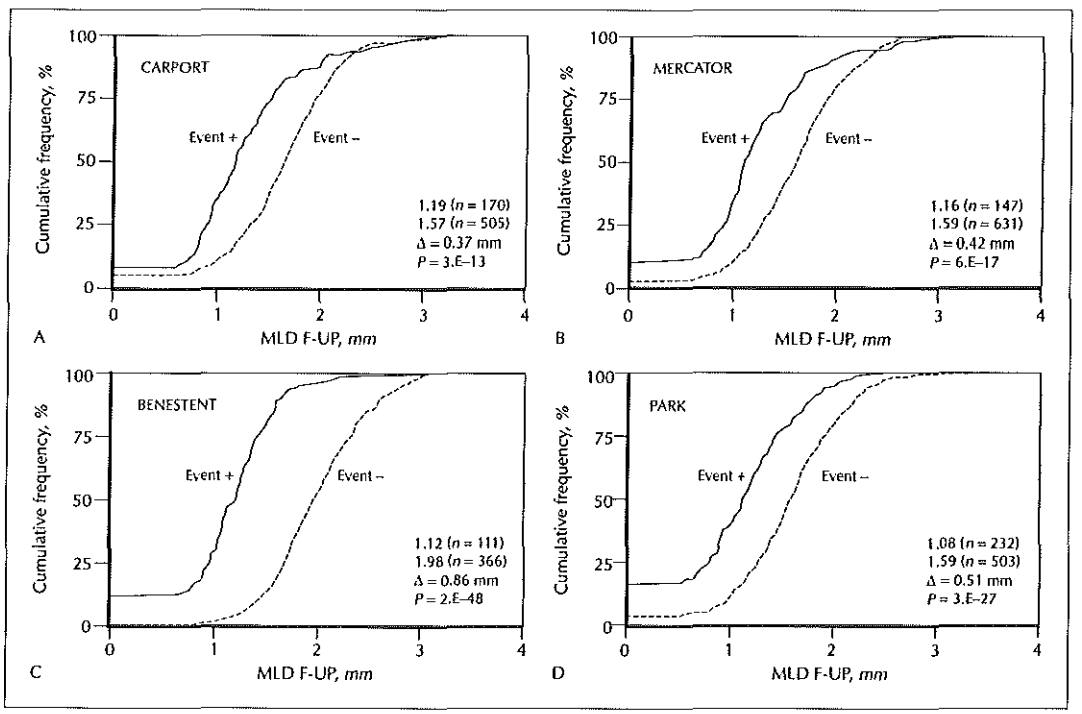

Figure 12-1. Quantitative coronary angiography (QCA) in the differentiation of event positive and event negative patient groups in CARPORT, MERCATOR, PARK, and BENESTENT. To test the validity of using QCA as a surrogate for clinical events in restenosis prevention studies, we compared the QCA results of those patients in whom a major clinical event (reintervention, bypass surgery, myocardial infarction, or death) occurred with the QCA results of those patients in whom a clinical event did not occur. The patients were taken from three neutral pharmacologic studies (CARPORT, MERCATOR, and PARK and from the patients who had received a stent in a positive device randomized trial (BENESTENT). QCA was highly effective in the separation of the clinical event–positive and clinical event–negative patient groups. These differences (up to 0.86 mm in BENESTENT) lend support for the policy of including QCA endpoints as either primary or secondary endpoints in the study of medium-term outcome following coronary interventional procedures. F-up—follow-up; MLD—minimal lumen diameter.

expected to be significantly higher in the absence of the controlled angiographic conditions of a prospective clinical trial coordinated by a core angiographic laboratory.

2. The average loss in luminal diameter at 6-month angiographic follow-up of patients treated by balloon angioplasty is approximately 0.30 mm [22–25].
3. If clinically effective, a pharmacologic agent that blocks one or more steps of the biologic cascade that leads to intimal hyperplasia might be expected to result in a 25% reduction of luminal loss at 6-month angiographic follow-up. The figure for estimated reduction of 25% is based on the probability that a drug, if highly effective, would reduce intimal hyperplasia by 50%. Given the recent evidence from intracoronary ultrasound (ICUS) studies by Mintz and coworkers [30] and ongoing work at the Thoraxcenter, indicating that intimal hyperplasia composes only 40% to 56% of the luminal renarrowing following coronary balloon angioplasty while the remainder of the renarrowing consists of late constriction of the vessel, a 25% reduction in luminal renarrowing is at least reasonable if not optimistic.
4. The natural variation in a patient population with 6-month angiographic results is large, ranging from a total occlusion at follow-up (MLD = 0 mm) to an increase in MLD during follow-up by remodelling (MLD > 3.5 mm). This has resulted in a standard deviation of MLD at follow-up for treated and control patients of more than ± 0.5 mm.
5. Thus, in the conduction of restenosis trials we are expecting QCA with, at very best, a clinical reproducibility of ± 0.20 mm, to be able to detect a difference of 0.06 mm (equivalent to the size of one pixel on QCA systems offering a high resolution and less than one pixel in other QCA systems) between the widely ranging (0 mm > 3.5 mm) treated and control patient groups.

It could therefore be proposed that we possibly are expecting too much by relying on QCA to detect a pharmacologic effect on restenosis following balloon angioplasty. Can we continue to justify the execution of further trials testing single pharmacologic agents on the prevention of restenosis following balloon angioplasty, knowing that it is highly unlikely that such drugs will reduce late vessel wall constriction?

In view of the above concerns, we should reconsider the application of QCA in studies on restenosis prevention. What measures can we take to increase our ability to detect a pharmacologic effect on restenosis?

Can we improve on the reproducibility of serial QCA analyses? A series of practical measures can be demanded by the core laboratory in the conduction of randomized angiographic trials to reduce the variability of radiographic acquisition and subsequent analysis. An outline of these measures is provided later in this chapter. Radiograph technology and image quality are continuously improving with each new generation of equipment. The resolution of digitally stored images has now greatly increased and in most systems the focal spot size can now be reduced to 0.4 mm. Although the tube would expire more quickly due to overheating if the focal spot was always set at the smallest setting, it might be reasonable to request that all angiograms for QCA trials be recorded using the smallest focal spot. This measure should reduce the point spread function and should thus reduce the tendency to overestimate small luminal diameters by QCA. All QCA systems undergo a continuous process of validation at core laboratories and subsequent refinement of algorithms and recalibration. The contribution of both the hardware components as well as the software algorithms should be considered as potential points for technical improvement in QCA performance. QCA validation is discussed later in this chapter. Can we improve on our pharmacologic strategies? Given the multiple pathways and phases of biologic cascade of restenosis, it is likely that only a combination of several drugs targeted for and administered during the different stages of the restenosis process will prove to be finally effective. Can we increase the substrate of our clinical model for the testing of potential restenosis preventative therapies? To determine whether balloon angioplasty provides the optimal substrate, we need to review the insights provided by QCA on luminal renarrowing following the application of different coronary interventional devices.

The Ideal Clinical Model for Testing Restenosis Preventative Therapies: Insights Provided by QCA and Matching

Analysis of QCA data from interventional studies using matching [31–35] as a surrogate for randomized trials has provided us with an accurate predictor of outcome of subsequent randomized trials and offers an effective mechanism for power calculations of prospective trials. For the testing of a specific hypothesis, the process of

matching can at times provide a more pure and effective model than a prospective clinical trial, as confounding variables can be removed provided that the pool of patients from which the ideal matches are selected is sufficiently large. Matching can overcome some of the inherent limitations of prospective randomized trials. For instance, in a prospective randomized trial it is difficult to decipher whether the greater restenosis after atherectomy or other device compared with balloon angioplasty is a result of the greater acute luminal gain or due to the mechanism of gain. In our most recent matching study we have demonstrated that not only does luminal loss increase with increasing extent of luminal gain [34,36] but also that luminal loss varies according to the mechanism of luminal gain [35]. Using the same QCA system that measured an average loss following balloon angioplasty of 0.30 mm as described above, we had previously found that the luminal loss following atherectomy is 0.68 mm [34]. When we subsequently matched for 1) vessel size, 2) acute procedural gain, and 3) MLD postprocedure in a second study [35], the mechanism of atherectomy (cutting) was found to induce a greater subsequent loss of 0.53 mm compared with the loss of 0.26 mm at 6 months following the stretching action in the matched balloon angioplasty patients. When the MLD postatherectomy was divided at the median into optimal atherectomy (MLD post > 2.47 mm) and suboptimal atherectomy (MLD post < 2.47 mm), the MLD at 6 months follow-up was 1.92 mm for optimal atherectomy and 1.67 mm for suboptimal atherectomy ($P < 0.05$) [35]. Of greater importance for our quest of the ideal clinical model for testing restenosis preventative therapies, we found that the loss at 6 months following optimal atherectomy was 0.86 ± 0.64 mm compared with 0.42 ± 0.59 mm for suboptimal atherectomy.

Clearly, even with a standard deviation of QCA measurements of ± 0.64 mm (which incorporates the reproducibility of ± 0.20 mm of serial clinical QCA measurements in a static population as well as the natural variability of the study population in angiographic outcome at 6 months), the likelihood of QCA detecting a 20% reduction in restenosis following atherectomy (0.17 mm) compared with a 20% reduction in restenosis following balloon angioplasty (0.09 mm) will be greater.

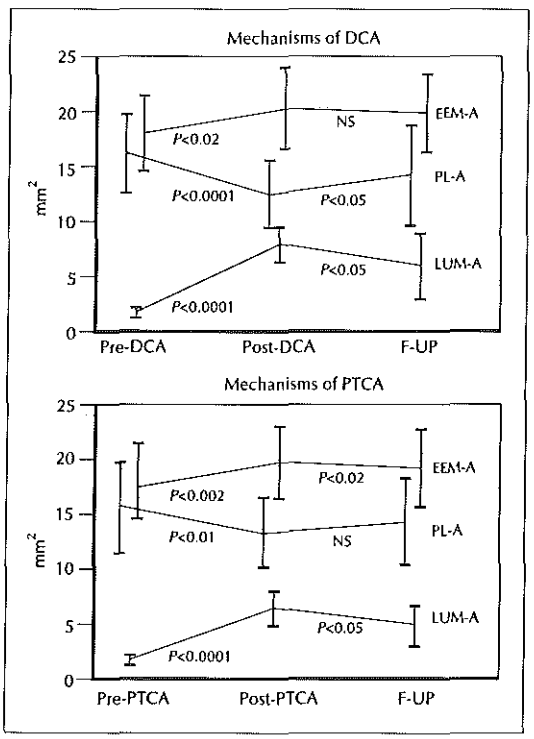

Figure 12-2. Mechanism of luminal renarrowing following percutaneous transluminal coronary angiography (PTCA) and directional atherectomy (DCA). Intracoronary ultrasound studies at the Thoraxcenter have compared the mechanism of luminal renarrowing following PTCA and following DCA. Luminal renarrowing (LUM-A) is due to a higher proportion of intimal hyperplasia (plaque area, PL-A) and a lower proportion of late vessel constriction (external elastic membrane area [EEM-A]) following DCA (28% late vessel wall constriction) compared with balloon angioplasty (44% late vessel wall constiction). These results have significant implications for pharmacologic attempts at restenosis prevention following different devices, given that a drug would be unlikely to effect late vessel wall constriction. F-up—follow-up; NS—not significant.

Additionally we have found, in an ongoing program of comparison by ICUS of the mechanism of restenosis following different coronary interventional devices, a higher proportion of intimal hyperplasia and a lower proportion of late vessel wall constriction (external elastic lamina area) in restenosis following atherectomy (28% late vessel wall constriction) compared with balloon angioplasty (44% late vessel wall constriction) (Fig. 12-2). Thus, if a drug was highly effective clinically and reduced intimal hyperplasia by 50%, this would result in an approximately 36% reduction in luminal renarrowing following atherectomy compared with an approximately 28% reduction following balloon angioplasty.

On the basis of the above findings we have adopted the optimal atherectomy model for the study of a pharmacologic agent for the prevention of restenosis in European Carvedilol Atherectomy Restenosis Evaluation (EUROCARE). This is a multicenter trial that will compare the efficacy of a polypharmacodynamic agent (the actions of which include strong antioxidant properties) in the prevention of restenosis using a QCA-derived variable as a primary endpoint (MLD at follow-up). Our adoption of the optimal atherectomy model has allowed us to reduce the number of patients required for recruitment in a randomized trial to 350 patients as well as increase the statistical power of our study compared with previous balloon angioplasty trials.

In the first study of QCA and matching of baseline stenosis characteristics, de Jaegere and coworkers [31] demonstrated that luminal loss following coronary stenting is greater (0.48 mm after Wallstent implantation) compared with a matched balloon angioplasty population (0.20 mm) [31]. This increased luminal loss following stenting was subsequently confirmed in two prospective randomized trials [37–39]. Furthermore, by the provision of a chronic radial force, early recoil and subsequent late vessel wall constriction following stenting is reduced to less than 20% (with likely greater reduction in vessel wall constriction from the more rigid mesh stents compared with the more flexible coil stents [39,40], and the restenosis substrate is thus likely to be a more pure form of intimal hyperplasia—the substrate against which most pharmacologic agents have been shown to be effective in preclinical trials.

In view of our somewhat shaken confidence in the sensitivity of QCA (lumenography) to detect a pharmacologic reduction in restenosis and given that a significant portion of the increase in plaque volume may be accommodated by outward expansion of the vessel wall [41], we have in EUROCARE also incorporated ICUS (murelography) imaging to compare plaque volume in the actively treated and placebo patients. Thus EUROCARE promises to be a showdown between the two imaging modalities. Should ICUS detect a reduction in plaque volume at 6 months plus or minus a greater luminal cross-sectional area at 6 months, and should QCA fail to detect a reduction inluminal renarrowing, our reliance on QCA to provide the primary endpoint (as the gold standard) of future clinical trials testing a single potential agent for restenosis prevention is likely to change.

Phases and Design of Restenosis Trials

Following an initial experience of successively negative trials characterized by variable trial design, power calculations, patient selection, and endpoints, a rational standardized three-phase approach to the prospective clinical assessment of potential pharmacologic agents for restenosis prevention was proposed [42].

Phase 1 comprised a small noncomparative pilot study (approximately 100 patients) using clinical endpoints only to demonstrate the safety of the drug in the setting of percutaneous coronary intervention and possibly to detect an efficacy trend that might be taken into consideration in the power calculations of phase 2.

In phase 2, providing the drug was shown to be safe in phase 1, a medium-sized controlled trial (approximately 600 patients) would be undertaken that was statistically powered to detect differences in QCA-derived variables as the primary endpoint. Clinical variables would also be studied as secondary endpoints although the trial would not be powered to detect a statistically significant reduction in major clinical event rate.

In phase 3, providing a significant improvement in angiographic outcome was demonstrated in Phase 2, a large clinical trial (approximately 2000 patients) would be undertaken without QCA to put the clinical efficacy of the drug to the test (as well as serendipitously putting the predictive value of QCA to the test).

Such screening of potential pharmacologic agents by medium-sized QCA trials, has yet to be demonstrated to be scientifically justified. Of interest was the approach taken in the design of the EPIC trial [43,44]. Rather than performing a QCA trial, the second phase of the above approach was bypassed and a large (2099-patient) clinical trial was directly undertaken. This approach has, in retrospect, at least for this pharmacologic agent (c7E3—a platelet IIb/IIIa

integrin antibody fragment), proven to be effective. A drug has been shown to be clinically efficacious without the expense (both temporal as well as fiscal) of incorporating follow-up angiography and QCA. However, in order to determine how this drug exerted a reduction in clinical event rates, rather than to determine whether this drug will be clinically effective, a QCA trial with c7E3 has now been undertaken (EPILOG). In addition to the luxurious position of testing the angiographic mechanism of action of c7E3 (*ie*, reduction in total occlusions (thrombosis) or reduction in global renarrowing), EPILOG will also serve to put QCA, the surrogate, to the test retrospectively.

A common path between these two alterntive approaches for the assessment of a potential pharmacologic agent for the prevention of restenosis, of phases 1, 2, 3 as proposed above and the 1, 3, 2 approach taken in the EPIC and EPILOG trials, might be the merging of phases 2 and 3, whereby the second (final) phase would consist of a clinical trial of 2000 patients and would include the performance of follow-up angiography with QCA in 600 of the 2000 patients. This strategy would be more economical in the long term and would lead more quickly and directly to a definitive result. Such economy and expedience in the execution of clinical trials could also be proposed for the merging of restenosis and progression trials, whereby the patients participating in a restenosis trial testing a pharmacologic agent that would be likely to reduce both restenosis and progression (*eg*, the antioxidant, carvedilol [EURO-CARE] or the HMGCoA reductase inhibitor, fluvastatin [FLARE] [45]) or a calcium antagonist [46—48] would be maintained on active treatment and undergo follow-up angiography at 6 months and at 3 years with QCA of all coronary segments.

Implications for Interventional Trials Derived from the Study of QCA in Progression and Regression Trials

Further evidence in support of the use of quantitative coronary angiography as a surrogate endpoint for clinical coronary events, arises from studies on progression and regression, where initially isolated angiographic evidence of progression has been subsequently followed during longer-term follow-up by higher clinical event rates. This positive predictive value of angiographic endpoints has been demonstrated for both visual assessment [49] as well as for semi-automated quantitative coronary angiography [11•,48]. Is the coupling of QCA and subsequent clinical events due to the observation of a paraphenomenon, or does the measurement of a severe coronary stenosis by QCA directly predict an increased risk of occurrence of a coronary event in this target vessel at the point of the minimal luminal diameter? Little and colleagues and other investigators have revealed that coronary occlusions that produce a myocardial infarction frequently occur at sites that previously contained minor, insignificant luminal narrowings and that the lesions with the severest stenosis are often found to be patent in such patients [50–54]. It has been proposed that angiographic evidence of progression or regression in one segment may be a marker of disease activity that may involve other coronary segments but not be apparent on the coronary angiogram [50••]. Whether this holds true for the demonstration by QCA of severely restenotic lesions (large luminal loss over 6 months) following intervention has yet to be clearly demonstrated. It has been proposed that the endoluminal cap of a restenotic lesion is more stable and less susceptible to fissuring than a primary atherosclerotic plaque of equivalent luminal diameter. Thus, it might be expected that the detection of restenosis following intervention by QCA might be more predictive of functional reversible ischemia, recurrence of angina and subsequent symptomatic need for revascularization, rather than predicting myocardial infarction and death.

QCA in Randomized Trials Comparing Interventional Devices: Dissociation Between QCA and Clinical Endpoints

Our trust in QCA to detect statistically significant differences in outcome in patients undergoing coronary interventional procedures has been partially restored by the simultaneous and mutually supportive positive QCA results of BENESTENT and STRESS, which used different QCA systems to compare angiographic outcome at 6 months in patients receiving a Palmaz-Schatz stent and patients undergoing balloon angioplasty alone [37–38]. The value of QCA was further strengthened by both of these studies as the reduction in QCA-determined restenosis was associated with a reduction in the number of clinical events in those patients randomly selected to receive a stent.

CAVEAT and CCAT also used different QCA systems (single worst view reported) to compare outcome following directional coronary atherectomy and following balloon angioplasty [55,56•]. CAVEAT included all coronary vessels while CCAT only included left anterior descending vessels. Assessment of acute angiographic outcome by

off-line QCA in the core laboratories resulted in an angiographic success rate (< 50% diameter stenosis) for atherectomy and for balloon angioplasty in CAVEAT of 89% and 80%, respectively and in CCAT of 98% and 91% respectively. While the pattern of relatively larger acute luminal gain following atherectomy was revealed by the off-line QCA analyses at the core laboratories of both trials, the difference between 89% and 98% for acute angiographic success rates for atherectomy between the two trials is more than would be expected given that the procedural policies of both trials were so similar. Although many explanations for this difference may exist, one possibility that should be considered is a systematic difference in the QCA systems used to analyze the trials in the core laboratories. It is of interest that in CAVEAT the mean residual diameter stenosis postatherectomy as assessed by the off-line QCA system at the core laboratory was 29% in comparison with 15% when assessed by the investigators.

CAVEAT reported an isolated significantly larger MLD in the proximal left anterior descending artery at 6 months in patients treated by atherectomy (MLD = 1.32 mm for atherectomy and 1.12 mm for balloon angioplasty ($P < 0.01$), however, a reduction in clinical events over the 6-month follow-up period was not conferred in these patients [55]. This uncoupling of angiographic and clinical outcome was found to persist when follow-up was extended to 1 year [57]. Such dissociation of angiographic and clinical results behests caution in the excessive reliance on QCA as a surrogate endpoint for clinical coronary events. Further caution on the reliability of QCA arises from a discordance between the angiographic results of CAVEAT with the angiographic results of CCAT, which reported no difference in either angiographic or clinical outcome at 6 months between the atherectomy (MLD at follow-up = 1.55 mm) and balloon angioplasty (MLD at follow-up = 1.61 mm) patients.

A paradoxical trend between QCA and clinical outcome was also seen in the PARK trial where despite a trend for reduced clinical events in the treated (ketanserin) patients compared with the control (placebo) patients, a trend in the opposite direction was seen in the QCA results whereby the luminal loss was greater in the treated patients (Fig. 12-3). Although the reasons for such a paradox between QCA and clinical outcome in a pharmacologic study may be complex, they again undermine the policy of exclusive reliance on QCA as the sole primary endpoint of interventional trials.

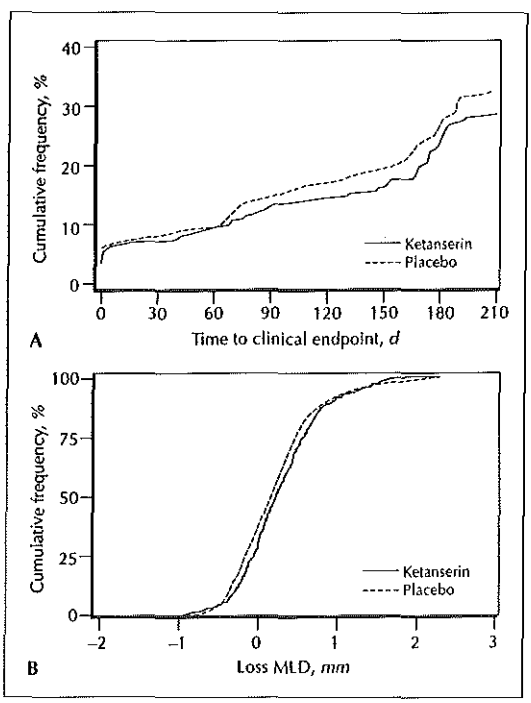

Figure 12-3. Paradox of quantitative coronary angiography (QCA) and clinical results in the PARK trial. A and B, Dissociation between QCA and clinical outcome was seen in the PARK trial where despite a trend for reduced clinical events in the treated (ketanserin) patients compared to the control (placebo) patients, a trend in the opposite direction was seen in the QCA results whereby the luminal loss was greater in the treated patients. Although the reasons for such a paradox between QCA and clinical outcome in a pharmacologic study may be multifactorial, they behest caution in the exclusive reliance on QCA as the sole primary endpoint of interventional trials. MLD—minimal luminal diameter.

A common finding in the QCA analysis of the four randomized device trials, CAVEAT, CCAT, BENESTENT, and STRESS was the relatively small vessel size reported. Although the inclusion criteria of the trials requested a vessel size of more than 3.0 mm (or ≥ 3.0 mm) as assessed on site by the investigator, the mean preprocedural reference vessel diameter as assessed by off-line QCA at the core angiographic laboratory was on average approximately 3.0 mm with an average standard deviation of approximately 0.47 mm for the four trials. In addition to possibly reflecting potential errors in the estimation of vessel size by the investigators on site, these results would also be consistent with a tendency of off-line QCA systems when calibrated by the catheter to underestimate measurements of large luminal diameter as suggested by several QCA validation studies. Appropriately, in none of these four device trials were patients excluded from the per protocol analysis by virtue of the measurement of a vessel size of less than 3.0 mm at the core angiographic laboratory.

APPLICATION OF ON-LINE QCA IN INTERVENTIONAL PRACTICE

The emergence of digital (subtraction) angiography has allowed the on-line performance of QCA measurements in the catheterization laboratory, so that a technique previously confined to research applications has been transformed into a practical technique, directly influencing clinical decision making in real time (Fig. 12-4).

In October 1993 we undertook a survey of interventional practitioners in Europe who had an experience of greater than 40 directional coronary atherectomy cases. At that time, 34 of the 36 interventionalists surveyed used on-line QCA, while only 24 of the 36 had experience with intracoronary ultrasound.

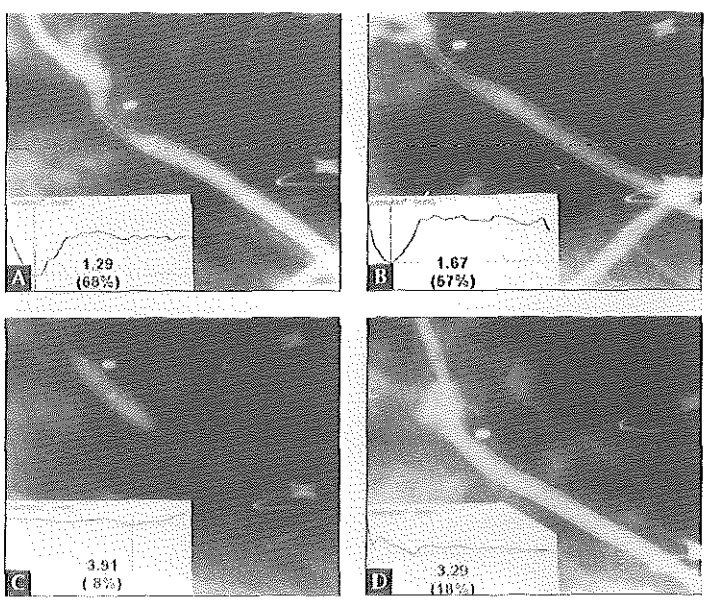

Figure 12-4. On-line quantitative coronary angiography (QCA) to guide interventional procedures. **A**, An ostial lesion of a saphenous vein jump graft was found to have a minimal luminal diameter (MLD) of 1.29 mm with a percent diameter stenosis of 68% and a length of 17 mm. A self-expanding less shortening coronary Wallstent of 4.5-mm nominal diameter and 29-mm nominal implanted length was selected to provide a stent to vessel difference of 0.4-mm diameter and a margin of 6 mm at the proximal and distal ends of the stent (to reduce the risk of misplacement by shortening of the Wallstent upon expansion). **B**, Following release of the radiolucent Wallstent a residual MLD of 1.67 mm was measured. **C**, A noncompliant balloon of 4-mm diameter was selected and inflated within the Wallstent to a peak pressure of 8 atmospheres during which the inflated balloon was found to have a uniform inflation with a MLD of 3.91 mm and a percent diameter stenosis relative to the mean balloon diameter of 8%. **D**, Final postprocedural measurement confirmed a residual MLD of > 3.00 mm and a percent diameter stenosis of < 20%, both of which have been shown to be associated with a reduced risk of subacute thrombosis.

During an interventional procedure on-line QCA can be used to provide an interpolated reference diameter to guide balloon-artery ratios [58,59] and the sizing of other devices. Recent studies using off-line QCA would indicate that appropriate stent sizing (oversizing) and inflation is of significant value and should effect long-term outcome [37,60].

The use of on-line QCA to confirm that an optimal result has been achieved has now become an integral component of interventional practice, particularly since the adoption of the bigger the better policy. The definition of angiographic (procedural) success is becoming more stringent (a moving target), and in EUROCARE, OARS, and BOAT this definition has changed from the traditional residual diameter stenosis of less than 50% to the new definition of less than 20% or 15% [35].

Other than to determine the diameter and length of a stent, the role of on-line QCA in the quantification of a threatened closure or dissection is limited. Clearly in the case of acute closure, on-line QCA can only provide the reference diameter of the proximal segment. In the case of a threatened closure, most information can be gleaned by serial visual assessment of dynamic parameters such as TIMI flow over time (by examining a sequence of images) [61–63]. The serial quantification of a static parameter such as the documentation of a reduction in MLD over 15 minutes by repeated on-line QCA can be of some help but is usually superfluous. The presence of a radiopaque guidewire in a dissected vessel further confounds QCA analysis as demonstrated in Figure 12-5. Edge-detection algorithms typically perform poorly and unpredictably in the case of extravasation of contrast, however, the recent development by van der Zwet and colleagues [8] of a gradient field transform algorithm that is capable of tracking dissections with extraluminal contrast and complex lesional morphology more accurately than minimal cost criteria algorithms may improve the value of on-line QCA in the assessment of threatened vessel closure.

Although it would be expected that the elimination of some steps in image acquisition and processing and the elimination of nonisocentric calibration should result in improved reliability of on-line QCA measurements, a recent study using phantom stenoses in porcine coronary arteries found that the accuracy and precision of one off-line QCA system was comparable with those obtained by an on-line QCA system using a different edge detection algorithm [64–66]. It seems, therefore, that basic concepts derived from the study of cinefilm images by reliable off-line QCA systems can be applied to on-line analysis to guide the operator during diagnostic and interventional procedures accepting a degree of discrepancy in absolute values according to the particular on-line and off-line QCA systems deployed [66]. With the recent introduction of interventional policies such as the bigger the better for balloon angioplasty and directional atherectomy and the change in policy from matching of stents to reference vessel size to a policy of oversizing, it could be considered that on-line QCA has become an essential requirement for optimal coronary interventional practice.

Although QCA can provide a measure of curvature, roughness, symmetry, and plaque volume, and indirect calculations of the hemodynamic significance of lesions [67•,68], these quantitative measurements have been inadequately validated and their current reliability appears to be no better than that provided by

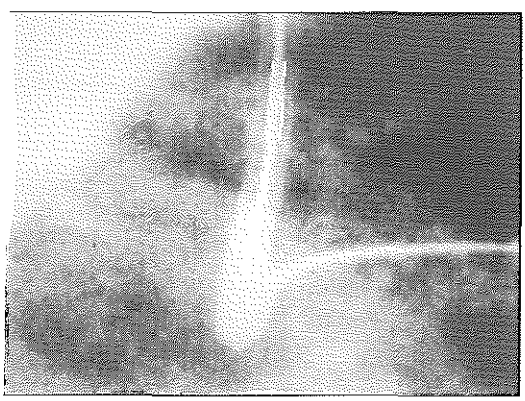

Figure 12-5. Tracking of a radiopaque guidewire by quantitative coronary angiography (QCA). Tracking of a radiopaque guidewire by QCA during catheter calibration in the contrast-empty state. The presence of a radiopaque guidewire in a catheter or coronary vessel may interfere with automated edge detection, in the absence of sufficient contrast medium.

visual qualitative assessments of lesion characteristics. We are currently assessing the agreement of semiautomated quantitative coronary measurements with traditionally derived visual assessments of ABC classifications. Agreement and correlation appear to be very poor for almost all parameters. Thus, despite the known poor interobserver agreement of visually assessed qualitative parameters, further improvements and research will be required before the use of computer-derived quantitative measurements of lesion and vessel morphological characteristics can be recommended.

Which QCA Variable Conveys the Most Information?

Prior to the introduction of QCA, the severity of coronary lesions used to be expressed in terms of percent diameter stenosis. Following the report that the restenosis process involves the normal reference segments immediately proximal and distal to the treated lesion [69], expression of restenosis rates in terms of percent diameter stenosis was subsequently found to be uninformative, at times deceptive (*eg*, pseudo regression [70]), and insensitive to the detection of a therapeutic effect in restenosis trials and imparted a reduction in statistical power of studies. The absolute minimal luminal diameter at follow-up is a static measurement providing an objective, reproducible and unambiguous parameter for the expression of the final angiographic outcome and conveys information of functional significance, while change in minimal luminal diameter provides a dynamic parameter to describe the process of luminal gain and loss. Determination of the reference vessel diameter, however, continues to be of value for the selection of device and stent size during on-line analysis and for obtaining direct comparisons between study groups in view of the known effect of vessel size on absolute luminal loss following intervention.

The conventional method of determination of the reference vessel diameter requires the user to select a reference position at a normal proximal point. In arteries with a focal obstructive lesion and clearly normal proximal and distal luminal diameters, selection of the reference point should be fairly reliable. However, in cases where the proximal part of the arterial segment contains both stenotic and ectatic areas, the selection may be difficult and unreliable. To overcome this subjectivity, an interpolated technique was developed to determine the reference diameter at the actual site of the stenosis without operator interference. The basic principle behind the technique is the computer estimation of the original diameter values over the obstructive region (assuming there was no coronary disease present) based on the diameter function. Following this approach the reference diameter is taken as the value of the polynomial at the position of the minimal luminal diameter. This objective and reproducible technique of reference vessel diameter determination is not yet available in all QCA systems but its value is becoming increasingly more recognized.

PRACTICAL MEASURES IN ANGIOGRAPHIC ACQUISITION AND QCA ANALYSIS FOR THE IMPROVEMENT IN REPRODUCIBILITY OF SERIAL QCA MEASUREMENTS

Pincushion Distortion

Pincushion distortion introduces a selective magnification of objects in the periphery of an image compared with those at the center. This can be overcome by the recording of a centimeter grid from each angiographic system to be analyzed off line. Some QCA systems can then memorize the degree of distortion by each system and make adjustments accordingly during each subsequent analysis. Furthermore, regions of interest should be filmed at the center of the image whenever possible. Fortunately the newer image intensifiers introduce significantly less pincushion distortion than previous ones.

S-Distortion

S-distortion, which results from geomagnetism and additional local magnetic field forces, varies considerably according to the angulation of the X-ray gantry. Corrective functions for such S-distortion are complex and have the potential to introduce more error than they promise to resolve.

Aspect Ratio

With the use of video as a storage medium for coronary angiograms, a new source of distortion and challenge arises for QCA—the aspect ratio. Non-CCD cameras (*eg*, vidicon or plumbicon) have an independent horizontal and vertical adjustment for magnetic beam deflection. This can give up to 10% differences between horizontal and vertical adjustment for magnetic beam

deflection. This results in up to a 10% difference between horizontal and vertical dimensions and thus the spatial orientation of the coronary segment becomes critically important. In addition to the horizontal and vertical gain in the X-ray camera, aspect ratio errors may also be introduced if the clock speed of the digitization board in the radiograph system is not adjusted for square pixel size. Furthermore, aspect ratio errors will occur if the aspect ratio of the frame grabber or the video digitizer in the QCA system is different than 1:1 (*eg*, in some systems it is 4:3). Most QCA systems offering pincushion distortion correction can now also correct for error in the aspect ratio (Fig. 12-6).

Differences in Angles and Height Levels of the X-ray Gantry

To improve the sensitivity of angiographic studies to detect change in luminal diameter over time, it is important that paired angiograms are acquired in the same views. This can be achieved by the automatic on-line recording of gantry settings and table height and selected X-ray exposure factors (kV, Ma) or written documentation on a technician's worksheet of the settings when on-line recording is unavailable. Attention to the table height and to the focal spot isocenter distance and the focal spot image intensifier distance will become increasingly more important if a drive toward isocentric calibration is to be effective.

Multiple Matched Views

When the method of QCA is geometric (edge detection) rather than videodensitometric, it is important that multiple orthogonal views (three for the left coronary artery and two for the right) be analyzed rather than a single worst view to provide a reliable analysis of eccentric lesions [71].

Differences in Vasomotor Tone

Because vasomotor tone may vary widely during consecutive coronary angiographic studies, it should be controlled at all times. Intracoronary nitrates should be administered immediately before pre- and post-procedural angiograms and at follow-up. Calcium antagonists are also

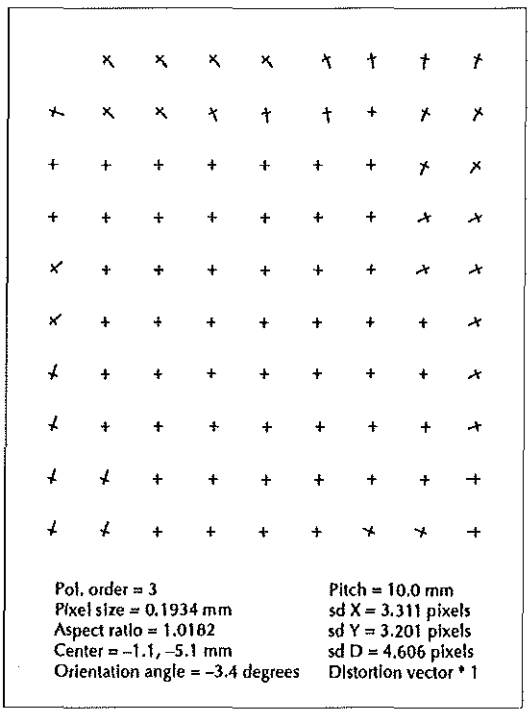

Figure 12-6. Aspect ratio and pincushion distortion. In addition to correcting for pincushion distortion, some quantitative coronary angiography (QCA) systems can also correct for the aspect ratio (difference in horizontal and vertical dimensions associated with videotape recordings of coronary angiograms). This is achieved by the recording of a centimeter grid at the beginning of a procedure. The detected and subsequently corrected or rectified points of intersection of the centimeter grid can be seen in the figure. The pincushion distortion from this radiograph system (Philips DCI) is relatively mild and typical for the current generation of radiograph hardware. It can be appreciated that the recording of the angiographic catheter in the center of the image and then the coronary stenosis in the center of the image will result in minimal distortion even when subsequently analyzed by a QCA system that does not correct for distortion.

given at some centers; however, their action may be of slower onset.

Influence of Contrast Agents on Vasomotor Tone

The vasodilatory effects of contrast agents on epicardial coronary artery tone appear to be smaller with nonionic compared to ionic agents. We therefore recommend the use of nonionic iso-osmolar contrast media for angiographic trials. Contrast concentration is also known to exert a marked effect on QCA measurements, and thus adequate vessel filling is essential for the reliability of serial QCA. This point is demonstrated in Figure 12-7 where the effect of 50% contrast and 100% contrast concentrations were compared in vitro in a multicenter study [72] of 10 QCA systems in North America and Europe.

Catheter as a Scaling Device

For off-line analysis, the guiding catheter is typically used as a scaling device for calibration of angiographic measurements. As the manufacturer's nominal size of catheters is unreliable, the external diameter of the catheter is measured by a precision micrometer. The image quality of the recorded catheter is dependent on the catheter material, the kilovoltage of the X-ray source and the concentration of the contrast agent. Nylon catheters have the largest effect on the angiographically measured size and are therefore not recommended for quantitative angiographic trials. The effect of the contrast-filling versus contrast-empty states are discussed later in this chapter. It is hoped that by the introduction of isocentric calibration techniques over the next few years (also discussed later in this chapter) many of the errors associated with catheter calibration will be avoided.

Length of the Analyzed Segment

Anatomic landmarks as bifurcations are used for the manual definition of start and endpoints of arterial segments to be analyzed to minimize the problem of nonidentical analyses.

Manual Corrections

Only very rarely is it necessary to enter either soft or hard corrections to the edge detection procedure. Corrections should be discouraged (particularly of the MLD) even in the presence of a dissection with extraluminal contrast, where the edge detection algorithm will typically include the extravasation in the presence of a continuous large channel connecting the true and false lumens and will typically exclude the extravasation in the presence of a discontinuous small connection between the true and false lumens. The computer registers for both the right and left hand contours, the length of the arterial segments that were manually corrected.

Frame Selection

An end-diastolic cine-frame is selected for quantitative analysis to avoid motion and blurring effects.

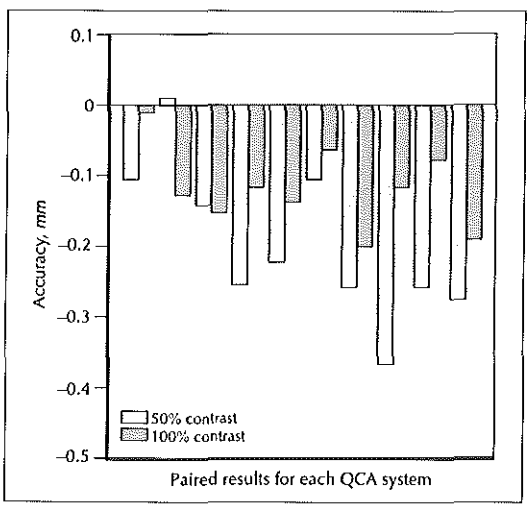

Figure 12-7. Effect of contrast concentration on quantitative coronary angiography (QCA) performance. As part of a multicenter QCA validation study, a series of phantom stenoses were recorded in vitro (plexiglass blocks). The stenosis channels were serially filled with 50% and 100% contrast and recorded on cinefilm. The cinefilm was then analyzed by off-line QCA at 10 core angiographic laboratories in North America and Europe. It can be seen that QCA measurements were most accurate when the stenoses were filled with 100% concentration of contrast.

CALIBRATION OF QCA MEASUREMENTS

Catheter Calibration

Whether calibration of QCA measurements should be based on contrast-empty or contrast-filled catheters has not yet been universally agreed upon [73–79]. Two studies, that have recommended the use of the contrast-empty state have adopted a similar methodologic approach and have been performed on the same QCA system that uses a fixed weighting of the first and second derivative [73,79]. After calibration by using a centimeter grid as a scaling device, QCA measurements of contrast-filled and contrast-empty catheters in vitro have been compared with the true external diameters of guiding catheters that have been measured by a precision micrometer (tolerance <0.001 mm). Such direct micrometer measurements of the external diameter of guiding catheters in a dry state at room temperature (20 °C less than the temperature at which catheters are recorded in vivo) result in a measurement of on average 0.025 mm smaller than the normal manufacturers' stated size [79]. Allowing for individual variations relating to the trilaminar composition of different catheters (Table 12-3), QCA measurements in the contrast-empty state have been found overall to provide the best agreement with the true external diameter of the catheters.

The methodologic approach of the above two studies [73,79], however, does not directly examine the reliability of QCA measurements when calibrated by a catheter, but rather addresses QCA measurements of catheters when calibrated by a centimeter grid. Furthermore, it should be remembered that ultimately QCA measurements are performed on contrast-filled vessels and not on the atherosclerotic walls of contrast-empty vessels. Although agreement of measurements of catheters by QCA and by micrometer were better when in the contrast-empty than in the contrast-filled state, they resulted in a smaller calibration factor (mm/pixell) [73,76,79]. Thus QCA measurements of coronary segments will be smaller when calibrated by contrast-empty catheters. We know that QCA systems underestimate measurements of coronary luminal diameters of >0.7 mm when calibrated by contrast empty catheters [64,72]. Although the reasons for this underestimation by QCA measurements probably relate to several technical factors, we have shown that when QCA

TABLE 12-3. TRILAMINAR COMPOSITION OF CORONARY GUIDING CATHETERS*

Manufacturer†	Series	Trilaminar composition
Bard	Illumen	Teflon, Kevlar braid, Pebax
Cordis	Diaventional	Trilon, Steel braid, Nylon
DVI	Brite Tip Atherectomy	Teflon, Polyurethane, Ultrax
Medtronic	Sherpa	Polyurethane, Steel braid, Teflon
Schneider	Soft Touch	Teflon, Steel braid, Polyurethane
Scimed	Triguide	Teflon, Steel braid, Trilon

*All of the above guiding catheters were found to be underestimated by quantitative coronary angiography (QCA) measurements. Underestimation was less when the catheters were analyzed in the contrast-empty state (-3%) compared with the contrast-filled state (-7%). The DVI atherectomy guiding catheter, which does not contain steel braiding, was found to be underestimated the most by QCA measurements (-7% in the contrast-empty state and -14% in the contrast-filled state). Use of angiographic guiding catheters as a scaling device for calibration of QCA measurements will thus result in smaller measurements of coronary stenoses when a contrast-filled catheter is used (*ie*, smaller calibration factor (mm/pixel).

†Cordis, Miami, FL; Medtronic, Minneapolis, MN; Schneider, Buelock, Switzerland; Scimed, Minneapolis, MN.

measurements of the same coronary luminal diameters are calibrated at the isocenter, this underestimation is significantly improved [72]. Thus until QCA systems no longer underestimate measurements of coronary luminal diameters, there are few compelling reasons to select the contrast-empty state during catheter calibration. This is perhaps particularly important during the conduction of an atherectomy trial, where luminal diameters will inherently be larger than those encountered in an exclusively balloon angioplasty trial.

In a study (perviously unpublished) to test whether such caution is warranted we compared QCA measurements of in vivo contrast filled phantom stenoses of known diameter in porcine coronary arteries when calibrated by three different techniques: 1) calibration on a contrast-filled guiding catheter, 2) calibration on the same guiding catheter in the contrast-empty state, and 3) calibration at the isocenter. The QCA system was an experimental edge detection algorithm [80] with variable weighting of the first and second derivative, which was designed to overcome the problem of overestimation of small diameters. The guiding catheter used was an 8-F Schneider (Buelach, Switzerland) guiding catheter that had previously been found in one of the above studies [79] to be most accurately measured by QCA in the contrast-empty state. The accuracy and precision for the three calibraton techniques are given in Table 12-4. Accuracy of QCA measurements of the coronary stenoses was poorest when calibrated by the contrast-empty catheter, improved slightly when calibrated by the contrast filled catheter (less underestimation of coronary luminal diameters), and was best when calibrated at the isocenter. The precision and standard error of QCA measurements was best during calibration by the contrast-filled catheter. While these results only have direct implications for one catheter and one QCA algorithm, they indicate a point in the process of QCA analysis that requires further research and clarification, and most importantly they indicate a potential point with significant scope for improvement in the reliability of QCA measurements. A comprehensive study on QCA calibration should be undertaken on several QCA systems to directly determine the accuracy and precision of QCA measurements of contrast-filled vessels when calibrated by contrast-empty catheters in vivo and when calibrated by contrast-filled catheters in vivo.

Isocentric Calibration

An improvement in the reliability of QCA measurements might be achieved by abandoning the use of the angiographic catheter as a scaling device entirely and aiming for isocentric calibration. In essence, the pixel size (mms) for each image intensifier field size is known (from the recording of a centimeter grid) and does not change throughout a procedure (nor indeed from day to day). By using a biplane radiograph system a coronary stenosis can be filmed at the isocenter by positioning the stenosis at the center of the image in both planes. When a coronary stenosis is filmed at the isocenter the errors

TABLE 12-4. CALIBRATION TECHNIQUES FOR QUANTITATIVE CORONARY ANGIOGRAPHY*

Calibration technique	Accuracy (signed differences), *mm*	Absolute mean error (unsigned differences), *mm*	Precision (SD of signed differences), *mm*	Standard error (standard error of the estimate), *mm*
Contrast-empty guiding catheter	-0.21	0.24	±0.23	±0.19
Contrast-filled guiding catheter	-0.18	0.22	±0.20	±0.17
At the isocenter (centimeter grid)	-0.08	0.20	±0.24	±0.24

*Comparison of three calibration techniques for quantitative coronary angiography. *In vivo* phantom stenoses of known diameter in porcine coronary arteries were used to compare the three techniques. A Schneider 8-F guiding catheter and an experimental edge detection algorithm with variable weighting of the first and second derivative were used for this comparison.

introduced by catheter calibration can be avoided. When an investigator fails to film the stenosis precisely at the center of the image in one of the planes (and thus inherently not at the isocenter of both planes), a complex mathematical formula can be applied to correct for the displacement from the isocenter [7]. If one accepts a deviation of approximately 1 cm from the center of the image in either plane this may still provide superior reliability of QCA measurements than that provided by catheter calibration, which currently does not correct for the out of plane distortion of the angiographic catheter, which is located in the coronary ostium. The coronary ostium will invariably be either further or nearer to the image intensifier than the coronary segment containing the stenosis. This source of absolute error will particularly effect the QCA measurement of stenoses located in the mid and distal segments in each of the three major coronary arteries, while QCA analysis of stenoses in the proximal segments (*ie*, American Heart Association classification segments 1,5,6,11 [81]) will be less susceptible to the calibration error introduced by out-of-plane distortion.

During application of a laserwire for the treatment of chronic total occlusions, biplane imaging is required to guide the direction of advancement of the laserwire to reduce the risk of perforation. In Total Occlusion Trial with Angioplasty assisted by Laser guide-wire (TOTAL) isocentric calibration will be used at the core angiographic laboratory, and should provide an indication of the relative merits and feasibility of noncatheter calibration for future interventional trials.

QCA BY GEOMETRIC AND VIDEODENSITOMETRIC TECHNIQUES

The two principle techniques for quantitative angiographic measurement are edge detection and videodensitometry. Only the edge-detection results of QCA measurements have been utilized in multicenter intervention trials to date. Edge detection involves the detection of luminal borders by weighting of the 1st and 2nd derivatives of the digitized brightness profile, which are converted into absolute values after calibration with an object of known diameter, such as the shaft of a guiding catheter. Because the observed morphology in a single-view angiographic image is critically dependent on the projection, the use of edge detection necessitates the incorporation of multiple matched orthogonal views to provide a three-dimensional approximation of the diseased segment.

More information can be extracted from a single view angiographic image by considering not only the relative changes in pixel brightness values upon which the edge detection technique is based, but also be integrating the absolute pixel brightness values. The intensity of the X-rays entering the image intensifier is in principle related to the absorption path length of the intervening medium by the Lambert-Beer law. The brightness intensity assimilated between two corresponding contour positions may thus provide a measure of the arterial cross-sectional area and is independent of the projection (in the transverse plane of the coronary segment). This method (videodensitometry) can be practically applied when the pixel brightness values are calibrated, *ie*, when the relationship between the pixel brightness values and the absorption path length (mm) of the contrast-filled artery is constituted. Videodensitometry assesses the relative area stenosis by comparing the density of contrast in the diseased and normal segments. The major limitation to videodensitometry is the strict requirement of an angiographic projection perpendicular to the long axis of the vessel (to prevent oblique cuts that would lead to overestimation of the luminal area) and the absence of overlapping, or closely parallel side branches or other vessels in the segment to be analyzed (which would interfere with the density of the lesion due to background subtraction). Densitometry is also more sensitive than edge detection to densitometric nonlinearities (X-ray scatter and veiling glare) and to inconsistent contrast filling of vessels. New techniques for the correction of background density irregularities have been recently developed [82]; however, their superior efficacy in improving the reliability of QCA measurements by videodensitometry has yet to be demonstrated by comparative studies.

Comparison of edge detection and videodensitometry in validation studies using phantom stenoses in vivo have shown promising results for videodensitometry, although random error (noise) rather than inaccuracy continues to be its primary limitation [83,84]. In a recent comparison by Escaned and coworkers [85] of the variability in QCA measurements by edge detection and videodensitometry of a single projection of clinical angiograms, the variability of videodensitometry measurements postangioplasty compared favorably with edge detection and indicated that by virtue of its independence of complex luminal morphology videodensitom-

etry might be of potential value in the clinical assessment of dissections [85,86].

The clinical application of videodensitometry in interventional research and practice has to date been limited. Videodensitometry may be used to detect intracoronary thrombus by a mismatch in cross-sectional area measurements from videodensitometry and edge detection in two planes. Detection of intracoronary thrombus may also be achieved by the use of pixel variance. A potential application of QCA by videodensitometry may be the derivation of volumetric measurements of coronary segments for the study of serial changes in diffusely diseased vessels [87]. This application, however, may prove to be of greater value for the study of progression-regression in coronary segments of small diameter (where ICUS catheters would wedge) rather than for the study of interventional cardiology [87].

Thus, although the option to perform measurements by videodensitometry is an added advantage for scientific research particularly for small lesions where accuracy of videodensitometry may be superior to edge detection and where ICUS catheters will wedge, videodensitometry could not be considered as an essential feature for a functional QCA laboratory.

Given the resolution and silver grain size in cinefilm, edge detection is unlikely to benefit significantly from the introduction of on-line QCA (typical pixel size with 5-inch image intensifier setting = 0.14 mm) whereby the process of cinefilm exposure and development is bypassed. Videodensitometry on the other hand, has been vulnerable to the nonlinearities between X-ray exposure and the densitometric characteristics of cinefilm that are only partly and crudely corrected by accepting a logarithmic rather than a linear relationship in densitometric analysis of cineangiograms. Given the 256 grey levels of digital imaging and the linear relationship between radiograph exposure and the pixel brightness value, it is likely that we can expect some improvement in the performance and reliability of videodensitometry with the advent of digital transfer of angiographic images to core laboratories and by the use of videodensitometry on-line in the catheterization laboratory.

VALIDATION

Although, today there are approximately ten commercially available QCA systems, there is as yet no standardized or universally agreed validation procedures to enable direct comparisons among QCA systems and the subsequent exchange and integration of data of angiographic studies from different core laboratories. QCA analysis involves the processing of an image through a series of technical steps involving both hardware and software components. Each step including the projector, magnification, camera, digital resolution as well as the edge detection algorithm effects the reliability of measurements. Importance should therefore be placed on the selection of the hardware as well as the software components when acquiring a QCA system, and the system should be calibrated after completion of the entire image processing chain. A comprehensive review of the hardware and software components for established QCA systems has been previously described by Johan Reiber [88]. It appears that most QCA systems are calibrated according to the results of in vitro validation studies. However it is only by the performance of in vivo validation studies that the conditions of heterogenous scatter and veiling glare encountered in the human thorax can be reproduced. Thus, development of QCA systems upon in vitro results may partly explain the overall poor results of QCA validation revealed by in vivo studies [72].

Qualitative coronary angiography validation studies can be stratified into those attempting to determine the accuracy and systematic errors of QCA measurements and those attempting to determine the reproducibility of repeated measurements in clinical practice. Both are of value and are mutually complementary. To determine the accuracy and the range over which overestimation and underestimation of QCA measurements occur, a series of stenoses of known diameter are required. These stenoses, which are usually made of plexiglass may be recorded in vivo or in vitro. The primary limitation of in vitro studies is their underestimation of the errors likely to be encountered in vivo or in clinical practice. The primary limitation of studies assessing reproducibility of QCA measurements of clinical angiograms is their inability to provide any measure of reliability. Thus a QCA system that is found to have excellent reproducibility of clinical angiograms might be perceived by the unwary as being reliable, even though if the same QCA system was submitted to in vivo validation studies using phantom plexiglas stenoses of known diameter the system might be found to be reproducibly unreliable, *eg*, underestimation of large diameters by 0.30 mm and overestimation of small diameters by 0.05 mm. Thus both forms of validation tests should be encouraged and are necessary if we are to eradicate the systematic and random errors currently encoun-

tered in both on-line as well as off-line QCA.

When reading the report of clinical trials, it is common to encounter a brief sentence stating that the QCA system deployed has been validated or that the QCA system has a reproducibility of O.OX mm. What does this mean? Were the validation studies performed with in vitro or in vivo models? How were the validated measurements calibrated? Was it the reproducibility for interobserver or intraobserver measurements? Was a preselected stop frame used and analyzed repeatedly at the same sitting or did the operator of the QCA system have to select the frame on each sitting in a blinded manner at 5 minutes, 2 hours, 30 days and 90 days apart [89,90•]? Given the magnitude of the clinical implications of QCA trials for interventional practice, reports of QCA trials should include an adequate description in the methods section of the likely overestimation and underestimation and reproducibility of the reported QCA results on the basis of in vivo QCA validation studies. Only then will the reader be able to determine the true angiographic outcome in the study population. This description of QCA was partly provided in the report of the CCAT trial, where in addition to detailed descriptions of the angiographic acquisition and angiographic analysis and calibration, was the inclusion in the manuscript of the results of the intraobserver reproducibility by the trial personnel for immediate reanalysis (0.07 mm) and for 25 paired angiograms analyzed 6 months apart (0.20 mm) [56•]. The demand for such measures and publication of quality control in the execution and reporting of multicenter angiographic trials is likely to increase over coming years.

Another problem contributing to the confusion over validation studies is the absence of a standardized set of cinefilms that could be used to test all QCA systems. In light of this problem, a cooperative validation study of QCA systems using the same set of in vitro and in vivo cinefilms calibrated by both the isocenter and with a catheter as a scaling device, was recently undertaken at ten centers in North America and Europe [72]. Marked variation in performance, among commercially available QCA systems as well as those that have been developed in house, was revealed. No system was found to be perfect and all systems either underestimated or overestimated measurements to varying degrees. The results of the study would suggest that it would be difficult for core laboratories using different software or hardware QCA components to directly share or merge data without the introduction of mathematical corrective functions for the results of each system.

A difficulty encountered in making direct comparisons between the performance of different QCA systems, even when validated by the same series of phantom stenoses, is deciding which statistical parameter is most discerning and informative. Traditionally, validation of QCA systems has been based on the statistical parameters of accuracy, precision, correlation coefficient, standard error of the estimate, and the equation of linear regression given by the intercept and slope. Although each parameter provides a unique index of a QCA system's performance, direct comparisons between QCA systems is confounded by the interdependence of all parameters and the application of one parameter in isolation can be misleading. Would it be possible to generate a single derived parameter to incorporate the essence of all the above parameters? Accepting that some parameters reflect minor problems that could be corrected by recalibration of the system and others reflect more serious problems of noise, it might be possible to convey the most essential information about a QCA system's performance by only one or two parameters, such as the correlation coefficient and the corrected standard error of the estimate after normalization of the measurements for an intercept of zero and a slope of one [66]. Applying this proposal of normalization for a y intercept of zero and a slope of 1 to the results of a recent multicenter QCA validation study [72] of the in vivo series of measurements calibrated by the catheter, a simplified model for the comparison of various quantitative coronary analysis systems is presented, based on the exclusive use of the corrected standard error of the estimate (SEEc) and correlation coefficient (r) (Table 12-5).

Clinical Application of QCA Validation Results

By modification of the principle of normalization of QCA measurements for an intercept of zero and a slope of one, the angiographic results of trials such as BENESTENT and STRESS could be merged and the angiographic results of CAVEAT and CCAT merged by the correction of their respective QCA results (by their known systematic errors from in vivo validation studies of the QCA systems used in each trial) for an intercept of zero and a slope of one. Thus if a hypothetical QCA system was found during an in vivo validation study with catheter calibration to overestimate small diameters and underestimate large diameters and thus have a

regression analysis of y = 0.20 mm + 0.80x then all angiographic results produced by that system would be normalized as true MLD = (measured MLD-0.20 mm)/0.80.

Following the application of this normalization for their respective QCA systems, the results of the two stent trials could be merged and the results of the two atherectomy trials merged. Clearly such normalization will not improve the reproducibility (random error) associated with each QCA system; however, the desensitizing effect on the trials exerted by the noise of each QCA system (high standard deviation of measurements) should be partially overcome by the increase in the total number of observations provided by the merging of the respective databases (thus reducing the standard error of the mean and increasing the sensitivity of the merged analyses).

Failure of the Parameter Accuracy to Convey the Systematic Error of a QCA System

The statistical parameter of accuracy can at times be misleading. Given that most QCA systems tend to overestimate small diameters and underestimate large diameters, the regression line of most QCA systems intersects the line of identity at a point above 0.5 mm on the X axis. An example of how the reliance on one or simple statistical parameters to convey an impression of the performance of a QCA system can be misleading is the use of accuracy. If in the conduction of a validation study the number of observations (phantom stenoses) above and the number of observations below the point of intersection of the regression and identity lines are equal, the reported accuracy for the QCA system may be close to zero. This would occur for example if the difference between QCA measurements and the true values above the point of intersection is -0.2 mm (underestimation) and the difference between QCA measurements and the true values below the point of intersection is + 0.2 mm (overestimation). This deception arises from cancellation of the signed differences of all measurements for the entire validated range. This inability of the parameter of accuracy to convey the systematic error of QCA measurements can be overcome by the reporting of the absolute mean error of QCA measurements. By

TABLE 12-5. NORMALIZATION OF THE STANDARD ERROR OF THE ESTIMATE FOR AN INTERCEPT OF ZERO AND A SLOPE OF ONE*

QCA system	Intercept, *mm*	Slope	Correlation	SEE, *mm*	Normalized SEEc, *mm*
1	0.19	0.74	0.89	±0.19	±0.27
2	0.14	0.76	0.96	±0.12	±0.16
3	0.15	0.69	0.89	±0.19	±0.27
4	0.04	0.66	0.91	±0.16	±0.24
5	0.00	0.83	0.98	±0.09	±0.11
6	0.34	0.58	0.91	±0.14	±0.23
7	0.12	0.63	0.90	±0.16	±0.25
8	0.05	0.71	0.87	±0.22	±0.31
9	0.17	0.57	0.91	±0.14	±0.24
10	0.20	0.60	0.83	±0.22	±0.36
Average	0.14	0.68	0.91	±0.16	±0.24

*Given the interdepence of all conventional statistical parameters for the description of quantitative coronary angiography (QCA) validation results, it becomes difficult to select which statistical parameters should be utilitzed for direct comparisons of different QCA systems. One approach would be to normalize the validation results of each QCA system under comparison for an intercept of zero and a slope of one. The normalized (corrected) standard error of the estimate (SEEc) for each QCA system would then be directly comparable between systems and provide an index of the noise or random error to be expected from each system after recalibration and elimination of systematic errors. The correlation coefficient will not alter during the normalization process and thus could be directly used for comparisons between QCA systems. We have applied this statistical proposal to the results of a recent multicenter QCA validation study whereby the results of ten different QCA systems are presented. The results are for an in vivo (porcine coronary arteries) series of phantom stenoses of known diameter and were calibrated using a guiding catheter positioned in the coronary ostium.

taking the unsigned differences, the deviation or error of each measurement from the true value is taken into account and conveys to the reader the systematic error to be expected from QCA measurements within the validated range. This point is illustrated in Figure 12-8, where for a hypothetical series of QCA measurements, the accuracy is 0.00 mm and the absolute mean error is 0.15 mm.

Many previous QCA validation studies have used the statistical approach proposed by Bland and Altman [89], however, this approach provides little additional information over linear regression analysis. Bland and Altman [91] designed their statistical method to display the agreement between two measurement systems in the absence of a golden standard and thus their approach is of limited value to a study when the true value of the measured objects is known. One method of addressing the problem of comparative validation would be to express accuracy and precision at any given true value of a phantom stenosis in a categorical manner. If a consensus was reached on the most relevant absolute value of diameter at which accuracy and precision of QCA systems should be compared (*eg*, 1.5 mm) then one value for accuracy and precision could be given for each QCA system. If, however, the regression line for a QCA system crossed the line of identity in the vicinity of this point (or near the midpoint of a validated range) then the derived accuracy value would appear deceptively favorable. Alternatively, a series of three accuracy and precision values could be given for each system for three true values of lumen dimension, *eg*, 1.0, 1.8, and 2.7 mm roughly corresponding to likely measurements of minimal luminal diameter pre- and postcoronary intervention and of reference vessel diameter.

QCA AND ANALOGUE VIDEOTAPE

With the increasing availability of digital (subtraction) angiography, many interventional suites have already entered the era of the filmless cath lab. While some radiograph systems have digital export facilities, most currently use analogue videotape for export and long-term storage of cineangiograms. Videotape offers the advantages of easy handling, instant replay, and low cost [92–95] and thus in many institutions videotape has been welcomed as a more convenient recording medium than 35 mm cinefilm. Despite the hasty replacement of cinefilm at many interventional suites, the suitability of video recordings for QCA has not yet been established. The limited shelf life of 7 years for videotape may render it unsuitable for important clincial trials on the results of which Food and Drug Administration approval for a device or pharmacologic agent may subsequently be sought.

Videotape may introduce additional noise and potentially worsen the reproductibility of QCA measurements by virtue of the introduction of the following additional steps in the data processing of angiographic images:

1. Video camera in X-ray image intensifier.
2. Analogue to digital conversion to provide digital angiographic images on hard disk (parallel Winchester disks for real time processing). These digital images may be compressed to increase the number of stored frames in an error-free or lossless compression format without resultant deterioration in precision of

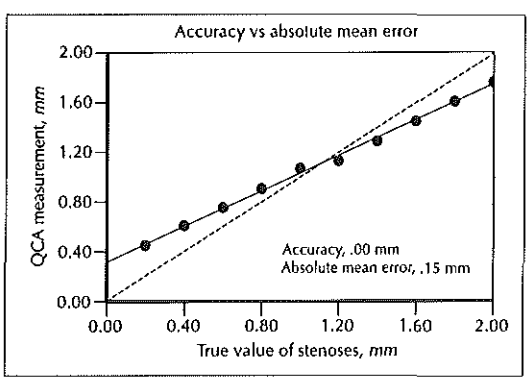

Figure 12-8. Accuracy of quantitative coronary angiography (QCA) measurements. Linear regression of a hypothetical QCA validation study where the accuracy reported for the QCA system is 0.00 mm even though 1) not a single individual measurement had an accuracy of 0.00 mm, and 2) the systematic tendency to overestimate small luminal diameters and underestimate large luminal diameters. This highlights the inadequacy of the term accuracy to portray the complete picture of a QCA system's performance and systematic errors, and supports the use of the parameter, absolute mean error, which is independent of the sign (±) of the individual QCA measurements.

QCA measurements, or filtered to provide edge enhancement (contrast).

3. Digital to analogue conversion for export to videotape with conservation of the edge enhancement if applied. The video-recorder itself may introduce additional high frequency noise.
4. Analogue to digital transfer (CCD camera in QCA hardware).

The imminent replacement of video cameras by CCD cameras in image intensifiers will provide more geometrically accurate images (thereby reducing pincushion distortion and avoiding the primary on-line analogue to digital conversion).

To determine the potential application and reliability of videotape recording for off-line QCA for clinical studies we recently carried out two studies. In the first we compared QCA measure-

TABLE 12-6. IN VITRO COMPARISON OF QUANTITATIVE CORONARY ANGIOGRAPHY MEASUREMENTS OF CINEFILM AND VIDEOTAPE RECORDINGS WITH AND WITHOUT EDGE ENHANCEMENT*

Recording medium	Accuracy, *mm*	Precision, *mm*	Correlation	Regression	SEE, *mm*
Cinefilm	-0.10	±0.08	0.997	y = 0.01 mm + 93x	±0.05
Video-N	-0.11	±0.18	0.987	y = 0.13 mm + 85x	±0.12
Video-E	-0.10	±0.11	0.992	y = -0.06 mm + 98x	±0.11

*Results of off-line quantitative coronary angiography (QCA) validation (CAAS II) of cinefilm and videotape recordings of in vitro stenoses. The videotape recordings tested were of normal images and of images that had undergone a process of on-line filtering—edge enhancement using a Philips DCI system. The random error (noise) of QCA analyses was least for cinefilm analyses and greater for videotape. The process of on-line edge enhancement was found to convey a reduction in random error (improvement in precision and standard error of the estimate [SEE] in subsequent off-line QCA analysis. Video-E—videotape recordings of edge enhanced angiographic images; Video-N—videotape recordings of normal (unfiltered) angiograpic images. *From* Ozaki and Coworkers [95]; with permission.

TABLE 12-7. AGREEMENT OF QUANTITATIVE CORONARY ANGIOGRAPHY MEASUREMENTS OF CLINICAL STENOSES BETWEEN CINEFILM AND VIDEOTAPE*

Comparison	Mean of differences (Agreement), *mm*	SD of differences, *mm*
Video-N—Cinefilm	0.14	±0.20
Video-E—Cinefilm	0.04	±0.13

*Results of off-line quantitative coronary angiography (QCA) validation studies where the results of QCA analyses of cinefilm were used as a reference for the assessment of QCA measurements of videotape recordings. The terms accuracy and precision, however, are not used as the true values of the coronary stenoses pre- and post-percutaneous transluminal coronary angiography are unknown. Video-E—videotape recordings of edge enhanced angiographic images; Video-N—videotape recordings of normal (unfiltered) angiographic images.

ments of cinefilm and videotape recordings of experimental stenoses of known diameter in vitro as well as comparing QCA measurements of the two recording media of clinical coronary artery stenoses pre or postballoon angioplasty [95]. All in vitro and clinical angiograms were recorded on a DCI X-ray system (Philips, Best, The Netherlands) in the Thoraxcenter catheterization laboratory and all off-line QCA analyses were performed on the CAAS II QCA system (Pie Medical, Maastricht, The Netherlands). The results of this study are presented in Tables 12-6 and 12-7. Videotape recording was associated with a deterioration in both accuracy and precision although edge enhancement of the images (filtering of the digitized images on the DCI system in the cath lab prior to their export (A to D transfer) on videotape, was seen to convey some improvement in the QCA measurements.

In our second study (previously unpublished) we undertook a multicenter trial of videotape recordings for QCA analysis. We compared the accuracy and precision of video recordings of in vitro stenoses from four different external cardiac catheterization laboratories and examined the effect of the application of edge enhancement (compared with normal processing) from each X-ray system. In this second study we also assessed the potential application of a signal averaging technique to reduce the additional noise of video recordings (*ie*, to raise the signal to noise ratio). The signal averaging technique consisted of the digitizing by the QCA system of multiple video frames of the same image (by using a custom-designed frame grabber) and averaging of their data (frozen images were recorded on videotape at a speed of one angiographic image per 25 frames of videotape). All in vitro stenoses (on a background of plexiglass blocks and copper plates) were filmed at the isocenter in the 7-inch image intensifier field size with the smallest focal spot size setting for each X-ray system (0.4 to 0.5 mm). Again the QCA system used for all off-line analyses was CAAS II. All QCA measurements were calibrated by the recording of a centimeter grid in each laboratory. The average pixel size during QCA analysis after optical magnification (x 2) and digitization of the video images was 0.19 mm (this is considerably larger than the typical pixel size of cinefilm recordings of 0.06 mm). Correction for pincushion distortion was applied to all video images prior to analysis. The results of this study are presented in Tables 12-8 and 12-9 and Figure 12-9.

Marked variability was seen from one catheterization lab to the next. In the X-ray system of catheterization lab 1, in addition to exerting a marked effect on accuracy (from 0.07 mm

TABLE 12-8. EFFECT OF ON-LINE EDGE ENHANCEMENT OF DIGITAL IMAGES EXERTS WIDELY VARIABLE AND UNPREDICTABLE EFFECTS ON SUBSEQUENT OFF-LINE QUANTITAIVE CORONARY ANGIOGRAPHY ANALYSIS OF VIDEOTAPE RECORDINGS*

	Normal processing, *mm*		Edge-enhanced, *mm*	
	Accuracy	Precision	Accuracy	Precision
Catheter lab 1	-0.08	±0.09	-0.12	±0.10
Catheter lab 2	0.07	±0.40	-0.05	±0.39
Catheter lab 3	0.07	±0.32	-0.03	±0.10
Catheter lab 4	-0.05	±0.10	-0.05	±0.19

*Results of off-line quantitative coronary angiography (QCA) measurements of in vitro stenoses on videotape recorded in four different catheterization labs. Marked variability was seen from one catheterization lab to the next. In the X-ray system of catheterization lab 3, in addition to exerting a marked effect on accuracy (from 0.07 mm to -0.03 mm) edge enhancement improved precision of off-line QCA measurements. In contrast, edge enhancement of the images in catheterization labs 1 and 2 had no effect on off-line QCA measurements and in catheterization lab 4 edge enhancement was associated with a deterioration in precision of off-line QCA measurements. On-line edge enhancement of digital images in catheterization laboratories may exert a significant effect on subsequent off-line QCA analysis of analogue videotape recordings of the enhanced images. The effect varies considerably from one X-ray system (and the filtering level selected) to another.

to -0.03 mm) edge enhancement improved precision of off-line QCA measurements. In contrast, edge enhancement of the images in catheterization labs 2 and 3 had no effect on off-line QCA measurements and in catheterization lab 4 edge enhancement was associated with a deterioration in precision of off-line QCA measurements. Thus, it appears that on-line edge enhancement of digital images in catheterization laboratories, exerts a significant effect on subsequent off-line QCA analysis of analogue videotape recordings of the enhanced images. This effect varies considerably from one X-ray system (and the filtering level selected) to another.

Signal averaging (by multiple frame grabbing) was found to convey no detectable improvement in the reliability of QCA measurements. The reliability of QCA measurements of videotape recordings vary significantly from one X-ray acquisition system to another. These results indicate that analogue videotape recordings of angiographic images are generally unsuitable for the conduction of interventional trials using off-line QCA at a core laboratory. Occasionally individual X-ray systems with particular edge enhancement filter settings may provide images of sufficient quality for off-line QCA of videotape recordings presumably due to faithful tracking by the off-line QCA edge detection algorithm of the enhanced edge previously inscribed by a reliable on-line edge-enhancement algorithm. Thus, centers with filmless cath labs with only analogue videotape export formats that wish to participate in multicenter interventional trials should be individually screened by appropriate QCA validation tests to determine the reliability of their angiographic images for off-line QCA.

FUTURE DIRECTIONS AND CONSENSUS

European and North American working groups are currently assessing potential digital and analogue storage media for the filmless catheterization laboratory. Storage media currently under consideration currently include hard disks, compact discs, optical disks, digital tape, and standard analogue tape. On the basis of availability, freedom of data compression and decompression requirements, videotape initially appeared attractive; however, the resolution and reliability of video formats with or without edge enhancement for off-line core lab quantitative angiographic analysis appears to be inadequate for research purposes, and compact disks will soon be widely available in catherization laboratories.

While a degree of loss may be acceptable for routine clinical purposes, the compression and decompression of angiographic images by a lossy

TABLE 12-9. RESULTS OF OFF-LINE QUANTITATIVE CORONARY ANGIOGRAPHY OF SIGNAL-AVERAGED IMAGES OF IN VITRO STENOSES RECORDED ON VIDEOTAPE*

	Number of frames averaged					
Filtration	16 frames	8 frames	4 frames	2 frames	1 frame	1 field (0.5 frame)
Catheter lab 1 normal processing	±0.09 mm	±0.13 mm	±0.12 mm	±0.11 mm	±0.11 mm	±0.13 mm
Catheter lab 1 edge enhanced	±0.10 mm	±0.08 mm	±0.07 mm	±0.12 mm	± 0.10 mm	±0.12 mm
Catheter lab 2 normal processing	±0.40 mm	±0.48 mm	±0.49 mm	±0.41 mm	± 0.44 mm	±0.47 mm
Catheter lab 2 edge enhanced	±0.39 mm	±0.15 mm	±0.16 mm	±0.17 mm	± 0.22 mm	±0.33 mm

*In vitro validation study of off-line quantitative coronary angiography (QCA) analysis (CAAS II) of videotape recordings from two catheter labs with normal video recordings and with the application of edge enhancement. Despite a subjective improvement in images (visual assessment), signal averaging of the video images by the use of a multiple frame grabber was not found to convey an improvement in the precision of off-line QCA measurements.

technique (which can achieve compression ratios from 10 to 1 to 80 to 1 (for monochrome images)) would be unacceptable for QCA purposes. Thus only error-free compression algorithms (which normally achieve a compression ratio from 2 to 1 to 10 to 1) should be used for angiographic images, which will subsequently be used for QCA analysis. Each compression algorithm offers different compression-decompression processing times as well as range of compression ratios. Fractal compression appears to be one of the most promising techniques for angiographic images. Further advances will be made when the manufacturers of radiograph systems agree on a common storage medium and software language (*eg*, Diacom) for digital exchange of angiographic images for QCA.

Over the past 2 years a group of international investigators have held meetings to address the current lack of standardization of data acquisition, analysis and validation for the conduction of progression-regression and restenosis trials. It is envisaged that the imminent report of this international QCA consensus group will provide guidelines for the design of future quantitative angiographic studies.

Until sources of systematic and random error in QCA measurements can be greatly reduced, we should consider an integrated approach for the assessment of coronary artery disease. QCA (static picture) should be combined with ICUS (murelography) as well as dynamic data such as Doppler or other flow measuring techniques (pressure wire).

While QCA offers objectivity and superior reproducibility compared with visual assessment, extensive improvements are required before QCA can be accepted as a reliable tool for the prediction of cardiac events. Wide differences exist in the performance of currently available QCA systems, highlighting the difficulties in attempting to make direct comparisons between absolute measurements of one angiographic study with those derived from a different QCA system or with online analysis in clinical practice.

Qualitative coronary angiography validation studies should be performed in a uniform and standardized manner to provide meaningful

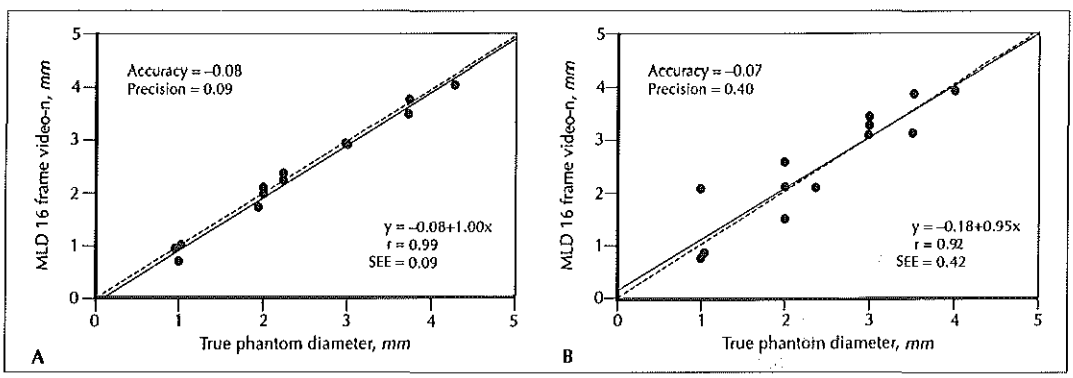

Figure 12-9. Multicenter validation study of quantitative coronary angiography (QCA) measurements of videotape images recorded at different catheterization laboratories. **A** and **B**, A series of phantom stenoses were recorded in vitro (plexiglass blocks) at different catheterization labs. The images were then recorded at each site onto analogue videotape and brought to a core angiographic laboratory where they underwent QCA analysis (CAAS II). QCA results of the videotape images varied markedly from one catheterization lab to another. In the figure, it can be seen that in catheterization lab 1 (**A**) (QCA measurements have been plotted against the true values on the graph) the results were of high quality where the process of analogue videotape recording subtended a minimal degree of random error (precision = ± 0.09 mm, standard error of the estimate [SEE] = ± 0.09mm). In contrast, in catheterization lab 2 (**B**) the process of analogue videotape recording introduced an unacceptable degree of random error (noise precision = ± 0.40mm, standard error of the estimate = 0.42mm). As to be expected in the absence of edge enhancement, video recording only introduced noise and did not result in a shift or systematic error of QCA measurements. Of particular interest are the values of accuracy reported for these two series of validation results, whereby the accuracy of QCA measurements of videotape images from catheterization lab 2 (0.07mm) is at least as good as for catheterization lab 1 (-0.08mm) and highlights the importance of understanding the relevance and meaning of the different statistical parameters used to describe measurement systems. MLD—minimal luminal diameter; video-N—videotape recordings of normal (unfiltered) angiographic images.

data that can be used to compare the performance of QCA systems, to guide the recalibration of QCA algorithms and to facilitate the maintenance of high standards of QCA for scientific studies and clinical practice.

Power calculations and study design of angiographic trials should be adjusted for the precision of the QCA system utilized to avoid the risk of failing to detect small differences in patient populations.

Results of validation studies should be given both as the normalized (corrected) values in addition to the absolute values of the statistical parameters. In the reporting of clinical angiographic studies, absolute values of luminal diameter and values of statistical significance for differences between study populations should be accompanied by the results of the appropriate validation parameters of the QCA system deployed to facilitate the interpretation of the study's findings.

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Chapter III

Comparative validation of quantitative coronary angiography systems: results and implications from a multicenter study using a standardized approach.

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Comparative Validation of Quantitative Coronary Angiography Systems

Results and Implications From a Multicenter Study Using a Standardized Approach

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Background Computerized quantitative coronary angiography (QCA) has fundamentally altered our approach to the assessment of coronary interventional techniques and strategies aimed at the prevention of recurrence and progression of stenosis. It is essential, therefore, that the performance of QCA systems, upon which much of our scientific understanding has become integrally dependent, is evaluated in an objective and uniform manner.

Methods and Results We validated 10 QCA systems at core laboratories in North America and Europe. Cine films were made of phantom stenoses of known diameter (0.5 to 1.9 mm) under four experimental conditions: in vivo (coronary arteries of pigs) calibrated at the isocenter or by use of the catheter as a scaling device and in vitro with 50% contrast and 100% contrast. The cine films were analyzed by each automated QCA system without observer interaction. Accuracy and precision were taken as the mean and SD of the signed differences between the phantom stenoses, and the measured minimal luminal diameters and the correlation coefficient (r), the SEE, the y intercept, and the slope were derived by their linear regression. Performance of the 10 QCA systems ranged widely: accuracy, +0.07 to +0.31 mm; precision, ±0.14 to ±0.24 mm; correlation (r), .96 to .89; SEE, ±0.11 to ±0.16 mm; intercept, +0.08 to +0.31 mm; and slope, 0.86 to 0.64.

Conclusions There is a marked variability in performance between systems when assessed over the range of 0.5 to 1.9 mm. The range of accuracy, intercept, and slope values of this report indicates that absolute measurements of luminal diameter from different multicenter angiographic trials may not be directly comparable and additionally suggests that such absolute measurements may not be directly applicable to clinical practice using an on-line QCA system with a different edge detection algorithm. Power calculations and study design of angiographic trials should be adjusted for the precision of the QCA system used to avoid the risk of failing to detect small differences in patient populations. This study may guide the fine-tuning of algorithms incorporated within each system and facilitate the maintenance of high standards of QCA for scientific studies. (*Circulation*. 1995;91:2174-2183.)

Key Words • angiography • coronary disease • stenosis

Clinical trials incorporating quantitative coronary angiography (QCA) have made a significant impact on the practice of interventional cardiology. They have reported the results of vessel size, lesion severity, and short- and long-term angiographic outcome of patients undergoing interventional procedures. On the basis of the BENESTENT, STRESS, CAVEAT, and CCAT trials, angiographic guidelines have been proposed for the application of interventional devices.[1-4] Furthermore, on the basis of restenosis prevention studies such as MARCATOR, PARK, and the US Angiopeptin trial and of progression-regression studies, pharmacological agents have been deemed to be ineffective because by the QCA approach a difference in minimal luminal diameter at follow-up has not been detected.[5,6]

The results of these trials, however, have been generated by different off-line QCA systems. It is not known whether their results are all of equal reliability and to what extent each system overestimates or underestimates the true coronary dimensions. To determine the reliability of the angiographic results of interventional, restenosis, and progression-regression trials, a validation of 10 QCA systems at major core angiographic laboratories in North America and Europe (including the core laboratories that performed the QCA for all of the above-mentioned trials) was undertaken.

QCA systems with poor precision may fail to detect small but significant differences in study populations, whereas QCA systems with poor accuracy may provide misleading results of absolute measurements of minimal luminal diameter. The results of studies based on unreliable QCA systems may not be directly comparable to those of more reliable systems. To render the results of angiographic studies meaningful and universally applicable, it is important that QCA systems be validated in a systematic and standardized fashion. Results of single-center validation studies will vary according to the individual characteristics of the models of the phantom stenoses used and their radiographic acquisition.[7-10] Without a standardized approach to validation, it becomes difficult to assess to what degree individual angiographic studies are reliable, the significance of their failure to detect relative changes in minimal luminal

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diameter, and how much weight should be attributed to absolute values of minimal luminal diameter derived from individual QCA systems. Furthermore, it is only by detailed validation studies that errors in QCA measurements can be identified and thereby provide guidance for the refinement of QCA systems.

To assess the QCA systems under radiographic conditions reflecting clinical practice in addition to those of optimal radiographic acquisition, phantom stenoses of known diameter were used as a reference both in vivo (after insertion in the coronary arteries of pigs) and in vitro (Plexiglas blocks). The QCA systems were assessed by their measurement of the absolute value (in millimeters) of the minimal luminal diameter within the artificial stenoses, which has previously been shown to be more reliable than relative measures (percent diameter stenosis) of coronary artery dimensions based on the definition of a reference contour.[11-13]

Methods

Phantom Stenoses

The phantom stenoses used in vivo as well as in vitro consisted of radiolucent acrylate and polyamide cylinders with precision-drilled circular lumens 0.5, 0.7, 1.0, 1.4, and 1.9 mm in diameter. Optical calibration of the stenosis channels using 40-fold magnification gave a tolerance of 0.003 mm. Parallel to the stenosis lumen, a second lumen 1.3 mm in diameter was drilled in the cylinders to enable their attachment to the tip of 4F Fogarty catheters (Vermed). The lumens of the Fogarty catheters contained a removable metallic stylet, which aided the intracoronary insertion of the phantoms as well as their positioning in the radiographic isocenter. Details of our experimental approach to QCA validation have been described.[14-16]

In Vivo Studies

The procedures followed were in accordance with institutional guidelines for animal studies. The phantom stenoses were inserted into the coronary arteries of anesthetized Yorkshire pigs (45 to 50 kg). Twelve-French introducer sheaths were surgically placed in both carotid arteries to allow the sequential insertion of the phantom stenoses on 4F Fogarty catheters and the insertion of the angiographic guiding catheter. To minimize the effect of respiration on angiographic acquisition, mechanical ventilation was temporarily discontinued immediately before each contrast injection. With two methods of calibration, two series of measurements were obtained for the in vivo series, providing an assessment of the variability of nonisocentric calibration.

In Vitro Studies

The phantom stenoses were serially inserted into a Plexiglas acrylate model to approximate the attenuation and beam hardening (peak kilovolt [kVp] level, 75 kV) produced by the human thorax.[17,18] The Plexiglas channel, including the artificial stenosis, was then filled with contrast medium (iopamidol 370, Bracco; 370 mg iodine/mL) at concentrations of 50% and then 100%. Each phantom stenosis filled with contrast medium was recorded on cine film. By use of two concentrations of contrast medium, two series of measurements were obtained for the in vitro series, allowing an assessment of the variability introduced by contrast concentration.

Calibration

All the in vitro cine frames were calibrated off-line by scaling from a steel object of 3-mm diameter recorded at the radiographic isocenter as previously described.[14-16] Both the 3-mm scaling object and subsequently the in vitro phantom stenoses were filmed precisely at the isocenter of the x-ray system.[19] The calibration procedures available in each off-line QCA system were applied to the images obtained by automated edge detection to produce the corresponding calibration factors (millimeters per pixel).

All in vivo frames were calibrated by scaling from the isocentric 3-mm steel object; subsequently, the analysis was repeated and frames were calibrated by scaling from the angiographic catheter, which was achieved by the nonisocentric radiographic acquisition of the unfilled tip of the contrast catheter (positioned at the coronary ostium as in routine clinical practice). A recent study using a centimeter grid showed that QCA measurements correspond to the outer diameter of the catheter and that the use of contrast-empty catheters (−2.9%) yields more accurate results than contrast-filled catheters (−7.1%).[20,21] The diameter of the nontapering part of each 8F polyurethane catheter was measured (diameters of the individual catheters ranging from 2.49 to 2.54 mm) with a precision micrometer (No. 293-501, Mitutoyo; accuracy, 0.001 mm), resulting in the respective calibration factors (millimeters per pixel). In the in vivo series, after the intracoronary insertion of each phantom stenosis and before angiographic recording, the radiopaque tip of the guide wire of the Fogarty catheter that was located in the side channel of each phantom was used as a marker in two planes to ensure that the phantom stenosis lay at the radiographic isocenter. The guide wire was then removed before coronary angiography.

Image Acquisition and Processing

A monoplane Philips Poly Diagnost C2 machine equipped with an MRC x-ray tube and powered by an Optimus CP generator (Philips Medical Systems International BV) was used for all radiographic imaging. The 5-in (12.5-cm) field mode of the image intensifier (focal spot, 0.8 mm) was selected, and the radiographic system settings were kept constant (kVp, mA, ms) in each projection. All phantoms were imaged in two projections sequentially and acquired on 35-mm cine film (CFE type 2711, Kodak) at a frame rate of 25 images per second with an Arritechno 90 cine camera (Arnold & Richter) with an 85-mm lens. The cine films were processed by a Refinal developer (Agfa-Gavaert) for 4 minutes at 28°C. The film gradient was measured in all cases to ensure that the optical densities of interest were on the linear portion of the sensitometric curve. From each angiogram that fulfilled the requirements of quantitative analysis (no superimposition of surrounding structures, no major vessel branching at the site of the phantom), a homogeneously filled end-diastolic coronary image was selected. Ten in vitro and 19 in vivo frames were suitable for quantitative analysis of the artificial stenoses.

Quantitative Angiographic Analysis

The cine films of the phantom stenoses were analyzed off-line by 10 QCA systems in nine participating centers. Each center had a unique combination of QCA software and hardware. The default settings of optical magnification, light-emitting diode settings, etc, at each core laboratory were used without alteration. It is assumed in this study that each core laboratory (through continuous internal quality control assessments) has established for itself the optimal settings and operations for its individual QCA system. The resultant pixel size after digitization depended on the video camera pixel matrix (Table 1) of each system and ranged from 0.07 to 0.20 mm/pixel. The list of participating centers and details of their QCA systems are given in alphabetical order in Table 1 (it should be noted that the subsequent results for the 10 systems are given in a different order anonymously). None of the QCA systems tested had been previously calibrated at prior validation testing with the type of phantom used. One of the investigators (E.M.v.S.) visited all the centers, bringing the same set of films for analysis to each center consecutively. The same set of preselected cine frames was analyzed at each center to avoid the introduction of any variability between QCA systems associated with frame selection by each operator.[22] A technician working at

TABLE 1. Details of QCA Systems

Site	Cine Projector	Optical Magnification of Cine Film Images	Camera (Video Converter)	Video Camera Pixel Matrix	QCA System
A	Vanguard XR35	Yes	Vidicon tube	Analogue	Artrek version 1.6; 1992
B	Tagarno 35AX	Yes	Vanguard TV-6	Analogue 525 line	Artrek version 1.6; 1992
C	Tagarno 35AX	Yes	Newvicon	Analogue	Artrek version 1.36; 1991
D	CAP 35B	Yes	Vidicon	Analogue	Artrek version 1.6; 1991
E	Arripro 35	Yes	CCD chip	756 581	AWOS
F	Tagarno 35CX	Yes	CCD array	1770 1330	CAAS I
G	Tagarno 35CX	Yes	CCD array	1770 1330	CAAS II
H	CAP 35E	Yes	CCD chip	512 480	CMS
I	Tagarno	Yes	CCD chip	512 480	In house
J	Tagarno 35CX	No	CCD chip	1320 1035	SM/SS

QCA indicates quantitative coronary angiography; CAP, cine angiography projector; CCD, charged coupled device; AWOS, artery work station; CAAS, coronary angiography analysis system; CMS, cardiovascular measurement system; and SM/SS, St Michael's/Sunnybrook system.

each center who was unaware of the true diameters of the phantom stenoses performed the automated QCA analysis of all cine frames in the presence of the investigator. To maintain scientific objectivity and to ensure that the direct comparisons between the 10 QCA systems were valid, operator intervention or editing of the automated edge detection was not permitted. An example of a contrast-filled phantom stenosis in vivo and its subsequent contours outlined by one of the QCA systems is given in Fig 1.

Statistical Analysis

The individual geometric measurements of minimal luminal diameter were compared with the true phantom diameters by simple subtraction and by linear regression analysis. The mean of the signed differences between measured values and the known diameter of the phantom stenoses was considered an index of accuracy and the SD of the differences an index of precision.

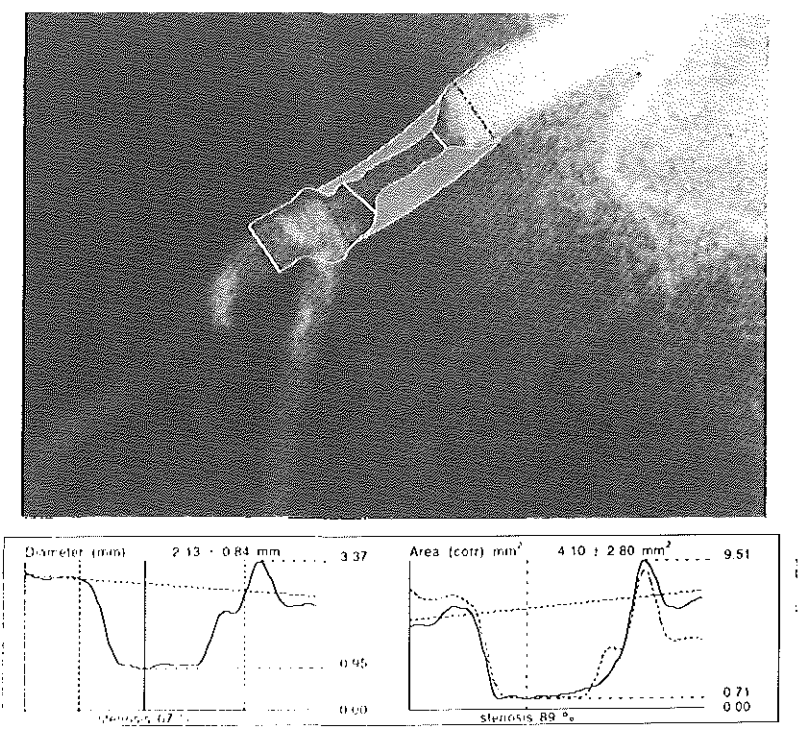

FIG 1. The borders of a coronary segment containing a phantom stenosis are outlined by the automated edge-detection algorithm of one of the validated quantitative coronary angiography systems. Diameter function is plotted at bottom of figure.

TABLE 1. (Continued)

Manufacturer of QCA	Correction for Pincushion Distortion	Digital Magnification to Image for Analysis	Final Pixel Matrix of QCA	Algorithm Principle
ImageComm, USA	No	Yes	512 480	1st and 2nd derivative
ImageComm, USA	No	Yes	512 480	1st and 2nd derivative
ImageComm, USA	No	Yes	512 480	1st and 2nd derivative
ImageComm, USA	No	Yes	512 480	1st and 2nd derivative
Siemens, Germany	No	Yes	512 512	Optimal convolution
Pie Medical, the Netherlands	Yes	No	512 512	1st and 2nd derivative
Pie Medical, the Netherlands	Yes	Yes	1770 1330	1st and 2nd derivative
Medis, the Netherlands	No	Yes	512 512	1st and 2nd derivative
Harvard University	Yes	Yes	512 512	1st and 2nd derivative
University of Toronto	No	No	1320 1035	Density profile of tracker boxes

Results

The individual indexes of accuracy and precision are given for all four validation series (in vivo with two calibration techniques and in vitro with two contrast concentrations) along with the average of their unsigned (absolute) values for all 10 QCA systems validated in Table 2. The averages for accuracy and precision, for correlation coefficient and SEE, and for intercept and slope for all 10 QCA systems are given in Table 3.

Indexes of Agreement

Accuracy of the 10 QCA systems ranged from 0.07 to 0.31 mm, and the correlation coefficient ranged from .96 to .89. The intercept of the regression line was positive for all 10 QCA systems and ranged from +0.08 to +0.31 mm, whereas the slope of the regression line for all 10 QCA systems was <1.0 and ranged from 0.86 to 0.64. Application of these regression lines indicates percentage accuracies for the 10 QCA systems ranging from +26% to −1% (mean, +7.2%) for measurements of lumen diameters of 0.5 mm, percentage accuracies from −7% to −24% (mean, −14.9%) for lumen diameters of 1.5 mm, and percentage accuracies from −11% to −29% (mean, −20.5%) for lumen diameters of 3.0 mm.

Indexes of Noise and Consistency

Precision of the 10 QCA systems ranged from ±0.14 to ±0.24 mm, and the SEE ranged from ±0.11 to ±0.16 mm.

An indication of the variability of performance among the 10 QCA systems can be visualized by comparing the results of the in vivo test calibrated by the catheter for two of the systems depicted in Fig 2.

Influence of the Validation Model

As expected, it can be seen in Table 2 that the performance of each individual system varied from one validation test to another. In the in vivo series, accuracy was better when calibrated at the isocenter than on catheter calibration in all 10 systems validated (see Fig 3). The method of calibration did not influence the precision or SEE of QCA. In the in vitro series, both

TABLE 2. Accuracy and Precision

	In Vivo Catheter		In Vivo Isocenter		In Vitro 50%		In Vitro 100%		Average	
	A	P	A	P	A	P	A	P	A	P
1	−0.09	0.23	0.07	0.21	−0.12	0.10	−0.01	0.18	0.07	0.18
2	−0.14	0.17	−0.01	0.18	0.01	0.16	−0.14	0.07	0.08	0.15
3	−0.20	0.24	−0.14	0.31	−0.16	0.17	−0.17	0.14	0.17	0.22
4	−0.35	0.23	−0.11	0.15	−0.28	0.06	−0.13	0.14	0.31	0.15
5	−0.19	0.13	−0.09	0.16	−0.25	0.13	−0.15	0.13	0.17	0.14
6	−0.13	0.26	−0.01	0.22	−0.12	0.14	−0.07	0.24	0.08	0.22
7	−0.30	0.25	−0.07	0.22	−0.29	0.13	−0.23	0.13	0.22	0.18
8	−0.28	0.26	−0.25	0.20	−0.41	0.18	−0.13	0.17	0.27	0.20
9	−0.33	0.26	−0.26	0.22	−0.29	0.20	−0.09	0.28	0.24	0.24
10	−0.24	0.30	−0.15	0.24	−0.31	0.17	−0.21	0.19	0.23	0.23

Accuracy (A) and precision (P) are the mean and SD of the differences (mm) between the measurement of luminal diameter derived by quantitative coronary angiography (QCA) and the true diameter of the phantom stenoses.

In vivo catheter indicates in vivo series of measurements calibrated by the catheter; in vivo isocenter, in vivo series of measurements calibrated at the isocenter; in vitro 50%, in vitro series of measurements with 50% contrast calibrated at the isocenter; in vitro 100%, in vitro series of measurements with 100% contrast calibrated at the isocenter; and average, average of the unsigned results.

Results for the QCA systems (1 through 10) are presented in Tables 2 and 3 in the same order anonymously and are in a different order than the systems detailed in Table 1.

TABLE 3. Summary of Validation Results

	Accuracy	Precision	Correlation	SEE	Intercept	Slope
1	0.07	0.18	.93	0.15	0.20	0.77
2	0.08	0.15	.96	0.12	0.17	0.82
3	0.17	0.22	.90	0.16	0.17	0.70
4	0.31	0.15	.96	0.11	0.11	0.79
5	0.17	0.14	.96	0.12	0.08	0.86
6	0.08	0.22	.94	0.12	0.31	0.64
7	0.22	0.18	.93	0.15	0.16	0.78
8	0.27	0.20	.92	0.16	0.11	0.73
9	0.24	0.24	.89	0.16	0.17	0.65
10	0.23	0.23	.91	0.16	0.18	0.67

Accuracy, precision, and parameters of linear regression (correlation, SEE, intercept, and slope) for the 10 quantitative coronary angiography (QCA) systems. The values given are the averages of the unsigned results from the four validation series (the in vivo series calibrated by the catheter; the in vivo series calibrated at the isocenter; the in vitro series with 50% contrast calibrated at the isocenter; and the in vitro series with 100% contrast calibrated at the isocenter).

Results for the QCA systems (1 through 10) are presented in Tables 2 and 3 in the same order anonymously and are in a different order than the systems detailed in Table 1.

accuracy and the SEE were found to improve when the concentration of the injected contrast was 100% compared with 50% during validation of 8 of the 10 systems.

Discussion

This study demonstrates the wide range of performance provided by 10 QCA systems currently in use in North America and Europe. The clinical implications of such widely different results are considerable and can be divided into the clinical implications of inaccuracy and the clinical implications of imprecision of QCA measurements.

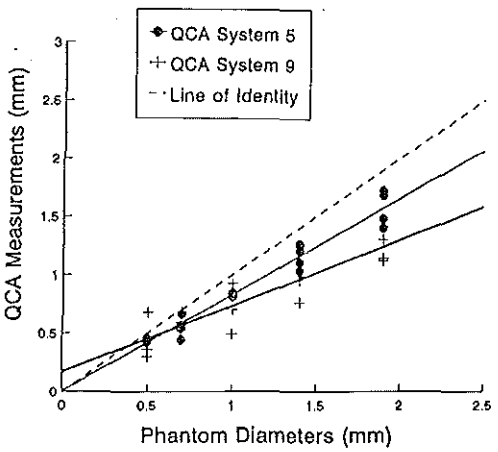

FIG 2. Graph showing in vivo data for two of the quantitative coronary angiography (QCA) systems validated. An indication of the variability of performance of the QCA systems validated is demonstrated by linear regression of the results for QCA systems 5 and 9. The raw data for the in vivo QCA analysis calibrated by the catheter as a scaling device has been plotted on the y axis with the true phantom stenosis diameters on the x axis. Each data point represents a single analysis of a cine frame from each angiographic sequence. The accuracy was −0.19 mm for system 5 and −0.33 mm for system 9; the precision was ±0.13 mm for system 5 and ±0.26 mm for system 9; the correlation was .98 for system 5 and .91 for system 9; and the SEE was ±0.09 mm for system 5 and ±0.14 mm for system 9.

Clinical Implications of QCA Inaccuracy

All systems were found to have a positive intercept (>0) and a slope of <1, indicating that many clinical studies to date using QCA may have overestimated the baseline minimal luminal diameter of their study populations and underestimated the acute gain in minimal luminal diameter after coronary intervention. For example, with QCA system 9, the linear regression analysis of which is displayed in Fig 2, a vessel of 2-mm diameter will be reported as 1.31 mm, and a procedural improvement in minimal luminal diameter from 0.5 to 1.9 mm will be reported as a luminal gain of only 0.77 mm. This may result in the establishment of angiographic guidelines that, when directly adopted in clinical practice using on-line QCA,[7,14,23,24] may lead to device-vessel mismatching and inappropriately aggressive luminal gains and when adopted in subsequent clinical trials may lead to inappropriate inclusion criteria. By underestimation in the range of typical reference vessel diameters (in addition to overestimation in the range of typical minimal luminal diameters), clinical studies reporting their QCA results exclusively in terms of percent diameter stenosis will be less instructive than studies disclosing the absolute values of the minimal luminal diameter. These findings contrast with visual assessments of luminal diameter, which tend to overestimate acute luminal gain

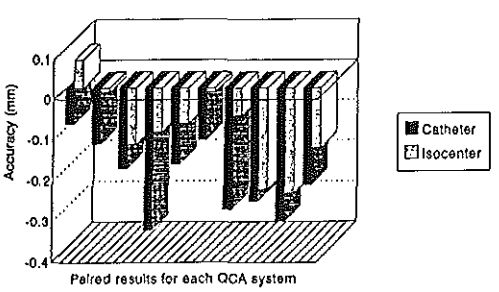

FIG 3. Bar graph showing effect of calibration on accuracy of the in vivo series. The accuracy of quantitative coronary angiography (QCA) is seen to improve during calibration at the isocenter compared with the use of the angiographic catheter as a scaling device. Solid bars indicate catheter; shaded bars, isocenter.

(it should be noted, however, that the variability between visual measurements has previously been shown to be many times higher than between QCA measurements[25-28]).

Measurements by some QCA systems were so different from the true phantom diameters and so different from other QCA systems that the direct pooling of absolute angiographic data from different core laboratories may be rendered invalid. Although little could be done to correct for the random error in QCA results before the sharing of data between core angiographic laboratories, application of a corrective function could be applied to compensate (recalibrate) for the known systematic errors of each QCA system. Specifically, the regression formula [y=a+b(x)] derived from standardized validation studies of each QCA system could be applied to the results of angiographic trials, thereby normalizing to an intercept of 0 and a slope of 1 for each core laboratory [corrected result=(measurement result−intercept)/slope]. Such a step might facilitate the meta-analysis of complementary intervention studies such as STRESS and BENESTENT or such as CAVEAT and CCAT.

Clinical Implications of QCA Imprecision

It could be proposed that poor accuracy or consistent overestimation or underestimation of absolute luminal diameters does not inherently abrogate the value of QCA in the detection of changes in serial angiographic studies, and perhaps the inherent noise (random error) of the system is more important for clinical trials. The high absolute values for precision (up to ±0.30 mm) and SEE (up to ±0.22 mm) provided by some systems indicate that calculation of study power and sample size for clinical studies should differ from one angiographic core laboratory to another. For example, for a two-limb angiographic restenosis study, a population size of 1022 patients would be required if QCA system 5 (precision, ±0.13 mm) were used, whereas a population size of 1356 patients would be required if QCA system 10 (precision, ±0.30 mm) were used to detect a difference in loss of minimal luminal diameter at follow-up of ≥0.10 mm (providing a value of α=.05 and a power of 90% and allowing for a patient dropout rate of 15%).[6,29,30] However, it should be acknowledged that the value of precision reflects not only the random error of measurements but also the systematic errors of a measurement system.[31] It may therefore be more appropriate to use the known SEE of a QCA system for the power calculations of clinical trials rather than the value of precision of the QCA system. In the absence of such adjustments in study design, differences between study groups may go undetected or fail to reach statistical significance if a QCA with a large random error is used.

The effect of the precision of a QCA system on the ability to clearly detect a difference among study populations can be seen graphically in Fig 4, in which a hypothetical study population has been analyzed by two different QCA systems, one with a poor precision and one with a good precision (the mathematical analysis used Lotus 1-2-3, Release 2.0 for Windows, Lotus 1993): The patient populations in graphs A and D are identical and represent a hypothetical study population in a restenosis trial 6 months after coronary intervention; one group of patients (treated with placebo) has "restenosis" (mean change in minimal luminal diameter at follow-up of 1.0 mm), and the other group does not have "restenosis" (mean change in minimal luminal diameter at follow-up of 0.0 mm) after successful treatment with a drug. Graphs B and E display the precision (0.08 and 0.30 mm) of two hypothetical QCA systems used to analyze the above study populations. Graphs C and F show the resultant measurements of the same study population by the two different QCA systems. In graph C, the significant difference between the two treatment groups (placebo and active drug) has been clearly detected by the highly precise QCA system. In graph F, the difference between the treatment groups has been lost (or the difference does not reach statistical significance) when analyzed by the imprecise QCA system. Similarly, a bimodal distribution of luminal renarrowing within a population may appear as unimodal when assessed by an imprecise QCA system.[32]

In Vivo Versus In Vitro Data

The tables of results provided in this report contain an average of the four validation tests for each QCA system. It is debatable, however, whether the results of in vivo tests (in which veiling glare and scatter are heterogeneous because of overlying structures) and in vitro tests (in which veiling glare and scatter are homogeneous) calibrated by different methods should be grouped together and thus attributed equal importance in view of their unique characteristics and implications.[17,18] Correlation between the different validation series was poor; however, this was to be expected, given the different combinations of hardware and software components of the 10 QCA systems (eg, different weightings of the first and second derivative would be expected to respond differently to the sharper change in brightness profile associated with 100% contrast or using a steel object for calibration). Although the contrast of the steel object was sharp, it was on the linear portion of the sensitometric curve, and, indeed, rather than resulting in a greater underestimation of stenosis measurements, QCA measurements calibrated by the steel object were associated (to a major or minor degree) with less underestimation of true diameters compared with catheter calibration, as shown in Table 2 and Fig 3. This finding of improved accuracy most likely results from the isocentric location of the steel calibration device rather than the catheter, which lay in the coronary ostium proximal to the coronary segment containing the stenosis as in clinical practice (with subsequent out-of-plane magnification). The results of the in vivo validation test calibrated by the catheter most closely reflect the practice of off-line analysis as performed in multicenter angiographic trials by a core laboratory, and in most of the 10 systems these results were poorer than those of the other three validation tests.

Influence of Hardware and Software Components of Each QCA System

The influence of the camera and cine-video converter on the final result of QCA analysis is highlighted by this study, which showed that although three centers had the same software package, remarkably different results were obtained because of their unique combinations of hardware components. Although our study was not designed to determine which components of the QCA chain were responsible for introducing the most noise, it is clear from our results that a core laboratory conducting follow-up studies should revalidate its QCA system whenever a hardware or software component is exchanged or upgraded.[33,34] This is of particular relevance

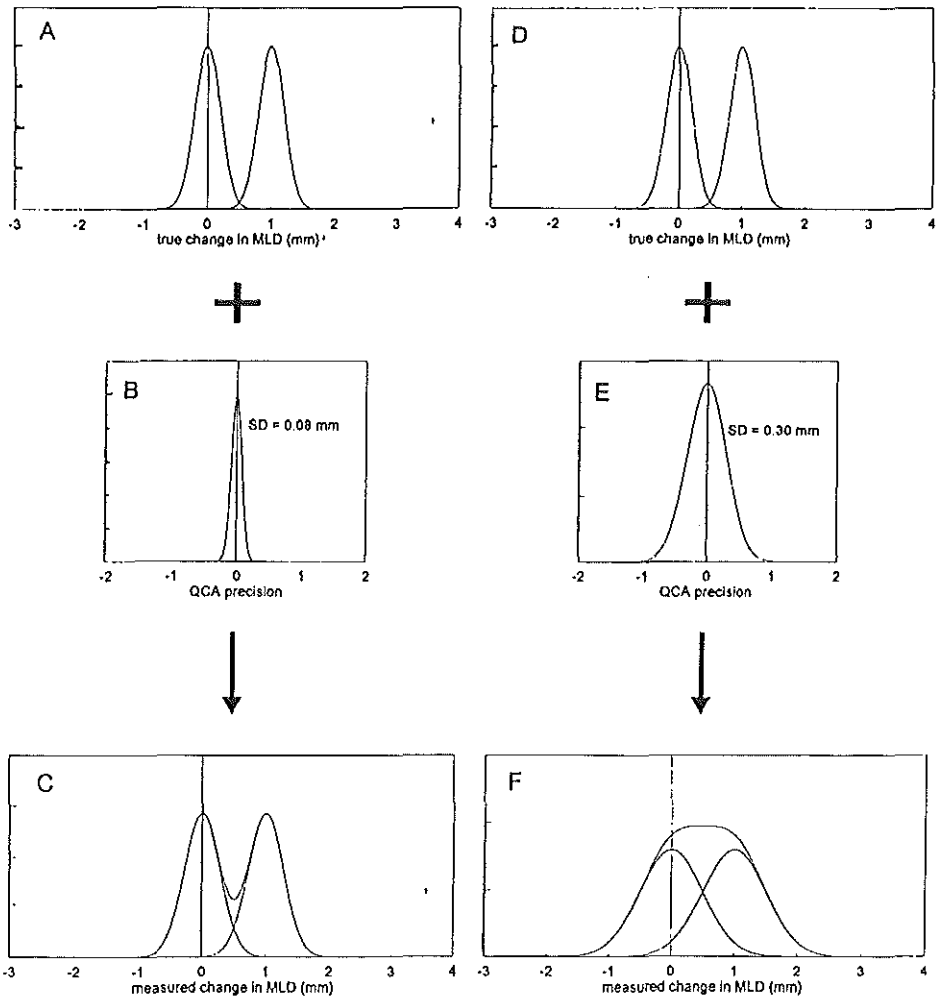

FIG 4. Graphs showing the effect of the precision of quantitative coronary angiography (QCA) systems on the ability to clearly detect a difference among study populations when a hypothetical study population (graphs A and D) has been analyzed by two different QCA systems: one with good precision (graph B) and one with poor precision (graph E). The difference between the treated and placebo patients has been detected (graph C) by the precise QCA system, whereas analysis by the imprecise QCA system (graph F) fails to detect the difference or fails to reach statistical significance (the mathematical analysis used Lotus 123, Release 2.0 for Windows, Lotus 1993). MLD indicates minimal luminal diameter.

to progression-regression trials, in which a QCA system 4 years old is likely to have been upgraded at the core laboratory by more modern versions of the software.

Positive Directions and the Future of QCA

The results of this study have already been used by the producers of some of the QCA systems to refine the algorithms incorporated within each system. Many of the systematic errors detected can be corrected by recalibration of the QCA software or tuning of the weighting of the first to the second derivative in the edge-detection algorithm,[35,36] whereas it would be expected to be more difficult to clear a system of noise, which usually reflects hardware impediments. Experimental algorithms currently under development include an adaptive dynamic weighting of the first and second derivatives to overcome the problem of overestimating measurements of small vessels and underestimating measurements of large diameters[37,37a] and a gradient field transform incorporating a "shortest-path" algorithm rather than a traditional smoothing "minimal-cost" algorithm to cope with the abrupt changes in luminal contour encountered after coronary angioplasty.[38]

Given the considerable time, effort, and cost of conducting restenosis and progression-regression trials, it seems reasonable to aim for a precision of clinical QCA measurements of ≤0.20 mm for the analysis of current multicenter angiographic studies. It is hoped that such an arbitrary threshold could be reduced over coming years when high-resolution digital x-ray cameras and high-resolution digital export formats (with lossless com-

pression) are widely available at all investigating centers. An additional proposal that could be considered for clinical studies to reduce the variability of QCA measurements would be for the investigators to reduce the setting of the focal spot size of the x-ray source to its smallest value (currently 0.4 mm in most x-ray systems) for the recording of the individual angiograms of patients participating in angiographic trials. Other steps for the reduction of variability of QCA measurements and the standardization of angiographic acquisition have been described in detail.[37,39-43]

Despite the variabilities in QCA measurements highlighted by this study, we should remain appreciative of the increased understanding of coronary artery disease afforded to us by the widespread application of QCA to scientific research and clinical practice. QCA has alleviated the subjectivity and high variability of visual assessments,[26,28,44-46] the errors and invalidity of the percent diameter stenosis for the assessment of progression/regression (pseudoprogression),[12,25,43] and the limitations of the dichotomous approach for the evaluation of restenosis.[13,31,47-56] The provision by QCA of objective and absolute measurements of coronary luminal diameter has significantly enhanced our approach to the assessment of noninvasive and invasive coronary interventions. It is hoped that the findings of our study will serve as a stimulus for the further improvement of QCA so that it may remain the gold standard and complementary technique to the new intracoronary imaging modalities for the acute and serial assessment of coronary artery dimensions.

Study Limitations

Although this study assessed the variability of measurements provided by automated QCA of a standardized set of cine films, it does not quantify the additional variability that might be introduced by variation in patient position and x-ray gantry settings during serial angiographic studies[40,57] (although this is now minimized by the design of most current trial protocols), the recording and developing of cine films at different institutions, frame selection (although this is now standardized by selection of end-diastolic frames[22,41]), and the occasional manual correction of detected contours (although this should be kept to an absolute minimum in angiographic core laboratories). The cumulative imprecision, including these factors, has been quantified in two clinical studies using one of the QCA systems validated and has been found in both studies to be ±0.20 mm (SD of measurements of serial angiograms).[25,58]

It can be seen in Fig 1 that although the contours of our phantom stenoses possessed an abrupt (90°) onset and termination, they were smooth over their 8-mm length. In clinical practice, many lesions are irregular, with rapidly changing arterial boundaries after coronary intervention. Given the use of a smoothing minimal-cost algorithm along scan lines perpendicular to the axis of the vessel, currently available QCA systems might be expected to fare less favorably if challenged with dissections and complex lesions compared with the angiographic stenoses presented in our study. Initial results with an experimental gradient-field transform algorithm provide hope that future QCA systems might be able to cope with more complex lesions.[38] This could perhaps be best tested in future validation studies by postmortem casts of diseased human coronary arteries with ulcerated plaques, dissections, and complex morphology.

The diameters of the phantom stenoses in this study (0.5 to 1.9 mm) were in the range of obstruction diameters of human coronary stenoses rather than typical reference vessel size. It is noteworthy that the average minimal luminal diameters before, immediately after, and at 6-month follow-up are 1.03, 1.78, and 1.48 mm for balloon angioplasty,[29] 0.98, 2.03, and 1.47 mm for directional coronary atherectomy,[3] and 1.07, 2.5, and 1.83 mm for stent implantation.[1] The positive intercept values of the regression line for all the systems in this study indicate that most QCA systems tend to overestimate in the lower range of luminal diameters (<1 mm). The slope (b), however, was <1 for all systems, indicating that for larger reference vessels, the QCA systems tested would underestimate the true lumen diameter. A standardized set of phantoms of large diameter should be produced for future multicenter studies to comprehensively examine the performance of QCA systems over the complete range of vessel size. The intracoronary insertion of phantom stenoses of large diameter may, however, prove to be difficult in the porcine model in view of the limited size of the coronary artery lumen.

Conclusions

This study has revealed wide differences in the performance of currently available QCA systems, highlighting the difficulties in attempting to make direct comparisons between absolute measurements of one angiographic study and those derived from a different QCA system or with on-line analysis in clinical practice. Power calculations and study design of angiographic trials should be adjusted for the precision of the QCA system used to avoid the risk of failing to detect small differences in patient populations.

QCA validation studies should be performed in a uniform and standardized manner to provide meaningful data that can be used to compare the performance of QCA systems, to guide the recalibration of QCA algorithms, and to facilitate the maintenance of high standards of QCA for clinical practice and scientific studies. The entire chain of a QCA system should be revalidated each time the version of QCA software is upgraded or a hardware component is exchanged.

In the reporting of angiographic studies, absolute values of luminal diameter and values of statistical significance for differences between study populations should be accompanied by the results of the appropriate validation parameters of the QCA system used so as to facilitate the interpretation of clinical studies.

Appendix

The following centers and investigators participated in this study (both the centers and investigators are given in alphabetical order).

Beth Israel Hospital, Boston, Mass: Donald Baim. Brigham and Women's Hospital, Boston, Mass: C. Michael Gibson. Cleveland Clinic, Cleveland, Ohio: Stephen Ellis, Eric J. Topol. George Washington University, Washington, DC: John Reiner, Allan Ross. Hôpital Universitaire Saint Jacques, Besançon, France: Jean Pierre Bassand. Mount Sinai Hospital, Toronto, Ontario: Allan Adelman. St Michaels Hospital and Sunnybrook Health Science Center, Toronto, Ontario: Paul W. Armstrong, Anatoly Langer, Normand Robert, Bradley Strauss, Martin Yaffe. Thomas Jefferson Hospital, Philadelphia, Pa: David Fischman, Sheldon Goldberg. Thoraxcenter, Rotterdam, the Netherlands: Carlo di Mario, Jürgen Haase,

David Keane, Eline Montauban van Swijndregt, Patrick W. Serruys, Cornelis Slager, Washington Cardiology Center, Washington, DC: Martin B. Leon, Jeffrey Popma.

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Chapter IV

In-vivo validation of an experimental adaptive quantitative coronary angiography algorithm to circumvent overestimation of small luminal diameters.

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Original Studies

In Vivo Validation of an Experimental Adaptive Quantitative Coronary Angiography Algorithm to Circumvent Overestimation of Small Luminal Diameters

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The reliability of quantitative coronary angiography (QCA) measurements is of fundamental importance for the study and practice of interventional cardiology. In vivo validation results have consistently reported a tendency for QCA systems to overestimate small luminal diameters. Such a systematic error may result in the underestimation of luminal gain during intracoronary procedures and in the underestimation of progression of coronary artery disease during longitudinal studies.

We report the in vivo validation results of an experimental adaptive edge-detection algorithm that was developed to reduce overestimation of small luminal diameters by incorporating a dynamic function of variable kernel size of the derivative operator and variable weighting of the first and second derivatives of the brightness profile. The results of the experimental algorithm were compared to those of the conventional parent edge detection algorithm with fixed parameters.

Dynamic adjustment of the edge-detection algorithm parameters was found to improve measurements of small (<0.8-mm) luminal diameters as evidenced by an intercept of +.07 mm for the algorithm with variable weighting compared to +0.21 mm for the parent algorithm with fixed weighting. A slope of <1 was found for both the parent and experimental algorithms with subsequent underestimation of large luminal diameters.

Systematic errors in a QCA system can be identified and corrected by the execution of objective in vivo validation studies and the consequent refinement of edge-detection algorithms. The overestimation of small luminal diameters may be overcome by the incorporation of a dynamic edge-detection algorithm. Further refinements in edge-detection algorithms will be required to address the issue of underestimation of large luminal diameters before the absolute values derived from QCA measurements can be considered accurate over the full range of clinically encountered luminal diameters.

Key words: coronary arteriography, quantitative coronary angiography, validation

INTRODUCTION

Computerized quantitative coronary angiography (QCA) has fundamentally altered our approach to the assessment of interventional techniques and strategies aimed at the prevention of restenosis and progression of coronary artery disease. The reliability of QCA measurements is therefore of central importance for the validity of angiographic trials and the application of their results to clinical practice.

Overestimation of small luminal diameters by automated QCA systems has been consistently reported for both edge detection, as well as videodensitometric algorithms [1–6]. The degree of reported overestimation varies according to the individual QCA system as well as the validation model (e.g., in vitro or in vivo, focal spot size of X-ray system). In a recent multicenter validation study of QCA systems at core angiographic laboratories in

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North America and Europe, we found that all 10 QCA systems validated, overestimated measurements of small luminal diameters [1]. The clinical implications of such overestimation include the reporting in clinical trials of smaller luminal gains than actually achieved at intervention, the underestimation of progression [8,9] of coronary artery disease in longitudinal studies, and the underestimation of the vasospastic response to ergonovine provocation tests [10]. Furthermore, in the analysis and interpretation of QCA validation studies, the overestimation of small luminal diameters by a given QCA system may partially compensate for the underestimation of large luminal diameters by QCA systems, resulting in the reporting of a highly favorable accuracy value for the QCA system, for the total range of diameters validated [7].

While one approach to overcome this phenomenon would be to provide a look-up-table for the results of small luminal diameter measurements based on regression analysis of in vivo validation studies, given the unpredictable degree of X-ray scatter in the thorax and possible motion blur of the heart, a dynamic modification of the edge-detection algorithm to address this issue would be scientifically preferable. We report in vivo validation results for an experimental QCA edge detection algorithm which was developed (University of Limburg), in an attempt to overcome the problem of overestimation of small luminal diameters by incorporating an adaptive correction function. The experimental algorithm was based on a conventional parent edge detection algorithm, with fixed weighting (50:50) of the first and second derivatives. A comparable approach to algorithm modification has been reported by Sonka et al. [13], who also used an edge operator that was dependent on the approximate diameter.

To determine the efficacy of the dynamic adaptive algorithm, we compared the quantitative measurements of this experimental algorithm with those obtained from the parent algorithm with fixed weighting for the same series of in vivo angiographic stenoses. Angiographic "phantom" stenoses of known diameter, mimicking human coronary artery obstructions, were serially inserted in the coronary arteries of anesthetized pigs and the QCA measurements of the cineangiograms obtained were compared with the known dimensions of the phantoms, to determine the reliability of the two QCA algorithms.

METHODS

Stenosis Phantoms

The stenosis phantoms consisted of radiolucent acrylate or polyimide cylinders with precision-drilled eccentric circular lumens of 0.5, 0.7, 1.0, 1.4, and 1.9 mm in diameter, as previously described [2,3]. The outer diameters of the cylinders were 3.0 or 3.5 mm and all were 8.4 mm in length. Acrylate was used to produce the phantoms with small stenosis diameters (0.5 and 0.7 mm), whereas the less fragile polyimide was better suited to the drilling of large stenosis diameters (1.0, 1.4, and 1.9 mm). Parallel to the stenosis lumen a second channel of 1.3 mm in diameter was drilled in the cylinders to attach them to the tip of 4 Fr Fogarty catheters (Vermed, Neuilly en Thelle, France). The central lumens of these catheters contained a removable metal stilette, which was used for intracoronary insertion of the phantoms, as well as for their positioning in the radiographic isocenter during the in vivo experiments.

Animal Preparation

Following an overnight fast, four cross-bred Landrace-Yorkshire pigs of 45–50 kg in weight were sedated with intramuscular ketamine (20 mg/kg) and intravenous metomidate (5 mg/kg). The animals were intubated and connected to a respirator for intermittent positive-pressure ventilation with a mixture of oxygen and nitrous oxide. Ventilator settings were adjusted during the experiments to maintain the arterial pH at 7.35–7.45, pCO_2 at 35–45 mm Hg, and the pO_2 at >150 mmHg. Anesthesia was maintained with a continuous intravenous infusion of pentobarbital (5–20 mg/kg/hr).

Valved introducer sheaths (12 Fr: Vygon, Ecouen, France) were surgically placed in both carotid arteries to allow sequential insertion of the angiographic guiding catheter and the stenosis phantoms. An 8 Fr introducer sheath was placed in a femoral artery for the introduction of a 7 Fr high-fidelity micromanometer (disposable microtip catheter, type 811/160, Cordis-Sentron, Roden, Netherlands). Jugular venous access was secured for the administration of medications and fluid. Each animal received an intravenous bolus of acetylsalicylic acid (500 mg) and heparin (10,000 IU), and a continuous infusion of heparin (10,000 IU/hr) was maintained throughout the procedure, to prevent the formation of an intracoronary thrombus.

Calibration of Quantitative Coronary Measurements

Two different calibration methods were applied to each series of quantitative coronary analysis measurements:

Conventional catheter calibration: The nontapering part of the tip of each 8F polyurethane guiding catheter (El Gamal, type 4, Schneider, MN) was measured (diameters of the individual catheters ranged from 2.49 to 2.54 mm) with a precision micrometer (No. 293-501, Mitutoyo, Tokyo, Japan; accuracy 0.001 mm). The catheter was then introduced into the ascending aorta via the left carotid artery and engaged in the ostium of the left

coronary artery. Before injecting contrast medium the catheter tip was flushed with saline and recorded on cinefilm for subsequent off-line QCA.

Calibration at the isocenter: A cylindrical metallic object (drill-bit) of known diameter (3.0 mm) was placed at the isocenter of the X-ray system and recorded on cinefilm. For the two QCA systems, the available calibration procedure using automated edge detection was applied to the images obtained, yielding the corresponding calibration factors (mm/pixel).

Coronary Angiography and Placement of Stenosis Phantoms in Vivo

After engaging the guiding catheter in the left main coronary artery, intracoronary isosorbide-dinitrate (1 mg) was administered to control coronary vasomotor tone before the insertion of the phantoms. The stenosis phantoms were serially wedged in the left anterior descending or left circumflex artery and positioned in the radiographic isocenter using the tip of the metal wire as a marker, which was removed prior to angiography. Coronary angiography was performed by ECG (R-wave)-triggered injection of 10 ml iopamidol 370 at 37°C with a programmed injection rate of 10 ml/sec (rise time = 0) through the 8 Fr guiding catheter, using a pressure injector. To minimize the effect of ventilation on angiographic acquisition, the respirator was disconnected during contrast injection.

Image Acquisition and Processing

Cineangiography was performed at 25 frames/sec on a monoplane Philips Poly Diagnost C2 machine equipped with an MRC X-ray tube and powered by an Optimus CP generator (Philips Medical Systems International BV, Best, Netherlands). The 5-inch (12.5-cm) field mode of the image intensifier (focal spot 0.8 mm) was selected, and the radiographic system settings were kept constant (kVp, mA, msec) in each projection. All phantoms were imaged at the isocenter sequentially in two projections, with particular care taken to minimize foreshortening of the segment of interest and acquired on 35-mm cinefilm (CFE type 2711, Kodak, Paris, France), using an Arritechno 90 cinecamera (Arnold & Richter, Munich, Germany) with an 85-mm lens. The cinefilms were processed by a Refinal developer (Agfa-Gavaert, Leverkusen, Germany) for 4 min at 28°C. The film gradient was measured in all cases to ensure that the optical densities of interest were on the linear portion of the sensitometric curve.

From each angiogram that fulfilled the requirements of image quality for automated quantification (no superimposition of surrounding structures, no major vessel branching at the site of the phantom position), a homogeneously filled end-diastolic coronary image was selected for off-line QCA. Twenty end-diastolic frames of the phantom stenoses were suitable for edge-detection analysis. A sufficiently long luminal coronary segment was selected for quantitative analysis on all images.

Automated Edge Detection Algorithms

The software for both the experimental and the conventional parent edge detection algorithms were loaded on the same QCA hardware components [2,11,15]. On both the conventional and experimental QCA system, a 6.9 × 6.9mm region of interest within the 18 × 24-mm cineframe is digitized into a 512 × 512-pixel matrix using a CCD-camera (8 bits = 256 density levels) resulting in a final resolution of 1,329 × 1,772 pixels. A correction for pincushion distortion [14] was applied for both series of analyses. For both systems, the user defines a number of centerline points within the arterial segment which are subsequently connected by straight lines, serving as a first approximation of the vessel centerline. The edge-detection algorithm is carried out in two iterations. First, the model is the initially defined centerline; second, the model is a recomputed centerline, determined automatically as the midline of the contour positions, which were detected in the first iteration.

The basic automated edge-detection algorithms for both the experimental and conventional parent algorithms are similar and are based on the first and second derivative functions applied to the brightness profiles along scanlines perpendicular to a model, using minimal cost criteria. For the conventional system, the weighting of the first and second derivatives is fixed at 50:50 for analysis of all luminal diameters. For the experimental algorithm, the following approach was adopted. A number of computer simulations were performed to gain insight into the parameters responsible for the overestimation at small vessel sizes. Theoretical density profiles of circular lumens were convolved with a gaussian function to reflect the X-ray system's blurring function. On these profiles, the edge detection algorithm was applied. It was observed that the computed diameters are larger than the true diameters below 1.5 mm. The overestimation increased with pixel size, the width of the blurring function, and the weight factor of the second derivative [16,17]. Also, the smaller the diameter, the larger the overestimation. On the other hand, a small kernel size of the derivative operator has a favorable effect on the results because it compensates for the limited number of pixels defining the extent of small diameters [15]. Note, however, that small kernel size makes the edge-detection algorithm more sensitive to noise in the image, as fewer pixels are involved in the computation. On the basis of these simulations, an algorithm was generated which adaptively varies the weighting of the first and second derivative and adjusts the kernel size as a function of the

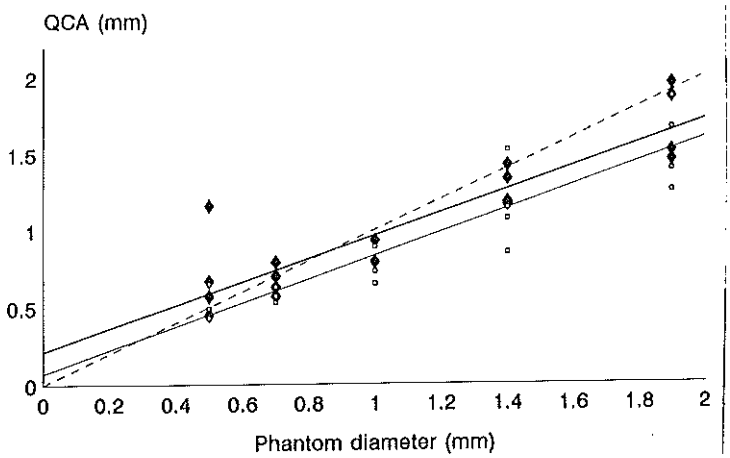

Fig. 1. QCA measurements calibrated by the angiographic catheter of the experimental and conventional edge-detection algorithms were plotted against the true values of the stenosis channels by linear regression. The results of the experimental algorithm are given as light squares and a light continuous regression line; the results of the conventional algorithm are given as dark diamonds and a dark continuous regression line; and the line of identity is represented by the interrupted line. Overestimation of small luminal diameters as seen with the conventional algorithm [y = 0.21 mm + 0.75 (x)] was avoided by the experimental algorithm by the incorporation of adaptive dynamic functions [y = 0.07 mm + 0.76 (x)].

approximate diameter measured in the first iteration. For small diameters, the ratio of the first to the second derivative was proportionally greater. Moreover, the kernel size of the derivative operator was adjusted to compensate for the limited number of pixels defining the extent of small diameters [15,16]. The experimental algorithm was adaptive only up to (and attenuated toward) a first iteration diameter measurement of 1.7 mm.

Measurement of the Obstruction Diameter

Once the contours of the stenosis phantoms were defined, the diameters of the artificial obstruction were automatically derived from the diameter function on each coronary analysis system. For the purpose of comparative validation, user interaction on the computerized reconstruction of phantom contours was excluded.

Statistical Analysis

Using both calibration methods (calibration at the isocenter and catheter calibration), the individual measurements for obstruction diameter obtained by the two QCA algorithms were compared with the true phantom diameters. The mean of the signed differences between the measurement values ("obstruction diameter") and the true diameters of the phantom stenoses was considered an index of accuracy and the standard deviation of the differences an index of precision. The mean absolute error was derived from the mean of the absolute (unsigned) differences between the measured values and the true diameters. The measured values were plotted against the true phantom diameters by linear regression. Measurements with the same algorithm of the same stenoses derived from calibration by the catheter and calibration at the isocenter were compared by Student's *t*-test for paired data.

RESULTS

The experimental algorithm with variable kernel size and variable weighting of the first and second derivative was found to be effective in the reduction of overestimation of QCA measurements of small luminal diameters. This improvement in the performance of QCA measurements of small luminal diameter is evidenced in Figures 1 and 2, where the results for the experimental algorithm are compared to those of the parent algorithm both when the measurements were calibrated by using the catheter as a scaling device (Fig. 1) and when measurements were calibrated at the isocenter (Fig. 2). The values of the linear regression analysis are presented in Table I.

When QCA measurements were calibrated by the catheter, the conventional edge-detection algorithm yielded an intercept of +0.21 mm and a slope of 0.75(x). This overestimation of small diameters was reduced by the experimental algorithm, which had an intercept of 0.07 mm and a slope of 0.76(x).

Calibration of QCA measurements at the isocenter for the conventional edge-detection algorithm, resulted in

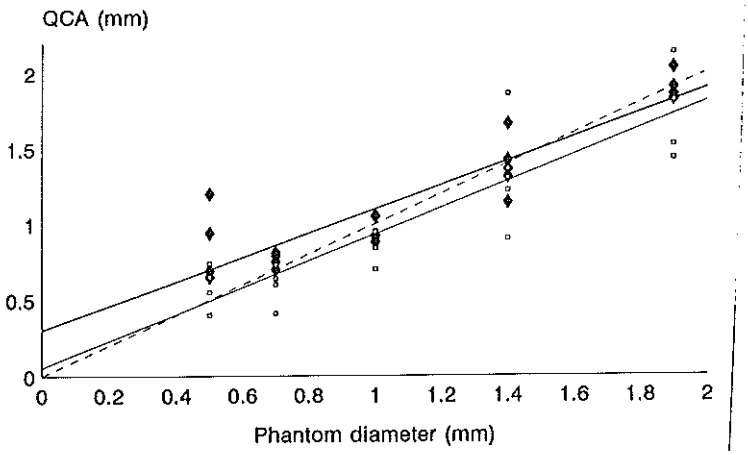

Fig. 2. QCA measurements calibrated at the isocenter of the experimental and conventional edge-detection algorithms were plotted against the true values of the stenosis channels by linear regression. The results of the experimental algorithm are given as light squares and a light continuous regression line; the results of the conventional algorithm are given as dark diamonds and a dark continuous regression line; and the line of identity is represented by the interrupted line. Overestimation of small luminal diameters as seen with the conventional algorithm [y = 0.30 mm + 0.80 (x)] was avoided by the experimental algorithm by the incorporation of adaptive dynamic functions [y = 0.05 mm + 0.88 (x)].

TABLE I. Luminal Diameter QCA Measurements Calibrated by Catheter or by Isocenter for Experimental and Conventional QCA Algorithms*

	Accuracy (mm)	Precision (mm)	Mean error (mm)	Correlation	SE (mm)	Regression (mm)
Conventional QCA catheter calibration	−0.06	±0.23	0.17	0.89	±0.20	0.21 + 0.75(x)
Experimental QCA catheter calibration	−0.21	±0.22	0.23	0.91	±0.19	0.07 + 0.76(x)
Conventional QCA isocenter calibration	0.07	±0.21	0.15	0.91	±0.19	0.30 + 0.80(x)
Experimental QCA isocenter calibration	−0.08	±0.24	0.20	0.89	±0.24	0.05 + 0.88(x)

*Note the lower intercept values for the regression line of the experimental algorithm which incorporates variable kernel size of the derivative operator and variable weighting of the first and second derivative of the brightness profile

both a greater positive shift (intercept) and a higher slope of +0.30 mm and 0.80(x), respectively. This overestimation of small diameters was reduced by the experimental algorithm, which had an intercept of 0.05 mm and a slope of 0.88(x).

Given the degree of overestimation of small diameters by the conventional system (particularly during calibration at the isocenter) in conjunction with the underestimation of larger diameters, it is not surprising that the overall accuracy (mean of the signed differences) for the validated range of 0.5–1.9 mm was more favorable for the conventional algorithm on account of the compensation [7] of the positive (small-diameter) and negative (large-diameter) signed values. Furthermore, despite the low slope of the conventional algorithm (0.75(x) and 0.80(x) for the catheter and isocenter calibration, respectively), the mean error [mean of the absolute (unsigned) differences between the measured values and the true phantom values] for the conventional algorithm (0.17 and 0.15 mm) was lower than for the experimental algorithm (0.23 and 0.20 mm), on account of the greater positive shift associated with the conventional algorithm and associated superior performance in larger luminal diameters.

DISCUSSION

The key findings of this study were (1) validation by the analysis of in vivo stenoses of a standard conventional QCA algorithm reveals a well-recognised problem of overestimation of small luminal diameters as well as underestimation of larger luminal diameters; (2) application of an experimental dynamic algorithm with adaptive weighting of the first and second derivative and an adjustive kernel size to circumvent the problem of overestimation of small luminal diameters results in a reduction in such overestimation of small (<0.8-mm) luminal diameters; (3) application of this experimental adaptive

algorithm to larger luminal dimensions (>0.8 mm) results in greater underestimation of measurements, particularly when calibrated by the catheter; and (4) although the reduction in measured diameter achieved by application of the adaptive algorithm is greatest for small luminal diameters and attenuated for larger diameters, the experimental algorithm in its current form (the algorithm is currently programmed to exert some activity up to diameters of 1.7 mm) confers no overall benefit for the whole range of 0.5–1.9 mm diameters validated on account of a greater underestimation of vessels >0.8 mm.

Overestimation of Small Luminal Diameters

Overestimation of small luminal diameters is a frequent finding of in vivo validation studies [1] and effective measures attempting to increase our understanding and to overcome such overestimation are required. The clinical implications of such overestimation of small luminal dimensions are significant. If in a clinical trial using the conventional algorithm, an improvement in coronary luminal diameter is achieved by balloon angioplasty or rotablator from 0.4 mm preprocedure to 1.8 mm postprocedure, a gain of 1.05 or 1.12 mm for catheter or isocentric calibration, respectively, will be attributed to the device, instead of a true luminal gain of 1.40 mm. Similarly, progression of a lesion in a longitudinal study from a minimal luminal diameter of 1.0–0.4 mm would be underestimated by the conventional algorithm (progression would be estimated to be 0.45 or 0.48 mm for catheter or isocentric calibration, respectively). In the current form of the experimental adaptive algorithm with variable weighting programmed up to a diameter of 1.7 mm, no significant benefit would be conveyed over the conventional algorithm – the luminal gain as above would be reported as 1.06 or 1.23 mm for catheter or isocentric calibration, respectively, and the progression as above would be reported as 0.46 or 0.53 for catheter or isocentric calibration, respectively.

The reasons for the overestimation of small luminal diameters by QCA systems remain unclear; potential factors include a point spread function relating to the focal spot size and limited resolution of the entire X-ray imaging chain [16] and too large a pixel size relative to the vessel diameter, as well as too great a kernel size of the derivative operator. While corrective numerical functions, based on the known pattern of underestimation or overestimation of QCA measurements, could be applied to the results of angiographic trials, it may be more effective and reliable to correct the systematic inaccuracies of a QCA system by the development and fine-tuning of dynamic adaptive algorithms.

We have demonstrated that the overestimation of luminal diameters of <0.8 mm can be effectively reduced by the incorporation of a dynamic function of variable kernel size of the derivative operator and variable weighting of the first and second derivative in the edge detection algorithm. The experimental edge detection algorithm, however, will require further modification to address the low slope of the system; i.e., the underestimation of larger luminal diameters before it could be adopted in clinical practice.

Calibration

The use of angiographic catheters for the calibration of quantitative coronary analysis systems may influence the outcome of luminal diameter measurements. Variations in catheter composition may result in varying X-ray attenuation [18–20] and therefore in differences in the automated detection of the contour points. In our study, only one type of catheter was used for calibration; therefore, the influence of different materials on calibration was excluded. The results of the present study show that the values using catheter calibration are smaller than those using calibration at the isocenter ($P < 0.001$). Theoretically, a greater distance between image intensifier and catheter tip than between image intensifier and isocenter would result in out-of-plane magnification producing smaller calibration factors (mm/pixel). This error can be circumvented by out-of-plane correction as proposed by Wollschläger et al. [21] or by calibration at the isocenter of the X-ray system.

QCA Validation Studies

Given the increasing role of QCA in the evaluation of interventional cardiology [7], it has become essential that the performance of QCA itself should undergo objective and scientific evaluation. While in vitro test series are more easily standardized, their results are not always representative of QCA measurements of clinical angiograms, as heterogeneous beam scattering and variable background density within the thorax and the potential influence of motion blur are unpredictable. In vivo validation studies on the other hand are of clinical relevance and provide an indication of the reliability of clinical angiographic trials, the significance of their failure to detect relative changes in luminal diameter and how much importance should be attributed to absolute values of luminal diameter derived from individual QCA systems. Furthermore, it is only by detailed validation studies that systematic errors in QCA systems can be identified and thereby provide guidance for the refinement of algorithms incorporated within QCA software.

Statistical Parameters for QCA Studies

Investigators reporting and readers interpreting QCA data should be familiar with the limitations of the conventional statistical parameters used to described QCA validation studies [7]. As recently described in detail [7],

the reporting of the "accuracy" of QCA measurements over a validated range may fail to convey the error to be expected from a given QCA measurement on account of cancellation of the signed differences of overestimated (below the intersection of the regression and identity lines) and underestimated (above the intersection of the regression and identity lines) measurements. This point may be revealed by the reporting of the absolute mean error, which is independent of the sign (+/−) of the differences between the true and measured values—it can be seen in the results of our study that the absolute mean error was consistently greater in value than the value of the accuracy for both the conventional and experimental algorithms (Table I). Alternatively, the reader might be well served by the provision of the accuracy of measurements at a number of different dimensions, rather than for the entire validated range as reported conventionally; review of Figure 2 clearly shows that the accuracy of measurements for dimensions of 0.4–0.8 mm is superior with the experimental algorithm, that the accuracy for dimensions of 1.0–1.2 mm is equivalent for the experimental and conventional algorithms, and for dimensions of 1.4–1.9 mm that the accuracy of measurements with the conventional algorithm is superior to those of the experimental algorithm in its current form. For the same reason, precision of QCA measurements will be dependent on the range of validated diameters, while the standard error of the estimate (SEE) will more closely reflect the random error or noise to be expected from the QCA system particularly after correction for an intercept of 0 and a slope of 1 (SEEc) [4,7,22].

CONCLUSION

Systematic errors in a QCA system can be identified and corrected by the execution of objective in vivo validation studies and the consequent refinement of edge-detection algorithms. The overestimation of small luminal diameters by QCA measurements may be overcome by the incorporation of an iterative algorithm with dynamic adjustment of the kernel size of the derivative operator and adaptive weighting of the first and second derivative of the brightness profile of the vessel in relation to the diameter to be detected. Further refinements in edge-detection algorithms will be required to address the issue of underestimation of large luminal diameters before the absolute values derived from QCA measurements can be considered to be accurate over the full range of clinically encountered luminal diameters.

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Chapter V

Insertion of balloon-mounted "stent" stenoses of up to 2.9mm in porcine coronary arteries for the in-vivo validation of quantitative coronary angiography.

David Keane, Wim van der Giessen, Yukio Ozaki, Ad den Boer, Patrick W Serruys.

(in review)

ABSTRACT :

Background. With the advent of "the bigger the better" policy and the increasing use of new alternative interventional devices associated with large luminal gains, the need arises for in-vivo phantom stenoses of large diameter for validation of quantitative coronary angiography measurements (QCA).

Objectives. To address this challenge and increase the direct clinical applicability of QCA validation results, we developed a new technique of in-vivo phantom stenosis deployment, permitting a range of stenoses of up to 2.89mm to be inserted in porcine coronary arteries.

Methods. Balloon-mounted single channel "stent stenoses" were introduced through the carotid arteries and positioned in proximal coronary segments under fluoroscopic guidance. Cineangiograms of the stenoses were recorded for QCA validation of an edge detection algorithm currently used for the analysis of interventional trials.

Results. For the QCA system validated, the accuracy over the entire range of 0.5 to 2.89mm stenoses was -.20mm compared to the previously reported accuracy of -.09mm for the same edge detection algorithm when validated over a smaller range of stenoses of 0.5 to 1.9mm.

Conclusions. The underestimation of QCA measurements (-.20mm) revealed by these new large diameter in-vivo stenoses, indicates that the development and fine tuning of QCA algorithms should no longer be based upon cinefilms of conventional in-vitro stenoses which fail to convey the heterogenous X-ray scatter and veiling glare encountered in-vivo and indicate that clinical angiographic trials to date (particularly those with stenting and atherectomy) may have underestimated the true luminal gain achieved by coronary interventional devices and underestimated the absolute luminal loss reported at 6 month follow-up.

INTRODUCTION :

Quantitative analysis of coronary arteriograms plays a major role in interventional cardiology and clinical research [1-10]. Validation of the accuracy and precision of quantitative coronary angiography (QCA) has traditionally been based upon the use of in-vitro models, whereby plexiglass blocks or water are used to approximate the beam hardening and attenuation of the X-ray beam in the human thorax [11]. In order to increase the quality and direct clinical applicability of QCA validation results, we have more recently reported the insertion of plastic stenoses in porcine coronary arteries to simulate the heterogenous scatter and veiling glare of the human thorax [12,13]. The range of phantom stenoses using this approach (from 0.5mm up to 1.9mm) has, however, been limited by both the technique used to deploy the stenoses as well as by the size of porcine coronary vessels.

Given that most QCA systems have been found to underestimate measurements of large diameter, the reported accuracy from validation studies using stenoses of 0.5 to 1.9mm diameter will be more favorable than those using a larger range of diameters. The 0.5 to 1.9mm range has, however, been in the range of human coronary stenoses undergoing conventional balloon angioplasty. The average minimal luminal diameter of coronary lesions pre- and post- balloon angioplasty and at six month follow-up as observed in multicenter trials are 1.03, 1.78 and 1.48mm respectively [14]. With the advent of coronary stenting and atherectomy and the recently introduced interventional policy of "the bigger the better" the minimal luminal diameter of lesions currently undergoing interventional treatment have become significantly larger : 1.07, 2.5 and 1.83 mm for stent implantation [15], and 1.29, 2.78 and 1.92mm for "optimal atherectomy" [16] for luminal diameters pre-procedure, post-procedure and at 6 month follow-up respectively.
This new direction in interventional practice demands that QCA systems also perform accurately in vessels with such large diameters.

In order to cover this new range of clinically encountered minimal luminal diameters, we expanded our QCA validation methodology by using a new technique of in-vivo "stent stenosis" deployment, allowing a range of stenoses of up to 2.89mm to be evaluated. The cinefilms obtained were used to validate QCA by edge detection and to determine the optimal image intensifier field size for angiographic studies.

METHODS :

Phantom stenoses. Seven phantom stenoses with diameters ranging from 0.5 to 2.9mm were studied. All phantom stenoses were constructed of radiolucent polyimide cylinders with precision-drilled circular lumens (tolerance of .003mm). The absolute internal diameters of the stenosis channels were measured to the nearest 0.001mm by a light profile projector (Mitutoyo PJ300, Tokyo, Japan). The stenosis channels were of 0.50, 0.69, 1.00, 1.41, 1.95, 2.49 and 2.89 mm diameter.

The construction of the 0.5 to 1.95mm series of phantom stenoses was of the same principle as previously reported [12,13]. These were designed for both ease of removal from the coronary artery as well as ease of insertion. Parallel to the stenosis lumen, a second channel of 1.3 mm in diameter was drilled in the cylinders to enable their attachment to the tip of 4 F Fogarty catheters (Vermed, Neuilly en Thelle, France). The lumens of the Fogarty catheters contained a removable metallic stilette, which aided the intracoronary insertion of the phantoms as well as their positioning in the radiographic isocenter.

We designed our new larger "stent stenoses" with the primary aim of keeping the outer diameter of the cylinders to a minimum usable size despite increasing the inner lumen of the stent stenosis. A single channel cylinder was constructed for deployment on an inflated angioplasty balloon. Once positioned in the coronary artery, the balloon was deflated and withdrawn and the facility to remove these larger phantom stenoses was thus forfeited.

The length of all stenosis channels was 8.4mm. The outer diameter of the cylinders for intracoronary insertion for the dual channel series of phantom stenoses, was 3.0mm for the 0.5 stenosis phantom, and 3.5mm for the 0.7 to 1.95mm phantom stenoses. For the single channel stent stenoses the outer diameter of the cylinders for intracoronary insertion was 3.0mm for the 2.49mm phantom stenosis and 3.5mm for the 2.89mm phantom stenosis.

Experimental Procedures. The procedures followed were in accordance with the institutional guidelines for animal studies and complied with the *Guide for the Care and Use of Laboratory Animals* [17]. All stenoses were inserted in the coronary arteries of two anaesthetized Yorkshire pigs (26 and 33kg). The animals were premedicated with ketamine hydrochloride. General anaesthesia was induced by enflurane and sodium pentobarbital. Sodium pentobarbital was also used to maintain general anaesthesia and finally at the end of each study to sacrifice the animal by overdose. Arterial blood gases, acid base balance, electrolytes and haemoglobin were serially monitored throughout the studies.

The animals were given aspirin 900mg intravenously at the beginning of the procedure. Heparin, 5,000iu, was given intravenously every hour. The phantom stenoses were bathed in heparin prior to intracoronary insertion and the operators gloves and angioplasty balloon were washed with heparin prior to handling of the phantom stenoses. Intracoronary isosorbide dinitrate (1mg) was administered prior to angiography of each phantom stenosis. Non-ionic contrast medium, iopamidol 755mg/ml (Iopamiro 370, BRACCO, Italy) was heated to 37^{0}C prior to intracoronary administration.

A 12 F and a 9F introducer sheath was surgically placed in the right and left carotid arteries respectively to allow the sequential insertion of the phantom stenoses mounted on Fogarty and balloon catheters and the insertion of the angiographic guiding catheter. An 8F soft tip guiding catheter (ELG4 S, Schneider, USA) was used for intracoronary contrast administration.

First the 0.5 to 1.95mm series of dual channel phantom stenoses were serially inserted and located at the radiographic isocenter (as previously described [12,13]). After arteriography (see below) they were removed from the coronary arteries. Then the larger series of single channel stent stenoses were inserted in the coronary arteries as follows: A guidewire (0.018", 270cm, Road Runner™, Cook Inc, Bloomington, IN) was first introduced into the coronary artery through the guiding catheter. The guiding catheter was then withdrawn and the tip of the guidewire was left in the distal segment of one of the three main coronary arteries. A single channel polyimide cylinder was then mounted on a noncompliant 3.5mm angioplasty balloon which was inflated to a pressure of 2 atmospheres prior to insertion through the 12 F carotid introducer, thereby providing a secure dumbell attachment of the stent stenosis as illustrated in **figure 1**. The balloon mounted stent stenosis was then advanced over the guidewire to be positioned in the proximal segment of the left anterior descending, circumflex or right coronary artery. After adjustment of the X-ray gantry to ensure that the stent stenosis lay at the radiographic isocenter, the balloon was deflated and withdrawn with the guidewire to allow coronary angiography. The latter single channel cylinders were retrieved post mortem by either reinsertion and reinflation of the balloon or by thoracotomy.

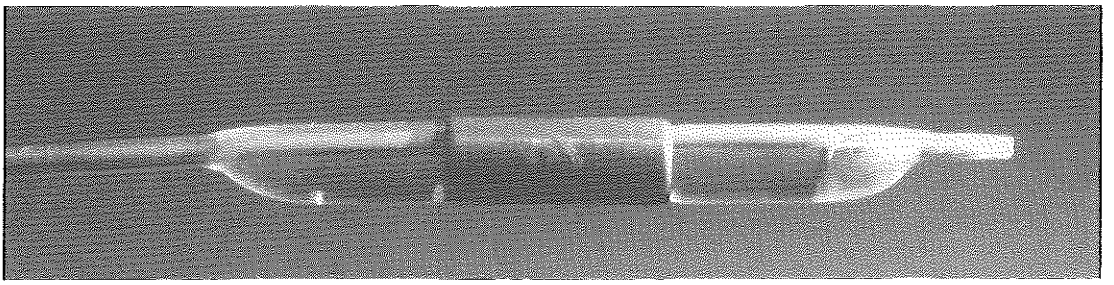

Figure 1. *A single channel polyimide cylinder with an inner diameter of 2.49mm can be seen to be firmly mounted on a balloon inflated to 2 atmospheres.*

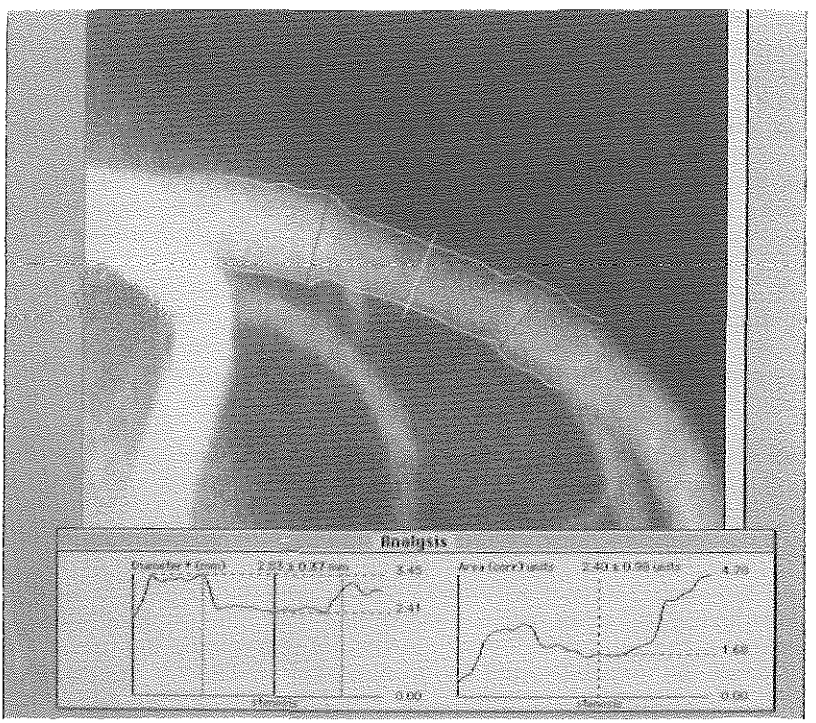

Figure 2. *Coronary angiographic image of the luminal stenosis induced by a single channel 2.49mm polyimide cylinder which has been positioned in the proximal segment of a porcine left anterior descending artery. QCA (edge detection) measurement of the segment containing the stenosis reveals an obstruction diameter of 2.41 mm*

Radiographic acquisition.
The cineangiograms were recorded on a Coroskop T.O.P. X-ray unit which incorporated a Polydoros IS/C generator and a Megalix 30/82 X-ray tube with a focal spot size of 0.4mm (Siemens A.G., Munich Germany, - 1994 release). Each intracoronary phantom stenosis was placed at the isocenter of the X-ray system and recorded in two orthogonal views in three image intensifier (II) field sizes 5" (13cm), 7" (17cm) and 9" (23cm) thus generating a total of 84 angiographic sequences for quantitative analysis.

The radiographic system settings were kept constant (kVp, mA, ms) in each projection. All stenoses were imaged in two projections sequentially and acquired on 35-mm cinefilm (CFE Type 2711, Kodak, Paris, France) at a frame rate of 25 images/s, using an Arritechno 90 cine camera (Arnold & Richter, Munich, Germany) with an 100 mm optical lens (over framing). The cinefilms were processed by a Refinal developer (Agfa-Gevaert, Leverkusen, Germany) for 4 minutes at 28°C. The film gradient was measured in all cases to ensure that the optical densities of interest were on the linear portion of the sensitometric curve.

Quantitative Angiographic Analysis.

Frame selection. The optimal angiographic frame from each of the 84 sequences was selected for QCA analysis. Frame selection was based on being end-diastolic, the absence of overlapping vessels, minimal foreshortening and homogenous filling of contrast - an example of a frame selected with automated contour detection is shown in **figure 2.**

Correction of pincushion distortion. Prior to the performance of the calibration and quantitative analyses of the stenoses, computerized correction for pincushion distortion was applied by the recording and subsequent off-line digitization of a centimeter grid.

Calibration. The QCA measurements were calibrated by the use of the guiding catheters as a scaling device as performed during the conduction of clinical interventional trials [8,9,15]. The nontapering catheter tips were measured with a precision-micrometer (Mitutoyo No.293-501, Tokyo, Japan; accuracy 0.001 mm) taking the average of repeated readings.

Automated Edge Detection. Cinefilms were quantitatively analyzed off-line in a core angiographic laboratory using the standard edge detection algorithm of the Cardiovascular Angiographic Analysis System (CAAS II; Pie Medical, Maastricht, The Netherlands) [18]. The entire 18 x 24 mm cineframe is digitized after optical magnification at a resolution of 1329 x 1772 pixels on a CCD camera. 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. The contour definition is carried out in two iterations. First, the user defines a number of centerline points within the arterial segment which are interconnected by a straight line, serving as the first model. Subsequently, the program recomputes the centerline, determined automatically as the midline of the contour positions which were detected in the first iteration. Manual correction of the automatically detected contours was neither necessary nor performed in this study (in routine practice at angiographic core laboratories, subjective manual correction of the detected contours at the minimal luminal diameter is kept to an absolute minimum e.g. in the case of complex dissections with contrast extravasation, which was not present in any of our porcine coronary angiograms).

"Minimal" versus "obstruction" diameter measurements. On the CAAS I, the parameter of "minimal luminal diameter" is taken as the shortest distance between the two luminal

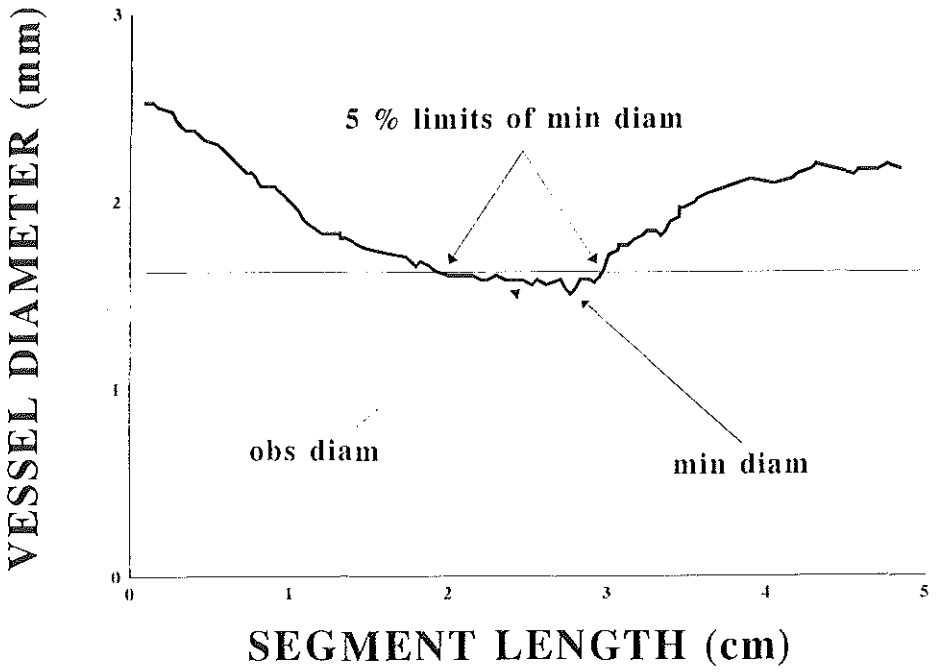

Figure 3. *The "minimal luminal diameter" (min diam) and the "obstruction luminal diameter" (obs diam) in the CAAS II system. The "minimal luminal diameter" is taken as the shortest distance between the two luminal contours i.e. the absolute minimum of the diameter function curve. The "obstruction diameter" is determined as the diameter of the vessel at the midpoint between the closest diameter positions on both sides of the minimum luminal diameter that exceed the minimum value by 5%.*

contours [19]. Thereby, the absolute minimum of the diameter function curve is provided. In addition to measuring the minimal luminal diameter, the CAAS II also calculates a so-called "obstruction diameter" [20]. The derivation of the "obstruction diameter" is illustrated in **figure 3** and is determined as the diameter of the vessel at the midpoint between the closest diameter positions on both sides of the minimum luminal diameter which exceed the minimum value by 5%. This additional variable has been created in an attempt to circumvent possible underestimations of the true value caused by quantum noise - its efficacy and reliability relative to the more conventional "minimal luminal diameter" measurement has not been previously validated.

Statistics. The QCA measurements for the minimal luminal diameter and the obstruction diameter were compared with the true phantom diameters to generate values for accuracy (mean of the signed differences) and precision (standard deviation of the signed differences) and by linear regression (true phantom diameter as the independent variable) to generate the indices of correlation, standard error of the estimate, intercept and slope.

RESULTS:

Accuracy and range of stenoses. The results of all analyses are presented in detail in **table 1.** Measurements for the entire range of phantom sizes (0.5 - 2.89mm) by QCA, using the conventional 5" and 7" image intensifier field sizes, revealed an accuracy of -.20mm. In contrast, analysis of only the 0.5 to 1.9mm range of phantom stenoses of our current study (i.e. excluding the 2.49 and 2.89mm cineframes) yielded an accuracy of -.16mm.

Regression analysis. Regression analysis of the results for the entire range of phantom stenoses yielded an intercept and slope of $y = .01 + .87(x)$ - see **figure 4.** The precision and standard error of the estimate, were $\pm$ .15mm and $\pm$ .12mm respectively.

Image intensifier field size. The results for the 5", 7" and 9" image intensifier field sizes are presented in **table 1.** As to be expected, no systematic deterioration in accuracy occurred with increasing pixel size from .063mm (7" image intensifier) to 0.082mm (9" image intensifier) while precision and standard error of the estimate (which are indices of random error and noise), both deteriorated with the 9" image intensifier setting. No improvement in precision or standard error of the estimate, however, was found when the image intensifer field size was reduced from 7" to 5" (when the pixel size decreased to .050mm).

"Minimal" versus "obstruction" diameter measurements. The validation results for the "minimal" and the "obstruction" diameter are given in **table 1.** A slight improvement in accuracy of edge detection of .02mm was found when measurement of the "obstruction" diameter (-.20mm) was compared to measurement of the "minimal" luminal diameter (-.22mm).

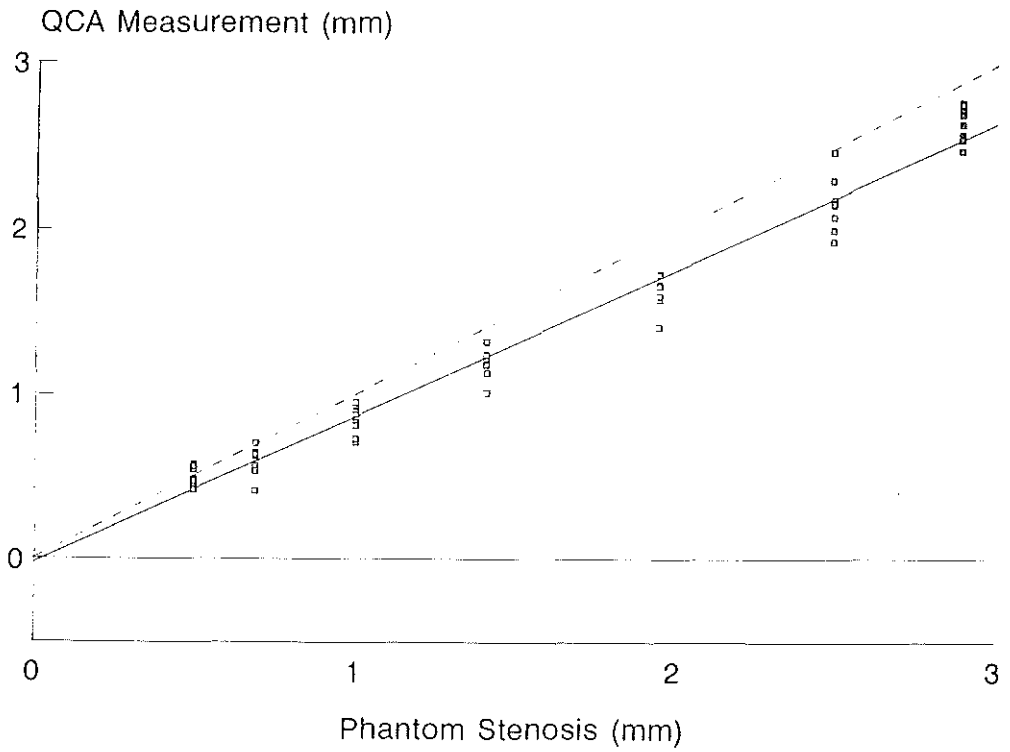

Figure 4. *The true diameters of the phantom stenoses on the X-axis have been plotted against their QCA measurements (obstruction diameter) on the Y-axis for the 5" and 7" image intensifier field sizes. The accuracy was -.20mm for the entire range validated (0.5 to 2.89mm) and the regression line has a slope of less than 1 (-.03 + .89(x)) indicating underestimation of large luminal diameters.*

	accuracy	precision	correlation	std error	regression	pixel size
5" image intensifier	-.21mm	±.15mm	.99	±.12mm	-.03mm +.88(x)	.050 ±.002mm
7" image intensifier	-.18mm	±.15mm	.99	±.12mm	-.02mm +.90(x)	.063 ±.003mm
9" image intensifier	-.18mm	±.21mm	.98	±.15mm	.09mm +.83(x)	.082 ±.003mm
"obstruction" luminal diameter	-.20mm	±.15mm	.99	±.12mm	-.03mm +.89(x)	.057 ±.007mm
"minimal" luminal diameter	-.22mm	±.16mm	.99	±.12mm	-.02mm +.87(x)	.057 ±.007mm
0.5 to 1.9mm phantom range	-.16mm	±.14mm	.98	±.08mm	.07mm + .78(x)	.057 ±.007mm

Table 1

- *Luminal diameter measurements for 5", 7" & 9" image intensifier settings.*
- *"Obstruction" versus "minimal" luminal diameter measurements for 5" and 7" image intensifier settings combined.*
- *Results of QCA measurements for the 0.5 to 1.9mm range of phantom stenoses only for 5" and 7" image intensifier settings combined.*

DISCUSSION:

Experimental Technique. In this study, we report a solution to technically overcome the limitations of earlier QCA validation studies by successfully inserting phantom stenoses of 2.5 and 2.9mm diameter on an inflated angioplasty balloon in vivo. Given that these large "stent" stenoses cannot be removed in-vivo, the maximum number of such single channel stent stenoses which could be deployed in a single animal is three (one in the proximal segment of the left anterior descending, the circumflex and the right coronary arteries). This limitation can be overcome by the prior insertion and withdrawal of dual channel phantom stenoses of smaller internal diameter using a fixed attachment to Fogarty catheters.

QCA results. Over a series of in-vivo stenoses from 0.5 to 2.9 mm in diameter, QCA measurements were associated with an accuracy of -.20mm and a precision of ± .15mm. Such a degree of underestimation of large luminal diameters (slope = .89(x)), is greater than previously detected by in-vivo validation studies using a smaller range of phantom stenoses and has significant implications for the interpretation of multicenter interventional trials.

Effect of increasing range of phantom stenoses on QCA measurements. By increasing the range of in-vivo phantom stenoses (0.5 - 2.89mm) we have revealed a greater underestimation (-.20mm) of measurements by QCA than demonstrated by our previous in-vivo validation studies (-.09mm) using a smaller phantom stenosis range of 0.5 to 1.9mm [12]. This finding results from two methodological differences. Firstly the cineangiograms in our previous studies were recorded on an older generation (1991) X-ray system with a larger focal spot size of 0.8mm (instead of the 0.4mm focal spot size used in our current study). This resulted in our previous studies in greater point spread function and a positive shift (intercept) with overestimation of very small diameters which partially compensated for the underestimation of larger values by bringing the overall accuracy (for the 0.5 to 1.9mm range) closer to zero (i.e. by cancellation of the signed differences). Secondly the absolute underestimation by edge detection increases with larger values and thus inclusion of stenoses of >2.0mm in our current study resulted in a greater underestimation for the entire range (0.5 to 2.89mm). This concept can be elaborated by considering a number of sample values: For a given QCA system with an intercept of .01mm and a slope of .87(x) it can be seen that measurement of a phantom stenosis of 1.00mm (typical pre-intervention minimal luminal diameter) will result in a reported QCA measurement of 0.88mm (accuracy of -.12mm) while measurement of a phantom stenosis of 2.8mm (typical post-optimal atherectomy minimal luminal diameter) will result in a reported measurement of 2.47mm (accuracy of -.33mm). It is thus clear that extension of the range of in-vivo phantom stenoses can result in the reporting of greater absolute inaccuracy for a QCA system. Furthermore our study confirms the degree of underestimation of larger diameters predicted from extrapolation of the regression line beyond the previously validated range (ie beyond 1.9mm).

Implications for clinical trials. While the degree of inaccuracy of QCA measurements of large luminal diameters revealed by our study has not been detected by previous validation studies using a smaller range of in-vivo stenoses, the tendency to underestimate luminal diameters of >1.0mm is not unique to the particular edge detection algorithm studied. In a recent validation study of 10 QCA systems at core angiographic laboratories in North America and Europe all were found to underestimate luminal diameters to some degree [21]. The clinical implications of the underestimation of large luminal diameters include the reporting in multicenter interventional trials of an underestimation of the true luminal gain

achieved at intervention and underestimation of the % diameter stenosis of all lesions. Furthermore, the degree of subsequent luminal loss at 6 month angiographic follow-up will also be underestimated. Such underestimation of luminal gain and subsequent loss and % diameter stenosis measurements will be particularly marked in interventional trials of devices associated with large luminal gains (e.g. the optimal atherectomy trials ; EUROCARE, BOAT, OARS [16]).

Until such time as QCA algorithms are developed and calibrated for images of in-vivo stenoses, rather than in-vitro images which fail to convey the heterogenous X-ray scatter and veiling glare of the thorax, it might be proposed that results of QCA measurements in angiographic trials should be transformed by a look-up-table based on the linear regression results of in-vivo validation studies (eg for CAAS II this would be y = -.03mm + .89(x)). Thus an angiographic trial using CAAS II reporting a mean luminal diameter of 2.5mm post intervention might be more appropriately reported as indicating a true luminal diameter of 2.81mm (i.e. (2.5mm +.03mm) / .89). Furthermore, the results of angiographic trials analyzed at different core laboratories with different QCA systems could be merged by correcting for the systematic error of each system as determined by in-vivo validation studies preferably using the same standardized set of in-vivo phantom cineangiograms. Application of such a normalization or corrective function to the results of each core angiographic laboratory might reveal that differences in luminal gain previously reported by different clinical studies for the same device may be greatly reduced. The inaccuracy in QCA measurements of large luminal diameters revealed by our study indicate that caution should be applied before directly applying the absolute results of multicenter angiographic trials to routine interventional practice in the catheterization laboratory, particularly in this new era of "the bigger the better" and widespread use of devices associated with large luminal gains in large vessels (eg stenting and atherectomy).

Image intensifier field size. We have shown that the use of either 5" or 7" image intensifier field sizes provide a resolution of adequate quality for quantitative coronary angiography and both should be permitted in the protocol of multicenter angiographic trials. The 9" field size was found to incur a minor loss in precision and standard error of QCA measurements without any change in accuracy or systematic shift. Therefore the occasional selection at an angiographic core laboratory of a 9" frame (when available) for quantitative analysis would be acceptable when the 5" or 7" angiographic sequences are found to be unsuitable for QCA analysis (eg due to poor contrast filling or vessel overlap), albeit accepting a slightly poorer precision for the individual analysis.

"Minimal" versus "obstruction" diameter measurements. We have demonstrated that for QCA measurements by the CAAS II system, the selection of the obstruction diameter rather than the minimal luminal diameter conveys an improvement in accuracy of .02mm. Even though this improvement is clearly small, we have now adopted the obstruction diameter rather than the minimal luminal diameter as the primary endpoint in on-going clinical trials.

Conclusion. To increase the direct clinical applicability of QCA validation studies for recently completed and ongoing interventional trials, the range of in-vivo phantom stenoses can be increased up to 2.9mm in porcine coronary arteries using a single channel "stent stenosis" technique in combination with our previously reported technique of insertion of dual channel phantom stenoses of smaller diameter. Extension of the range of phantom stenoses significantly affects the reported accuracy for a given QCA system and directly supports the implications from previous studies using smaller in-vivo stenoses that automated QCA algorithms underestimate large diameters in-vivo and thus underestimate acute luminal gain and subsequent chronic luminal loss following interventional procedures.

The results of this study are of particular relevance to the interventional policy of "the bigger the better" and widespread use of devices associated with large luminal gains in large vessels (eg stenting and atherectomy).

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Chapter VI

Comparison of Coronary Luminal Quantification obtained from both Geometric and Videodensitometric Quantitative Angiography and from Intracoronary Ultrasound pre and post Coronary Intervention.

Yukio Ozaki, David Keane, Carlo Di Mario, Edoardo Camenzid, Jose Baptista, Pim de Feyter P, Jos RTC Roelandt, Patrick W Serruys.

(In review)

ABSTRACT:

Objectives. The aim of this study was to determine whether coronary luminal area obtained from intracoronary ultrasound (ICUS) agree with measurement obtained by edge-detection (ED) or videodensitometric (VD) quantitative angiography pre and post coronary intervention, and which factors play a role in the discordance between ICUS and quantitative angiographic measurement.

Background. While the primary role of intracoronary ultrasound (ICUS) may be the imaging of coronary mural pathology, precise quantification of luminal cross sectional area (MCSA) would offer a significant advantage.

Method. One hundred thirty patients who underwent successful balloon angioplasty (BA, n = 100) or directional atherectomy (DCA, n = 30) were examined pre and post intervention. Minimal cross sectional area (MCSA) obtained from the three quantitative techniques were compared by the mean and standard deviation of their signed differences.

Results. Vessel size and lumen obtained after intervention was significantly larger in DCA than BA. MCSA obtained by ICUS was significantly larger than MCSA measured by ED and VD both pre and post BA or DCA. Correlation of MCSA measurements by ICUS and ED was 0.59 pre BA and 0.57 pre DCA, which deteriorated to a correlation of 0.48 post BA and 0.41 post DCA. The correlation between ICUS and VD was 0.50 pre BA and 0.48 pre DCA, the correlation between ICUS and VD was 0.63 post BA and 0.58 post DCA. Post intervention better correlation was shown between ICUS and VD than that between ICUS and ED.
One hundred lesions were classified according to the degree of vessel damage post BA. While the correlation between measurements obtained from ICUS and ED was 0.13 in lesions with angiographic dissection, 0.40 in the presence of angiographic haziness and 0.71 in the absence of dissection and haziness, the correlation between measurements obtained from ICUS and VD was 0.31 in lesions with angiographic dissection, 0.60 in the presence of haziness and to 0.76 in smooth lumen. The agreement both between ICUS and ED, and between ICUS and VD deteriorated in lesions with dissection.

Conclusions. MCSA obtained by ICUS is significantly larger than MCSA obtained from both ED and VD. Agreement between ICUS and ED considerably deteriorated after intervention. The complex morphological changes induced by angioplasty may augment the discordance of MCSA measurements by ICUS and quantitative angiography. VD may provide an acceptable alternative for ED in lesions with complex morphological changes induced by intervention. The absolute values of lumen dimensions obtained from ICUS, ED and VD after angioplasty should be interpreted with care, especially when used to decide on the necessity for further intervention.

INTRODUCTION :

While quantitative coronary angiography is still the golden standard in interventional cardiology, many pathologic studies indicate that angiography may underestimate the extent and severity of atherosclerotic disease (1-4). Intracoronary ultrasound is felt to be more sensitive than angiography in the qualitative assessment of vessel wall morphology including the detection of calcium deposits and plaque rupture (5-15). Intracoronary ultrasound may provide useful information in the guidance of coronary intervention procedure (16-18). Precise quantitative analysis of luminal cross sectional area by intracoronary ultrasound would offer a significant advantage. Previous studies have provided conflicting evidence on whether quantitative measurement derived from ICUS agree with the measurement obtained from quantitative coronary angiography (5,6,10,19-22).

To clarify whether intracoronary ultrasonographic measurement agrees with quantitative coronary angiography, and which factors may play a role in the discordance between ultrasound and quantitative angiographic measurement, we compared minimal cross sectional luminal area obtained from intracoronary ultrasound and both edge-detection and videodensitometric quantitative angiography.

METHODS :

Patients. One hundred sixty-eight patients who had intracoronary ultrasound (ICUS) examination pre balloon angioplasty (BA) or pre directional coronary atherectomy (DCA) at the Thoraxcenter were candidates for this study. Twenty-three of these patients were excluded because intracoronary ultrasound (ICUS) examination post intervention was not performed. Fifteen patients were excluded from the study because either their angiographic or ultrasound recordings were of inadequate quality for quantitative analysis. The remaining 130 patients were selected for the study. Of these 130 patients, 100 patients were treated with BA and the remaining 30 patients underwent DCA. Pre intervention, total occlusion of the target lesion was observed in 7 patients and the ultrasound catheter completely occluded the coronary lesion (cross sectional area of less than 1.61mm^2 with a 4.3Fr ultrasound catheter or cross sectional area of less than 0.73mm^2 with a 2.9Fr ultrasound catheter) in 87 patients. Pre intervention intracoronary ultrasound images were analyzed in the remaining 36 patients. Post intervention ICUS measurements were carried out in all 130 patients.

Balloon angioplasty (BA) or directional coronary atherectomy (DCA). All patients received full anticoagulant therapy including intravenous aspirin and heparin before intracoronary ultrasound examination and intervention. Coronary angiograms were recorded on cinefilm after the intracoronary administration of isosorbide dinitrate (1 - 2mg). A 0.014 inch high torque floppy guide wire (Advanced Cardiovascular Systems, Santa Clara) was inserted to guide the ultrasound catheter and the balloon or atherectomy catheter. The size of balloon or atherectomy device was determined to match the vessel reference diameter obtained from on-line quantitative angiographic measurement.

Table 1. Baseline clinical characteristics

	BA	DCA	p value
Patients	100	30	
Male/female	81/19	27/3	ns
Age (years)	60 ± 10	57 ± 9	ns
Stable / Unstable angina	53/47	16/14	ns
Coronary vessel	100	30	
RCA	31(31%)	7(23%)	ns
LAD	47(47%)	19(64%)	ns
LCX	18(18%)	4(13%)	ns
SVG.	4 (4%)	0(0%)	ns
Lumen measurement by edge-detection (mm)			
MLD pre	1.14 ± 0.41	1.23±0.44	ns
RD pre	2.88 ± 0.65	3.06 ±0.75	.001
MLD post	2.11 ± 0.54	2.87 ±0.65	.001
RD post	2.99 ± 0.71	3.66 ±0.59	.001
Lumen area measured ICUS (mm^2)			
MCSA pre	3.36 ± 0.99	2.77 ±1.00	ns
MCSA post	5.19 ± 1.90	7.67 ±2.25	.001

BA; balloon angioplasty, DCA; directional coronary atherectomy, LAD; left anterior coronary atery, RCA; right coronary artery, LCX; left circumflex coronary artery, MLD; minimal luminal diameter, RD;reference diameter, MCSA; minimal cross sectional area.

Quantitative coronary angiography (QCA). The new version of the computer-based Coronary Angiography Analysis System (CAAS II)(23,24) was used to perform the edge-detection (ED) and videodensitometric (VD) quantitative analysis. In the CAAS analysis which has previously been described elsewhere (24-28), the entire cineframe of size 18 x 24 mm is digitized at a resolution of 1329 x 1772 pixels. Correction for pincushion distortion is performed before analysis. To standardize the method of analysis pre and post 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 matched views after the administration of isosorbide dinitrate (29-30).

Edge-detection (ED) QCA Analysis. Boundaries of a selected coronary segment are detected using a weighted sum of the first and second derivative functions on the brightness profile of each vessel scan line automatically (22,23). The absolute diameter of the stenosis (in mm) is determined using a contrast free guiding catheter as a scaling device (32). Using the diameter function, the luminal diameter at the site of lesion (minimal luminal diameter; MLD) and a computer-derived estimation of an interpolated reference vessel diameter (RD) at the site of the lesion was determined. Minimal cross sectional area (MCSA) was calculated from the value of minimal luminal diameter (πr^2) obtained from the edge-detection analysis in multiple matched views pre and post intervention.

Videodensitometric (VD) QCA Analysis. Videodensitometric measurement is based on the relationship between the attenuating power of the lumen filled with contrast medium and the X-ray image intensity (23,33). Using this relationship, a videodensitometric profile which is proportional to the cross-sectional area 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 non-diseased area. Conversion of the individual videodensitometric profiles to absolute values was performed after a transformation of the videodensitometric profile found in a cross-sectional area of non-diseased segment, assuming a cross-sectional area at any point is proportional to the densitometric profiles at the point. Minimal cross sectional area (MCSA) was calculated from the average value obtained from the videodensitometric system in multiple matched views.

Qualitative angiographic assessment. Qualitative coronary angiographic assessment was performed by the consensus of at least two experienced angiographers. Angiographic dissection was defined as a dissection classification type B, C, D, E and F (34).

Image Acquisition of Intracoronary Ultrasound (ICUS). Following selective coronary angiography, a mechanical intracoronary ultrasound imaging catheter (30-MHz, 4.3Fr or 2.9Fr, CardioVascular Imaging Systems, Sunnyvale, CA) was introduced over a 0.014 inch guidewire. After the imaging catheter was passed into and beyond the lesion, a slow manual continuous pull-back was started to obtain an initial assessment of the target lesion. A second pull-back was performed using a motorized pull-back device with a constant speed of 1.0 mm/second. A simultaneous fluoroscopic image of the position of the ICUS catheter-tip was continuously displayed using a split screen format. Side branches 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 (ICUS). Luminal area was defined as the integrated area central to the intimal leading edge echo. Images with minimal cross sectional area (MCSA) were selected from the pull-back sequence by reviewing the position of the ICUS catheter on the angiographic image using the split screen format and by review of the time log and audio recording of the procedure.

Qualitative assessment of Intracoronary ultrasound (ICUS). Presence of calcium was graded into three categories - calcium free, focal deposit (<90 degrees of the vessel circumference), and moderate or diffuse (>90 degrees). Lumen morphology after intervention was graded into three categories; a smooth lumen was defined as a regular and even shape of the lumen; an irregular lumen was defined as an uneven or rough border of the lumen or partial tear and crack of the plaque toward the media; and a dissection was defined as a split or tear behind the plaque (7,8).

Interobserver variability. To determine the interobserver variability of ICUS measurements, 30 lesions were independently measured by two observers. The mean signed difference and correlation of the measurements of cross sectional area was $0.02 \pm 0.37 mm^2$ and 0.97 respectively.

Statistical analysis. While previous studies (5,6,10,19-22) applied linear regression analysis in comparison between ICUS and angiographic measurements, Bland and Altman (35) have recommended the use of the mean and standard deviation of the signed differences between two measurement systems as an index of agreement between two systems in the absence of the known true values. Thus, we took the mean and standard deviation 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 using the paired Student's t-test and correlation coefficient.

RESULTS :

Part 1 - results for all lesion types :

Baseline characteristics comparison between BA and DCA. The clinical characteristics of the patients are provided in Table 1. While no difference was found in age, gender, anginal symptoms (36) and distribution of diseased vessel between the BA group and the DCA group, reference diameter (RD) pre and post intervention and minimal luminal diameter (MLD) post intervention obtained from edge-detection quantitative angiography was significantly larger in the DCA than in the BA patients. While pre intervention MCSA obtained from ED, VD and ICUS was not different between the BA and DCA groups, post intervention MCSA was significantly larger in the DCA than in the BA patients as determined by all three measurement systems.

Comparison between ICUS and ED pre and post BA. While pre BA (26 lesions) the mean value of MCSA was 3.36 $\pm$0.99mm^2 derived by ICUS and 1.12 $\pm$0.96mm^2 obtained by edge-detection (ED) measurements, post BA (100 lesions) mean MCSA was 5.19 $\pm$1.90mm^2 derived by ICUS and 3.48 $\pm$1.76mm^2 by ED. The figures 1a and 1b display the agreement between measurements obtained from ICUS and ED according to the statistical approach proposed by Bland and Altman (35). Pre BA the mean difference between the two measurements was 1.43 $\pm$1.12mm^2. Post BA (Fig 1a) the mean difference was 1.71 $\pm$1.87mm^2. Post BA the agreement between the two measurement systems deteriorated in comparison with pre BA. MCSA obtained by ICUS was significantly larger than MCSA measured by ED both pre and post BA ($p<.001$ and $p<.0001$ respectively). The correlation coefficient of measurements by the two techniques was 0.59 pre BA and 0.47 post BA respectively.

Comparison between ICUS and ED pre and post DCA. While pre DCA (10 lesions) mean MCSA was 2.77 $\pm$1.00mm^2 derived by ICUS and 1.19 $\pm$0.81mm^2 by ED, post DCA (30 lesions) mean MCSA was 7.67 $\pm$2.25mm^2 derived by ICUS and 6.49 $\pm$2.56mm^2 by ED. Pre DCA the mean difference between the two measurements was 1.33 $\pm$1.02mm^2. Post DCA (Fig 1b) the mean difference was 1.18 $\pm$2.62mm^2. The correlation coefficient was 0.59 pre DCA and 0.41 post DCA. MCSA derived from ICUS was significantly larger than MCSA measured by ED both pre ($p<.01$) and post ($p<.05$) DCA. The correlation between the two measurement systems deteriorated after DCA in comparison to pre DCA.

Comparison between ICUS and VD pre and post BA and DCA. Mean MCSA determined by videodensitometry (VD) was 1.32 ±1.02mm^2 pre BA (26 lesions) and 1.16 ±0.72mm^2 pre DCA (10 lesions) ; and 3.92 ±1.82mm^2 post BA (100 lesions) and 4.44 ±2.35mm^2 post DCA (30 lesions). MCSA obtained by ICUS was significantly larger than MCSA measured by VD both pre and post BA and DCA. The correlation coefficient of the ICUS and VD measurements was 0.50 pre BA and 0.48 pre DCA, and 0.63 post BA and 0.58 post DCA. The mean difference and standard deviation between the two measurements was 1.15 ±1.12mm^2 pre BA and 1.32 ±1.00mm^2 pre DCA, and 1.27 ±1.61mm^2 post BA and 0.83 ±2.08mm^2 post DCA. Fig 2 displays the comparison of measurements between ICUS and VD. Post intervention the agreement between ICUS and VD was better than the agreement between ICUS and ED (Fig 1). An example of ICUS, ED and VD measurements post intervention can be seen in Figure 3.

Part 2 - results according to qualitative lesion characteristics :

Role of angiographic dissection in the agreement between ICUS and ED after BA (Table 2). One hundred lesions post BA were classified according to the following angiographic features (Table 2); a) presence of angiographic haziness, b) presence of dissection, and c) absence of haziness and dissection. The correlation coefficient of ICUS and ED quantitative measurements was 0.71 in lesions without haziness or dissection, 0.40 in lesions with haziness, and 0.12 in lesions with angiographic evidence of dissection.

Table 2. Comparison of agreement between measurements of ICUS and edge detction QCA according to lesion characteristics in 100 patients undergoing Balloon Angioplasty

	Mean difference (mm^2)	Standard deviation (±mm^2)	Correlation coefficient (r)
Lesion characteristics on angiography			
Absence of dissection and haziness (n=47)	1.16	1.48	.71
Presnce of haziness (n=26)	2.44	2.00	.40
Presence of dissection (n=27)	1.96	2.14	.13
Lesion characteristics on ultrasound			
Smooth lumen (n=32)	1.28	1.64	.63
Irregular lumen (n=38)	1.53	2.00	.49
Presence of dissection (n=30)	2.39	1.81	.24
Calcium free lesion (n=26)	1.75	1.83	.71
Focal calcium lesion (n=42)	1.71	1.38	.37
Moderate to diffuse calcium lesion (n=32)	1.67	2.44	.15

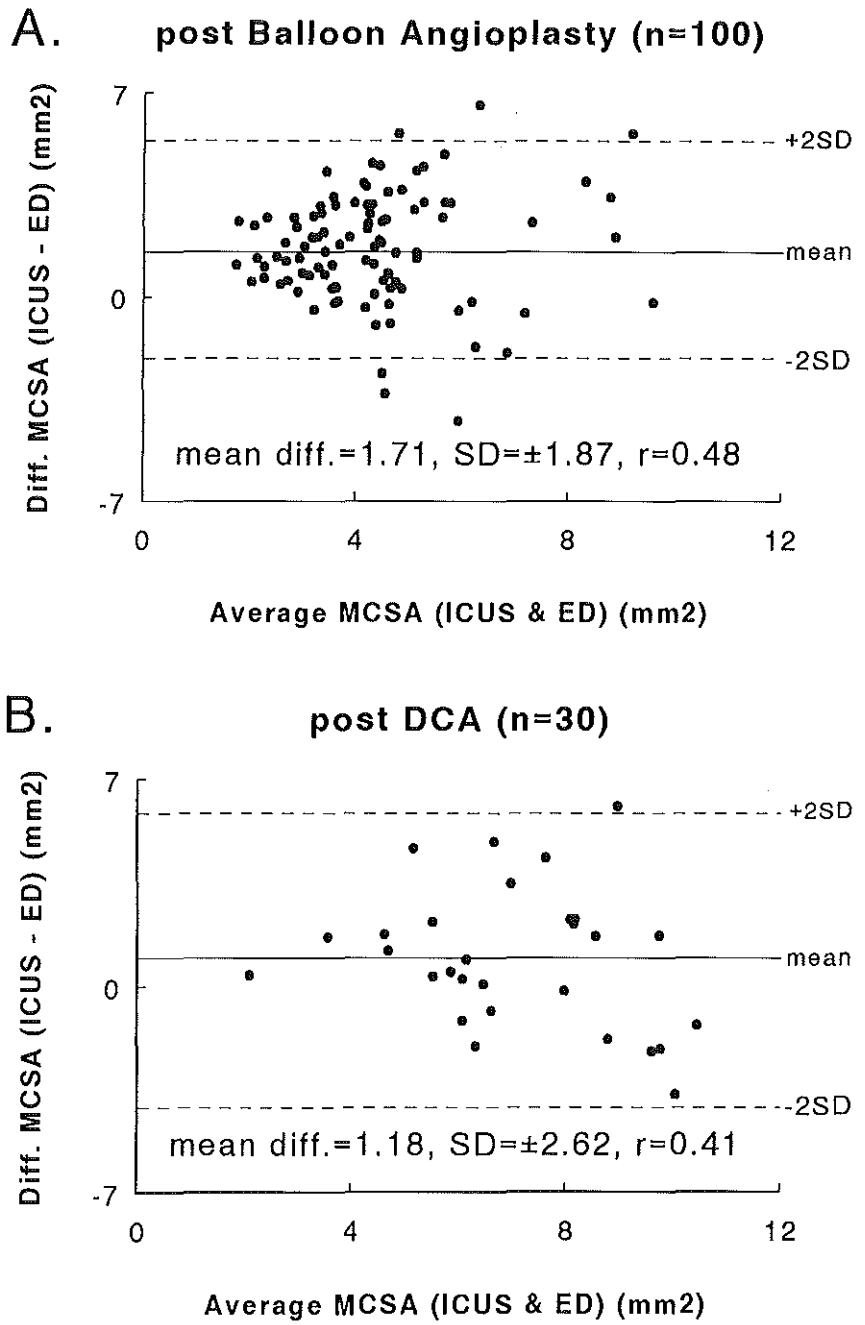

Figure 1. *The agreement between ICUS and edge detection QCA (ED) post BA (A) and post DCA (B) according to the statistical approach proposed by Bland and Altman (35).*

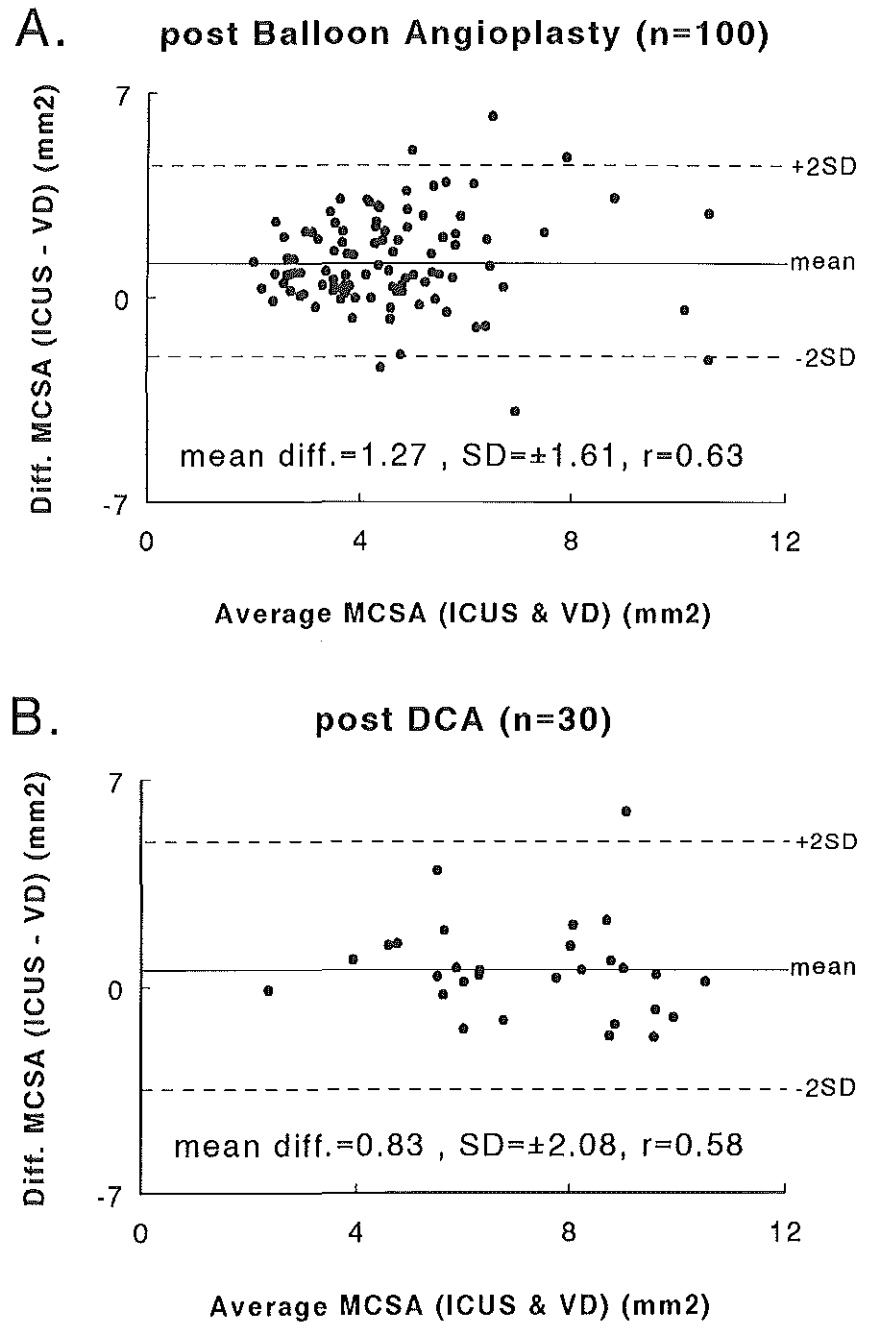

Figure 2. *The agreement between ICUS and videodensitometry QCA (VD) post BA (A) and post DCA (B) according to the statistical approach proposed by Bland and Altman (35).*

One hundred lesions post BA were graded according to their morphological pattern as assessed by intracoronary ultrasound examination. The correlation of ICUS and ED quantitative measurements was 0.63 in lesions with a smooth lumen as determined by ultrasound, 0.49 in lesions with an irregular lumen, and 0.24 in lesions with ultrasound evidence of dissection. Lesions post BA were classified according to the degree of calcium deposits on ultrasound examination. The correlation of ICUS and ED measurements was 0.71 in calcium free lesions, 0.37 in the presence of focal calcium deposits, and 0.15 in the presence moderate to diffuse calcification. Thus the presence of dissection or calcium was associated with a deterioration of agreement between ICUS and ED measurements.

Comparison of the agreement between ICUS and VD in dissected lesion post BA (Table 3). The relationship of ICUS and ED measurements was examined in one hundred lesions post BA according to their angiographic features (Table 3); The correlation of ICUS and ED measurements was 0.76 in lesions without dissection or haziness, 0.60 in lesions with haziness and 0.31 in lesions with angiographic evidence of dissection.

Table 3. Comparison of agreement between measurements of ICUS and Videodensitoetry QCA in 100 patients undergoing Balloon Angioplasty

	Mean difference (mm^2)	Standard deviation ($\pm mm^2$)	Correlation coefficient (r)
Lesion characteristics on angiography			
Absence of dissection and haziness (n=47)	1.02	1.40	.76
Presence of haziness (n=26)	1.54	1.76	.60
Presence of dissection (n=27)	1.48	1.79	.31
Lesion characteristics on ultrasound			
Smooth lumen (n=32)	0.98	1.53	.73
Irregular lumen (n=38)	1.14	1.72	.63
Presence of dissection (n=30)	1.76	1.47	.43
Calcium free lesion (n=26)	1.25	1.53	.81
Focal calcium lesion (n=42)	1.24	1.49	.43
Moderate to diffuse calcium lesion (n=32)	1.33	1.85	.42

The relationship of ICUS and ED measurements were also examined in lesions post BA according to their morphological pattern as assessed by ultrasound. The correlation of ICUS and ED measurements was 0.73 in lesions with a smooth lumen, 0.63 in lesions with an irregular lumen, and 0.43 in the presence of ultrasound evidence of dissection. especially in the presence of angiographic or ultrasound evidence of dissection. The correlation of ICUS and VD measurements was 0.81 in calcium free lesions, 0.44 in the presence of focal calcium deposits, and 0.42 in the presence moderate to diffuse calcification.

The agreement and correlation of VD and ICUS measurements was higher than the agreement and correlation of ED and ICUS measurements especially in lesions with moderate to diffuse calcium (Table 2). A similar pattern was seen when lesions treated by DCA were categorised according to their morphological characteristics (see **Table 4**).

Table 4. Comparison of agreement between measurements by ICUS, edge detection QCA (ED) and videodensitoemtry QCA (VD) in 30 patients undergoing Directional Coronary Atherectomy

	Mean difference (mm^2)	Standard deviation ($\pm mm^2$)	Correlation coefficient (r)
ICUS versus ED			
Lesion characteristics on ultrasound			
Absence of haziness and dissection (n = 19)	1.15	2.52	0.52
Presence of haziness or dissection (n = 11)	1.24	2.92	0.12
Lesion characteristics on ultrasound			
Smooth lumen (n = 8)	0.68	1.99	0.74
Luminal Irregularity or dissection (n = 22)	1.37	2.84	0.25
Calcium free lesion (n = 12)	0.67	1.99	0.68
Focal to diffuse calcium lesion (n = 18)	1.53	2.97	0.24
ICUS versus VD			
Lesion characteristics on ultrasound			
Absence of haziness and dissection (n = 19)	0.92	1.81	0.71
Presence of haziness or dissection (n = 11)	0.68	2.57	0.27
Lesion characteristics on ultrasound			
Smooth lumen (n = 8)	0.52	1.77	0.80
Luminal Irregularity or dissection (n = 22)	0.95	2.21	0.44
Calcium free lesion (n = 12)	0.33	1.40	0.84
Focal to diffuse calcium lesion (n = 18)	1.16	2.42	0.40

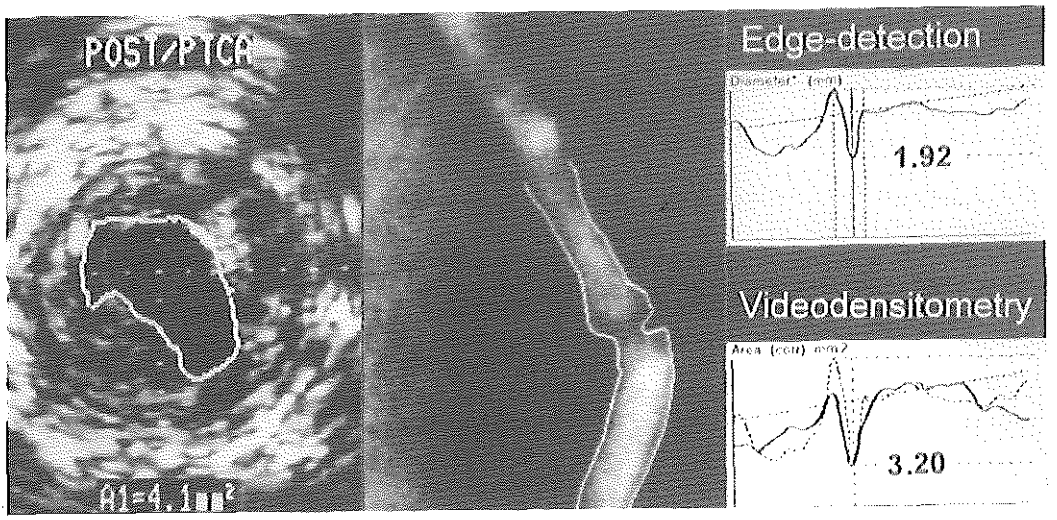

Figure 3. *Quantitative angiographic analysis by edge detection (ED) and videodensitometry (VD) and ICUS analysis post balloon angioplasty BA in the middle segment of the left circumflex coronary artery. The ICUS image (right side) shows an irregular lumen with partial rupture of a soft eccentric plaque. The elliptical and irregular shape of the lumen may explain the discordance between measurements of the minimal lumen cross sectional area (MCSA) obtained from ICUS (4.1 mm2) and edge-detection QCA (minimal luminal diameter of 1.92mm (MCSA 2.99 mm2)) and videodensitometric QCA measurement (3.20 mm2). To overcome the limitation of single view quantitative angiography the average of multiple matched views was utilized.*

DISCUSSION :

The unique features of our study design were as follows: 1) This is the first study to compare both edge-detection and videodensitometric quantitative angiographic measurements with ICUS measurements. 2) The agreement of measurements in the absence of the known true luminal dimensions was compared using the method proposed by Bland and Altman (35). 3) The influence of both luminal and vessel wall morphology on the relationship of ICUS and quantitative angiographic measurements was examined 4) An attempt at intracoronary ultrasound examination as well as quantitative angiography was made in all lesions both pre and post intervention. 5) The study population was the largest ever performed for the purpose of comparison of ICUS and quantitative angiographic measurements.

The principle findings of our study were as follows: 1) MCSA obtained by ICUS was significantly larger than MCSA measured by either edge-detection or videodensitometric quantitative coronary angiography both pre and post BA and DCA. 2) The agreement between ICUS and ED deteriorated considerably after both BA and DCA. 3) The complex morphological changes induced by angioplasty contributed to the discordance of the agreement of two measurement systems. 4) ICUS measurements were found to provide a better agreement with videodensitometry than with edge detection, particularly in lesions with complex morphological changes post intervention.

Agreement between ICUS and ED-QCA in previous studies. Previous studies have provided conflicting evidence on whether luminal measurements obtained from intracoronary ultrasound agree with edge detection quantitative angiographic (ED-QCA) measurements in human coronary arteries. In general, previous studies which examined the relationship of the ICUS and ED-QCA measurements in normal coronary segments reported a favourable correlation between the two quantitative imaging modalities (5,10), while those studies which included lesions post angioplasty reported a poor correlation of the two measurement techniques (6,21,22).

Role of vessel wall disruption post intervention and calcification on the agreement between ICUS and QCA measurements. Our study clearly demonstrates that luminal area obtained by ICUS was significantly larger than both ED and VD with considerable deterioration of the agreement after BA and DCA. The agreement deteriorated in proportion to the grade of damage induced by intervention in both ED and VD compared with ICUS. A progressive deterioration in the relationship of ICUS and QCA measurements was seen in accordance to the presence of an irregular lumen, luminal haziness, or dissection. Thus exclusive reliance upon either QCA or ICUS measurements for the guidance of coronary interventional techniques and the determination of post intervention results may be unreliable. A similar progressive fall in the relationship between ICUS and QCA measurements was seen in accordance with the degree of vessel wall calcification. Of interest, Fitzgerald et al. (7) indicated that calcium has a direct role in promoting dissection by increasing shear stress within the plaque during coronary angioplasty, and thus the deterioration of agreement between ICUS and QCA in calcified lesions may indirectly relate to the predisposition to the occurrence of dissection or haziness induced by intervention. In our study population, 31% of lesions with moderate to diffuse calcification developed angiographic evidence of intraluminal haziness and 41% developed a dissection post intervention.

Contributing factors to the discordance of ICUS and QCA measurements. A number of factors may have contributed to the observed discordance of ICUS and QCA measurements. The dissected lumen which may not be completely filled by contrast medium on account of a poorly communicating channel between the true and the false lumen or on account of nearly stagnated blood in the false lumen which may contribute to the relative underestimation by contrast angiography measurements. Ultrasound fall-out due to guide wire artifact and elliptical angulation of the ultrasound catheter within the longitudinal axis of the vessel may augment the discordance of ICUS cross sections with QCA measurements. Additionally, introduction of the ultrasound catheter may itself result in tacking back of dissections and stretching or dilatation of the vessel (Dotter effect) and thereby result in a larger lumen during ICUS examinations post intervention compared to the less invasive technique of contrast angiography.

QCA by videodensitometry provided a better agreement and less relative underestimation in relation to ICUS measurements than QCA by edge-detection. The underestimation by edge detection relative to ICUS measurements may reflect the propensity of the contour detection algorithm to trace the change in brightness profile in the contrast-weak channel between the true and false lumens (37) while ICUS measurements and measurements by videodensitometry in multiple views may have included the contribution of the false lumen. Such a phenomena, however, would not account for the relative underestimation be edge detection in the pre-intervention phase. It may also be possible that the interventional cardiologist tends to select angiographic projections which best demonstrate both the stenosis pre intervention and the residual stenosis post intervention, - "worst view" angiography. ICUS and videodensitometry are not projection-dependent and both would provide a measure of the "depth" as well as the "width" of the lumen cross section. Edge-detection, however, only provides a measure of one diameter (the "width") of the lumen and assumes a elliptical cross section. Even after averaging of multiple matched views as performed in our study, the assumed average cross section may have been based upon multiple "worst views" which although they were per-protocol $>30^0$ apart, they were not necessarily truly orthogonal views, and thus the "worst view" was not necessarily balanced by the "best view". Such a limitation to quantitative angiography by edge-detection has been an inherent limitation to all coronary interventional trials and attempts to address this limitation by three-dimensional imaging in truly orthogonal views (with catheter- independent isocentric calibration) are currently under evaluation (38-40). Of interest, in a recent study evaluating the performance of ten edge-detection QCA systems at core laboratories in North America and Europe, all ten edge detection QCA systems were found to underestimate the known true dimension of symmetrical phantom stenoses in porcine coronary arteries in-vivo (28).

Conclusion. Minimal lumen cross sectional area measurements obtained by intracoronary ultrasound are significantly larger than measurements provided by both geometric and videodensitometric quantitative coronary angiography both before and after intervention. Agreement between intracoronary ultrasound and geometric quantitative angiographic 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. Videodensitometry may provide an acceptable alternative for edge-detection quantitative coronary angiography in lesions with complex morphology. Exclusive reliance upon the absolute values of coronary lumen dimensions derived from intracoronary ultrasound alone or from geometric or videodensitometric quantitative angiography alone to guide coronary interventional procedures or to determine post interventional results may be unreliable.

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ANGIOGRAPHIC & CLINICAL EVALUATION

Chapter VII

Structural design, clinical experience, and current indications of the Coronary Wallstent.

David Keane, Peter de Jaegere, Patrick W Serruys.

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STRUCTURAL DESIGN, CLINICAL EXPERIENCE, AND CURRENT INDICATIONS OF THE CORONARY WALLSTENT

David Keane, MB, Peter de Jaegere, MD, and Patrick W. Serruys, MD

STRUCTURAL DESIGN

The Wallstent (Schneider, Bülach, Switzerland) has a stainless steel tubular mesh design with longitudinal flexibility. A total of 18 to 20 monofilaments 0.07- to 0.10-mm thick are used to fabricate each coronary Wallstent, resulting in a metallic surface area in the expanded state of approximately 20%[6] and a metallic cross-sectional area 0.062 mm².[15] This relatively high metallic surface area (compared with 8% for the new advanced cardiovascular system [ACS] stent) may be of theoretical importance as it appears likely that stents of lower metallic surface area are less thrombogenic and cause less inflammatory response in the vessel wall. The intersections of the filaments of the mesh structure are not fixed or soldered together, thereby affording greater longitudinal flexibility in comparison with that of the Palmaz-Schatz mesh design. Vessel splinting is, thus, not prominent in either native or vein graft coronary vessels following Wallstent implantation. Early concerns of friction from metal surfaces rubbing together at points of filament intersection appear to be unwarranted, and signs of such complications have not emerged from clinical studies.

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The stainless steel alloy is cobalt-based, and energy dispersion spectrometric studies have identified elements of chromium, iron, nickel, and molybdenum in addition to cobalt,[15] thus indicating that the Wallstent consists of a more heterogenous alloy than many other metallic coronary stents. The radiopacity of the Wallstent during conventional cineangiography is relatively low (compared with that of the tantalum Wiktor and Strecker stents); however, with advances in digital pulsed fluoroscopy, the Wallstent mesh can usually be identified (at 50 kV) even after removal of the radiopaque markers of the delivery system.[15] Unlike some other stainless steel stents (e.g., Palmaz stent) but similar to tantalum stents (e.g. Strecker stent), the Wallstent has been found not to move or deflect during MR imaging, even under high magnetic field strengths.[13, 19] However, as stents become incorporated into the vessel wall after several weeks, MR imaging of patients with ferromagnetic stents is probably safe after a suitable period has elapsed to ensure stable positioning of the device.[13]

The Wallstent is self-expanding and, therefore, does not require a balloon for deployment. This may be particularly advantageous in friable, diffusely diseased bypass grafts at high risk for embolization with balloon angioplasty. Instead, the Wallstent is mounted on a

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low-profile catheter and is maintained in a collapsed state until it is progressively released by the retraction of its rolling membrane (Fig. 1). The doubled-over restraining membrane and delivery mechanism prevent accidental release of the stent, and a partially deployed Wallstent can often be withdrawn proximally or removed entirely.[6]

Dilatation of a balloon within the Wallstent is normally performed after its release to accelerate early expansion, to ensure symmetrical and adequate apposition of the stent against the vessel wall, and to dissipate thrombus within the stent (Fig. 2). The Wallstent is thought to continue to expand until an equilibrium is reached between the elastic recoil of the vessel wall and the radial force of the stent.[1]

The low profile of the Wallstent compares favorably with that of stents which require balloon mounting. The outer diameter of the coronary stent–mounted delivery catheter of the Wallstent is 1.57 mm (Schneider, Bulach, Switzerland) in comparison with 1.65 mm for the preballoon-mounted Palmaz-Schatz mesh stent (Johnson & Johnson, Paris, France) and 2.13 mm for the balloon-mounted Gianturco-Roubin coil stent (Cook, Bloomington, IN). This feature increases the versatility of the Wallstent and, coupled with its longitudinal flexibility, results in its aptitude to negotiate proximal vessel tortuosities and points of small luminal diameter. Furthermore, its low profile permits introduction of the Wallstent through an 8-F guiding catheter (0.077-inch internal diameter), and, thus, exchange of the femoral sheath and guiding catheter during the bailout management of an acute occlusive

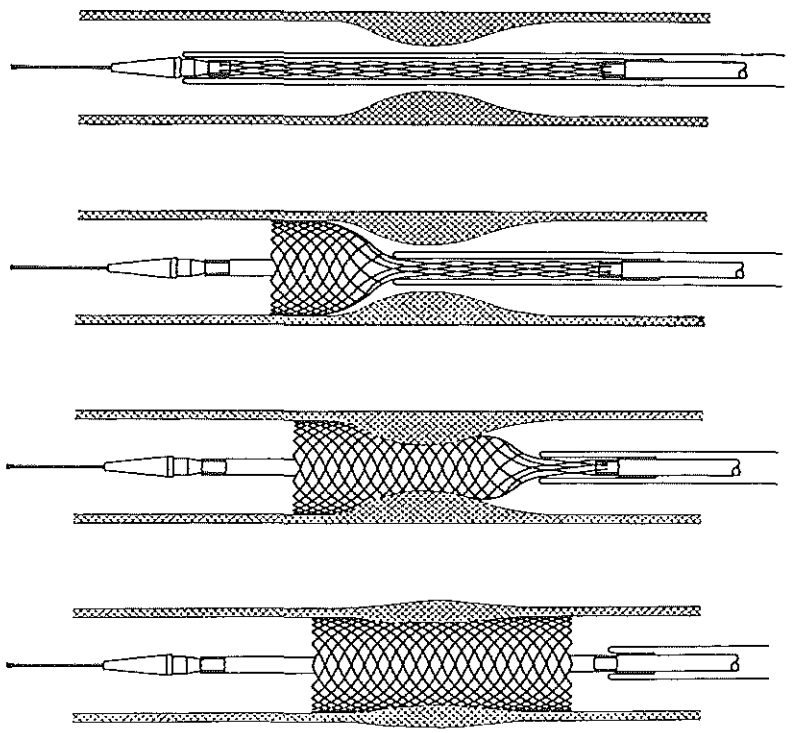

Figure 1. Deployment of the Wallstent requires the advancement of the Wallstent over a 0.014-in or 0.018-in guidewire across the lesion. The distal marker band should be positioned slightly beyond the distal edge of the stenosis to account for distal shortening of the stent during expansion. The central and proximal markers approximately define the final position of the stent. The rolling membrane is inflated with contrast medium to 4 atmospheres prior to its gradual retraction to facilitate the smooth and progressive release of the self-expanding stent.

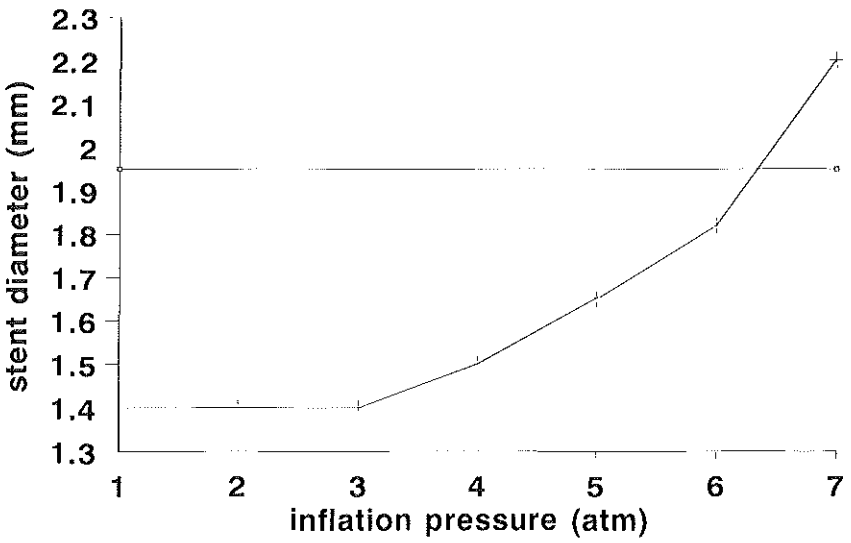

Figure 2. A balloon dilatation is normally performed within the Wallstent after its release to optimize deployment. This plot of inflation pressure against the diameter of the Wallstent in vitro indicates that inflation pressures should be kept under 4.5 atmospheres to avoid significant alteration of the mesh configuration of the expanded Wallstent.

dissection with the Wallstent is rarely necessary. This compares favorably with the Gianturco-Roubin coil stent for which, normally, a 9-F guiding catheter (internal diameter 0.089 inches) is required for introduction of a Flexstent larger than 3.0 mm [this undesirable exchange of guiding catheters and sheaths during bailout management might be overcome by the recent development of the Lumax 8-F guiding catheter (Cook), which has a relatively large internal lumen of 0.086 inches and allows delivery of the 4.0-mm Flexstent stat].

An additional feature of the Wallstent is the wide range of sizes available for coronary vessels, ranging from 2.5 to 6.0 mm in diameter in the expanded state with lengths of 15 to 30 mm. This range of diameters is adequate for two reasons. First, stenting of vessels 2.5 mm or less in diameter appears to carry an unacceptable risk of subacute thrombosis, and a Wallstent size of 0.5 mm greater than the vessel size is required for optimal results to ensure that sufficient radial force is exerted on the vessel wall to prevent stent migration and to overcome elastic recoil. Second, few vessels are of greater diameter than 5.5 mm, even among coronary vein grafts. Wallstents of greater than 6.0 mm in diameter are available, but they are usually deployed in peripheral vessels. The large range of lengths available for the Wallstent may be particularly advantageous. It is helpful for the treatment of long dissections and to avoid the deployment of more than one stent for long dissections, a factor known to increase the risk for early thrombosis[3] and subsequent late restenosis (particularly at the site of stent overlap where the metallic burden on the vessel wall is highest.[16]) Also, the large range of lengths permits the selection of a Wallstent of greater length than the lesion, thus reducing the risk of failing to cover the entire lesion length.

The length of the Wallstent may shorten significantly upon expansion. This may result in a failure to cover a lesion and necessitate the deployment of a telescoping second Wallstent to cover a stenosis or dissection. To overcome the difficulty of unpredictable longitudinal shortening following radial expansion, the design of the coronary Wallstent has recently been modified to produce a device which is less prone to shortening (the less shortening Wallstent). This is achieved at a cost of some loss of radial strength. Its technical features are depicted in Figure 3. The

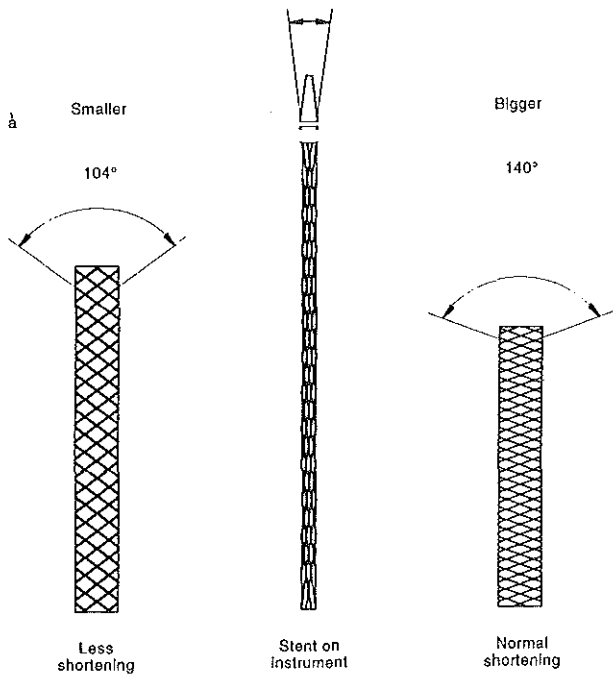

Figure 3. To overcome the problem of marked shortening of the Wallstent upon expansion, the design of the mesh has been modified to produce the Less Shortening Wallstent. The braiding angle of the mesh has been been reduced from 140° to 104°. This is associated with an overall lower density of metal struts per unit length but carries a cost of lower radial support.

less shortening Wallstent undergoes approximately 25% shortening upon expansion, and the braiding angle of its mesh is 104 degrees in comparison with 140 degrees for the normal shortening Wallstent. The follow-up phase of the first clinical study to evaluate this modified design has just been completed. All previously reported experience with the Wallstent has involved the earlier normal shortening design.

EXPERIMENTAL STUDIES OF THROMBOGENICITY AND POLYMERIC COATING

The primary reservation concerning clinical use of the Wallstent has been a relatively high incidence of acute thrombosis. This most likely relates to its high stent-to-vessel surface area. It is unlikely that the stainless steel alloy of Wallstents is more thrombogenic than the composition of other metallic stents.

Among the stainless steel alloy stents, differences in thrombogenicity have not been found. In an exteriorized arteriovenous silicone shunt model in baboons, the thrombogenicity of the chromium-free stainless steel Palmaz-Schatz stent was compared with that of the chromium-based stainless steel Wallstent. The Palmaz-Schatz stent accumulated $4.37 \pm 0.68 \times 10^9$ platelets/cm, which was not statistically different from the Wallstent, which accumulated $3.91 \pm 0.42 \times 10^9$ platelets/cm.[8]

Although no thrombotic occlusions were observed within 4 weeks in a noncomparative study of a tantalum stent (Wiktor) in the coronary arteries of 10 pigs,[20] evidence for lower thrombogenicity of tantalum in comparison with stainless steel stents has not been found in comparative in vitro and in vivo studies despite theoretical differences in ionic charge between tantalum and stainless steel. In an in vitro study by Hearn et al,[5] no significant difference in thrombogenicity was found between noncoated tantalum and stainless steel stents exposed to human blood. Further work from Emory University in both extracorporeal baboon and intracoronary porcine models has confirmed that stainless steel stents are not more thrombogenic than tantalum stents.[14a]

In an effort to reduce the incidence of stent thrombosis, the surface of the Wallstent was

modified in 1989 to incorporate a polymer coating (BioGold). In vivo research at the Thoraxcenter has indicated that this polymeric coating may reduce the thrombogenicity of the Wallstent.[21] In this comparative study in porcine coronary arteries, thrombogenicity (by angiography) at 1, 4, and 12 weeks and vessel wall histology at 12 weeks were studied in 15 polymer-coated Wallstents placed with no medication and 48 uncoated Wallstents placed with the administration of acenocoumarol (16 stents), aspirin (16 stents), and no medication (16 stents). A 38% thrombotic occlusion rate within 1 week (uncoated Wallstents with no medication) was prevented by polymeric coating and by acenocoumarol but not by aspirin. Histologic analysis showed no difference in the thickness of the neointimal hyperplasia between the groups, and the BioGold polymer did not induce an inflammatory reaction. This experimental histologic finding is supported by the retrospective angiographic comparison of those patients who received an uncoated Wallstent before August 1989 versus those patients in whom a polymeric-coated stent was implanted after August 1989, in which the BioGold coating was found to have no significant relationship on late restenosis.[16] The efficacy of this coating in the reduction of subacute thrombosis, however, has yet to be demonstrated clinically.

EARLY CLINICAL EXPERIENCE WITH THE WALLSTENT

Valuable clinical experience with coronary stenting was gained from a six-center European study of the Wallstent which was undertaken in the 1980s.[12, 14] Between March 1986 and January 1988, 117 Wallstents were implanted in the native coronary arteries (94 stents) or saphenous vein bypass grafts (23 stents) of 105 patients. Seventy-one stents were implanted after dilatation of a restenotic lesion, 14 were placed as bailout therapy for an acute occlusion following balloon angioplasty, 5 were deployed after angioplasty for chronic occlusion, and 27 were included as an adjunct procedure to primary balloon angioplasty.

It is not surprising that this early experience was fraught with the controversy of anticoagulant management. Regimens ranged from the use of subcutaneous heparin to routine intracoronary urokinase. Many of the initial patients in this early experience were not started on an oral anticoagulant regimen post-stenting, and a few patients did not receive aspirin, whereas others were maintained on coumadin, aspirin, dipyridamole, and sulfinpyrazole. Even today, 8 years later, the strategies proposed for anticoagulant therapy post-stenting continue to differ widely without international consensus.[7]

The overall mortality rate for the group at 1 year was 7.6% (eight deaths). Of these deaths, six were most likely the result of stent occlusion. Stent occlusion was angiographically confirmed at implantation in two of the six patients and after 24 hours in one patient, whereas in the other three, sudden death occurred at 48 hours, 11 days, and 6 weeks, respectively, after stent implantation.

Quantitative angiography (cardiovascular angiography analysis system [CAAS]) revealed that, overall, the minimum luminal diameter improved from 1.21 ± 0.56 mm to 1.88 ± 0.43 mm after balloon angioplasty and then further to 2.48 ± 0.51 mm immediately after stent implantation. Angiographic follow-up was obtained in 90% of patients at a mean of 5.7 ± 4.4 months. At follow-up, the diameter for the whole group (95 patients) had decreased to 1.68 ± 1.20 mm. The validity of including or excluding total occlusions from an angiographic follow-up analysis of restenosis following balloon angioplasty is unclear in view of the unconfirmed mechanisms of total occlusion.[7, 22] With coronary stenting, it seems more likely that total occlusions may represent a different phenomenon than typical restenosis in view of the frequently documented occurrence of thrombotic occlusions in the early period following stent implantation. When the total occlusions (27 stents in 25 patients) were removed from the angiographic follow-up group, the minimal luminal diameter at follow-up was 2.26 ± 0.78 mm. Ten stents in nine patients of this group and one segment proximal to a stent had a diameter stenosis of more than 50% at follow-up for a total restenosis rate of 14% of patients in whom the Wallstent was patent at follow-up.

LATER CLINICAL EXPERIENCE WITH THE WALLSTENT

The previously described results from the early experience, which was pioneering not only for the Wallstent but also for all coronary stenting, were compared with the subsequent

results of the period from February 1988 to March 1990.[16, 17] In addition, the cumulative clinical experience gained from 265 patients (308 lesions) from March 1986 to March 1990 was analyzed according to whether the Wallstent was implanted in a native coronary artery or bypass vein graft (Fig. 4).[16, 17] The selection of cases during the early and late periods differed significantly, with a higher proportion of bypass vein grafts and primary stenoses in the later period (1988 to 1990).

Early occlusions following Wallstent implantation were less frequent in later years (10% of stents) than in the early experience (18% of stents). This may relate to the adoption of a more effective and standardized anticoagulant regimen, increased operator experience, and refined patient/lesion selection in the later years. In the combined early and later experience, early occlusions were documented in 18% of native coronary arteries compared with 7% of bypass vein grafts. The lower incidence of thrombotic occlusion in vein grafts may reflect, in part, that most of these vein graft stents were implanted during the later period when the anticoagulation period was more aggressive and, in part, the greater vessel size (recent studies indicate that thrombotic occlusion is less likely to occur in vessels larger than 3.25 mm compared with vessels smaller than 3.25 mm^3).

Quantitative angiographic follow-up was obtained in 82% of all patients. The outcomes for native and bypass vessels are compared in Table 1. It has been proposed that the higher late restenosis rate in vein grafts may be the price for lower early occlusion rates.[17] By diminishing the formation of early occlusive thrombus with more effective anticoagulation, the residual nonoccluding thrombus could form the substrate for late restenosis.[17] This hypothesis is not supported by a more recent observation that the presence of thrombus at the time of balloon angioplasty is not associated with greater luminal loss at follow-up if total occlusions at follow-up are excluded from the analysis.[22]

To gain a perspective of these relative results of the Wallstent in bypass vein grafts and native coronary arteries, it is worth, for comparative purposes, to consider the results of a provisional report of early ischemic events in bypass vein grafts and coronary arteries following implantation of the Gian-

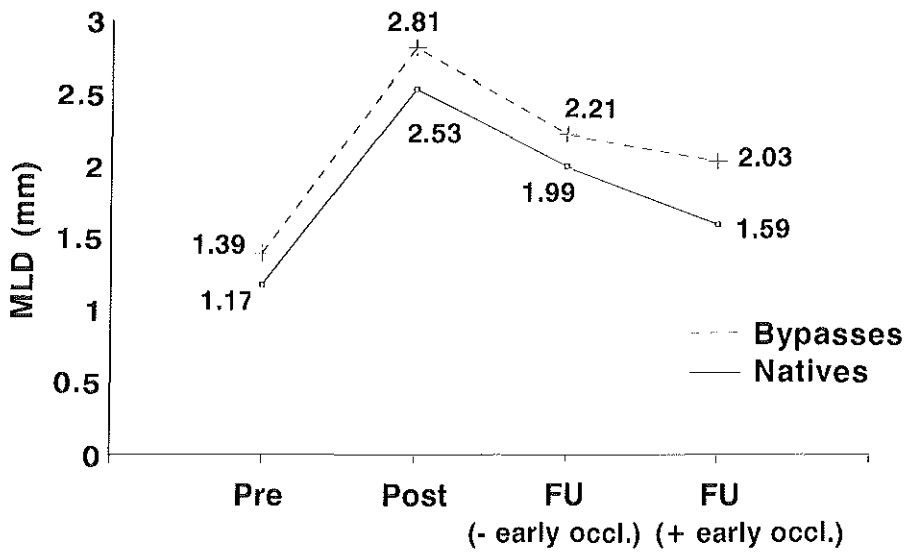

Figure 4. Minimal luminal diameter (MLD) of native coronary arteries and bypass vein grafts preprocedure, postprocedure and at follow up. The mean values have been calculated with and without the inclusion of the early in-hospital occlusions. (*From* Strauss BH, Serruys PW, Bertrand ME, et al: Quantitative angiographic follow-up of the coronary wallstent in native vessels and bypass grafts (European experience—March 1986 to March 1990). Am J Cardiol 69:475–481, 1992; with permission.)

Table 1. EARLY AND LATE RESULTS FOLLOWING WALLSTENT IMPLANTATION*

Vessel	Percent Early Occlusion	Percent Restenosis
Native coronary artery	19	39
Bypass vein graft	8	18

*Although the early occlusion rate for vein grafts was lower than that for native coronary arteries, the restenosis rate (>50% diameter stenosis) per patient was higher in bypass vein grafts than in native coronary arteries. There was no difference in the late occlusion rate between the two vessel types (16 lesions).[17]

turco-Roubin coil stent.[18] Periprocedural (<24 hours) ischemic events occurred in 2% of vein grafts compared within 8% of native arteries ($P=0.07$), and the rate of later ischemic events at 1 to 90 days was at least as favorable for vein grafts as it was for native arteries.[18] Interpretation of these results, however, is confounded by differing clinical indications and lesional characteristics between the two vessel types and by the subsequent greater requirement for the deployment of multiple stents in bypass vein grafts.

CLINICAL EVALUATION OF THE LESS SHORTENING WALLSTENT

One of the factors thought to have contributed to the high rate of stent occlusion in the European registry of the coronary Wallstent in the 1980s was the frequent deployment of more than one stent to cover the target lesion. This factor attributed to the high degree of shortening of the Wallstent upon expansion. To overcome this limitation, the design of the Wallstent was modified to reduce the degree of shortening with the development of the Less Shortening Wallstent. A small study was undertaken to determine the safety and efficacy of implanting this new Wallstent for the management of saphenous vein coronary bypass graft stenoses. Between November 1991 and March 1993, the Less Shortening Wallstent was implanted in 29 patients at 6 centers in the Netherlands, Germany, and Belgium.[6a]

Thirty-five Wallstents were electively deployed in aorto-coronary vein grafts in 29 patients. Stent deployment was successful in 35 of 36 attempts in 30 lesions. In 5 of the 30 lesions, a second stent was required to cover the proximal portion of the lesion. Angiographic success (< 50% residual diameter stenosis as determined by offline quantitative coronary angiography) was achieved in all 29 patients. During the in-hospital phase, no major adverse cardiac event occurred (reintervention, re-CABG, myocardial infarction, or death), and 5 patients had hemorrhagic complications. Following hospital discharge, one patient had a subacute stent occlusion associated with symptoms and elevated cardiac enzymes at 11 days, another patient had symptoms and elevated cardiac enzymes (CK 300 U/l) at 22 days with a patent stent, five patients required balloon angioplasty within the 6 month follow-up period (four for restenosis and one for stent occlusion), and one patient underwent re-CABG for a native artery stenosis distal to the anastmosis of the patent stented vein graft. The results of this introductory study suggest that the new Less Shortening Wallstent may be associated with a reduction in the requirement for multiple stent deployment and a lower rate of thrombotic occlusion in comparison to its pioneering prototype. On the basis of these results, a number of larger multicenter clinical trials have been initiated to further evaluate the new coronary Wallstent.

CURRENT INDICATIONS

Based on the data described previously the Wallstent is a versatile stent which, by virtue of its longitudinal flexibility and low profile, can be deployed with a high degree of success in complex lesions of both native coronary arteries and bypass vein grafts.

Despite strict clinical indications that have been proved by prospective randomized trials, it could be proposed that there are, as yet, no absolute indications for coronary stenting. Indeed, traditional balloon angioplasty itself, the gold standard with which stenting frequently is compared, 17 years after its introduction[4] has yet to establish unequivocally its current indications in randomized, comparative morbidity and mortality trials in preference to medical therapy and bypass surgery.[2,9-11]

Thus, it may be more appropriate in this relatively early era of coronary stent evolution to refer to clinical applications and contraindications. Fewer patients are required and randomization is not essential to detect contraindications to coronary stenting, whereas absolute indications for coronary stenting are more difficult to establish. Currently, these contraindications include persistent intracoronary thrombus (after intracoronary administration of thrombolytic therapy

and, when necessary, confirmation with angioscopy) and contraindications to anticoagulant therapy. Relative contraindications include a vessel size of less than 3.0 mm, excessive proximal tortuosity where introduction of the stent would be unlikely to succeed, deployment of a stent in an unprotected left main coronary artery, and the absence of in-house cardiac surgical back-up.

It is unclear if an indication is established by a large randomized trial for one stent, whether the same results can be expected from a stent of similar design. In view of the relatively early stage of the clinical evaluation (8 years) of coronary stenting and the fundamental differences in metal surface area, strut composition (with or without coating), stent profile, delivery system, expansile mechanism, longitudinal flexibility, radial strength, and design among mesh stents (Wallstent, Palmaz-Schatz, and Strecker) and among coil stents (Wiktor, Gianturco-Roubin, and ACS), it seems that, for at least the present, each stent will have to prove its efficacy and safety for each clinical indication. Furthermore, although the coating of currently available stents continues to necessitate systemic anticoagulant therapy, the absolute indications for coronary stenting are likely to remain limited.

The clinical conditions in which the coronary Wallstent has been applied (usually as an adjunct to balloon angioplasty) during observational studies include the elective treatment of primary stenoses, restenoses, and chronic occlusions in native coronary arteries, the elective treatment of primary stenoses in vein grafts, and the bailout management of acute vessel closure following coronary intervention. By virtue of the high early thrombotic rate in native vessels and the high restenosis rate in vein grafts, it seems that, currently, the only condition in which implantation of a coronary Wallstent can be justified outside of a randomized trial are the bailout management of acute nonthrombotic occlusion (dissection) following interventional procedures in native vessels of 2.5 mm or greater diameter and, possibly, the elective treatment of bypass vein grafts with friable lesions. In light of its unique mechanical properties, the Wallstent might be expected to excel over stents of different design in long lesions in large-diameter vessels associated with proximal tortuosity.

Upcoming prospective randomized trials with the new less shortening Wallstent should determine whether the Wallstent has been a victim of the pioneering era of clinical evaluation during the early learning phase of coronary stenting associated with inadequate anticoagulation regimens, inappropriate patient selection, and multiple stent placement (on account of stent shortening), or whether exposure of the coronary artery to the relatively large stent surface area of the Wallstent presents an unacceptably high early thrombogenic burden or, possibly, late excessive stimulus to vessel wall hyperplasia in bypass vein grafts.

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Chapter VIII

Five year clinical and angiographic follow-up of the Coronary Wallstent.

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(in review)

ABSTRACT

Objectives : This study was conducted to assess the long-term angiographic outcome of the first series of stents (Wallstents) implanted at our institution between March 1986 and December 1987.

Background : While the short-term (six months) angiographic outcome of coronary stents have been extensively reported, uncertainties persist concerning the long-term tolerance of these metallic foreign bodies as well as the evolution of intimal hyperplasia after the six month period.

Methods : Twelve patients in whom Wallstent deployment had been free of thrombotic complications and free of restenosis at 6-months, underwent long-term angiographic follow-up at five years. Absolute and percent obstruction diameters within the stented segments were measured by quantitative coronary angiography.

Results : Minimal luminal diameter increased from 1.21 +/- 0.43 mm to 2.34 +/- 0.13 mm immediately after intervention and then slightly decreased to 2.12 +/- 0.27 mm at six months and to 1.66 +/- 0.50 mm at five years. Percent diameter stenosis decreased from 59.1 +/- 10% pre-stenting to 24.2 +/- 10% immediately post-stenting and by 6 month angiographic follow-up percent diameter stenosis had increased to 32.8 +/- 10%, without further change at five years (34.9 +/- 12%). Only one patient had > 50% diameter stenosis at 5 years (53% diameter stenosis), thus indicating that from six months to five year follow-up, progression of the minimal luminal diameter within the stent(.46 +/- .30 mm) was not greater than progression in the reference vessel diameter of the stented coronary segment (.68 +/- .62 mm). Intimal hyperplasia within the stent averaged (0.35 +/ -0.13 mm) at 5 years.

Conclusion : The results of this limited series of patients do not lend support to the hypothesis that atherosclerosis within coronary stents may be accelerated or prolonged beyond six months.

INTRODUCTION

Although the concept of implanting a tubular metallic structure in a coronary segment to maintain vessel patency after luminal dilatation was introduced by Dotter in 1964 (1), its clinical application in humans was not undertaken until 1986 (2). The self-expanding woven mesh Wallstent (**Figure 1**) was the first to be used in human studies for this purpose (2). Despite the occurrence of a high rate of acute and subacute thrombosis, this initial experience helped to define the clinical and angiographic criteria for patient selection as well as to refine their anticoagulant management.

Whereas a 6-months angiogram is considered as a valid endpoint for assessing the result of balloon angioplasty based on long-term follow-up studies (3,4,5), it is undetermined whether the time course of restenosis is similar after the implantation of a metallic stent. Although six months angiographic follow-up of patients at the five centers evaluating the Wallstent has been reported (6,7), no further angiographic follow-up has been performed to assess whether luminal renarrowing within the Wallstent actually ceases after this period.

Histological studies of synthetic arterial grafts and non-degradable stents have indicated that release of mediators and smooth muscle cell growth factors can continue even after complete endothelialization of the foreign material has occurred (8-13). Abundant myofibrillar cells and macrophages, the harbingers of the restenosis process, have been found to originate in the immediate vicinity of the individual stent struts adjacent to the internal elastic lamina and to fan out to fill the neointimal tissue in an evenly distributed fashion. On the basis of such post-endothelialization findings it has been proposed that by damaging the internal elastic lamina, stents render this natural barrier more permeable to the migration of smooth muscle cells and provide a permanent stimulus to smooth muscle proliferation and thus both accelerate and prolong the restenosis process (14).

To assess whether the continued exposure to the metallic surface and sustained pressure (barotrauma) associated with coronary stents provide a permanent stimulus for neointimal proliferation, we addressed the 5-years angiographic outcome of patients in whom a Wallstent was implanted at our institution and in whom a subacute occlusion or restenosis at 6 months had not occurred. Our study population included the first patient ever to have received a stent (**Figure 2**).

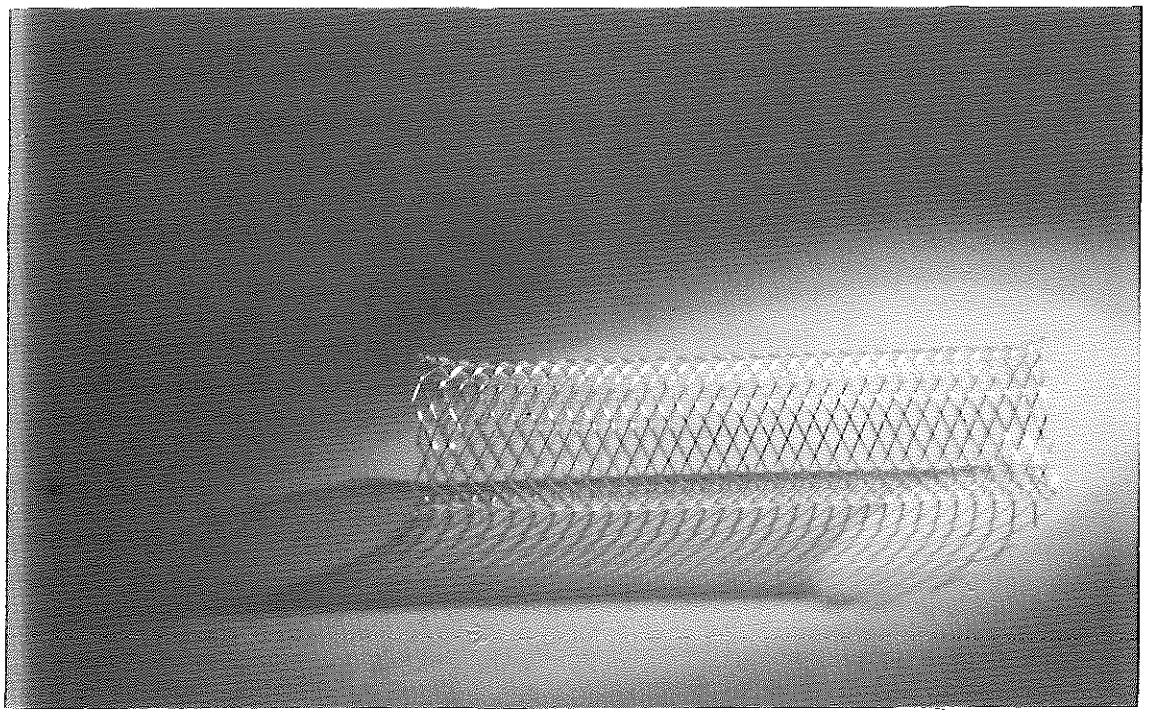

Figure 1.

Coronary Wallstent

METHODS

Study population. Between March 1986 and December 1987, 27 stents were implanted after dilatation of a restenotic lesion in native coronary arteries in 27 patients at our institution (6). Of this pioneering experience, eight patients developed thrombotic occlusion within 2 weeks and four patients developed restenosis at 6 month follow-up (> 50% diameter stenosis). Thus fifteen patients were free of acute complications and late restenosis at 6 months and represented our population study. Baseline characteristics and lipid profile are shown in Table 1.

Stent design. The design of the stent and its method of implantation have been previously described (2,6,15). Briefly, it is a self-expanding, stainless steel, woven mesh endovascular prosthesis which can be positioned in the coronary artery according to the standard over-the-wire technique through an 8 or 9 French guiding catheter. It is constructed of 16 wire filaments, each 0.08 mm wide, constrained in an elongated configuration on a 1.57 mm delivery catheter, the distal and being covered by a removable rolling membrane. The prosthesis returns to its unconstrained original diameter as the rolling membrane is withdrawn. The unconstrained stent diameter was selected to be 0.5 mm larger than the visual estimate of the coronary artery diameter.

Quantitative coronary angiography. The initial procedure as well as the six-months' follow-up angiograms were recorded on 35 mm cinefilm and the five year follow-up angiograms were recorded on analogue videotape (16). All angiograms were analysed at a core laboratory (Cardialysis, Rotterdam) by means of a computer-assisted cardiovascular angiography analysis system (CAAS) as described elsewhere (17). Briefly, a selected frame area encompassing the coronary segment of interest is optically magnified and digitized. A computer-assisted automated edge detection technique is applied to determine the vessel contour based on the weighted sum of the first and second derivative functions applied to the digitized brightness information after correction for pincushion distortion. A calibration factor based on a computer analysis of the non-tapering part of the contrast-empty catheter is calculated, and absolute MLD as well as the interpolated reference diameter based on a computed estimation of the original diameter of the artery at the level of obstruction are measured accordingly. Percent diameter stenosis is then derived from the observed and reference diameter values.

In addition to the above off-line quantitative analyses at the core laboratory, the five years follow-up angiograms were studied on-line using the Automated Coronary Analysis (ACA)

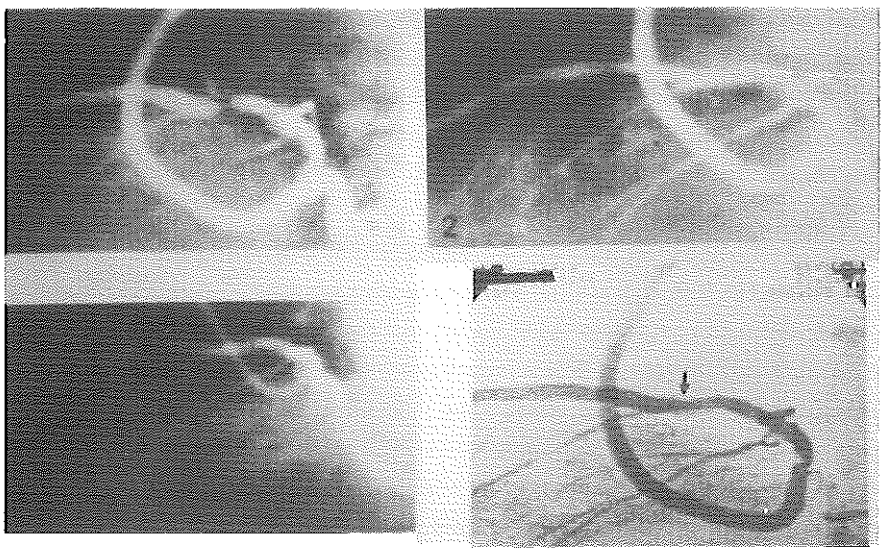

Figure 2.

First coronary stent implantation in a human in March 1986:

1) Upper left panel : Restenotic lesion in the proximal left anterior descending artery

2) Upper right panel : Immediate result post implantation of a Wallstent

3) Lower left panel : Six month angiographic follow-up.

4) Lower right panel : Five year angiographic follow-up.

software package of the Philips Digital Cardiac Imaging (DCI) system, as described elsewhere (18). These latter on-line assessments were preferred for manual tracing on the metallic stents which were more reliably detected on the original digital radiographic images. This enabled the following analyses to be made:

- *Observed stent diameter* : computed after manual drawing of the stent contour along the vessel wall.
- *Stent expansion* : calculated as the (ratio of observed diameter/nominal unconstrained stent size* 100).
- *Mean intimal thickness* : calculated as half the difference between observed stent diameter and mean luminal diameter within the stent. This last measurement is computed as the reference luminal diameter when the start-point and the end-point are selected at the proximal and distal extremity of the stent lumen.

Other stent parameters assessed were : contour aspect, qualified as parallel or divergent, lumen regularity, radiopacity, presence of calcification in proximity to the stent and the fate of side branches originating at the site of the stent.

Statistical analysis. All continuous variables are expressed as mean values ± standard deviation. Individual comparisons of MLD, percent stenosis and reference segment diameter between phases of follow-up were made by two-tailed t-tests for paired data. A correlation coefficient was calculated to assess possible relations between quantitative variables. A p value less than 0.05 was considered significant.

RESULTS

Clinical data. Among 15 patients eligible for long-term angiographic restudy, twelve (10 males, 2 females) underwent coronary angiography at a mean of 60.9 +/- 7.0 months after stent implantation (48 - 75 months). The 3 remaining patients refused catheterization and were asymptomatic and had a negative treadmill exercise test. Of the 12 patients who underwent long-term angiographic follow-up, 10 were asymptomatic and 2 had class I angina pectoris according to the Canadian Cardiovascular Society. One patient had experienced recurrent angina 3 months after stenting and had been found to have significant left main-stem disease for which he had undergone bypass surgery.

Table 1.

Baseline Characteristics of The Study Population

No of patients	15
Mean age (yr)	66.6 +/- 9.4
Gender (M/F)	13/2
Smokers	11
Serum cholesterol baseline	270 +/- 32
Serum cholesterol follow-up	238 +/- 28
No of stents	15
Stent size	
- 3.0 mm	2
- 3.5 mm	11
- 4.0 mm	2
Implanted site	
- LAD :	10
- LCxA :	2
- RCA :	3
Indication for stent	
- Restenosis :	15

Qualitative angiographic data. The vessel lumen within the stent was regular in 5 patients and irregular in 7. The luminal irregularities in the 7 patients were due to the presence of narrowing at the distal portion of the stent in 4 patients, at the mid portion of the stent in 2 others and throughout the stent in the remaining patient.

Side branches originating from the stented segment were patent in 8/8 patients without a reduction in blood flow. The stent itself remained radiopaque in all cases, and no calcification was seen in proximity to the stents. No disruption of the metallic structure of the stent was seen. By the time of the control angiogram, two patients who were in class I angina had developed new lesion involving small vessels.

Quantitative angiographic data. Mean MLD increased from 1.21 +/- 0.43 mm before dilatation to 2.34 +/- 0.13 mm immediately after stent placement ($p < .01$) and subsequently decreased slightly (n.s.) to 2.12 +/- 0.27 mm at 6 months. At 5 years the mean MLD had decreased to 1.66 +/- 0.50 mm indicating a progression of atherosclerosis from 6 months to 5 years of .46 +/- .30 mm within the stent ($p = .01$) (**Figure 3**)*.
Mean reference segment diameter was 2.92 +/- 0.47 mm before dilatation, 3.12 +/- 0.33 mm immediately post stenting (n.s.) and 3.18 +/- 0.36 mm at six months (n.s.). At 5 years the mean reference segment diameter had decreased to 2.50 +/- 0.37 mm indicating a progression of atherosclerosis from 6 months to 5 years of .68 +/- .62 mm in the coronary segment containing the stent ($p < .01$).
The percent diameter stenosis decreased significantly from 59.1 +/- 9.8% before to 24.2 +/- 10.0% immediately post-stenting ($p < .01$), and was 32.8 +/- 9.9% at 6 months ($p < 0.5$) and 34.9 +/- 11.5% at 5 years (n.s.). Thus no significant deterioration (2.1%) occurred in diameter stenosis after 6 months (**Figure 4**). While one patient had > 50% stenosis within the stent at long term follow-up, the absolute change in percent diameter stenosis from 6 months to 5 years in this patient was only 4.6%.
Percent stent expansion at 5 years was 89.6 +/- 4% (82.5 - 95.4). Mean intimal thickness within the stent was 0.35 +/- 0.13 mm (0.18 - 0.55). Negative correlation (-.79) was found between the initial stent/artery size ratio and 5-years percent diameter stenosis, but no significant correlation with ultimate MLD, stent expansion or intimal thickness was found.

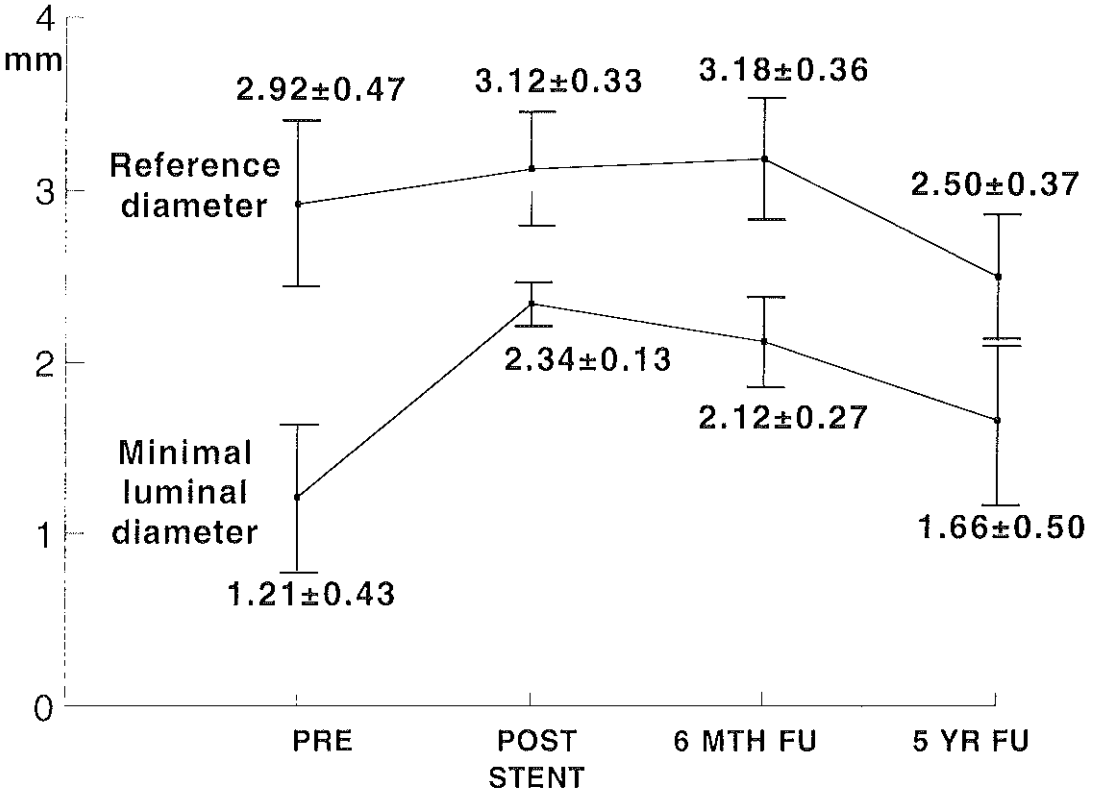

Figure 3.

Serial evolution of average minimal luminal diameter (MLD) and mean reference vessel diameter (RVD).

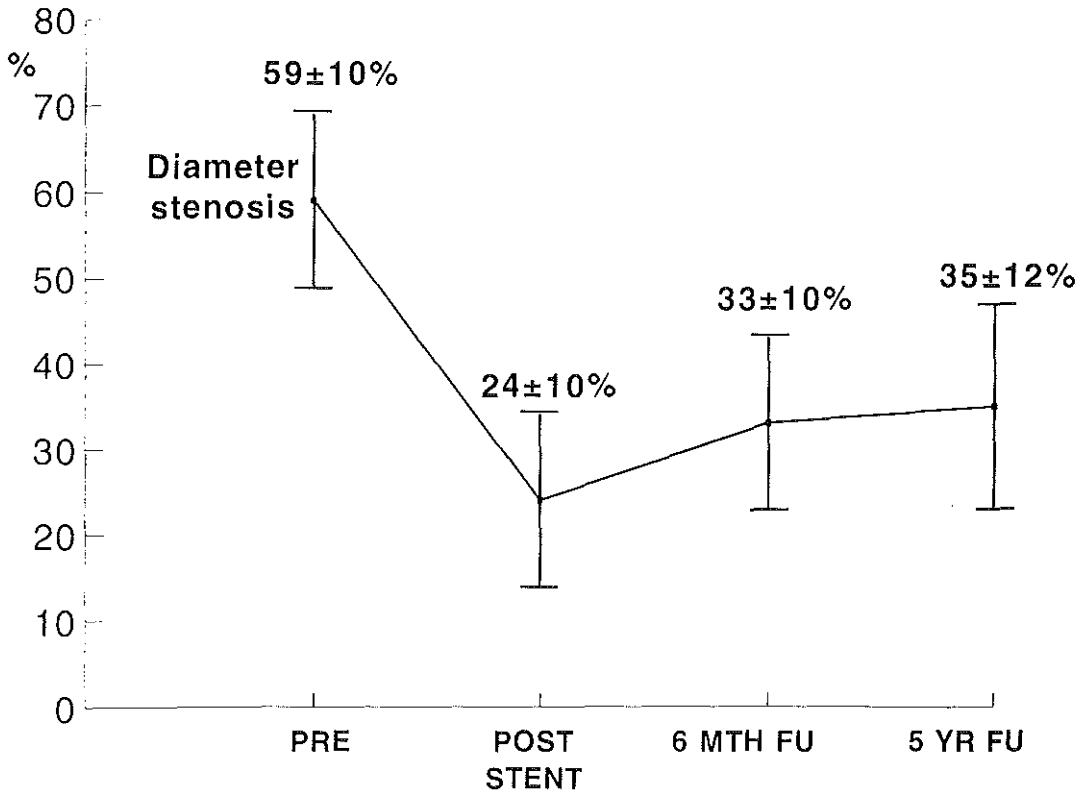

Figure 4.

Serial evolution of average percent diameter stenosis (%DS).

DISCUSSION

Time course of restenosis and comparison with balloon angioplasty. This study clearly shows that the restenotic process after stent implantation is time-limited and does not appear to progress after the period of six months follow-up. Questions had always raised concerning the long-term tolerance of a stent and its interaction with the vessel wall constituents (19,20). Six-month angiographic follow-up was always considered in the literature as describing the ultimate outcome of any stent (6,21-26)). This was proven to be true with balloon angioplasty, so that restenosis rate is almost always based on 6-months' angiogram (3,27). A part from one angiographic study addressing the one year outcome of Palmaz-Schatz stents (28), clinical but not angiographic issues of implanted stents after 6 months have been reported (29). Clinical follow-up, however, does not accurately reflect the restenosis process, as we know from balloon angioplasty, that silent restenosis may be present even in the presence of negative treadmill exercise testing and that silent restenosis may effect long-term prognosis (30-34).

The intentional oversizing in our first series of coronary stents may have resulted in more severe acute injury to the vessel wall, a more profound denuding effect and more extensive disruption of the internal elastic lamina, all factors associated in experimental studies with a more severe hyperplastic reaction (35-37). The time course of this response, however, which is greater than that induced by a conventional balloon (26), seems to follow the same pattern as PTCA. Whereas most series addressing the late outcome after dilatation emphasize the long-term benefits provided by the balloon (38-40) and some show that percent stenosis may event tend to decrease after six months (27), few cases of late restenosis have been reported (27,41).

Experimental studies of different animal models show that, shortly after stent implantation, a thin layer of platelets and fibrin becomes adherent to the deendothelialized surface and neointima which covers the stent struts progressively thickens to reach its maximum after about 8 weeks (35,42). Medial atrophy and inflammatory infiltrates are the other prominent features described in short follow-up experimental studies (35). Although smooth muscle cell proliferation under denuded areas may continue at rates up to 50 times the control one for periods longer than 12 months (43), the neointima have been shown to undergo rapid growth during the first two months before progressively thinning over the ensuing 6 to 9 months (42).

Determinants of intimal hyperplasia. The magnitude of the hyperplastic response to injury varies and depends on, among other factors, the stent to artery ratio, stent design and animal models (44). The constituent metal type does not appear to exert different effects on smooth muscle cell proliferation (37). Some animal studies suggested that a thinner metallic structure, like that of the Palmaz-Schatz stent, may induce only limited proliferative reaction (45,46). However, in human studies using the same device, maximal intimal hyperplasia averaged 400 - 450 u in thickness and reached more than 650 u event within those stents free of restenosis (47,48). Previously published data on the Wallstent" revealed similar degrees of intimal thickness (200 - 500u) (2,10). Factors associated with abnormally excessive progression of intimal hyperplasia include multiple stents per lesion, saphenous bypass graft site and excessive over-sizing of the stent (49). In our patients, one single stent was implanted at one site, in a native coronary segment. Intentional stent oversizing was correlated neither with ultimate intimal thickness nor with MLD changes between 6 months and 5 years, indicating that the factors able to modulate cellular response cease to operate after the first few months.

Qualitative angiographic features of the Wallstent at 5 years. Radiological characteristics of the Wallstent were unchanged by time, side branches were still patent at ultimate control, as has been described with other stents (50) and no angiographic calcifications were seen around it, which suggests its long-term tolerance by the human body.

Study limitations. By examining the luminal renarrowing process beyond the 6 month period in a limited number of patients who did not develop a thrombotic occlusion or undergo reintervention at the stent site, we have inherently studied a selected population of patients. It is conceivable that patients who develop a significant renarrowing within 6 months of stent implantation, might be more predisposed to a prolonged restenosis process, however, in order to study such a population it would be necessary to withhold reintervention for five years - a stance difficult to justify in patients with recurrent symptoms.

CONCLUSION

Contrary to previous concerns over the long-term effect of a metallic foreign body exerting prolonged barotrauma in the coronary arterial wall, 5 year angiographic follow-up after Wallstent implantation in patients without restenosis at 6 months suggests that progression of atherosclerosis within the stent may not be accelerated. Such angiographic evidence provides hope that the short-term benefits which have been recently demonstrated in randomized trials of metallic stents may be maintained in the long - term. Over the next few years, similar long-term angiographic studies should be undertaken with other stent designs to determine whether the implications of our study can be generalized or only limited to the self-expanding stainless steel mesh stent.

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Chapter IX

Clinical and angiographic outcome following implantation of the new Less Shortening Wallstent in aorto-coronary vein grafts : Introduction of a second generation stent in the clinical arena.

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Clinical and Angiographic Outcome Following Implantation of the New Less Shortening Wallstent in Aortocoronary Vein Grafts: Introduction of a Second Generation Stent in the Clinical Arena

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One of the factors felt to have contributed to the high rate of stent occlusion in the European registry of the coronary Wallstent in the 1980s was the frequent deployment of more than one stent to cover the target lesion. This resulted from a high degree of shortening of the Wallstent upon expansion. To overcome this limitation the design of the Wallstent was modified to reduce the degree of shortening. We report the results of a study of the first patients to undergo implantation of the new Less Shortening Wallstent. Thirty-five Wallstents were electively deployed in aortocoronary vein grafts in 29 patients. Stent deployment was successful in 35 of 36 attempts in 30 lesions. In five of the 30 lesions, a second stent was required to cover the proximal portion of the lesion. Angiographic success (< 50% residual diameter stenosis as determined by off-line quantitative coronary angiography) was achieved in all 29 patients. During the in-hospital phase, no major adverse cardiac event occurred (reintervention, re-CABG, myocardial infarction, or death) and five patients had hemorrhagic complications. Following hospital discharge, one patient had a subacute stent occlusion associated with symptoms and elevated cardiac enzymes at 11 days, another patient had symptoms and elevated cardiac enzymes (CK 300 U/l) at 22 days with a patent stent, five patients required balloon angioplasty within the 6 month follow-up period (four for restenosis and one for stent occlusion), one patient underwent re-CABG for a native artery stenosis distal to the anastomosis of the patent stented vein graft. The results of this introductory study suggest that the new Less Shortening Wallstent may be associated with a reduction in the requirement for multiple stent deployment and a lower rate of thrombotic occlusion in comparison to its pioneering prototype. On the basis of these results, a number of larger multicenter clinical trials have been initiated to further evaluate the new coronary Wallstent.
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Introduction

To date, revascularization procedures for diseased aortocoronary bypass vein grafts have been associated with poor clinical and angiographic outcome.[1,2] Repeat coronary artery bypass graft surgery (CABG) is technically more difficult, is associated with a higher morbidity and mortality, and has inferior long-term clinical results when compared with a first bypass operation.[3–5] While the immediate results of balloon angioplasty has been shown to be favorable in patients with discrete lesions in venous bypass grafts,[6,7] results have been unfavorable in diffusely diseased, ulcerated, or thrombosed venous grafts. Furthermore, it appears that the rate of restenosis is high, varying from 40% to 70% depending on the site of the lesions and overall extent of disease in the graft.[8–14]

In our previous study of vein graft revascularization with the Medinvent Wallstent (Lausanne, Switzerland) in 26 patients and the polymer-coated Biogold

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Wallstent in 43 patients between 1988 and 1990,[2] we reported a procedural success rate of 100% (postprocedural diameter stenosis of < 50%). Despite this initial technical advantage and despite the implementation of a comprehensive antithrombotic regimen (pre- and intraprocedural intravenous heparin and dextran, immediate postprocedural intracoronary urokinase and postprocedural intravenous heparin [3–5 days], acenocoumarol [3–6 months], aspirin [300 mg/day], and dipyridamole [300–450 mg/day]) the rate of in-hospital thrombotic occlusion was 10%. Of 53 patients who had no major in-hospital complications and underwent follow-up angiography at 4.9 months, restenosis (as defined by > 50% diameter stenosis) was present in 25 (47%), three of whom had stent occlusions. The primary reason for this excessively high rate of stent occlusion was felt to reflect the patient selection. The patients had not been recruited within the rigorous inclusion/exclusion criteria of a prospective trial but rather had been selected outside the confines of a protocol for compassionate use often in patients with unstable angina and end-stage disease who had been turned down from surgery.

Furthermore, the Medinvent Wallstent was characterized by a high metallic surface area, a high level of radial force and marked shortening upon deployment. The high degree of shortening resulted in difficulty in predicting the final location and extent of the deployed stent and thus necessitated the deployment of multiple stents in a large proportion of patients as exemplified in the above series where, 136 stents were implanted in 69 patients (30 single stents in single lesions, 90 multiple stents in single lesions, and 16 multiple stents in multiple lesions). The resultant augmented accumulative metallic surface area of multiple stents is felt to have also have contributed to the higher rate of subacute thrombosis in the above series.[2] For this reason, the design of the Wallstent was modified to reduce the degree of shortening associated with stent expansion. The braiding angle of the stainless steel mesh was reduced from approximately 140° to approximately 104° with a reduction in shortening to approximately 25% of the stent's length; the degree of shortening and final braiding angle of this new Less Shortening Wallstent varies according to the degree of expansion of the deployed stent and the stent:vessel size ratio. An inherent advantage of this modification is a reduction in the metallic surface area of the expanded stent albeit at a cost of a concomitant reduction in radial force.[15–17]

In view of the previous history of a prohibitive risk (10%) of stent thrombosis with its predecessor, it was felt that a feasibility and safety trial of the new Less Shortening Wallstent should be undertaken in a controlled context including monitoring by a safety committee that was independent from both the investigators as well as industry and had the mandate to terminate the trial at any stage of recruitment.

Methods

Study Design. The study was a noncomparative observational series in 29 patients undergoing implantation of the less shortening coronary Wallstent between November 1991 and March 1993 in six investigating centers. Patients with recurrent angina who had undergone saphenous vein coronary artery bypass graft surgery (SV-CABG) at least 60 days prior to the current admission were considered for inclusion. The key features of the study population were as follows: Patients had to be suitable candidates for a second surgical bypass procedure. The patient's history, signs, and investigations had to indicate that the current clinical symptoms were attributable to myocardial ischemia, for which the graft stenosis was principally suspected as being the culprit lesion. Patients had to give signed informed consent that emphasized the critical importance of 6-month angiographic follow-up. The inclusion and exclusion criteria are listed in Table 1.

Technical Considerations. The new less shortening coronary Wallstent (Schneider-USA, Minneapolis, MN, USA) has an uncoated stainless steel tubular

Table 1. Inclusion and Exclusion Criteria

Inclusion Criteria	Exclusion Criteria
(1) a flow (run-off) in the target vessel of at least TIMI grade 2	(1) a lesion which encompassed the distal anastomosis (either end-to-end or side-to-side
(2) a stenosis length of < 20 mm, with the unconstrained dimension of the stent providing a margin of at least 4 mm on either side of the lesion	(2) a target vessel which does not regionally supply a major vascular bed
(3) a vessel size of 3.5–5.5 mm in diameter	(3) a target vessel with significant distal disease
	(4) more than one previous angioplasty at the proposed stent implantation site

mesh design. Eighteen to twenty 0.07–0.10 mm thick monofilaments are used to fabricate each coronary Wallstent resulting in a metallic surface area in the expanded state of approximately 20%[18] and a metallic cross-sectional area 0.062mm^2.[19] The intersections of the filaments of the mesh structure are not fixed or soldered together, thereby providing greater longitudinal flexibility. The outer diameter of the coronary stent-mounted delivery catheter of the Wallstent is 1.57 mm, which compares favorably to other stents.[17] The low profile of the Wallstent permits its introduction through an 8Fr guiding catheter (0.077 inch internal diameter).

The Wallstent is self-expanding and, therefore, does not require a balloon for deployment. This may be particularly advantageous in friable, diffusely diseased bypass grafts at high risk of embolization with balloon angioplasty. Instead, the Wallstent is mounted on a low profile catheter and is maintained in a collapsed state until it is progressively released by the retraction of its rolling membrane.[17] The doubled-over restraining membrane and delivery mechanism prevent accidental release of the stent.

An additional feature of the Wallstent is its wide range of available sizes for coronary vessels of up to 6.0 mm diameter in the expanded state with lengths of up to 40 mm. Wallstents of > 6.0 mm diameter are available but they are usually deployed in peripheral vessels and the biliary tree and have a reduced longitudinal flexibility. The large range of lengths available for the Wallstent may be particularly advantageous: first for the treatment of long lesions in diffusely diseased vein grafts; second to avoid the deployment of more than one stent—a factor known to increase the risk of early thrombosis[20] and subsequent late restenosis (particularly at the site of stent overlap where the metallic burden on the vessel wall is highest[21]); and third it permits the selection of a Wallstent of greater length than the lesion thus reducing the risk of failing to cover the entire lesional length.

Definitions.

—*Angiographic success* was defined as a postprocedural (Wallstent implantation) residual diameter stenosis of < 50% as determined by quantitative coronary angiography at the core laboratory using the average of multiple matched views.

—*Procedural success* was defined as an angiographic success in the absence of any of the following in-hospital major adverse cardiac events; re-PTCA, re-CABG, myocardial infarction, or death.

—*Restenosis* was defined as a diameter stenosis of > 50% in the treated lesion as determined by quantitative coronary angiography at the core laboratory using the average of multiple matched views.

—*Study end points:* The primary clinical end point of the trial was the occurrence of any of the following four major adverse cardiac events; re-PTCA, re-CABG, myocardial infarction (cardiac enzymes more than twice the upper limit of normal) or death. The primary angiographic end point was the restenosis rate at angiographic follow-up. The secondary clinical end point was anginal symptoms at 6 month follow-up.

Anticoagulant Therapy. Investigators were encouraged to commence the patient on anticoagulant therapy 1 or 2 days before the planned procedure. However, when the investigator proceeded directly to intervention after diagnostic angiography, anticoagulant therapy was started on the day of the procedure itself. The pharmacological protocol was as follows:

—Aspirin (not enteric coated) 325–500 mg daily before the procedure and 80–100 mg daily permanently after the procedure.

—Dipyridamole beginning 1 or 2 days prior to stent implantation and continuing for 6 months thereafter.

—Warfarin 5 mg daily beginning 1 or 2 days prior to implantation and adjusted to maintain an international normalized ratio (INR) of 2.2–4.1 (at an international sensitivity index of 2.4).

—Nifedipine 30–60 mg (slow release) once daily beginning the day of the procedure.

—Heparin intravenously. A bolus of 10,000–20,000 IU was given at the beginning of the intervention and subsequently monitored every 30 minutes to maintain the activated clotting time (ACT) greater than 300 seconds until the procedure was completed. The sheath was removed when the ACT fell below 150 seconds. One hour after sheath removal, heparin was restarted to maintain the partial thromboplastin time (PTT) at 1.5–2.0 times normal. The heparin was continued for 5 days or until the INR was greater than 2.2.

—Dextran intravenously. Following a preceding test dose of dextran 1 (Promit) 20 mL over 2–15 minutes, low molecular weight dextran (dextran 40) was administered for 2 hours before the procedure at a rate of 100 mL/hr. At the start of the procedure, the dose of dextran was reduced to 75 mL/hr. Dex-

tran was discontinued 3 hours after sheath removal or after a maximum of 1 L had been administered.

Quantitative Coronary Angiography. Angiograms were obtained immediately pre- and postprocedure (Wallstent implantation) and at 6-month follow-up. At least three projections (of > 30° apart) of the coronary segment scheduled for stent implantation were recorded on cinefilm before intervention. The same projections were repeated after the intervention and at follow-up angiography. The angiograms were recorded in such a way that they were suitable for quantitative coronary angiography (QCA).[22,23]

The quantitative analysis of the aortocoronary vein graft stenoses pre- and postprocedure and at 6-month follow-up was performed by an off-line semiautomated edge-detection system (Cardiovascular Angiography Analysis System, CAAS—Pie Medical, Maastricht, The Netherlands) at a core angiographic laboratory (Cardialysis, Rotterdam, The Netherlands) after digitization of the cineangiograms.[24,25] The average of multiple matched views with orthogonal projections is reported whenever possible. Correction for pincushion distortion was enabled by the prerecording on cinefilm of a centimeter grid in all participating catheterization laboratories. All measurements were calibrated by the use of the angiographic guiding catheter in the contrast-empty state. The accuracy and precision of this QCA system has been found to be −0.09 mm and ± 0.23 mm during measurements of in vivo phantom stenoses using catheter calibration[26] and the reproducibility of measurements of serial clinical angiograms with this QCA system[27,28] at this core angiographic laboratory[27] has been found to be ± 0.20 mm.[27,28]

Statistics. Descriptive statistical methods have been used to report the results. As one patient had two lesions treated within the one graft, the results of quantitative coronary angiography of this patient are taken as the mean value for the two lesions.

Results

Four of the 29 patients broke the inclusion/exclusion criteria for the following four reasons:

(1) Two separate segments in the same graft were treated by the implantation of Wallstents (one Wallstent at each lesion)—one patient.

(2) Another segment in a native coronary artery underwent concomitant intervention—one patient.

(3) Previous implantation of stents in coronary arteries—one patient.

(4) One patient was 78 years old.

The mean age of the patients was 62.5 years (27 male, 2 female). Four patients had unstable angina. The mean age of the grafts was 9.5 years and 19 of the grafts had multiple distal anastomoses. Four of the lesions had calcification and four of the stenoses were recurrent following a previous intervention at the same site. The clinical features of the patients and vein graft characteristics are given in Table 2.

Stent Deployment. Stent deployment was successful in 35 of 36 attempts in the 29 patients. More than one stent was used in seven patients; in five patients the stent was placed too distally and only partially covered the lesion and subsequent implantation of an overlapping second stent covered the lesion entirely in all four patients. In one patient, two stents were implanted in two separate lesions within the same vein graft, and in another patient the stent delivery system was inserted and removed without implantation due to inability to release the stent. The mean nominal stent diameter and nominal implanted stent length were 4.50 ± 0.61 mm and 26.86 ± 4.03 mm, respectively.

Table 2. Clinical Characteristics of Study Population

Total Number of Patients	29
Male/Female	27/2
Age	62.5 (40–78 years)
Smokers	10
Hypertension	7
Hypercholesterolemia	15
Diabetes	1
Angina stable/unstable	25/4
Prior myocardial infarction	18
Prior PTCA (to same or other segment)	11
Prior PTCA at target site	4
Age of bypass grafts	9.5 (2–18 years)
Distribution of grafts:	
Left anterior descending	10
Left circumflex	9
Right coronary artery	10
Multiple distal anastomoses ("jump" grafts)	19
Number of lesions stented	30
Portion of graft stented	
Ostial	14
Body	12
Distal	4
Calcified lesions	4
Balloon dilatation within stent	25

Procedural Success. Procedural success as defined by < 50% residual diameter stenosis in the absence of any in-hospital major adverse cardiac event (re-PTCA, re-CABG, myocardial infarction, or death) was achieved in all 29 patients.

In-Hospital Complications and Events. The following in-hospital complications occurred: femoral hemorrhage—three patients (of these three patients, two required transfusions and one required surgical removal of the femoral sheath); hematuria—two patients (one of these patients had nephrolithiasis and the other had benign prostatic hyperplasia); acute occlusion of the native right coronary artery after concomitant balloon angioplasty at this arterial segment (protocol violation), which was successfully managed during the primary interventional procedure by bailout stent (Palmaz-Schatz) placement.

Complications and Events Following Discharge. Eight major adverse cardiac events occurred in seven patients within 6 months of stent implantation. These consisted of repeat balloon angioplasty to the originally stented site in five patients; Q wave myocardial infarction in one patient (the peak creatine phosphokinase (CK) was 885 U/L and was associated with stent occlusion 11 days poststenting, which was managed by balloon angioplasty); non-Q wave myocardial infarction in one patient (the peak CK was 300 U/L at 22 days poststenting and was associated with a patent stent—minimal luminal diameter of 2.66 mm); and repeat coronary artery bypass graft surgery due to a stenosis in the native coronary artery distal to the graft anastomosis in the presence of a patent stented site in the vein graft in one patient. In addition to the above events within the 6-month study period, an additional patient presented with increased symptoms at 8 months, which was managed by balloon angioplasty to the stented segment. While no patient had residual angina at the time of hospital discharge, seven patients had angina at 1- and 6-month follow-up visits.

Quantitative Coronary Angiography. Coronary angiograms suitable for quantitative analysis were obtained in all 29 patients pre- and poststent implantation. Follow-up angiography was obtained at 6 months or sooner if clinically necessitated in 25 patients. Four patients refused follow-up angiography.

Off-line quantitative analysis of the 29 patients gave

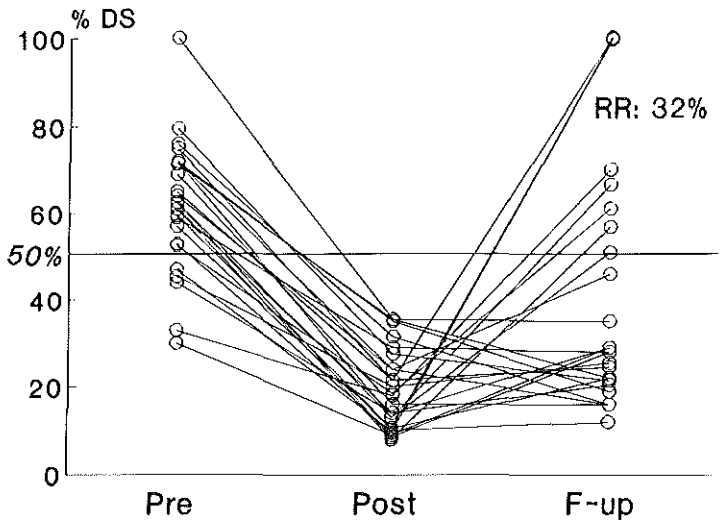

Figure 1. Changes in percent diameter stenosis (%DS) from prestenting through poststenting to follow-up for the 25 patients with angiographic follow-up. Procedural success (< 50% diameter stenosis poststenting) was achieved in all patients. Restenosis (> 50% diameter stenosis at follow-up) occurred in eight of the 25 patients yielding a restenosis rate RR of 32%. In four patients a significant improvement in minimal luminal diameter was observed at follow-up (see text).

an average vessel size of the saphenous vein grafts prestenting of 3.66 ± 0.89 mm. This indicated a ratio of the nominal stent diameter to vessel diameter of 1.27 and a nominal stent diameter to vessel diameter difference of 0.84 ± 0.64 mm. In the 29 patients, minimal luminal diameter (MLD) prestenting was 1.32 ± 0.68 mm, which increased to 2.98 ± 0.71 mm poststenting. Angiographic success as defined by < 50% residual diameter stenosis postprocedure by quantitative coronary angiography at the core laboratory was achieved in all 29 patients.

Restenosis as defined by > 50% diameter stenosis at follow-up by quantitative coronary angiography at the core laboratory occurred in 8 of the 25 patients with angiographic follow-up providing a restenosis rate of 32%. Of the eight patients, three had total occlusions (one total occlusion was associated with a myocardial infarction at 11 days and the other two total occlusions were observed at 6-month follow-up). The mean loss in luminal diameter over follow-up of the 25 patients was 0.64 ± 1.11 mm resulting in a MLD at follow-up of 2.31 ± 1.13 mm. The net gain index for the 25 patients was 0.25 ± 0.35, whereby net gain index = (gain in MLD at intervention—loss in MLD at follow-up)/vessel size. The individual changes in percent diameter stenosis from prestenting through poststenting to follow-up for the 25 patients is displayed in Figure 1 where it can be seen that while eight of the patients had greater than 50% diameter stenosis at follow-up, further improvement in stent diameter stenosis occurred in other patients over the follow-up period. At follow-up, the absolute MLD had increased from the poststenting value in seven patients. In four of these patients the absolute increase in MLD was ≥ 2 standard deviations of the clinical reproducibility of the QCA system in serial angiographic studies (i.e., ≥ 0.40 mm).

Discussion

In this series, deployment of the new Less Shortening Wallstent was successful in 35 of 36 attempts. Historically the procedural success for deployment of the Wallstent has always been high, reflecting its technical performance.[29–31] The unique trackability offered by the Wallstent results from three features:(1) low profile (1.57 mm); (2) longitudinal flexibility; and 3) the smooth rolling membrane (covering sheath), which protects the struts until the stent is across the lesion to be stented.[17]

Because the Wallstent is not a balloon expandable stent, precise positioning can be technically exacting as evidenced by the use of multiple stents. This is particularly critical for ostial lesions. Deployment of a second Less Shortening Wallstent was required (to cover the proximal portion of the lesion) in five of the 30 lesions stented (16.6%), which compares favorably to the previously described vein graft experience with the original Wallstent design (136 stents deployed in 74 lesions).[2] This problem was primarily encountered by those operators on the learning curve of Wallstent deployment and was not seen with the more experienced operators.

The 3.4% (by patient) incidence of subacute stent occlusion (one subacute occlusion at 11 days post stenting) in our current study again compares well with the previously reported incidence of early (acute and subacute) occlusions with the original Wallstent design (8% by patient in vein grafts and 19% by patient in native arteries).[2,30,31] Although, the reasons for subacute occlusions poststenting are multifactorial, it is likely that the lower requirement for multiple stent deployment in addition to a slight reduction in metallic surface area per stent associated with the less shortening design of the new Wallstent may have contributed to the low incidence of subacute stent occlusion.

The incidence of bleeding events in our series was high. This may relate to the aggressive anticoagulation policy adopted in our study protocol, which was advised by the manufacturer of the device (Schneider, Bulach, Switzerland) and by the independent safety committee of the trial. This was felt to be necessary in view of the previously high rate of subacute occlusion observed with the previous Wallstent design as described above.

The mean residual percent diameter stenosis poststenting in our 29 patients was 20.6 ± 9.8%, with a percent diameter stenosis of > 30% in five of the 29 patients. This is lower than our current stent practice and recently we have defined angiographic success as < 20% diameter stenosis for upcoming interventional trials.[23,32,33] The increasing use of intracoronary ultrasound to guide stent deployment and ensure maximal and uniform stent expansion and apposition to the vessel wall should further reduce the incidence of subacute thrombosis and improve long-term angiographic outcome.

Because of the low profile of the Wallstent, a large

amount of predilitation is not required. This reduced the risk of disruption of friable degenerating tissue within the grafts. This was reflected by the low incidence of patients in whom an acute elevation of cardiac enzymes occurred poststent implantation; no patient had a significant elevation of CK during the in-hospital phase while two patients (8.3%) had an elevation at 11 and 22 days post stenting as described earlier. This incidence compares favorably with the CAVEAT II experience of CK elevation following directional coronary atherectomy in venous bypass grafts.[34]

In addition to the relatively low rate of restenosis (32%) in this series of vein graft lesions,[8–14] it is of interest to note the occurrence of a negative loss in luminal diameter (i.e., further expansion of the lumen) over a 6-month follow-up in seven patients. In four of these patients the negative loss was ≥ two standard deviations of the clinical reproducibility of QCA measurements at the core laboratory (i.e., ≥ 0.40 mm[27,28]) and thus is highly likely to represent a significant expansion in luminal diameter in these patients. This most likely reflects the self-expanding nature of the Wallstent, which may continue to expand after deployment.[35]

The results of this introductory study suggest that the new Less Shortening Wallstent may be associated with an improvement in requirement for multiple stent deployment and a lower rate of thrombotic occlusion in comparison to its pioneering prototype. On the basis of these results, a number of larger multicenter clinical trials have been initiated to further evaluate the new coronary Wallstent.

Acknowledgments: Patients undergoing implantation of the Less Shortening Wallstent in bypass vein grafts were enrolled at the Thoraxcenter, Rotterdam NL (12 patients), Academisch Ziekenhuis Leiden NL (10 patients), Kardiologische Gemeinschaftspraxis, Am Roten Kreus Krankenhaus, Frankfurt G (3 patients), St Antonius Ziekenhuis, Nieuwegein NL (2 patients), Université Catholique de Louvain, Bruxelles B (1 patient), Ziekenhuis Aalst, Aalst B (1 patient).

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Chapter X

Clinical and angiographic outcome following implantation of the Palmaz-Schatz stent in small coronary arteries.

Implications for vessel selection and stent sizing.

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(in review)

ABSTRACT

Background: While recently completed trials indicate that stent implantation may improve both clinical and angiographic outcome following coronary intervention, it is unknown if such advantages are conveyed in coronary vessels of < 3.0mm diameter.

Methods: To determine whether small vessel size subtends an increased risk of adverse cardiac events during and following elective stent placement, we performed both a categorical and continuous analysis of vessel size using an intention-to-treat approach in the patients who were randomized to receive a Palmaz-Schatz stent (n = 259) or to undergo balloon angioplasty alone (n = 257) in the BENESTENT trial.

Results: Using a categorical approach we divided the stent population into two groups according to vessel size >3.00mm (n = 118) and <3.00mm (n = 132). In small vessels the stent to vessel diameter ratio was significantly higher (1.23) than in large vessels (1.07) with subsequent significantly greater relative gain (Rel Gain = procedural improvement in minimal luminal normalized for vessel size), however, the loss index (late loss at follow-up / acute procedural gain) was significantly greater in small vessels ($p < .001$). Small vessel size conveyed a significantly higher ($p < .05$) risk of adverse cardiac events including procedural failure (procedural failure = procedural cross-over, >50% residual diameter stenosis, or occurrence of in-hospital event), subacute thrombosis (SAT), and myocardial infarction (MI), need for revascularization (rePTCA & CABG), and occurrence of any cardiac event during 6 month follow-up.

For those patients randomized to balloon angioplasty, a similar pattern between vessel size and need for revascularization was seen, however, small vessel size was not associated with a higher rate of bailout stent, post-procedural abrupt vessel closure or subsequent MI during follow-up in the balloon angioplasty population.

Logistic regression indicated that decreasing vessel size (as a continuous variable) was associated with an increasing risk of cardiac events for both the stent and balloon angioplasty populations.

Conclusion: While recent studies have indicated a favourable clinical outcome following elective coronary stent placement, the relative merits of coronary stenting may be reduced in vessels of <3.00mm diameter.

INTRODUCTION

Two recently completed randomized trials, BENESTENT [1] and STRESS [2], comparing elective coronary stent implantation with balloon angioplasty, have indicated that stent implantation may improve both clinical and angiographic outcome following coronary intervention. Analyses of previous non-randomized data of coronary stenting have provided conflicting evidence on the outcome of stenting in small coronary vessels. The results of previous analyses have been obscured by a number of confounding variables in their study populations including diverse indications for coronary stent implantation (bailout, suboptimal result, and elective), diverse lesion characteristics (restenotic lesions and primary lesions in native arteries and vein grafts), and diverse clinical status (unstable and stable angina).

The per protocol inclusion criteria of the BENESTENT trial required that the size of the target coronary vessel be more than 3.0mm as determined by the investigator and the STRESS trial required a vessel size of greater than or equal to 3.0mm. Despite such per protocol inclusion criteria, quantitative coronary angiographic analysis (QCA) at the trial core laboratories indicated a mean vessel size of 3.00 and 3.01mm in the BENESTENT and STRESS trials respectively. It is unknown whether the relative advantages conferred by coronary stent implantation are limited to large vessels and specifically if the rate of subacute stent thrombosis and the degree of lumen renarrowing is different in small vessels following stent implantation.

To determine whether small vessel size conveys an increased risk of adverse cardiac events during and following elective stent placement and following balloon angioplasty, we performed both a categorical and continuous analysis of vessel size using an intention-to-treat approach in the patients who were randomized to receive a Palmaz-Schatz stent or to undergo balloon angioplasty alone in the BENESTENT trial.

METHODS

Details of the methodology and primary outcome of the BENESTENT trial have been previously published [1]. For inclusion patients were required to have stable angina due to a single de novo lesion in a native coronary artery. The target lesion needed to be < 15mm long and to be located in a vessel of more than 3.0mm in diameter (as determined by the investigator) which supplied a normal functioning myocardium. Patients with an ostial lesion, a lesion at a bifurcation, or a lesion in a previously grafted vessel were excluded from the study, as were patients in whom an intracoronary thrombus was suspected.

Balloon angioplasty was performed according to the routine practice of the investigators. Deployment of the Palmaz-Schatz stent was performed with either the premounted sheathed Stent Delivery System or with a bare stent which was crimped by the operator on a standard angioplasty balloon. Following stent implantation, additional intrastent balloon inflations were often performed. Post intervention all patients who received a stent were managed with intravenous heparin, warfarin, and acetylsalicylic acid.

Quantitative coronary angiography. Quantitative coronary angiography at the core angiographic laboratory (Cardialysis, Rotterdam, The Netherlands) was performed on the Cardiovascular Angiography Analysis System (CAAS - PIE Medical, Maastricht, The

Table 1

Clinical Characteristics of Patients with Small and Large Coronary Vessels

Stent & Balloon Populations Combined

	Vessel Size >3.00mm n = 236	**Vessel Size <3.00mm** n = 266	**p-value Chi Sq.**
Female Gender	15%	23%	.02
Diabetes Mellitus	6%	7%	n.s.
Smoker	25%	23%	n.s.
Previous Myocardial Infarction	22%	17%	n.s.
Left Anterior Descending Artery	53%	72%	<.001

Netherlands) [3-13]. Calibration of the quantitative analyses was achieved by the use of the guiding catheter as a scaling device [14-20]. Vessel size was measured at each study phase after the administration of intracoronary nitrates. Standardization of angiographic procedures was adhered to during acquisition by the investigator and during analysis at the core laboratory in order to reduce the variability of serial quantitative angiographic measurements [21,21]. Rather than using an operator selected reference point, CAAS determines the size at the target coronary segment using a computer derived interpolated reference diameter [4,10,21]. The interpolated reference diameter is derived from the edge-detected diameter function of the non-stenotic 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 analysed coronary segment. The interpolated reference vessel diameter is taken as the value of the reconstructed diameter function at the position of the minimal luminal diameter. The advantages of this approach is 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. The limitation of this technique is in ostial lesions where a proximal segment is unavailable, however, in BENESTENT ostial lesions were excluded per protocol. All measurements of both vessel size as well as minimal luminal diameter were the mean values of multiple matched projections.

Angiographic Indices. In order to make valid comparisons between coronary vessels of different size the following angiographic indices were examined :
Vessel Size = Interpolated reference diameter pre intervention
MLD = minimal luminal diameter of the angiographic segment analysed
Acute Gain = MLD post intervention - MLD pre intervention
Late Loss = MLD at 6 month follow-up - MLD post intervention
Relative Gain = Acute gain normalised for (divided by) vessel size
Relative Loss = Late Loss normalised for (divided by) vessel size
Net Gain Index = Relative Gain - Relative Loss
Loss Index = Late Loss normalised for (divided by) Acute Gain

Clinical events. Procedural failure was defined as procedural cross-over, >50% residual diameter stenosis, or occurrence of in-hospital event. Clinical events analyzed for both the in-hospital phase and subsequent follow-up to 7 and 12 months included: 1) cardiac death (one patient in the balloon group committed suicide and this was therefore not included under cardiac death), 2) myocardial infarction, 3) coronary artery bypass surgery, 4) reintervention, 5) abrupt vessel closure. Abrupt vessel closure following balloon angioplasty typically occurs during the interventional procedure or within 6 hours of the procedure [23-32], while following coronary stent placement abrupt vessel closure due to stent thrombosis is delayed up to 14 days with a median of 4-5 days and therefore may not occur until the patient has been discharged from hospital [33-41]. Following stent placement in the BENESTENT trial subacute stent thrombosis (within 14 days of stent implantation) was diagnosed in 10 patients. In eight patients, occlusion of the vessel was demonstrated angiographically, while in two cases the diagnosis was clinical. Of these latter two patients, one sustained an acute myocardial infarction which was successfully treated by systemic thrombolytic therapy with electrocardiographic evidence of reperfusion. In the second case the patient presented to his local hospital with chest pain and ST elevation on ECG and died before angiography could be performed.

Statistical analysis. From the total intention-to-treat population of BENESTENT [1], 502 patients (252 assigned to balloon angioplasty and 250 assigned stent implantation) in whom vessel size was quantified were included in our analysis. Using a categorical approach we divided the stent and balloon angioplasty populations into two groups each according to vessel size >3.00mm and <3.00mm. Odds ratio with 95% confidence intervals were calculated for the development of a clinical event for both small vessels (<3.00mm) and large vessels (>3.00mm). The influence of vessel size on clinical and angiographic outcome was examined using the technique of multivariate logistic regression, allowing for the influence of minimal lumen diameter pre (MLD-pre), minimal luminal diameter (post), as well as the clinical variables diabetes mellitus, gender, and previous myocardial infarction. A p value of <.05 was taken as an indicator of statistical significance.

RESULTS

In the stent group 118 patients had a vessel size of > 3.00mm and 132 patients a vessel size of <3.00mm. In the balloon angioplasty group 118 patients had a vessel size of >3.00mm while 134 patients had a vessel size of < 3.00mm. The clinical characteristics of the patients with small (<3.0mm) and large (>3.0mm) coronary vessels are compared in **table 1**. Patients with small vessels were more likely to be female (23% versus 15% for patients with small and large coronary vessels respectively, p<.05). Small coronary segments were more commonly located in the left anterior descending artery (72% versus 53% for small and large vessels respectively, p<.001).

The angiographic outcome and clinical outcome of patients with small or large coronary vessel size in the stent and balloon angioplasty groups are compared in **tables 2 and 3** respectively. The individual vessel size of the patients who developed abrupt vessel closure in the both the stent and balloon angioplasty populations are displayed in **figure 1**.

Stent population. In small vessels the stent (nominal) to vessel diameter ratio was higher (p<.01) with consequent greater relative gain compared to large vessels (p<.05). At 6 month angiographic follow-up, however, the relative loss and loss index were greater in small vessels (p<.001 and p<.01 respectively).

In patients randomized to stent implantation, small vessel size conveyed a significantly higher (p<.05) risk of adverse cardiac events including procedural failure, subacute thrombosis (SAT), myocardial infarction (MI), need for revascularization (rePTCA & CABG), and occurrence of any cardiac event during follow-up to 7 or 12 months.

In the stent population, logistic regression indicated that decreasing vessel size (as a continuous variable) was associated with an increasing risk of cardiac events for the stent population. The relationship of vessel size and probability of a clinical event post stent implantation is displayed in the logistic regression curve in **figure 2**.

Table 2

Angiographic Outcome for Small and Large Vessels

Stent	Vessel Size >3.00mm n = 118	Vessel Size <3.00mm n = 132	p-value
Stent : Vessel Ratio	1.07 ±.11	1.23 ±.17	<.01
Acute Gain	1.49 ±.44mm	1.28 ±.38mm	<.001
Relative Gain	0.44 ±.13	0.49 ±.15	.02
Late Loss	0.59 ±.52mm	0.71 ±.60mm	.10
Relative Loss	0.17 ±.15	0.27 ±.24	<.001
Loss Index	0.40 ±.41	0.59 ±.57	<.01
Net Gain	1.32 ±.44mm	1.01 ±.41mm	<.001

Balloon	Vessel Size >3.00mm n = 118	Vessel Size <3.00mm n = 134	p-value
Balloon : Vessel Ratio	1.02 ±.11	1.18 ±.12	<.01
Acute Gain	1.01 ±.39mm	0.90 ±.31mm	.02
Relative Gain	0.30 ±.12	0.34 ±.11	.01
Late Loss	0.24 ±.49mm	0.37 ±.45mm	.04
Relative Loss	0.07 ±.14	0.14 ±.17	.03
Loss Index	0.31 ±.70	0.42 ±.76	.25
Net Gain	0.93 ±.43mm	0.77 ±.32mm	.001

Table 3

Clinical Outcome for Small and Large Vessels

Stent	Vessel Size >3.00mm n = 118	Vessel Size <3.00mm n = 132	p-value Chi Sq.
Subacute Stent Thrombosis	1	9	.02
Cardiac Death	0	2	.18
Myocardial Infarction	1	9	.02
CABG	4	11	.10
Re-intervention	11	23	.06
CABG or Re-intervention	14	31	.02
CerebroVascular Accident	0	0	n.s.
Any Clinical Event - 7 Months	15	36	.004

Balloon	Vessel Size >3.00mm n = 118	Vessel Size <3.00mm n = 134	p-value Chi Sq.
Ballout Stent during procedure	4	9	n.s.
Abrupt Vessel Closure post procedure	3	4	n.s.
Cardiac Death	0	0	n.s.
Myocardial Infarction	6	5	n.s.
CABG	4	6	n.s.
Re-intervention	17	41	.002
CABG or Re-intervention	21	46	.003
CerebroVascular Accident	1	1	n.s.
Any Clinical Event - 7 Months	26	54	.002

Balloon angioplasty population. The balloon (nominal) to vessel ratio was significantly greater in small vessels ($p < .01$) with consequent greater relative gain in small vessels. As in the stent group, small vessel size was associated with greater subsequent relative loss and a higher loss index at 6 month angiographic follow-up.

For those patients randomized to balloon angioplasty, small vessel size was associated with a greater requirement for subsequent revascularization. Unlike the stent group, small vessel size in the balloon angioplasty group was not associated with a higher rate of procedural crossover (bailout stent), post procedural abrupt vessel closure or subsequent myocardial infarction during follow-up to 7 or 12 months.

As for the stent population, logistic regression indicated that decreasing vessel size (as a continuous variable) was associated with an increasing risk of cardiac events for the balloon angioplasty population.

DISCUSSION

The key findings of this study are ; 1) during both stent implantation as well as balloon angioplasty, smaller coronary vessels are treated with relatively larger devices (higher device : vessel ratio) with consequent greater acute relative gain in lumen diameter ; 2) smaller vessels subsequently sustain greater relative loss and a higher loss index (luminal renarrowing over 6 months normalized for vessel size and gain respectively); 3) In both the stent and balloon groups this greater relative loss in lumen diameter is associated with a greater requirement for revascularization procedures during follow-up; 4) While in those patients undergoing stent implantation smaller vessel size is associated with a greater risk of procedural failure, subacute stent thrombosis, and myocardial infarction during follow-up, in patients undergoing balloon angioplasty smaller vessel size is not associated with a significantly higher risk of bailout stent, procedural failure, abrupt vessel closure or myocardial infarction during follow-up.

Previous studies. Sutton et al. on behalf of the Gianturco-Roubin Intracoronary Stent Investigator Group undertook an analysis of predictors of adverse events after acute and elective coronary stenting on a pooled registry database [36]. They found vessel size of patients who experienced an adverse clinical event post stenting to be 3.16 ±0.59mm compared to a vessel size of 3.06 ±0.62mm in those patients without an event ($p = .14$ on univariate analysis and $p = .0001$ on multivariate analysis). In a stepwise logistic regression model, they found larger vessel size was associated with an increased odds ratio for a clinical event of 2.87 (95% C.I. 1.74 - 4.71). These findings are at variance to expectations and to the results of our current study. The potential confounding variables which may have contributed to the findings of the study by Sutton et al include ; the absence of a single standardized core angiographic laboratory ; vessel size was determined by calliper measurement in an adjacent coronary segment in the single worst view ; the pooling of native artery with bypass graft results ; and the spectrum of indications for stent implantation (predominantly for the acute management of dissections and the elective management of restenotic lesions).

Schomig et al., in a report of their experience with the Palmaz-Schatz stent in bailout therapy, found the difference in vessel size between patients who developed a subacute

Vessel Size in Patients with Abrupt Vessel Closure following Balloon Angioplasty and following Stent Implantation

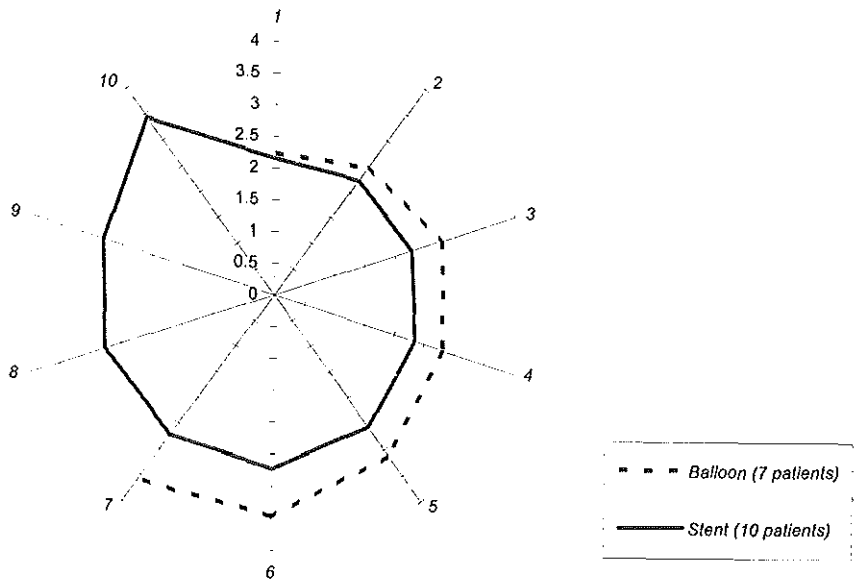

Figure 1
Polar plot of the individual vessel size of each of the patients who developed an abrupt vessel closure following balloon angioplasty (7 patients) and following stent implantation (10 patients). While small vessel size was associated with a higher risk of subacute thrombosis, vessel size was not predictive of abrupt vessel closure following balloon angioplasty.

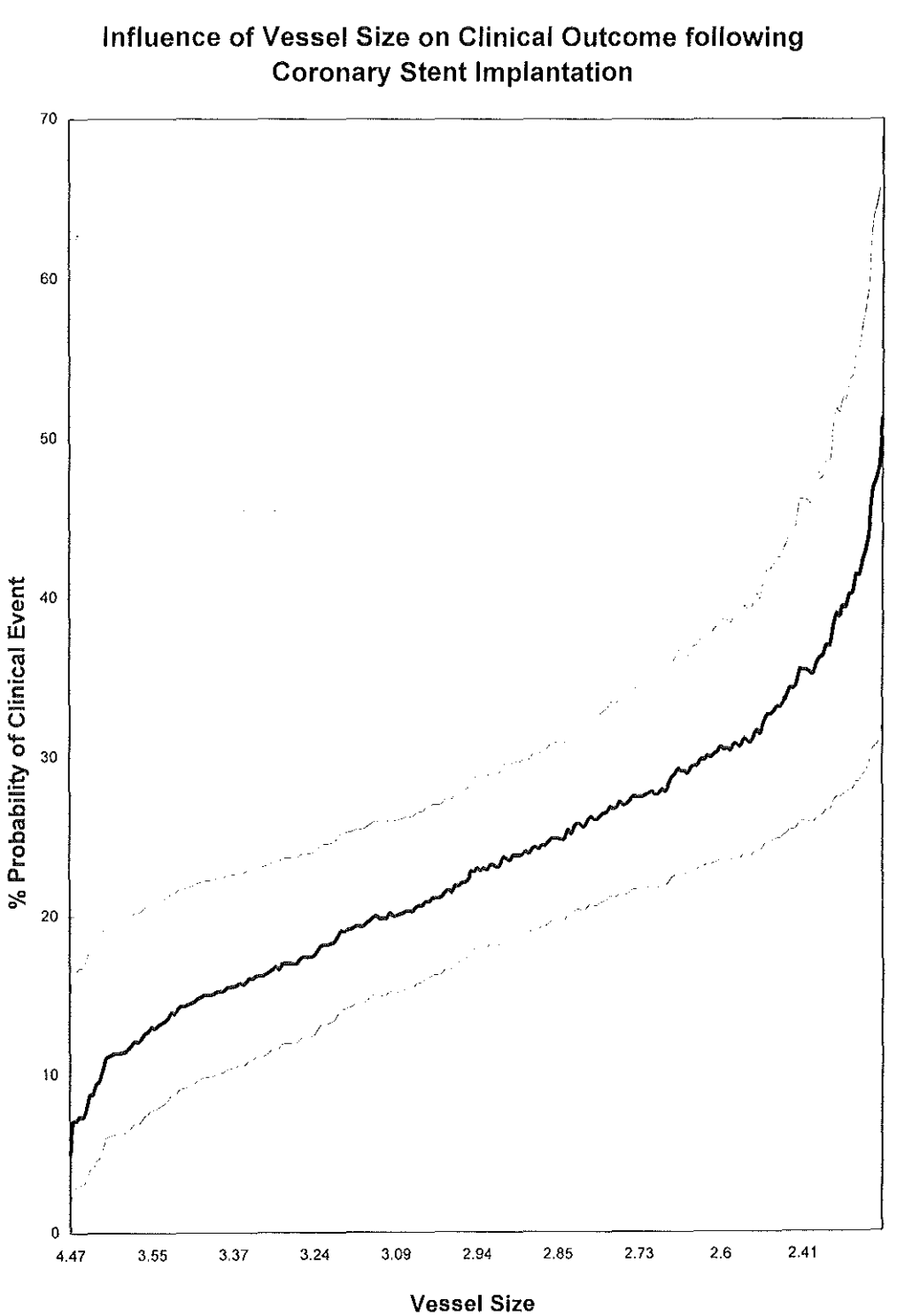

Figure 2
By logistic regression, decreasing coronary vessel size (as a continuous variable) was associated with an increasing probability of a clinical event over 7 months post stent implantation.

stent occlusion (n=21) and those without a subacute occlusion (n=280) was not statistically significant (3.1 ±0.4mm and 3.3 ±0.6mm, p=.16) [43].

In a previous univariate relative risk analysis from our group of restenosis following implantation of the coronary Wallstent, vessel size was not found to be predictive of restenosis. In a more recent analysis from our group of the influence of vessel size on the restenosis process following successful (per protocol) balloon angioplasty, vessel size was found after normalization for confounding variables to exert an independent negative effect on luminal loss and a positive effect on minimal lumen diameter at 6 month angiographic follow-up [43]. These findings are consistent with those of our present study of a greater relative loss and loss index in vessels <3.0mm in patients undergoing balloon angioplasty in the BENESTENT trial and might be predicted from geometrical or mechanical considerations.

Clinical implications. The precise reasons as to why operators select a higher device to vessel ratio in smaller vessels is not clear and may possibly relate in part to the common practice of visual guidance of interventional procedures rather than the more reliable guidance of on-line quantitative coronary angiography to provide absolute measures of both vessel size as well as minimal lumen diameter [20].

Our study has shown that while the relative influence of vessel size on acute and 6 month angiographic outcome is similar for stent implantation and balloon angioplasty, the influence of small vessel size on adverse clinical events is different for stent implantation and balloon angioplasty. Specifically, while small vessel size is not associated with an increased risk of abrupt vessel closure or myocardial infarction following balloon angioplasty, small vessel size is associated with an increased risk of abrupt vessel closure and myocardial infarction post stenting. Current approaches to reduce the risk of subacute stent thrombosis by the development of stent coatings [44-46] and the introduction of improved antiplatelet regimens [47-50] may be expected to improve the outcome of stenting in smaller coronary vessels. Until such expectations are confirmed by prospective studies in vessels of < 3.0mm, balloon angioplasty may continue to be the elective procedure of choice in smaller vessels.

Conclusion: While recent studies have indicated a favourable clinical and angiographic outcome following elective coronary stent placement, the relative merits of coronary stenting over balloon angioplasty may be reduced in vessels of <3.0mm diameter.

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APPENDIX

BENESTENT Study Group

The following institutions and investigators participated in the BENESTENT study. The number of patients enrolled at each center are given in parenthesis:

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8) Sart-Tilman, Centre Hôspitalier Universitaire, Liège, Belgium (32): V Legrand,
9) Hôpital de la Citadelle, Liège, Belgium (19): P Materne, J Boland,
10) Instituto Cardiovascular de Buenos Aires, Buenos Aires, Argentina (19): J Belardi, J Berrocal, R Piraino
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12) Centro Cuore, Milano, Italy (11): A Colombo, L Maiello,
13) CHUV, Lausanne, Switzerland (11): JJ Goy, E Eeckhout,
14) Middelheim Ziekenhuis, Antwerpen, Belgium (10): P van den Heuvel, F van den Brande,
15) Gregorio Maranon, Madrid, Spain (10): J Delcan, E Garcia,
16) Ziekenhuis de Weezenlanden, Zwolle, The Netherlands (8): H Suryapranata, J Hoorntje,
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18) Hospital Maggiore, Trieste, Italy (8): S Klugmann, E Della Grazia, A Salvi,
19) Hôpital Cantonal Universitaire, Genève, Switzerland (7): P Urban, E Camenzind
20) Academisch Ziekenhuis Groningen, The Netherlands (6): P den Heijer, R van Dijk,
21) Academisch Medisch Centrum, Amsterdam, The Netherlands (6): J Piek, K Koch,
22) Christian Albrechts University, Kiel, Germany (6): R Simon, F Herrmann,
23) Centre Cardiologique du Nord, Paris, France (5): MC Morice, T Royer,
24) James Hospital, Dublin, Ireland (5): P Crean,
25) Catharina Ziekenhuis, Eindhoven, The Netherlands (3): H Bonnier, J Koolen, F Bracke,
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27) CHUR, Nancy, France (2): N Danchin, Y Juillière,
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Chapter XI

A quantitative angiographic study of inflation and recoil of the Gianturco-Roubin stent in native coronary arteries :

Results of a learning phase with implications for stent sizing and deployment.

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(in review)

ABSTRACT

Background: The Gianturco-Roubin stent is composed of a balloon-expandable stainless-steel incomplete coil with a clamshell configuration. Its low metallic surface area is achieved by a relatively large distance between its transversely parallel struts. To determine the acute expansile and elastic properties of the stent in-vivo, we studied the behaviour of the stent during deployment in native coronary lesions by detailed quantitative coronary angiographic analysis.

Methods: Thirty-nine Gianturco-Roubin stents were implanted in the native coronary arteries of 35 patients between October 1992 and October 1994 for the management of primary lesions, restenotic lesions, and acute or threatened closure after primary balloon angioplasty. All lesions were predilated by primary coronary angioplasty prior to stent deployment. A nominal (manufacturer's) stent size of on average .61 ±.61mm greater than the reference vessel diameter was selected. This report includes our early learning experience with this stent design and the performance of an additional high pressure intrastent inflation of a non-compliant balloon was only performed latterly in eight of our patients. Computerised quantitative coronary angiography was performed on the inflated balloon and inflated stent as well as pre and post balloon and stent dilatations.

Results: Neither the mean nor the minimal luminal diameter achieved post stenting matched the nominal diameter of the Gianturco-Roubin stent. Acute procedural changes in minimal luminal diameter were from 1.10 ±.53mm pre-intervention through 2.87 ±.51mm during balloon inflation to 1.56 ±.78mm post primary balloon angioplasty. Minimal luminal diameter subsequently increased significantly during stent inflation to 2.97 ±.42mm but fell to a final result of 2.56 ±.39mm post stent deployment. Performance of an additional high pressure intrastent inflation with a non-compliant balloon resulted in a significant improvement in final angiographic outcome (2.68 ±.34mm, $p < .05$). Analysis of the standard deviation of the diameter and analysis of the difference between the minimal and mean diameter (as indices of lumen irregularity) of the inflated balloons and stented segments indicated a non-uniform stent expansion and recoil. Recoil post stenting of the minimal luminal diameter was 15.7 ±11.6% (0.34 ±.68mm), while elastic recoil post stenting of the mean diameter was 8.9 ±9.3% (0.30 ±.33mm).

Conclusions: Inflation and recoil of the Gianturco-Roubin stent is not uniform which may relate to the large interstrut distance (with protrusion of intima or plaque between the struts) and use of a highly compliant premounted balloon. Even with a policy of stent oversizing (stent vessel ratio = 1.23 ±.25mm), a residual diameter stenosis of 20% may persist. This study supports the recent change in interventional practice from matching the size of the Gianturco-Roubin stent to the vessel diameter to the new policy of stent oversizing, and the performance of post delivery high pressure intrastent inflations with a non-compliant balloon under the guidance of on-line QCA.

INTRODUCTION :

Seven different metallic coronary stents, each of unique design, are currently available for clinical implantation. These can be loosely grouped into different design categories, the mesh stents (The Less-Shortening Wallstent [1,2], Palmaz-Schatz [3,4],), the intermediate design of the AVE Micro (zig-zag axial struts), and the coil design (Gianturco-Roubin [5,6], Wiktor [7], Cordis, Multilink). While the mesh stents generally offer strong radial support (particularly the AVE Micro and Palmaz-Schatz stents) and have more longitudinal or oblique orientation of their struts, they do have a large metallic (particularly the Wallstent and Palmaz-Schatz) and therefore potentially thrombogenic surface area. In contrast, the coil stents offer a relatively low metallic burden and a greater degree of longitudinal flexibility and a lower propensity to shorten upon expansion. These potential advantages of coil stents, however, come at a price of potentially providing lower circumferential support. Furthermore, the coil stents have a more transverse orientation of their struts and thus provide less longitudinal continuity in their scaffolding of the vessel wall. In an attempt to reduce this limitation of coil stents, the struts of the Wiktor, Cordis and ACS stents have been crenulated to increase the longitudinal scaffolding provided to the vessel wall. In the case of the Gianturco-Roubin coil stent, however, the stainless steel wire is straight and not crenulated. Instead, the Gianturco-Roubin stent is composed of .006 inch wire wrapped in a serpentine manner so that every 360° the wire makes a 180° turn. The resultant series of parallel U and inverted U-shaped loops allows the coil to expand in a clam-shell manner. The transversely parallel struts of the Gianturco-Roubin stent, however, are spaced at a distance of 1mm to each other (**figure 1**). To determine the acute expansile and elastic properties of the Gianturco-Roubin stent and the effect such large interspacing of the transversely oriented straight struts may have on the behaviour of the Gianturco-Roubin stents in-vivo, we performed detailed quantitative angiographic analysis before, during and following deployment of the Gianturco-Roubin stent in the native coronary arteries of 35 patients.

METHODS :

Patient population. Thirty nine Gianturco-Roubin stents were successfully implanted in the native coronary arteries of 35 patients for the management of primary lesions, restenotic lesions, and acute or threatened closure after primary balloon angioplasty. The average age of the patients was 57 ±10 years and 30 of the 35 patients were male. Eleven of the patients had a previous balloon angioplasty at the site of the target lesion. Three of the patients had peviously undergone coronary artery bypass surgery. Nine of the patients had a history of myocardial infarction. No patient had left ventricular ejection fraction below 40% and no patient had diabetes mellitus. Qualitative angiographic assessment of the target lesions pre-intervention revealed that 8 of the lesions were ACC / AHA [8] type A, 21 lesions were type B, 6 of the lesions were type C. The clinical characteristics and qualitative angiographic profile of the coronary lesions are given in **Table 1**.

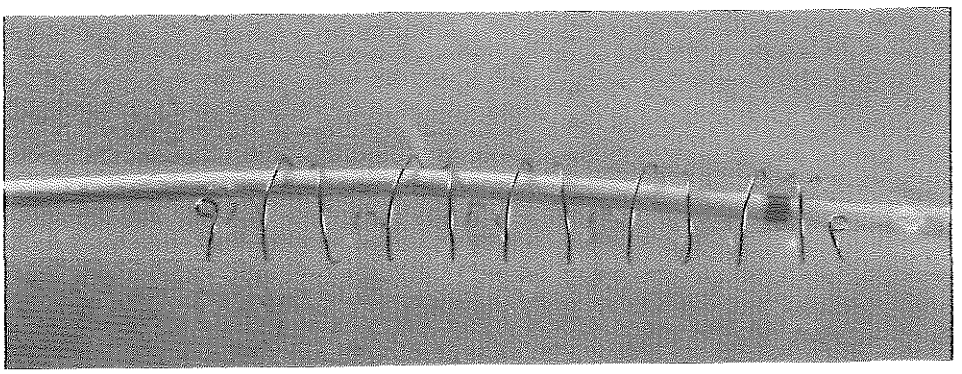


Figure 1. *The Gianturco-Roubin coronary flexible stent is composed of a monofilamentous, surgical stainless steel wire, 0.006 inch in diameter, wrapped in a serpentine manner around a compliant polyethylene balloon catheter so that every 360^0 the wire makes a 180^0 turn [6]. This results in a series of interdigitating U and inverted U-shaped loops and allows the coil to expand in a clam-shell manner as the balloon is inflated .*

Table 1

Clinical Characteristics and Procedural Details

Age	57 ± 10 years
Gender	30 male / 5 female
Hypertension	8 patients
Hypercholesterolaeima	12 patients
Smoking history	
Never	12 patients
Previous	10 patients
Current	13 patients
Number of diseased coronary vessels	
1 vessel disease	22 patients
2 vessel disease	9 patients
3 vessel disease	4 patients
Coronary vessel	
left anterior descending artery	19 patients
right coronary artery	11 patients
left circumflex	5 patients
Pre-balloon angioplasty ACC / AHA Lesion Type	
A	8 lesions
B	21 lesions
C	6 lesions
Indication for stenting post balloon angioplasty	
elective management of restenosis ;	7 patients
unplanned management of a suboptimal result ;	4 patients
bailout of dissection with threatened closure (TIMI [11] flow 2 or 3);	17 patients
bailout of acute vessel closure (TIMI flow 0 or I);	7 patients

Interventional procedure. During the primary balloon angioplasty procedure the maximal inflation pressure was 11.3 ±3 atm.'s with an average of 3.8 ± 1.8 inflations performed. The indication for stenting was elective management of restenosis [7] following previous balloon angioplasty in 7 patients, unplanned management of a suboptimal result of balloon angioplasty in 4 patients, bailout management [9] of a dissection with threatened [9,10] closure (TIMI [11] flow 2 or 3) in 17 patients, and bailout management of an acute closure (TIMI flow 0 or I) in 7 patients. An attempt to cover the full extent of the lesion or dissection was made in each patient. In four of the lesions, a second stent was required to cover the length of the dissection. Three of the stents had a length of 12mm while the other 36 stents were 20mm long. A policy of selecting a nominal stent diameter greater than the vessel size was practised throughout the study. The nominal (manufacturer's) diameter of the stents deployed were 3.64 ±.45mm [range 3.0 to 4.0mm]. The maximal inflation pressure with the premounted balloon to deploy the stent was 6.6 ±2.0 atm.'s with a total number of 3.8 ±1.8 inflations of the premounted balloon being performed.

This report includes our early learning experience with this stent design (commencing in October 1992) and during our two year period of evaluation of the Gianturco-Roubin stent

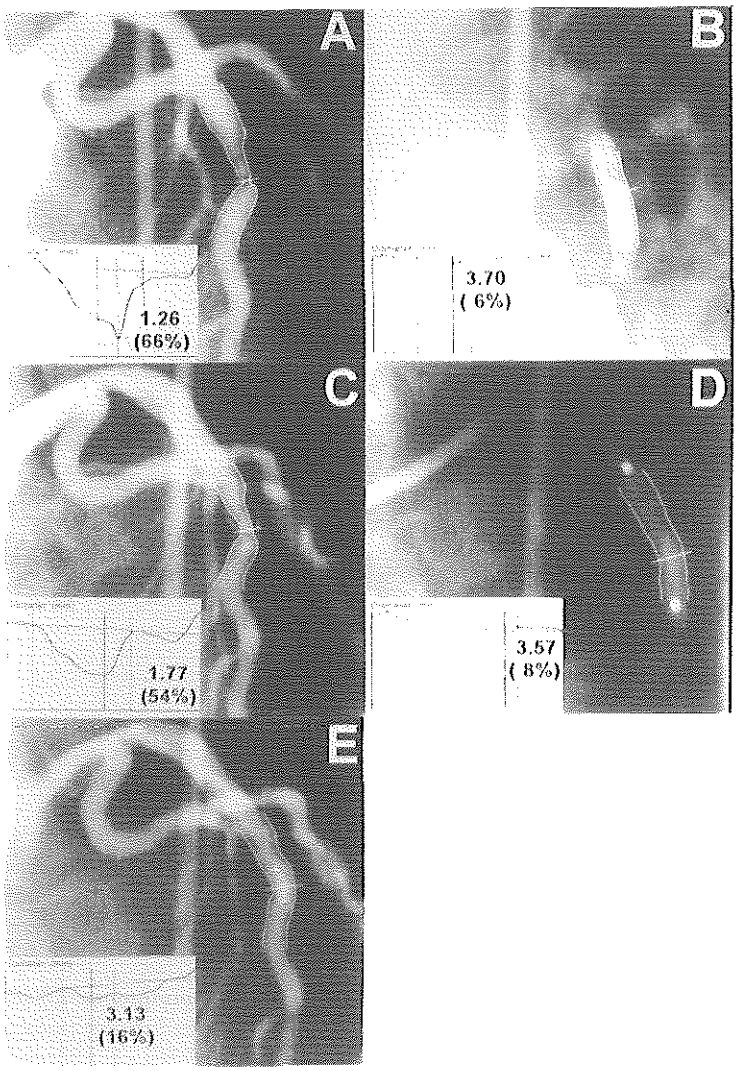


Figure 2a-e. Quantitative coronary angiographic analysis was performed pre-balloon inflation (A), during balloon inflation (B), post-balloon inflation (C), during stent inflation (D), and post-stent deployment (E).

information became available from studies at the University of Alabama to indicate that the performance of an additional high pressure intrastent inflation of a non-compliant balloon should be performed routinely in nearly all patients undergoing implantation of a Gianturco-Roubin stent. Accordingly following delivery of the stent on the premounted balloon, additional high pressure (13.3 ±3.7atm.'s) intrastent inflations of a non-compliant balloon was performed latterly in eight of our patients.

Contrast coronary angiography was performed after the administration of intracoronary nitrates pre-intervention, post-balloon angioplasty, post stent deployment, and post additional inflation of a non-compliant intrastent balloon. Angiograms were also recorded without luminal contrast at peak inflation pressure after waisting of the angioplasty balloon and waisting of the stent balloons were deemed by the operator to have disappeared.

Quantitative angiographic analysis. Subsequent computerised quantitative coronary angiographic measurements on the cineangiograms were conducted on the inflated balloon. and inflated stent as well as pre and post balloon and stent dilatations, thus providing a total of five consecutive procedural phases of quantitative analysis 1) pre balloon angioplasty; 2) during balloon inflation; 3) post balloon angioplasty; 4) during stent inflation; and 5) post stent deployment (**figure 2a-e**). During analysis of the body of the inflated angioplasty balloons and intrastent deployment balloons, the 1mm tapered balloon terminals beyond the limits of the stent were not included. The quantitative angiographic parameters of the analyzed segment which were studied at each procedural phase were the minimal luminal diameter [12,13], the mean luminal diameter [12,13], the standard deviation of the luminal diameter (as an indicator of the irregularity of the luminal borders), and the interpolated reference vessel diameter of the coronary segment.

The computerized quantitative coronary angiographic analysis of the cineangiograms was performed with the Coronary Angiography Analysis System (CAAS II) [14]. After the selection of views which were most suitable for quantitative angiography (e.g. absence of overlapping side branches and foreshortening [15,16]), a 6.9 x 6.9mm region of interest within the 18 x 24mm cineframe is digitized into a 512 x 512 pixel matrix using a CCD-camera (8 bits = 256 density levels) resulting in a final resolution of 1329 x 1772 pixels. A correction for pincushion distortion was applied for all analyses by the recording of a centimeter grid at each image intensifier setting at each interventional suite in our cardiac catheterisation laboratory prior to the study [14]. To initiate the analysis the operator defines a number of centerline points within the arterial segment which are subsequently connected by straight lines, serving as a first approximation of the vessel centerline. The edge detection algorithm is carried out in two iterations. First, the model is the initially defined centerline and second, the model is a recomputed centerline, determined automatically as the midline of the contour positions which were detected in the first iteration.

Calibration of all angiographic measurements was achieved by the use of the coronary guiding catheter as a scaling device [17]. The non-tapering part of the tip of each guiding catheter was measured with a precision-micrometer (No. 293-501, Mitutoyo, Tokyo, Japan; tolerance 0.001mm). The calibration procedure using automated edge detection was applied to the images obtained, yielding the corresponding scaling factor (mm/pixel).

Statistical analysis. Recoil post stent deployment was calculated for both the minimal and mean diameters from quantitative analysis of the intrastent deployment balloon recorded at peak inflation pressure and the luminal diameter post stent deployment as follows :

(minimal diameter of the inflated stent - minimal luminal diameter post stenting) * 100

minimal diameter of the inflated stent

and

(mean diameter of the inflated stent - mean luminal diameter post stenting) * 100
mean diameter of the inflated stent

Student's t-test for paired data was used to compare quantitative angiographic parameters of the same patients at different procedural phases. A p value of $<.05$ was taken as an indication of statistical significance.

RESULTS :

The average vessel size was found to be 3.04 ±.52mm pre-intervention which was .61 ±.61mm smaller than the nominal stent size thus indicating a stent : vessel size ratio of 1.23 ±.25. While vessel size did not change during primary balloon angioplasty, the vessel diameter increased significantly to 3.28 ±.36mm following stent deployment ($p<.05$). The final residual percent diameter stenosis post stenting was 22 ±8%. Neither the mean nor the minimal luminal diameter finally achieved post stenting matched the selected nominal diameter of the Gianturco-Roubin stent.

The dynamic changes in minimal (and mean) luminal diameters at each procedural phase are displayed in **figure 3** and changes in all angiographic measurements are given in **table 2.** The minimal luminal diameter was found to increase from 1.10 ±.53mm pre-balloon to 2.87 ±.51mm during balloon inflation and subsequently to decrease to 1.56 ±.78mm post primary balloon angioplasty. Minimal luminal diameter subsequently increased during stent inflation to 2.97 ±.42mm but fell to a final result of 2.56 ±.39mm post stent deployment. In the eight patients in whom an additional high pressure inflation was performed with a non-compliant balloon, the minimal luminal diameter was found to further improve significantly changing from 2.28 ±.42mm following stent delivery to 3.39 ±.48mm during high pressure inflation (Swiss Kiss) to a final angiographic result of 2.68 ±.34mm ($p < .05$).

Uniformity of stent inflation. Although the inflated primary angioplasty balloons and intrastent deployment balloons were filmed at peak pressure when waisting of the balloons were felt to have disappeared by the operator, marked differences were observed between the minimal diameter and the mean diameter and large standard deviations of the diameter of the maximally inflated balloons and stents were observed (**figure 3**). The minimal diameter of the primary angioplasty balloon during peak inflation pressure was .29 ±.23mm smaller than the mean diameter of the inflated balloon and the standard deviation of the diameter of the inflated balloon was .17 ±.11mm (**table 2**). During peak inflation of the pre-mounted intrastent deployment balloon, the minimal diameter of the inflated stent was .37 ±.20mm smaller than the mean diameter of the inflated stent and the standard deviation of the diameter of the inflated stent was .19 ±.07mmm. In those patients in whom an additional inflation of a non-compliant intrastent balloon was performed the minimal diameter of the inflated stent at peak pressure was .20 ±.06mm smaller than the mean diameter of the inflated stent and the standard deviation of the diameter of the inflated stent was .13 ±.03mmm

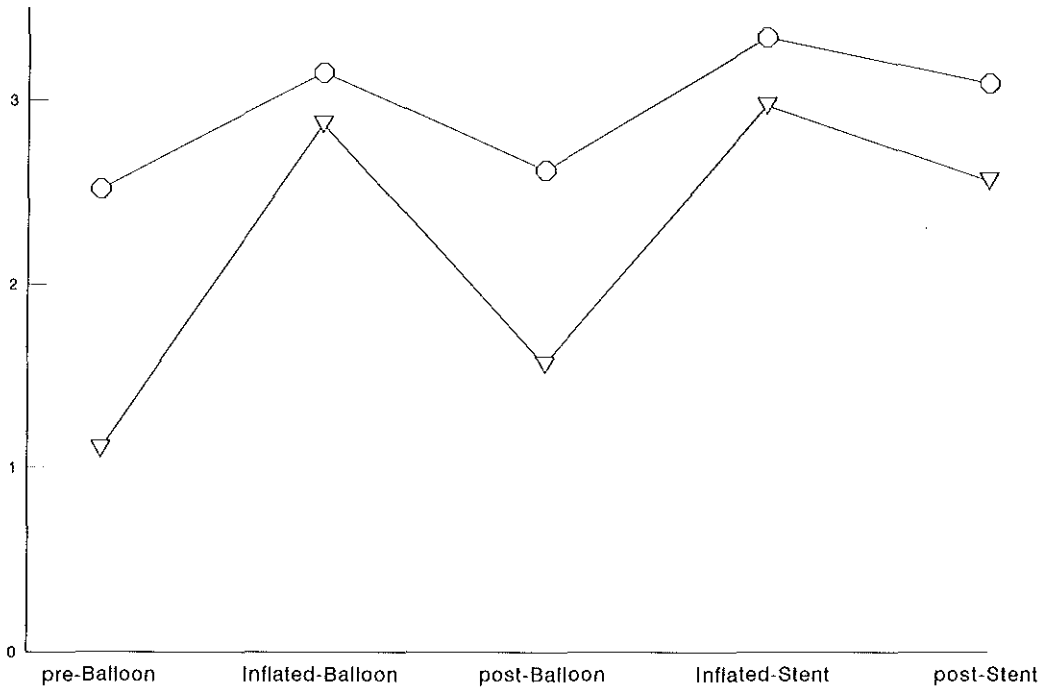


Figure 3. Serial intraprocedural changes in minimal and mean luminal diameter measurements for all patients studied. The minimal luminal diameter of the treated lesion can be seen to decrease (recoil) following deflation of the primary angioplasty balloon and following deflation of the stent deployment balloon.

Table 2

Results of quantitative angiographic analysis at each of five intraprocedural phases

	Pre-balloon	Balloon inflation	Post-balloon	Stent inflation	Post-stent
Min Lum Diam (MLD)	1.10 ±.53mm	2.87 ±.51mm	1.56 ±.77mm	2.97 ±.42mm	2.56 ±.39mm
Mean Lum Diam (MeanLD)	2.52 ±.46mm	3.15 ±.46mm	2.62 ±.57mm	3.34 ±.37mm	3.09 ±.37mm
MeanLD-MinLD	1.35 ±.51mm	0.29 ±.23mm	1.00 ±.35mm	0.37 ±.20mm	0.53 ±.17mm
Standard Dev of Lum Diam (SDD)	0.65 ±.16mm	0.17 ±.11mm	0.59 ±.22mm	0.19 ±.07mm	0.34 ±.11mm
Interpolated Ref Vessel Diam (IVD)	3.04 ±.52mm		3.05 ±.63mm		3.28 ±.36mm
% Diam Stenosis (%DS)	62% ±15%		49% ±22%		22% ±8%

Following stent deployment acute recoil of the minimal luminal diameter of the stented segment was 15.7% ±11.6%, which was significantly larger than recoil of the mean luminal diameter of the stented segment, 8.9 ±9.3% (p<.001). The interpolated reference vessel diameter (IVD) [14] was seen to increase following stent deployment. With an interventional policy of stent oversizing, neither the mean nor the minimal luminal diameter reached the nominal size of the stents deployed (3.64 ±.45mm).

Stent recoil of the minimal and mean diameter. Diameter measurements of the intrastent deployment balloon during peak inflation pressure were compared with the diameter measurements of the resulting stented lumen after removal of the deployment balloon. Recoil of the minimal luminal diameter was significantly greater than recoil of the mean luminal diameter of the stented segment. Recoil post stenting of the minimal luminal diameter was 15.7 ±11.6% (0.48 ±.35mm), while elastic recoil post stenting of the mean diameter was 8.9 ±9.3% (0.30 ±.33mm) (p < .001). In those patients in whom an additional inflation of a non-compliant intrastent balloon was performed recoil of the minimal luminal diameter was 20.6 ±6.3% (0.71 ±.27mm) and recoil of the mean diameter was 11.65 ±8.0% (0.44 ±.33mm) (p < .001).

DISCUSSION :

The key findings of our study are ; firstly, that despite a policy of oversizing by 0.61 ±.61mm of the Gianturco-Roubin stent, a final residual diameter stenosis of 22 ±8% was found to persist; secondly, that elastic recoil post deployment of the Gianturco-Roubin stent is significant and inhomogeneously distributed and will vary considerably in value according to whether recoil of the minimal diameter or mean diameter is considered; and thirdly, quantitative angiographic analysis of the lumen diameter throughout the stented segment indicates that the longitudinal scaffolding of the vessel wall may not be uniform over the length of the Gianturco-Roubin coil stent.

Stent sizing. We have demonstrated that when the Gianturco-Roubin stent is deployed in-vivo, the stent rarely achieves its nominal diameter (as determined by the manufacturer's in-vitro testing). Even when an additional post-deployment high pressure intrastent inflation of a non-compliant balloon is performed, neither the minimal nor the mean diameter of the stented segment reaches the nominal diameter of the stent. Potential contributing factors to these findings might include a) an additional high pressure intrastent inflation of a non-compliant balloon was only performed latterly in eight of our patients when the angiographic result was deemed by the operator to be suboptimal rather than being routinely performed in all patients, b) use of the pre-mounted highly compliant polyethylene delivery balloon to deploy the stent, which by protruding through the 1mm interstrut intervals may not exert an adequate and uniform expansile force directly on the stainless steel coils, c) inability of this coil stent when deployed as a single unit (i.e. without telescoping or overlapping multiple stents) to eliminate recoil throughout the stented segment, d) a policy of selecting a stent of greater nominal diameter than the size of the target vessel will make it more difficult to fully expand the stent to reach its nominal diameter than if a stent of equal size to the vessel diameter is selected, and e) a systematic tendency of QCA measurements to underestimate large lumen diameters has been recently recognised [18,19], although this would primarily limit the reliability of the absolute values of measurement more than limit the reliability of relative measurements of changes in luminal diameter throughout the procedural phases.

Quantitative angiographic analysis of coronary stenting. The QCA system employed in our study provides an interpolated reference diameter measurement [14] rather than a less reproducible and less objective manual selection of a proximal or distal diameter point by the QCA analyst. It can be seen from **Table 2**, that while the reference vessel diameter did not change from 3.04 ±.52mm pre-intervention to post primary balloon angioplasty (3.05 ±.63mm), the reference vessel diameter did increase significantly after stent deployment to 3.28 ±.36mm ($p < .05$). This increase in vessel size post stenting may result from improved flow and dilatation of the segment distal to the stent, or may relate to the contribution of maximally dilated intrastent subsegments to the assimilation of the interpolated reference vessel diameter. As a result of the increase in interpolated vessel diameter post stenting, the reported final residual diameter stenosis is 22%, rather than a residual diameter stenosis of 16% if the pre-intervention vessel size was considered. Of interest in the BENESTENT trial [20], where the same QCA system was used to measure luminal diameters, the reference vessel increased significantly from 2.99 ±.45mm pre-intervention to 3.16 ±.43mm post implantation of a Palmaz-Schatz stent, as a result of which the post stent residual diameter stenosis was reported as 22% rather than a value of 17% if the pre-intervention vessel size was considered. In contrast, however, in the STRESS trial [21] where vessel size was taken as an average of manually selected proximal and distal diameter points, vessel size was reported as not to have increased from pre-intervention (3.03 ±.42mm) to post Palmaz-Schatz stent deployment (3.05 ±.40mm) with a reported residual diameter stenosis of 19%. Thus for the evaluation of an

interventional device which results in an increase in the interpolated reference vessel diameter, assessment of acute angiographic outcome should not be limited to the residual % diameter stenosis, but also consider the absolute improvement in minimal luminal diameter. Furthermore, guidance of stenting procedures by visual assessment rather than the performance of on-line QCA may fail to appreciate the absolute gain in luminal diameter in addition to failing to appreciate non-uniform and inadequate balloon inflation and subsequent stent expansion [16].

Previous studies. Our findings are consistent with those recently reported by the group at the University of Alabama at Birmingham in a study of sizing of the Gianturco-Roubin stent [22] and lend support to their recommendation of a change in interventional practice from matching the stent size to the vessel size to a policy of stent oversizing. While, they recommended a stent oversizing by 0.0 to 0.4mm [22], we feel that when the Gianturco-Roubin is deployed as a single unit without overlapping multiple stents, oversizing by ≥0.5mm may be required to improve the final angiographic outcome. While the highly compliant pre-mounted polyethylene balloon provides the unsheathed Gianturco-Roubin stent with a more firm grip on the delivery system and thereby reduces the risk of premature stent dislodgement, the subsequent performance of a high pressure intrastent inflation of a non-compliant balloon may be required to obtain an optimal result. Given that the nominal diameter of the pre-mounted polyethylene balloon is 0.5mm greater than the nominal size of the Gianturco-Roubin stent, it is important that when adopting a policy of stent oversizing that initial delivery inflation pressures with this balloon should not exceed the recommended delivery inflation pressure of 4-6 atm.'s in order to avoid the risk of distal dissection by the unrestricted expansion of the compliant balloon beyond the distal limits of the stent [23,24].

Following the adoption of the current strategy of routine additional high pressure intrastent inflations of a non-compliant balloon, the primary function of the pre-mounted compliant balloon is now more limited to safely deliver and position the stent in the target lesion, rather than to optimize stent deployment and it could therefore now be proposed that the balloon diameters achieved during the initial inflation of the pre-mounted compliant balloon should not be used by the operator to estimate the final angiographic potential of the stent. Furthermore, if a 3.5mm Gianturco-Roubin stent is placed in 3.0mm vessel then a non-compliant balloon of 3.5mm should be used for high pressure inflations. Further studies will be required to determine the effect of oversizing by ≥0.5mm on restenosis over six months [23 -25]. It is likely that the degree of oversizing of different stents should be related to the distribution of radial force exerted by each individual stent design and that a general guideline for sizing of all stent designs would be inappropriate.

Elastic recoil. A difference of .37mm between the minimal diameter and the mean diameter of the inflated intrastent balloon and a difference of .56mm between the minimal luminal diameter and the mean luminal diameter post stent deployment was observed [12,13]. Explanations for the variability in stretch and recoil throughout the stented lesion may include that atherosclerotic lesions in native coronary arteries may have a non-uniform distribution of elastic and non-distensible tissue and secondly that the design of the Gianturco-Roubin stent may be inherently predisposed to the protrusion through its 1mm interstrut spacing of the compliant polyethylene balloon during inflation and subsequent encroachment of the vessel wall into the lumen after stent deployment. Determination of elastic recoil by assessment of the mean diameter of the stented segment alone will underestimate the residual functional significance of recoil which is primarily determined by recoil of the minimal luminal diameter. This finding is of relevance for the guidance of stent deployment by on-line QCA in clinical practice as well as for the design of future studies on the acute angiographic outcome following stent deployment.

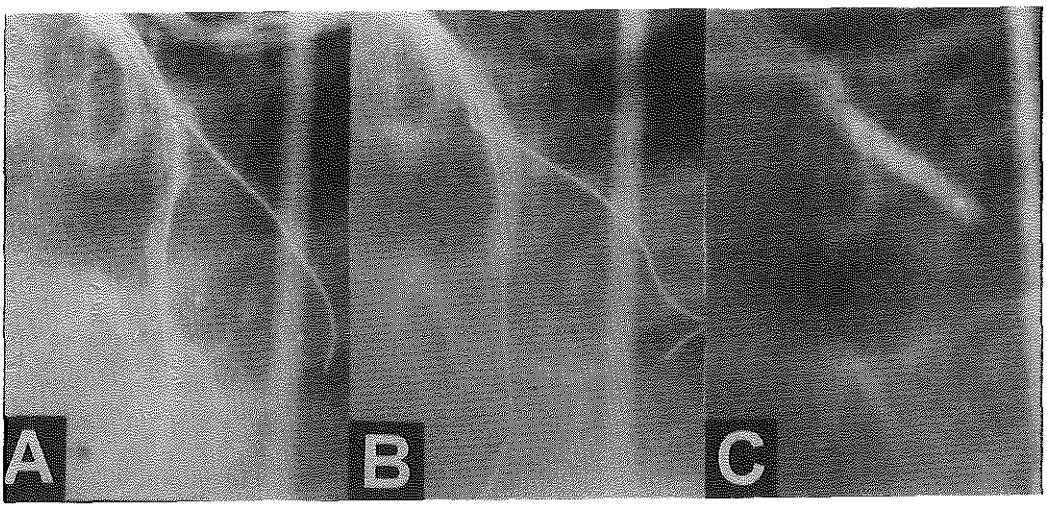
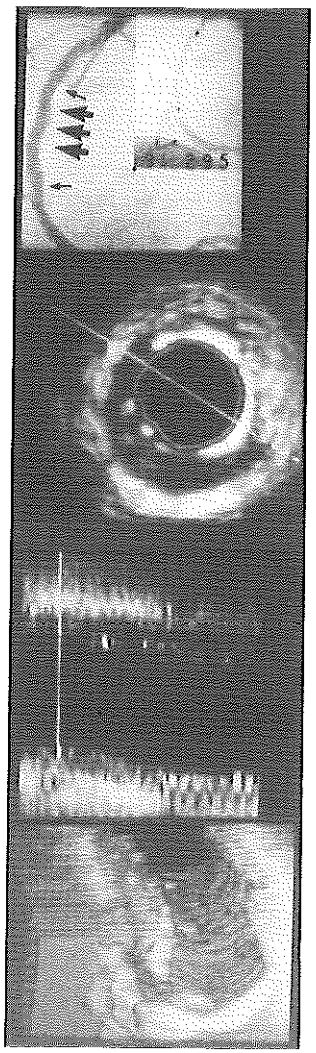


Figure 4a-c. *The large interstrut distance of 1mm of the Gianturco-Roubin stent allows the performance of interventional procedures in a sidebranch of the stented coronary segment through the strut intervals. Fig 4a; an occlusive dissection in the bifurcation of the left anterior descending (LAD) and diagonal (D1) arteries occurred following primary balloon angioplasty. Fig 4b; a 20mm Gainturco-Roubin stent is placed in the LAD covering the segments proximal and distal to the diagonal artery. Fig 4c; the second guidewire in the diagonal artery is withdrawn and then readvanced inside the Gianturco-Roubin stent and through the strut intervals back into the diagonal artery. An AVE Micro stent is then advanced over the guidewire through the strut intervals into the diagonal artery where it is successfully deployed. Such a procedure would not be possible through a stent without large interstrut intervals.*

In a previous study from our group of acute recoil following implantation of the Wiktor stent (a crenulated tantalum coil stent) in restenotic lesions in native coronary arteries following previously successful balloon angioplasty using the same automated edge-detection QCA system, recoil of the mean diameter was found to be 8.2% (0.25 ±.32mm), while recoil of the minimal luminal diameter was not reported [26]. In a study by Haude et al. on acute recoil following implantation of the Palmaz-Schatz stent in restenotic lesions in native coronary arteries, a manual (eye-hand) edge detection methodology was used and recoil was defined as the difference between the maximal balloon size assuming uniformity along the entire length of the inflated balloon and the subsequent residual minimal lumen diameter [27]. With this methodology recoil following implantation of the Palmaz-Schatz stent was reported to be 3.5% (0.10 ±.07mm) [27]. In a different study by Schömig et al of patients treated by implantation of the Palmaz-Schatz for the management of dissection complicating balloon angioplasty, elastic recoil was defined as the difference between the maximally inflated intrastent balloon diameter and the resulting final minimal lumen diameter, however, it was not stated as to whether the mean or minimal intrastent balloon diameter was analysed [28]. In this latter report, elastic recoil following Palmaz-Schatz implantation was found to be 16% (.51 ±34mm) [28]. The discrepancy (3.5% versus 16%) between the two reports [27,28] of elastic recoil following implantation of the Palmaz-Schatz stent, highlight the importance of defining whether the minimal or the mean diameter of the intrastent balloon is taken for determination of recoil and that uniformity of balloon inflation should not be assumed [12,13]. Until a standardized quantitative angiographic analytical approach is adopted by independent studies attempting to examine recoil post stenting, direct comparisons of the compliance of different stent designs in vivo cannot be drawn. Furthermore, direct interstent comparisons should await the execution of stent studies in equivalent patient population groups (e.g. in patients undergoing elective stent placement for restenosis or patients undergoing bailout stenting of dissected primary stenoses).

Stent design. While our quantitative angiographic analysis of the Gianturco-Roubin stent would indicate that the lumen of the stented segment may not be uniformly expanded, it should be acknowledged that the acute and long-term clinical results associated with implantation of the Gianturco-Roubin coronary stent have been extensively reported particularly in the bailout management of acute and threatened closure following balloon angioplasty and have been found to be at least comparable to those of other stents [5,6,10,9,29-32]. The reported favorable clinical results may in part result from some of the positive aspects of the structural design of the Gianturco-Roubin stent. Potential advantages of the large 1mm intervals between the parallel struts of the Gianturco-Roubin stent include the following: Firstly, the metallic (and thus the thrombogenic) surface area of the stent is thereby reduced (10% surface area in the expanded state). Secondly, the large interstrut intervals allows the stent following optimal deployment to be embedded more deeply into the the intimal layer of the vessel wall thereby further reducing the metallic surface area exposed to the lumen [6]. Thirdly, the free proximal and distal terminals of the stent are felt to embed into the vessel wall which may provide the stent with longitudinal grip and stability to prevent recoil caused by spiralling of the coil stent and to prevent migration of the stent during or after deployment. Fourthly, the larger interstrut distances reduce the amount of "jailing" of side branches, whereby the ostia of side branches remain unobstructed with minimal risk of occluding side branches and rendering it possible to perform an interventional procedure in a side branch through the strut intervals (see **figure 4**). Fifthly, the longitudinal flexibility of the stent is enhanced. Sixthly the parallel transverse orientation of the non-crenulated struts results in the Gianturco-Roubin stent being the only stent which does not shorten longitudinally upon radial expansion. Seventhly the parallel strut orientation offers a transverse mechanical advantage over oblique and axially orientated strut designs for the resistance of radial compression.

Figure 5.



Top panel : Coronary angiogram of a right coronary artery in which a Gianturco-Roubin stent (arrows) was placed for the management of a long dissection. The radiopaque markers (inset image) of the premounted stent-delivery balloon are located 1-2mm beyond the limits of the stent.

Second panel from top : Intracoronary ultrasound cross-sectional image within the stented coronary segment revealing a soft plaque of low echogenicity between 4 - 11 o'clock and a highly echogenic strut of the coil stent which is seen to be symmetrically deployed and in apposition to the vessel wall throughout the visualised transverse arc.

Third panel from top : A longitudinal reconstruction of the sequential intracoronary ultrasound data sets which were acquired using an automated pull-back device showing a widely patent lumen and well deployed stent

Bottom panel : A blood-speckle identification program (Echovision, CVIS, Sunnyvale, CA, USA) which distinguishes between the varying backscatter pattern of flowing blood cells in the vessel lumen and the more stable pattern of the vessel wall, has been used for three-dimensionsal reconstruction of the ICUS data sets which are displayed here in a "clam-shell" view [34]. In order to obtain a three-dimensional image the voxels (image volumetric elements) identified as part of the blood pool by the automated detection are removed. Note the slight artefact in the proximal left side behind the stent where part of the low echogenic plaque has been misinterpreted as part of the blood pool.

Study Limitations. A prospective policy of inflation of a non-compliant balloon following delivery of the Gianturco-Roubin stent in all patients might have produced additional improvement in the acute angiographic results in our patients. We have now adopted this policy for stents of all design. While we use on-line QCA for guidance of all stent procedures, intracoronary ultrasound guidance of stent deployment was only performed in a minority of our patients undergoing Gianturco-Roubin stent deployment (see **figure 5**). The additional and independent value of intracoronary ultrasound for the guidance of stent deployment has, however, yet to be firmly established as most studies reporting the value of intracoronary ultrasound have not used on-line QCA to first optimize the angiographic result prior to ultrasonic evaluation [33,34,35]. It is likely that intracoronary ultrasound may be of greater value for the deployment of poorly radiopaque stents such as the Gianturco-Roubin stent compared to radiopaque stents such has the AVE Micro stent, where expansion of the individual struts can clearly be seen in orthogonal radiographic projections. The imminent introduction of on-line ECG-gated three-dimensional reconstruction [36] of intracoronary ultrasound images may present a significant advance in the acute evaluation of stent deployment and of the mechanical behaviour in-vivo of different stent designs.

CONCLUSIONS :

Detailed quantitative angiographic analysis reveals that inflation and recoil of the Gianturco-Roubin stent are not uniform which may relate to the large interstrut distance and use of a highly compliant pre-mounted balloon. Even with a policy of oversizing (stent size 0.61 ±.61mm > vessel diameter), a residual diameter stenosis of 22% may persist when the Gianturco-Roubin stent is used as single unit without overlapping of multiple stents. Following delivery of the Gianturco-Roubin stent on the pre-mounted balloon to the target stenosis, performance of a high pressure intrastent inflation with a non-compliant balloon may improve the angiographic result. This study supports the recent change in interventional practice from matching the size of the Gianturco-Roubin stent to the vessel diameter to the new policy of stent oversizing, and the performance of post delivery high pressure intrastent inflations with a non-compliant balloon under the guidance of on-line QCA.

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Chapter XII

GRACE - Gianturco Roubin stent in Acute Closure Evaluation: Substrate, challenges, and design of a randomized trial of bailout therapy.

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GRACE—Gianturco-Roubin Stent Acute Closure Evaluation: Substrate, Challenges, and Design of a Randomized Trial of Bailout Management

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The Substrate—Abrupt and Threatened Vessel Closure

Coronary interventional techniques carry a significant risk of abrupt vessel closure either during or soon after the procedure. Abrupt closure can be defined as a sudden obstruction in a coronary artery resulting in either a complete or critical reduction in blood flow.[1,2] Typically acute closure is accompanied by chest pain and or electrocardiographical evidence of myocardial ischemia. Although most reported series of abrupt vessel closure have been devoted to those complicating the most common percutaneous transluminal coronary technique, namely balloon angioplasty,[1–10] abrupt vessel closure may result from all coronary interventional techniques[11–18]—even though many of the newer devices may have been partly designed to improve the procedural success rates for coronary lesions with high risk features.[19]

The timing of periprocedural coronary artery occlusion following balloon angioplasty varies among reports. In the NHLBI report of the experience at 15 centers from the period of 1985–1986, 72% of occlusions occurred inside and 28% occurred outside the catheterization laboratory.[2] In a series of abrupt vessel closure in 109 patients, Lincoff et al.[7] reported a median time from first balloon inflation to vessel closure of 27 minutes with a range of 0 minutes to 5 days.

The determination of the true incidence of acute occlusion has been hampered not only by the use of different criteria to define acute occlusion, but also in the selection of the study population in which the incidence was reported. The principle reports have excluded either none, some, or all of the following patient groups: acute myocardial infarction; out-of-laboratory events; unsuccessful balloon angioplasty; and balloon angioplasty in saphenous vein grafts. Consequently, the reported acute closure rates have varied from 2% in a study adopting all of the above exclusion criteria[6] to 8.3% in a study with none of the above exclusion criteria.[7] Of eight series with different exclusion criteria, each involving > 1,000 patients, reflecting an accumulative experience from 1979–1991,[1–3,6–10] the weighted and crude averages of their reported incidence of abrupt closure following balloon angioplasty were both 5.3%. Nonetheless, these data often do not include cases where vessel closure is either silent or accompanied by mild or atypical symptoms. Nor do they necessarily include patients who die, show ECG or enzyme evidence of myocardial infarction, or for a variety of reasons are referred for coronary artery bypass surgery. Accordingly, abrupt closure after balloon angioplasty has probably been underestimated in most previous studies.

The clinical consequences of abrupt vessel closure are significant. The NHLBI Registry reported that 20% of all deaths, 40% of myocardial infarctions, and 25% of coronary artery bypass operations recorded at

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1 year follow-up occurred in the 6.8% of patients who had periprocedural coronary occlusion.[7,20]

Mechanism of Abrupt Vessel Closure

Once arterial spasm has been excluded by the intracoronary administration of nitroglycerine, abrupt vessel closure is found to be predominantly caused by either dissection, thrombus, or a combination of both. Although contrast angiography has detected intraluminal thrombus in up to 44% of patients with coronary occlusion, often superimposed upon medial dissection,[7,8,19,21] angiography appears to be a suboptimal imaging modality for the study of the mechanism of acute vessel occlusion.[19,22] In an angiographic study of 109 patients with abrupt vessel closure, Lincoff et al,[7] diagnosed dissection in 28% of patients, thrombus in 20% of patients, an additional combination of thrombus and dissection in 7% of patients, and were unable to determine the mechanism of acute closure in 45% of patients.

The sensitivity of the above contrast angiographic studies (particularly with respect to thrombus recognition) would appear to be low in the light of recent studies using intravascular imaging modalities. In an angioscopic study by Jain et al,[23] of ten patients with an acute occlusion following balloon angioplasty, intravascular thrombi were observed at the site of the acute occlusion in nine of the ten patients and were occlusive in two patients; fragmented plaque and tissue flaps secondary to dissection of the arterial wall was seen in all ten patients and were occlusive in eight patients; seven of the occlusive dissections were associated with nonocclusive mural thrombi, and the two occlusive thrombi were associated with superficial (nonocclusive) dissections; only one patient had evidence of an occlusive dissection without thrombus present.[23] Thus, although the primary cause of acute closure was most often an occlusive dissection, nonocclusive intracoronary thrombi were associated with these dissections in all but one of ten cases.[23] It is likely that the mechanism of acute occlusion during and following the use of the newer interventional devices differs from that of balloon angioplasty (e.g., following stent implantation, spasm and dissection appear less frequently than acute and subacute thrombus formation).

These angioscopic findings throw into question the principle that thrombus presents a relative/absolute contraindication to stenting. Indeed many issues concerning the interaction between intracoronary thrombus (which has been previously underestimated by contrast angiography) and coronary stents have yet to be addressed. Is angioscopically detected thrombus different from angiographically detectable thrombus—is it purely a matter of volume? Should intracoronary thrombolytic therapy be routinely administered prior to, following, or instead of coronary stent implantation? What precisely happens to thrombus when compressed by a balloon or stent? Is such compressed (? dispelled) thrombus less likely to propagate within a stent than uncompressed thrombus by reduction in surface area of the thrombus? It seems likely that the higher rate of thrombotic occlusion seen after bailout stenting compared to elective stenting of primary lesions, relates at least in part to the higher preexisting burden of thrombus in threatened and acute occlusions. The extent of vessel wall damage and release of "tissue factors" responsible for platelet activation and thrombus formation almost certainly also play a role.

Little is known of the incidence of medial hematoma in the absence of dissection and while intravascular ultrasound may be our only tool for diagnosing nondissected hemorrhage in the media, we will remain unable to determine the true incidence of such a diagnosis in total occlusions until the advent of forward scanning intravascular ultrasound technology. Perhaps this mechanism in addition to acute recoil may contribute to those lesions that are currently referred to as a suboptimal result.

Therapeutic Strategies for Abrupt Vessel Closure

Although the reported therapeutic strategies for acute occlusion include standard balloon,[24–25] perfusion balloon,[26–29] and laser balloon angioplasty,[30] intracoronary stenting,[31] directional coronary atherectomy,[32] thrombolytic therapy,[33,34] ultrasonic dissolution, catheter reperfusion,[35,36] and intraaortic balloon counterpulsation,[37] currently, the two most frequently practiced approaches are balloon angioplasty and stenting. These latter two management strategies are under comparison in the GRACE trial (Gianturco-Roubin stent Acute Closure Evaluation) (Gianturco-Roubin stent, Cook Inc. Bloomington, IN, USA). The

GRACE trial will address the immediate and long-term efficacy and safety of urgent stent implantation in the setting of failed balloon angioplasty or other interventional devices. The control limb will be randomized to prolonged and/or repeated balloon dilatation with a minimal accumulative postrandomization inflation time of 15 minutes.

It may be tempting to believe that stenting offers a more definitive and, therefore, more effective solution than balloon angioplasty for acute and threatened vessel closure. Before this stance should be adopted universally, however, scientific evidence that can only be provided by a randomized trial is required to confirm whether this preconception is indeed true. It is also critical that we learn to identify which categories of threatened closure are most and least suitable for bailout coronary stenting or prolonged and/or repeated balloon angioplasty. Much of our confidence in stenting has evolved from experience gained in elective stenting. The favorable clinical and angiographic results of coronary stenting (with the Palmaz-Schatz mesh stent [Johnson & Johnson Interventional Systems, Warren, NJ, USA]) obtained in the recent Benestent[38] and STRESS (STent in REStenosis Study)[39] studies apply only to elective stenting of single proximal primary lesions ideally suited to stenting in native coronary vessels of > 3.0-mm diameter in patients with stable angina. The lesions that are most likely to develop abrupt closure following intervention are those lesions that are known to increase the risk of subacute thrombosis following coronary stenting i.e., long lesions, type C lesions containing intracoronary thrombus or dissection[40–42] and thus our confidence in stenting should be checked until we learn of the results of prospective randomized trials using standard definitions of comparative treatment of angiographically unattractive vessels with threatened and total occlusions (e.g., what is the best management strategy for a threatened closure of a complex distal lesion of 15-mm length in a small vessel of 2.5-mm diameter with proximal tortuosity and possible thrombus?).

Our current preconceptions of the results for the bailout management of acute or threatened closure by stenting or prolonged and repeated balloon angioplasty may be distorted by several confounding variables. Results to date have been based on noncomparative observational series that have been plagued by (often retrospective) definitions of threatened vessel closure.[40] In addition, different case selection, end point definitions and stages of device development between previously reported observational series make conclusions difficult. For this reason a prospective randomized trial of bailout management has become necessary in order to make a valid scientific judgement on the optimal bailout strategy. The GRACE inclusion criteria permits a range of vessel closure criteria with individual subanalyses planned for totally occlusive dissections, and, at the opposite end of the spectrum of entry criteria, "the suboptimal result" with > 50% diameter stenosis.

The Gianturco-Roubin stent is a stainless steel coil stent that is premounted on a highly compliant balloon. While its longitudinal flexibility is excellent, the primary limitation of the current prototype is its relatively high profile, which may limit its deployment in distal lesions. Proximally tortuous vessels, especially if calcified, necessitate the exchange of the guiding catheter or guidewire during the bailout procedure. The efficacy of the Gianturco-Roubin stent in the management of acute and threatened vessel closure has been documented in several observational series.[43–46] In one such series reported by Roubin et al.,[43] deployment of the stent was attempted in the bailout management of 115 patients with acute (10% of vessels) or threatened closure at a single center between 1989 and 1991 by operators experienced at stent deployment. Angiographic success (< 50% residual diameter stenosis) was obtained in 93% of vessels. In three patients, it was not possible to track a stent into the lesion on account of diffusely diseased, calcified and/or tortuous proximal segments. In two other vessels, stents had been successfully deployed in the right coronary artery proximally and attempts at deployment of a second stent through the proximal stent failed. In all five cases the nondeployed Gianturco-Roubin stent was removed from the patient. Overall in-hospital mortality was 1.7% and coronary artery bypass surgery was required in 4.2%; Q wave myocardial infarction occurred in 7% and non-Q wave myocardial infarction in 9%. Stent thrombosis occurred in 7.6%. A major hemorrhagic event occurred in 10% of patients; these consisted of four gastrointestinal bleeds, two retroperitoneal hemorrhages, and six local groin hematomas. Additional complications relating to anticoagulation therapy post stenting included pericardial tamponade in one patient (who had also received intracoronary urokinase). Another 13 patients required a transfusion of one or more units. Six percent of patients required vascular surgical repairs, four for expanding pseu-

doaneurysms, and one for failure to control femoral arterial bleeding. Four other patients developed local femoral arterial complications; three pseudoaneurysms and one arteriovenous fistula, none of which required surgical intervention. Thus it can be seen that while coronary stenting may achieve an acceptable immediate angiographic result in a high percentage of patients, the cost in terms of clinical events is significant. These events relate primarily to the delicate balance between the thrombogenicity of the stented vessel and the induced hemorrhagic consequences of anticoagulation.

What can we expect from repeated and/or prolonged balloon dilatation? Most of the large series of abrupt vessel closure treated by balloon angioplasty were reported before the widespread availability of the autoperfusion catheter and the coronary stent. Thus, the effect of technical advances and evolving patient selection should be taken into consideration when comparing noncontemporaneous series of balloon angioplasty with more recent stent series. In a single center experience reported by de Feyter et al.[1] of bailout management of acute vessel closure of 104 patients between 1986 and 1988, repeat redilatation with a standard balloon was attempted in 95 patients. Of these 95 patients, angiographic success was obtained in only 33 patients (3 of whom subsequently reoccluded). The overall mortality for the 104 patients treated in this prestent era was 6% and the myocardial infarction rate (combined non-Q wave and Q wave) was 36%. Clearly these results are less favorable than those reported more recently for bailout stenting. Perhaps the most significant difference in the above two series of bailout management by repeat balloon dilatation reported by de Feyter et al.[1] and by stenting reported by Roubin et al.[43] is the very different inclusion criteria. In the series reporting outcome for repeat balloon dilatation all patients had either a complete (TIMI flow 0) or critical reduction in flow (TIMI flow 1 or 2), while in the series reporting outcome for bailout stenting only 10% had TIMI flow 0 or 1 and only another 16% had TIMI flow 2. This major difference in inclusion criteria again serves to emphasize the scientific invalidity of drawing hard conclusions on the comparative efficacy of two devices on the basis of nonrandomized observational series. Despite the apparent limitations of stenting, the need to pursue carefully performed clinical studies is compelling. In a recent report[44] of the multicenter experience of the Gianturco-Roubin stent, 156 patients with established acute closure (TIMI 0 or I flow) were identified. In this cohort, stenting resulted in a relatively favorable outcome with a 2.69 mortality (7.7% emergency coronary artery bypass surgery and 7.6% incidence of myocardial infarction (3.8% Q wave).

With the advent of the perfusion balloon, results of small series would indicate that the prolongation of the inflation time (to approximately 18 minutes) permitted by the perfusion balloon conveys a therapeutic advantage over the shorter inflation times (approximately 11 minutes) of conventional repeated balloon dilatation.[47] Further prolongation of inflation time of a perfusion balloon to several hours, however, appears to convey no further advantage.[48]

Accepting the above caveats, it might be cautiously expected that those patients in the GRACE trial who are randomized to prolonged and/or repeated balloon inflation would be unlikely to have such a high angiographic success rate compared to those randomized to stenting. However, for those patients who do respond to repeat balloon dilalation without crossing over to stenting, the subsequent clinical event rates are likely to compare very favorably with those patients assigned to stenting.

A key feature of the GRACE trial (possibly of more benefit to the balloon limb) is a minimal period of waiting 15 minutes after obtaining angiographic success by bailout management to ensure that the vessel patency is maintained. In a report by Satler et al.[49] of 1,000 consecutive cases, who underwent repeat angiography 10 minutes after the last balloon inflation of elective balloon angioplasty, partial or total loss of the initial gain was observed in 7% of cases requiring further balloon dilatation. A second period of 10 minutes was allowed before the final angiographic study. In this series, the incidence of abrupt vessel closure after patients left the catheterization laboratory was $< 1\%$, suggesting that repeat dilatation may prevent subsequent abrupt vessel closure in patients with early loss of the initial improvement after balloon angioplasty.

Lessons Learned from Prestudy and the Concept of the Evolving Protocol

One important aspect of the trial design is the inclusion of a prestudy phase of over 200 patients during which investigators must exhibit proficiency at im-

plantation of the Gianturco-Roubin stent. Before commencing the formal GRACE trial, the investigator must have a less than 5% rate of subacute closure or thrombosis and < 10% rate of hemorrhagic complications during the prestudy. Furthermore, investigators should have enough potential patients to meet the minimum cases per institution criterion. This design concept represents a new direction in interventional trials with emphasis on optimal performance by all investigators at the upper plateau of the learning curve.

Significant procedural experience has been gained during the GRACE prestudy at the 21 participating centers. Over 300 stents have been implanted in over 250 patients. While investigators with less previous stent experience were encouraged to begin the prestudy with elective stenting of primary lesions, over two thirds of the stents of the prestudy have been implanted for the nonrandomized bailout management of acute or threatened closure. Thus the procedural experience gained during the prestudy should serve well the randomized phase.

Given the rapid evolution of coronary stenting and the enthusiastic embracement of new developments in this field, the results of any clinical trial of coronary stenting are almost redundant before the completion of the randomization and follow-up. A trial of bailout therapy such as the GRACE trial would be particularly prone to rapid developments in coronary stenting, given that even at centers with a high volume of interventional procedures the incidence of abrupt vessel closure remains low and thus recruitment of 250 patients is likely to require 12 months. To overcome this risk, the GRACE trial has attempted to adopt evolving clinical strategies learned during the conduction of its prestudy. When the first draft of the protocol was written in 1992, anticoagulation poststenting by the administration of intravenous heparin for several days followed by the administration of warfarin for 3 months was practiced almost universally and this standard regimen was, therefore, incorporated in the original study protocol. During the GRACE prestudy, alternative approaches to reduce the incidence of thrombotic occlusion were developed in Europe by investigators participating in GRACE. A survey of the preferred anticoagulation practice of the GRACE participants revealed that some of the centers no longer prescribed warfarin routinely post elective or bailout stenting. The use of ticlopidine had been adopted in many of the French centers as an alternative to warfarin[50–52] and the use of intravascular ultrasound to confirm optimal and symmetrical stent expansion was introduced in an Italian center to reduce the incidence of subacute thrombosis.[53] To ensure that the results of the randomized phase of the GRACE trial would have implications for current practice, those investigators who had established these alternative anticoagulation strategies in their routine practice were permitted to do so in the trial by a revision of the GRACE protocol.

The issues of stent sizing and postdeployment dilatation have also continued to evolve. During the writing of the original GRACE protocol in 1992, most investigators matched the nominal (labelled) stent size to the vessel size (i.e., to the diameter of the "normal" proximal and distal segments) and postdeployment dilatation with another balloon was not routinely performed. Quantitative coronary angiographic studies at the University of Alabama and at the Thoraxcenter of patients in the prestudy of GRACE[54] revealed a significant degree of under expansion that follows low pressure deployment of the Gianturco-Roubin coil stent by the premounted highly compliant polyethylene balloon. As a result, the GRACE protocol on stent sizing was revised to advise a policy of stent oversizing (by 0.5-mm) and when necessary to perform further dilatations with a noncompliant balloon or to implant additional Gianturco-Roubin stents to increase the total radial force. Preliminary quantitative coronary angiographic analysis of the baseline data of those patients that have recently entered the randomized phase of GRACE has confirmed that the policy of stent oversizing has indeed been adopted.

Conclusion

The need for a multicenter randomized trial to study the clinical success of stenting versus prolonged and/or repeated balloon inflation for the treatment of acute closure is apparent. The rapid developments in the clinical practice of stenting have presented exciting challenges for the design and execution of such a trial. The experiences from a prestudy and a flexibility of the protocol to accommodate evolving strategies of stent practice, should ensure that the results of the randomized phase of GRACE will have clinical relevance for the practice of coronary stenting by operators who are advanced along the plateau of the procedural learning curve.

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Chapter XIII

The Bailout Stent.

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The Bailout Stent

Is a Friend in Need Always a Friend Indeed?

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When invited to write an editorial on bailout stenting, many titles came to mind—"The Double-Edged Sword," "Friend or Foe," and "Jekyll and Hyde"—to convey the current balance of the efficacy and the risk associated with bailout stent therapy. Rather than consolidating the role of stenting in the emergency management of abrupt or threatened occlusion following coronary interventional procedures, the observational study reported by Hearn and colleagues in this issue of *Circulation*[1] raises further questions over the benefit-to-risk ratio of bailout stenting.

See p 2086

Abrupt vessel closure occurs during coronary balloon angioplasty in 5.6% of patients, whereas an additional 1.7% of patients develop an occlusion during the following 24-hour period.[2] The mechanisms of abrupt coronary occlusion include a combination of dissection, subintimal hemorrhage, thrombus formation, vasoconstriction, and elastic recoil.[3] When acute coronary occlusion persists, it leads to myocardial infarction in about 40% of cases and death in about 4%.

In the early experience of balloon angioplasty, abrupt occlusion was managed by emergency coronary artery bypass surgery. In contrast to elective surgery, however, emergency surgery was found to convey a high morbidity and mortality risk. As experience with balloon angioplasty grew, the practice of immediate redilatation was developed. While prolonged balloon inflation with or without a perfusion balloon or laser balloon angioplasty offered an alternative to emergency surgical management, they rarely achieved definitive success. Thrombolytic therapy (either intravenous or intracoronary) has been anecdotally successful. However, the overall experience has been disappointing. Moreover, if the patient proceeds to emergency surgery, prior thrombolytic therapy may complicate the operation. Despite these strategies, abrupt closure after coronary intervention continues to result in unacceptable morbidity and mortality. With such room for improvement, stenting with its scaffolding properties opened a new avenue, and while initially viewed by some as a bridge to surgery, it is now heralded by many as the path to avoid surgery.

The opinions expressed in this editorial comment are not necessarily those of the editors or of the American Heart Association.

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The Paradox

Considerable overlap exists between the lesional characteristics predisposing to abrupt closure following coronary interventional procedures and the relative contraindications to elective stenting (and thus it could be thought that the bailout stent gives coronary stenting a bad reputation): Univariate and multivariate analyses of qualitative and quantitative criteria have shown that severe, long, complex lesions, at a branch or bend point, of ACC/AHA type B, C, containing intracoronary thrombus or dissection and unstable angina lead to an increased likelihood of acute closure following balloon angioplasty. While factors found to predict subacute thrombosis after stent implantation have included bailout indication (odds ratio, 5.4), lesion length, type C lesion, stent size <3.25 mm, residual thrombus, and unstable angina.[4,5]

Unfortunately, in the setting of an abrupt vessel closure attended by acute ischemic consequences, an operator is unable to electively select only those vessels and lesion characteristics that are ideally suited to stent implantation. Thus, vessels containing characteristics that might normally be regarded as relative contraindications to stenting frequently impose themselves on the interventionist who is left with a choice of either stenting under unfavorable conditions or adopting an alternative, less-effective strategy known to carry a higher risk. Stenting in bailout management could be considered the best of a bad lot. In large vessels, subtending a substantial amount of myocardium, which develop a totally occlusive dissection, the case for bailout stenting appears clear (white), whereas for small vessels <2 mm developing a subocclusive thrombosis following intervention, the preference for stenting over alternative nonsurgical strategies is weak (black). Unfortunately, like many aspects of medicine, most cases fall into a "gray" intermediate category.

Empty Threats?

Studies of emergency therapy are inherently confounded by terminology and the quality of data acquisition. In the case of bailout stenting, although the term "acute closure" of a vessel appears steadfast and clear, the term "threatened closure" appears soft and open to interpretation by the operator. Indeed, a threatened event such as an "impending myocardial infarction" is a diagnosis that in reality can only be confirmed after the event if intervention is withheld. In the observational study reported by Hearn et al, the definition of threatened occlusion included either static or dynamic elements.[1] A static component such as a large dissection

will remain subjective, whereas the incorporation of an evolving process such as a recorded decrease in luminal diameter or change in TIMI grade flow over time offers a more rigorous approach. In most reports on bailout stenting, outcome for threatened occlusion has been grouped to include a wide spectrum of angiographic, ECG, or clinical criteria, thus rendering the results difficult to interpret and limiting their direct applicability to clinical practice.

The Learning Curve and the Legacy

The historical series of bailout coronary stenting reported by Hearn et al[1] reflects the early experience of coronary stenting. Between September 1987 and December 1990, Gianturco Roubin stents were implanted in 103 patients. In view of the approximately 3- to 6-year time span from stent implantation to publication of the results, the report is to some extent of limited relevance to the current practice of coronary stenting. The design of the pioneering series necessitated the referral to bypass surgery of all nine patients in the first phase of the study and an additional nine patients in phase II in whom potential closure would have incurred a significant risk of mortality. Their rate of emergency coronary artery bypass surgery for ongoing ischemia after stent implantation was 11 of 98 patients (11%) in whom stenting was attempted and in whom surgery was not mandated by the study protocol. Their rates of in-hospital q wave myocardial infarction and mortality after stenting were 4.9% and 4.0%, respectively. It is not possible to decipher whether their results with bailout stenting improved over the 3-year study period as the sequential breakdown of their results is presented in only two phases, with the first phase containing only the first nine patients as above.

In a second single-center observational series of bailout therapy with Gianturco Roubin stents in 115 patients between October 1989 and June 1991 involving an operator previously experienced with Gianturco Roubin stent implantation, the in-hospital rates for emergency bypass surgery, q-wave myocardial infarction, and mortality were 4.2%, 7%, and 1.7%, respectively.[6] A comparable outcome was subsequently reported in a multicenter study of similar design.[7] These results were favorable considering that in a meta-analysis of nine series of bailout stent therapy incorporating an accumulative experience of five different stent prototypes in 464 patients from 1986 through 1991, mean rates of in-hospital emergency bypass surgery, myocardial infarction, and mortality were 8.4%, 10.6%, and 4.1%, respectively.[8]

The Prospects

Clearly, the results of the above bailout studies compare poorly with those reported for elective stenting from the same era. It would also be envisaged that over recent years the outlook for all stenting has improved due to advances in procedural and postprocedural management. Following the observations that subacute thrombosis and restenosis occur more frequently in stents of smaller size and the quantitative angiographic observations that even during maximal stent inflation the nominal manufacturer's size of a stent is rarely achieved and that recoil immediately after stent implantation is the order of 20%,[9] policies have changed from matching stent size in the reference vessel diameter to a policy of choosing a stent of slightly larger nominal size than the reference vessel size to compensate for the above limitations. On the basis of a large databank at the Thoraxcenter of balloon angioplasty procedures, only approximately 20% of the population would be able to receive a stent of more than 3.0 mm under a policy of strict matching for vessel size. In the series reported by Hearn et al[1] a stent size of >3.0 mm was chosen in only 16% of patients which compares with the series of Roubin et al where 17% of stents deployed were >3.0 mm.[6] The stent sizing chosen by Hearn et al may, however, have been influenced by their process of patient selection whereby patients were selected if they had "lesions that, if closed after stent placement, would not result in massive myocardial ischemia or hemodynamic instability." It is noteworthy that the recent Benestent I and STRESS trials on elective stenting excluded vessels of <3.0 mm.

A second change in policy is the criterion of procedural success. In the report of Hearn et al,[1] procedural success was defined as <50% residual diameter stenosis. As with other interventional techniques the current aim in coronary stenting is now changing to achieve a "zero" percent residual diameter stenosis. This latter change in policy is likely to have a major effect in both short- and long-term outcome after coronary stenting particularly in patients receiving a stent of small size.

Accurate implementation of both the new stent-sizing policy and the policy of greater luminal gain (the bigger the better) has recently been made possible by the almost ubiquitous presence of on-line computerized quantitative coronary angiography in the interventional suite.

The advent of intracoronary imaging has further improved procedural management. Intracoronary ultrasound can be used to detect asymmetrical stent expansion or residual dissection behind a stent, whereas angioscopy can provide valuable information on stent deployment with the detection of luminal encroachment at sites of articulation in a mesh stent or protrusion of intima between struts in a coil stent, both of which may be ameliorated by the placement of a second stent or prolonged or high-pressure inflation of a noncompliant balloon within the stent. Furthermore, angioscopy can detect the development of thrombus within a stent that can be treated with intracoronary urokinase or t-PA. As a reflection of its practical value, angioscopy altered management in 18 cases in a recent series of 50 stent implantations (unpublished data from the Scripps Clinic and Research Foundation and the Arizona Heart Institute).

The postprocedural hazard of subacute thrombosis continues to curb enthusiasm for coronary stenting. Once solved, the inherent complications of our current approach to its prevention will be obviated, ie, internal hemorrhage and local femoral arterial complications. While the development of material that is less thrombogenic than stainless steel and tantalum has so far been disappointing, local coating of struts with heparin may offer some hope[10] and will be addressed by the ongoing pilot phase of the Benestent II trial. In the meantime, the optimization of anticoagulant control by the use of the coagulant markers. TAT and F_{1+2} have helped to drastically reduce the incidence of subacute

thrombosis.[5,11] Furthermore, improved mechanisms of achieving local hemostasis by Vasoseal® and collagen plugs in addition to the use of mechanical devices such as Femostop® and clamping devices, have facilitated uninterrupted anticoagulant therapy following stent implantation. Recently, some investigators have opted to not anticoagulate patients receiving large-diameter stents after optimal deployment has been confirmed by intracoronary imaging.[12] However, the safety of this approach has not been determined.

The Selection

All series of bailout stenting have reported a high implantation success rate, which is remarkable taking into account the technical difficulties that may be encountered in a bailout situation. Disappearance of angiographic landmarks and spasm of the vessel segment may render stent delivery and correct positioning difficult. The selection of the diameter, length and type of stent, and selection of the guide wire and guiding catheter may all influence deployment success. In the case of acute takeoff and tortuosity, longitudinal flexibility of the stent is desirable.

Stent selection may also be guided by mural tomographic information provided by intracoronary ultrasound. Lesions characterized by excessive elastic recoil may require a "hard" stent with strong circumferential support such a mesh stent with sturdy metallic struts, whereas lesions that have been extensively disrupted may require only a "soft" stent with a lighter architecture and minimal metallic surface area. The precise effect of lesional characteristics and the role of intracoronary ultrasound in the determination of stent requirements are an area of future research.

'In Doubt—Let's Randomize'

Are randomized trials of bailout coronary stenting ethical? A fractured radius is currently managed by fixation in a plaster of Paris. Yet the need for a randomized controlled trial of fixation of limb fractures has been deemed to be unnecessary. As we feel confident from observational studies that bailout stenting can be effective in the prevention of myocardial infarction and the preemption of emergency bypass surgery, how can randomized trials of bailout stenting be warranted? Until such time as the thrombotic and hemorrhagic sequelae of coronary stenting can be overcome, randomization of patients to the nonstenting limb of a controlled trial seems ethical. The policy proposed by Andreas Gruntzig and echoed by Spencer King—"in doubt—Let's randomize"—still appears reasonable.

The Gianturco Roubin Stent Acute Closure Evaluation (GRACE) trial will address the immediate and long-term efficacy and safety of urgent stent implantation in the setting of failed balloon angioplasty or other interventional device. The control limb will be randomized to prolonged and/or repeated balloon dilatation. One important aspect of the trial design is the inclusion of a prestudy phase on 200 patients during which investigators must exhibit proficiency at implantation of the Gianturco Roubin stent. Before commencing the formal GRACE trial, the investigator must have a less than 5% rate of subacute closure or thrombosis and less than 10% rate of hemorrhagic complications during the prestudy. Furthermore, investigators should have enough potential patients to meet the minimum cases per institution criterion. This design concept represents a new direction in interventional trials in keeping with the upcoming directional atherectomy trials EURO-CARE (<20% residual stenosis required) and OARS and BOAT, with emphasis on optimal performance by all investigators at the upper plateau of the learning curve.

The Showdown

To convincingly evaluate the relative merits and demerits of bailout stenting, large, multicenter randomized trials need to be conducted exclusively by experienced operators at high-volume centers over a short period of time and reported expeditiously to have an impact on current practice.

Acknowledgment

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Chapter XIV

The new AVE Micro coronary stent as a single stent or as a complementary device for multiple stenting.

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ABSTRACT :

Background. The range of short lengths (4 to 16mm), the radiopacity of the stent struts, and the premounted balloon-expandable user-friendly delivery system, render the new AVE Micro stent suitable for either the treatment of short focal dissections as a single device or for the treatment of long complex dissections as a complementary device in combination with longer stents of different design. In particular, the short design of the Micro stent render it ideal for improving the inflow and outflow of longer stents and for bridging the gap between both proximally and distally deployed stents.

Methods. We report our experience with this novel stent as a versatile component of a multiple stent strategy for the treatment of complex coronary dissections. Deployment of 36 AVE micro stents was attempted in 28 coronary lesions in 25 patients who developed acute or threatened closure after balloon angioplasty. Fourteen stents were deployed in the left anterior descending artery, 12 in the circumflex, and 10 in the right coronary artery. Twelve of the 28 lesions were at ostial or bifurcation sites. All patients were managed with intravenous and oral anticoagulant therapy post intervention. Luminal dimensions at the site of the Micro stent deployment were measured using a computer-based quantitative coronary angiography system (CAAS II). The acute angiographic results as well as the thirty day clinical event rate are reported.

Procedural outcome. Stent deployment was successful in 35 of 36 attempts (98%). In one patient the attempted stent deployment was unsuccessful and the patient was managed by emergency coronary artery bypass surgery while in twenty-four patients stent deployment was successful. In five of the twenty-four patients Micro stents were deployed as a single device to treat short dissections while in nineteen patients Micro stents were deployed as part of a multiple stent strategy for long dissections. In four of the nineteen patients who received multiple stents, all of the stents were Micro. In fifteen of the patients the Micro stent was deployed in combination with longer stents of different design. In ten patients Micro stents were advanced through proximally deployed stents and in four patients stents of different design were advanced through proximally deployed Micro stents. In no patient did stents become caught in other stents during stent delivery, however, in one patient following successful delivery of the Micro stent to the target site proximal migration of the stent occurred during the deployment process.

Clinical events. The patient who underwent emergency coronary artery bypass surgery made an otherwise uneventful post-operative recovery. The clinical course of the 24 patients in whom stent deployment was successful was free of coronary re-intervention, bypass surgery and death. A myocardial infarction was observed in 2 patients (8%), in one 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 prior to stent implantation. A femoral haemorrhage and haematuria requiring blood transfusion was observed in one patient (4%). No subacute occlusion was observed. Event-free survival at 30 days following stent implantation was 88% (22 of 25 patients).

Angiographic outcome ; Minimal luminal diameter (MLD) was 0.79 ±0.56mm pre BA, 2.67 ±0.40mm during balloon inflation, 1.21 ±0.62mm post BA, 3.26 ±0.47mm during stenting, 2.70 ±0.48mm post stent, 3.42 ±0.46mm during balloon inflation post stenting (Swiss Kiss), and 2.85 ±0.44mm post Swiss Kiss. Average percent diameter stenosis was reduced from 70% pre BA through 55% post BA to 16% post stenting. During the initial stent implantation, stent recoil was 0.56±0.31mm (17±9% of MLD during stent inflation). A Swiss Kiss was performed in 14 Micro stents with an average pressure of 14±3 atmosphere and residual stenosis was reduced from 2.54mm (20% diameter stenosis) to 2.85mm (15% diameter stenosis) in these lesions. Angiographic success (<30% residual diameter stenosis) was achieved in all stented lesions.

Conclusion. The results of this early experience would indicate that the new AVE micro stent may be deployed as either a stand-alone stent or as complementary device for multiple stenting with a high procedural success rate and a minimal learning curve. Specifically the Micro stent can be successfully passed through other proximal stents which have been optimally deployed. While primary deployment of this new balloon-expandable stent significantly reduced residual diameter stenosis and restored coronary flow after failed BA, performance of additional high-pressure intra-stent balloon inflations (Swiss Kiss) may optimize the angiographic outcome.

INTRODUCTION :

One of the major risks associated with balloon angioplasty (BA) is acute or threatened closure of the coronary artery. When acute coronary occlusion persists following balloon dilatation, 27 to 40% of the patients sustain a myocardial infarction and 4 to 5% of the patients die [1-8]. Several non-randomized studies have suggested that deployment of the Wallstent [9,10], Gianturco-Roubin stent [11-15], or Palmaz-Schatz stent [16,17,18] may be of value in the bailout management [20,21] of acute or threatened closure following BA. Given the spectrum of structural design and metallic composition of currently available stents it cannot be presumed that clinical results obtained with one stent will be necessarily matched by stents of alternative design and each stent will thus have to undergo individual clinical evaluation. 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. This short stent represents a new direction in coronary stent design characterized by a simple balloon expandable deployment technique, 0.008" stainless steel struts with moderate radiopacity, a zig-zag structure, and is composed of 4mm welded and unconnected segments providing a range of lengths from 4 to 16 mm (see **Figure 1**).

This study reports our early experience with the AVE micro stent in the clinical arena. Clinical events up to thirty 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 at the site of the Micro stent deployment were made at 7 intraprocedural phases; pre primary balloon angioplasty, during primary balloon inflation, post balloon angioplasty at the time of acute or threatened vessel closure, during stent inflation, post stent deployment, during high pressure intra-stent balloon inflation (Swiss Kiss), and final post Swiss Kiss, using a quantitative coronary angiographic analysis system (CAAS II).

METHODS :

Patients : To determine the feasibility and safety of deployment of this new stent, we deployed 36 AVE micro stents in 28 native coronary artery lesions in 25 patients who developed acute or threatened closure after balloon angioplasty (BA). Clinical characteristics of the study population are provided in Table 1. Average age was 55 $\pm$7 ranging from 45 to 68 years old and 21 patients were male. Sixteen patients had stable angina and the remaining 9 patients had unstable angina [21]. Of the 9 patients with unstable angina 4 patients had Braunwald type II and 5 had type III [21].

Criteria of acute and threatened vessel closure : Post BA lesion morphology was categorized according to the dissection criteria proposed by Huber et al [22] and coronary flow distal to the lesion was classified according to the TIMI criteria [23]. 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 greater than 50% [22,23].

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

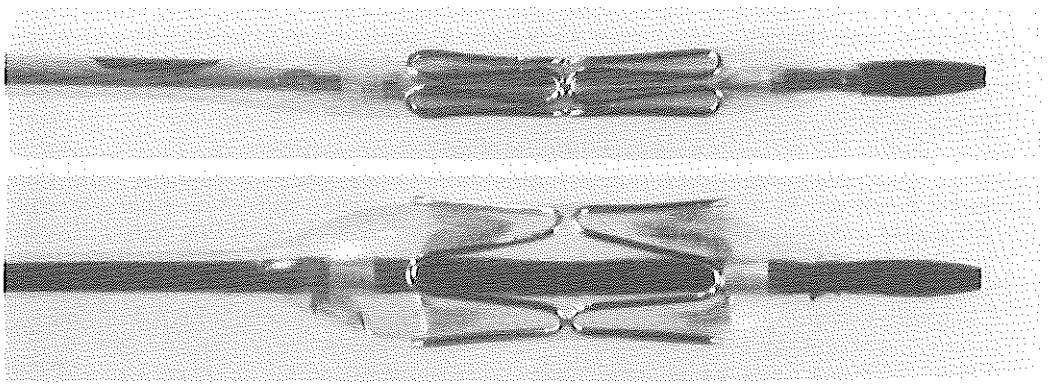

Figure 1. *A 8 mm AVE Micro stent. The AVE micro stent is a pre-mounted balloon-expandable stainless steel stent composed of 4mm welded or unconnected segments.*

Table 1. Clinical characteristics of 25 patients

	Number of Patients (25)
Gender, male	21
Angina pectoris type*	
Stable	16
Unstable	9
Prior MI	10
Prior BA	11
Prior CABG	2
Coronary risk factors;	
Hypercholesterolemia	12
Systemic hypertension	10
Cigarette smoking	9
Diabetes	3

*MI; myocardial infarction, BA; balloon angioplasty, CABG; coronary artery bypass grafts, *Angina pectoris classification [21].*

Balloon Angioplasty and Stent Implantation : Balloon angioplasty and stent deployment were performed according to standard clinical practice by the femoral approach at the Thoraxcenter (Rotterdam, The Netherlands). The coronary stents were delivered on a pre-mounted balloon catheter. The size of the balloon is .25mm 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 36 stents used in 28 lesions, 13 were of 3mm diameter, 19 were 3.5mm and 4 were 4mm in diameter. Of the 36 stents 9 were 4mm in length, 22 were 8mm, 2 were 12mm, and 3 were 16mm in length.

During the primary balloon angioplasty, the nominal balloon diameter was 3.04 ±0.41mm and the maximum inflation pressure given was 9.6 ±3.1 atmospheres. Following initial deployment of the stent high pressure inflations (14.6 ±3.1 atmospheres) to optimise stent expansion (Swiss Kiss) were made with balloons of 3.58 ±0.52mm nominal diameter.

The coronary position of the Micro stent relative to the other multiple stents and the order of deployment of the multiple stents is provided in Table 3.

Anticoagulant therapy : At the beginning of the procedure, patients were given an intravenous bolus dose of 10,000 i.u. of heparin, and subsequently 5,000 i.u. as required to maintain the ACT (activated clotting time) > 300s throughout the procedure. The post intervention anticoagulant regimen was conventional [24] : One hour following removal of the femoral sheath, a heparin intravenous infusion was commenced to maintain the APTT (activated partial thromboplastin time) between 70 to 90s until oral anticoagulant therapy (Coumadin) had achieved a PT INR (prothrombin time international normalised ratio) of 2.5 to 3.5. Coumadin was prescribed for three months post stent implantation and aspirin indefinitely [24].

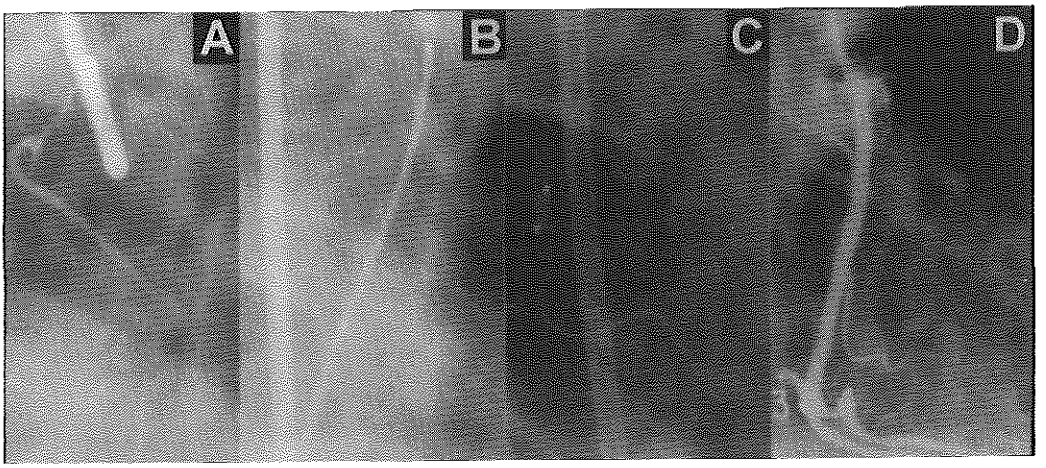

Figure 2. *Reconstruction of a right coronary artery by multiple stenting following successful recannalization of a chronic total occlusion [A]. Following successful advancement of a guidewire through the proximal occlusion, balloon angioplasty was performed throughout the epicardial course of the vessel. Two Wallstents (nominal diameters 6.0 and 5.5 mm, nominal length 45 and 45 mm when maximally expanded) were placed in AHA segments 1 and 2 (proximal and mid right coronary artery) [B]. Two manually crimped Palmaz-Schatz stents (15mm nominal length) were placed in AHA segment 3 (distal right coronary artery) leaving a short unstented gap between the distal end of the Wallstent and the proximal end of the Palmaz-Schatz stent. A single AVE Micro stent (diameter 4.0mm, length 4.0mm) was deployed to bridge the unstented gap using the radiopacity of the short thick struts to aid the precise positioning and to avoid overlap with the other stents [C]. Contrast angiography of the resultant vessel reveals a continuity of vessel calibre throughout the reconstituted artery with an appropriate degree of tapering [D].*

Quantitative coronary angiographic analysis : The new version of the computer-based Coronary Angiography Analysis System (CAAS II)[25,26] was used to perform the quantitative analysis. In the CAAS analysis which has previously been described elsewhere [26-29], the entire cineframe of 18 x 24 mm is digitized at a resolution of 1329 x 1772 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 after the administration of isosorbide dinitrate [30,31] at each stage of the procedure.

Study endpoints and definition : The primary clinical endpoint 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 less than 30% residual diameter stenosis following 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 : Paired Student's t-test was used to compare sequential changes at the same segment in the same patients. A p value of less than 0.05 was considered significant.

RESULTS :

Lesion characteristics : The angiographic characteristics of the treated lesions are given in table 2. Of 28 lesions, 10 lesions were the left anterior descending coronary arteries, 8 were the right coronary arteries and the remaining 10 lesions were the circumflex coronary arteries. Five of the lesions were ostial and seven were at sites of major bifurcation. Pre balloon angioplasty, the lesions were categorized according to the AHA/ACC Task Force criteria [32]. Of the 28 lesions, 3 lesions were type A, 17 were type B, and the remaining 8 lesions were type C. Post primary balloon angioplasty, at the time of acute or threatened vessel closure 3 lesions had a type A dissection (with $>50\%$ diameter stenosis), 1 a type B dissection (with $>50\%$ diameter stenosis), 14 a type C dissection, 1 a type D dissection, 8 a type E dissection and 1 a type F dissection [22]. At this pre-stent phase, TIMI flow [23] was grade 0 in 1 lesion, grade 2 in 9 lesions and grade 3 in 18 lesions and the angiographic appearance of intracoronary thrombus (intraluminal filling defect) was present in 8 lesions [33].

Table 2. Angiographic lesion characteristics of 28 lesions

	Number
Location of lesions	
LAD	10
RCA	8
LCX	10
Portion of artery stented	
ostial or major bifurcation site	12
middle segment	16
Modified AHA/ACC classification*	
type A	3
type B1	6
type B2	11
type C	8
Type of dissection before stent**	
type A	3
type B	1
type C	14
type D	1
type E	8
type F	1
TIMI flow before stent***	
TIMI 0	1
TIMI 1	0
TIMI 2	9
TIMI 3	18
Thrombus before stent****	8
Indication for stenting	
Threatened closure	27
Acute complete occlusion	1

*BA; balloon angioplasty, CABG; coronary artery bypass grafts, LAD; left anterior coronary artery, RCA; right coronary artery, LCX; left circumflex coronary artery. *AHA/ACC task force [32], **Dissection classification [22], ***TIMI flow [23], ****Presence of thrombus[33].*

Procedural outcome : Stent delivery was possible in 35 of 36 stents (97%). In one patient the stent could not be advanced beyond a curved branch point to the target stenosis in the mid-left 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 unwelded 4mm unit of the 12mm stent migrated proximally into the mainstem of the left coronary artery. This 4mm unit was then expanded fully in the left mainstem and the patient had an uneventful clinical course.

In five of the twenty-four patients Micro stents were deployed as a single device to treat short dissections while in nineteen patients Micro stents were deployed as part of a multiple stent strategy for long dissections. The Micro stent was used to both improve the inflow and outflow of longer stents of different design as well as to bridge the gap between longer proximal and distal stents. In table 3, the relative position and order of deployment of each of the Micro stents are listed individually. In four of the nineteen patients who received multiple stents, all of the stents were Micro. In fifteen of the patients the Micro stent was deployed in combination with longer stents of different design. In ten patients Micro stents were advanced through proximally deployed stents and in four patients stents of different design were advanced through proximally deployed Micro stents. In no patient did stents become caught in other stents during stent delivery. An example of the stent implantation to the lesion of dissection after BA can be seen in **Figure 2.**

In-hospital events : One patient in whom stent delivery was unsuccessful underwent emergency bypass surgery and made an uneventful post operative recovery. The clinical course of the other 24 patients in whom stent deployment was successful was free of coronary re-intervention, bypass surgery and death. A myocardial infarction was observed in 2 patients (8%), in one 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 prior to stent implantation. A femoral haemorrhage and haematuria requiring blood transfusion was observed in one patient (4%). All patients remained event free post hospital discharge and thus the event-free survival at 30 days follow-up was 88% (22 of 25 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 0.79 ±0.56mm pre primary balloon angioplasty to 1.21 ±0.62mm post balloon angioplasty at the time of dissection. Implantation of the AVE micro stent increased the MLD to 2.70 ±0.48mm ($p<.001$). The changes in MLD from pre primary balloon angioplasty through stent implantation to post Swiss Kiss are displayed in **Figure 3.** In 16 lesions which required post stent balloon dilatation (Swiss Kiss) MLD increased significantly from 2.54 ±0.46mm (pre Swiss Kiss) to 2.85 ±0.44mm (post Swiss Kiss, $p<0.01$). Absolute value of the acute stent recoil in the initial implantation (MLD during stent inflation - MLD post stent) was 0.56 ±0.31mm and acute recoil ratio of this stent (MLD during stent inflation - MLD post stent / MLD during stent inflation) was 17±9%.

Angiographic success was achieved in all lesions with successful deployment of the stent. Thus, the angiographic success rate of all lesions attempted was 96% (27 of 28 lesions). Average percent diameter stenosis decreased significantly from 70% pre intervention to a final residual value of 16% post 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 20% pre Swiss Kiss to 15% post Swiss Kiss ($p<.05$).

Table 3

Patient	Vessel AHA segment	Combination of Multiple Stents	Order of Deployment of Micro Stent
1	RCA-1 & 3	Micro / Micro	distal then proximal
2	RCA-2	Micro / Micro	distal then proximal
3	CX-11	Micro / Micro	distal then proximal
4	LAD-6	Micro / Micro / Micro	middle then proximal then distal
5	LAD-6	PS / Micro	Micro before PS
6	CX-13	GR / Micro	Micro after GR
7	LAD-9	GR / Micro	Micro after GR
8	CX-13	sPS / Micro	Micro after sPS
9	RCA-1	Micro / WS	Micro after WS
10	RCA-3	WS / Micro	Micro after WS
11	LAD-6	PS / Micro	Micro after PS
12	RCA-1	Micro / PS	Micro before PS
13	LAD-6viaSVG	WS / Micro	Micro after WS
14	LAD-6	sPS / sPS / Micro	Micro after sPS
15	CX-13	PS / Micro / Micro	2 Micros after PS
16	RCA-1	Micro / Micro / PS	2 Micros before PS
17	LAD-7	Micro / Micro / Micro / PS	3 Micros before PS
18	RCA-2	WS / WS / Micro / PS / PS	Micro after WS and PS
19	CX-11	PS / PS / Micro / Micro / Micro / PS	3 Micros after 2 prox & before dist PS

Multiple stenting with AVE Micro stent in combination with other AVE Micro stents (patients 1 - 4) and in combination with longer stents of different design (patients 5 - 19).
RCA = right coronary artery | LCX = left circumflex artery | left anterior descending artery | AHA segment No. 1-16 = coding system of the American Heart Association for coronary segment location | viaSVG = native coronary artery with proximal occlusion stented through saphenous vein graft | Micro = AVE Micro stent | WS = Wallstent | sPS = sheathed Palmaz-Schatz stent on premounted delivery system | PS = bare Palmaz-Schatz stent crimped by operator on a standard angioplasty balloon | GR = Gianturco-Roubin stent

DISCUSSION :

The key findings of this early experience were as follows: 1) Delivery to the target lesion of the radiopaque premounted AVE Micro stent as a stand-alone stent or as a complementary device for multiple stenting can be achieved in a high proportion of cases (27 of 28 lesions) ; 2) Following delivery of the stent (27 lesions), angiographic success as defined by <30% residual diameter stenosis can be achieved in a high proportion of cases (27 of 27) ; 3) Acute recoil following dilatation of the micro stent in vivo compares favourably with other stents [34,35] ; 4) Despite the bailout indication for stenting, deployment of this low metallic surface area stent (8.4%) resulted in a low risk of acute or subacute stent thrombosis (0 of 27 stented lesions).

Successful delivery of the micro stent may be attributed to two characteristics of the stent design. Firstly the 1.65mm profile of the micro stent in its unexpanded balloon-mounted state compares favourably with that of other stents and thus an intraprocedural exchange of the guiding catheter or guidewire should rarely be necessary. Secondly, the unconnected junctions of the modules and the 4mm and 8mm length of the individual modules provide the stent with hinge joints and very limited rigid segments to aid the negotiation of tortuous vessels. The monorail delivery system and the ease of identifying the individual .203mm thick struts further enhance the deployment of the Micro stent. The oblique longitudinal orientation of the Micro stent struts reduce the chance during multiple stenting of the struts catching in other stents despite the absence of a protective sheath.

Conventionally multiple stenting is performed by the deployment of the most distal stent first. This conventional order of deployment avoids the potential risks associated with passage of stents through other stents whereby the struts of the stents may catch. Recently, the importance of optimal stent deployment for the reduction of risk of subsequent subacute stent thrombosis has been increasingly recognized. Optimal deployment entails maximal stent and vessel expansion, apposition of the stent struts against (or embedded into) the vessel wall at all points, and the obtainment of a symmetrical lumen. Such optimal deployment has the additional benefit of facilitating and reducing the risks associated with the advancement of additional low profile stents through stents which have already been deployed proximally - see Table 3.

The proximal migration during inflation of a 4mm segment of an unconnected 12mm stent into the left mainstem in one 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.

Although 24 of 28 lesions had dissection type C, D, E, and F after primary balloon angioplasty, stenting was effective in tacking back the dissection flap and restoring TIMI 3 flow in all 27 lesions stented. While 8 of the lesions with threatened closure had angiographic evidence of intracoronary thrombus prior to 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 3.5mm 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 [36,37].

Two of our patients (8%) had significantly elevated creatine phosphokinase (CPK) levels and ECG changes of myocardial infarction. In one of these two patients stent implantation was performed within 24 hours of the onset of an acute Q-wave myocardial infarction and the patient became asymptomatic post stenting and CPK levels continued to decline post stenting without a further rise. In the other patient acute vessel closure had been present for 58 minutes prior to stent deployment. This patient had no further chest pain post stent implantation and the peak CPK level in this patient was 720 iu/l. Lincoff et al. indicated that peak CPK levels directly related to the time to stent placement after the onset of vessel closure and significant CPK elevation was commonly observed when vessel closure persisted for more than 49 minutes [13]. Thus, the elevated CPK

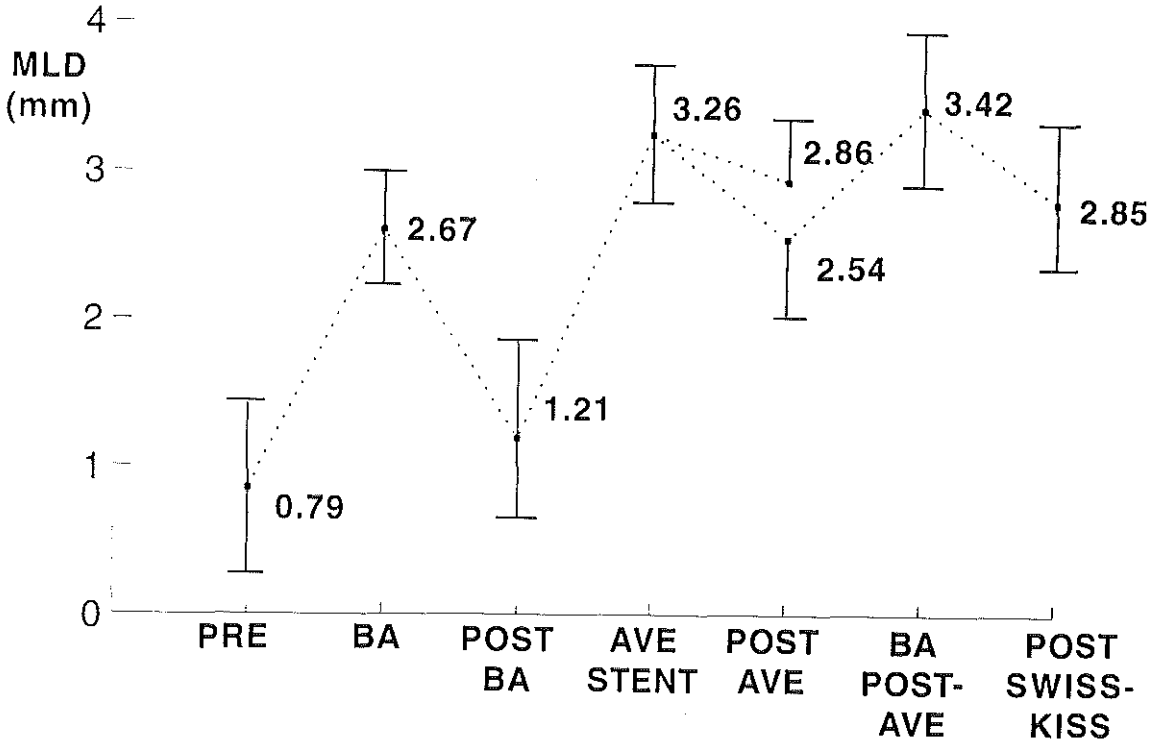

Figure 3. Changes of minimal luminal diameter (MLD) in 28 lesions from pre-procedure through stent implantation. Swiss Kiss (see text) was carried out in 16 lesions. MLD improved significantly after AVE stent implantation and after the performance of a Swiss Kiss (14.6 ±3.1 atmospheres).

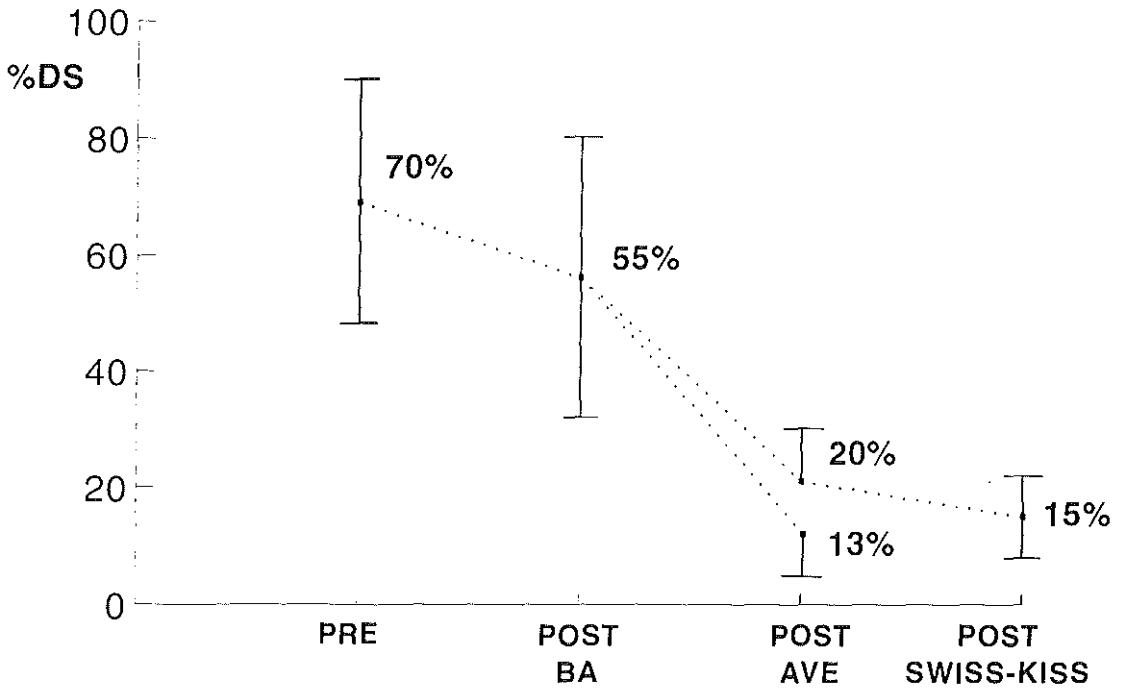

Figure 4. Changes in percent diameter stenosis (% DS) from pre procedure to post stent implantation in 28 lesions. A Swiss Kiss with high pressure (14.6 ±3.1 atmospheres) was performed in 16 lesions and the percent diameter stenosis improved from 20% to 15%.

levels in our two patients were felt to reflect their clinical events prior to stent deployment rather than the occurrence of an acute or subacute thrombosis post stenting.

Both single center and multicenter observational series of bailout stenting have been reported for the Wallstent [10], Palmaz Schatz stent [11-15], Gianturco Roubin stent [16-18]. These have been associated with a deployment success rate of 89 to 98%, a myocardial infarction rate of 4 to 43%, a CABG 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 Multilink (A.C.S. - Advanced Cardiovascular Systems) stents. While the structural design of the above stents can be grouped into two 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 stents may be more suited to the elective treatment of primary or recurrent stenoses with strong elastic recoil in non-tortuous vessels.

This study revealed sequential changes of luminal diameter from pre primary intervention, through stent implantation, to the performance of a Swiss kiss. Percent diameter stenosis decreased from 70% (pre balloon angioplasty) through 55% (post balloon angioplasty) to 15% (post Swiss kiss). While previous in-vitro testing of this stent has found recoil to be 8.7 % for the 3.5mm diameter stent, in this quantitative angiographic study of the stent in diseased coronary arteries in-vivo we found recoil to be $17 \pm 9\%$ (0.56mm) with an average stent diameter of 3.37mm. Furthermore, the post stent MLD achieved matched or was greater than the nominal stent size in only 4 of 27 stented lesions. The performance of a high pressure (14 atmospheres) Swiss kiss may result in an increase in MLD by 0.31mm, and may be a useful complementary technique when on-line quantitative angiographic analysis is available to guide the optimization of stent deployment.

Conclusion. Early experience with the new AVE micro stent would indicate that delivery of the stent to the target lesion and the subsequent achievement of optimal angiographic results can be expected in a high proportion of cases with the use of additional high pressure intrastent balloon inflations when necessary. The Micro stent may effectively serve as a stand-alone stent or as a complementary device for multiple stenting where it can be used to improve the inflow and outflow of longer stents of different design or to bridge the gap between proximal and distal stents. The proximal migration during inflation of a 4mm segment of an unconnected 12mm stent into the left mainstem in one 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. The safety of deploying the AVE micro stent for the management of threatened or acute vessel closure as indicated by the low rate of clinical events in this early series indicate that further clinical evaluation of the stent is warranted.

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Chapter XV

Does the method of transluminal coronary revascularization influence restenosis ? : Balloon angioplasty, directional coronary atherectomy, Wiktor stent, and Wallstent compared.

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Br J Clin Pract 1995;49:7-15.

DOES THE METHOD OF TRANSLUMINAL CORONARY REVASCULARISATION INFLUENCE RE-STENOSIS? BALLOON ANGIOPLASTY, ATHERECTOMY AND STENTS COMPARED

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SUMMARY Luminal renarrowing after successful coronary angioplasty is now recognised as a continuously distributed process which is determined largely by the extent of luminal increase achieved at angioplasty. In this study an alternative analytical approach is applied to determine whether luminal renarrowing following coronary intervention is related to the mechanism of luminal increase (ie by balloon, by atherectomy, by a self-expanding stainless steel mesh stent, or by a balloon-expandable tantalum coil stent). The results confirm the known proportional relationship between luminal renarrowing during follow-up and luminal improvement at intervention, regardless of the device used. However, significant differences were observed between the devices, which may reflect device-specific characteristics of the hyperplastic response to vessel injury and may have clinical implications.

Since its inception, balloon angioplasty has been plagued by what has now become known as the 'Achilles heel' of re-stenosis[1] which, according to current (albeit incomplete) understanding, appears to consist of the healing response of the vessel wall to the injury imparted during treatment.[2] Attempts to prevent or control this phenomenon have taken the form of clinical trials of a plethora of pharmacological agents,[3] and have in addition led to technological advances culminating in the development of a succession of alternative devices for primary transluminal revascularisation.[4] No pharmacological trial has yet provided the antidote to re-stenosis[3] and, despite optimism over alternative percutaneous revascularisation devices, none of the new strategies has thus far fulfilled its expectations in preventing luminal renarrowing.[5-9]

Clinical trials comparing directional atherectomy with conventional balloon angioplasty have reported no significant reduction in the categorically defined angiographic re-stenosis rate by atherectomy and no significant acute or long-term clinical benefit of this device. Trials evaluating the Palmaz-Schatz stent have reported improved clinical and angiographic outcome, but this reduction (rather than prevention) in luminal renarrowing came at the price of an increased rate of haemorrhagic complications; full reports and comprehensive analyses of findings of these trials are awaited.

Observational studies comparing stent implantation with directional atherectomy and balloon angioplasty have concluded that the device is essentially irrelevant: it is, rather, the acute angiographic result that is the most important predictor of long-term results. Our group has previously performed comparative studies on patient groups treated by different devices by 'matching' each patient for lesion location, severity and vessel size with a comparable patient treated by balloon angioplasty.[10-14] In these studies, differences in expected relative luminal loss were detected between directional atherectomy- and balloon angioplasty-treated patients, as well as between patients treated by the Wallstent or balloon angioplasty and those treated by excimer laser or balloon angioplasty.

This clinical study was intended to compare the effect on late re-stenosis of balloon angioplasty, directional atherectomy and implantation of a Wallstent (self-expanding stainless steel mesh stent[15]) or Wiktor stent (balloon-expandable tantalum coil stent), by using previously described quantitative angiographic parameters of relative luminal gain and loss as angiographic correlates of vessel wall injury and hyperplastic response (re-stenosis).

METHODS

For the purposes of this study, clinical and quantitative angiographic data were obtained from already completed prospective multicentre clinical trials[16-20] and ongoing clinical experience at our centre.[9,14,21,22] The study population consisted of 1234 patients (1452 lesions) who had been treated by balloon angioplasty, 120 patients (123 lesions) who had undergone directional coronary atherectomy, 104 patients (110 lesions) in whom an endoluminal self-expanding stainless steel mesh stent was implanted, and 100 patients (101 lesions) treated by balloon-expandable tantalum coil stent implantation for native coronary artery disease. Pertinent baseline demographic data are given in Table 1.

The balloon angioplasty patients had been enrolled in two separate European multicentre placebo-controlled re-stenosis prevention trials, the details of which have already been published.[16,17] In each of these trials the pharmacological agent under investigation was found to have no significant effect on the process of luminal renarrowing, so all the patients were pooled for the purposes of the present study. Entry criteria for these two studies were similar, all patients scheduled for angioplasty with angiographically proven native primary coronary artery disease affecting single or multiple vessels and with clinical symp-

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Table 1. Demographic data for the four patient groups. Male/female ratios, age, treated vessel and frequency of diabetes are similarly distributed. The directional atherectomy and balloon-expandable stent groups have a greater frequency of class III and IV and unstable angina, and no chronic total occlusions were treated by either of these devices. Lesion type varies widely between groups

	Balloon angioplasty	Directional atherectomy	Balloon-expandable stent	Self-expanding stent
Patients	1234	120	100	104
Lesions	1435	123	101	110
Male/female (%)	987/247 (80/20)	97/23 (81/19)	85/15 (85/15)	87/17 (84/16)
Age (years)	56.4 ±9	57.6 ±10.8	56.6 ±11.7	57 ±11
Lesion type				
primary	100%	70%	0	14%
restenosis	0	25%	100%	49%
bail-out	0	5%	0	33%
Vessel				
LAD	47%	65%	52%	55%
RCA	30%	22%	34%	35%
LCX	23%	13%	14%	10%
Total occlusion	4%	0	0	4%
Diabetes	7%	6%	12%	5%
Classes III or IV angina	52%	73%	68%	50%
Unstable angina	12%	51%	?%	26%

toms of stable or unstable angina pectoris being considered for inclusion. Specific exclusion criteria and procedural details can be found in the original publications.[16,17] Only those having a successful dilatation, defined by the operator as a reduction in lesion severity to <50% diameter stenosis, were actually included in the trials for the ultimate assessment of angiographic outcome. Eventually a total of 1234 patients with 1452 lesions had full angiographic follow-up.

Patients undergoing implantation of the Wallstent were recruited at six centres involved in a non-randomised trial: for the treatment of acute coronary artery occlusion during balloon angioplasty (14%), as an adjunct to suboptimal angioplasty (19%), re-stenosis after angioplasty (49%), and primary coronary artery disease (18%, of which 4% were for chronic total occlusion).[7,8,18] The Wiktor stents were implanted for symptomatic angiographically documented re-stenosis after balloon angioplasty in a multicentre trial.[20] The respective implantation methodology and anticoagulation regimens have been described.[7,19,23] Patients experiencing in-hospital stent occlusion (<14 days after implantation) were excluded, as this is a consequence of a thrombotic event, not intimal hyperplasia, and is not of interest in this study.

Directional atherectomy, using the Simpson atherectomy catheter, was performed at two specialised institutions: as a primary procedure in 70% patients, as a bailout after complicated balloon angioplasty in 5%, and for re-stenosis after previous intervention in 25%. The atherectomy procedure has been described in detail elsewhere.[9,21]

Quantitative coronary angiography

Coronary angiography was performed before and immediately after intervention and at 6 month follow-up. The angiograms were recorded using a fixed table system and 35 mm cinefilm at a minimum speed of 25 frames/sec according to the guidelines of the core angiographic laboratory, whereby a series of previously reported measures were taken to reduce variability in radiographic acquisition.[24,25] All cineangiograms were analysed using the computer-assisted cardiovascular angiographic analysis system (CAAS, validated and described in detail elsewhere[26-31]) (Figure 1).

Angiographic variables

In this study we examined the relationship between luminal improvement at intervention and luminal renarrowing during follow-up for lesions treated by balloon angioplasty, directional atherectomy or stent implantation; to that end, per-lesion analysis (to include the potential influence of all treated lesions, where multilesion intervention was performed) was done using the following parameters:[9,32-35]

Figure 1. Depicts the difference in % diameter stenosis (%DS) measurement by conventional 'user-defined' reference diameter (RefD) proximal and/or distal to the lesion and the automated interpolated reference diameter (IRD), provided by the Cardiovascular Angiographic Analysis System (CAAS). The computer algorithm automatically measures the diameter along each scanline (every 0.1 mm) of the detected contours of the segment, proximal and distal to the lesion (excluding the lesion itself). Then a polynomial function reconstructs the contours over the diseased segment (shown as smooth, thick, slightly tapering lines). The IRD is the diameter of the reconstructed contours at the minimal luminal diameter (MLD), giving a %DS of 66%

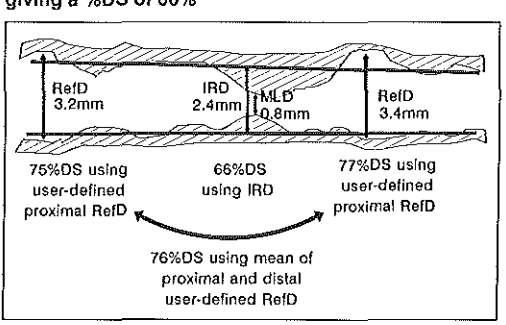

Table 2. Relevant quantitative angiographic measurements, given as means ±standard deviation (95% CI)

	Balloon angioplasty *n*=1435 (95%CI)	Directional atherectomy *n*=123 (95%CI)	Balloon-expandable stent *n*=100 (95%CI)	Self-expanding stent *n*=110 (95%CI)
MLD preintervention (in mm)	1.02 ±0.37* (1.0-1.04)	1.17 ±0.39 (1.13-1.21)	1.11 ±0.31 (1.04-1.18)	1.21 ±0.54 (1.11-1.31)
MLD postintervention (in mm)	1.78 ±0.36* (1.76-1.80)	2.46 ±0.42 (2.37-2.55)	2.43 ±0.33† (2.36-2.50)	2.60 ±0.51 (2.50-2.70)
MLD at follow-up (in mm)	1.50 ±0.57* (1.47-1.53)	1.78 ±0.63 (1.65-1.91)	1.71 ±0.66 (1.57-1.85)	1.89 ±0.90 (1.72-2.06)
Vessel size (IRD preintervention) (in mm)	2.63 ±0.54* (2.60-2.66)	3.25 ±0.64 (3.12-3.38)	2.86 ±0.49‡ (2.76-2.96)	3.10 ±0.61 (2.99-3.21)
Gain in MLD at intervention (in mm)	0.76 ±0.40* (0.74-0.78)	1.29 ±0.49 (1.19-1.39)	1.32 ±0.32 (1.25-1.39)	1.39 ±0.63 (1.27-1.51)
Loss in MLD during follow-up (in mm)	0.28 ±0.51* (0.25-0.31)	0.67 ±0.67 (0.53-0.71)	0.71 ±0.60 (0.58-0.84)	0.71 ±0.92 (0.54-0.88)
Relative gain (in MLD at intervention) (in mm)	0.29 ±0.16* (0.28-0.30)	0.42 ±0.20 (0.38-0.46)	0.47 ±0.13 (0.44-0.50)	0.46 ±0.19 (0.43-0.49)
Relative loss (in MLD at intervention) (in mm)	0.1 ±0.21* (0.10-0.12)	0.26 ±0.24 (0.21-0.31)	0.23 ±0.28 (0.18-0.28)	0.23 ±0.25 (0.18-0.28)
Net gain index at follow-up (in mm)	0.18 ±0.21 (0.17-0.19)	0.19 ±0.20 (0.15-0.23)	0.21 ±0.23 (0.16-0.26)	0.23 ±0.31 (0.17-0.29)

*Significant difference between PTCA and each of the other three groups, $P<0.05$ for each comparison (Student's *t*-test).
† Significant difference between the balloon-expandable stent group and each of the other three groups ($P<0.05$).
‡ Marginally significant difference between the balloon-expandable and self-expanding stent groups ($P=0.048$).
IRD = interpolated reference diameter; MLD = minimal luminal diameter; PTCA = percutaneous transluminal coronary angioplasty

- Gain = (MLD postintervention - MLD preintervention)
- Loss = (MLD postintervention - MLD at follow-up)
- Relative gain = gain/vessel size
- Relative loss = loss/vessel size
- Net gain index = (MLD at follow-up - MLD preintervention)/vessel size.

where MLD is the minimal luminal diameter, and the vessel size is represented by the interpolated reference diameter preintervention (Figure 1); 'gain' and 'loss' respectively represent the absolute improvement in MLD achieved at intervention and the absolute change during follow-up, measured in mm; 'relative gain' and 'relative loss' depict these absolute changes in luminal diameter, normalised for the vessel size in each individual case; 'net gain index' is a measure of the ultimate net effect of the intervention in question, in terms of the change in minimal luminal diameter from pre-procedure to follow-up, normalised for the vessel size.

As the main focus of interest was the relationship between luminal improvement at intervention and deterioration during follow-up, only those lesions having an identifiable increase in MLD, defined as a relative gain greater than 0, were included. Consequently, of 1452 lesions treated by balloon angioplasty with satisfactory angiographic follow-up, 1435 were included, as well as 122 of 123 treated by atherectomy and all lesions in both stent groups.

Statistical methods

Statistical analyses were carried out using a standard commercially available statistical package (BMDP statistical software, University of California, Berkeley, CA).

The data obtained by quantitative angiographic analysis are given as means ±SD and SEM. Patient groups were compared by analysis of variance: for differences regarding minimal luminal diameter pre- and postintervention and at follow-up, for vessel size (interpolated reference diameter preintervention), for absolute gain and loss in minimal luminal diameter, relative gain and relative loss in minimal luminal diameter, and net gain index. If significant differences were found by analysis of variance, the Student *t*-test was applied to all possible intergroup comparisons to pinpoint sources of difference.

Pearson's correlation coefficient is used to assess the association between relative gain and relative loss for each patient group. A least-squares linear regression analysis of relative loss on relative gain was performed in each group and resultant regression equations compared by analysis of variance. To examine for possible hidden differences between the patient groups treated by the different devices, with regard to the relative gain/relative loss relationship at various levels of relative gain, the patient groups were subdivided into 'small', 'moderate' and 'large' relative gain increments by obtaining the lower and upper quartiles for relative gain for each group, and then taking the means of these as the cut-off points.

RESULTS

Mean quantitatively derived values, with standard deviations and 95% confidence intervals are given in Table 2, for minimal luminal diameter pre- and postintervention and at follow-up, for vessel size (interpolated reference diameter preintervention), for absolute gain and loss in MLD, relative gain and relative loss in MLD, and net gain index, with respect to each patient group. The mean values for the absolute measurements of MLD pre- and postintervention and at follow-up, for vessel size (interpolated reference diameter preintervention), and for absolute gain and loss in MLD are significantly less for the balloon angioplasty group than for each of the other three groups. There are no significant differences between the directional atherectomy, self-expanding stainless steel stent and balloon-expandable tantalum coil stent groups for any of these variables, except that the mean vessel size in the balloon-expandable stent group is significantly smaller than in the atherectomy and self-expanding stent groups and the mean MLD postintervention in the balloon-expandable stent

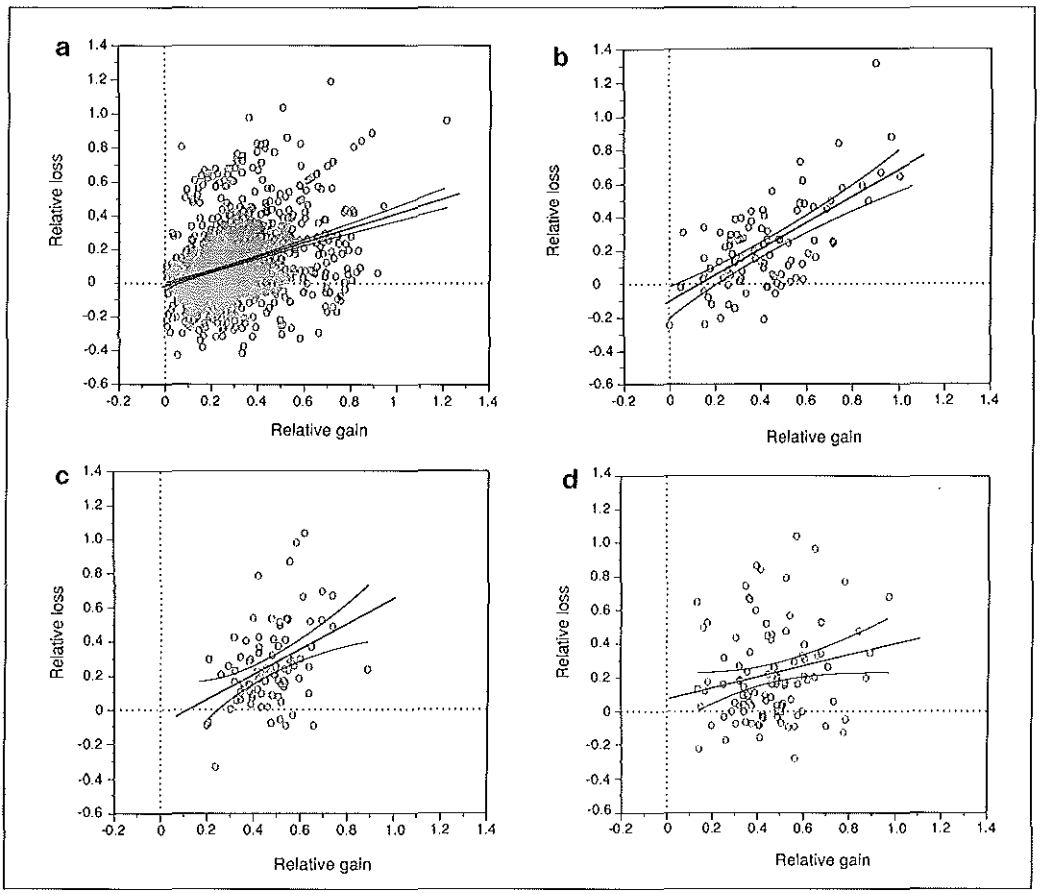

Figure 2. a,b,c,d: Scatterplots of relative loss on relative gain for lesions treated by balloon angioplasty (a, *n*=1435), directional coronary atherectomy (b, *n*=123), balloon-expandable tantalum coil stent implantation (c, *n*=101) and self-expanding stainless steel mesh stent implantation (d, *n*=110), with regression lines and their 95% confidence limits superimposed. Although there is considerable data scatter in each graph, which is reflected by the relatively weak coefficients of correlation, the association between these variables is strikingly statistically significant; more notably, least-squares regression reveals a definite linear dependency of relative loss on relative gain, for each treatment group, as described by their respective regression lines and *P* values

Table 3. Regression and correlation coefficients for the relative gain/relative loss relationship for each group

	Balloon angioplasty	Directional atherectomy	Balloon-expandable stent	Self-expanding stent
Line slope	0.43	0.78	0.75	0.33
Intercept	- 0.02	- 0.10	- 0.09	0.07
Pearson's product moment correlation coefficient *r*	0.34	0.68	0.39	0.21
Significance value *P* of both correlation and regression	<0.00005	<0.00005	0.0002	0.03

group is less than in the self-expanding stent group.

The mean relative gain achieved by balloon angioplasty and the mean relative loss are both significantly less than for any of the three other treatment modalities, which do not themselves differ significantly with respect to these parameters. The mean net gain index does not vary significantly between the four patient groups.

Examination of the balloon angioplasty group with regard to the relationship between relative gain and relative loss produces a correlation coefficient r=0.34 (P<0.00005). Linear regression analysis yields a regression equation (y=bx+a) of: relative loss = 0.43 relative gain -0.02 (P<0.00005) (Figure 2). Regression equations for the other three groups are shown in Table 3 and illustrated in Figure 2. Analysis of variance reveals a significant difference between the regression lines (P=0.00002). Results of intergroup comparisons are shown in Table 4 and the four regression lines plotted in Figure 3. Direct comparisons between all possible group combinations, also by analysis of variance, are shown in Table 4 and the four regression lines plotted in Figure 3. Significant differences are observed between the balloon angioplasty group and both the

directional atherectomy and balloon-expandable tantalum coil stent groups, and also between the directional atherectomy and self-expanding stent groups. A trend towards a significant difference is observed between the balloon angioplasty and self-expanding stent groups.

Subdivision of the patient groups (to further analyse overall differences and to examine for possible hidden differences between the groups, with regard to the relative gain/relative loss relationship) according to the method previously described, produces cut-off points of 0.3 and 0.5 for 'small', 'moderate' and 'large' relative gain. Where relative gain was 'small' (<0.3) there were 845 lesions in the PTCA group, 41 in the directional atherectomy group, 13 in the balloon-expandable stent group, and 16 in the self-expanding stent group; for 'moderate' relative gain (0.3–0.5) the corresponding group sizes were 443, 47, 46, and 51; where relative gain was 'large' (≥0.5) there were 147 in the PTCA group, 34 in the directional atherectomy group, 42 in the balloon-expandable stent group, and 43 in the self-expanding stent group. Analysis of variance of regression between the subgroups is shown in Table 4. Overall differences observed between the balloon angioplasty and both the directional atherectomy and balloon-expandable tantalum coil stent groups as well as the difference between the directional atherectomy and the self-expanding stent group appear to be explained by differences encountered where RG ≥0.5 (P=0.001, P=0.06 and P=0.08 respectively). The balloon angioplasty and self-expanding stent groups differ significantly where RG <0.3 (P=0.01).

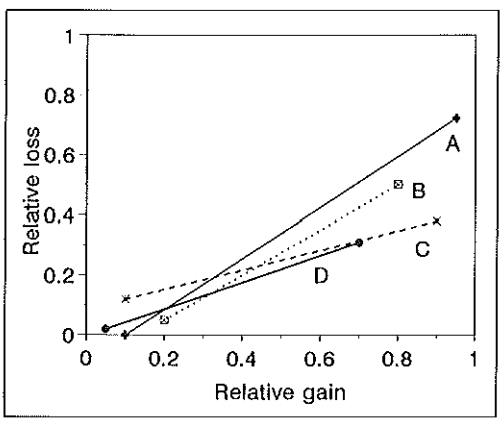

Figure 3. Linear regression plots for all four patient groups (A = directional atherectomy; B = balloon-expandable stent; C = self-expanding stent; D = balloon angioplasty) superimposed. Analysis of variance reveals significant differences between the respective regression lines, as explained in the text

Intergroup comparisons at the various levels of relative gain to detect the actual, as opposed to predicted, differences in relative loss between the patient groups are shown in Table 5 and Figure 4. A pattern of increasing mean relative loss is apparent, from small, to moderate, to large relative gain. In fact the incremental increase in relative gain is associated with significant increases in relative loss for the balloon angioplasty group (P<0.01 for each 'step up' in relative gain). Where RG is large (0.5), a statistically significant difference is detected for relative loss between the balloon angioplasty and directional atherectomy groups, and a trend towards a difference is apparent between balloon angioplasty and Wiktor stent groups.

DISCUSSION

Our group and others have shown that luminal renarrowing over 6 months is related to the extent of luminal gain (injury) achieved at coronary intervention.[32,34,37–43] While others have reported no influence of the nature of the device used for intervention on the degree of late luminal renarrowing, our findings suggest otherwise. Definite differences have been shown here between balloon angioplasty, directional coronary atherectomy and stent implantation with respect to the degree of renarrowing (relative loss), which may be anticipated as progressively greater degrees of luminal increase (relative gain) achieved with these different devices. The use of relative gain, relative loss and net gain index (rather than absolute changes) in luminal diameter adjust for the known confounding influence of significant differences in vessel size between the patient groups treated by the different devices, which render the subsequent differences observed for absolute luminal gain at intervention and loss during follow-up difficult to interpret.

Although balloon angioplasty does not generally achieve as great a mean relative gain as the other three devices, which do not differ significantly, balloon angioplasty is also not attended by the same degree of relative loss, so that the

Table 4. Outcome of analysis of variance of the relative gain/relative loss relationship between the patient groups, given as P values. The overall differences between the regression lines are shown in the first column; the next three describe the differences between the patient groups at various levels of relative gain. Small, moderate and large relative gain levels were defined by first obtaining the lower and upper quartiles for relative gain in each group, and taking the means of these values as the respective lower and upper cut-off points

	Overall differences	'Small' (<0.3) relative gain	'Moderate' (0.3-0.5) relative gain	'Large' (>0.5) relative gain
PTCA *vs* DCA	0.00007*	0.52	0.45	0.001*
PTCA *vs* balloon-expandable stent	0.0009*	0.74	0.24	0.06†
PTCA *vs* self-expanding stent	0.06†	0.01*	0.35	0.44
DCA *vs* balloon-expandable stent	0.98	0.51	0.37	0.58
DCA *vs* self-expanding stent	0.04*	0.15	0.91	0.08†
Balloon-expandable *vs* self-expanding stent	0.20	0.48	0.76	0.60

*Statistically significant difference.

†Clear, although not statistically significant difference.

DCA = directional coronary atherectomy; PTCA = percutaneous transluminal coronary angioplasty

ultimate net benefit (net gain index) was found to be similar for each treatment modality in this study.

Linear relationship of relative gain and relative loss

Despite the relatively weak correlation there is an undoubtedly linear relationship between relative gain at intervention and relative loss during follow-up for each treatment device, as illustrated by the regression lines (Figure 3), with the clear message that the greater the improvement in minimal luminal diameter achieved by intervention — regardless of the device used — the greater the subsequent magnitude of luminal renarrowing. This maxim is essentially in agreement with the pathological information provided by the porcine model employed by Schwartz *et al*,[36] and has now been reported by many investigators.[37-43]

Differences between groups treated by different devices

With regard to comparison of the devices assessed in this study (Figure 2), a therapeutic procedure where the regression line describing the relative gain/relative loss relationship has a gentle slope (bisecting the origin) might be considered in general preferable to one that is attended by a steep slope. By this scheme, directional atherectomy and balloon-expandable stent implantation are associated with less favourable profiles than balloon angioplasty or self-expanding stent implantation. Analysis of variance of the regression lines reveals a highly significant difference (P=0.00002), which is interpreted as demonstrating that the relationship between relative gain in minimal luminal diameter at intervention and relative loss during follow-up for the respective patient populations, of which the four groups in this study are samples, cannot be described by the same regression line.

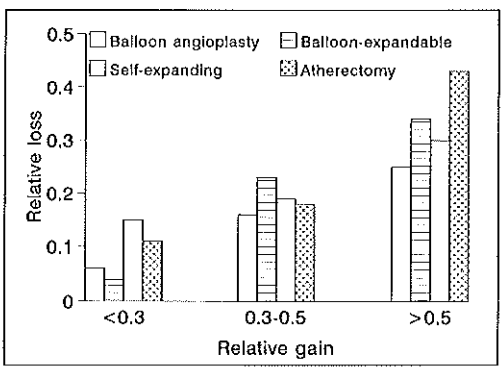

Figure 4. Intergroup comparisons are shown at the various levels of relative gain (RG) to detect the actual, as opposed to predicted, differences in relative loss between patient groups. A pattern of increasing mean relative loss is apparent, from small to moderate to large RG. The incremental increase in RG is associated with significant increases in relative loss for the balloon angioplasty group (P<0.01 for each 'step up' in RG). Where RG is large (0.5), a statistically significant difference is detected for relative loss between balloon angioplasty and directional atherectomy groups, and a trend towards a difference is apparent between balloon angioplasty and Wiktor stent groups

Comparisons between the patient groups to characterise this overall difference with regard to the relative gain/relative loss relationship (Table 3) reveal that the atherectomy and balloon-expandable stent groups are similar (P=0.97), and that both groups differ significantly from the balloon angioplasty group (P=0.00007 and P=0.0009 respectively). In addition, the directional atherectomy group (but not the balloon-expandable stent group) differs significantly from the self-expanding stent group (P=0.04). There is also a clear, although not actually 'significant', difference between the balloon angioplasty and self-expanding stent groups (P=0.06), which is apparently explained by the difference between the groups at the lower levels of relative gain (P=0.01). This may be due to the fact that in all cases of self-expanding stent implantation in this study a relative gain greater than 0.13 was achieved, whereas 15% (n=238) of lesions treated by balloon angioplasty that had been considered successfully dilated (diameter stenosis <50% as assessed by the interventionalist) were associated with a relative gain of less than this. The overall differences observed between the balloon angioplasty group and the directional atherectomy and balloon-expandable stent groups are, conversely, explained by differences at the upper end of the relative gain spectrum (≥0.5). These observations may relate to the inherent methodological properties of the devices for the mechanical achievement of increase in luminal dimensions whereby there may be differing degrees of occult trauma imparted to the vessel wall by the different devices, to attain a given proportional luminal improvement, that become most apparent at higher levels of relative gain.

Mechanistic considerations

Directional atherectomy. It could be hypothesised that the type and extent of injury imparted by the traumatic removal of tissue during directional coronary atherectomy, with exposure to the circulation of extensive areas of denuded intimal, medial or even adventitial layers,[41,45] create

Table 5. Mean relative loss values ±standard deviation and 95% CI of the mean for each patient group with regard to 'small', 'moderate' and 'large' increments of relative gain, as derived from the mean of the lower and upper relative gain (RG) quartiles for each group

	Balloon angioplasty (95%CI)	Directional atherectomy (95%CI)	Balloon-expandable stent (95%CI)	Self-expanding stent (95%CI)
Mean relative loss at 'small' (<0.3) RG	0.06 ±0.17* (0.05-0.07)	0.11 ±0.17† (0.05-0.17)	0.04 ±0.23 (-0.13-0.40)	0.15 ±0.25 (0.02-0.27)
Mean relative loss at 'moderate' (0.3-0.5) RG	0.16 ±0.20* (0.14-0.18)	0.18 ±0.17† (0.13-0.23)	0.23 ±0.17 (0.18-0.28)	0.19 ±0.25 (0.11-0.25)
Mean relative loss at 'large' (>0.5) RG	0.25 ±0.29*‡¶ (0.19-0.29)	0.43 ±0.30†‡ (0.32-0.54)	0.34 ±0.28¶ (0.25-0.43)	0.30 ±0.33 (0.20-0.44)

*Significant difference in relative loss with incremental increase in relative gain in the balloon angioplasty group (P<0.01).

†Significant difference in relative loss with incremental increase in relative gain in the directional atherectomy group (P<0.05).

‡Significant difference between the balloon angioplasty and directional atherectomy groups (P<0.003).

¶Trend towards a significant difference between the balloon angioplasty and balloon-expandable stent groups (P=0.056).

a large substrate for an aggressive healing response to re-endothelialise the resultant 'wound' surface.[2] Also, the potential local turbulence and shear-force altering effects of an irregular, scalloped luminal configuration (as often persists after successful directional atherectomy[46,47]), may delay re-endothelialisation and thus promote excessive neointimal formation.[48] The extent of the ensuing intimal thickening may thus be more directly dependent on the depth and magnitude of injury[49] than is the case for the other devices.

Balloon angioplasty. It is not difficult to imagine that the extent and depth of vessel wall disruption caused by lesion stretching and tearing during balloon angioplasty[52] depends, to a greater or lesser extent, on a large number of individual factors such as lesion length and symmetry, plaque composition (proportion of loose connective and dense fibrous or calcified tissue) and volume, vessel curvature and elasticity, presence of thrombus or intimal dissection.[53-55] The angiographic relative gain in minimal luminal diameter may not therefore reflect the degree of intimal injury so accurately, and thus is not quite so clearly associated with subsequent relative loss (luminal renarrowing) as is observed with atherectomy. Furthermore, although (as previously mentioned) we have found relative gain to be the greatest single determinant of luminal renarrowing in stepwise multivariate regression analysis, a number of other clinical, lesion and procedural factors have been reported to be predictive of or associated with a greater risk of re-stenosis: unstable angina, shorter duration of angina, angina class (III or IV), lesion length >10 mm, eccentricity, pre-procedural lesion severity, location in a bend, smaller arterial size, calcification, residual transstenotic gradient >20 mmHg, angiographically visible thrombus after angioplasty etc.[34,56-59] The influence of these factors attenuates the relationship between relative gain and relative loss, to variable degrees, in these patients. In addition, the luminal contour immediately after successful balloon angioplasty often adopts an irregular non-circular configuration and is much more often disrupted by intimal dissection than is appreciated by angiography.[53,55,60-62] Measurement of the minimal luminal diameter, and thus relative gain and relative loss values, are therefore subject to potential imprecision after balloon angioplasty, particularly when compared with stent implantation, where the lumen postintervention tends to assume a smoother and more circular configuration,[47,63] and also perhaps when compared with directional atherectomy, after which luminal disruption and dissection is less often observed by intravascular ultrasound.[64,65]

Stent implantation. The use of an implantable endoluminal prosthesis, whether a *balloon-expandable tantalum coil* or *self-expanding stainless steel mesh*, introduces additional compounding factors such as the scaffolding effect of the device, the embedding effect of the wires, the long-term presence of a foreign body (with its inherent thrombogenic effect and inability to mount an appropriate physiological response), the potential molecular effect of the electrical charge of the stent molecules, as well as the unquantifiable persisting barotraumatic injury of the self-expanding stent on the vessel wall.[19,66,67] As a further entangling issue, the smoothing effect of the stent in reducing turbulence and shear stress[19,68] may facilitate rapid endothelial recovery and therefore retard smooth muscle cell proliferation,[48] although the luminal contour several weeks after stent implantation may adopt an indented, undulating appearance (with potential turbulence effects), depending on the helical structure. These and other as yet unknown considerations dilute the association of vessel wall injury and tissue response in stented patient groups with a consequently relatively weak correlation between luminal improvement after stent implantation and renarrowing during follow-up.

Despite the apparent graphic difference between the regression lines of the two stent groups, analysis of variance reveals no statistically significant difference (P=0.2). This is due to the wide 95% confidence intervals of the regression line for each group, which might constrict somewhat with the addition of further patients or in fact be a feature of the multifarious nature of the vessel wall injury and subsequent response provoked by implantation of appropriately sized endoluminal prostheses. The group treated by self-expanding stainless steel mesh stent implantation in this study is non-homogeneous, with a mixture of emergency implantations (for acute or threatened vessel closure during balloon angioplasty), re-stenotic and primary lesions, and the balloon-expanding stent group consists exclusively of re-stenotic lesions. These lesion categories are reported to be associated with differing long-term angiographic outcome,[69-72] which might contribute to the differences observed between the two groups. However, a previously published relative risk analysis for re-stenosis in the patient group treated by implantation of self-expanding stainless mesh stent demonstrated no significant differences in re-stenosis rates (by two commonly used re-stenosis criteria) between the three lesion categories.

It must also be recognised that the inclusion of re-stenotic lesions only, in our group treated by implantation of this stent, may contribute to the observed differences between the tantalum coil stent and balloon angioplasty groups, even though the evidence indicating a significantly different response to repeat wall injury in such patients is somewhat conflicting and thus far not wholly conclusive.[8,57,69,72]

Where relative gain is in the moderate range (0.3–0.5), there is no obvious long-term advantage of any device, as evidenced by the similar predicted and actual relative loss for all four groups in that range.

Limitations. The coronary angiogram is a two-dimensional luminal silhouette, providing only indirect evidence of the milieu in a coronary vessel, which may undergo profound disruption after intervention, in the absence of angiographic abnormality.[53,60] This is a limitation of all angiographically based studies, which we have attempted to minimise by the use of an automated contour detection system for quantitative angiographic analysis, to provide objective, reproducible and absolute measurements of luminal dimensions. Accepting this inherent limitation of coronary angiography we believe that relative gain and relative loss represent the best available angiographic correlates of arterial wall injury and intimal hyperplasia respectively.

The effect of other clinical, procedural and lesion-related characteristics on the relative gain/relative loss relationship was not considered. It is conceivable that the apparently greater frequency of unstable angina in each of the patient groups treated by directional atherectomy and balloon-expandable tantalum coil stent implantation contributes to the differences observed between these groups and the balloon angioplasty group. Also, the balloon angioplasty group comprises exclusively primary lesions, whereas the atherectomy and self-expanding stent groups

include a mixture of primary, 'bailout' and re-stenotic lesions, and the balloon-expandable stent group comprises re-stenotic lesions only, which may contribute to the between-group differences observed. However, in reply to these points, a number of recent studies from our group (including stepwise regression analysis of multiple clinical, angiographic and procedural factors) have found luminal improvement at intervention or 'relative gain' to be the strongest determinant of luminal renarrowing or relative loss.[32,34,35,79] We were thus most interested in exploring a dynamic relationship between these isolated variables as a clinical evaluation of the injury/hyperplasia hypothesis.

The imbalance in patient numbers between the balloon angioplasty group and the other three might be considered to contribute to the observed intergroup differences in the relative gain/relative loss relationship. Furthermore, some of the atherectomy and self-expanding stent data represent the initial clinical experience with these devices, whereas the angioplasty data are obtained from recent European clinical trials, which may also have some bearing on intergroup differences. On the other hand, additional differences might become apparent between the two stent groups or between the directional atherectomy and self-expanding stent groups with larger patient numbers, as the wide 95% confidence intervals for mean values and line slopes in the stent groups would most likely be reduced if these groups were larger. Perhaps amalgamation of similarly acquired quantitative angiographic data from other institutions would solve this shortcoming.

We accept that the correlation coefficients describing the relative gain/relative loss association are weak. This demonstrates the limitation of applying simple geometric principles to describe a compound, multifactorial phenomenon. However, tests of the significance of the association between relative gain and relative loss are strikingly significant for balloon angioplasty, directional atherectomy and balloon-expandable stent groups and mildly significant for the self-expanding stent group, demonstrating that these variables are clearly related beyond chance. Similarly, the regression equations describing their interrelationship clearly illustrate a linear dependency of relative loss on relative gain. We recommend application of this approach to homogeneous patient groups treated by different devices to ascertain more refined information with respect to various clinical syndromes.

CONCLUSION

Differences in the relative gain/relative loss relationship between the devices studied may reflect the inherently disparate intensity of wall injury characteristic of each, in the achievement of their beneficial effects, which become particularly evident at a higher scale of luminal improvement. Despite these differences, none of the devices evaluated demonstrates the qualities of an ideal device, which would not provoke any untoward luminal renarrowing in response to maximisation of luminal increase during angioplasty. The ultimate routes to the prevention of restenosis, therefore, cannot lie solely in devices to achieve increasing luminal improvements, but must be via an approach integrating pharmacologists, histopathologists, molecular biologists, geneticists as well as interventionalists in the development of an 'agent'[78,79] for the control or prevention of the tissue response to the apparently unavoidable injury imparted to the vessel wall during the revascularisation process.

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Chapter XVI

Coronary lumen quantification at 6 month follow-up of the new radiopaque Cordis stent : An experimental and clinical study with quantitative coronary angiography and intracoronary ultrasound.

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(in review)

ABSTRACT :

Background. While the radiopacity of tantalum stents may facilitate their deployment in coronary arteries, the outline of the radiopaque stent struts embedded in the vessel wall may interfere with the reliability of automated quantitative angiographic analysis of the stented lumen in the presence of intimal hyperplasia at 6 month angiographic follow-up.

Methods. To determine the reliability of geometric (edge-detection) quantitative angiographic analysis (QCA) of restenosis within the 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, plexiglass phantom vessels with concentric stenosis channels ranging from 0.75 to 3.0 mm in diameter and with a reference diameter of 3.0mm were imaged both prior to and following their insertion in tantalum stents. For the experimental series, measured values of minimal luminal diameter (MLD) and of the reference diameter obtained from QCA and ICUS were compared with the true diameters of the plexiglass vessel to determine the accuracy and precision of measurements. In the clinical series the agreement of QCA and ICUS measurements were studied in twenty-three patients who had undergone coronary implantation of the Cordis stent and twenty-three patients who had undergone balloon angioplasty 6 months previously. Measurements of the reference vessel diameter by QCA were based on a computer derived interpolated diameter which assimilates the diameter of the entire length of the analysed segment, while measurement of the reference vessel diameter by ICUS was based on measurement at one point.

Results. *Experimental results for minimal luminal diameter.* The reliability of QCA measurements deteriorated in the presence of the radiopaque stent (accuracy of QCA fell from -.07mm to -.12mm), while the reliability of lumen measurements by ICUS was independent of the presence of the radiopaque stent (-.12mm and -.13mm prior to and following introduction of the stent respectively).
Experimental results for reference vessel diameter and % diameter stenosis. Without the stent, the average MLD obtained from QCA of the 1.00mm plexiglass vessel was 1.00 ±.01mm and the 3.00mm reference vessel diameter was 2.81 ±.05mm providing a 64 ±1% diameter stenosis. Following introduction of the stent, the average MLD was 0.99 ±.06mm and the average reference vessel diameter was 3.36±0.17mm providing a diameter stenosis of 71 ±2%. ICUS measurements (2.77mm) of the reference vessel diameter (3.00mm) were unaffected by the presence of the stent.
Clinical series. The agreement of ICUS and QCA measurements (ICUS - QCA) was poorer in the balloon angioplasty patients (.68mm ±.42mm) compared to the stented patients (-.05mm ±.42mm). Similarly, the correlation of ICUS and QCA measurements was .40 in the balloon angioplasty population and .60 in the stented patients.

Conclusion. In the 6 month follow-up of patients who have undergone implantation of the highly radiopaque Cordis tantalum stent, assessment of restenosis can be reliably quantified by QCA by the use of the minimal luminal diameter rather than the percent diameter stenosis. Assessment by QCA of the reference diameter of the stented coronary segment at follow-up should not be performed in the interpolated mode but may in the case of this highly radiopaque stent be more accurately performed by the selection of reference points outside the stent. Alternatively for the conduction of multicenter studies the pre-intervention interpolated reference vessel diameter may be utilized for the determination of the relative loss and net gain index. While ICUS measurements are unaffected by the radiopaque stent, the poorer accuracy of ICUS measurements, the mechanical problem of ICUS catheter wedging in stenoses of < 1.00mm, and the substantial cost of ICUS catheters will restrict the widespread application of ICUS for the assessment of intrastent restenosis.

INTRODUCTION :

The increasing use of coronary stents for the elective prevention of restenosis and the bailout management of acute or threatened vessel closure following coronary angioplasty has resulted in a greater need for reliable quantitative measurement of angiographic outcome. While most of the currently available stents are of moderate radiopacity, the new tantalum Cordis stent is highly radiopaque. Although during the interventional procedure itself, the strong radiopacity of the tantalum stent facilitates the exquisite positioning of the stent in the target lesion and the subsequent precise placement of additional non-compliant balloons for high pressure intrastent inflations, the radiopaque stent struts may interfere with the assessment of restenosis within the stent at angiographic follow-up.

In a previous in-vitro study by our group comparing the effect on videodensitometric quantitative angiographic measurements of a stainless steel stent (Palmaz-Schatz, Johnson & Johnson, NJ), a cobalt alloy stent (Wallstent, Schneider, Bulach, Switzerland), and a tantalum stent (Wiktor, Medtronic, MN), it was found that the radiopaque tantalum stent (Wiktor) resulted in a consistent overestimation of the minimal luminal cross-sectional area by 9-56% compared to the control values (varying with the contrast concentration and size of the phantom vessel) [1]. Furthermore, in the quantitative angiographic analysis of the multicenter Wiktor restenosis study, it was found that automated edge detection was unreliable in 8% of patients at angiographic follow-up requiring operator interaction [2,3]. The new Cordis tantalum stent has a greater impact on the radiopacity of the contrast-filled lumen than the Wiktor tantalum stent on account of its more dense and highly crenulated strut configuration.

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 manually traced intracoronary ultrasound measurements of the vessel lumen with and without the radiopaque stent in both an in-vitro plexiglass restenosis model as well in the 6 month follow-up of patients who had undergone implantation of the Cordis stent and patients who had undergone balloon angioplasty 6 months previously.

METHODS :

PART I EXPERIMENTAL SERIES

Experimental image acquisition of plexiglass restenosis model with and without stent.
For the in-vitro assessment of restenosis measurements within a new radiopaque stent, phantom vessels were filmed prior to and following their insertion in balloon-expanded Cordis stents of 3.5 mm nominal diameter. The phantom vessels were composed of radiolucent plexiglass cylinders (45 mm 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 [4-8]. The length of each phantom stenosis channel was 5 mm and the adjacent "normal reference" channel length of the proximal and distal segments was 20 mm. The plexiglass channel including the artificial stenosis was filled with contrast medium (iopamidol 370; 370 mg iodine/ml (Bracco, Milano, Italy)). Cinefilm acquisition was performed with additional plexiglass blocks (50 mm anteriorly and 50 mm posteriorly). These plexiglass blocks provide a more appropriate kV-level and a scatter medium which more closely approximates the radiological scatter of the human thorax during angiography. Angiograms were performed using a 5" field of the image intensifier, with separate recordings using two different focal spots (0.4mm and 0.7mm). The radiographic system settings

were kept constant (kV, mA, x-ray pulse width) for each radiographic acquisition. All phantoms were imaged at the radiographic isocenter of the X-ray gantry [9] and acquired on 35-mm cinefilm (Kodak CFE Type 2711, Paris, France). For each of the seven phantom vessels, 10 cineframes were selected both prior to and following their insertion in the Cordis stents providing a total of 140 cineframes for quantitative analysis.

PART II CLINICAL SERIES

Coronary balloon angioplasty. Balloon angioplasty was performed using 8 French polyurethane catheters in 23 lesions of 23 patients at the Thoraxcenter, Erasmus University, Rotterdam. The size of balloon was selected to match the reference vessel diameter obtained from on-line quantitative angiographic analysis after the intracoronary administration of isosorbide dinitrate. Of the 23 lesions treated, a 2.5mm diameter balloon was used in 6 lesions, a 3.0mm in 10 lesions, a 3.5mm in 6 lesions and a 4.0mm balloon in 1 lesion. Of the 23 lesions, 11 were in the left anterior descending coronary artery (LAD), 5 in the left circumflex coronary artery (LCX), and 7 in the right coronary artery (RCA). The follow-up angiogram and intracoronary ultrasound (ICUS) examination were performed at 6 $\pm$2 months after balloon angioplasty.

Coronary stent implantation. Following predilatation, implantation of a new radiopaque coronary stent (Cordis, Miami, U.S.A) was performed using 8 French polyurethane catheters in 23 lesions of 23 patients at Kokura Memorial Hospital, Kitakyushu, Japan. Twenty-one stents were implanted in 21 lesions of 21 patients and four stents were deployed in two lesions of two patients (two stents in each lesion). Of the 25 stents used in 23 lesions, 14 stents were 3.0mm in diameter and 11 stents were 3.5mm in diameter. Of the 23 lesions, 11 were in the LAD, 5 in the LCX, and 7 in the RCA. The follow-up angiographic and ICUS examination were performed at 6 $\pm$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 [10-12] prior to manual injection of contrast medium (iopamidol 370; 370 mg iodine/ml) at 37°C. The 5" field of the 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 per second. An average of 2.6 cineframes per patient were selected for quantitative angiographic analysis. Minimal luminal diameter (MLD), reference vessel diameter (RD) and luminal dimension at the proximal and distal extremities of the radiopaque stent were measured.

Quantitative angiographic analysis. Cinefilms from both the experimental and clinical series were quantitatively analyzed using the computer-based Cardiovascular Angiographic Analysis System (CAAS II; Pie Medical, Maastricht, The Netherlands) [4-8,13-17]. Prior to 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 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 (Mitutoyo No.293-501, Tokyo, Japan; accuracy 0.001 mm). In the experimental study a sufficiently long segment of the plexiglass cylinders including the phantom stenosis with or without the stent was selected for analysis. In the clinical study frames without foreshortening nor overlapping side branches were selected [19,20]. 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 x 24 mm is digitized at a resolution of 1329 x 1772 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 [17]. The contour definition is carried out in two iterations. First, the user defines a number of centerline points within the arterial segment which are interconnected by a straight line, serving as the first model. Subsequently, the program recomputes the centerline, determined automatically as the midline of the contour positions which were detected in the first iteration. 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 was changed of the light emitting diode (LED) which regulated the image brightness during digitization of the cineframe. Manual correction of the automatically detected contours was not performed in either the experimental phantom nor the clinical studies. Minimal luminal diameter (MLD) and reference diameter (RD) were quantified in multiple matched views.

Image Acquisition of Intracoronary Ultrasound (ICUS). Following selective coronary angiography, a mechanical intracoronary ultrasound imaging catheter (30-MHz, 4.3Fr or 2.9Fr, CardioVascular Imaging Systems, Sunnyvale, CA) was introduced over a 0.014 inch guidewire. In the experimental series, a slow manual pull-back 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 pull-back (CardioVascular Imaging Systems, Sunnyvale, CA) with a constant speed of 0.5 mm/second was started 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 (ICUS). Luminal area was defined as the integrated area central to the intimal leading edge echo. Images with minimal cross sectional area (MCSA) in the stent were selected from the pull-back sequence by reviewing the position of the ICUS catheter on the angiographic image. Contrary to the QCA measurements, calculation of the reference vessel diameter by ICUS is based on a point measurement and is not interpolated. Minimal luminal diameter and reference vessel diameter was calculated from MCSA (πr^2). To determine the interobserver variability of ICUS measurements, 30 lesions were independently measured by two observers. The mean signed difference and correlation of the measurements of cross sectional area was 0.02 $\pm$0.37mm^2 and 0.97 respectively.

Statistical analysis. In the experimental study, the individual measurements of MLD were compared with the true phantom diameter using the paired Student's t-test and linear regression. 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 standard deviation of the differences an index of precision.
In the clinical study, the mean and standard deviation of the signed differences between measurements of MLD derived from QCA and from ICUS were used as an index of agreement between measurements. This statistical approach to the comparison of two measurement systems has been previously recommended by Bland and Altman [21].

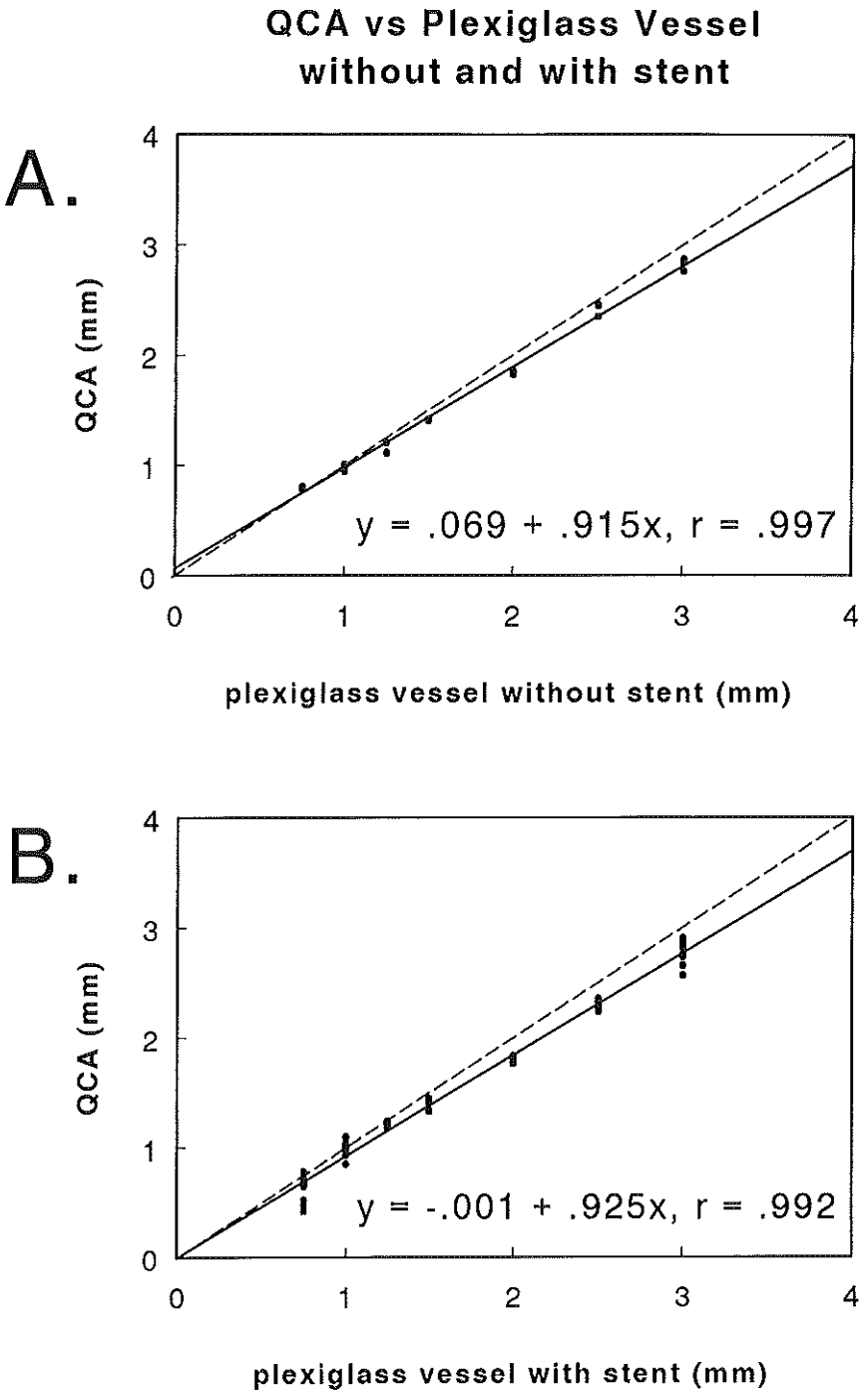

Figure 1. *QCA measurements obtained from 70 cineframes of the plexiglass restenosis model without (figure 1a) and subsequently with (figure 1b) insertion of the vessel in the tantalum stent. The measurement values have been plotted against the true diameter of the contrast-filled lumen of the plexiglass vessel (linear regression).*

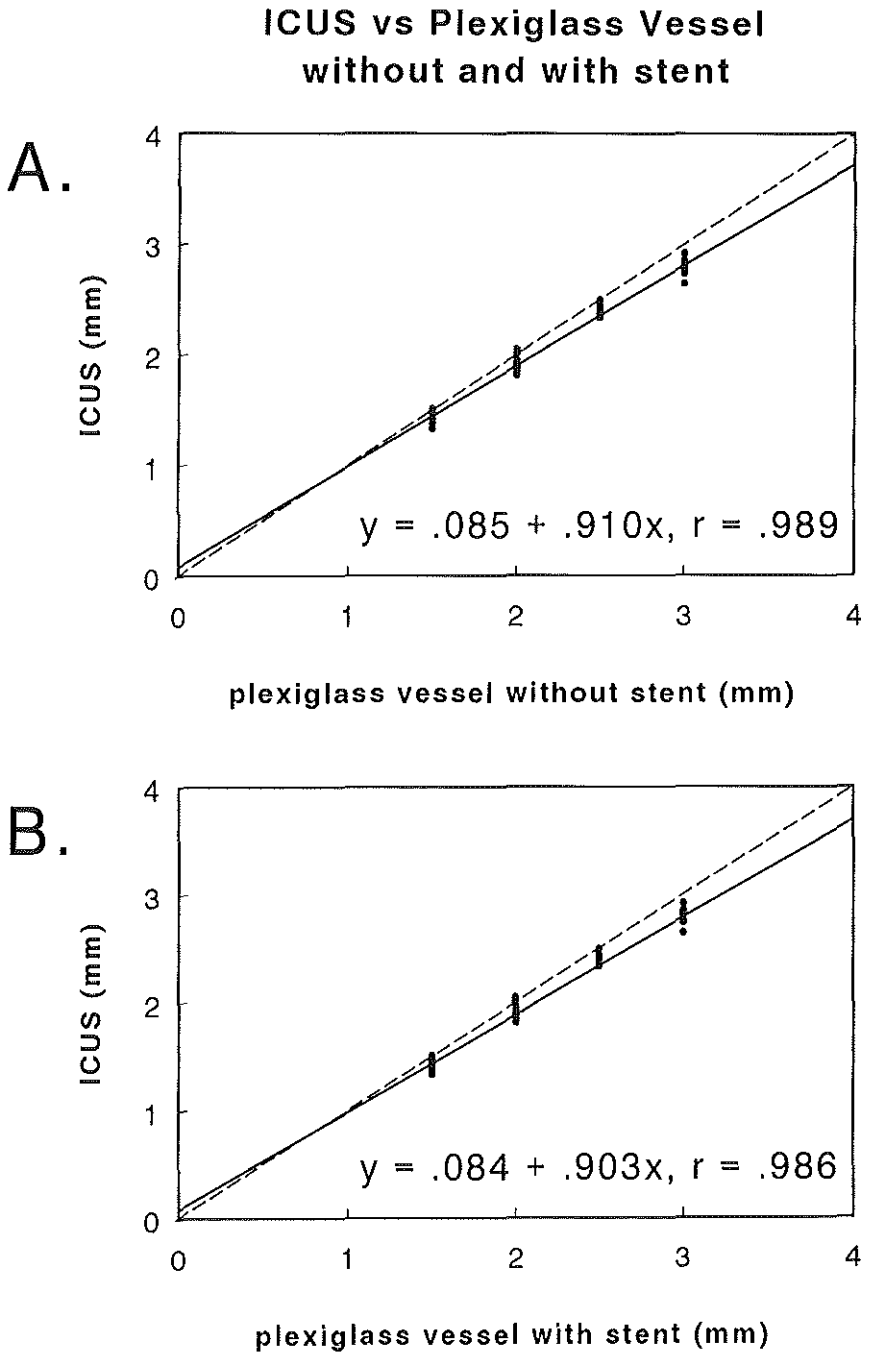

Figure 2. *ICUS measurements obtained from 40 frames of the plexiglass restenosis model without (figure 2a) and subsequently with (figure 2b) insertion of the vessel in the tantalum stent. The measurement values have been plotted against the true diameter of the contrast-filled lumen of the plexiglass vessel (linear regression).*

RESULTS :

PART I - EXPERIMENTAL SERIES

Experimental results for minimal luminal diameter. The results for measurements of the minimal luminal diameter within the plexiglass vessel with and without the stent are presented in **table 1** and in **figure 1 a & b** (QCA) and **figure 2 a & b** (ICUS). Prior to positioning the plexiglass vessels in the stents, measurements of the phantom vessel lumen by QCA were more accurate than ICUS. The reliability of QCA measurements, however, deteriorated in the presence of the radiopaque stent (accuracy of QCA fell from -.07mm to -.12mm), while the reliability of lumen measurements by ICUS was independent of the presence of the radiopaque stent (-.12mm and -.13mm prior to and following introduction of the stent, respectively).

Measurement	*Accuracy*	*Precision*	*Significance*	*Correlation*
QCA without stent	*-0.07*	*±0.08*	*p<.001*	*0.997*
QCA with stent	*-0.12*	*±0.10*	*p<.001*	*0.992*
ICUS without stent	*-0.12*	*±0.09*	*p<.001*	*0.989*
ICUS with stent	*-0.13*	*±0.11*	*p<.001*	*0.986*

Table 1. *QCA and ICUS measurements values of the minimal luminal diameter were compared to the true luminal diameter of the plexiglass vessel (1.00mm).*

Experimental results for reference vessel diameter and % diameter stenosis. Results of reference vessel measurements by QCA and ICUS are displayed in **figure 3 a & b.** Measurement by QCA of the reference vessel diameter within the stent was significantly larger than without the stent ($p < .001$) and the percent diameter stenosis was consequently significantly more severe with the stent than without the stent ($p < .001$). Without the stent, the average MLD obtained from QCA of the 1.00mm plexiglass vessel was 1.00 ±0.01mm and the reference vessel diameter was 2.81 ±0.05 mm providing a 64 ± 1% diameter stenosis. Following introduction of the plexiglass vessel in the stent, the average MLD was 0.99 ±0.06mm and the average reference vessel diameter was 3.44 ±0.10mm providing a diameter stenosis of 71 ±2%. ICUS measurements (2.77mm) of the reference vessel diameter (3.00mm) were unaffected by the presence of the stent.

An example of automated quantitative angiographic analysis of the contrast-filled plexiglass vessel without and with the tantalum stent is provided in **figure 4.**

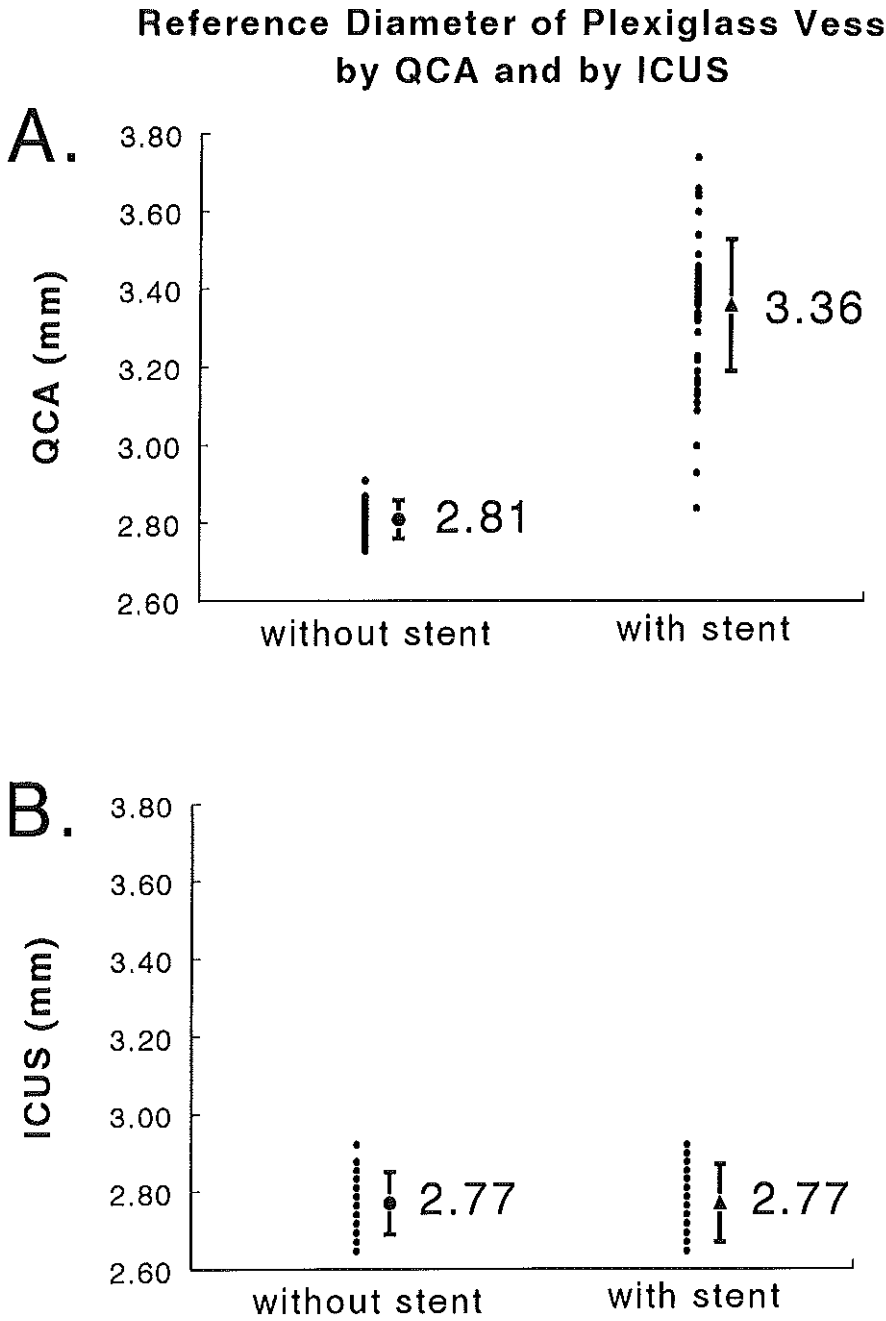

Figure 3. *Comparison of reference diameter obtained from QCA (3a) and ICUS (3b) without and with the radiopaque stent. While measurement obtained by QCA of the reference vessel diameter within the stent was significantly larger than without the stent ($p<0.001$), ICUS measurements were unaffected by the radiopaque stent (n.s.).*

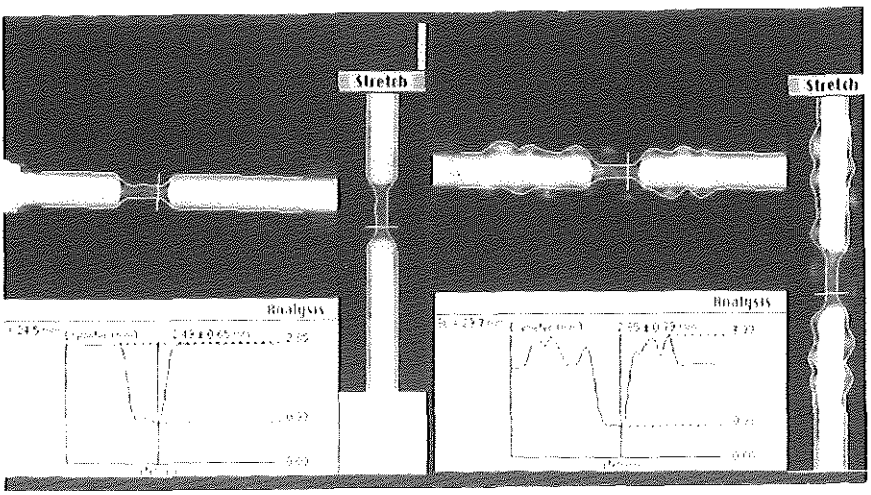

Figure 4. *The contrast-filled lumen of the plexiglass vessel is shown without the stent in the left panel and following insertion of the vessel within the radiopaque stent in the right panel. Automated quantitative angiographic analysis was found to faithfully track the contour of the stenotic segment (true value = 1.00mm) in both the absence and subsequent presence of the stent (minimal luminal diameter = 0.99mm and 0.98mm, respectively). Automated quantitative angiographic analysis of the normal reference vessel diameter (true value = 3.00mm), however, was significantly effected 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 3.77mm following introduction of the stent. The overestimation of the reference vessel diameter in the presence of the stent resulted in an exaggeration of the severity of the percent diameter stenosis.*

PART II - CLINICAL SERIES

The results of measurements of MLD from ICUS are plotted against those from QCA for the balloon angioplasty and coronary stent patients in **figure 5 a** and **figure 5 b** respectively. Of the 23 stented lesions, 3 showed signs of catheter wedging of the ICUS catheter and in the remaining 20 lesions minimal cross sectional area and MLD was measured. Of the 23 balloon angioplasty lesions, 8 showed a signs of catheter wedging. The agreement of ICUS and QCA measurements (ICUS - QCA) was poorer in the balloon angioplasty patients (.68mm ±.42mm) compared to the stented patients (-.05mm ±.42mm). Similarly, the correlation of ICUS and QCA measurements was .40 in the balloon angioplasty population and .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 the each radiopaque stent (46 measurements) from ICUS are plotted against those from QCA in **figure 6.** The agreement between the two sets of measurements at the extremity of the stent was -0.06mm ±0.42mm (mean and standard deviation of the signed differences) associated with a correlation coefficient of 0.63.

An example of angiographic measurement of the MLD of a patient with a new radiopaque stent can be seen in **figure 7.** The difference between ICUS and QCA measurements was small both at the site of the MLD and at the stent extremity.

DISCUSSION :

The principle findings of our study were : a) in the plexiglass restenosis model, QCA provided more accurate measurements of minimal luminal diameter than ICUS; b) following introduction of the plexiglass vessel in the radiopaque stent, the accuracy of QCA measurements deteriorated while the accuracy of ICUS measurements of both the minimal luminal diameter as well as the reference vessel diameter was unaffected by the radiopaque stent; c) measurements by QCA of the interpolated reference vessel diameter of the plexiglass vessel were rendered inaccurate by the presence of the radiopaque stent and resulted in the overestimation of the severity of the % diameter stenosis; d) in the 6 month follow-up of patients post coronary intervention, agreement of ICUS and QCA measurements was higher in patients who were stented compared to those who underwent balloon angioplasty alone.

Comparison between ICUS and edge-detection QCA measurement. Previous studies which examined the relationship of the ICUS and QCA measurements in normal coronary segments reported a favourable correlation between the two quantitative imaging modalities [22,23], while those studies which included lesions post balloon angioplasty reported a poor correlation of the two measurement techniques [24-26]. Complex morphological changes caused by balloon angioplasty may result in a deterioration of agreement between the two measurement systems post balloon angioplasty. As it is assumed that coronary lumen may be more circular and smooth post stent implantation than those post balloon angioplasty, the better agreement obtained between ICUS and QCA measurements may be conveyed by the lumen symmetry enforced by stent implantation.

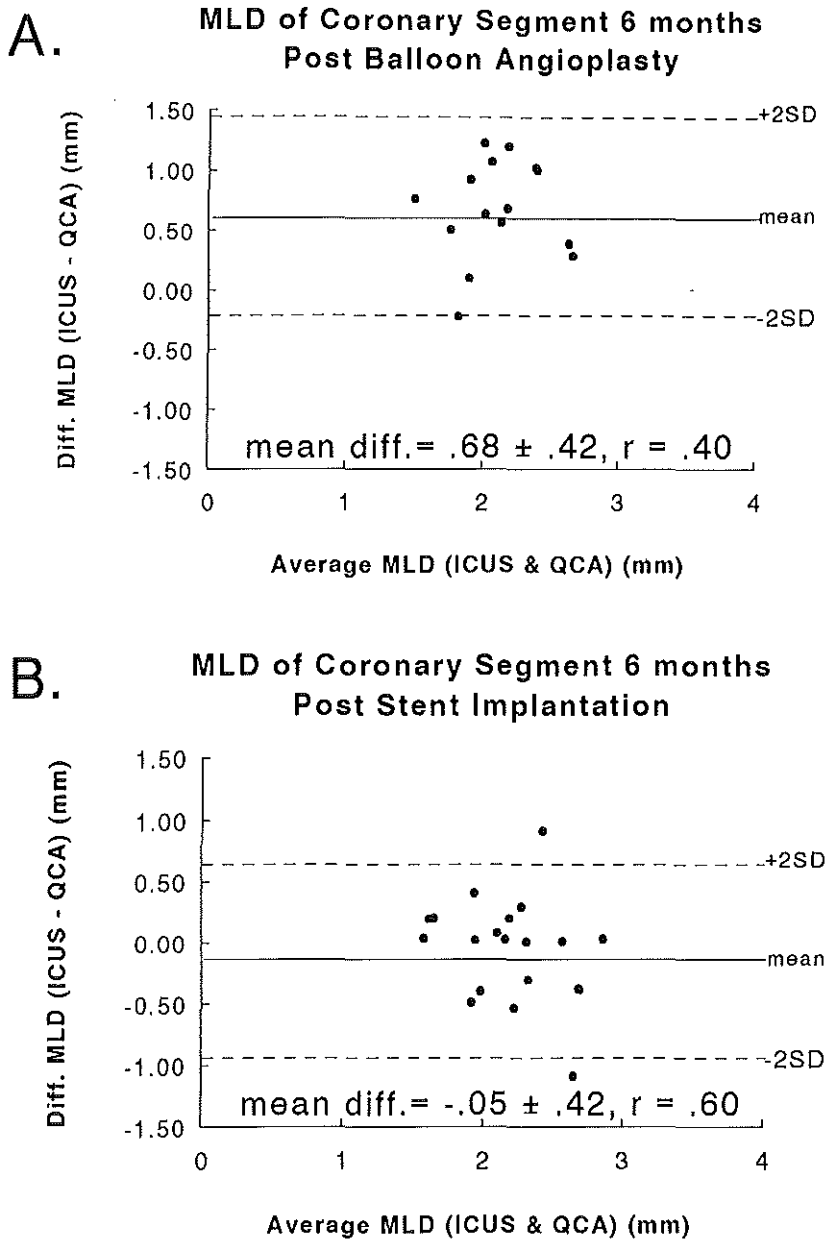

Figure 5. *The figures display the agreement between measurements obtained from geometric QCA and ICUS according to the statistical approach proposed by Bland and Altman (21) at 6 month follow-up of patients who had undergone balloon angioplasty (5a) and of patients who had undergone implantation of the radiopaque stent (5b). In 5a the difference 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. In 5b 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 the stented patients.*

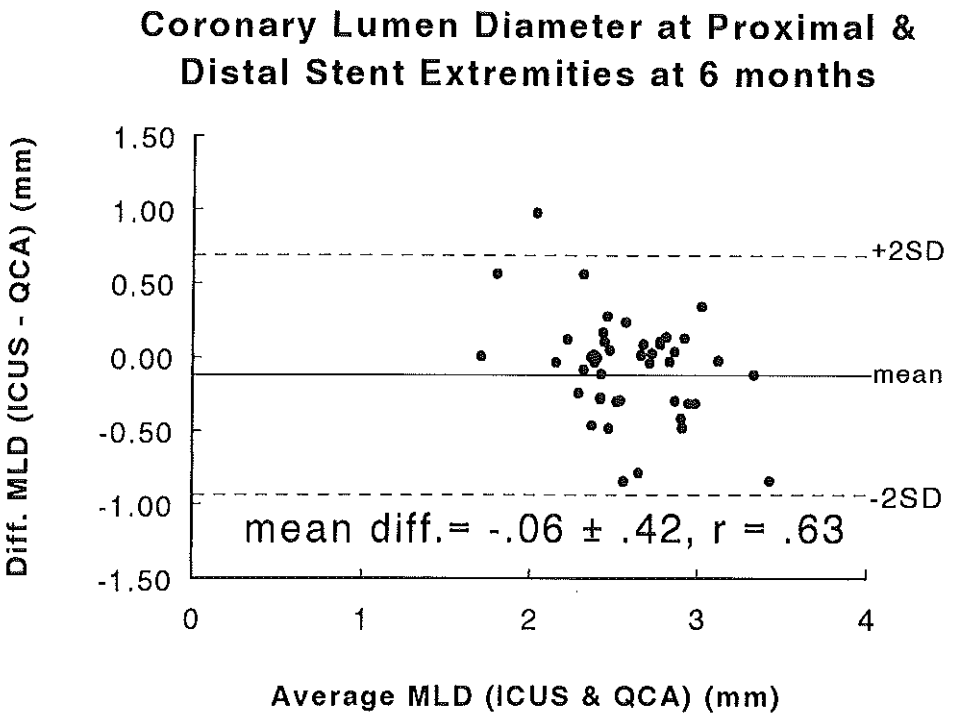

Figure 6. *The figure displays the agreement between measurements obtained from QCA and ICUS at the 46 proximal and distal extremities of the 23 stents at 6 month follow-up according to the statistical approach proposed by Bland and Altman [21]. The differences between ICUS and QCA measurement values have been plotted against their mean value.*

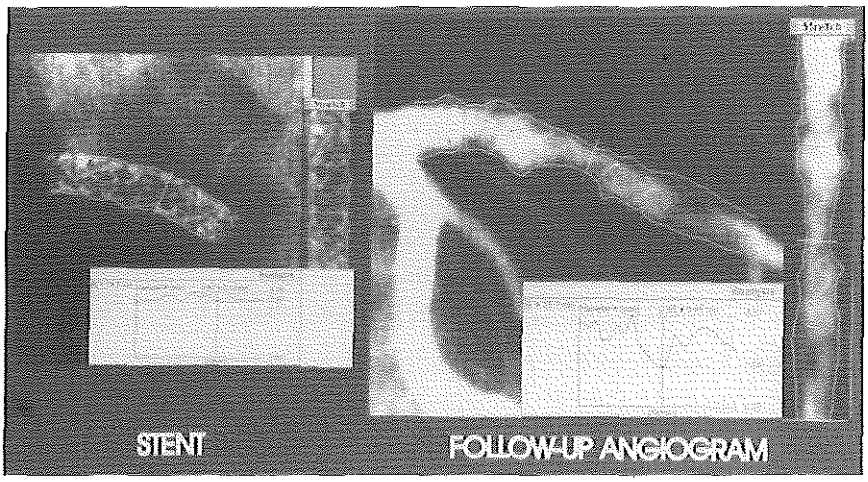

Figure 7. *At six month follow-up angiography, the radiopacity of the tantalum stent can be traced by automated edge detection without contrast media (left panel). In this patient, automated edge detection of the minimal luminal diameter appeared to function reliably following contrast injection (right panel).*

Limitation of QCA. During QCA measurement of the minimal luminal diameter within a stented vessel segment, the automated edge detection algorithm will trace the true diameter of the contrast-filled lumen at the point of most severe stenosis in between the radiopaque stent struts i.e. in the interstrut intervals. QCA measurements of the minimal luminal diameter will thus remain reliable for two reasons; firstly 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; and secondly 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 measurements by automated edge detection may be unreliable for two reasons; firstly, beyond the subsegment of maximal restenosis the outer contour of the radiopaque stent struts lie 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; and secondly the interpolated reference vessel diameter is based on multiple scanlines over a large extent of the analysed segment which will incorporate both scan lines which do and scanlines which 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 [4-8,13-17]. The interpolated reference diameter is derived from the edge-detected diameter function of the non-stenotic 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 analysed coronary segment. The interpolated reference vessel diameter is taken as the value of the reconstructed diameter function at the position of the minimal luminal diameter. The advantages of this approach is 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. 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 Cordis stent (or an average of both) may prevent the overestimation of vessel size associated with use of the default interpolated reference vessel diameter mode.

Limitation of intracoronary ultrasound. ICUS can provide clinically useful information on lesion and vessel characterization as well as for the guidance of optimal stent deployment [27-30]. However, the 2.9 French size of the ultrasound catheter restricts the application of ICUS for lumen quantification to lesions of >1.0mm in diameter on account of mechanical wedging of the catheter. In our study 3 of 23 stented lesions and 8 of the 23 lesions previously treated by balloon angioplasty showed signs of catheter wedging and these measurements were therefore excluded from analysis (these proportions (3/23 and 8/23) would be consistent with expectations of the different long-term angiographic outcome conveyed by the two interventional techniques). Thus while ICUS may be useful immediately post intervention for assessment of stent deployment, by the time of 6 month follow-up those lesions with significant restenosis may be unsuitable for ICUS evaluation. Furthermore, as the price of ultrasound catheters remain expensive (approximately $1,600), it is difficult to justify the use of ICUS for the follow-up of all stented patients.

Implications. For patients undergoing 6 month angiographic follow-up of this new radiopaque stent, measurements by QCA of the minimal luminal diameter may be performed reliably. When a QCA system is used which 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 overestimated unless a manually selected reference point(s) proximal and/or distal to the tantalum stent is used. Alternatively for the determination of relative loss (absolute loss in minimal luminal diameter normalised for vessel size) the interpolated reference vessel diameter measured pre intervention may be used.

At the time of stent implantation and thus prior to 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 measurements during stent deployment. Thus determination of the absolute (MLD post - MLD pre) and relative (MLD post - MLD pre normalised for reference vessel diameter pre) gain achieved at stent implantation, the absolute (MLD post - MLD follow-up) and relative (MLD post - MLD follow-up normalised for reference vessel diameter pre) loss in minimal luminal diameter over 6 months, and the loss index (loss / gain) (restenosis process) as well as measurement of the absolute minimal luminal diameter at follow-up (final outcome) should be feasible with QCA in patients undergoing implantation of this tantalum stent.

Conclusion. In the 6 month follow-up of patients who have undergone implantation of the highly radiopaque Cordis tantalum stent, assessment of restenosis can be reliably quantified by QCA by the use of the minimal luminal diameter rather than the percent diameter stenosis. Assessment by QCA of the reference diameter of the stented coronary segment at follow-up should not be performed in the interpolated mode but may in the case of this highly radiopaque stent be more accurately performed by the selection of reference points outside the stent. Alternatively for the conduction of multicenter studies the pre-intervention interpolated reference vessel diameter may be utilized for the determination of the relative loss and net gain index. While ICUS measurements are unaffected by the radiopaque stent, the poorer accuracy of ICUS measurements, the mechanical problem of ICUS catheter wedging in stenoses of < 1.00mm, and the substantial cost of ICUS catheters will restrict the widespread application of ICUS for the assessment of intrastent restenosis.

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Chapter XVII

Comparative quantitative mechanical, radiographic, and angiographic analysis of eight coronary stent designs

David Keane, Johan Schuurbiers, Cornelis J Slager, Yukio Ozaki,
Ad den Boer, Nico Bruining, Patrick W Serruys

(in review)

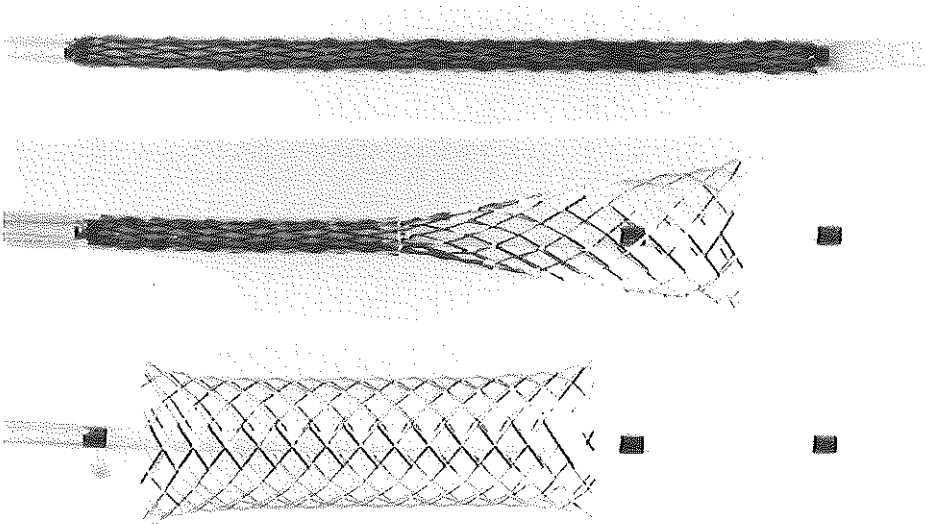
Abstract

Background. Although all coronary stents currently undergoing clinical evaluation are metallic, each stent is unique in design with resultant variable radial compliance and different degrees of radiopacity. In the selection process of an individual stent for an individual patient, the clinician should be familiar with the technical characteristics of each stent. The mechanical characteristics of stents are important to gain insight into the altered vessel wall compliance and the force exerted by the stent wires on the vessel wall post stent implantation while the radiographic characteristics are of clinical importance for the facilitation of the deployment procedure and the analysis of the angiographic outcome.

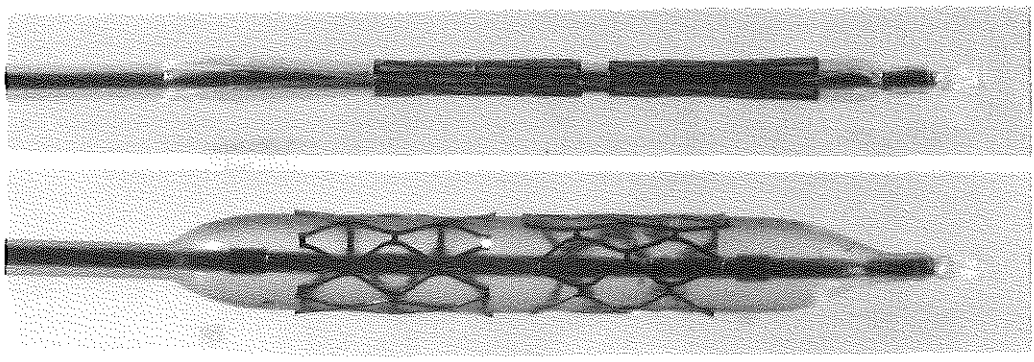
Methods. To enable the comparison of the relative advantages and disadvantages and potential clinical niche of each stent design, we performed a comparative analysis of all the stents which are currently available for clinical evaluation. We performed our study in three parts : In part I, to gain insight into the range of radial compressibility proffered by each of the currently available coronary stents we investigated 8 self- and balloon-expandable stents by measuring the Pressure-Diameter ratio relation in vitro in a customized measurement system. In part II, we determined the relative radiopacity of each stent by comparing the video signal of a lineplot through the radiographic profile of each stent successively. In part III, we determined the influence of each metallic stent on the reliability of automated quantitative angiographic measurements by both the geometric (edge detection) and densitometric techniques of the contrast-filled vessel lumen.

Results. Our study revealed marked variability among the currently available stents in terms of their radial compliance, their radiopacity, and their interference with the reliability of automated quantitative angiographic measurements by both geometric (edge detection) as well as videodensitometric techniques. The findings of our studies were consistent with the expectations from the strut thickness and configuration and the metallic composition of each stent design. The comparative results may be of relevance for the selection of different stents for different coronary indications and the analysis of subsequent angiographic outcome.

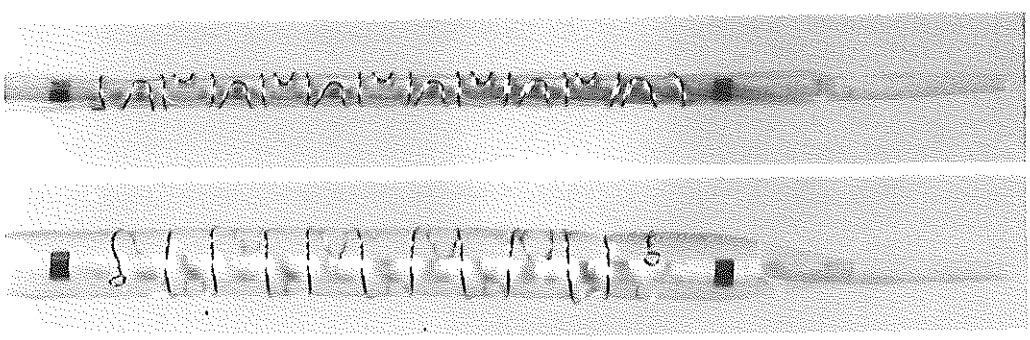
Self-expanding Less-Shortening Wallstent



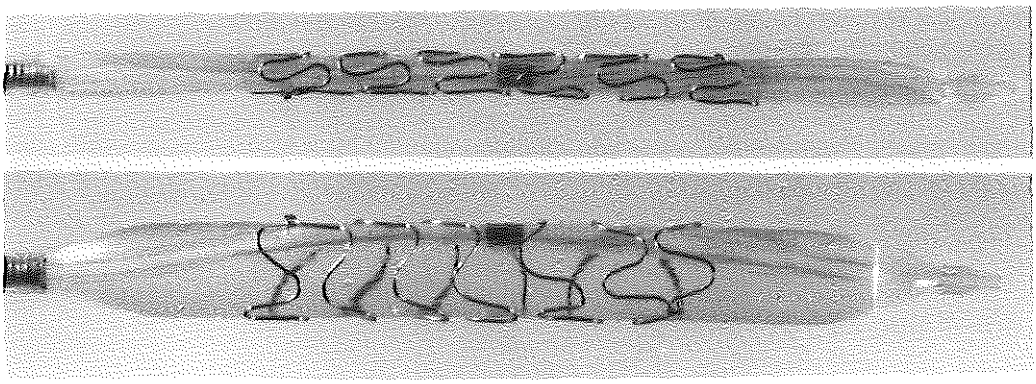
Palmaz-Schatz stent



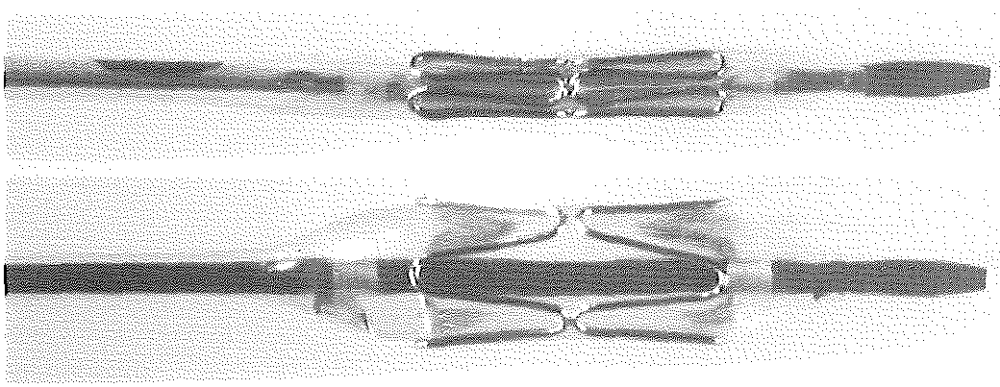
Gianturco-Roubin stent



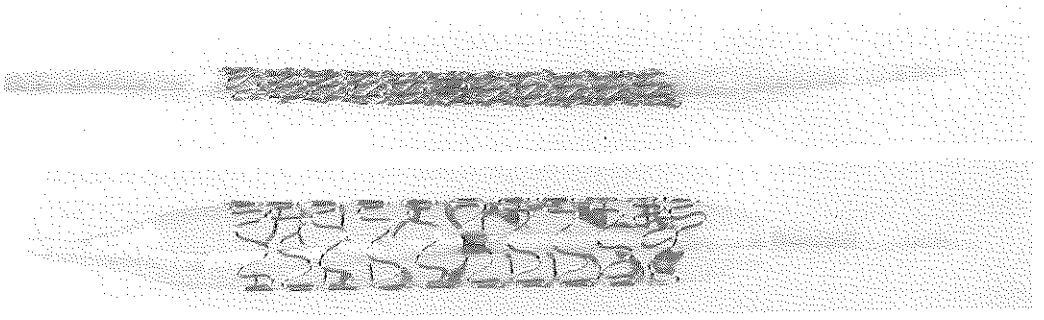
Wiktor stent



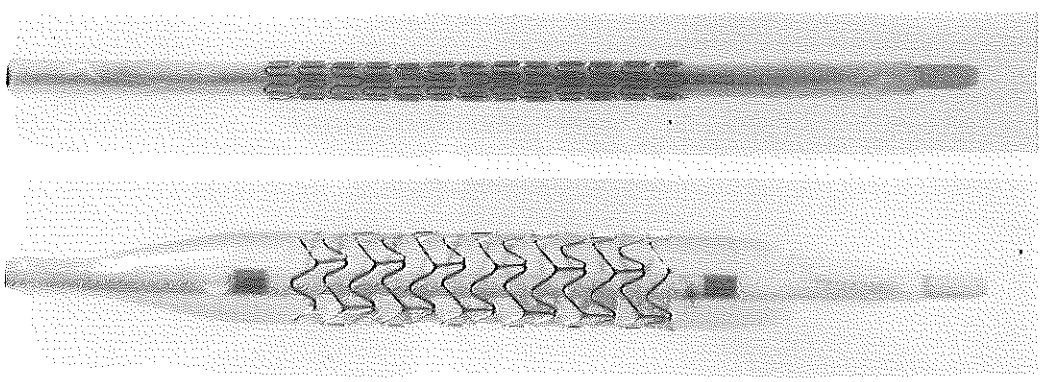
AVE Micro stent



Cordis stent



Multilink stent



INTRODUCTION

Coronary stents are intended to scaffold the coronary vessel wall, tacking back intimal dissections post balloon angioplasty and preventing acute and chronic recoil with consequent reduction in restenosis over 6 months. Although all coronary stents currently undergoing clinical evaluation are metallic, each stent is unique in design with resultant variable radial compliance and different degrees of radiopacity. In the selection process of an individual stent for an individual patient, the clinician should be familiar with the technical characteristics of each stent. While the range of diameters, lengths and profile of each stent are readily available and easily compared among the different stent designs there is yet no standardized information on the relative mechanical behaviour or the comparative radiographic features of each stent design.

To enable the comparison of the relative advantages and disadvantages and potential clinical niche of each stent design, we undertook a comparative analysis of the mechanical behaviour and radiographic features of the all the stents which are currently available for clinical evaluation. We performed our study in three parts :

In part I, to gain insight into the range of radial compressibility proffered by each of the currently available coronary stents we investigated 8 self- and balloon-expandable stents by measuring the Pressure-Diameter ratio relation[3] in vitro in a customized measurement system.

In part II, we determined the relative radiopacity of each stent by comparing the video signal of a lineplot through the radiographic profile of each stent successively.

In part III, we determined the influence of each metallic stent on the reliability of automated quantitative angiographic measurements by both the geometric (edge detection) and densitometric techniques of the contrast-filled vessel lumen.

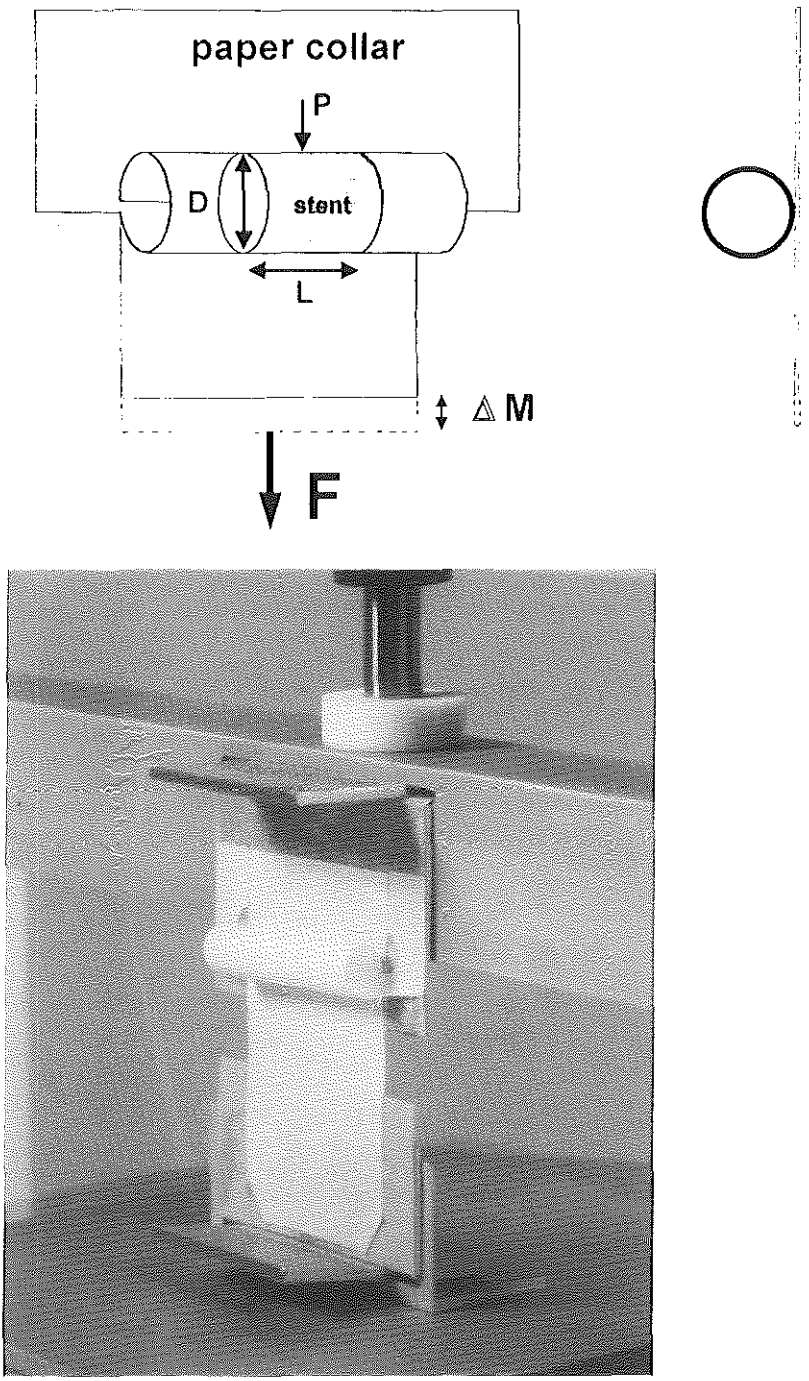


Figure 1
Paper collar used to exert a radial pressure (P) on the stent with an outer diameter D by pulling with an calibrated force (F). The resulting displacement M is measured with a micrometer.

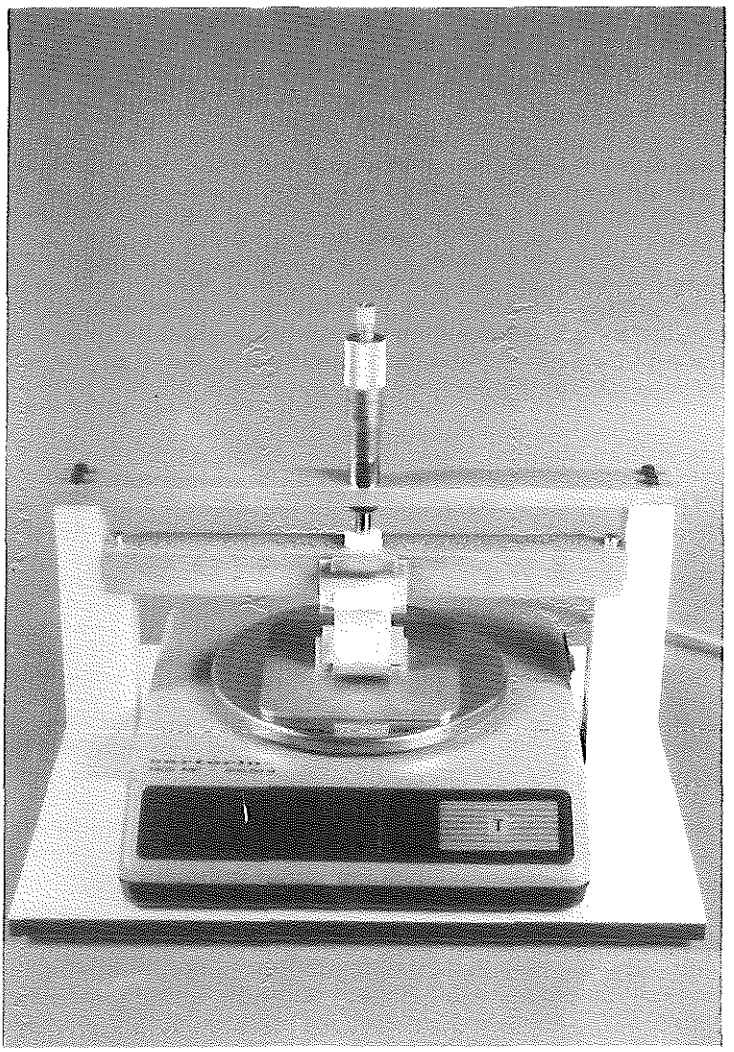


Figure 2
Measurement apparatus. The bar with the collar assembly is pushed against the micrometer by 2 springs. Vertical translation of the bar is achieved by rotation of the micrometer.

METHODS

PART I

RADIAL COMPLIANCE

Measurement apparatus. The basic method used to deform the stents was described by Fallone et al. and consisted of a wrap-a-round collar of the nonelastic paper backing of Scotchal® film [1,2]. We used nonelastic coated low-friction paper (3M, St.Paul, MN) collar with a 30mm width (**Figure 1**). We fixed the upper end of the paper collar to a bar which was pushed up by springs against a micrometer (Mitutoyo 0-25 mm, resolution 0.01mm). The micrometer was mounted on a frame and vertical translation of the bar was achieved by rotation of the micrometer spindle. The lower end of the collar was fixed onto a weight of 300 gr which was positioned on a balance (Sartorius 1409 MP, resolution 0.01 g) (**Figure 2**).

Measurement procedure. First the micrometer reading was calibrated using a glass tube with a reference diameter (Dref) of 7.3 mm while a force of 0.05 Newton (N) was applied to the collar. When measuring stents with diameters different from the glass tube, the relation between the micrometer reading and the stent diameter was defined by:

$$D = Dref - \frac{M - Mref}{\pi} \qquad (1)$$

where D is the actual stent diameter and M the corresponding micrometer reading, and Dref and Mref represent the diameter of the glass tube and the corresponding micrometer displacement reading respectively.

Stiffness of the system itself was determined by repeated (n = 4) measurement of the force-displacement curve using a stainless steel tube with an outer diameter of 4.1 mm, a wall thickness of 0.6 mm and a length of 47 mm. After inserting the tube in the collar, a force (0.1 to 1 N), was applied to the collar with 0.1 N increments by adjustment of the micrometer.

Stents. The force-displacement curve of a self-expandable cobalt-based alloy Wallstent (Schneider, Bulach, Switzerland) and 7 balloon-expanded stents, the original single-articulation stainless steel Palmaz-Schatz design and the new multiple helicoid articulation stainless steel Palmaz-Schatz design (Johnson & Johnson Interventional Systems NJ), the stainless steel Gianturco-Roubin (Cook, IN - stainless steel), the tantalum Wiktor (Medtronic, MN - tantalum), the stainless steel Micro (Applied Vascular Engineering CA), the tantalum Cordis (Cordis FL - tantalum), and the stainless steel Multilink (Advanced Cardiovascular Systems CA) was measured. After inserting the expanded stent in the collar, a lightsource was used to illuminate the inner side (lumen) of the collar in order to visualize the collar wall approaching the stent struts. After the micrometer was adjusted until the stent struts were in apposition with the collar, the balance was tared. The micrometer reading reflected the initial expanded outer diameter of the stent according to *equation 1*. A force from 0.1 to 1N in 0.1N increments indicated by the balance, was applied to the collar by micrometer adjustment. The corresponding displacement was measured by the micrometer reading. All stent diameter measurements were corrected for the elasticity of the system by subtracting

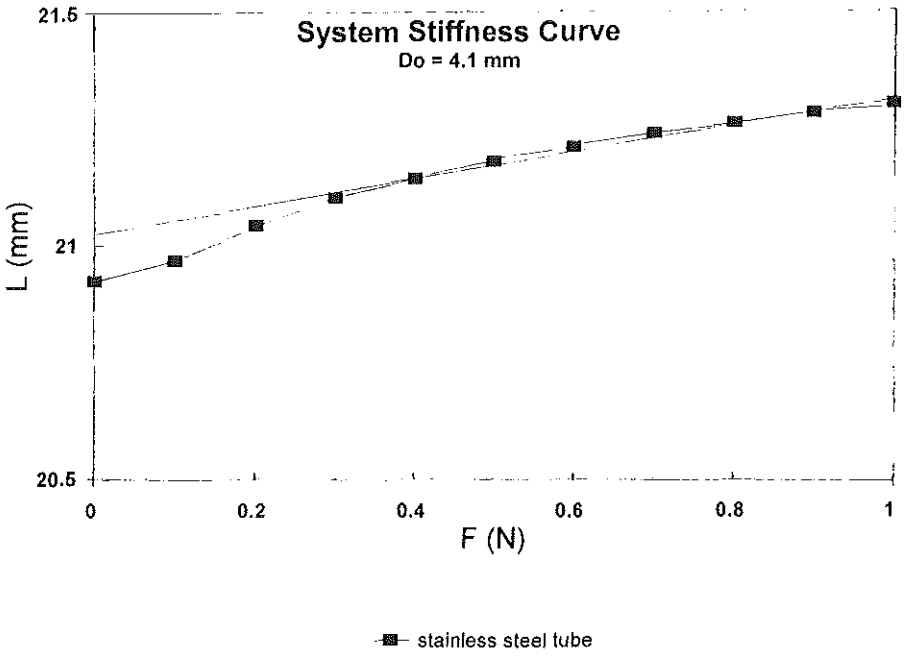


Figure 3
Elasticity of the system illustrated by the force-displacement curve of a stainless steel tube with a diameter of 4.1 mm. Note the nonlinear region caused by shape-adaptation of the collar.

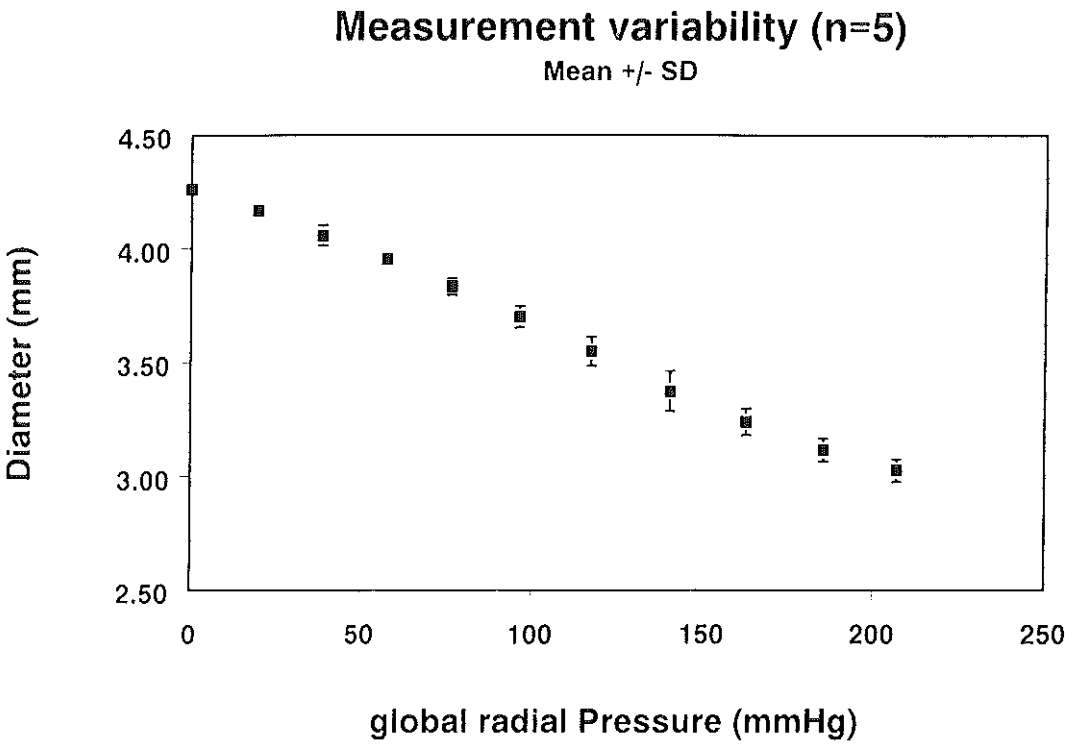


Figure 4
Measurement variability and mean diameter(D) of the Wallstent calculated from repeated (n = 5) measurement of the force-displacement curve is plotted against the global radial pressure (P)

the lengthening of the collar as measured on the stainless steel tube at the corresponding forces. The length of the stents was measured at zero force and at maximal force (1N) applied to the collar using a calliper.

Pressure calculation: To allow for comparison of different types of stents, we normalized for the length of each stent by introducing the global radial pressure. At the intermediate steps the length of the stents used in the radial pressure calculations was achieved by linear interpolation. If we neglect the thickness of the collar and stent, the applied force F on the collar results in a wall tension T in the stent of:

$$T=\frac{F}{L} \qquad (2)$$

where F is the applied force on the collar and L the length of the stent. According to Laplace's law the relation between tension T and pressure P is:

$$P=\frac{2T}{D} \qquad (3)$$

where P is the global radial pressure, T is the wall tension and D the stent diameter. Substitution of *(2)* in *(3)* gives:

$$P=\frac{2F}{LD} \qquad (4)$$

In order to express the pressure P in mmHg, the applied force F in N and the length L and diameter D in mm, *(4)* results in:

$$P=\frac{F}{68LD}CDOT \quad \text{(mmHg)} \qquad (5)$$

To account for the varying initial stent diameters, the global radial pressure was related to the relative stent diameter Dr :

$$Dr=\frac{D}{Do} \qquad (6)$$

with Do being the stent diameter at the initial force of 0.1N and D the actual stent diameter.

Analysis of the linear force-displacement curve of the stainless steel tube resulted in a stiffness (F/L) of 4 N/mm, for the measurement setup **(Figure 3)**. The mean variability of the displacement measurement on the stainless steel tube (n=4) over a force range of 0.1 to 1N expressed as the standard deviation was $\pm 27\mu m$.

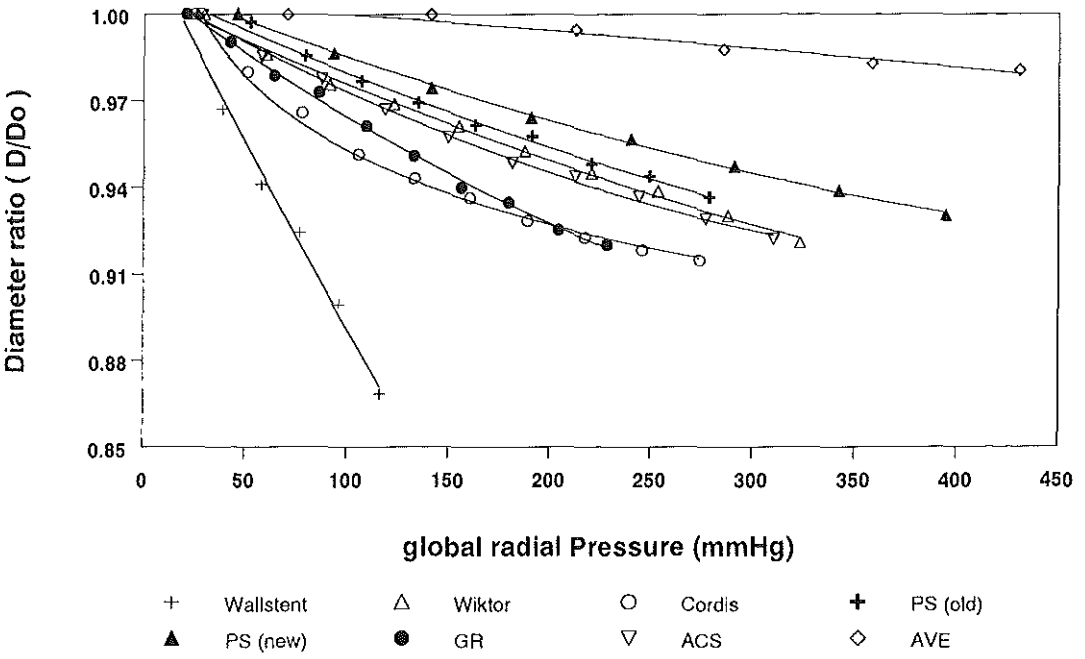


Figure 5
Relative diameter (D/Do) of 8 different self- and balloon-expandable stents is plotted against the global radial pressure (P).

The variability of the method was evaluated by repeated measurement (n = 5) of the force-displacement curve of the Wallstent over a 0-200 mmHg pressure range. Repeated measurement showed a very low variability with a mean relative error of < 1.4% (SD) of the measured mean diameter (**Figure 4**).

The nonlinear region in the force-displacement curve of the stainless steel tube results from adaptation of the paper strip to the shape of the tube and deformation of the paper strip especially at the positions where it is fixed. The stiffness (F/L) of the system in the linear region was 4 N/mm. Correcting the measurements for the relative low stiffness of the paper collar assembly introduces an additional error which will be small, because of the very low variability in the system stiffness measurement using a stainless steel tube (27μm). The estimated increase in variability of the diameter measurements introduced by this correction is 8.6 μm (27 / π). As repeated measurements of the force-displacement curve of the Wallstent demonstrated a low variability in the measured diameter, we expect the measurement error introduced by the limited stiffness of the system, and the variability in the stent diameter measurements are small.

Due to construction restraints and the limited flexibility of the paper collar some force is needed to adapt the collar to a circular shape. The mean force to deform the collar in the measured diameter range was .075 $\pm$.0125 N. For stent diameters smaller than 2.5 mm the force to deform the paper collar steeply rises, however, all coronary stents are $\geq$ 2.5mm and this should therefore not limit the application of the method to coronary stent analysis.

The relative diameter (D/Do) of 8 different self- and balloon-expandable stents were plotted against the global radial pressure (P) (**figure 5**).

PART II

COMPARATIVE RADIOPACITY

The eight stents under comparison were aligned on plexiglass blocks to provide a kilovoltage of 70kV and recorded on fluoroscopy on a Coroskop T.O.P. X-ray unit which incorporated a Polydoros IS/C generator and a Megalix 30/82 X-ray tube with a focal spot size of 0.4mm (Siemens A.G., Munich Germany). Using the HONIE software function of the HICOR system (Siemens), the videosignal of each stent was analyzed and compared. With this system, a moveable (joystick) plotline was drawn to pass through the struts of each metallic stent in the transverse axis of the stent and thus the oblique or longitudinal axis of the struts. The displayed videosignal for each stent was compared and the order of alignment of the eight stents was switched until a consecutive descending order of radiopacity was achieved from left to right (**figure 6**).

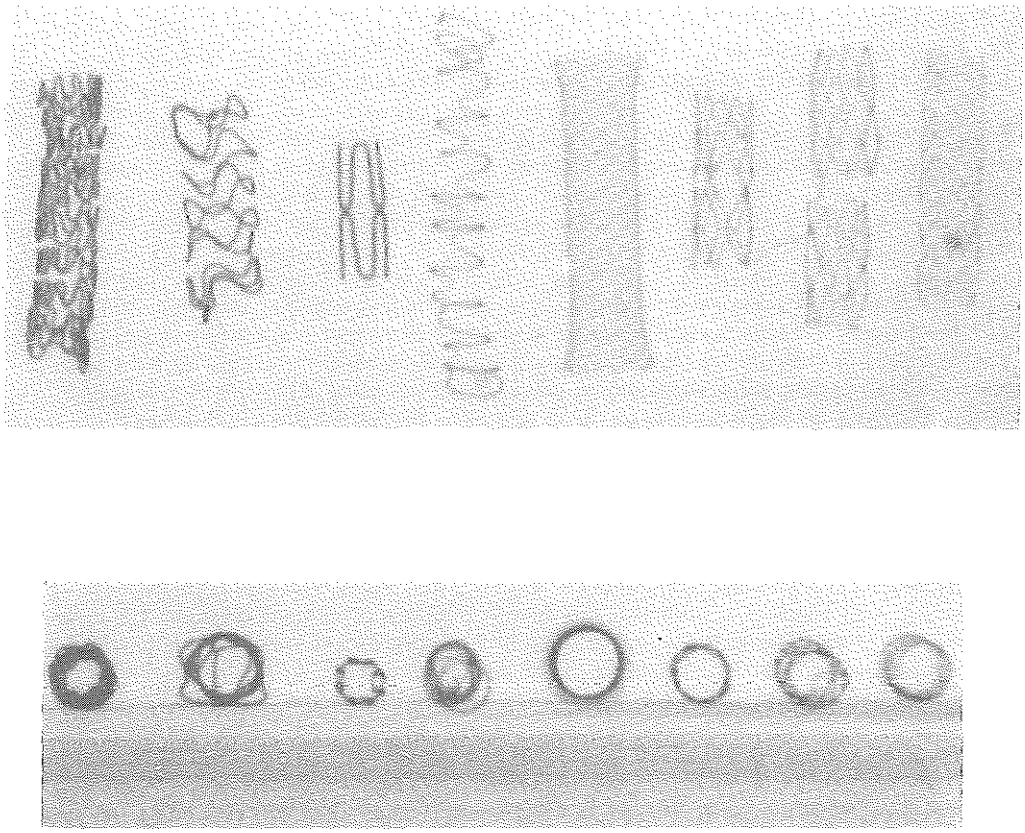


Figure 6 a & b
Relative radiopacity of eight coronary stents were compared using a line plot of their video signal. In order of decreasing radiopacity from left to right the stents were 1) Cordis, 2) Wiktor, 3) AVE Micro stent, 4) Gianturco-Roubin, 5) Wallstent, 6) new Palmaz-Schatz design, 7) old Palmaz-Schatz design (thinner strut diameter than new Palmaz-Schatz), 8) Multilink.

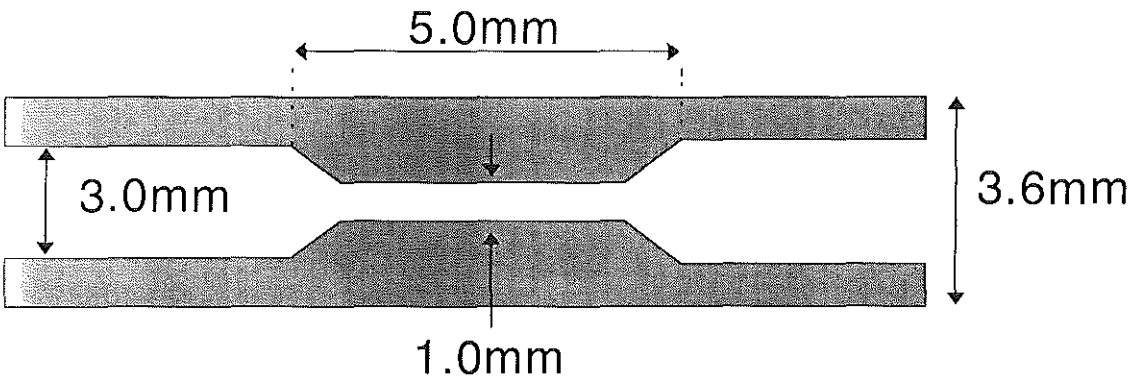
PART III

COMPARATIVE GEOMETRIC AND DENSITOMETRIC QUANTITATIVE ANGIOGRAPHY

For the in-vitro assessment of the effect of each metallic stent on the reliability of automated quantitative angiographic measurements by both videodensitometry as well as by edge detection (geometric) techniques we compared measurements of a contrast filled plexiglass vessel which was inserted in each stent consecutively. The radiolucent plexiglass vessel had normal reference vessel diameter segment (3.00mm in diameter and 20mm in length) as well as a stenosis segment (1.00mm in diameter and 5mm in length). The total length of the plexiglass vessel was 45mm and the outer diameter was 3.6mm (**figure 7**). The plexiglass channel including the artificial stenosis was filled with contrast medium (iopamidol 370; 370 mg iodine/ml (Bracco, Milano, Italy)). Cinefilm acquisition was performed with additional plexiglass blocks (50 mm anteriorly and 50 mm posteriorly). These plexiglass blocks provide a more appropriate kV-level and a scatter medium which more closely approximates the radiological scatter of the human thorax during angiography. Angiograms were performed using a 5" field of the image intensifier, with separate recordings using two different focal spots (0.4mm and 0.7mm). Each stent was imaged at the radiographic isocenter of the X-ray gantry (17) and the radiographic system settings were kept constant (kVp, mA, ms) for each stent. The images were acquired on 35-mm cinefilm (Kodak CFE Type 2711, Paris, France) using an Arritechno 90 cine camera (Arnold & Richter, Munich, Germany) with an 100 mm optical lens (over framing). The cinefilms were processed by a Refinal developer (Agfa-Gevaert, Leverkusen, Germany) for 4 minutes at 28°C. The film gradient was measured in all cases to ensure that the optical densities of interest were on the linear portion of the sensitometric curve. For each of the eight stents and for the plexiglass vessel without a stent, 10 cineframes were selected providing a total of 90 cineframes for quantitative analysis.

Quantitative angiographic analysis. Cinefilms were quantitatively analyzed using the computer-based Cardiovascular Angiographic Analysis System (CAAS II; Pie Medical, Maastricht, The Netherlands) [5-14]. Prior to 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. Quantitative measurements were calibrated by the use of an isocentrically-recorded contrast-free catheter tip as a scaling device [16-21]. The nontapering catheter tip was measured with a precision-micrometer (Mitutoyo No.293-501, Tokyo, Japan; accuracy 0.001 mm). A sufficiently long segment of the plexiglass cylinders including the phantom stenosis with or without the stent was selected for analysis.

Geometric (edge detection) QCA. In the CAAS II system, the entire 18 x 24 mm cineframe is digitized at a resolution of 1329 x 1772 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. The contour definition is carried out in two iterations. First, the user defines a number of centerline points within the vessel which are interconnected by a straight line, serving as the first model. Subsequently, the program recomputes the centerline, determined automatically as the midline of the contour positions which were detected in the first iteration. If the automatically detected contour did not faithfully track the border of the lumen, the level was changed of the light emitting diode (LED) which regulated the image brightness during digitization of the cineframe. Manual



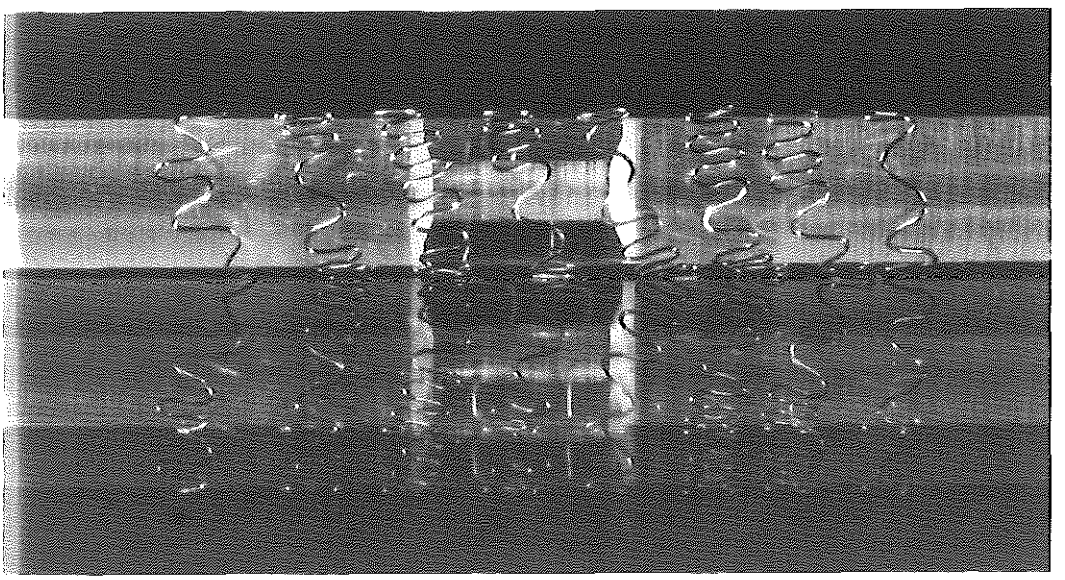


Figure 7. The phantom plexiglass vessel served as an in-vitro model for intrastent restenosis by the insertion of the model into each expanded stent. Quantitative angiographic measurements were made of the contrast-filled lumen without the stent (control measurements) and subsequently within each stent.

correction of the automatically detected contours was not performed in either the experimental phantom nor the clinical studies.

Videodensitometric QCA. Videodensitometric measurement is based on the relationship between the attenuating power of the lumen filled with contrast medium and the X-ray image intensity [11-14]. Using this relationship, a videodensitometric profile which is proportional to the cross-sectional area 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 non-diseased area. Conversion of the individual videodensitometric profiles to absolute values was performed after a transformation of the videodensitometric profile found in a cross-sectional area of non-diseased segment, assuming a cross-sectional area at any point is proportional to the densitometric profiles at the point. Minimal luminal diameter was calculated from the minimal luminal cross sectional area.

The individual measurements of the minimal luminal diameter, the mean luminal diameter, and the maximal luminal diameter were compared with the true phantom diameter using the paired Student's t-test and linear regression. The mean of the signed differences between the true phantom diameters and the individual MLD values derived from measurements of QCA was considered an index of accuracy and the standard deviation of the differences an index of precision. The percent deviation of QCA measurements for each stent was calculated from the measurement of the plexiglass vessel when analyzed in the absence of any stent (control QCA measurement).

RESULTS

PART I

In part I the radial compressibility of 8 different metal balloon-expandable and self-expandable stents were measured (**figure 5**). The results of the measurements indicated that Wallstent was the most compliant stent while the AVE Micro stent proffered the greatest resistance to compression. The radial compliance of the new Palmaz-Schatz design and the Wiktor stent were equivalent and second to the AVE Micro stent, while the compliance of the Gianturco-Roubin, ACS, old Palmaz-Schatz, and Cordis stent were similar and in an intermediate third category as displayed in **figure 5.**

PART II

The relative radiopacity of each stent design can be visualized in **figure 6.** The two tantalum stents were found to be the most radiopaque while the thin strutted stainless steel Multilink (ACS) stent was found to be the least radiopaque. In order of decreasing radiopacity the stents were 1) Cordis, 2) Wiktor, 3) AVE Micro stent, 4) Gianturco-Roubin, 5) Wallstent, 6) new Palmaz-Schatz design, 7) old Palmaz-Schatz design (thinner strut diameter than new Palmaz-Schatz), 8) Multilink.

PART III

The results of the computer-based quantitative angiographic (QCA) measurements of the contrast-filled plexiglass vessel without any stent and subsequently within each of the eight stents are presented in **table 1a&b** and **table 2a&b.**

In measurement of the minimal luminal diameter in the contrast-filled 1.00mm stenosis (**table 1a**), it was found that the superimposition of the struts of the AVE Micro and the new Palmaz-Schatz design occasionally drew the automated edge detection algorithm inside the outer border of the contrast-filled lumen due to a further increase in the brightness profile of the digitized image. On videodensitometric analysis (**table 1b**), the additional increase in brightness caused by the highly radiopaque tantalum Cordis stent had a marked effect on measurement of the lumen resulting in a significant increase in the measured value (in the presence of the Cordis stent the 1.00mm lumen was measured to be 1.32mm instead of the 0.99mm measurement value when the stenosis of the plexiglass vessel was analyzed in the absence of any stent.

In measurement of the mean and maximal value of the 3.00mm segment of the plexiglass vessel, it was found that the two tantalum stents (Cordis and Wiktor) resulted in an increase in the measurement value. The effect was much greater by both the geometric and densitometric techniques for the Cordis stent, compared to the Wiktor stent. For the edge detection technique this was seen to be due to the tracking by the algorithm of the outer edge of the tantalum stents which lay in close proximity to but external to the contrast filled lumen. Given the previously described [20] tendency of automated quantitative angiographic techniques to underestimate large diameters (-0.26mm in this study for the 3.00mm segment) , the absolute numerical effect in mm's of the increase in measurement value associated with the tantalum stents was limited.

Table 1a. Comparison of the minimal luminal diameter of the plexiglass vessel with 1.00 mm stenosis without and subsequently with each of the 8 stents

	Edge-detection			Videodensitometry		
	Accuracy	Deviation	Precision	Accuracy	Deviation	Precision
Plexiglass vessel without stent	-.01		±.01	-.01		±.01
Cordis	-.02	(-1%)	±.03	.33	(34%)	±.08
Wiktor	-.05	(-3%)	±.04	.03	(4%)	±.06
AVE	-.11	(-10%)	±.03	-.07	(-6%)	±.06
GR	-.06	(-4%)	±.05	-.04	(-3%)	±.04
Wallstent	-.06	(-5%)	±.04	-.06	(-5%)	±.04
PS (new)	-.10	(-9%)	±.04	-.10	(-9%)	±.04
PS (old)	-.02	(-1%)	±.02	-.01	(0%)	±.03
ACS	-.01	(0%)	±.03	-.01	(0%)	±.03

(%) = % difference between the stented vessel and vessel without stent

Table 1b. Comparison of minimal luminal diameter in plexiglass vessel of 3 mm diameter without and subsequently with each of the 8 stents

	Edge-detection			Videodensitometry		
	Accuracy	Deviation	Precision	Accuracy	Deviation	Precision
Plexiglass vessel without stent	-.26		±.03	-.26		±.03
Cordis	-.20	(3%)	±.05	.27	(19%)	±.12
Wiktor	-.27	(0%)	±.04	-.23	(1%)	±.03
AVE	-.30	(-1%)	±.09	-.25	(0%)	±.03
GR	-.31	(-1%)	±.05	-.27	(0%)	±.04
Wallstent	-.26	(0%)	±.01	-.31	(-2%)	±.04
PS (new)	-.28	(0%)	±.07	-.25	(0%)	±.03
PS (old)	-.30	(-1%)	±.05	-.29	(-1%)	±.02
ACS	-.27	(0%)	±.04	-.26	(0%)	±.02

(%) = % difference between the stented vessel and vessel without stent

Table 2a. Comparison of mean vessel diameter in plexiglass vessel of 3 mm diameter without and subsequently with each of the 8 stents

	Edge-detection			Videodensitometry		
	Accuracy	Deviation	Precision	Accuracy	Deviation	Precision
Plexiglass vessel without stent	-.26		±.04	-.25		±.03
Cordis	.20	(17%)	±.22	.42	(24%)	±.12
Wiktor	-.22	(2%)	±.03	-.15	(4%)	±.03
AVE	-.25	(0%)	±.07	-.21	(1%)	±.03
GR	-.27	(0%)	±.05	-.24	(0%)	±.03
Wallstent	-.26	(0%)	±.01	-.28	(-1%)	±.03
PS (new)	-.24	(1%)	±.06	-.23	(1%)	±.03
PS (old)	-.28	(-1%)	±.05	-.27	(-1%)	±.02
ACS	-.24	(1%)	±.04	-.24	(0%)	±.02

(%) = % difference between the stented vessel and vessel without stent

Table 2b. Comparison of maximal vessel diameter in plexiglass vessel of 3 mm diameter without and subsequently with each of the 8 stents.

	Edge-detection			Videodensitometry		
	Accuracy	Deviation	Precision	Accuracy	Deviation	precision
Plexiglass vessel without stent	-.24		±.01	-.23		±.03
Cordis	.64	(32%)	±.09	.59	(30%)	±.08
Wiktor	-.16	(3%)	±.02	-.07	(6%)	±.02
AVE	-.19	(2%)	±.09	-.17	(2%)	±.06
GR	-.26	(-1%)	±.05	-.21	(1%)	±.04
Wallstent	-.25	(0%)	±.01	-.25	(-1%)	±.02
PS (new)	-.22	(1%)	±.06	-.21	(1%)	±.03
PS (old)	-.23	(0%)	±.06	-.25	(0%)	±.01
ACS	-.21	(1%)	±.04	-.23	(0%)	±.03

(%) = % difference between the stented vessel and vessel without stent

DISCUSSION

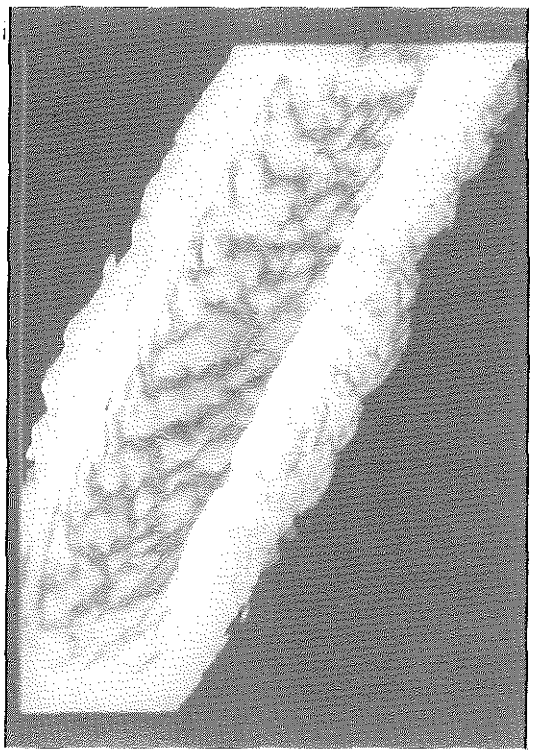
Our studies have clearly demonstrated that the mechanical behaviour, radiographic profile, and effect on computer-based quantitative angiographic analysis vary markedly among currently available coronary stent designs.

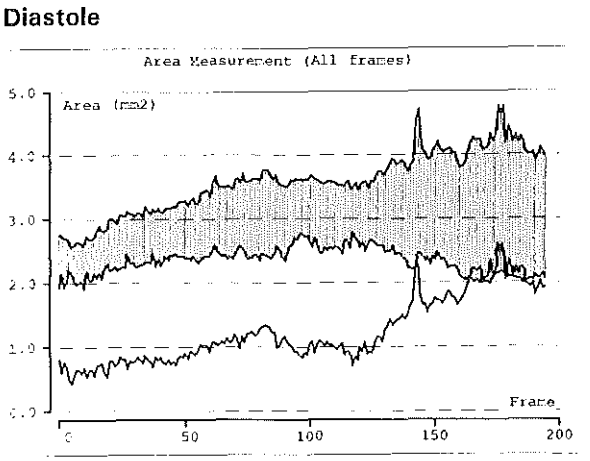
Radial compliance.
The mechanical characteristics of stents are important to gain insight into the altered vessel wall compliance and the force exerted by the stent wires on the vessel wall post stent implantation. Intracoronary ultrasound studies have demonstrated compliance of healthy coronary vessels with marked diastolic to systolic differences in lumen dimensions. Implantation of a stent would be expected to restrict the compliance of the stented coronary segment. The degree of radial compliance of a stent will be dependent upon the strength of the metal alloy, the thickness of the stent struts, the proximity of successive struts (i.e. the interstrut interval), the angle of orientation of the struts against the vessel wall, and the presence of either welded or free interstrut junctions.

The compliance mismatch between the coronary vessel and the metallic stent might be expected to result in focally accentuated shear stress or barotrauma in the vessel wall especially at the proximal and distal extremities of the stent. This may be more marked recently following the introduction of the interventional policy of "bigger is better", the selection of oversized stents, and the optimization of stent deployment by ultrasound-guided high pressure intrastent inflations of non-compliant balloons. While it may therefore be felt that a degree of compliance might be desirable in a stent, it should also be considered that the exertion of sustained radial force by the stent on the vessel wall may be required to withstand elastic recoil and vascular spasm and to prevent stent migration following deployment. Results of detailed quantitative angiographic studies of patients undergoing stent implantation suggest that stents do demonstrate a degree recoil upon deflation of the stent deployment balloon.

In our study, except for the Wallstent and AVE stents the relation between the radial pressure and diameter ratio appears to be nonlinear (**figure 5**). This nonlinear behaviour results in part from adaptation of the stent to the cylindrical shape of the collar during the pressure build-up. Such a deviation of the stent surface from a cylindrical shape, may result in a nonuniform distribution of the applied radial pressure on the stent wires. This can be appreciated in **figure 6**, where the axial photograph of the lumen of all the stents reveals that both the Wallstent and AVE Micro stent were symmetrically expanded and thus the radial force exerted by each strut would have been recruited simultaneously by the cylindrical collar. The inhomogenous expansion of stents may result in non-uniform distribution of radial force throughout the stented coronary segment.

The comparative results of our in-vitro measurement are not necessarily directly applicable to the dynamics of deployed stents in-vivo. In particular it should be noted that our low friction model allows the longitudinal extension of stents upon compression. While stents with primarily transverse orientation of their struts (e.g the Gianturco-Roubin stent) do not undergo significant changes in length upon radial expansion or compression, other stent designs such as the Wallstent undergo significant lengthening upon radial compression. Once deployed in the vessel wall, the Wallstent struts would be expected to become embedded in the intima of the vessel wall and the coronary vessel itself would thereby be expected to resist longitudinal extension. This supposition may be indirectly assessed by the use of quantitative ECG-





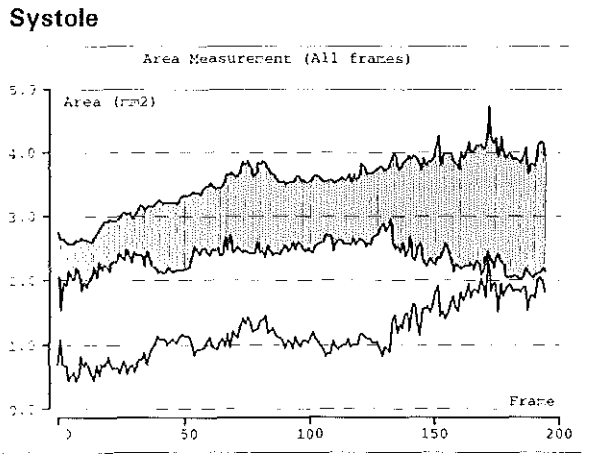


Figure 8. *Quantitative ultrasonic analysis of compliance within a stented coronary artery.*

Left panel; *ECG-gaited three-dimensional reconstruction of an intracoronary ultrasound recording within a Wallstent in a native coronary artery. Images were acquired using a motorized pull-back device (CVIS). Filtering of the ultrasonic data sets has been applied during off-line post-processing of the image to enhance the back scatter from the metallic struts of the stent.*

Upper right panel ; *Automated measurements of luminal and medial area in end-diastole analyzed over 200 frames at an interval of 0.1mm / frame indicating a diastolic luminal volume of 46.79 mm^3*

Lower right panel ; *Automated measurements of luminal and medial area in end-systole analyzed over 200 frames at an interval of 0.1mm / frame indicating a systolic luminal volume of 47.16 mm^3*

This data adds support to the concept that the Wallstent demonstrates low compliance in-vivo when significant elongation of the stent is restricted by the atherosclerotic wall of the coronary artery in which the stent is embedded

gaited three dimensional [22,23] intracoronary ultrasound analysis of stented segments (**figure 8**). By comparing the systolic and diastolic intrastent diameters and volumes in a native coronary artery immediately following Wallstent implantation it can be seen that no significant cyclical changes can be seen within the stented segment, thus supporting the concept that the compliance of the Wallstent following deployment in a coronary vessel wall behaves differently than in our low-friction in-vitro measurement system [4].

Despite the limited direct applicability of the reported absolute in-vitro results to in-vivo expectations for stents which undergo elongation upon radial compression, the system described does offer a simple and standardized approach to compare the radial compressibility of stents. Refinement of the apparatus may be achieved by the incorporation of a corrugated collar which might offer longitudinal friction or resistance to stent elongation or alternatively the testing of each stent in an excised coronary vessel from an autopsy specimen or animal model.

It should be noted that the interaction of the radial compliance of a stent and the prevention of vessel recoil and subsequent restenosis in-vivo has yet to be demonstrated. Furthermore additional studies are required to address the influence of the distribution of radial force (a coil stent with large interstrut intervals e.g. Gianturco-Roubin stent versus a dense mesh e.g. Wallstent) exerted by stents on angiographic outcome.

Relative radiopacity.
While the radiopacity of tantalum stents may facilitate their deployment in coronary arteries, the outline of the radiopaque stent struts embedded in the vessel wall may interfere with the reliability of automated quantitative angiographic analysis of the stented lumen in the presence of intimal hyperplasia at 6 month angiographic follow-up. While most of the currently available stents are of moderate radiopacity, the new tantalum Cordis stent is highly radiopaque. Although during the interventional procedure itself, the strong radiopacity of the tantalum stent facilitates the exquisite positioning of the stent in the target lesion and the subsequent precise placement of additional non-compliant balloons for high pressure intrastent inflations, the radiopaque stent struts may interfere with the assessment of restenosis within the stent at angiographic follow-up.

Effect of metallic stents on automated quantitative angiography
The new Cordis tantalum stent was found to exert a greater impact on the radiopacity of the contrast-filled lumen than the Wiktor tantalum stent on account of its more dense and highly crenulated strut configuration. In a previous in-vitro study by our group comparing the effect on videodensitometric quantitative angiographic measurements of a stainless steel stent (Palmaz-Schatz, Johnson & Johnson, NJ), a cobalt alloy stent (Wallstent, Schneider, Bulach, Switzerland), and a tantalum stent (Wiktor, Medtronic, MN), it was found that the radiopaque tantalum stent (Wiktor) resulted in a consistent overestimation of the minimal luminal cross-sectional area by 9-56% compared to the control values (varying with the contrast concentration and size of the phantom vessel) [23]. Furthermore, in the quantitative angiographic analysis of the multicenter Wiktor restenosis study, it was found that automated edge detection was unreliable in 8% of patients at angiographic follow-up requiring operator interaction [24,25]. Our results would indicate that videodensitometry is unlikely to offer a more reliable alternative to geometric QCA measurements in the presence of tantalum stents.

CONCLUSIONS

We have demonstrated that marked variability exists among the currently available stents in terms of their radial compliance, their radiopacity, and their interference with the reliability of automated quantitative angiographic measurements by both geometric (edge detection) as well as videodensitometric techniques. The comparative results may be of relevance for the selection of different stents for different coronary indications and the analysis of subsequent angiographic outcome.

ACKNOWLEDGEMENTS

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Conclusion

Chapter XVIII

Different stents for different coronary lesions.

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INTRODUCTION

Coronary stents were developed to overcome the two primary limitations of balloon angioplasty, namely, abrupt vessel closure and late restenosis. Coronary stents achieve the acute maintenance of vessel patency following failed balloon angioplasty by the provision of a scaffolding lattice to tack back intimal flaps and seal the dissected vessel wall. Following procedurally successful balloon angioplasty, coronary stents prevent late recoil and consequent restenosis by mechanically enforced remodelling and resetting of the vessel size of the stented segment.

Although coronary stent implantation commenced in 1986, only one indication (elective treatment of primary lesions in native coronary arteries) for one stent (Palmaz-Schatz) has to date been evaluated by the rigorous process of the randomized trial [1,2]. BENESTENT [1] and STRESS [2] have indicated that coronary stenting may indeed be effective in the reduction of the restenosis rate at six months compared to balloon angioplasty. This reduction in restenosis rate is achieved despite the accommodation of a greater absolute loss in lumen diameter over six months in stented patients. Such an achievement is made possible by the even greater gain in lumen diameter achieved at the time of stent implantation compared to the procedure of balloon angioplasty alone in addition to the prevention of late recoil of the stented vessel wall.

While following balloon angioplasty abrupt vessel closure due to dissection and thrombus formation typically occurs while the patient is still in the cardiac catheterization laboratory or within the first 4 - 6 hours [3-13], stent implantation may delay the onset of abrupt vessel closure due to thrombotic stent occlusion which typically occurs at a median time of 3 - 5 days post stenting [1,2]. This delayed risk of thrombotic occlusion on the metallic coronary stent has necessitated the administration of systemic anticoagulant therapy with an associated increased risk of haemorrhagic events [1,2]. Approaches to address these limitations of stenting include the substitution of anticoagulant therapy (heparin and coumadin) by effective antiplatelet therapy (ticlopidine and aspirin) [14-16] and the current drive towards optimal stent deployment guided by on-line quantitative coronary angiography [17,18] in multiple projections and / or intracoronary ultrasound [19-23] (**figure 1**), and at some centers guided by angioscopy [24,25] (**figure 2**). Additional measures include the use of improved femoral haemostatic devices [26-29] and the application of stent coatings [30] which were initially introduced for clinical evaluation on the Wallstent (polymer coating, {BioGold, PlasmaCarb Inc., Bedford, NH, U.S.A.}) from 1989 through 1991 [31,32, 49], and more recently on the Palmaz-Schatz stent (heparin coating {Carmeda AB, Stockholm, Sweden}) [33].

Apart from BENESTENT and STRESS the available data on all other stents and all other indications for coronary stenting arises from non-comparative studies and registry data. Results of ongoing randomized trials on elective stenting in native coronary arteries of primary lesions (START[34]), total occlusions (SICCO), and restenotic lesions (REST [35]), and in vein graft lesions (SAVED), and randomized trials on bailout stenting of acute and threatened vessel closure (GRACE[36], TASC II [37]), should become available in 1996. With enthusiasm unabated by the current paucity of prospective controlled randomized data, the clinical practice of coronary stenting has marched on in accordance with interpretation of non-comparative series of clinical applications with strikingly different inclusion / exclusion criteria, only occasionally presented with historically-matched case controls [38], and in accordance with the level of restrictions exerted by national or federal regulatory bodies. Accordingly the current indications for coronary stenting include 1) bailout therapy of acute and threatened vessel closure [39-45], 2) non-elective

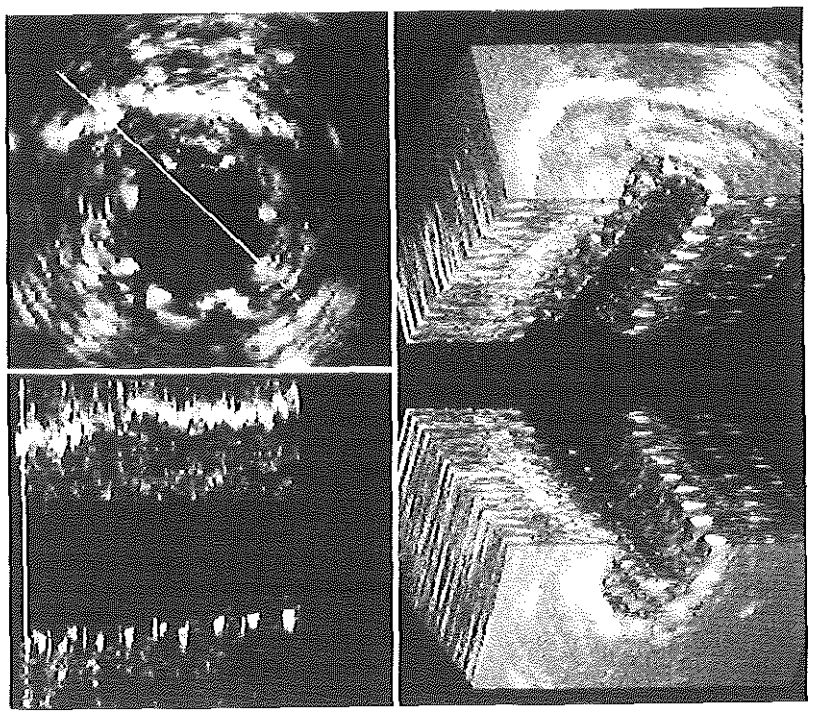

Figure 1
Intracoronary ultrasound (ICUS) images of a Wallstent in an aortocoronary bypass graft. A blood-speckle identification program (Echovision, CVIS, Sunnyvale, CA, USA) which is able to distinguish between the varying backscatter pattern of flowing blood cells in the vessel lumen and the more stable pattern of the vessel wall, has been used for three-dimensionsal reconstruction of the ICUS data sets. In addition to the transverse and longitudinal views a true three dimensional view is displayed (right side), presenting the data in a cylindrical format which has been opened longitudinally ("clam-shell" view) [85]. Stent deployment can be checked and offer guidance for additional high pressure intrastent inflations of a non-compliant balloon when necessary. In this patient the Wallstent was found to be symmetrically expanded.

improvement of the suboptimal angiographic result of primary balloon angioplasty [45], and 3) elective stenting of primary lesions in native coronary arteries [1,2] and saphenous vein grafts [32, 49,46-53], restenotic lesions [54, 56], and total occlusions [55].

Given the spectrum of clinical indications and coronary lesions amenable to stent therapy, there is clearly a need for more than one stent design. Following the recent introduction of the Less Shortening Wallstent, Multilink (ACS), AVE Micro, and Cordis stents and the recent withdrawal of the Strecker stent, there are now seven different coronary stents available for clinical evaluation. The scaffolding lattice of each stent differs markedly in configuration (**figure 3**) varying in the balance between the presentation of as minimal a metallic surface area as possible to lower the thrombogenic burden and the provision of strong radial force. The stents can be categorized into the mesh stents characterized by strong and extensive scaffolding of the vessel wall (Wallstent, Palmaz-Schatz, AVE Micro, (Strecker)) and the coil stents characterized by a low metallic surface area and predominantly transverse strut orientation (Gianturco-Roubin, Wiktor, Multilink, Cordis). The AVE Micro and ACS Multilink stents only loosely belong to such simplistic categories and the detailed structural design of each stent will be individually discussed later in this chapter while the key features of each stent are presented in tables 1-3. Within each category each stent offers a unique structural profile and consequently conveys its own clinical advantages and disadvantages. When selecting a stent for an individual patient with an individual indication and lesion the operator needs to take a number of patient and procedural related factors into consideration as well as to consider the structural properties and delivery system of each available stent. This chapter aims to rationalize coronary stent selection and to focus on the clinical and technical guidelines to help the operator select the most appropriate stent for each patient. In the first section, the requirements of each of the current indications for stenting are considered in relation to the clinical setting, the vessel and lesion characteristics, and procedural details. In the second section of this chapter the suitability of each of the currently available stents to meet the requirements of each indication and lesion is critically reviewed.

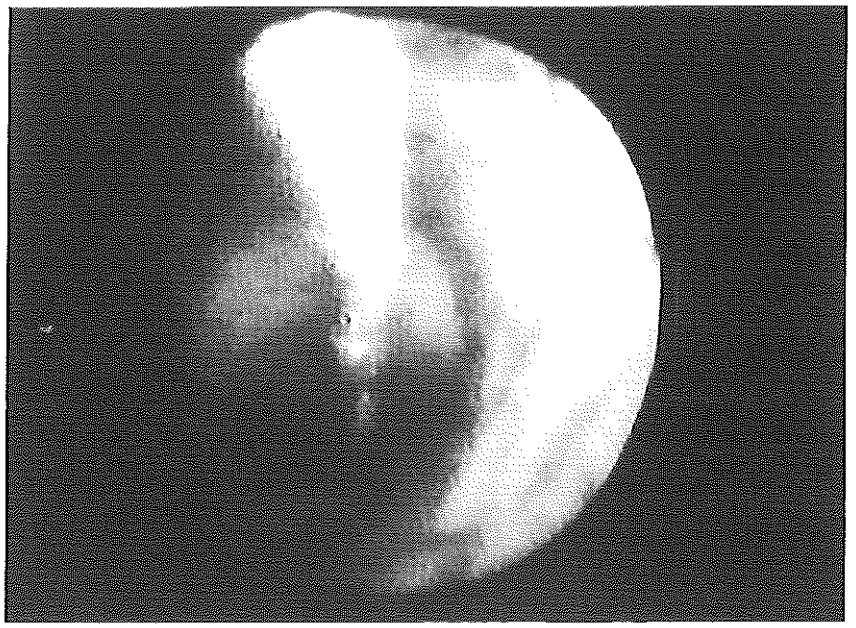

Figure 2
Angioscopic examination following optimal deployment of a Wallstent demonstrating the mesh lattice of the stent struts (left side) which has been well opposed to the vessel wall and a symmetrical lumen. No protrusion of intimal flaps or thrombus are seen. The guidewire can be seen to run axially in the center of the lumen.

SECTION I

Indication.
For bailout stenting the threatened or acute vessel closure typically results from a subocclusive or occlusive intimal flap accompanied by a varying degree of intracoronary thrombus [57]. Extensive dissections are more likely to be induced by aggressive angioplasty performed in accordance with the "bigger is better" policy. Thus at the time of stent implantation the tough primary lesion has already been "cracked" and the immediate "bailout" function of the stent becomes one of tacking back the dissected flap rather than overcoming recoil. Therefore in the bailout setting, the selection of a coil stent should be adequate without the necessity of a mesh stent with strong radial force and high metallic surface area. It is of interest to note that the incidence of subacute stent thrombosis following emergent stent placement in multicenter experience over the same period of 1988 - 1991 was 16% for the Palmaz-Schatz mesh stent [45] compared to 8.7% for the lower metallic surface area Gianturco-Roubin coil stent [42].

In the case of the suboptimal result (acute recoil with or without medial haemorrhage) after coronary angioplasty which may previously have been taken as >50% residual diameter stenosis but is now more commonly taken as >25% residual diameter stenosis, a stent proffering strong radial support will be required. Similarly a strong radial force will be required for elective stent placement where the primary objective is to reset the vessel size at the point of the lesion and to enforce mechanical remodelling thereby improving the accommodation of intimal hyperplasia and to prevent late recoil over the ensuing 6 months [58,59]. The selection of a mesh stent with extensive scaffolding (sieve) will prevent encroachment on the lumen by intimal protrusion acutely and may contribute to the reduction in lumen renarrowing due to intimal hyperplasia over 6 months through the interstrut intervals [1,2,54, 56]. In both the case of "touching-up" the suboptimal angiographic result of primary angioplasty as well as in the case of elective primary stent placement, selection of a stent with a relatively high metallic surface area should not be of major concern and the obtainment of a large lumen with laminar flow should be the primary aim.

Clinical setting.
The thrombogenic state of the coronary artery is felt to progressively increase when going from the setting of stable angina, through unstable angina, to acute myocardial infarction. In a study comparing the outcome of stenting in patients with unstable angina and patients with stable angina [60], instability of symptoms was not found to convey a negative outcome. This finding, which was in contradistinction to previous findings with balloon angioplasty, was felt to possibly relate to the sealing of dissections or to the use of full conventional anticoagulation in all patients in this series [60]. In an analysis of the multicenter registry data on the Gianturco-Roubin stent [43], angiographic evidence of intracoronary thrombus was found to be predictive of subsequent adverse clinical events following elective stent placement but not after bailout stenting. Herrmann et al, however, in an analysis of a multicenter experience of emergent placement of the Palmaz-Schatz stent, found angiographic evidence of intracoronary thrombus to be associated with a significantly higher risk of subsequent subacute thrombosis [45]. The very limited number of reported patients who have been stented in the setting of myocardial infarction render conclusions on this last frontier for stenting premature [61-64]. Thus the impact of the

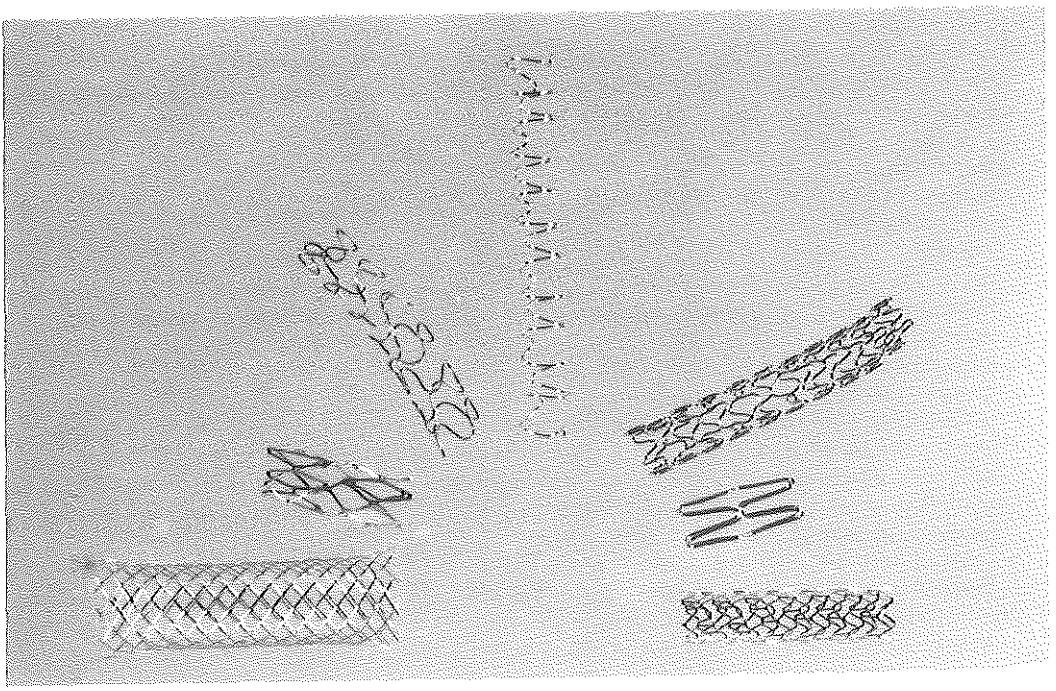

Figure 3
The seven coronary stents which are currently available for clinical evaluation.

thrombogenic state or stability of symptoms on outcome following coronary stent implantation remains to be clearly defined by prospective studies. While it might appear advantageous to select a stent with a low metallic surface area in patients with a profile of increased risk for acute / subacute thrombotic occlusion, it is likely that the procurement of an optimal angiographic result with high laminar flow is of greater importance than the metallic (thrombogenic) burden of the stent used to achieve such a result.

Vessel size.
Further to our increased understanding of the importance of vessel size as well as the minimal diameter of the lesion on acute and longterm outcome, on-line quantitative coronary angiography (QCA) has become an integral component of optimal stent deployment [17]. On-line QCA data is used to guide both the prestenting or priming balloon inflations as well as for appropriate stent sizing. Depending on the structural design of the individual stent selected, a nominal (manufacturer's stated) stent size of 0.1 to 0.5mm larger than the vessel size is selected. In a patient with a vessel size of > 4.0mm only two of the currently available stent designs have an adequate range of stent sizes to cover such a vessel, namely the Wallstent and the Palmaz (unarticulated) "biliary" stent. Stenting of larger vessels is associated with a higher procedural success rate and improved clinical outcome compared to stenting of smaller vessels. Furthermore the reported lower complication rate for elective stenting in the right coronary artery [65] may in part relate to the large size of the right coronary artery.

In addition to vessel size considerations, the coronary flow of the target vessel is also of prognostic importance post stenting. Stenting in a vessel with poor distal run-off supplying an infarcted myocardial region or stenting in the presence of poor left ventricular function is associated with a higher risk of subsequent subacute stent thrombosis [66].

Vein graft versus native coronary artery.
When stenting a venous bypass graft, the scaffolding properties of the stent as well as the stent size should be taken into consideration. Old bypass grafts frequently contain extensive friable tissue prone to embolization in the subtended coronary arterial bed. It is unlikely that a coil stent with a large interstrut distance such as the Wiktor or Gianturco-Roubin stent would provide sufficient scaffolding of the vein graft wall to prevent such embolization of friable tissue. In contrast the cross-hatched mesh design [32] of the Wallstent [49] and to some extent the Palmaz-Schatz stent [50-53] offers greater protection against the risk of embolization by virtue of their shorter interstrut distance and higher metallic surface area. The absence of side branches in the shaft of vein grafts obviates any concern of jailing of vessels by the stent mesh. Although long lesions located in the body (shaft) of coronary vein grafts are particularly well treated by the Wallstent, lesions located at the ostium of vein grafts are unsuited to Wallstent implantation on account of movement of the stent and proximal shortening which normally occur during retraction of the rolling membrane and expansion of the Wallstent. Thus for ostial lesions where exquisite positioning is required to avoid protrusion of the proximal terminal of the stent into the aorta, a balloon expandable and preferably radiopaque stent may produce more predictable results particularly for those operators without extensive experience in Wallstent deployment. For lesions located in the distal segment of "jump" (sequential) vein grafts, it is important that a stent with a sufficiently long delivery system be selected.

Chronic total occlusions.
To date published results for stenting of chronically occluded vessels have been limited to non-comparative series [55]. Following successful recanalization of vessels with chronic total occlusions, it is often found that the entire vessel is extensively diseased in either a

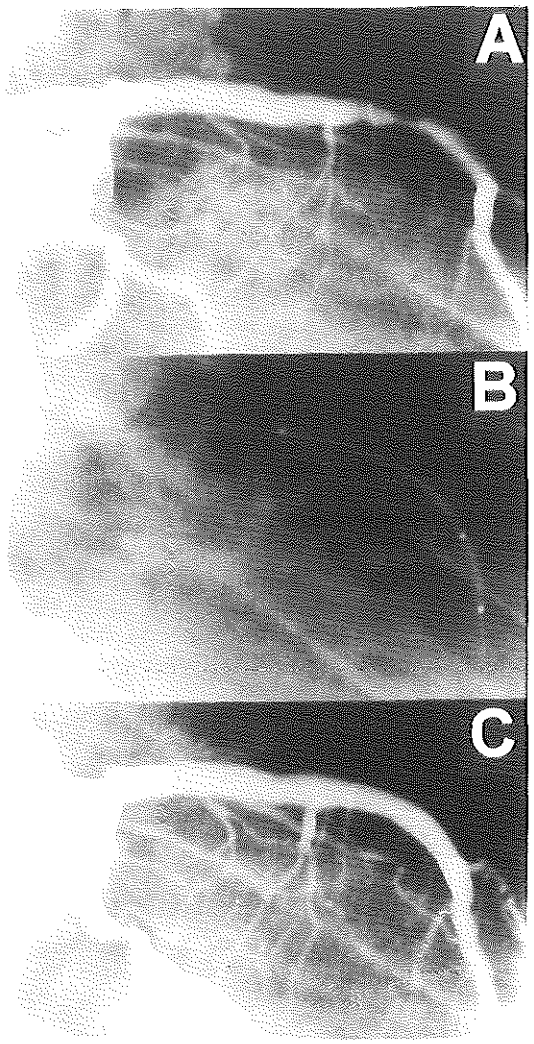

Figure 4

A *Focal lesion in the left anterior descending artery prior to directional coronary atherectomy*

B *A Less Shortening Wallstent was delivered to treat a dissection induced by atherectomy*

C *Final angiographic outcome reveals a smooth-contoured stented segment with no loss of side-branches and absence of vessel splinting which may be seen following deployment of more rigid stents*

diffuse or segmental manner. Recently we have adopted a policy of resetting the size [67] of the entire vessel, whereby we select a long Wallstent (35mm nominal length when fully expanded) with a nominal diameter of 1.5mm larger than the maximal diameter of the vessel (MVD) obtained from the diameter function of the on-line QCA. When grossly oversized, the axial shortening of the Wallstent is further reduced resulting in a final deployed length of up to 40mm. When necessary a second (and rarely a third) Wallstent is deployed to ensure that the entire length of the reconstructed vessel is expanded. The flexibility and continuity of large diameter of the resultant stented vessel results in an entire reconstruction of the epicardial vessel. Whether such enforced mechanical remodelling of the vessel results in an improved accommodation of intimal hyperplasia in patients so treated remains to be determined by long-term angiographic follow-up.

Lesion length and location.
Given the limited range of lengths available for most of the currently available stents, long coronary lesions and spiral dissections are normally managed by the tandem implantation of multiple stents. In the case of the Palmaz-Schatz stent overlapping or telescoping of sequential stents should be avoided while for coil stents with low metallic surface area such as the Gianturco-Roubin stent, overlapping of multiple stents may occasionally be advantageous to provide additional radial support.

For short lesions located immediately proximal or distal to a vessel curve, attention must be paid to ensure an adequate inflow or outflow of the stented segment. For this reason it may on occasion be necessary to deploy a stent of significantly longer nominal length than the apparent lesion length to avoid the extremity of the stent being directed at the outer wall of the vessel curvature. This is particularly the case for more rigid stents such as the Palmaz-Schatz stent, where splinting by the stent of the previously curved vessel segment is angiographically evident. For lesions located in tortuous segments, the preference for a flexible stent is clear. Similarly for distal lesions located in vessels with proximal tortuosity, flexibility and low profile of the stent delivery device will be required.

Concerns have previously been expressed over the outcome of side branches located in the stented segment. Two recent papers reporting the outcome of side branches arising from Palmaz-Schatz stented coronary segments have provided reassuring data over this concern [68,69]. From these reports it appears that side branch occlusion following stent placement occurs infrequently (< 10%), the occluded side branches usually have preceding ostial disease, their occlusion typically does not result in myocardial infarction, and the occluded side branches are usually found to have recanalised at 6 month angiographic follow-up [68,69]. "Jailing" the ostium of major side branches by stent struts whereby intervention in the affected side branch is precluded arises in stents with a fine lattice such as the Wallstent, Palmaz-Schatz, Multilink, and Cordis stents, while the Gianturco-Roubin and Wiktor stents have sufficiently large interstrut intervals to make interventional procedures in major side branches possible.

As in vein grafts, lesions located in the ostium of native coronary arteries require exquisite stent delivery to avoid the risk of proximal migration and protrusion. Thus a balloon-expandable radiopaque stent should be selected for such lesions.

Multiple stenting.
In general, when it is felt that more than one stent [18, 70] will be required to treat a long lesion or spiral dissection, it is advisable to begin with the placement of the most distal stent. Occasionally, however, placement of a single proximal stent will eliminate the distal extension of the false lumen and obviate the necessity for multiple stenting. When a

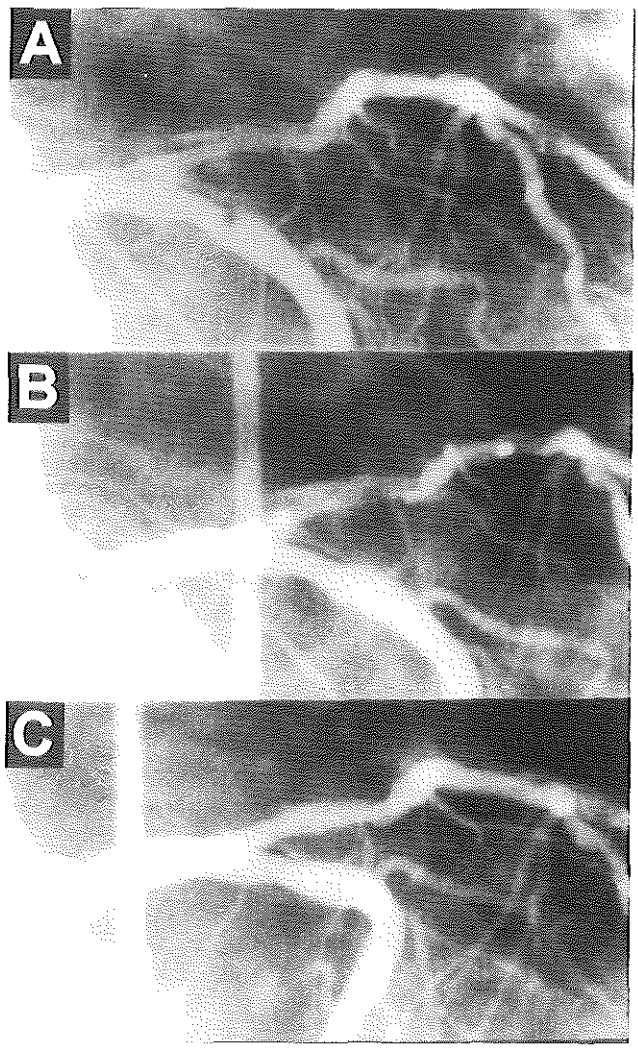

Figure 5

A *Dissection following balloon angioplasty in the proximal left anterior descending artery*

B *Following delivery of a Gianturco-Roubin Flexstent through a Superflow 8F Judkins guiding catheter to the target vessel, the radiopaque markers (located 1mm proximal and distal to the stent extermities) facilitate the final positioning of the stent prior to inflation of the delivery balloon*

C *Contrast angiography post stent deployment demonstrates preservaion of the vessel curvature in the stented segment*

second distal stent is to be passed through a proximally deployed stent, the profile and trackability of the second stent becomes of paramount importance. A stent with a low profile which is preferably sheathed to avoid catching of struts in the proximally deployed stent should be selected. Flexibility of the second stent will also reduce the risk of the second stent failing to pass through the proximally deployed stent.

Guiding catheter and guidewire.
In the case of non-elective stenting, the guiding catheter and guidewire in-situ which have been used during the primary coronary angioplasty procedure may have a bearing on the stent to be selected. If a regular lumen 8 French guiding catheter has been used, selection of a stent with a high profile (e.g. 3.5 or 4.0 mm Gianturco-Roubin stent) will not be possible without necessitating the exchange of the guiding catheter. Similarly, exchange to an extra support .018" guidewire may be required for the advancement of the Gianturco-Roubin delivery system (premounted balloon) through a proximally tortuous vessel. Such technical limitations of the Gianturco-Roubin stent will soon be overcome by the introduction of a lower profile 2nd generation device.

TABLE 1

Coronary Stent	Design	Deployment	Premounted	Sheathed	Delivery	First Clinical Implantation
Wallstent	Wire mesh	Self-expanding	balloon not required	sheathed	over-the wire	1986 [39] 1991 (Less Shortening Wallstent) [32, 49]
Palmaz-Schatz	Slotted tube 0-2 articulations	Balloon-expandable	pre-mounted & free	sheathed & unsheathed	over-the-wire over-the-wire or monorail	1988 [76,45] 1994 (Heparin coated helicoid connection) [33]
Gianturco-Roubin	Incomplete coil clam shell loop	Balloon-expandable	premounted	unsheathed	over-the-wire	1989 [41]
Wiktor	Sinusoidal helical coil	Balloon-expandable	premounted	unsheathed	over-the-wire or monorail	1991 [54]
Multilink	Multiple rings with multiple links	Balloon-expandable	premounted	sheathed	over-the-wire	1993 [83]
Cordis	Sinusoidal helical coil	Balloon-expandable	premounted	unsheathed	over-the-wire	1994
AVE Micro	Zig-Zag axial struts 4mm units	Balloon-expandable	premounted	unsheathed	monorail	1994

Wallstent - Schneider Bulach, Switzerland | Palmaz-Schatz - Johnson & Johnson, Warren, New Jersey, USA | Gianturco-Roubin - Cook, Bloomington, Indiana, USA | Wiktor - Medtronic, Minneapolis, Minnesota, USA | ACS - Advanced Cardiovascular Systems, London, U.K. | Cordis, Cordis, Miami, Florida, USA | AVE Micro, Advanced Vascular Engineering, Santa Rosa, California, USA.

TABLE 2

	Profile (mm)	Diameters (mm)	Lengths (mm)	Shortening (%)	Metallic SA (%)
Wallstent	1.57	3.5 - 6.0	12 - 35	25%	-
Palmaz-Schatz	1.65	3.0, 3.5, 4.0 (pre-mounted) 3.0, 3.5, 4.0, 5.0, 6.0 (unmounted)	8, 9, 14, 15, 18	2.5-25%	<20%
Gianturco-Roubin	1.78 / 2.13 (2.0-3.0 / 3.5 & 4.0)	2.0, 2.5, 3.0, 3.5, 4.0	12, 20	0%	10%
Wiktor	1.75	3.0, 3.5, 4.0	16	-	8.8%
Multilink	1.37	3.0, 3.25, 3.5	15	3%	7%
Cordis	1.27 - 1.52 (3.0 - 4.0)	3.0, 3.5, 4.0	15	10%	15%
AVE Micro	1.65	3.0, 3.5, 4.0	4, 8, 12, 16	2%	8.4%

Profile - profile of stent delivery system | Metallic SA - metallic surface area of stented coronary segment when the stent is expanded to its nominal diameter

TABLE 3

Coronary Stent	Metal composition	Strut Thickness	Relative Radiopacity* (1-7)	Position of radiopaque markers
Wallstent	Cobalt based alloy	.07-.10 mm	5	Distal & proximal & intermediate for expected final length
Palmaz-Schatz	316 L Stainless Steel	.102 mm	6	Distal & proximal (premounted)
Gianturco-Roubin	316 L Stainless Steel	.152 mm	4	Distal & proximal
Wiktor	Tantalum	.127 mm	2	Central
Multilink	316 L Stainless Steel	.056 mm	7	Distal & proximal
Cordis	Tantalum	.127 mm	1	Central
AVE Micro	316 L Stainless Steel	.203 mm	3	Distal & proximal

*Relative radiopacity score (1-7) - based on ongoing comparative densitometry studies by Keane et al. at the Thoraxcenter.
A relative score of 1 = most radiopaque, while a relative score of 7 = least radiopaque.

SECTION II

Currently Available stents

The currently available stents, a description of their design, and the year of their clinical introduction are listed in table 1. For comparative purposes the key structural features and technical details of the different stents are provided in tables 2 & 3. In the absence of prospective randomized interstent comparative trials, it is difficult to draw conclusions on the relative merits and demerits of each stent design, however, individual experience and registry data from each stent allow preliminary impressions to be made on the advantages and limitations of each stent.

Wallstent

The Wallstent was the pioneer of stents [39, 83] through which we learnt the risk profile and indications for coronary stenting and the necessity and adverse effects of antithrombotic measures. In a European cooperative registry in the late eighties [46,47], both a quantitative angiographic as well as clinical Wallstent database was built up from which predictors of subacute thrombotic occlusion and restenosis were identified in both vein grafts as well as native arteries [71]. In 1991, the new Less Shortening Wallstent was developed through a change in the braiding angle [32, 49] and results of the first clinical implantation of this second generation stent in coronary vein grafts have been promising [49]. The unique advantages of the Wallstent include the extensive range of diameters and lengths available, thereby allowing the Wallstent to be used for the management of long spiral dissections, and for vessel reconstruction. The sheathed "balloon-less" delivery system in combination with the free unconnected wire mesh design, render the Wallstent one of the most trackable, pushable and flexible stents (**figure 4**) for negotiating vessel tortuosity and passing through proximally deployed stents. Its fine cross-hatched mesh (**figures 2 & 3**) design provides excellent scaffolding properties which is particularly well suited to entrap friable material in diffusely diseased vein grafts (**figure 1**), however, the fine mesh also raises questions over the "jailing" of major side branches. Its primary limitations are the longitudinal shortening of the stent upon radial expansion and motion of the stent during retraction of the rolling membrane rendering the stent less suitable for ostial lesions.

Palmaz-Schatz Stent

The Palmaz-Schatz stent has been extensively investigated in a broad range of coronary lesions [19-22,45,50-53,55,62,68,69,72-78]. It is the only stent to date to have completed prospective randomized trials comparing the clinical and angiographic outcome with that of balloon angioplasty [1,2]. The angiographic results following Palmaz-Schatz stent implantation are predictable and the slotted tube design (**figure 3**) allows the performance of high pressure intrastent balloon inflations without risk of structural deformation. The low radiopacity of the Palmaz-Schatz stent, however, can render the positioning of a non-compliant balloon for post deployment high pressure intrastent inflations difficult. The availability of a free unmounted Palmaz-Schatz stent which can be crimped by the operator on any balloon provides more procedural versatility and results in a lower profile during stent delivery. It does, however, increase the risk of losing the stent during deployment and in general the unmounted Palmaz-Schatz stent should not be

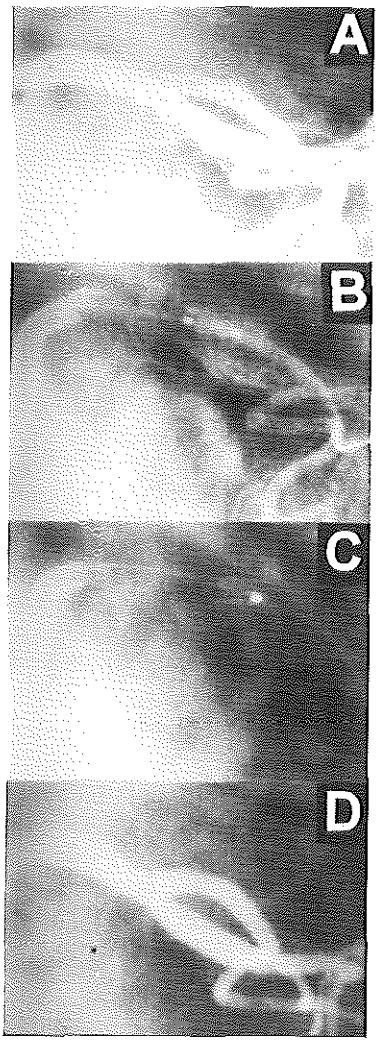

Figure 6

A *Short dissection in the origen of the left circumflex coronary artery following balloon angioplasty*

B *An AVE Micro stent is delivered to the target vessel through an 8F Amplatz guiding catheter, the two radiopaque markers at the extremities of the are clearly seen*

C *Following delivery of the stent, the thick radiopaque stainless steel struts facilitate the precise positioning of a short non-compliant balloon (single marker) within the stent for subsequent high pressure inflations and optimization of stent deployment*

selected when attempting to pass through another stent which has been deployed proximally on a bend. This limitation arises partly as a result of the rigidity of the Palmaz-Schatz stent, which is only partially compensated by the newer helicoid connections. The connected tubular segments of the Palmaz-Schatz stent negotiate vessel bends like the carriages of a train rather than the continuity of flexibility proffered by the Wallstent and coil stent designs. When multiple Palmaz-Schatz stents are implanted in tandem, overlap of the stents should be avoided. The Palmaz-Schatz stent is particularly suited for focal lesions in nontortuous coronary segments.

Gianturco-Roubin Stent

Prior to obtaining FDA approval for non-investigational clinical use, most of the clinical data on the Gianturco-Roubin stent was gathered in single and multicenter registries in the U.S.A. [38,8, 41-44]. The indication for the Gianturco-Roubin stent for which most data has been gathered is for the bailout of subocclusive and occlusive dissections following balloon angioplasty in native coronary arteries. The data gathered compares well with historical controls treated by repeated and prolonged balloon angioplasty alone and results of the first randomized trial of the Gianturco-Roubin in bailout therapy (GRACE) are awaited with interest [36]. The principle advantages of the Gianturco-Roubin stent include its range of lengths and longitudinal flexibility. While the relatively large interstrut intervals of 1mm (**figure 3**) raise questions over the suitability of this stent for the management of friable vein graft lesions, the advantages of the Gianturco-Roubin stent design include minimal risk of "jailing" side branches and the potential to perform coronary interventional procedures in side branches through the interstrut spaces. While this stent excels in long dissections in curved coronary segments (**figure 5**), its more generalised use is hindered by the high profile of the current prototype.

Wiktor Stent

The available clinical data on the Wiktor stent arises from observational studies and registry data [54,56,79-82], the principle registry of which has been in the management of restenotic lesions. Like the Gianturco-Roubin stent, the Wiktor stent is a coil stent (**figure 3**) which offers marked flexibility and thus conformability with the vessel curvature, however, also like the Gianturco-Roubin stent, the Wiktor stent is unlikely to excel in the treatment of friable vein grafts on account of the large interstrut interval of the Wiktor stent and subsequently reduced scaffolding properties. The radiopacity of the Wiktor stent allows exquisite positioning of the stent in ostial and focal lesions, while the flexibility of the stent makes it suitable for short dissections on curved coronary segments. The recent introduction of the option of a monorail delivery system improves the user-friendliness of the device. The limitations of the current prototype of the Wiktor stent include the availability of only one length, the limited scaffolding properties with the potential for the protrusion of intimal flaps through the interstrut intervals, and occasionally the radiopacity of this tantalum stent can interfere with on-line quantitative angiographic analysis of the stented segment.

Multilink Stent

The ACS stent [39, 83] currently has the least clinical experience of the currently available stents and is undergoing its first 100 patient registry which is being conducted at five European centers. The advantages of this new stent include the flexibility and low profile (**Table 1**) of the sheathed stent and delivery system. Although the Multilink stent design manages to provide remarkable scaffolding properties (**Figure 3**), the metallic burden to the

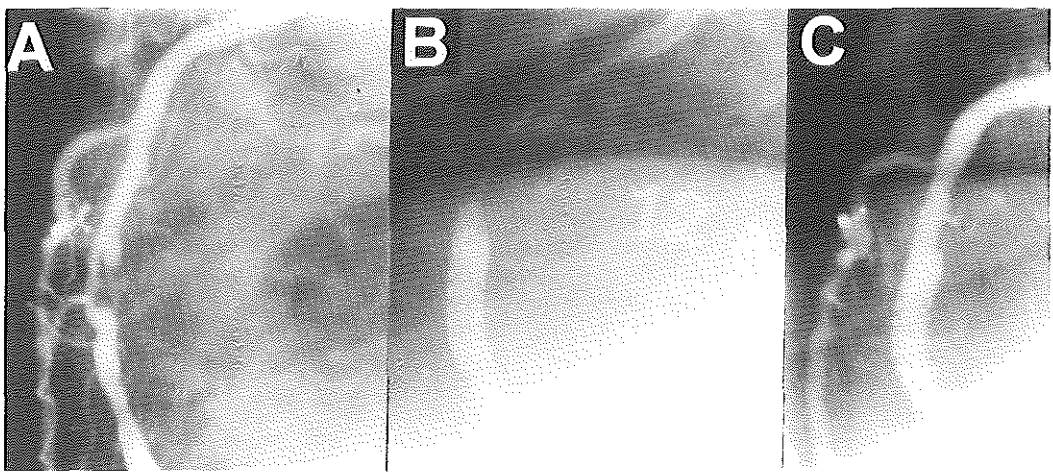

Figure 7

A *Complex lesion of the mid-segment of the right coronary artery*

B *Positioning of the Cordis stent was facilitated by the radiopacity of the tantalum struts which are clearly seen during inflation of the contrast-filled intrastent balloon to 12 atmospheres*

C *Angiography post stent deployment reveals the stent struts to be embedded in the vessel wall external to the contour of the contrast-filled lumen*

stented vessel remains very low by virtue of the small diameter of the corrugated struts. The limitations of the stent include its radiolucency (**Table 3**) rendering the positioning of non-compliant balloons for post-delivery high pressure intrastent inflations very difficult. The current availability of only one length of 15mm, means that the 1st prototype can only be used for very focal lesions. Following some minor modifications this stent may offer some significant advantages over the earlier generation of stent designs. The attachment of radiopaque tips on the stent would present a significant enhancement.

AVE Micro Stent

The AVE Micro stent is now undergoing clinical evaluation in a large number of countries [84]. The high degree of radiopacity (**Table 3**) and balloon expandable deployment should render the stent ideal for exquisite positioning in highly focal and ostial lesions (**Figure 6**), however, by virtue of the longitudinal (axial) orientation of its eight struts, the 4mm AVE Micro stent units may be prone to proximal migration and protrusion and therefore preferably longer welded AVE Micro stents should be deployed in ostial locations. The customized range of short lengths make the AVE Micro stent ideal as an adjunctive complementary device for multiple stenting, filling in the gaps between longer stents and improving the inflow or outflow of longer stents. Despite the absence of a protective sheath, the low profile and longitudinal strut orientation, make the AVE micro stent one of the easiest stent to pass through other proximally deployed stents. The monorail delivery system increases the user-friendliness of the device which has a short learning curve. The strong radial support proffered by the thick struts should make the stent suitable for the prevention of recoil and restenosis. Care should be taken, however, to avoid the positioning of junctions between the unconnected 4mm units at the site of the minimal lumen diameter of lesions in order to prevent intimal protrusion.

Cordis Stent

The Cordis stent continues to undergo early evaluation in the clinical arena. The principle investigator of this stent has been Masakio Nobuyoshi and colleagues in Kyoto, Japan where over 80 Cordis stents have now been deployed. Like the A.C.S. stent, the Cordis stent offers some advantages over the first generation stents by virtue of its low profile, flexibility, and comprehensive scaffolding properties. The absence of a protective sheath on the delivery system, however, increases the possibility of stent dislodgement or disruption during delivery. The operator should be aware of the protrusion of the delivery balloon beyond the limits of the Cordis stent if inflations of higher pressure are considered. While the strongly radiopaque tantalum struts (**Table 3**) allow exquisite positioning (**Figure 7**) of the stent in short dissections in curved coronary segments, the radiopacity may pose problems for on-line quantitative angiographic assessment, particularly during assessment of luminal renarrowing at 6 month angiographic follow-up.

CONCLUSIONS

Clearly none of the currently available stents is ideal or free from limitations. Moreover, no stent should be expected to serve all indications and all coronary lesions. It is probably appropriate for each interventional center to adopt two or three different stent types. Use of all seven currently available stents at one center may result in unfamiliarity of each operator with all stents and prolonged learning curves. Rationalization of the selection of stents at each center should be based upon the case mix of the interventional practice. Tertiary referral centers with a high volume of complex lesions including chronic total occlusions, long lesions in diffusely diseased vessels, and vein graft reconstructions may wish to have the Wallstent (which requires extensive experience for optimal deployment) in their stent armamentarium, while secondary referral centers with a standard interventional case mix and smaller patient volume might be adequately served by more user friendly stents with a shorter learning curve. Each center will require 1) at least one standard mesh stent with strong radial support such as the Palmaz-Schatz stent or AVE Micro stent primarily for recoil and restenosis prevention and lesions in straight coronary segments, and 2) at least one flexible coil stent primarily for dissections and lesions located in tortuous vessels.

Given the increasing demands for accountability of cost:benefit efficacy in interventional cardiology, it might be proposed that centers not participating in research studies should include one low budget economical stent in their selection for "straight forward lesions" in routine practice. If each stent will be expected to prove its own clinical indications and niche by randomized trials comparing them to either conventional balloon angioplasty or with previously established stent prototypes, the ultimate cost of each stent design will continue to represent a significant consideration in stent selection. The three most important considerations in the stent selection process for the individual patient, however, should continue to be 1) will the stent have an appropriate profile and trackability to be safely and successfully delivered to the individual coronary segment ? 2) is the structure of the stent appropriate for the indication ? , and 3) will the dimensions of the selected stent allow the achievement of an optimal angiographic resul ?

Key points for clinical practice

- The aim of obtaining <50% residual diameter stenosis post intervention has changed to one of < 25% residual diameter stenosis for balloon angioplasty and to one of 0% residual diameter stenosis for coronary stenting
- The achievement of optimal angiographic results obtained at the time of coronary stent implantation confers a reduced risk of subsequent adverse clinical events
- Optimal stent deployment can be obtained by the guidance of on-line quantitative coronary angiography in multiple projections aiming for <0% diameter stenosis in all views using the interpolated reference vessel diameter
- Any additional benefit conferred by the routine use of intracoronary ultrasound over the optimal use of on-line quantitative coronary angiography in multiple projections alone for the guidance of stent deployment has yet to be demonstrated.
- The specific role of coronary stenting in vessels of < 3.0mm diameter has yet to be addressed by prospective studies. It is hoped that the development of thromboresistant (e.g. heparin-coated, heparin-eluting) stents may have a significant impact in this domain.
- The results of early studies by highly experienced investigators on the feasibility of coronary stenting without post-procedural anticoagulant therapy by the combination of optimal stent deployment in vessels of >3.0mm and effective antiplatelet therapy (ticlopidine and aspirin) are promising but await confirmation by large international multicenter studies to determine if this can be safely achieved routinely at less experienced centers.
- A stent size of at least equal to or greater than the reference vessel diameter as measured by on-line quantitative coronary angiography, should be selected. The degree of stent oversizing, however, should vary according to the structural design of the stent
- Caution should be exerted over the inflation to high pressures of premounted compliant balloons which extend beyond the extremities of the stent
- Exchange of the premounted delivery balloon for a non-compliant balloon (of shorter length and occasionally of larger diameter) for the performance of post-delivery high pressure intrastent inflations may be required to achieve an optimal angiographic result
- Particular attention should be paid to ensure an optimal inflow and outflow of (rigid) coronary stents especially when placed in proximity to a vessel curvature
- Axial shortening of stents upon radial expansion varies from 25% for the mesh design of the Wallstent to 0% for the coil design of the Gianturco-Roubin stent
- The length of the selected stent should be longer than the lesion to be covered in order to provide a proximal and distal margin of more than 2mm after allowance for axial shortening of the stent upon radial expansion.
- For vein grafts, a stent with an adequate range of diameters and adequate scaffolding lattice such as the Wallstent or Palmaz biliary stent should be selected.

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SAMENVATTING

Na implantatie van de eerste coronaire stent door Jacques Puel in Toulouse in 1986, heeft de stent zich, via pionierswerk in de tachtiger jaren en via gerandomizeerde trials in de negentiger jaren, een prominente plaats verworven in de huidige praktijk van de interventie cardiologie. De conventionele stent vertegenwoordigt de mechanische benadering van een biologisch probleem. De coronaire stent kan een dissectie aanleggen en de normale bloedstroom in vaten met een dreigende of acute afsluiting herstellen, en het voorziet in een methode om angioplastiek van primaire vernauwingen en restenotische lesies in zowel natieve kransslagaders als in aorto-coronaire bypass-grafts te optimaliseren.

Ons onderzoek heeft zich primair gericht op het vastleggen van harde klinische eindpunten (reïnterventies, bypass-chirurgie, hartinfarcten en doden), en op kwantitatieve coronair angiografie (QCA). QCA tijdens de interventie procedure is een leidraad naar optimale stent ontplooiing, en biedt de mogelijkheid de winst aan diameter en de recoil na stentimplantatie te kwantificeren. Bij angiografische follow-up geeft QCA een maat voor het restenoseringsproces in de stent en veranderingen in dimensies van het proximaal en distaal van de stent gelegen vat.

Deel I van dit proefschrift beschrijft de betrouwbaarheid van QCA, en deel II beschrijft de resultaten van kwantitatief angiografische en klinische evaluatie van de korte en lange termijn uitkomst bij electieve en bail-out stent implantaties in natieve kransslagaders, en van primaire stent implantatie in veneuze aorto-coronaire bypass-grafts.

In hoofdstuk II worden de resultaten van 3 studies weergegeven (de relatie tussen klinische eindpunten en QCA, catheter calibratie voor QCA metingen, en de toepassing van signal-averaging voor analoge videotape analyse). Hoofdstuk III geeft een vergelijking weer van 10 QCA systemen die gebruikt worden in leidende core-labs in de Verenigde Staten, Canada en Europa. De tendens om grote diameters te onderschatten en kleine diameters te overschatten werd bij alle systemen gezien. In hoofdstuk IV beschrijven we de resultaten van een methode om de overschatting van kleine diameters teniet te doen door de introductie van een dynamisch edge detection algoritme. In hoofdstuk V rapporteren we een nieuwe techniek om een coronaire "stent-stenose" te plaatsen om QCA-meting van grote diameters in varkens te mogelijk te maken. In hoofdstuk VI vergelijken we de uitkomsten van videodensitometrische en geometrische QCA techniek, met de uitkomsten van intracoronair ultrageluid in patiënten tijdens een coronaire interventie.

Deel II van dit proefschrift evalueert de stents die momenteel klinisch worden toegepast (hoofdstukken VII - IX: Wallstent, hoofdstuk X: Palmaz-Schatz stent, hoofdstuk XI en XII: Gianturco Roubin stent, hoofdstuk XIII: de bail-out stent, hoofdstuk XIV: de AVE Micro stent, hoofdstuk XV: de Wiktor stent en de Wall stent, en in hoofdstuk XVI: de 6 maands resultaten van de Cordis stent gebaseerd op zowel QCA als intracoronair ultra-geluid. In hoofdstuk XVII worden de mechanische en radiografische eigenschappen van alle zeven momenteel beschikbare stents, inclusief de ACS en Cordis stent vergeleken, en op basis hiervan wordt in hoofdstuk XVIII voor elke type stent een potentiële plaats binnen het klinisch toepassingsgebied voorgesteld.

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British Cardiac Society

International Congress on Rate Adaptive Cardiac Pacing and Implantable Defibrillators

North American Society of Pacing and Electrophysiology

American College of Cardiology

American Heart Association

European Society of Cardiology

World Congress of Cardiology

MANUSCRIPT PUBLICATIONS

1 Umans V, Keane D, Foley D, Boersma E, Melkert R, Serruys PW. Optimal use of directional coronary atherectomy is required to ensure long-term angiographic benefit: A study with matched procedural outcome after atherectomy and angioplasty. J Am Coll Cardiol 1994;24:1652-9.

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