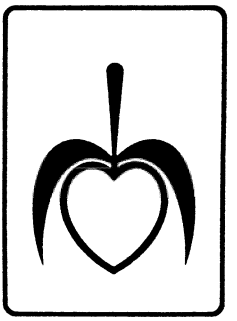
# QUANTITATIVE CORONARY ANGIOGRAPHY IN CLINICAL PRACTICE



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# QUANTITATIVE CORONARY ANGIOGRAPHY IN CLINICAL PRACTICE

*edited by*

PATRICK W. SERRUYS, DAVID P. FOLEY *and* PIM J. DE FEYTER
*Thoraxcenter, Erasmus*
*University Rotterdam, Rotterdam*
*The Netherlands*

with a foreword by

SPENCER B. KING III
*Director, Andreas Gruentzig,*
*Cardiovascular Center,*
*Emory University, Atlanta,*
*Georgia,*
*U.S.A.*

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# Contents

# List of Contributors

Alfred E.R. Arnold
Department of Cardiology
Medisch Centrum Alkmaar
Wilhelminalaan 12
1815 JD ALKMAAR
The Netherlands
Co-authors: Patrick W. Serruys

Nicolas Danchin
CHU Nancy-Brabois
Rue du Morvan
F-54511 VANDOEUVRE-LES-NANCY
France
Co-authors: Yves Juilliere, David P. Foley and Patrick W. Serruys

Peter P. de Jaegere
Thorax Center, EE 2332
Erasmus University
P.O. Box 1738
3000 DR ROTTERDAM
The Netherlands
Co-authors: Bradley H. Strauss, Marie-Angèle Morel, Pim J. de Feyter and Patrick W. Serruys

Pim J. de Feyter
Thorax Center, EE 2332
Erasmus University
P.O. Box 1738
3000 DR ROTTERDAM
The Netherlands
Co-authors: Jeroen Vos, Carlo Di Mario, Patrick W. Serruys and Jos R.T.C. Roelandt

Bernard De Bruyne
Cardiovascular Center
O.L.V.-Hospital
Moorselbaan 164
B-9300 AALTST
Belgium
Co-authors Chapter 10: Nico H.J. Pijls, Pascal J. Vantrimpont, Walter J. Paulus, Stanislas U. Sys and Guy R. Heyndrickx
Co-authors Chapter 15: Nico H.J. Pijls and Guy R. Heyndrickx

Carlo Di Mario
Thorax Center, EE 2332
Erasmus University
P.O. Box 1738
3000 DR ROTTERDAM
The Netherlands
Co-authors Chapter 4: Jürgen Haase, Javier Escaned, Eline Montauban van Swijndregt and Patrick W. Serruys
Co-authors Chapter 16: Pim J. de Feyter, Johan C.H. Schuurbiers, Peter P. de Jaegere, Robert Gil, Håkan Emanuelsson, Cornelis J. Slager and Patrick W. Serruys
Co-authors Chapter 19: Sipke Strikwerda, Robert Gil, Pim J. de Feyter, Nicolas Meneveau and Patrick W. Serruys
Co-authors Chapter 37: Jos R.T.C. Roelandt, Peter P. de Jaegere, Pim J. de Feyter and Patrick W. Serruys

Håkan Emanuelsson
Division of Cardiology
Sahlgrenska Hospital
S-413 45 GÖTEBORG
Sweden
Co-authors: Michal Dohnal, Carl Lamm, Carlo Di Mario and Patrick W. Serruys

Javier Escaned
Thorax Center, EE 2332
Erasmus University
P.O. Box 1738
3000 DR ROTTERDAM
The Netherlands
Co-authors Chapter 5: Jürgen Haase, David P. Foley, Carlo Di Mario, Ad den Boer, Eline Montauban van Swijndregt and Patrick W. Serruys
Co-authors Chapter 36: Pierre Doriot, Carlo Di Mario, David P. Foley, Jürgen Haase, Jose Baptista, Nicolas Meneveau, Ad den Boer, Jos R.T.C. Roelandt and Patrick W. Serruys

David P. Foley
Thorax Center, EE 2332
Erasmus University
P.O. Box 1738
3000 DR ROTTERDAM
The Netherlands
Co-authors Chapter 6: Jaap Deckers and Patrick W. Serruys
Co-authors Chapter 32: Walter R.M. Hermans, Victor A.W.M. Umans, Benno J. Rensing, Peter P. de Jaegere, Javier Escaned, Pim J. de Feyter and Patrick W. Serruys

Jürgen Haase
Thorax Center, EE 2332
Erasmus University
P.O. Box 1738
3000 DR ROTTERDAM
The Netherlands
Co-authors: David Keane, Carlo Di Mario, Javier Escaned, Cornelis J. Slager and Patrick W. Serruys

Claude Hanet
Department of Cardiovascular Pathology
University Clinic Saint Luc
Avenue Hippocrate 10
UCL 10/28.81
B-1200 BRUSSELS
Belgium
Co-authors: Robert Dion and William Wijns

Walter R.M. Hermans
Department of Cardiology
Refaja Hospital Dordrecht
Van der Steenhovenplein 1
3317 NM DORDRECHT
The Netherlands
Co-authors Chapters 7 and 26: Benno J. Rensing and Patrick W. Serruys
Co-authors Chapter 25: David P. Foley and Benno J. Rensing

Spencer B. King III
Andreas Gruentzig Cardiovascular Center
Emory University Hospital
Suite F606
1364 Clifton Rd., NE
ATLANTA, GA 30322
U.S.A.

Eugène P. Mc Fadden
Department of Cardiology B
CHU Lille
59037 LILLE Cedex
France
Co-authors: C. Bauters, P. Quandalle, Michel E. Bertrand and Jean-Marc Lablanche

Yukio Ozaki
Thorax Center, EE 2332
Erasmus University
P.O. Box 1738
300 DR ROTTERDAM
The Netherlands
Co-authors: David Keane, Jürgen Haase, Fumimaro Takatsu and Patrick W. Serruys

Nico H.J. Pijls
Department of Cardiology
Catharina Hospital
P.O. Box 1350
5602 ZA EINDHOVEN
The Netherlands
Co-authors: K. Lance Gould, Bernard De Bruyne, Hans J.R.M. Bonnier, G. Jan Willem Bech, Guy R. Heyndrickx, William Wijns, Richard L. Kirkeeide and Mamdouh I. El Gamal

Johan H.C. Reiber
Department of Diagnostic Radiology
University Hospital Leiden
Building 1, C2–S
P.O. Box 9600
2300 RC LEIDEN
The Netherlands
Co-authors: Pieter M.J. van der Zwet, Gerhard Koning, Craig D. von Land, Bert van Meurs, Jan J. Gerbrands, Beert Buis and Ad E. van Voorthuisen

Benno J.W.M. Rensing
Thorax Center, EE 2332
Erasmus University
P.O. Box 1738
3000 DR ROTTERDAM
The Netherlands
Co-authors Chapters 24 and 27: Walter R.M. Hermans and Patrick W. Serruys

Patrick W. Serruys
Thorax Center, EE 2332
Erasmus University
P.O. Box 1738
3000 DR ROTTERDAM
The Netherlands
Co-authors: Edward S. Murphy and Nico H.J. Pijls

Cornelis J. Slager
Thorax Center, EE 2332
Erasmus University
P.O. Box 1738
3000 DR ROTTERDAM
The Netherlands
Co-authors: Jürgen Haase and Johan C.H. Schuurbiers

Sipke Strikwerda
Thorax Center, EE 2332
Erasmus University
P.O. Box 1738
3000 DR ROTTERDAM
The Netherlands
Co-authors: Eline Montauban van Swijndregt and Patrick W. Serruys

Harry Suryapranata
Department of Cardiology
Hospital "De Weezenlanden"
Groot Wezenland 20
8011 JW ZWOLLE
The Netherlands
Co-author: Patrick W. Serruys

Victor A.W.M. Umans
Thorax Center, EE 2332
Erasmus University
P.O. Box 1738
3000 DR ROTTERDAM
The Netherlands
Co-authors Chapter 8: Walter R.M. Hermans, Jean-Paul R. Herrman, Jaap Pameyer and Patrick W. Serruys
Co-authors Chapter 28: David P. Foley, Annie Robert, Pascal Quaedvlieg, Eline Montauban van Swijndregt, William Wijns and Patrick W. Serruys

Marc M.J.M. van der Linden
Thorax Center, EE 2332

Erasmus University
P.O. Box 1738
3000 DR ROTTERDAM
The Netherlands
Co-authors Chapter 13: Jürgen Haase and Patrick W. Serruys
Co-authors Chapter 35: A.H.M.M. Balk and Pim J. de Feyter

Marcel van den Brand
Thorax Center, EE 2332
Erasmus University
P.O. Box 1738
3000 DR ROTTERDAM
The Netherlands
Co-authors: Maarten L. Simoons, Addy van Miltenburg, M.J. de Boer, Pim J. de Feyter and the European Cooperative Study Group

Jeroen Vos
Thorax Center, EE 2332
Erasmus University
P.O. Box 1738
3000 DR ROTTERDAM
The Netherlands
Co-author: Pim J. de Feyter

Felix Zijlstra
Department of Cardiology
Hospital "De Weezenlanden
Groot Wezenland 20
8011 JW ZWOLLE
The Netherlands
Co-authors: Menko Jan de Boer , Jan C.A. Hoorntje, Johan H.C. Reiber and Harry Suryapranata

# Foreword

No technique in cardiology is more discussed and less used clinically than quantitative coronary arteriography. This is a serious error. In the early days of coronary angiography, the appearance of coronary stenoses on cineangiography was so imprecise that angiographers were urged to read films while they were being played at rapid frame rates. Stopping in film usually resulted in an image that was blurred beyond recognition. Although film quality improved rapidly, the habits of angiographers more interested in performance of the procedure than its interpretation continued to ignore the vast amount of data available on the angiographic film. In recent years, angiographic systems have evolved to the point that quantification of the degree of obstruction is not only possible but is necessary in order to promote proper communication in clinical practice.

Perhaps the greatest stimulus to the development of quantitative coronary arteriography came with the advent of interventional cardiology. When Gruentzig began to alter arterial obstructions with balloons, he also measured those changes from optically magnified images. Quantification became the gold standard even if not universally applied.

Much of the impetus for state of the art quantitative coronary arteriography came from the Thoraxcenter in Rotterdam and the principal cheerleader for its application in clinical medicine has been Patrick Serruys. Dr. Serruys, in this book, brings together many of those who have made significant contributions to the development of coronary anteriography.

The angiographer reading this volume will be impressed by the breadth of the treatment of the subject. The volume begins with chapters discussing the validation of the method and progresses through a discussion of physiologic correlates of coronary artery dimensions. Coronary flow and flow reserve judged angiographically and the relationships of pressure and flow to the angiographic findings are treated in depth. The important area of vasomotion in both large conduit arteries as well as resistance vessels completes the extensive evaluation of the technique itself. The editor then selected those who have applied the technique in clinical settings. The use of quantitative coronary arteriography in primary myocardial infarction, in cases of compli-

cations of interventional techniques and assessing results with new interventional technologies such as atherectomy, stents, and laser angioplasty is extensively explored.

The crucial role of quantitative arteriography in evaluating restenosis trials is an area in which the editors has great experience. Application of consistent quantitative angiographic core laboratories to drug restenosis trials has allowed for highly precise measures of luminal dimensions in the late follow-up period. Important consistencies have been found between trials of various ineffective drug regimens. Quantitative coronary arteriography has also helped investigators understand the proliferative process following these interventions by precisely defining the luminal results of the procedure and the changes in dimensions found over the follow-up period. Although quantitative coronary arteriography has made major contributions, the authors are equally appreciative of the limitations of the technique and conclude the book with chapters on intravascular ultrasound, the new technology vying for the title of "gold standard".

This volume will be of enormous help to those angiographers involved in the design of clinical trials as well as those trying to provide a better assessment of their clinical results. Those who choose to use such methods will produce data which will be of signficant value in management of their patients. Documentation of results will improve communication among physicians and those outside of medicine with a strong interest in patient outcome so they can better understand the value of collecting precise clinical information. Kluwer Academic Publishers, in producing this book, continue their tradition of making available the best thinking regarding the status of modern technology in cardiology at a time when that information is most needed. Both editors, authors and publisher are to be congratulated for an excellent contribution to the understanding of the clinical value of a valuable and underused tool.

Spencer B. King III

# Introduction

In 1986 the undersigned, Patrick W. Serruys and Cees J. Slager wrote our first book on Quantitative Coronary and Left Ventricular Cineangiography: Methodology and Clinical Applications, that was entirely based on work carried out at the Thoraxcenter. At that time 40% of the clinical chapters were devoted to the quantification of left ventricular function and the remaining chapters to quantitative coronary arteriography (QCA). However, over the last decade the scale in our common technological and clinical research interests has definitely tipped over towards QCA. This is clearly evident from the four books that we have edited since then in the Kluwer series Developments in Cardiovascular Medicine. These books describe exclusively the developments in the analytical QCA software packages and their clinical applications. Likewise, this new book from the Thoraxcenter covers the advantages, limitations and applications of QCA in clinical practice, covering work performed at the Thoraxcenter as well as at other cardiological centers.

Of course, this shift in interest is not unexpected. Two major clinical developments have stimulated this enormous growth in QCA clinical research. First of all, the exponential rise in interventional catheterization procedures following the first coronary balloon dilatation (PTCA) by Andreas Gruentzig in 1977 Since that time, PTCA has established itself as a routine revascularization procedure with a known restenosis rate of approximately 33%, depending on the criteria used. Since then many multicenter restenosis prevention trials have been carried out in attempts to solve this restenosis problem. At the same time the number of QCA Core-laboratories have mushroomed worldwide without a well defined Quality Assurance program on the quality of these labs established.

Many new approaches have been invented over the last decade to recanalize the obstructed coronary arteries, including thrombolysis in the acute myocardial infarction situation with various pharmacological agents, and various recanalization devices, such as stents, mechanical atherectomy devices, lasers, etc. To study the efficacy, restenosis rates and other limitations of these approaches, carefully acquired coronary arteriographic data pre- and

immediate post-intervention as well as at follow-up need to be interpreted in great detail.

Secondly, there has been an enormous growth in the development and use of cardiovascular drugs directed at the regression or no-growth of existing coronary artery disease, or the delay in the formation of new lesions. These approaches require the precise comparison of the arterial dimensions in a control group versus those in a treated group studied over a long period of time (typically 2–3 years).

It has been well accepted that the conventional visual interpretation of coronary arteriograms is no longer acceptable to study the efficacy and limitations of all these different intervention procedures. The results must be evaluated in an objective and reproducible manner on the basis of absolute parameters describing accurately the baseline coronary morphology and subsequent changes therein. The off-line cinefilm-based approaches for QCA has been used exclusively in such clinical research studies. In parallel to and triggered by these clinical applications, major developments have taken place in these QCA-systems. There has been a definite shift from the more traditional PDP and Vax computers to workstations and very powerful personal computers (PC's), characterized by decreased cost and highly increased performance. In addition, major advances have taken place in the development of the analytical software packages. Progress has been made towards more routinely applicable user-interfaces, more robustness of the software itself coupled with a higher degree of automation (less user interaction) and reproducibility in the derivation of the clinically relevant parameters.

in addition, there has been a significant progress in X-ray imaging technology. Image quality is continually improving due to the availability of higher quality X-ray sources, image intensifiers, TV chains, the use of pulsed fluoroscopy, and real-time image enhancement. It is now also possible to store the dynamic pictorial information on-line in digital format at high spatial and temporal resolution. The application of gap filling techniques allows a reduction in the acquisition frame rates with a concomitant reduction in X-ray radiation dose. Quantitative data on coronary arterial dimensions can now be made available at the time of the catheterization procedure (on-line) measured directly from digitally acquired arteriograms.

However, sofar these on-line techniques have been used predominantly for clinical decision making, balloon and stent sizing, etc.

From the QCA data functional measures have also been derived such as pressure gradients at various assumed flow values, the stenotic flow reserve (SFR), etc. These approaches have always been difficult to validate. More recently, major developments in guide wire technology have allowed much more reliable intracoronary pressure and Doppler flow measurements. This will allow integrated approaches for the assessment of coronary pathophysiology.

Finally, Intravascular Ultrasound (IVUS) has emerged as a new technique to study the morphology of the coronary vessels. Of course, both QCA and

IVUS have their own advantages and limitations. It will be interesting to see how IVUS will compete with QCA, and how these can complement each other.

As the majority of new catheterization laboratories are equipped with digital imaging systems, on-line quantification of coronary morphology, flow reserve and left ventricular function will become feasible with state-of-the-art analytical packages featuring a high success score and a short processing time. The use of these analytical software packages is expected to increase significantly in the coming years. This process may be accelerated if quality assurance issues are demanded by insurance companies and/or government agencies. As patients who have been involved in clinical research studies are followed up over longer periods of time, more prognostic information about the progress of coronary artery disease will become available. Therefore, it is not unlikely that in the future the results from QCA will be used by the more general cardiologists to predict any future sequelae. Further developments in analytical software packages are directed among others at the processing of the entire coronary tree with the automated selection of significant lesions. These results will then be presented in coronary reporting schemes to be included in the patient's status. Such a graphical representation can then be transferred to the referring physicians leading towards a wider dissemination of the QCA message.

Johan H.C. Reiber

*PART ONE: Validation of QCA: In vitro and in vivo, off-line and on-line studies*

# 1. Why and how should QCA systems be validated?

JOHAN H.C. REIBER

Whichever QCA analytical software package is being used, it will always produce numbers describing the morphology of the coronary segment analyzed. It will be clear that extensive validation studies need to be carried out to demonstrate the strengths and weaknesses, as well as the clinical validity of such analytical packages. The more we learn about QCA, the more it becomes clear that such validation studies must be well designed, properly carried out and analyzed statistically. In general, the following sequence of studies, which will be described in more detail in the following paragraphs, needs to be performed: 1) Assessment of the accuracy and precision of the edge detection technique; 2) Assessment of the reproducibility of the results from the image analysis procedure; 3) Assessment of the short-, medium-, and long-term variabilities; and 4) Assessment of the interinstitute or -laboratory variability. It has been well accepted that the results from validation studies should be described in terms of the mean signed differences (accuracy) and the standard deviation (precision) of these signed differences (measurement 1 – measurement 2; not absolute differences) between the actual and measured values or between the values from repeated measurements [1,2]. Finally, for laboratories involved in longitudinal coronary arteriographic studies a strictly controlled Quality Assurance (QA) program is of eminent importance.

**Assessment of the accuracy and precision of the edge detection technique**

– Evaluation studies using plexiglass phantoms with circular tubes or 'vessels' ranging in size from 0.5 mm to 5.0 mm either with or without obstructions and performed under different imaging conditions (various concentrations of the contrast agent, different kV-levels) must be carried out. The phantom must be acquired with an X-ray scattering medium, e.g. a 10 cm stack of plexiglass or a corresponding water basin. A straight "vessel" segment must be analyzed over a sufficient length, e.g. 2 cm, providing a mean value and



*P.W. Serruys, D.P. Foley and P.J. de Feyter (eds.), Quantitative Coronary Angiography in Clinical Practice*, 1–6.

a standard deviation per segment. The precision per segment is defined by the standard deviation of the signed differences between each measured diameter in the diameter function of the segment and the measured average diameter of the segment; this standard deviation is a measure for the irregularity of the detected contours. In other words, this precision measure represents an uncertainty range for the diameter measured at a discrete position, such as the minimal lumen diameter (MLD). To obtain an overall measure for the phantom acquired under a certain imaging condition, the mean difference values can be averaged over all segments providing an overall accuracy value, and the pooled standard deviation provides an overall precision value [3]. It is important to realize that the overall precision should not be based on the standard deviation of the signed differences between the mean diameter value of a segment and its true value; this would result in too optimistic values! For an edge detection technique to be acceptable, the overall accuracy value should be close to zero, which means that no significant over- or underestimations, or systematic errors occur; the overall precision in absolute vessel sizes should be on the order of 0.10–0.13 mm.

However, this overall analysis is not sufficient to demonstrate the success of a particular edge detection technique. The averaging process may hide local inaccuracies; for example, overestimations for the small vessel sizes may cancel out underestimations for the larger sizes. Therefore, it is of utmost importance to show the results for the individual vessel segments as well. An excellent way to do this, is by means of the difference plots as have been suggested by Bland and Altman [4]. Such plot allows a rapid and easy interpretation of the efficacy of the edge detection technique for all the individual vessel sizes; 'local' inaccuracies will be readily apparent.

Precision numbers decrease when the degree of contour smoothing is increased, resulting in smoother contours. At first glance this would seem to be a positive characteristic of the contour detection algorithm. It is clear though, that by increasing the degree of contour smoothing the performance of the algorithm to accurately measure the minimal lumen diameter of an obstruction, particularly those of short severe obstructions, will deteriorate. The degree of smoothing necessary is rather critical: too little smoothing results in very irregular contours which may have a tendency to follow all kinds of irregularities, too heavy smoothing results in missing of abrupt changes in the vessel sizes at obstructions. It is therefore important that the algorithms are also tested on 'vessel' tube phantoms that contain obstructions. Preferably, these obstructions should taper to one single minimal diameter. If, on the contrary phantoms are used that contain obstructions of constant diameter over a certain length, the minimum of all obstruction diameters is chosen, leading to a systematic underestimation of the MLD.

– To allow a clinically more realistic evaluation, this plexiglass phantom should be positioned on the chest of a patient over the heart and acquired during a routine catheterization procedure. The same analyses as described above can be carried out. This will result in an increase in the standard

deviation values, i.e. a lower precision due to inhomogeneous background, usually lower signal-to-noise ratio, etc.

– The ultimate test is an in vivo animal study with hollow plastic cylinders of various luminal sizes inserted in the coronary arteries [5,6]. Again the same analyses procedures as described earlier should be followed. Under these truly clinical conditions, precision values on the order of 0.20 mm or larger should be expected.

– If densitometric validation studies are carried out, the hypothesis that the results are independent of the angiographic views in which these studies were acquired, must be tested.

## Assessment of the reproducibility of the results from the image analysis procedure

Once the accuracy and precision of the edge detection technique have been established and found to be acceptable, the next issue is the assessment of the inter- and intraobserver variabilities on a set of routinely acquired coronary arteriograms. Frames to be analyzed will, in general, be selected by one of two users; the images selected for calibration do not need to be the same as the images in which the coronary segments are analyzed. For the inter-observer study, the selected frames are analyzed by the two observers independently from each other. For the intra-observer study, the same set of images are analyzed several weeks later by one of the two observers without using knowledge from the first analysis session [7]. From the inter- and intraobserver data, the mean signed differences (accuracy) and the standard deviation of these differences (precision) are calculated. Again the differences should not be statistically significantly different from zero, and the standard deviation values as small as possible. Precision values in absolute dimensions on the order of 0.12–0.14 mm are nowadays common.

## Assessment of the short-, medium- and long-term variabilities

The inter- and intraobserver variability measurements proposed above are obtained from selected frames of coronary arteriograms. Additional sources of variability are included with repeated acquisition of coronary arteriograms followed by quantitative analysis of these images. Such studies will more closely resemble the situations in which these packages will be applied in routine clinical practice. For these purposes we can define three kinds of studies, the socalled short-, medium- and long-term variability studies. The short-term variability is defined by the variability in measured arterial dimensions from repeated acquisition and quantitative analysis of coronary arteriograms taken 5 min apart with unchanged geometry of the X-ray system. The medium-term variability is defined by the variability in measured arterial

dimensions from repeated acquisition and quantitative analysis of the coronary arteriograms with the first arteriogram taken at the beginning of the catheterization procedure and the second arteriogram taken at the end. Between these repeated arteriograms, the X-ray system settings will be changed various times for the acquisition of other angiographic views (and of the left ventriculograms).This means that the X-ray system needs to be returned to the initial arteriographic view for the repeat study. Finally, the long-term variability is defined by the variability in measured arterial dimensions from repeated acquisitions and quantitative analysis with the first and the second arteriograms taken at two separate catheterization sessions. The time period between the two sessions should preferably not exceed 6 months to exclude the effects from progressive coronary artery disease. It will be clear that standardized acquisition protocols need to be followed to minimize the number of error sources [7]. Standardization items include among others the use of a coronary vasodilator, preferably a nonionic contrast agent, maximal and reproducible inspiration by the patient, careful read out and resetting of the rotation and angulation angles of the gantry, etc. From our experience, the short-, medium- and long-term variabilities in absolute vessel dimensions will be on the order of 0.20 mm or higher. The increased variabilities are most likely due to the variations in the calibration factor assessed on the basis of the contrast catheter.

**Assessment of interinstitute or -laboratory variability**

With the widespread use of QCA in different laboratories, the question comes up how well the results from these core-laboratories correlate. Two core-labs may use the same equipment, but differ in the image quality of the coronary arteriograms and/or in the way the angiograms are analyzed (frame selection, standardization in the selection of the coronary segments, dedication in the actual analysis of the images, etc.). On the other hand, two labs may use different QCA equipment, but otherwise have the same level of sophistication in the coronary arteriographic acquisition and analysis procedures. The worst situation is present if two labs use different equipment and have different image quality, different approaches in the analysis procedures, etc. Sofar very little has been done to assess these interlaboratory variabilities. The first reports now begin to appear and demonstrate that Quality Assurance (QA) is something that we need to think about very seriously [8]. One approach that we have taken to teach the users about the basic principles of QCA, and about standardized acquisition and analysis procedures, is by organizing Quantitative Coronary and Left Ventricular Cine and Digital Angiography (QCLA) training courses, whereby a great deal of attention is given to hands-on training on the equipment under the supervision of faculty members. This has shown to be very effective in transferring our QCLA experience to the (potential) users.

**Quality Assurance (QA) in longitudinal coronary arteriographic studies**

The quality of the results of such studies are necessarily dependent upon the quality of the underlying arteriographic images. It has been clear that proper 'calibration' of the participating catheterization laboratories will improve the consistency and reliability of the image data, and that truly corresponding segments from multiple views can be compared with precision. To determine the quality of the X-ray imaging chain and the possible changes therein over a study period, appropriate calibration programs have been developed for catheterization laboratories. Items which are measured include, among others:

1) accuracy and precision of the rotation and angulation read-out devices;
2) accuracy and precision of tower height and table read-out devices;
3) resolution of the X-ray system based on the modulation transfer function analysis and on the basis of line-pair phantoms;
4) determination of the large detail detectability (LDD) of the X-ray system using the MEDIS X-ray phantom;
5) signal-to-noise ratio in the phantom images;
6) spatial distribution and degree of pincushion distortion;
7) the quality of the cinefilm development process;

The derived data from these measurements are stored in a QA-database, allowing trend analysis from follow-up calibration procedures which are carried out at regular time intervals. As soon as it becomes evident that one of the parameters will fall outside of the normal ranges, preventive maintenance procedures can be initiated. On the basis of these objective data, cardiac catheterization laboratories can have their performance assessed and submit this data in order to be selected for inclusion in a clinical trial (Quality Acceptance Program).

**Concluding remarks**

From the above it will clear that assessing the strengths and weaknesses and the validity of a new QCA analytical software package is not a trivial task anymore. In addition to all these variability measurements, a great deal of attention must also be given to the user interface, to the amount of manual corrections that need to be carried out to the detected contours in routinely acquired arteriograms and the simplicity with which these corrections can be applied, to the success score in tracking complex lesions, etc. Quality Assurance programs are now being set up to test the quality of QCA core-laboratories and the quality of the catheterization laboratories participating in multi-center trials.

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# 2. Accuracy and precision of quantitative digital coronary arteriography; observer-, as well as short- and medium-term variabilities

JOHAN H.C. REIBER, PIETER M. J. VAN DER ZWET, GERHARD KONING, CRAIG D. VON LAND, BERT VAN MEURS, JAN J. GERBRANDS, BEERT BUIS, and AD E. VAN VOORTHUISEN

## Introduction

Over the last decade and particularly in the last few years, intervention cardiology has grown at an unforseen pace. In addition to the now "conventional" intervention techniques such as thrombolysis and balloon dilatation, other rapidly evolving techniques for transluminal revascularization or recanalization, such as stent implantation, laser ablation, mechanical atherectomy approaches, etc. have been and are being developed and validated at many research centers. In parallel to and partly triggered by these clinical developments, there has been a significant progress in X-ray imaging technology. Image quality is continually improving due to the availability of higher quality X-ray sources, image intensifiers, TV chains, the use of pulsed fluoroscopy, and real-time image enhancement. It is now also possible to store the dynamic pictorial information on-line in digital format at relatively high spatial and temporal resolution [1–3]. The application of gap filling techniques allows a reduction in the acquisiton frame rates with a concommitant reduction in X-ray radiation dose. These clinical and technical forces running in parallel, put pressure on the availability of quantitative data on coronary artery dimensions at the time of the cardiac catheterization procedure (on-line) or shortly thereafter on the basis of the digitally acquired arteriograms, as well as off-line from 35 mm cinefilm.

In the on-line situation, the system will function as a tool providing the interventional cardiologist with quantitative morphologic and functional data useful for the selection of the appropriate sizes of recanalization devices (e.g. intracoronary balloons, stents, atherectomy catheters, lasers etc.). In addition, the effect of an intervention (e.g. PTCA) can be assessed directly during the procedure; the angiographer can continue with the procedure until a quantitatively assessed acceptable result in terms of morphology and/or function has been obtained. Therefore, this approach is particularly useful for diagnostic and/or therapeutic decision making during the catheterization procedure. Naturally, coronary morphology can also be assessed quantitatively after the catheterization procedure as long as the digital data



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remain available. Coronary quantification based on the off-line 35 mm cinefilm approach is still used almost exclusively for long-term intervention studies (e.g. directed at studying the effect of a drug, diet, etc. on the regression or progression of coronary artery disease), because of the inherently higher spatial resolution of the cinefilm [4–8], and the fact that a practical and universally available long-term storage medium with the same degree of transportability, durability and cost of cinefilm still does not exist for digital images.

Recently, we have developed the Automated Coronary Analysis (ACA-)-package, for coronary quantification for the Philips Digital Cardiac Imaging (DCI-)system [9–11]. To be able to apply this package also in the on-line situation, it should satisfy the following requirements: 1) minimal amount of user-interaction in the selection and processing of a coronary segment; 2) computationally fast (total processing time in the order of 15 seconds or less); and 3) high success-score; preferably in at least 90% of the cases the user should agree with the first obtained automatically determined results and not feel the necessity to manually edit the contours of the arterial segments, particularly at the lesion, to change reference positions, etc.

Despite the high degree of automation in the quantitative analysis of the coronary segments with the ACA-package, definite measurement variabilities continue to exist. Potential error or variability sources come from either the analysis procedure or the acquisition procedure. Important error sources in the analysis procedure include the manual definition of the beginning and end points of the segment to be analyzed, possibly manual corrections to the otherwise automatically detected outlines, frame selection, etc. Most of these variabilities can be assessed with a well-conducted inter- and intra-observer variability study. In clinical practice, it is not sufficient to only know the reproducibility of a QCA package on the same set of images. One should know what the overall variability is with repeated angiography and analysis. In the acquisition procedure there are many sources of variabilities, reason why a standardized approach on image acquisition and analysis is of utmost importance in QCA. All the relevant acquisition error sources will be discussed in detail in the Discussion section.

In this chapter, we describe the basic principles of this ACA-package, as well as the results from various evaluation studies. Extensive validation studies have been carried out directed at: 1) assessment of the accuracy and precision of the edge detection technique based on appropriate hardware phantoms; 2) assessment of inter- and intra-observer variabilities; and 3) assessment of short- and medium-term variabilities with repeated coronary arteriographies and quantitative analysis.

## Methods

With the Philips DCI digital coronary arteriograms can be acquired at 12.5, 25 or 50 frames/s for a 50 Hz configuration and at 15, 30 or 60 frames/s for

a 60 Hz system at matrix sizes of $512^2 \times 8$ bits and $512 \times 480 \times 8$ bits, respectively. The entire analysis procedure consists of the following steps:
1) calibration of the image data;
2) definition of coronary segment to be analyzed;
3) automated path line detection;
4) automated contour detection of the arterial segment;
5) derivation of the clinically relevant parameters; and finally,
6) presentation of the results.
These steps will be briefly clarified in the following sections; since calibration is based on the same basic principles as arterial analysis, it will be described third.

*Definition of coronary segment to be analyzed*

The first step in the analysis procedure is the selection of an appropriate frame. The following criteria are important for the frame selection process:
1. The arterial segment should be well-filled with contrast medium. This is usually achieved by selecting an image from the second or third cardiac cycle following the contrast administration.
2. To avoid motion blur, the image should preferably be selected in the diastasis or end-diastolic phase of the cardiac cycle.
3. The obstructed coronary segment should be clearly visible, preferably without any overlap from other vessels or sidebranches.

In order for the method to be applicable in an on-line and routine clinical environment, the user should preferably provide only two points of the arterial segment to be analyzed: the start point and the end point. User-interaction is performed with the mouse of the DCI. These points do not need to be close to the actual center of the vessel, any place *within* the vessel is acceptable. Standardization of the procedure will result in the highest accuracy and precision of the measurements. We thus advocate to define these points at the bifurcations of the major arterial segments, such as the LAD prox, LAD mid, segments etc., as recommended by the American Heart Association [12].

*Automated path line detection*

In the ACA-package, an arterial path connecting the start and end points is computed automatically using an innovative tracer algorithm in a minified version of the image [9,11]. This arterial path functions as a rough model for the subsequent contour detection, so it does not need to follow the actual centerline of the vessel. For that reason, we shall refer to this line tracer path as the pathline. A combination of two algorithms is used for the automated detection of the pathline of the selected segment: the tracer algorithm, and the box algorithm, which have been described in detail elsewhere [9]. Figure 1 shows the results of this technique for a proximal segment of a left anterior descending (LAD) artery. This pathline is acceptable if all points remain

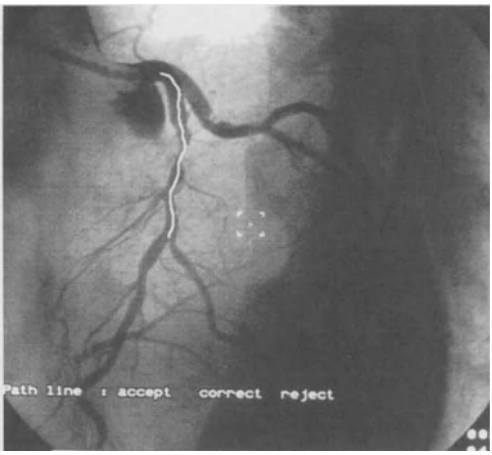


*Figure 1.* Arterial path line detected automatically between manually defined beginning and end points of the proximal segment of a left anterior descending artery (LAD).

within the assumed arterial boundaries. On the rare occasion that the detected pathline does not follow the path that the user had in mind, (s)he can define additional points in the missing part of the arterial segment in an iterative manner. The program then searches for a new path, from the start point, via the correction point, to the end point. On the DCI, the pathline is presented in the original nonmagnified image.

*Automated contour detection of the arterial segment*

The next step is the contour detection procedure which is carried out in two iterations, the first one in the original nonmagnified $512^2$ image, the second iteration in a digitally magnified image. The contour detection technique itself is based on resampling the image perpendicular to a model (the pathline in the first iteration), computing a cost coefficient matrix representing for each point in the resampled matrix the edge strength defined by the weighted sum of the first- and second derivative values in the brightness levels computed along the scanline, and applying the socalled minimal cost contour detection technique to the cost coefficient matrix [5,11]. This technique has been shown to be very robust, which is particularly useful for images with low signal-to-noise ratios, and computationally fast [13]. This first iteration of the contour detection procedure provides a first approximation of the arterial boundaries. The contour detection algorithms are applied to the original, white-compressed images.

As a next step, an automatically defined region of interest (ROI) of size $256 \times 256$ pixels ($256 \times 240$ pixels for NTSC system) centered around the

defined arterial segment is digitally magnified by a factor of two with bilinear interpolation. If the length of the selected arterial segment was chosen such that the digitally magnified segment would not fit within the $512^2$ matrix size, digital magnification is not carried out and the second iteration is performed at the original resolution; this will of course negatively influence the accuracy of the measurements. The contours detected in the first iteration function as models for the contour detection in the second iteration either in the magnified or nonmagnified image. To correct for the limited resolution of the X-ray imaging system, the 1st- and 2nd-derivative functions which are used for the calculation of the edge strength for each pixel are modified in the second iteration based on an analysis of the point spread function of the imaging chain. This is of particular importance for the accurate measurement of small vessels [11]. The finally detected contours are subsequently transformed back to the magnified or nonmagnified image. Figure 2 shows the final results of the contour detection algorithm applied to the example of Fig. 1. If the user does not agree with one or more parts of the detected contours, manual corrections can be applied after the second iteration. Two possibilities have been implemented. If the erroneous part can be approximated by a straight line, the user erases this part using the mouse. Next, the two remaining contour parts are connected by a straight line and the contour detection technique is again applied in a restricted area around this part (3rd iteration), so that in the end all contour points are based upon the actual grey level distribution in the image. If this straight line approximation is not applicable, the user erases the erroneous part and manually redraws the correct contour as accurately as possible. However, if this corrected part deviates significantly from the initial erroneous contour part, the contour detection process is also repeated in a restricted area around this redrawn part. This means that in the majority of the cases, the finally accepted contour will be based on the actual grey level distribution in the image: the user only identified the unacceptable contour parts. All these manual interactions have been made as user-friendly as possible.

*Derivation of the clinically relevant parameters*

After the final contours have been detected and possibly corrected, relevant clinical parameters are assessed. From the left- and right-hand contour positions of the arterial segment a new accurate centerline is computed. Next, the diameter function or profile of the arterial segment is determined by measuring the distances between the two contours for every second position along this centerline. The diameter of the vessel at a particular centerline position is defined as the length of the chord between both contours taken perpendicular to the local centerline direction.

From these data the following parameters are automatically calculated: the site of maximal percent diameter stenosis and the corresponding lesion diameter (which does not necessarily correspond with the minimal vessel

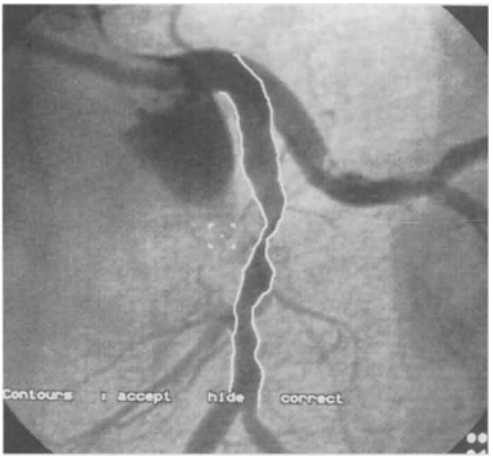


*Figure 2.* Result of the contour detection algorithm. The arterial contours were detected automatically with the minimum cost algorithm.

diameter, as the lesion is selected by the *maximal percent* diameter stenosis). To be able to automatically determine the reference diameter value, a best estimation of the 'nondiseased' size of the vessel is determined from the diameter function by the so-called iterative linear regression technique. This reference diameter function represents a best approximation of the nondiseased state of this segment by excluding the ectatic and obstructed regions. The reference diameter value is then taken as the value from the reference diameter function as measured at the site of obstruction. This automated approach has been found to be very reproducible.

On the basis of this reference diameter function, and the actual arterial contours, the reference contours are reconstructed. Spline functions are used to obtain a best fit of the reference contours around the actual arterial contours, satisfying the reference function.

From the obstruction and reference diameters, the percentage diameter and area stenosis (assuming circular cross sections) are derived. The length of the obstruction and the area of the atherosclerotic plaque are calculated from the differences between the luminal and reference diameter functions and contours, respectively. The symmetry of the stenosis is defined by the ratio of the plaque area at the left hand side of the vessel divided by the plaque area at the right hand side of the vessel. The symmetry value ranges from 0 (asymmetric) to 1.0 (symmetric). Finally, the transstenotic pressure gradients at different flows (ml/s) and the stenotic flow reserve (SFR) are calculated from the arterial dimensions according to Kirkeeide and Gould [14].

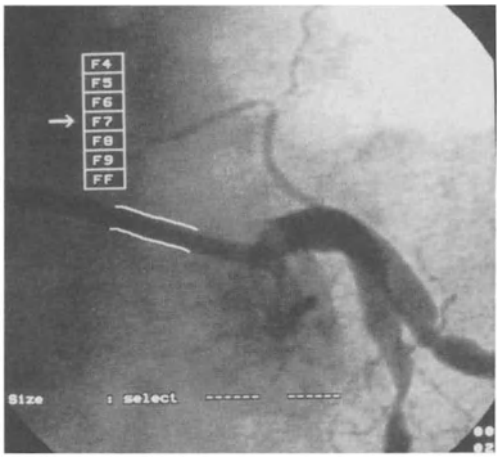


*Figure 3.* Example of the detected contours along a nontapered portion of the catheter segment. A priori information has been used in the edge detection process resulting in two parallel curves.

### *Calibration*

Image calibration is performed on the contrast catheter either in the same frame in which the arterial segment was analyzed if a sufficiently long nontapering part of the catheter is visible, or in another frame of the same image run. The catheter part to be analyzed should also be free from any disturbing objects, such as contrast dye in the aortic valve, other catheters, etc. Basically, a similar procedure is followed for the automated edge detection of a nontapering portion of the contrast catheter as was described for an arterial segment; *a priori* information is used in the edge detection procedure for the catheter segment knowing that this portion is the projection of a cylindrical structure. This means that the two contours are always running in parallel, without necessarily being straight lines. On the basis of the average diameter of the catheter segment in pixels and the known size of the catheter in French, the calibration factor in mm/pixel is computed (Fig. 3). Typical values for digital images of size $512 \times 512$ pixels acquired at a 7″ image intensifier mode are 0.18–0.23 mm/pixel.

### *Presentation of the results*

All the results are presented on two pages (Figs 4A and 4B). The first result page (Fig. 4A) shows the actual arteriographic image with the arterial boundaries superimposed, the diameter function with the straight line being the interpolated reference diameter function, demographic data in the top panel, and the most important derived parameters in the bottom panel.

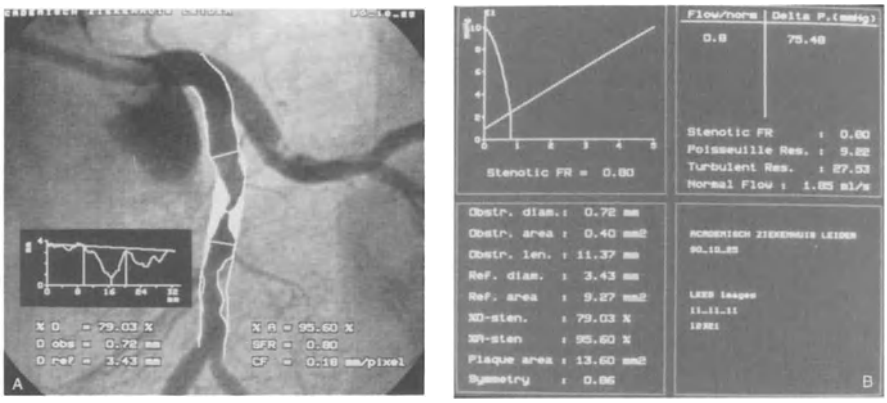


*Figure 4.* Final result of the analysis of the coronary segment of Fig. 1. The first results page shows the automatically detected luminal contours, the computer-defined reference contours, and the diameter function (Fig. 4A). The calibration factor CF = 0.18 mm/pixel refers to the pixel size in the original nonmagnified image. In Fig. 4B the derived parameters are presented on the second results page.

The second result page (Fig. 4B) provides a complete overview of all parameters derived. These include in the lower left quadrant obstruction and reference diameters and areas (assuming circular cross sections), percent diameter and area stenoses, obstruction symmetry, area of the atherosclerotic plaque and length of the obstruction. Functional information is given in the upper right quadrant: normal flow (ml/s) based on the assumption of a constant flow velocity of 20 cm/s and taking into account the computed reference area, the Poisseuille and turbulent resistances, as well as the radiographic Stenotic Flow Reserve (SFR-)value. Finally, pressure gradients (mmHg) are given for various normalized flow situations up to the SFR-value.

## Materials

Before this ACA-package can be applied with confidence in daily practice or for clinical research purposes, extensive validation studies need to be carried out. We have always advocated to perform the following basic validation steps: 1) phantom studies under different conditions to test the accuracy and precision of the contour detection technique; 2) repeated analysis of a set of clinical coronary arteriograms to assess the inter- and intra-observer variabilities; and 3) determination of the short- and medium-term variabilities in the repeated angiographic acquisition ànd quantitative analysis of clinical coronary arteriograms. The materials used are described in more detail in the following paragraphs.

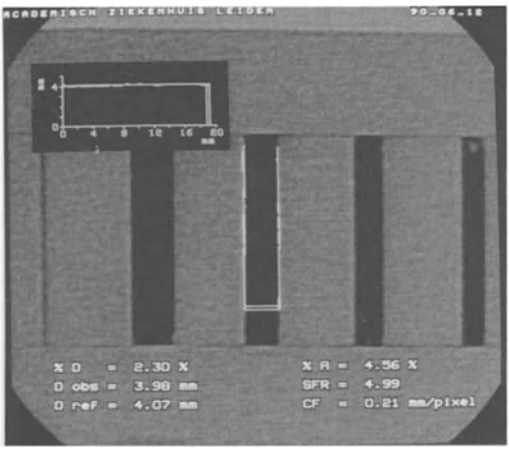


*Figure 5.* Example of the vessel phantom acquired in the 7" image intensifier mode, at 100% contrast concentration and at 70 kV. The detected contours for the tube with a true size of 4.04 mm are superimposed on the images. In this case a mean diameter of 4.03 mm and a standard deviation of 0.06 mm were found.

### *Vessel phantom*

The accuracy and precision of the contour detection technique was assessed on the basis of a plexiglass phantom (from Richard L. Kirkeeide, Ph.D., Houston, USA) consisting of a total of eleven tubes of known diameters (range 0.660–5.055 mm). The phantom was filled with 100% and 50% of the contrast agent (Iopamiro$^{R}$ 370) and acquired at 70 and 90 kV in both 5″ and 7″ imaging modes of the image intensifier (II). Figure 5 is an example of a vessel phantom image acquired in the 7″ II-mode, at 100% contrast concentration and at 70 kV. From each tube a portion with a length of approximately 2 cm was analyzed. Using a special research version of the ACA-package the mean diameter over this segment and the associated standard deviation of the diameter relative to the mean diameter was provided. The overall quality of the contour detection applied to the vessel phantom is described by the overall mean signed difference (accuracy) between the measured and true values, and by the pooled standard deviation (precision) of the individual measurements. A negative accuracy is associated with an underestimation of the vessel size.

### *Reproducibility on routine coronary arteriograms*

To assess the inter- and intra-observer variabilities of the ACA-package, 16 routinely acquired digital coronary arteriograms were used with a total of 39

obstructions. Images were selected in the diastasis period by one observer (GK) and per image one or more coronary obstructions were analyzed in a standardized manner, i.e. from one major bifurcation to the following one according to the recommendations by the AHA; this one set of images was analyzed by two observers (GK, HR) independently of each other. For each coronary segment a corresponding calibration factor was obtained on the basis of the contrast catheter. The image selected for calibration was not necessarily the same as the image in which the obstruction was measured. Criteria for the calibration frame selection included: 1) nontapering segment of the catheter visible with a sufficient length (approximately 2 cm); and 2) catheter not obscured by contrast flowing back into the aorta. As a result, the catheter image was usually selected in the early phase of the cardiac study. This same set of images was reanalyzed at average five weeks later by one of the two observers (GK) without using knowledge from the first analysis session. This means that for both the inter- and intra-observer variability studies the users defined the beginning and end points of the coronary segments based on the bifurcations visible in the images, but without knowing the precise positions of these reference points from the corresponding analyses. From these inter- and intra-observer data the mean signed differences (accuracy) between the repeated measurements, and the standard deviation of these differences (precision) were calculated.

*Short- and medium-term variabilities*

The inter- and intra-observer variability measurements described above were obtained from selected frames of digital coronary arteriograms. An additional source of variability can be included by repeated acquisition of coronary arteriograms followed by quantitative analysis of these images. Such studies will more closely resemble the situations in which the ACA-package will be applied in routine clinical practice. For these purposes we defined two kinds of studies, the socalled short- and medium-term variability studies. The short-term variability is defined by the variability in measured arterial dimensions from repeated acquisition and quantitative analysis of digital coronary arteriograms taken five minutes apart with unchanged position of the geometry of the X-ray system. The medium-term variability is defined by the variability in measured arterial dimensions from repeated acquisition and quantitative analysis of the digital coronary arteriograms with the first arteriogram taken at the beginning of the catheterization procedure and the second arteriogram taken at the end. Between these repeated arteriograms the X-ray system settings were changed various times for the acquisition of other angiographic views (and of the left ventriculograms). This means that the X-ray system had to be returned to the initial arteriographic view for the repeat study. For both types of studies the following acquisition protocols were followed. Immediately prior to each study a coronary vasodilator (5 mg isosorbide dinitrate sublingually) was administered to standardize the coron-

*Table* 1. Distribution of coronary vessels analyzed in the short- and medium-term variability studies.

| | Short-term variability | Medium-term variability |
|---|---|---|
| Number of obstructions | 41 | 40 |
| Number of patient studies | 15 | 15 |
| Major coronary vessels | | |
| RCA | | |
| prox | 9 | 10 |
| mid | 3 | 3 |
| distal | 3 | 1 |
| LAD | | |
| prox | 5 | 5 |
| mid | 5 | 4 |
| distal | 2 | 2 |
| Cx | | |
| prox | 5 | 5 |
| distal | 6 | 8 |
| Sidebranches | | |
| Obtuse marg. | 1 | - |
| Postero lateral branch | 1 | 1 |
| Diagonal branch | 1 | 1 |

ary vasomotor tone [15]. In addition, a nonionic contrast agent (Omnipaque$^{R}$ 350) was used. For the medium-term variability study the X-ray system settings (rotation angle, angulation angle, table height, tower height, kV-level, etc.) were documented.

For the short-term study a total of 41 coronary obstructions were acquired and analyzed from 15 digital coronary arteriograms. The distribution of the coronary vessels in which these obstructions were found is listed in Table 1. For the medium-term study 40 obstructions were acquired and analyzed from 15 digital coronary arteriograms; the distribution of the vessel segments is also given in Table I. A total of 37 coronary obstructions and images could be included in both short- and medium-term studies.

Similarly as described earlier for the reproducibility study, for both the short- and medium-term studies images were selected in the diastasis period from corresponding cardiac cycles relative to the moment of contrast injection. Again per image one or more coronary obstructions were analyzed in the standardized manner.

### *Statistical analysis*

The accuracy is defined as the mean signed differences between the true and measured values or between the values from repeated measurements, while the precision is defined as the standard deviation of these differences. For

*Table* 2. Mean difference and overall standard deviation of the measurements applied to images of the vessel phantom, as measured on the DCI.

| II Mode | Contrast concentration (%) | Load (kV) | Mean differences (mm) | Pooled standard deviation (mm) |
|---|---|---|---|---|
| 7″ | 100 | 70 | −0.001 | 0.096 |
| 7″ | 100 | 90 | −0.013 | 0.110 |
| 7″ | 50 | 70 | −0.021 | 0.130 |
| 7″ | 50 | 90 | −0.015 | 0.136 |
| 5″ | 100 | 70 | −0.021 | 0.095 |
| 5″ | 100 | 90 | −0.005 | 0.082 |
| 5″ | 50 | 70 | −0.041 | 0.104 |
| 5″ | 50 | 90 | −0.025 | 0.118 |

the phantom studies with a total of eleven "vessel" segments analyzed, the overall variability is defined as the pooled standard deviation calculated from the standard deviation values of the individual vessel segments. The overall accuracy is defined as the average value of the accuracy data obtained from the individual segments. A difference was defined to be statistically significant for $p < 0.01$.

## Results

### *Vessel phantom*

The results of the vessel phantom study are shown in Table 2. For each of the two image intensifier modes (5″ and 7″), contrast concentrations (50% and 100%) and kV-setting of the X-ray system (70 and 90 kV) the mean differences between the measured and true diameter values, and the pooled standard deviations of these differences have been listed. Under all circumstances the ACA-package slightly underestimates the true sizes of the vessel segments; the maximal difference, however, is −0.041 mm only. The precision values range from 0.082 mm for the 5″ II-mode, 100% contrast concentration and 90 kV-load, to 0.136 mm for the 7″ II-mode, 50% contrast concentration and 90 kV-load. For all cases the variability as assessed from a 5″ II-mode is smaller than from the corresponding study on a 7″ II-mode (p = n.s.). Similarly, the studies acquired with 100% contrast concentration are associated with a smaller variability than the corresponding 50% concentration studies (p = n.s.). Finally, images acquired at 70 kV show a smaller variability than the corresponding ones acquired at 90 kV, except for the 5″ II-mode and 100% contrast concentration.

To provide some further insights in the individual measurements, the results for the different phantom studies are given in Figs. 6A-D. The true

diameters of the segments are plotted along the x-axis and the mean differences with respect to the true values along the y-axis. The two horizontal lines represent the pooled standard deviation values with respect to the overall mean difference computed from all the individual standard deviation values for the 100% and 50% contrast concentration measurements. These figures make clear that the usual roll-off at the smaller sizes does not occur. This is due to the correction technique for image blur applied in the contour detection procedure. This means that obstruction values down to 0.66 mm can be measured with high accuracy and precision.

*Inter- and intra-observer variabilities on routine coronary arteriograms*

The inter- and intra-observer variabilities as assessed from the total of 39 coronary obstructions are presented in Table 3. From these data it can be observed that the precision in the obstruction measurements for the inter- and intra-observer studies is only 0.11 and 0.10 mm, respectively, and in the automatically determined reference diameters 0.13 and 0.13 mm, respectively. The inter- and intra-observer precision for the percentage diameter stenosis is 5.64 and 3.18%, respectively.

The inter- and intra-observer variabilities in the obstruction length are very much comparable at 1.46 mm and 1.22 mm, respectively. The variability values for the area of the atherosclerotic plaque were equal at 1.29 $mm^2$. Finally, the variabilities in the derived stenotic flow reserve (SFR) were 0.36 and 0.21, respectively.

*Short- and medium-term variabilities*

The results for the short- and medium-term (ST and MT) variabilities are presented in Table 4 The variabilities in the calibration factor are 0.007 and 0.012 mm/pixel, respectively. This corresponds to coefficient of variation values of only 3.2% and 5.5%, respectively. These values are roughly double those assessed from the inter- and intra-observer variability studies.

The precision values of the obstruction diameters have increased to 0.19 and 0.18 mm, respectively, and those of the interpolated reference diameters to 0.22 and 0.34 mm, respectively. The variabilities in the percentages diameter and area stenoses are approximately equal to the corresponding values for the inter-observer study. The obstruction length variabilities for the ST and MT studies are very similar at 2.00 and 1.98 mm, respectively. These values are slightly larger than those obtained for the observer variability studies. Likewise, the area plaque precision values increased slightly from 1.92 $mm^2$ for the ST-study to 2.35 $mm^2$ for the MT-study. The last value is almost double the value obtained from the inter-observer study. The SFR-values are all very similar: 0.43 and 0.38 for the ST and MT-studies, respectively, and 0.36 for the inter-observer study.

The 40 coronary segments analyzed for the medium-term study were

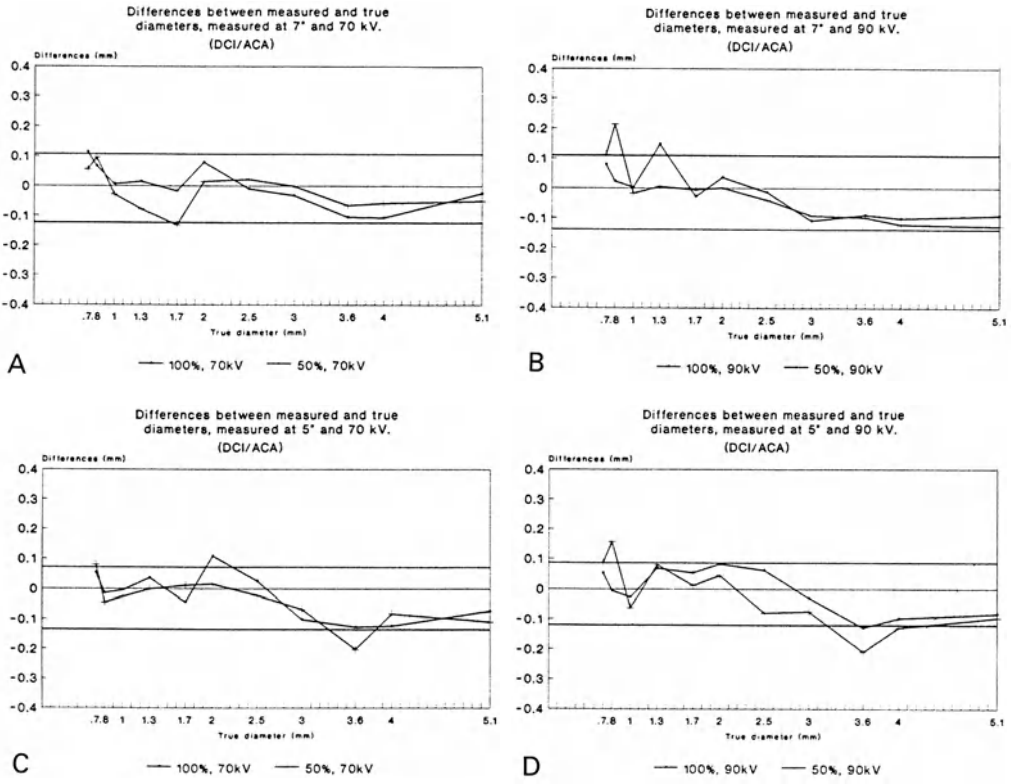


*Figure 6.* Differences (ordinate) between measured and true dimensions of the vessel phantom as a function of the vessel size (abscissa) as assessed under the various imaging conditions. Figure 6A and 6B show the data for 7″ image intensifier size and 70 kV and 90 kV, respectively. In Fig. 6C and 6D similar data is shown for the smaller 5″ image intensifier mode.

*Table 3.* Inter- and intra-observer variabilities in the repeated analysis of digital coronary analysis.

| | Range | Inter-observer (N = 39) | | Intra-observer (N = 39) | |
|---|---|---|---|---|---|
| | | Acc. | Prec. | Acc. | Prec. |
| Calibration factor (mm/pixel) | 0.160–0.240 | −0.001 | 0.003 | 0.000 | 0.005 |
| Obstruction diam. (mm) | 0.63–2.85 | −0.02 | 0.11 | 0.03 | 0.10 |
| Reference diam. (mm) | 1.56–4.08 | −0.01 | 0.13 | 0.03 | 0.13 |
| Percentage diam. sten. (%) | 21.45–79.90 | 0.25 | 5.64 | −0.19 | 3.18 |
| Percentage area sten. (%) | 38.29–95.95 | −0.23 | 6.60 | −0.03 | 3.39 |
| Obstruction length (mm) | 3.71–35.90 | −0.24 | 1.46 | 0.36 | 1.22 |
| Area of plaque ($mm^2$) | 1.24–35.13 | −0.03 | 1.29 | 0.22 | 1.29 |
| Stenotic flow reserve | 0.68–4.87 | −0.05 | 0.36 | 0.06 | 0.21 |

*Table 4.* Short-term and Medium-term intra-observer variabilities of the DCI-ACA package as assessed from routine digital coronary arteriograms.

| Parameter | Mean value | Short-term (N = 41) | | Medium-term (N = 40) | | Unit |
|---|---|---|---|---|---|---|
| | | Acc. | Prec. | Acc. | Prec. | |
| Calibration factor | 0.217 | −0.002 | 0.007 | 0.003 | 0.012 | mm/pixel |
| Obstruction diam. | 1.69 | 0.00 | 0.19 | 0.03 | 0.18 | mm |
| Reference diam. | 3.18 | −0.02 | 0.22 | −0.02 | 0.34 | mm |
| Percentage diam. sten. | 46.47 | −0.57 | 5.61 | −0.47 | 5.28 | % |
| Percentage area sten. | 69.18 | −0.88 | 6.09 | −0.96 | 5.96 | % |
| Obstruction length | 9.21 | 0.30 | 2.00 | −0.53 | 1.98 | mm |
| Area of plaque | 7.00 | 0.20 | 1.92 | −0.06 | 2.35 | $mm^2$ |
| Stenotic flow reserve | 3.65 | 0.03 | 0.43 | 0.02 | 0.38 | |

selected from a total of 24 different angiographic projections. Based on the X-ray geometry data we found the following mean difference ± standard deviation in resetting the angiographic views for the rotation and angulation angles: $-0.04° \pm 0.20°$ and $+0.04° \pm 0.55°$, respectively.

## Discussion

A new approach for the on-line quantification of coronary arterial dimensions from digital arteriograms is presented. For such an approach to be acceptable in a routine clinical environment requires far more stringent criteria than for an off-line technique. The user-interaction should be reduced to an absolute minimum, the contour detection procedure should be highly reliable, robust and accurate, clinically relevant parameters should be presented to the user with a minimum of additional steps necessary, and finally the processing time should be acceptable, so that the actual processing during the catheterization procedure becomes feasible with a minimal amount of waiting time involved.

These requirements have been met in the ACA-package described. Two versions of the package exist, the short ACA-package and the standard ACA-package. In the short-ACA package the only user-interaction requested is the manual definition of the start and end points of the arterial segment to be analyzed. All the other steps of automated contour detection and presentation of the results are subsequently performed automatically, i.e. this version does not allow any corrections to the detected pathline or contours. This short ACA-package, therefore, is recommended in those situations where the user does not expect any interactions, for example in situations with minimal overlap of the segment with other structures, relatively clear definition of the segment, good image quality, etc. If the results are not satisfactory, the user can start the standard ACA-package, which provides features for pathline and boundary corrections. Experiences in routine prac-

tice must demonstrate in which percentages of the cases the short and standard versions are applicable.

The pathline tracer has been found to meet the design criteria set [9]. In a validation study including 78 short and 25 long coronary arterial segments, the pathline was accepted after the first iteration in 89,3% of the cases; in 99.0% of the cases two iterations sufficed. This compares very favorably with other techniques described sofar [16], such as the manual definition of a number of centerline points within the segment followed by linear interpolation, and the socalled circle method which does not allow the kind of segment standardization as we propose [17].

The automated contour detection using the minimal cost criteria has been shown to be reliable and reproducible. The great advantage of this approach is that all the edge information along an arterial segment is taken into account in the definition of these outlines, i.e. the edge position for a particular scanline is not based on the edge strength for that scanline alone. Furthermore, we have developed a new version of the automated contour detection procedure to be able to correct for the limited frequency response of the imaging chain, by modifying the kernels for the computation of the first and second derivative functions. The phantom study indeed has made clear that the sizes of the plexiglass phantom can be determined reliably down to 0.66 mm. If such correction is not applied, the measured values would overestimate the true values below a size of about 1.2–1.3 mm. Another very useful feature of this new contour detection procedure is the fact that portions of the contour which need to be corrected according to the user, are updated by the program itself by searching for a new contour portion in a limited search region, after the old erroneous contour part has been deleted by the user. This means that in the majority of the cases, all contour points, whether initially corrected or not, are derived from the actual pictorial information using the minimum cost contour detection method. This leads to an improvement in the accuracy and precision of the technique, since the influence of human interaction is minimized.

The inter- and intra-observer variability study made clear that the precision of the technique is excellent with precision values for the absolute diameter data better than 0.13 mm, which is slightly more than $\frac{1}{2}$ pixel value in the 7″ image intensifier mode. This high precision is also due to a very accurate and precise calibration procedure. The catheter detection process combines two important features: 1) the use of the minimal cost contour detection technique in an iterative manner; and 2) the use of a priori information about the shape of this object. A precision of 0.003 mm/pixel in the inter-observer study means a coefficient of variation of only 1.46%; for the intra-observer variability study the coefficient of variation was found to be 2.43%.

The obstruction precision values at 0.11 and 0.10 mm, respectively, are of course excellent and correspond very closely to the cinefilm variability of 0.10 mm as assessed on the filmbased system CAAS [5]. We believe that

these values represent the lowest values of precision that one can obtain with any coronary quantification system, i.e. the precision is on the order of 1/2 pixel value. It should be mentioned that the edge detection algorithms for the DCI and CAAS are similar in general terms, but have otherwise been optimized for the corresponding characteristics of the digital and cinefilm images, respectively. The interpolated reference diameter variability was found to be 0.13 mm for both the inter- and intra-observer studies and is slightly higher than found earlier from cinefilm (user-defined reference 0.12 mm and interpolated approach 0.10 mm on the CAAS)[5]. The higher variability in this reference diameter value can be explained by the fact that it is a derived value which is influenced by the length of the segment analyzed, to some although small degree by the positions of the starting and end points of the pathline, etc. However, if the standardized approach for the selection of the segments is followed as advocated, this dependency will be minimal. It should be mentioned that the basic algorithms for the calculation of the reference diameter functions on the DCI and CAAS are different. The most likely explanation for the higher ACA variability in the reference diameter value as compared to the CAAS data, is the more sparse sampling of the diameter values along the centerline.

Definite advantages of this automated approach for the selection of the reference diameter are: 1) there is no user-interaction involved which makes it more reproducible and certainly quicker; 2) the reference diameter is taken at the site of the obstruction, and not proximal or distal which may result in an over- or underestimation of the size for a tapering segment, respectively.

The inter-oberserver variability values in the percentages diameter and area values is better than 6.6%; the corresponding intraobserver variability is better than 3.39%. It should be stressed that the relative parameters percent diameter and area stenoses are not very sensitive parameters. For example, changes occurring in the calibration factor which translate directly into absolute vessel dimensions, have no effect on the % D-stenosis value since both the numerator and the denumerator in the formula for the % D-stenosis value change. Only changes occurring in the obstruction and/or reference diameters which are not related, have some effect on the % D-stenosis values.

Finally, the precision values for the obstruction length, area of plaque and stenotic flow reserve value are rather good. The small accuracy values of Table III for both the inter- and intra-observer studies clearly demonstrate that no systematic differences between the observers or between the repeated measurements exist.

The short- and medium-term variability studies have shown a significant increase in the variability of the obstruction diameter value to 0.19 and 0.18 mm, respectively. Causes for the increase in variability as compared to the observer-variability data with repeated analysis of selected images can only be attributed to sources of error or changes in the acquisition procedure. In general, in the angiographic data acquisition procedure the following

sources of variation can be distinguished: 1) differences in the rotation and angulation angles and the height levels of the X-ray gantry at the time of repeated angiography; 2) change in position of the patient with respect to the X-ray equipment; 3) differences in the position of the diaphragm and therefore of the heart with different degrees of inhalation; 4) differences in the vasomotor tone of the coronary arteries; 5) variations in the quality of mixing of the contrast agent with the blood; 6) differences in angiographic image contrast due to different settings of the wedge-filter and the X-ray shutters; 7) deviations in size of the catheter as listed by the manufacturer with the true size; and 8) differences in the image quality of the imaged contrast catheters. For the ST-study only items 2–5 and 8 apply, for the MT-study 1–6 and 8.

The data on the differences in rotation and angulation angles presented for the medium-term variability study made clear that repositioning of the X-ray system to the appropriate angiographic view can be done very accurately and precisely with the modern electronic read-out devices. The only remaining uncertainties that were not checked are the table and tower height. However, these have only an effect on the magnification which is almost entirely corrected for by the catheter calibration procedure. The position and orientation of the patient on the table (item 2), of course, remains an unknown parameter. During a complete cardiac catheterization procedure the patient will move a little bit, with any rotation along the long axis of the patient being of most concern. We have no absolute data on the magnitude of this error source, but believe it to be small. The only possibility to be sure about the constancy of the orientation of the patient under the X-ray gantry would be by using laser positioning devices as applied in radiotherapy and nuclear medicine. However, this would not be very practical in the catheterization laboratory and not realistic in view of the otherwise small remaining error. During the coronary angiographies the patients were requested to hold their breath to obtain an optimal image quality (item 3). Although the degree of breath holding cannot be standardized perfectly, the fact that breath holding is performed, leads to a standardization of the angiographic procedure and therefore to a minimization of the variabilities.

As far as item 4 is concerned, coronary vasomotor tone was standardized to the best of our knowledge in this study. Item 5 was concerned with the variations in the quality of the mixing of the contrast agent with the blood. This may have an effect on the variability of the measurements, but not different for the short- or medium-term study. Item 6 is concerned with any possible deviations in the sizes of the catheters as listed by the manufacturer with their true sizes. In general, this is hardly of any concern if the actual sizes of the catheters are measured with a micrometer, and of no concern in this study, as the same catheters were used for the contrast administration in the repeated runs for the short-term or medium-term studies, respectively. The item that apparently caused most of the variability in this study is the image quality of the catheter in the different runs and the subsequent

calculations of the calibration factors. Any deviation in a calibration factor will translate directly into a deviation in the obstruction diameter and indirectly also into the reference diameter. Table IV makes clear that the precision of the calibration factor in the short- and medium-term study is approximately double and triple of that from the observer variability study, respectively. Apparently, this is the major contributor to the higher variability in the obstruction diameter values.

The largest variabilities occur in the assessment of the automated reference diameter values at 0.22 and 0.34 mm for the ST and MT-studies, respectively. For the CAAS cinefilm analyses, a medium-term variability of 0.15 mm was found [5]; this represented data from the best controlled repeated study and can be compared with our present medium-term study. We have noticed already that the current implementation of the reference diameter function apparently introduces more variability than the earlier one. On the other hand, the relatively large variability in the calibration factor again contributes significantly to this reference diameter variability. On the CAAS a much higher variability of 0.28 mm was also found for the user-defined reference data for the medium-term study.

On the other hand, the variabilities in the percent diameter stenosis are again very similar to the inter-observer variability at 5.61% and 5.28% for the short- and medium-term studies, respectively. Likewise, the variabilities in the obstruction length, plaque area and stenotic flow reserve have increased slightly when compared to the observer variability data as one would expect, but are very acceptable.

The entire analysis procedure, including calibration when carried out in the same frame selected for the coronary segment, takes only approximately 15 seconds on the Philips DCI-SX. When separate frames need to be selected for calibration and vessel analysis, additional time is needed to select the appropriate frames. However, these data make clear that the execution times of these packages are now so short, that the other user manipulations such as selection of the appropriate frames and administration of the derived results, have now become the limiting factors in the quantitative analysis of coronary arteriograms.

In conclusion, a new analytical technique has been made available to the angiographer for the objective assessment of the optimal choice of recanalization devices and for the instantaneous assessment of the effects of such recanalization procedures during the catheterization procedure based on digital coronary arteriograms of size $512^2$ pixels (PAL) or $512 \times 480$ (NTSC) with 8 bits of density levels.

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# 3. How reliable are geometric coronary measurements? In vitro and in vivo validation of digital and cinefilm-based quantitative coronary analysis systems

JÜRGEN HAASE, DAVID KEANE*, CARLO DI MARIO, JAVIER ESCANED, CORNELIS J. SLAGER and PATRICK W. SERRUYS

## Introduction

While quantitative coronary angiography may not completely predict the functional significance of luminal narrowings [1], computer-assisted geometric analysis represents an effective and the most readily applicable approach to evaluate the severity of coronary artery stenoses. An increasing number of digital and cinefilm-based analysis systems is now commercially available [2,3] requiring critical evaluation and a series of validation studies have recently been performed [4–13]. For the purposes of both scientific research and clinical practice, the question arises whether each system requires separate validation and which of the geometric parameters is most suitable for the purpose of quality control.

The experimental work on validation of quantitative coronary analysis systems, which has been carried out at the Thoraxcenter, clearly demonstrates that even modification and refinement of software packages, especially when edge detection algorithms are adapted to different imaging systems, may result in differences in accuracy and precision [12, 13]. Therefore, the evaluation of geometric coronary analysis systems appears to be a continuous process which has to be updated whenever a new software version is released. However, these requirements are alleviated by the fact that the validation of geometric coronary measurements can be built up on one critical parameter, the "minimal luminal diameter" or "obstruction diameter", which is obtained by fully automated computation and has proven to be the most reliable measure for changes in coronary artery dimensions [14–16].

In this chapter, we report the validation of geometric measurements on the first and second version of the Cardiovascular Angiography Analysis System (Pie Medical, Maastricht, Netherlands), the Automated Coronary Analysis package of the Digital Cardiac Imaging system (Philips, Best, Ne-

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therlands), and the Cardiovascular Measurement System (Medis, Nuenen, Netherlands).

To validate these quantitative analysis systems both in vivo and in vitro, angiographic stenosis "phantoms" of known diameter, mimicking human coronary artery obstructions, were first serially inserted in a polyethylene model to simulate the radiographic scatter of the human thorax in vitro and then used for percutaneous intracoronary implantation in anaesthetized pigs [11–13]. The edge detection analysis of angiographic images from these artificial stenoses was compared with the known dimensions of the phantoms to assess accuracy, precision and reliability of the respective system. To estimate the potential influence of standard calibration techniques on the outcome of geometric coronary measurements, analyses with calibration carried out at the radiographic isocenter were compared with those using the angiographic catheter for calibration.

## Methods

### *Stenosis phantoms*

The stenosis phantoms were produced at the Workshop of the Erasmus University Rotterdam and 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 (Fig. 1). The outer diameters of the cylinders were 3.0 or 3.5 mm, the length was 8.4 mm. Optical calibration of the stenosis lumens using 40-fold magnification gave a tolerance of 3 μm, demonstrating the perfect suitability of these phantoms to serve as a reference for validation. Acrylate was used to produce the phantoms with small stenosis diameters (0.5, 0.7 mm), whereas the less fragile polyimide was better suited to the drilling of large stenosis diameters (1.0, 1.4, 1.9 mm). Parallel to the stenosis lumen a second hole of 1.3 mm in diameter was drilled in the cylinders to attach them to the tip of 4 F Fogarty catheters (Vermed, Neuilly en Thelle, France). The central lumens of these catheters contained a removable metal wire, which was used for intraluminal insertion of the phantoms as well as for their positioning in the radiographic isocenter during the in vivo experiments (Fig. 2).

### *In vitro experiments*

The stenosis phantoms were serially inserted in the center of cylindrical plexiglass models (diameter 25 mm, length 120 mm) with a concentric channel of 3.0 mm in diameter. The plexiglass channel including the artificial stenosis was then filled with contrast medium (iopamidol 370, Bracco, Milano, Italy; 370 mg iodine/ml) at a concentration of 100%. Digital as well as cinefilm

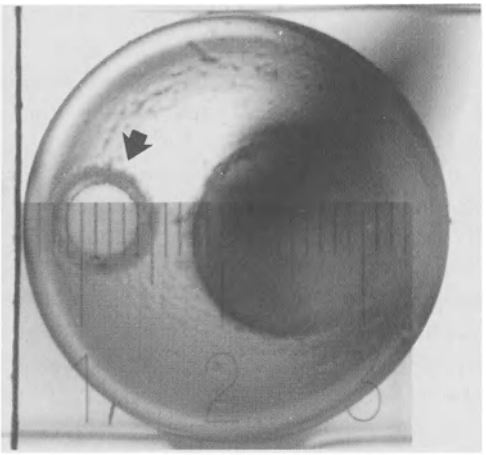


*Figure 1.* View at the opening (arrow) of the stenosis channel of a 0.5 mm plexiglass phantom (outer diameter 3.0 mm).

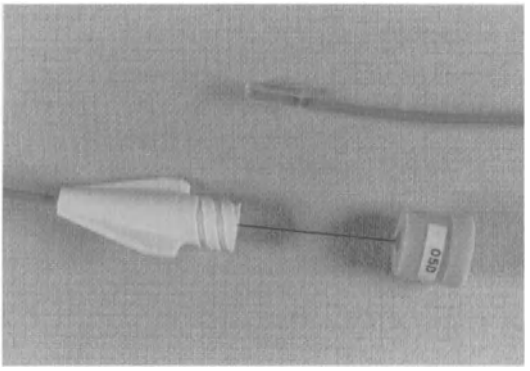


*Figure 2.* Phantom catheter with removable metal wire. At the tip of the catheter the 0.5 mm phantom is mounted (arrow).

acquisition was performed with an additional thickness of plexiglass blocks (12.5 cm anterior and 5 cm posterior to the models) to approximate the density of water. The addition of plexiglass blocks resulted in a more appropriate kV-level (75 kV) and in a scatter medium which more closely approximated the radiological scatter in the human thorax during fluoroscopy. Each phantom filled with contrast medium was recorded on the Digital Cardiac Imaging system (DCI) as well as on conventional cinefilm.

*Animal preparation*

Following an overnight fast, 4 cross-bred Landrace-Yorkshire pigs of average weight 45–50 kg were sedated with intramuscular ketamine (20 mg/kg) and intravenous metomidate (5 mg/kg). The animals were intubated and connected to respirator for intermittent positive pressure ventilation with a mixture of oxygen and nitrous oxide. Ventilator settings were adjusted during the experiments to maintain normal arterial pH (7.35–7.45), pCO2 (35–45 mmHg) and pO2 (>150 mmHg). Anaesthesia was maintained with a continuous intravenous infusion of pentobarbital (5–20 mg/kg/h).

Valved introducer sheaths (12F: Vygon, Ecouen, France) were surgically placed in both carotid arteries to allow sequential insertion of the angiographic guiding catheter and the stenosis phantoms. An 8F introducer sheath was placed in a femoral artery for the introduction of a 7F 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/h) was maintained throughout the procedure to prevent clot formation.

*Calibration of the quantitative coronary analysis systems*

During the in vivo experiments two different calibration methods were applied to each quantitative coronary analysis systems.

A. 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 both digitally and on cinefilm. For each system the available calibration procedures using automated edge detection were applied to the images obtained, yielding the corresponding calibration factors (mm/pixel).
B. Conventional catheter calibration: The non-tapering part of the tip of each 8F polyurethane guiding catheter (El Gamal, Type 4, Schneider, Minneapolis, USA) was measured (diameters of the individual catheters ranging 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 DCI and cinefilm for subsequent measurement by automated edge detection with the digital as well as the cinefilm-based coronary analysis systems.

*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 the coronary vasomotor tone prior to the insertion of the phantoms. A baseline angiogram was then carried out, for orientation purposes. Coronary angiography was performed by ECG-triggered injection of 10 ml iopamidol 370 at 37°C with an injection rate of 10 ml/second (rise time = 0) using a pressure injector. To minimize the effect of ventilation on angiographic acquisition, the respirator was disconnected during contrast injection.

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.

*Image acquisition and processing*

Simultaneous digital and cine-angiography was performed at 25 frames per second. Particular care was taken to minimize foreshortening of the segment of interest in the in vivo setting and to avoid overlap with other vessels or structures. The 5″-field mode of the image intensifier (focal spot 0.8 mm) was selected and the radiographic system settings were kept constant (kV, mA, x-ray pulse width) in each projection. All phantoms were imaged isocentrically. The digital angiograms were acquired on the Philips DCI system which employs a matrix size of 512 × 512 pixels. The horizontal pixel size was 200 μm and the density resolution was 8 bits (256 density levels). The images were stored on a 474 MB Winchester disk. From each digital angiogram which fulfilled the requirements of image quality for automated quantitation (no superimposition of surrounding structures, no major vessel branching at the site of the phantom position), a homogenously filled end-diastolic coronary image was selected and quantitative analysis of the stenosis phantom was performed on-line (Fig. 3) with the new Automated Coronary Analysis (ACA) analytical software package (17).

The corresponding 35–mm cineframes (CFE Type 2711, Kodak, Paris, France) were routinely processed and used for off-line analysis with the first and the second version of the Cardiovascular Angiography Analysis System (CAAS I and CAAS II) as well as with the Cardiovascular Measurement System (CMS).

On both versions of the CAAS [18, 19], a 6.9 × 6.9 mm 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 1329 × 1772 pixels. On the first version of the CAAS a correction for pincushion distortion is applied. Digitization of cinefilm images on the CMS (20) is carried out with a CAP-35E cine-video converter (Medis, Nuenen, The Netherlands). The pixel matrix of the CCD-camera used in this converter

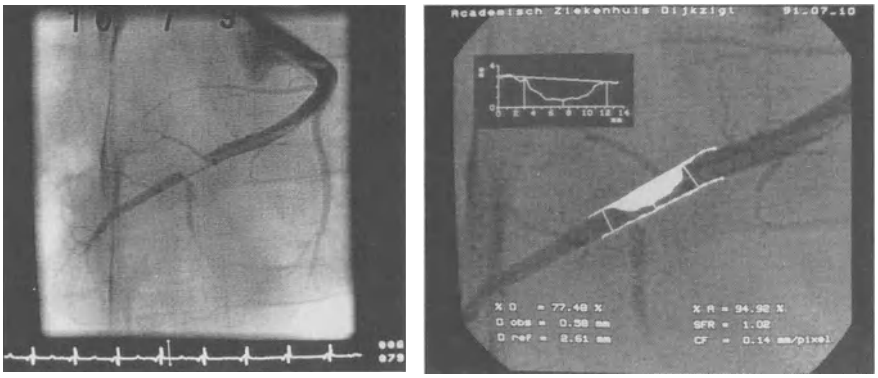



*Figure 3.* Angiographic visualization of the artificial coronary obstruction produced by a 0.7 mm stenosis phantom in the left anterior descending artery (left) with subsequent digital measurement of MLD (right).

(760 horizontal × 576 vertical) is different from the final pixel matrix of the CMS system (512 × 512).

*Automated contour detection*

Ten in vitro and 20 corresponding end-diastolic in vivo frames of the phantom stenoses were suitable for edge detection analysis both digitally and from cinefilm. A sufficiently long luminal segment was selected for quantitative analysis on all images; care was taken to define the same segment length on corresponding digital and cinefilm images. On the CAAS system 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 [18]. On the DCI as well as on the CMS system, the user is requested to define only a start and an end point of the vessel segment, and a centerline through the vessel between these two points is subsequently defined automatically. On each system the basic automated edge detection techniques are similar; they are based on the first and second derivative functions applied to the brightness profiles along scanlines perpendicular to a model using minimal cost criteria [17, 20].

In CAAS I and CAAS II, 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.

With DCI, the edge detection algorithm is also carried out in two iterations and two spatial resolutions. In the first iteration the scan model is the initially detected centerline and edge detection takes place at the 512 × 512 matrix resolution. Here, the contours detected in the first iteration function as scan models. In the second iteration, the region of interest centred around the

defined arterial segment is digitally magnified by a factor of two with bilinear interpolation. On the CAAS II as well as on the ACA-package of the DCI system, the edge detection algorithm is modified to correct for the limited resolution of the entire x-ray imaging chain [17, 19]. By these modifications a more accurate determination of vessel sizes less than 1.0 mm diameter is provided.

The contour detection software of the ACA-package (as implemented on the DCI system) was subsequently refined and incorporated into the CMS for adaptation to cinefilm.

*Measurement of minimal luminal diameter/obstruction diameter*

Once the contours of the stenosis phantoms were defined, the diameter of the artificial obstruction were automatically derived from the diameter function on each coronary analysis system.

On the CAAS I, the classical parameter of "minimal luminal diameter" is taken as the shortest distance between the two luminal contours [18]. Thereby, the absolute minimum of the diameter function curve is provided. To circumvent possible underestimations of the true value caused by quantum noise, the CAAS II delivers a so-called "obstruction diameter" [19] which is determined as the vessel diameter at the midpoint between the closest diameter positions on both sides of the minimum luminal diameter that exceed the minimum value by 5%. On Fig. 4 this definition of the obstruction diameter is illustrated using a schematic diameter function curve of a coronary artery stenosis.

On the commercially available software package installed on the DCI as well as on the CMS system, the "obstruction diameter" does not necessarily represent the minimum of the diameter function curve but refers to the diameter measured at the site of maximum percent diameter stenosis [21]. Here, the tapering of the vessel is taken into account to define the site of a coronary obstruction, however, the absolute value of minimal luminal diameter is not available to the operator and currently it is not possible to correlate the potentially significant different values of obstruction diameter as obtained with the DCI or the CMS system and the true minimal luminal diameter. On Fig. 5, the difference in definition between minimal luminal diameter (MLD) as available on CAAS I and the obstruction diameter (OD) as defined on DCI and CMS is illustrated.

For the purpose of comparative validation, any user interaction on the computerized reconstruction of phantom contours was excluded and the selection of the site of stenosis was automated. However, when a degree of obstruction due to cellular material or partial thrombosis was obvious within the phantom channel the site of minimal luminal diameter or obstruction diameter assessment was then user-defined. Examples of digital and cinefilm-based measurements of a 1.9 mm stenosis phantom on corresponding images is shown in Fig. 6

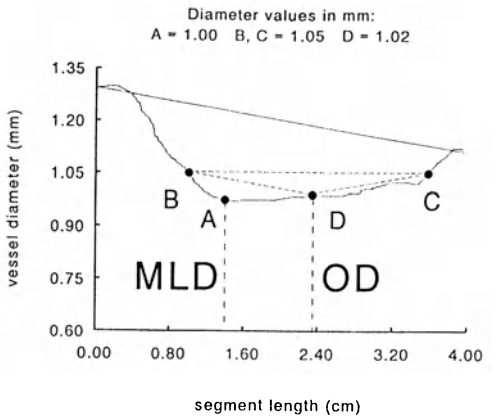



*Figure 4.* Definition of "obstruction diameter" on CAAS II: Schematic display of the diameter function curve of a coronary artery stenosis with illustration of the so-called "geometric center" of the obstruction, defined as the middle (D) between the two closest diameter values which exceed the minimal luminal diameter (A) of the stenosis by 5% (B,C). At position D, the "obstruction diameter" (OD) is calculated (OD = obstruction diameter, MLD = minimal luminal diameter).

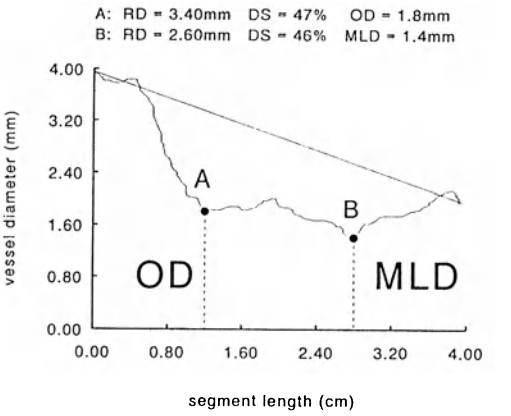



*Figure 5.* Definition of "obstruction diameter" on DCI and CMS: Schematic display of the diameter function curve of a coronary artery obstruction. The minimum of the diameter function curve is located at position B. Due to the tapering of the vessel, B is not necessarily identical to the site of maximum percent diameter stenosis represented by position A where the obstruction diameter is defined (OD = obstruction diameter, MLD = minimal luminal diameter, RD = reference diameter, DS = percent diameter stenosis).

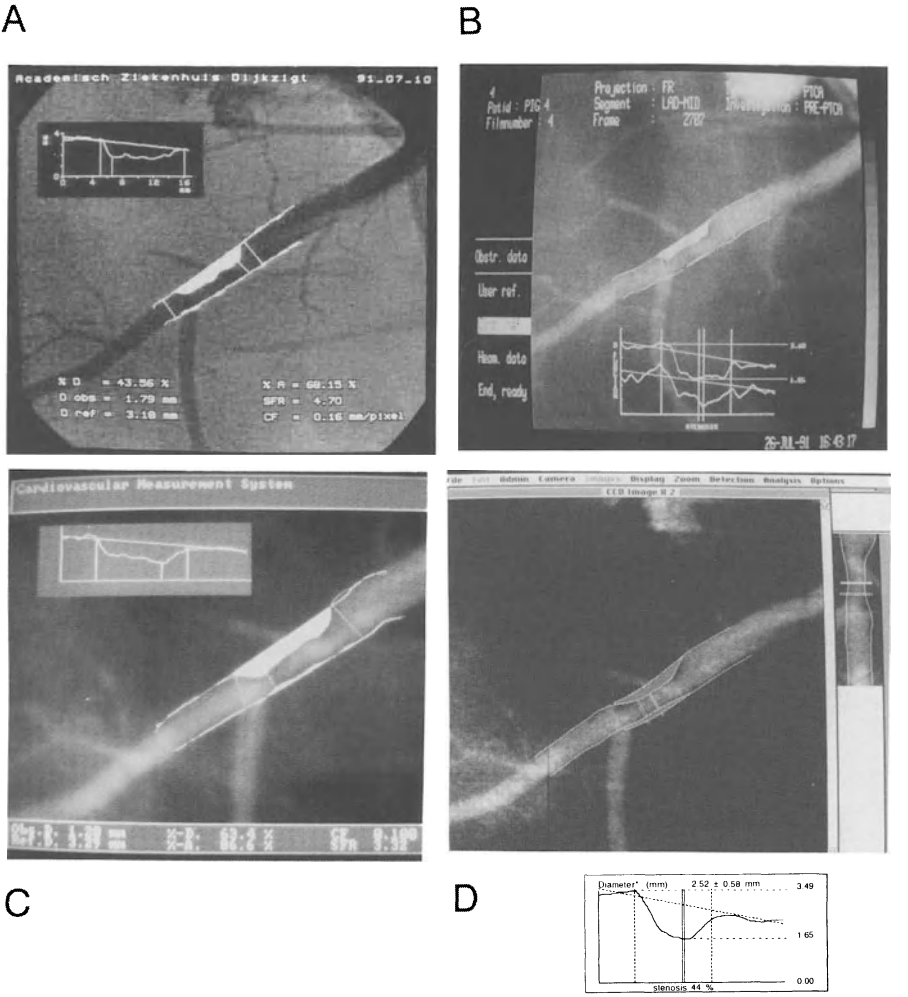



*Figure 6.* Angiographic image of a 1.9 mm stenosis phantom with automated geometric coronary measurement on DCI (A), CAAS I (B), CMS (C), and CAAS II (D) on corresponding end-diastolic images. The vessel diameter function as obtained with the CAAS II is displayed in the bottom graph.

### *Statistical analysis*

Using both calibration methods (calibration at the isocenter, catheter calibration) the individual data for minimal luminal diameter or obstruction diameter obtained by the respective system were compared with the true phantom diameters by a t-test for paired values. The mean of the signed differences between measured diameters and individual reference values was considered an index of accuracy and the standard deviation of the differences

an index of precision. The measured values were plotted against the true phantom diameters and linear regression analyses were applied. Precision values from both calibration techniques were compared using Pitman's test [22].

The standard deviation of the mean value from 15 or 30 geometric and videodensitometric measurements on the same angiographic phantom was considered a measure of reproducibility. From two systems, these values were calculated separately for all five stenosis phantoms. The mean reproducibility was defined as the mean value from those five reproducibility values.

## Results

### *A. In vitro validation of obstruction diameter assessments*

With the new version of the CAAS, the in vitro assessment of obstruction diameters yielded an accuracy of 0.001 mm and a precision of ±0.11 mm. As illustrated by Fig. 7 A, there was a high correlation between obstruction diameter values and true phantom diameters ($r = 0.98$, $y = 0.18 + 0.82x$, $SEE = 0.08$) with a slight tendency to underestimate large phantom sizes.

Using the DCI, we obtained an accuracy of 0.11 mm and a precision of ±0.06 mm with an excellent correlation between measured values of obstruction diameter and reference diameters ($r = 0.99$, $y = 0.03 + 0.91x$, $SEE = 0.05$), as depicted in Fig. 7 B.

The corresponding cinefilm-based measurements on the CMS, gave an accuracy of 0.18 mm and a precision of ±0.14 with relatively good correlation ($r = 0.97$, $y = 0.06 + 0.75x$, $SEE = 0.09$), although the diameters of large stenosis phantoms were underestimated ($p < 0.01$), as illustrated by Fig. 7 C. The difference in variability from DCI and CMS measurements was statistically significant ($p < 0.05$).

### *B. In vivo validation of obstruction diameter assessments*

*Assessment of minimal luminal diameter on CAAS I*

The results of in vivo validation using the first version of the CAAS system are illustrated by Fig. 8 A. Calibrated at the radiographic isocenter, the assessment of minimal luminal diameter gave an accuracy of −0.07 mm and a precision of 0.21 mm with a non-significant trend towards over-estimation of small phantom diameters ($r = 0.91$, $y = 0.30 + 0.79x$, $SEE = 0.19$). Using catheter calibration (Fig. 8 B), the corresponding measurements yielded an accuracy of 0.09 mm with a precision of ±0.23 mm and tended to underestimate large phantom sizes ($r = 0.89$, $y = 0.19 + 0.74x$, $SEE = 0.19$).

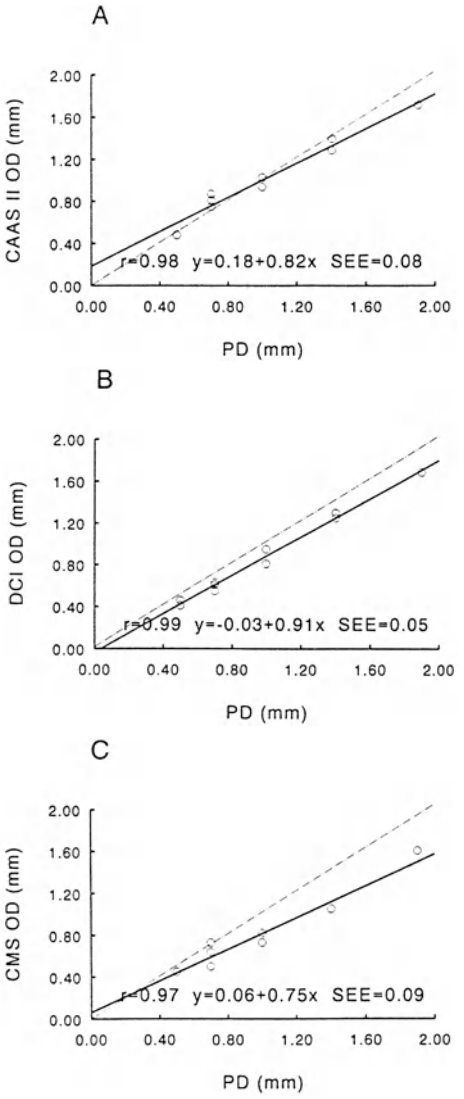



*Figure 7.* In vitro validation of geometric coronary measurements using 100% contrast medium: The individual obstruction diameter values (OD) obtained by CAAS II (A), DCI (B), and CMS (C) are plotted against the known diameters of the stenosis phantoms (PD). The graphs include the lines of identity as well as the individual results from the linear regression analyses.

*Assessment of obstruction diameter on CAAS II*

As demonstrated by Fig. 8, the over-estimation of small phantom diameters is less pronounced with the new version of the CAAS. Using this version with calibration at the isocenter (Fig. 8 C), the assessment of obstruction

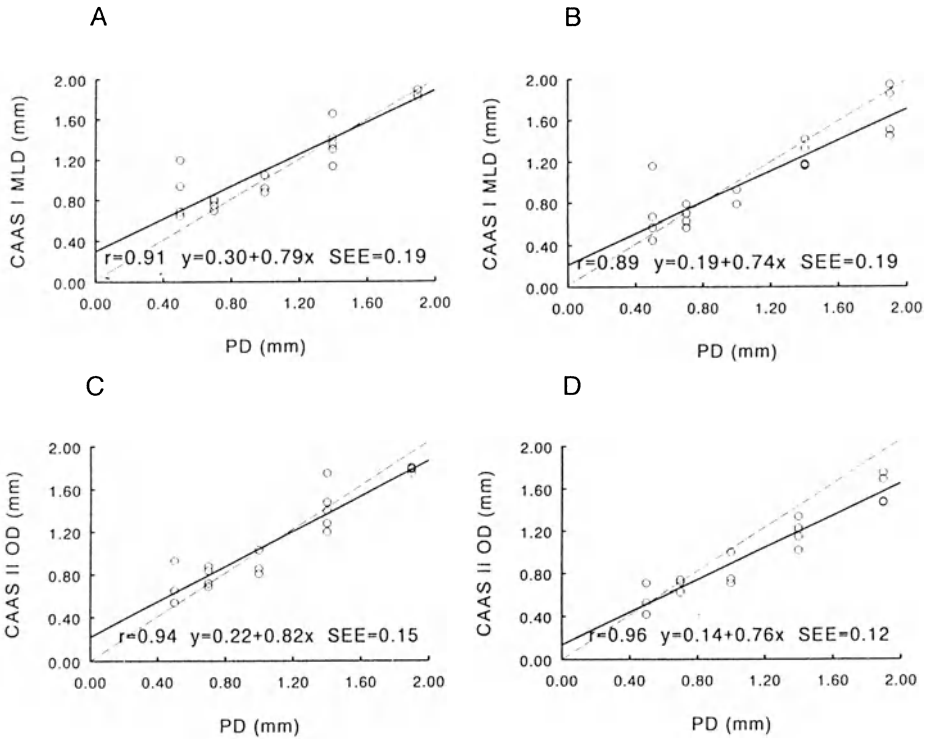



*Figure 8.* In vivo validation of geometric coronary measurements by CAAS I and CAAS II: The plot of measured minimal luminal diameter values (MLD) or obstruction diameter values (OD) against known phantom diameters (PD) obtained by CAAS I with calibration at the isocenter are displayed in graph A, the corresponding plot with catheter calibration is displayed in graph B. Graphs C and D show the results from CAAS II using calibration at the isocenter and catheter calibration, respectively.

diameters gave an accuracy of −0.01 mm and a precision of ±0.18 mm with high correlation between measured values and true phantom diameters ($r = 0.98$, $y = 0.18 + 0.82x$, SEE = 0.08). With catheter calibration (Fig. 8 D), an accuracy of 0.14 mm and a precision of ±0.17 mm was obtained. In this series, the measurement points of the smallest phantom diameters lay rather close to the line of identity, while large diameters were significantly underestimated ($p < 0.05$) producing a relatively low slope of the regression line ($r = 0.96$, $y = 0.14 + 0.76x$, SEE = 0.12).

*Assessment of obstruction diameter on DCI*

Using calibration at the isocenter, the assessment of obstruction diameters by the digital system (Fig. 9 A) gave an accuracy of 0.08 mm and a precision of ±0.15 mm with high correlation between measured values and true phantom sizes ($r = 0.96$, $y = 0.08 + 0.86x$, SEE = 0.14). Catheter calibration (Fig.

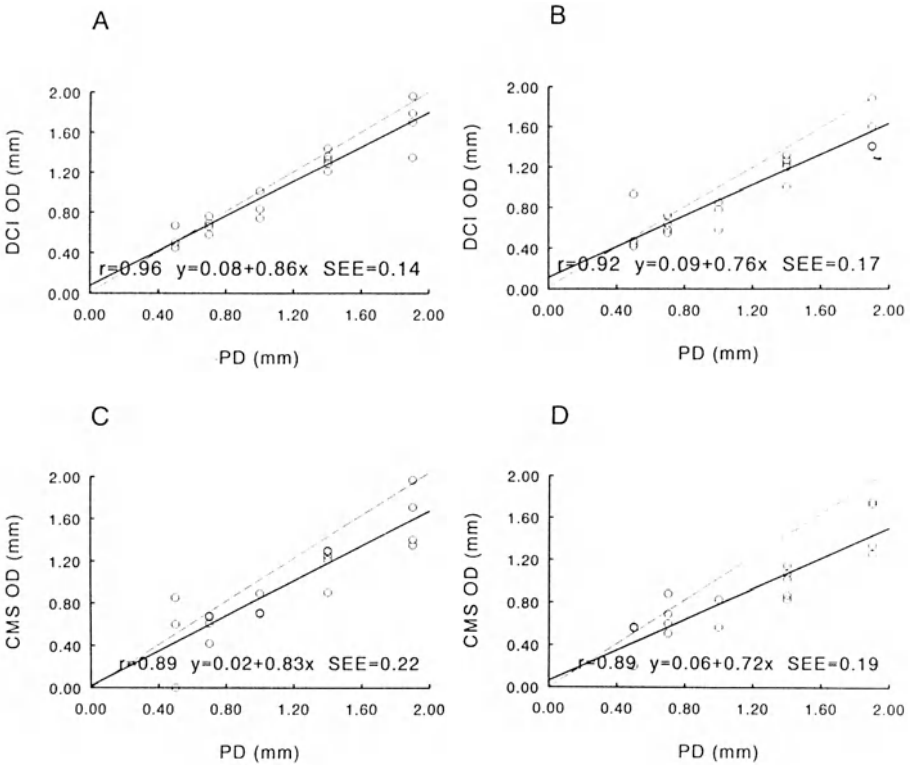



*Figure 9.* In vivo validation of geometric coronary measurements by DCI and CMS: The plot of measured obstruction diameter values (OD) against known phantom diameters (OD) obtained by DCI with calibration at the isocenter are displayed in graph A, the corresponding plot with catheter calibration is displayed in graph B. Graphs C and D show the results from CMS using calibration at the isocenter and catheter calibration, respectively.

9 B) yielded an accuracy of 0.18 mm and a precision of ±0.21 mm ($r = 0.92$, $y = 0.09 + 0.76x$, SEE = 0.17). The tendency towards underestimation of phantom diameters with calibration at the isocenter ($p < 0.05$) was more pronounced when catheter calibration was applied ($p < 0.001$).

*Assessment of obstruction diameter on CMS*

The corresponding cinefilm-based measurements on the CMS are displayed in Fig. 7 C and D. Calibrated at the radiographic isocenter (Fig. 9 C), the assessment of obstruction diameters yielded an accuracy of 0.18 mm and a precision of ±0.23 mm ($r = 0.89$, $y = 0.02 + 0.83x$, SEE = 0.22). The underestimation of large phantom sizes was statistically significant ($p < 0.01$). Compared with DCI, the CMS measurements showed a higher degree of variability ($p < 0.05$). Using catheter calibration (Fig. 9 D), we found an accuracy

of 0.26 mm and a precision of ±0.24 mm ($r = 0.89$, $y = 0.06 + 0.72x$, SEE = 0.19) with an even more pronounced tendency to underestimate true phantom diameters ($p < 0.001$).

The results from the in vitro and in vivo validation using CAAS, DCI, and CMS, are summarized in Table 1 A and B, respectively.

*Reproducibility of geometric coronary measurements*

The results from 30 repeated obstruction diameter assessments of each stenosis phantom on the new version of the CAAS and from 15 repeated measurements with the CMS are depicted in Fig. 8. Using the CAAS II (Fig. 10 A), the variability of measurements was ±0.07 mm with the 1.4 mm phantom, ±0.09 mm with the 0.5 mm, 0.7 mm, and 1.0 mm phantoms, and ±0.10 mm with the 1.9 mm stenosis phantom, resulting in a mean reproducibility of ±0.09 mm. From CMS (Fig. 10 B), the variability of measurements was ±0.06 mm with the 0.5 and 1.4 mm phantom, ±0.07 mm with the 0.7 mm and 1.9 mm phantom, and ±0.12 mm with the 1.0 mm phantom, resulting in a mean reproducibility of ±0.08 mm.

## Discussion

Continuous improvement of software packages and their adaptation to different imaging systems implies potential changes of accuracy, precision and reliability of automated geometric coronary measurements [2, 3]. To meet the requirements of quality control, each new version of a quantitative coronary analysis system should undergo in vitro and in vivo validation in a way that allows the user to objectively compare the respective systems [12]. In vitro test series can easily be standardized, however, their results are not always representative for the outcome of computerized measurements on angiographic images from human coronary artery dimensions, because beam scattering from surrounding tissue and the potential influence of motion blur are unpredictable. On the other hand, an identical scaling of measured diameters for in vitro and in vivo validation is desirable if the impact of these factors on the reliability of automated measurements is to be clarified.

To solve this problem, a unique experimental approach has been applied using identical stenosis phantoms for in vitro testing as well as for serial insertion in porcine coronary arteries with subsequent quantitative analysis of the respective angiographic images [11–13]. This experimental approach served for the comparative validation of the first and the second version of the Cardiovascular Angiography Analysis System (CAAS I and CAAS II), the Automated Coronary Analysis Package of the Digital Cardiac Imaging System (DCI) as well as for the Cardiovascular Measurement System (CMS).

In the primary description of the CAAS system (CAAS I), an accuracy of −0.03 mm and a precision of ±0.09 mm is reported from in vitro assessment of minimal luminal diameter using plexiglass phantoms [18]. The focal

*Table 1.* Results of the in vitro (A) and in vivo (B) validation of quantitative coronary analysis systems

A. In vitro validation

| System | Accuracy | Precision | Difference | Correlation | Linear regression analysis | Standard error of estimate |
|---|---|---|---|---|---|---|
| CAAS II | 0.001 | 0.11 | N.S. | r = 0.98 | y = 0.18 + 0.82x | SEE = 0.08 |
| DCI | 0.11 | 0.06 | N.S. | r = 0.99 | y = −0.03 + 0.91x | SEE = 0.05 |
| CMS | 0.18 | 0.14 | $p < 0.01$ | r = 0.97 | y = 0.06 + 0.75x | SEE = 0.09 |

B. In vivo validation

| System | Calibration | Accuracy | Precision | Difference | Correlation | Lin.regression analysis | SEE |
|---|---|---|---|---|---|---|---|
| CAAS I | Isocenter | −0.07 | 0.21 | N.S. | r = 0.91 | y = 0.30 + 0.79x | 0.19 |
| | Catheter | 0.09 | 0.23 | N.S. | r = 0.89 | y = 0.19 + 0.74x | 0.19 |
| CAAS II | Isocenter | −0.01 | 0.18 | N.S. | r = 0.94 | y = 0.22 + 0.82x | 0.15 |
| | Catheter | 0.14 | 0.17 | $p < 0.05$ | r = 0.96 | y = 0.14 + 0.76x | 0.12 |
| DCI | Isocenter | 0.08 | 0.15 | $p < 0.05$ | r = 0.96 | y = 0.08 + 0.86x | 0.14 |
| | Catheter | 0.18 | 0.21 | $p < 0.001$ | r = 0.92 | y = 0.09 + 0.76x | 0.17 |
| CMS | Isocenter | 0.18 | 0.23 | $p < 0.01$ | r = 0.89 | y = 0.02 + 0.83x | 0.22 |
| | Catheter | 0.26 | 0.24 | $p < 0.001$ | r = 0.89 | y = 0.06 + 0.72x | 0.19 |

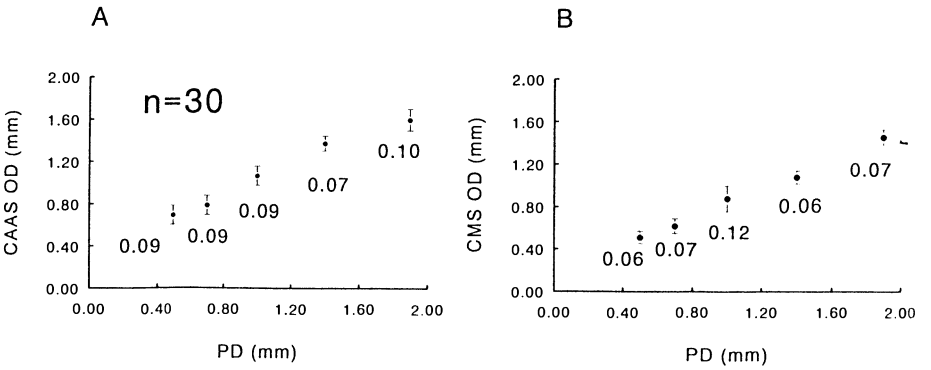



*Figure 10.* Reproducibility of the CAAS II (A) and the CMS system (B): Mean values from 30 measurements of obstruction diameter obtained by the CAAS II and from 15 measurements obtained by the CMS on one representative frame of each size of the stenosis phantoms (0.5, 0.7, 1.0, 1.4, 1.9 mm) are plotted with the respective standard deviation as a measure of reproducibility against the true phantom diameters.

spot size related tendency to over-estimate small luminal diameters [23] has not yet been corrected in this first version. CAAS II, however, incorporating special algorithms to correct for this over-estimation, gave an accuracy of 0.001 mm and a precision of ±0.11 mm in our series. The improvement of measurement reliability is confirmed by the results from our in vivo validation [11, 13]. While CAAS I gave an accuracy of −0.07 mm and a precision of 0.21 mm with calibration at the isocenter ($r = 0.91$, $y = 0.30 + 0.79x$, SEE = 0.19), corresponding measurements with CAAS II yielded an accuracy of −0.01 mm and a precision of ±0.18 mm ($r = 0.94$, $y = 0.22 + 0.82x$, SEE = 0.15). As illustrated by Fig. 6 B and D, catheter calibration, on the other hand, reveals a tendency towards underestimation of larger diameters with both versions, although less pronounced with CAAS II. The high level of reproducibility throughout the range of all phantom sizes, as demonstrated with the new version, is comparable to current digital as well as cinefilm-based quantitative coronary analysis systems [12, 24, 25].

The same experimental approach was used to compare the new cinefilm-based CMS with the DCI system. This comparison was of particular interest, because the edge detection software of the CMS has primarily been developed for the Automated Coronary Analysis package of the Philips Cardiac Imaging system and was subsequently refined for application to cinefilm. The measurement of obstruction diameter in our study reveals a change of accuracy values from 0.11 to 0.18 mm when the edge detection algorithm designed for digital images is applied to conventional cineframes. This loss of accuracy is combined with a significant underestimation of true phantom diameters ($p < 0.01$) is particularly evident with large phantom diameters as illustrated by a decrease of the slope of the regression line from 0.91 to 0.75 in Fig. 5

B and 5 C, respectively. Furthermore, we observed an increase of variability from ±0.06 mm to ±0.14 mm ($p < 0.05$).

The result of this in vitro comparison was further supported by our animal experiments in which we serially implanted the same phantom stenoses into porcine coronary arteries. When the edge detection algorithm was applied to cinefilm analysis and calibrated to the radiographic isocentre (corresponding to the in vitro trial) we found a change in accuracy values of obstruction diameter measurements from 0.08 mm to 0.18 mm and an increase of variability from ±0.15 mm to ±0.23 mm ($p < 0.05$). The underestimation of true phantom diameter values which was already present with digital measurements ($p < 0.05$) was more pronounced when the edge detection algorithm was applied to the corresponding cineframes ($p < 0.01$). When the imaging systems were calibrated with the angiographic catheter, we found a change of accuracy values from 0.18 mm (digital measurements) to 0.26 mm (cinefilm-based measurements), while the variability increased from ±0.21 mm to ±0.24 mm. It appears from Fig. 9 B and D that these differences are explained by a higher degree of scatter as well as by a more pronounced underestimation of large phantom diameters.

The variable shape of human coronary artery stenoses [26] has prompted the use of non-circular stenosis phantoms for the validation of quantitative coronary angiographic analysis systems. This approach seems to be particularly relevant for the measurement of minimal cross sectional area by densitometry [27]. Cylindrical phantoms which have been used for our experiments, however, fulfil the requirements for the application of 2-dimensional geometric measurements and therefore are eminently satisfactory as a surrogate of coronary obstructions.

In order to be able to compare in vivo results with those obtained from in vitro assessments, we performed geometric measurements using two calibration methods: calibration at the radiographic isocenter which was used for in vitro settings, and catheter calibration which represented the calibration technique conventionally used in clinical studies [28].

The use of angiographic catheters for the calibration of quantitative coronary analysis systems may influence the outcome of luminal diameter measurements, because varying catheter composition may result in varying x-ray attenuation [29] and therefore in differences in the automated detection of the contour points. In our in vivo study, only one type of catheter was used for calibration and therefore the influence of different materials on calibration was excluded. Another geometric error is introduced if the planes of calibration and measurement are not identical [30]. This error can be circumvented by out-of-plane correction as proposed by Wollschläger [31], or by calibration at the isocenter of the x-ray system.

The results of the present study show that, in general, the values of both digital and cinefilm measurements using catheter calibration are smaller than those using calibration at the isocenter. 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. A similar effect might have been produced by pincushion distortion for which DCI and CMS are not corrected. Both factors could explain smaller values of measurement when catheter calibration was applied.

The loss of accuracy as well as the increase of variability occurring when an edge detection algorithm is transferred from a digital to a cinefilm-based analysis system may at least in part be explained by differences in the grey scale representation on digital and cinefilm images. If refinement of an algorithm is guided by simultaneous in vitro and in vivo validation studies, a correction for those differences should be possible. In case of the CMS system, the mismatch between the matrix of the CCD camera (760 H × 576 V) and the AD-converter (512 × 512) might have additional impact on the outcome of corresponding geometrical measurements.

In spite of the above mentioned disadvantages, the adaptation of the edge detection algorithm from digital to cinefilm-based analysis did not affect the high reproducibility of automated geometric coronary measurements. The reproducibility of obstruction diameter measurements with the CMS system ranged from ±0.06 mm to ±0.12 mm which corresponds to the reproducibility of the digital system [24, 25] and is comparable to the values obtained from the new version of the CAAS (Fig. 8).

In principle, the use of "minimal luminal diameter" or "obstruction diameter" as the parameter of choice for comparison with true phantom diameters can be criticized. The size of the stenosis channel theoretically could be underestimated if the measurements of the automatic edge detection algorithm are influenced either by the presence of cellular debris collected in the phantom lumen during insertion, or by the development of micro-thrombosis, or by the presence of noise from the acquisition system. These occurrences may also explain the frequency of underestimation of the true lumen by different techniques [7]. In our experimental study, the minimal luminal diameter or obstruction diameter has been selected for the comparative validation of various quantitative coronary analysis systems because it represents a non-arbitrary measurement obtained by fully automated analysis of the entire coronary segment.

In conclusion, the present comparative investigation has demonstrated that geometrical coronary measurements can be applied with a high degree of reliability. Superior in vivo results are obtained when systems are calibrated using a well defined structure at the radiographic isocenter. Conventional catheter calibration, in general, results in a slightly lower level of accuracy and precision. Furthermore, the transformation of an edge detection algorithm from a fully digital to a cinefilm-based system can lead to an impairment of measurement accuracy which is independent from calibration techniques. Refinement of an algorithm for the application to another imaging system should be guided by the results of simultaneous in vitro and in vivo validation studies in order to guarantee a high level of measurement reliability.

**Appendix: On the use of the parameters accuracy and precision for validation of QCA systems** *by Cornelis J. Slager, Jürgen Haase and Johan C.H. Schuurbiers*

The traditional choice to use the parameters accuracy and precision as a quality index to compare Quantitative Coronary Angiography (QCA) systems needs a critical review. Especially when comparing results of different validation studies the use of these parameters may easily lead to incorrect conclusions. When comparing a set of measurement values with known true values, accuracy is defined as the mean of all signed differences between these values and precision as the standard deviation of these differences. At hand of a series of 8 numerical examples, shown in Figure 1, some of the characteristics of these parameters will be explained. For a comparison the linear correlation coefficient (r) and the standard error of the estimate (SEE) will be discussed as well. Investigated variables are:

- range of the true values, which vary respectively from 1 to 5 and from 1 to 7 both with an increment of 1. For each true value two measurement values are defined. Thus for both ranges the number of measurements is 10 and 14 respectively.
- slope of the relation between measurement and true values.
- shift of the relation between measurement and true values.
- noise, accomplished by adding +0.5 to the previously defined measurement values.

In Figure 1, we observe:

*left column, from top to bottom*:

- For $y = x$, all parameters describe the system to be perfect.
- Adding a shift, i.e. $y = x + 1.5$, only influences accuracy.
- Adding noise to $y = x$, does not influence accuracy. The minor difference between SEE and precision (SD) has to do with a different correction for the number of measurements. For an infinite set of measurements both parameters will equal 0.5. Correlation coefficient slightly improves by extending the range.
- Adding shift and noise gives a combination of the above.

*right column. from top to bottom*:

- A systematic measurement error characterized by $y = 0.5\ x$, yields a score for both precision and accuracy different from zero, which also appears to be dependent on the range of data. SEE remains to be zero.
- Now adding a shift, i.e. $y = 0.5\ x + 1.5$, again influences accuracy. As shown accuracy may even become zero, suggesting a perfect system!
- Adding noise to the set $y = 0.5\ x$, again increases the value for precision. Now precision, because of its sensitivity to the systematic error, gives a higher value than the SEE. When compared to the set $y = x$, SEE has the same value but the correlation coefficient decreases because the addition of noise has a greater weight at the slope = 0.5 situation.

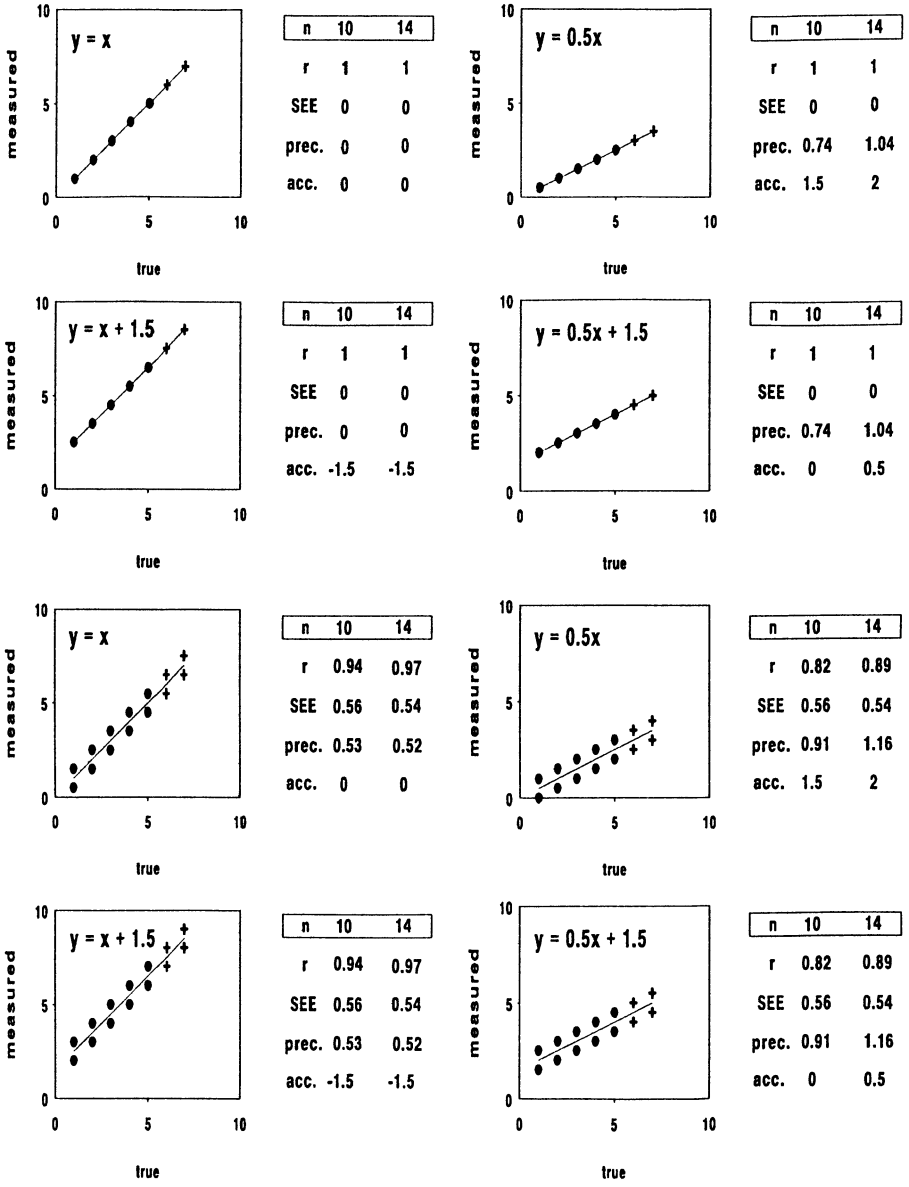
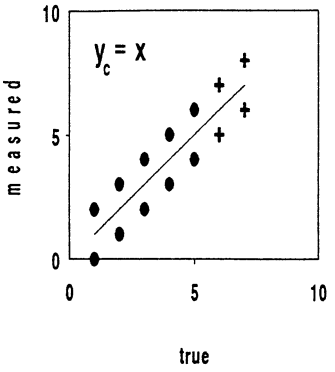



*Figure A1.*

– Adding shift and noise gives a combination of the above.

In a practical measurement system, the random error consists of an absolute noise contribution, as discussed in the presented examples, and of a relative noise contribution, being related to the true value.




| n | 10 | 14 |
|---|---|---|
| r | 0.82 | 0.89 |
| SEE | 1.12 | 1.08 |
| prec. | 1.05 | 1.04 |
| acc. | 0 | 0 |

*Figure A2.*

Considering only the contribution of the absolute noise the following conclusions can be made:
- accuracy is dependent on shift, range and slope.
- precision is dependent on noise, range and slope.
- correlation coefficient is dependent on the noise related to the mean measurement values. In the presence of only absolute noise, extending the range will raise the correlation coefficient up to 1.
- SEE is dependent on the absolute noise values.

For these reasons, a comparison of different QCA systems on the basis of the parameters accuracy and precision is influenced in an ambiguous way by the choice for the range of true reference values and by the combined effect of slope and shift of the relation between measurement and true values. The choice for using the terms precision and accuracy is also confusing as e.g. adding noise to the system increases the value of precision. Furthermore an accuracy of zero is not intuitively associated with an optimal system. Extending this discussion to the contribution of relative noise does not change these conclusions.

A better method to compare measurement quality of systems can be obtained by correcting for the systematic error, indicated by the slope and intercept of an obtained regression equation. Thus the normalized relation between corrected measurement values and true values will show a slope = 1 and a shift = 0. Accuracy will then be zero. Precision and SEE will be almost equal, both expressing a measure in absolute terms for the unpredictable error which is still present in the corrected system. The correlation coefficient gives a measure for the unpredictable error in relation to the mean measurement values.

As an example the corrected relation of $y = 0.5\ x + 1.5 + 0.5$ (Figure 1, right column, third from above) is shown in Figure 2 as $y_c = x$. When compared with $y = x$ (Figure 1, left column, third from above), the absolute error of the corrected system, indicated by precision and SEE, is doubled

while the correlation coefficient decreased because of the relative increase of noise in the considered range.

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# 4. Validation of videodensitometry in the assessment of stenosis phantoms: an in vitro and in vivo study

CARLO DI MARIO , JÜRGEN HAASE, JAVIER ESCANED, ELINE MONTAUBAN VAN SWIJNDREGT and PATRICK W. SERRUYS

## Introduction

Computer-assisted automatic assessment of luminal contours (edge detection) is the technique normally used in quantitative angiography. The accuracy of the measurements with edge-detection, however, can be impaired by the presence of eccentric lesions or of lesions of complex lumen geometry. Under these conditions densitometry has a potential advantage because of its independence from the shape of the lesion.

In vitro studies have demonstrated a high accuracy of videodensitometry in the measurement of hole phantoms [1–6] and its superiority to edge-detection in the measurement of eccentric stenosis [7–8]. The clinical application of this technique, however, has produced conflicting reports on its reliability as an alternative to the geometric approach [7–15].

To determine the accuracy and to understand the limitations of these two quantitative angiographic techniques, the comparison must be performed with a lumen of known size.

Aim of this study was the validation and the comparison of the videodensitometric and geometric techniques of a computer-based automatic quantitative angiographic analysis system (CAAS System) in an in vivo experimental setting simulating a diagnostic coronary angiogram. For this purpose stenosis phantoms with circular lumens covering the entire range of clinically relevant coronary stenoses (diameter: 0.5–1.9 mm) were inserted into the coronary arteries of 6 closed-chest pigs and a standard selective cineangiography was performed. In order to better distinguish the role of the non ideal conditions of examination present during an in vivo angiographic acquisition from the inherent limitations of the geometric and videodensitometric quantitative angiographic techniques the same stenosis phantoms were inserted into different sized plexiglass tubes filled with different concentrations of contrast medium (50% and 100%) and examined using the same radiographic equipment and comparable radiologic parameters.



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**In vitro and in vivo validation of the videodensitometric measurements**

*A. Methods*

*Coronary phantoms*

Precision drills of 0.5, 0.7, 1.0, 1.4 and 1.9 mm were used to create circular holes in a series of cylinders of acrylate (Perspex) and polyamide with a length of 8.4 mm and an external diameter of 3.0 and 3.5 mm, tapered at the distal end to facilitate insertion. This material was chosen because of its extremely high radiolucency and suitability to precision drilling. An optical calibration with a 40 fold magnification showed a mean difference of $3 \pm 23$ μm between the drills used and the resulting lumens, with an almost perfect circularity of the lumens. The cylinders were mounted at the tip of 4 French radiolucent catheters containing a movable radiopaque guide-wire for catheter insertion.

*In vitro experimental setting*

The previously decribed coronary stenosis phantoms were wedged into the plexiglass tubes. Plexiglass tubes with an internal diameter of 3.0 and 3.6 mm were used for the stenosis phantoms with an internal diameter of 0.5 to 1.4 mm, using the two series of phantoms with an external diameter of 3.0 and 3.5 mm. The 1.9 mm phantom was inserted into a 4.0 mm plexiglass tube.

The plexiglass models containing the stenosis phantoms were positioned vertical on the radiologic table with a fixed distance of 15 cm from the image intensifier. The focus-to-object distance was maintained at 90 cm throughout the procedure. A circular highly radiopaque copper phantom of known diameter (3 mm) positioned at the same distance from the image intensifier was used for calibration. Plexiglass blocks of known thickness (17.5 cm) were added to obtain a kilovoltage level comparable to the levels observed during the in vivo angiographic acquisition. All phantoms were filled using undiluted (100% iopamidol 370, iodine concentration 370 mg/100 ml) and diluted (50% iopamidol/50% saline, iodine concentration 185 mg/100 ml) contrast medium.

*Radiographic setting*

A single plane Philips Poly Diagnost C2 was used, equipped with a MCR X-ray tube and powered by an Optimus CP generator. The 0.8 mm focal spot and the 5–inch (12.5 cm) field of view of the cesium-iodine image intensifier were used for all angiograms. The pulse width was maintained unchanged at 5 ms. The kVp and mA range was automatically adjusted according to the thickness of the imaged object (mean 76 kVp) and cinematography was performed using the "lock-in" mode. Angiograms were filmed at 25 frames/s using an Arritechno 90 cinecamera with an 85 mm lens. A

Kodak CFE cinefilm was used and developed with an Agfa Refinal developer 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.

*Animal preparation*

Studies were performed in accordance with the position of the American Heart Association on research animal use and under regulations of the Erasmus University Rotterdam. After sedation with intramuscular ketamine and intravenous metomidate 6 cross-bred Landrace-Yorkshire pigs (HVC, Hedel, The Netherlands) of either sex (45 to 55 kg) were intubated and connected to a respirator for intermittent positive pressure ventilation with a mixture of oxygen and nitrous oxide. Anesthesia was maintained with intravenous pentobarbital. The right carotid artery was cannulated with a 12 French valved sheath for the insertion of the stenosis phantoms. The left carotid artery was used for the insertion of the angiographic coronary catheter and the left jugular vein for administration of drugs or fluids when necessary. To prevent clot formation, all the animals were treated with an intravenous bolus of acetylsalicylic acid (500 mg) and heparin (10,000 I.U.) and a continuous intravenous infusion of heparin 10,000 I.U./hour.

*In vivo image acquisition*

After intracoronary administration of 1 mg of isosorbide-dinitrate and performance of a preliminary left coronary angiography for orientation, the catheter with the stenosis phantom mounted was advanced into the left coronary artery until a wedge position in either the left anterior descending or the left circumflex artery was obtained. The guide-wire used for the insertion of the radiolucent catheter was then totally removed. An 8 French El-Gamal guiding catheter was engaged into the ostium of the left coronary artery and selective coronary arteriography was performed by power injection of 10 ml of iopamidol (iodine content 370 mg/ml) at 37°C with an injection rate of 10 ml/s (Medrad Mark V pressure injector). Ventilation was transiently interrupted during the acquisition of the angiograms. Before the angiogram, the catheter was filmed unfilled for calibration purposes. To increase the calibration accuracy a catheter with minimal distal tapering and a highly radiopaque polyurethane jacket (Schneider Shiley Soft-Touch) was chosen and the tip was measured at the end of the procedure with a micrometer. The insertion of the entire range of stenosis phantoms was attempted in all animals. The choice of the radiographic projection was aimed at avoiding foreshortening and overlapping of contiguous vessels on the stenotic segment.

*Quantitative analysis*

A cineframe with an optimal stenosis filling (end-diastolic for the in vivo cineangiograms) was selected for analysis with the CAAS System (Pie Medical, Maastricht, The Netherlands). A $6.9 \times 6.9$ mm region of interest was

selected from the 18 × 24 mm image area on the 35 mm cineframe and digitized into a 512 × 512 pixel matrix with 256 grey levels. The image calibration factor was calculated using the circular copper phantom (in vitro) or the coronary guiding catheter (in vivo) as a scaling device in each projection.

*Contour analysis*: The inner diameter of the plexiglass tubes and of the porcine coronary arteries as well as the lumen of the stenosis phantoms was calculated with an automatic contour detection technique. A weighted first and second derivative function with predetermined continuity constraints was applied to the brightness profile of each scanline perpendicular to the vessel centerline [16]. Manual correction of the automatically determined contours is possible with the used system but was completely avoided in these measurements. The obstruction diameter was defined by the minimal value in the diameter function. The geometric cross-sectional area was computed from this obstruction diameter assuming a circular cross-section. A user-defined diameter was selected in the plexiglass tube opposite to the side of insertion of the phantoms (in vitro) or in a normal coronary segment distal to the stenosis (in vivo) as a reference diameter for the calculation of percent diameter and cross-sectional area stenosis and as a calibration of the densitometric measurement (Figs 1, 2). The automatic mode for the calculation of this reference diameter from the integration of the segments proximal and distal to the stenosis (interpolated technique) could not be used because of the bias for the densitometric measurements induced by the presence of the phantom-mounting catheter in the proximal segment of the plexiglass tube or coronary vessel.

*Videodensitometry*: The brightness profile of each scanline perpendicular to the centerline of the vessel lumen was transformed into an absorption profile by means of a simple logarithmic transfer function to correct for the Lambert-Beer law. The background contribution was estimated by computing the linear regression line through the background points directly left and right of the detected contours [17]. Subtraction of this background portion from the absorption profile yielded the net cross-sectional absorption profile. By repeating this procedure for all scan-lines the cross-sectional area function was obtained. An absolute reference densitometric area value was calculated using the diameter measurements obtained from the edge detection technique assuming a circular configuration in a user-defined reference segment distal to the stenosis (Figs 1, 2). The densitometric minimal cross-sectional area could then be calculated by the ratio of the density levels at the reference area and at the narrowed segment. The densitometric minimal lumen diameter was calculated from the densitometrically determined cross-sectional area assuming a circular model. Densitometric percent diameter and cross-sectional area stenosis were calculated from the densitometric measurements of stenosis and reference segment. The phantom derived corresponding values were calculated from the known dimensions of the phantoms and the geometric measurements of the reference segment.

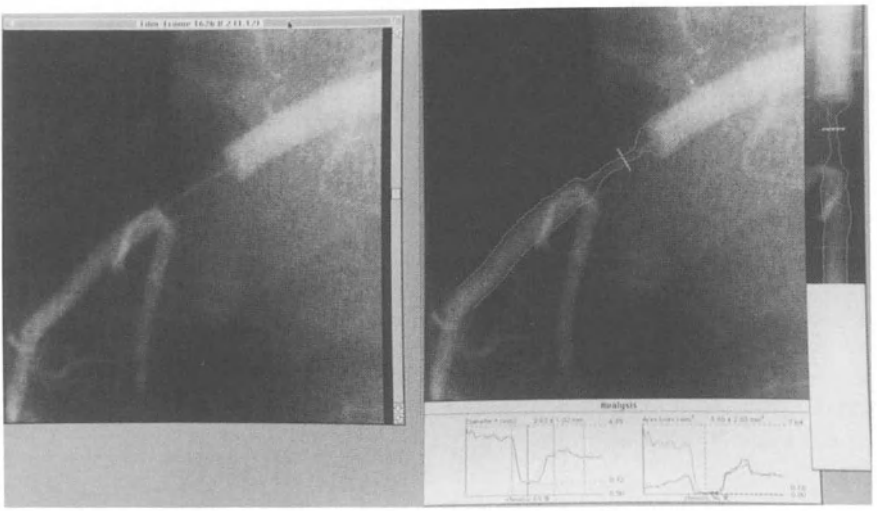

*Figure 1.* Magnified image of the middle segment of the left anterior descending artery in the left lateral view after insertion of the 0.5 mm stenosis phantom. The automatically detected vessel contours are displayed in the figure on the right. The two graphs below show on the x-axis the segment length, from proximal to distal, and on the y-axis the lumen diameter (on the left) and the lumen cross-sectional area measured with videodensitometry (on the right). The lumen of the stenosis phantom was overestimated with edge detection. Note the distal diameter defined as a reference for the absolute videodensitometric measurements.

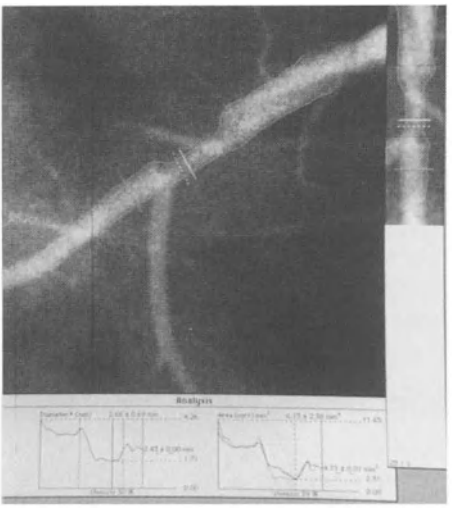

*Figure 2.* Magnified image of the middle segment of the left anterior descending artery in the same projection after insertion of the 1.9 mm stenosis phantom.

*Statistical analysis*
The minimal lumen diameter, minimal cross-sectional area and percent cross-sectional area stenosis measured both with the geometric and the densitometric technique were compared with the corresponding values of the stenosis phantoms using a paired t-test (two-tailed) and linear regression analysis. The mean differences between geometric and densitometric minimal lumen diameter and cross-sectional area and corresponding phantom dimensions were calculated and considered an index of the accuracy of the measurements, while the standard deviation of the differences was considered an index of precision. These differences were also plotted against the size of the phantoms according to the method proposed by Bland and Altman (modified) [18]. The standard deviations of the differences with the geometric and densitometric technique were compared using a Pitman's test. A p value $< 0.05$ was considered to be statistically significant.

## Results

### *A. In vitro*

Nine cineangiograms were filmed with the phantoms filled with 100% contrast and 10 after filling with 50% contrast. In the two cineangiograms performed with the 0.5 mm phantom filled with 50% contrast, the stenosis lumen showed a very poor opacification of the lumen so that the automatic contour detection technique failed to appropriately detect the centerline of the vessel and the contours of the stenosis. These two clearly erroneous measurements were considered as missing data in the statistical analysis.

*Minimal lumen diameter*
Both edge detection and videodensitometry underestimated the stenosis phantom diameter (mean difference = $-0.05 \pm 0.16$ mm and $-0.09 \pm 0.13$ mm, respectively, ns), (Fig. 3). Similar differences were observed in the measurements obtained with the phantoms filled with undiluted and 50% contrast. Edge detection obtained different results according to the dimension of the measured lumen, with a clear trend towards an overestimation of the stenoses of smaller diameter and an underestimation of the stenoses of larger lumen diameter. This observation may explain the higher correlation coefficient and the slope closer to 1 observed with videodensitometry when linear regression analysis was used to compare the true phantom lumen and the geometric and videodensitometric measurements (Fig. 4).

*Minimal luminal cross-sectional area and percent area stenosis*
The mean difference of the angiographically measured minimal cross-sectional areas and the phantom lumen cross-sectional area was $-0.15 \pm 0.30$ $mm^2$ and $-0.12 \pm 0.31$ $mm^2$ for the geometric and densitometric techniques, respectively.

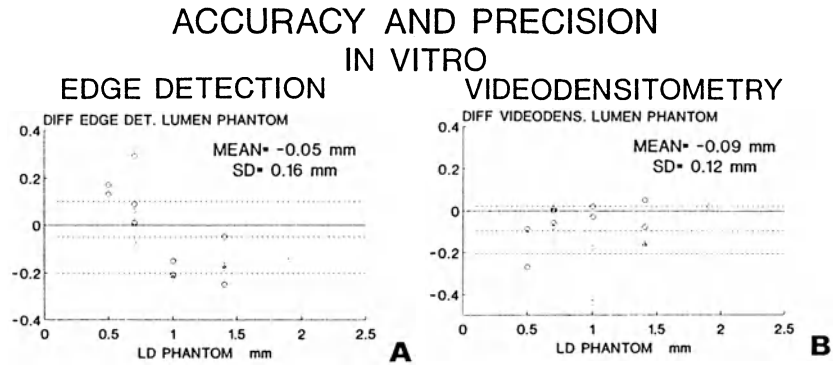


*Figure 3.* The signed differences between minimal lumen diameter measured in vitro with edge detection and with videodensitometry and phantom lumen diameter (LD) are plotted against the lumen diameter of the phantoms (on the x-axis, 0.5, 0.7, 1.0, 1.4 and 1.9 mm). The dashed lines indicate the mean difference and the standard deviation of the signed values.

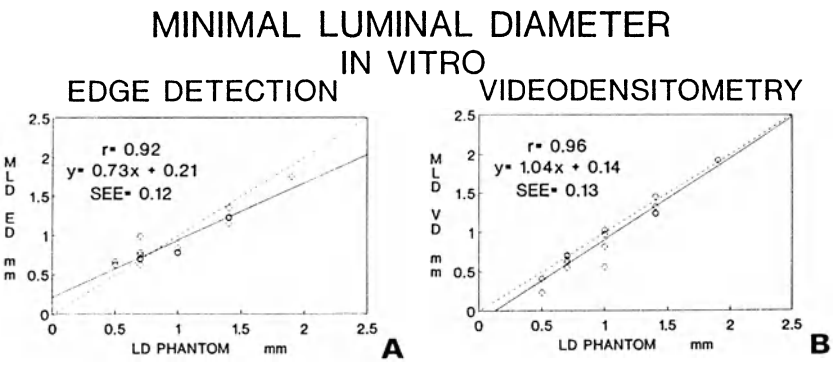


*Figure 4.* Linear regression analysis of the phantom lumen diameter (LD) vs the minimal lumen diameter (MLD) measured in vitro with edge detection (ED) and videodensitometry (VD). The dashed line and the continuous lines correspond to the line of identity and the line of regression, respectively.

Linear regression analysis was used to compare true percent cross-sectional area stenosis calculated from the known cross-sectional areas of the phantom and the plexiglass tube lumens and from the measured geometric and videodensitometric corresponding values (Fig. 5). The percent area stenosis measured with both techniques showed a high correlation with the true values ($r = 0.94$ for both methods) but the videodensitometric measurements were better aligned along the line of identity ($Y = 2 + 0.98\ X$) than the corresponding geometric measurements ($Y = 27 + 0.71\ X$).

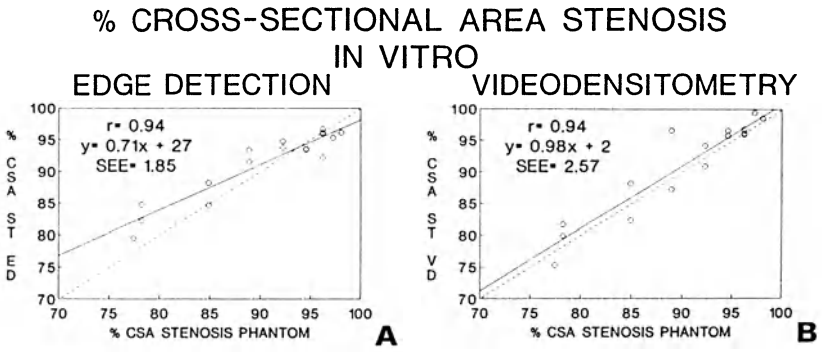


*Figure 5.* Linear regression analysis of the phantom percent cross sectional area (CSA) stenosis measured in vitro with edge detection (ED) and with videodensitometry (VD). The dashed lines and the continuous lines correspond to the line of identity and the line of regression, respectively.

## *B. In vivo*

Forty-two coronary cineangiograms were obtained after intracoronary insertion of the stenosis phantoms. Three cineangiograms were excluded because of the presence of dye streaming around the incompletely wedged stenosis phantom. Eleven angiograms (26%) were considered to be of insufficient diagnostic quality for quantitative analysis because of: side-branches overlapping the stenotic segment (3), foreshortening of the stenotic segment (4); inadequate arterial filling (4). This last finding was observed in 3 phantoms with a lumen diameter of 0.5 mm and in one 0.7 mm stenosis phantom. The results of the quantitative analysis of the remaining 28 cineangiograms (67%) are reported in the following paragraphs.

### *Minimal lumen diameter*

In Fig. 6 the minimal lumen diameter measured with the geometric and densitometric techniques is compared with the phantom diameter using a linear regression analysis. The lower correlation coefficient and higher SEE of videodensitometry (Fig. 6B) was largely due to the inability of this technique to detect a difference between mean intraluminal density and density of the adjacent background in two angiograms of the smaller phantoms (0.5 and 0.7 mm). In both cases a precise measurement was possible with the geometric technique. When these measurements were excluded from the analysis (Fig. 6C) videodensitometry showed a regression coefficient and SEE similar to the geometric approach, with the regression line almost aligned with the line of identity ($Y = 1.02\,X - 0.10$).

Both edge detection and videodensitometry underestimated the phantom diameter (mean difference = $-0.06 \pm 0.14$ mm and $-0.11 \pm 0.20$ mm, re-

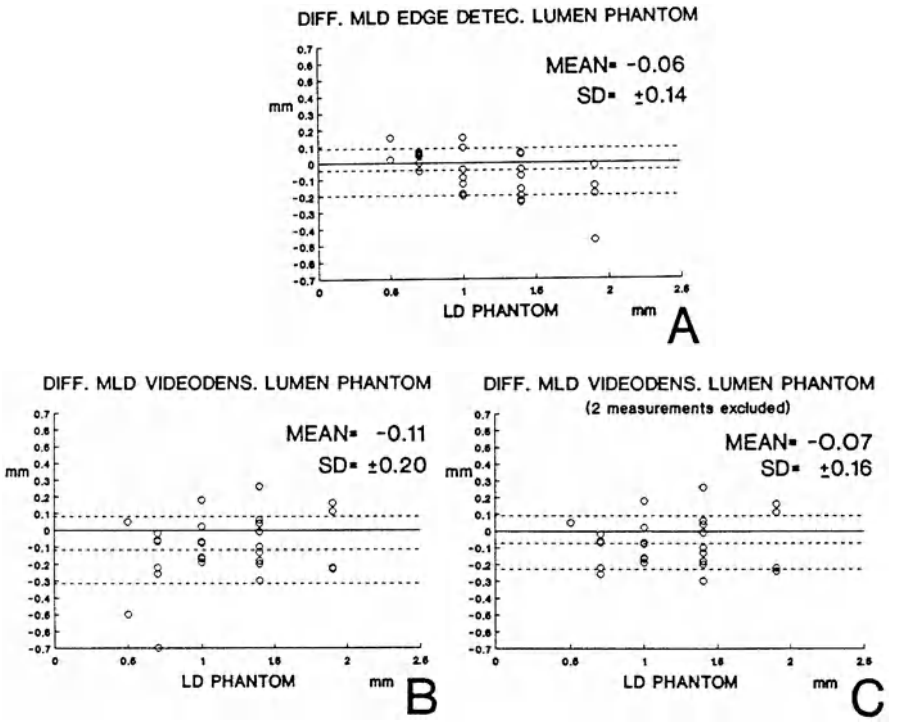


*Figure 6.* Linear regression analysis of the lumen diameter (LD) of the phantom vs the minimal lumen diameter (MLD) measured in vivo with edge detection (ED),(A) and videodensitometry (VD),(B). The dashed lines indicate mean and standard deviation of the difference.

Figure C shows the videodensitometric results when the two failed measurements (aligned on the x-axis in Figure B) are excluded. Redrawn from Di Mario et al. Am Heart J 1992; 124: 1181–89, with permission.

spectively, ns), (Fig. 7). When the results, however, were compared without the two previously described failures of the densitometric approach, the mean difference and standard deviation measured with videodensitometry ($-0.07 \pm 0.16$ mm) was comparable with the previously reported mean difference obtained using the geometric approach.

*Minimal luminal cross-sectional area*

The absolute cross-sectional areas of the stenosis phantoms were correlated with the quantitative angiographic measurements of minimal cross-sectional area (Fig. 7). The discrepancies between corresponding geometric and densitometric measurements were observed mainly in the range of the smaller phantom sizes and had therefore a reduced impact on the calculated correlation coefficient (0.94 with both techniques). A slightly larger SEE, however, was observed with the densitometric technique (0.31 $mm^2$ vs 0.24 $mm^2$ with the geometric technique).

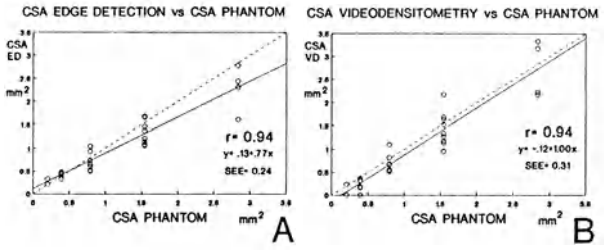


*Figure 7.* Linear regression analysis of the phantom cross sectional area (CSA) measured with edge detection (ED), (Fig. A), and videodensitometry (VD), (Fig. B). The dashed lines and the continuous lines correspond to the line of identity and the line of regression, respectively. Redrawn from Di Mario et al. Am Heart J 1992; 124: 1181–89, with permission.

The mean difference of the angiographically measured minimal cross-sectional area and the phantom lumen cross-sectional area was $-0.15 \pm 0.30$ $mm^2$ and $-0.12 \pm 0.31$ $mm^2$ for the geometric and densitometric techniques, respectively.

*Percent cross-sectional area stenosis*

The percent cross-sectional area stenosis calculated for the phantoms and the corresponding geometric and videodensitometric measurements showed a high correlation, with a correlation coefficient of 0.93 for both techniques (SEE = 5% with the geometric technique and 6% with the densitometric technique).

Edge detection and videodensitometry overestimated the phantom derived percent cross-sectional area stenosis, with a mean difference between angiographic and phantom derived percent cross-sectional area stenosis of $2 \pm 6\%$ for both techniques.

## Are the results of these experimental studies applicable in the routine clinical angiographic acquisition?

*In vitro studies*

Several in vitro studies have confirmed that densitometry has the potential to measure differences in density between large and narrow phantom lumens and that the calculated percent cross-sectional area stenosis is highly correlated with the corresponding phantom derived measurement [2–6]. Furthermore, these studies have confirmed that videodensitometry has potential advantages in the measurement of eccentric lesions from a single plane angiogram [7, 8] and that absolute values can be obtained from the comparison of the density of a reference area measured with edge detection [17] or of a thin-wall contrast filled angiographic catheter [2]. Phantoms with a large

lumen diameter were less accurately measured with videodensitometry, most likely due to the non-linearity between iodine content and optical density of the radiographic image induced by the spectral hardening of the polyenergetic x-ray beam [1]. On the contrary, in vitro videodensitometry has advantages in the measurement of stenoses smaller than 1 mm. In this range edge-detection tends to overestimate the minimal luminal diameter while more precise measurements are obtained with videodensitometry. Our observations confirm this finding also for stenosis <0.75 mm, not analyzed in previous studies. In our experience, however, using radiographic parameters comparable to those required for clinical studies, phantoms with a lumen diameter of 0.5 mm filled with 50% contrast medium were not analyzable with any of the quantitative angiographic techniques used. In phantoms of larger lumen or in 0.5 mm phantoms filled with undiluted contrast videodensitometry showed a slightly lower accuracy but a higher precision than edge detection. It is noteworthy that the relative measurements of stenosis cross-sectional area, only based on the measured minimal videodensity at the site of the stenosis and in a reference area, were more strictly correlated with the true percent cross-sectional area reduction using videodensitometry than edge detection.

The in vitro measurement of radiographic phantoms, however, can not reproduce some of the sources of error of the videodensitometric approach in vivo. Arterial branches overlapping or parallel to the analyzed segment impairing the measurement of the density of the lumen or of its background, patient structural noise inducing an inhomogeneous background, lack of orthogonality of the vessel with the radiographic beam, inhomogeneous filling of the vessel during injection are conditions which can not be assessed in in vitro studies. Also some of the most important sources of non-linearity of densitometry such as scatter/veiling glare and beam hardening are accentuated or more difficult to correct for in vivo [19].

*Clinical studies*

The promising results of the in vitro application of videodensitometry, the development of interventional techniques inducing complex lumen irregularities of the treated stenosis and the diffusion of digital angiography with the possibility of on-line videodensitometric measurements have stimulated the interest for this technique of quantitative analysis. Single-plane videodensitometry was found to be an accurate and convenient method for quantifying stenosis severity in eccentric coronary lesions [7, 8]. The shaggy and rough appearance of the dilated segment after balloon angioplasty with the presence of haziness of the luminal contour is a challenge to quantitative angiography. Initial reports have suggested that the use of videodensitometry can overcome these limitations of the geometric technique in the immediate evaluation of the results of balloon angioplasty [10, 11]. Other reports, however, showed comparable quantitative angiographic measurements with both techniques

[13]. Doubts concerning the possibility to reliably assess vascular dimensions from one projection and, in general, concerning the accuracy of videodensitometry were raised by the observation of a poor correlation between the videodensitometric measurements of the same segment in two projections after angioplasty [14]. Balloon angioplasty, however, must be considered as a critical condition for the application of any quantitative angiographic technique and videodensitometry can also provide unreliable measurements because of inadequate mixing due to blood turbulence or intraluminal dissections [20, 21, 22]. Not surprisingly, the large discrepancies of the edge detection and videodensitometric measurements immediately after angioplasty are largely reduced after stent implantation, probably because of remodelling of the stented segment into a more circular configuration and because of sealing of wall dissections [23]. Similarly, a poor correlation between videodensitometry and edge detection is present in the evaluation of the irregular channel obtained after lasing in comparison to the results obtained after balloon dilatation [24].

Clinical studies, however, can evaluate only the variability of repeated measurements in the same or in different projections. A more complete comparison of the usefulness and limitations of the two techniques is possible only if a lumen of already known dimension is measured with angiography.

*Previous in vivo phantom studies: comparison with the present results*

Simons et al. [25] measured with a videodensitometric technique a large series of coronary stenoses induced by the inflation of Silastic cuffs in dogs and compared these results with the measurements of the pressurized histologic cross-sections. Although a good correlation between videodensitometry and histology measurements was demonstrated, a relatively large mean difference (+18.5% difference in the measurement of the stenosis diameter) was observed.

The use of pre-shaped intracoronary phantoms can reduce the variability induced by the inaccuracies of the measurement of the true stenotic lumen. This approach, however, is outweighed by the more troublesome phantom insertion procedure, thus explaining the limited number of analyzable angiograms in our series (28 corresponding measurements) and in the series reported by Wiesel [26] and Mancini [27] (14 measurements in 10 dogs and 25 measurements in 16 dogs, respectively). Wiesel [26] observed a mean difference between calculated cross-sectional area and known phantom lumen cross-sectional area of 0.65 $mm^2$ with videodensitometry and of 0.54 $mm^2$ with the geometric technique, with correlation coefficients of 0.76 and 0.70, respectively. The larger differences and lower correlation values in comparison with the results of our study can be explained by the different sizes and shapes of some of the stenosis lumens and by the lower number of pixels/mm available in the digitized image.

More similar phantoms (circular lumen with a diameter ranging from 0.83

to 1.83 mm) were inserted by Mancini et al. [27] into the coronary arteries of open chest dogs. When the analysis was performed on the cinefilm the SEE of the linear regression analysis of true phantom diameter and corresponding geometric measurements was equal to 0.24 mm ($r = 0.87$). Although no direct data was provided concerning the accuracy of the videodensitometric measurements, the videodensitometric minimal cross-sectional area and percent area stenosis were significantly correlated with the coronary flow reserve assessed using electromagnetic flowmeters, yielding a correlation similar to the geometric measurements.

A peculiarity of our study was that we were able to examine phantoms of small lumen diameter (0.5 and 0.7 mm). The angiographic examination of these high-grade stenosis phantoms, however, was not possible in all cases because the reduced flow rapidly induced ischemic changes and intraluminal thrombosis. Furthermore, in 4 cases the visualization of these severe stenosis phantoms was so poor to preclude any quantitative measurement. Also in two cases correctly analyzed with edge detection, however, videodensitometry could not identify the low density of the small phantom lumen. The results from the database of our Laboratory, collecting quantitative angiographic measurements from more than 4,600 patients included in large multicenter trials [28, 29], show that in more than 10% of the cineangiograms before coronary angioplasty densitometry fails to measure the lumen diameter because of the combined effect of low density of a severe stenosis, dense background and/or presence of parallel vessels interfering with the background subtraction. Figure 8 reports the results of linear regression in the analysis of 1,000 consecutive measurements of minimal luminal cross-sectional area before balloon angioplasty using edge detection and videodensitometry. A large series of negative measurements were obtained with videodensitometry, especially in the range of minimal luminal cross-sectional areas $<1$ mm$^2$.

With the exception of some of the measurements of the most severe lesions, the accuracy and precision of the videodensitometric results was comparable with the accuracy and precision of the geometric results. In this study, however, only cineangiograms with an optimal orientation of the incident X-rays to the evaluated segment, without overlapping vessels and with an adequate homogeneous lumen filling were analyzed. It is noteworthy that more than 1/4 of the in vivo cineangiograms had to be excluded because of the presence of these three conditions which are likely to reduce to a greater extent the accuracy of the videodensitometric measurement rather than that of the geometric measurements. The corresponding videodensitometric and geometric measurements of minimal luminal cross-sectional area before angioplasty in a large unselected series from a recent multicentric quantitative angiographic study [30] showed a correlation which was much more poor than the correlation observed in both our in vitro and in vivo experience, with the presence of negative videodensitometric measurements in 8.2% of the cases (Fig. 9). These findings suggest that the applicability of

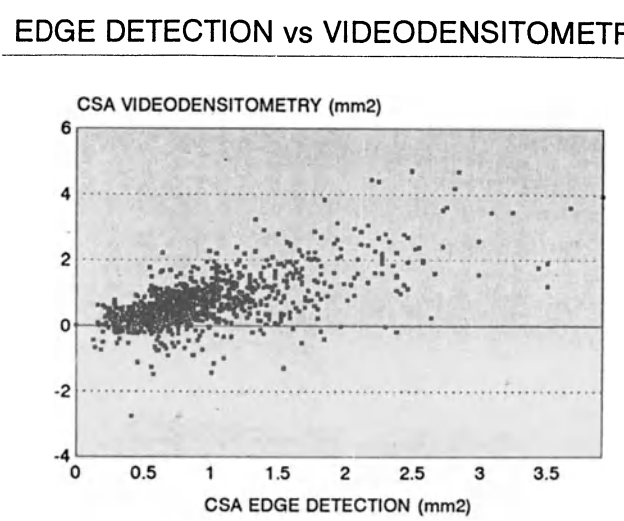


*Figure 8.* Linear regression analysis of 1,000 consecutive measurements of minimal luminal cross-sectional area (CSA) before balloon angioplasty analyzed in the QCA Core Laboratory of Rotterdam. The cases with total occlusion were excluded from analysis. Note that videodensitometry measured negative cross-sectional areas in a significant number of cases, especially in the smaller stenosis range. Courtesy of Dr. WRM Hermans.

videodensitometry to the analysis of large series of cineangiograms from clinical trials is more limited than that of edge detection, especially in the examination of stenosis of small diameter.

*Limitations of the study*

The use of phantoms of regular circular lumen limits the possibility to detect advantages of the densitometric technique in the evaluation of eccentric or irregular stenosis. Although this evaluation is of interest, the aim of this study was more simply to establish whether videodensitometry is able to measure coronary lesions with an accuracy comparable to that of the geometric technique, despite the well known limitations of densitometry in the in vivo application and without the cumbersome and still investigational corrections proposed for the scatter and veiling glare [30, 31]. Beam hardening, another well-known limitation of this technique, is a function of iodine density which is proportional to vessel thickness. Consequently, the results obtained in the examination of this series of small size lumen phantoms are not applicable to larger vessels.

In this study, in order to obtain a completely automatic measurement, the minimal luminal diameter and minimal cross-sectional area and not the average of the corresponding values measured over the obstruction segment were

chosen for the comparison with the lumen diameter of the stenosis phantom. This approach, however, possibly explains the moderate underestimation with both techniques as a consequence of quantum noise or intraluminal microthrombosis interfering with the angiographic measurements.

Videodensitometry can only detect percent differences between two vascular segments. Unfortunately, only in vitro the cross-sectional area of the reference diameter was known. In vitro the fully densitometric measurements of percent cross-sectional area were almost superimposable to the true percent cross-sectional area stenosis. The calculation of absolute videodensitometric measurements of the stenosis is based on the geometric measurement of the luminal cross-sectional area of the reference segment. This value is therefore dependent, as an integration of densitometric and edge-detection measurements, on the accuracy of the geometric measurement of the reference segment. In the in vitro experience the moderate underestimation of the reference diameter, squared in the calculation of the corresponding cross-sectional area, may explain the larger underestimation of absolute minimal luminal diameter and minimal cross-sectional area with videodensitometry in comparison to edge detection. Inaccuracies in the geometric measurement can be caused by an erroneous calculation of the magnification factor using the catheter as a scaling device. Unfilled catheters, with a highly radiopaque wall and without tapering of the measured segments were used to minimize some of the possible sources of error [32–35]. Inaccuracies induced by an out-of-plane position of the catheter, however, can not be easily corrected. More accurate calibration methods such as the isocentric technique [36] have been proposed but they are more cumbersome and of difficult application in clinical practice.

The correction for pincushion distortion was performed using a square grid filmed in the anteroposterior position as a reference [16]. Another possible source of distortion in image intensifier tubes, determined from the rotational distortion due to the geomagnetic field [37], is more difficult to be corrected because it varies in all the different image amplifier positions. The effect of this type of distortion on small object dimensions, however, is normally negligible.

## Conclusions

The geometric and videodensitometric techniques of quantitative angiographic analysis showed a high accuracy and precision in the measurement of stenosis hole phantoms of various severity (diameter 0.5–1.9 mm) both in vitro and after in vivo insertion in porcine coronary arteries. Minimal lumen diameter and cross-sectional area measured with both techniques slightly underestimated the true phantom diameter and cross-sectional area. The geometric approach more reliably measured the phantom lumens of smaller diameter.

## Acknowledgements

The collaboration of the Experimental Laboratory, Thoraxcenter, Rotterdam (Drs. P.D. Verdouw, W.J. van den Giessen and R. van Bremen) and of the Technical Staff of the Cardiac Catheterization Laboratory (Mr. A. den Boer and R. van den Perk) is gratefully acknowledged. I am indebted to Dr. WRM Hermans for the use of the quantitative angiographic database of the QCA Core Laboratory of Rotterdam for the preparation of Fig. 8.

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# 5. Videodensitometry in percutaneous coronary interventions: a critical appraisal of its contributions and limitations

JAVIER ESCANED, JÜRGEN HAASE, DAVID P. FOLEY, CARLO DI MARIO, AD DEN BOER, ELINE MONTAUBAN VAN SWIJNDREGT and PATRICK W. SERRUYS

## Introduction

The rapid development of percutaneous coronary revascularization techniques, such as balloon angioplasty, atherectomy and stenting, has created new demands for quantitative angiography. These include the need for reducing the time dedicated to quantitative analysis during interventional procedures, as well as obtaining reliable measurements in unfavorable conditions, such as in vascular segments with complex luminal morphology resulting from percutaneous intervention [1–5]. The role that videodensitometry may play in the solution of these problems has barely been explored and is still unclear, although from a theoretical point of view it may offer at least two major potential contributions [6]. Firstly, when videodensitometry is used measurements can be performed from any angiographic projection, facilitating data collection and avoiding cumbersome and time-consuming analysis in orthogonal angiographic projections. Secondly, since luminal cross sectional area is calculated directly from the densitometric profile, no assumptions on luminal morphology are required, a fact that may contribute to a more realistic appraisal of the result of the intervention. The reliability of these appealing features in clinical practice, although supported by the theoretical background of the technique and by experimental work, is still controversial [7–15].

In this chapter we intend to perform a critical appraisal of the potential strengths and applications of videodensitometry technique that are appealing for the interventional cardiologist, as well as the problems underlying current state-of-the-art of the technique. Some of the theoretical principles of videodensitometry that are relevant for the understanding of these aspects are also discussed. Finally, the potential use of combined geometric and videodensitometric quantitative angiographic analysis is discussed.

Quantitative coronary angiography was born as an attempt to reduce the variability associated with visual quantification of stenosis severity and to extrapolate information on their hemodynamic severity [16–20]. During the last decade, the generalization of the use of percutaneous revascularization



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using balloon angioplasty and other techniques such as coronary atherectomy and stenting has potentiated the use of coronary angiography. As a result of the growing complexity of these procedures, the information obtained has to be used not only to provide the operators with reliable information as to the severity of the stenosis, but also on aspects relevant to procedural decisions. Matching the size of the interventional device to the artery is required in order to reduce vessel damage during recanalisation that may lead to acute vessel occlusion and late restenosis [21, 22]. Objective information on the changes in luminal dimensions obtained by the technique during the procedure may be required in order to decide on whether discontinuation of the procedure or further recanalisation is needed [2, 4]. For the researcher, quantitative angiography is a basic tool in assessing not only the primary efficacy of a particular technique, but also to assess luminal renarrowing in the long term [23].

As a result of these requirements, the use of on-line quantitative angiographic analysis is now experiencing an exponential growth. Most available digital angiographic systems have in-built algorithms for automated quantification of coronary stenosis. However, since the application of the methodology used in off-line angiographic analysis is cumbersome and time consuming during interventional procedures, the development of new, simplified forms of analysis are required. Furthermore, a similar degree of accuracy is needed during all the stages of the interventional procedure.

To understand the potential contribution of videodensitometry to these problems, in this chapter we review the basic principles underlying its technique. The original contributions from our group on the use of videodensitometry found in the text are based in the use of the Coronary Angiography Analysis System, which has been discussed in detailed in other chapters of this book and elsewhere [24–27].

## Estimation of luminal area using edge detection and videodensitometry

The basic difference between videodensitometric and geometric analysis of the angiogram is that the former measures luminal area measurements while the latter yields luminal diameters. Luminal diameters are widely used given the ease of measurement and the fact that, at first glance similar information to that used during visual interpretation of the angiogram or hand held calipers is conveyed. This similarity may be more illusory than real, as the work by Fleming et al. [28] has demonstrated that a better correlation exists between visual estimation of stenosis severity and luminal area derived from quantitative analysis. A potential advantage associated with the use of area measurements is that it may yield more relevant physiologic information that luminal diameters [29–33]. However, the calculation of luminal area from geometric analysis of the angiogram is cumbersome and not always accurate, the most obvious limitation being that lumen morphology is not always

circular or elliptical while such asumption is a prerequisite for the calculation of luminal area from geometric diameter measurements [5, 34, 35].

Although it is well known that the lumen of atherosclerotic vessels can show a variety of cross-sectional morphologies, it seems that in non-complicated segments circular or moderately elliptical lumina are predominant [34]. Plaque ulceration, fissuring and thrombosis can, however, cause major changes in luminal geometry in segments containing complicated plaques [36, 37]. More importantly, balloon angioplasty and other percutaneous interventions yield extremely complex luminal morphologies as a result of tearing of the intima and atherosclerotic plaque, dehiscence of plaque from the media, and disruption of the deep layers of the vessel wall [5, 35–40].

On these grounds, different solutions have been proposed to solve the problem derived from using geometric measurements obtained in different views to calculate the dimensions of non-circular lumina. These include using the lowest value as an estimate of luminal size [41], producing average values [42], or calculating luminal area using an elliptical model [43]. In those approaches the use of true orthogonality of the angiographic views yields a more accurate estimate than that obtained from non-orthogonal views [44], although such condition may be difficult to fulfill in clinical practice.

One of the advantages of videodensitometry relies on the fact that luminal area is calculated without making assumptions on lumen morphology [6]. Videodensitometry is based in the existing relationship between the attenuating power of the lumen filled with contrast medium and the X-ray image intensity. From this information a densitometric profile which is proportional to the cross-sectional area of the lumen is obtained, irrespective of its morphology. Luminal area is calculated using mathematical expressions such as

$$\text{Cross sectional area} = (d/\mu C)\Sigma \ln(Io/I)i,$$

where d is the separation between pixels along the profile direction, $\mu$ is the attenuating coefficient for the contrast material in the artery, C is the concentration of iodine within the artery, Io is the intensity of the X-ray beam in the absence of the attenuation in the artery, and I is the intensity of the X-ray beam after passing through the artery. Lets review some of the limitations and potential sources of error that stem from this basic theoretical background.

The first obvious requirement to obtain a reliable correlation between luminal dimensions and videodensity is that a complete replacement of blood by contrast medium during each injection should be obtained by the operator. Streaming of contrast would affect not only the detection of the true luminal borders but also the concentration of iodine within the artery (C in the above mentioned formula) and therefore the calculation of luminal area from the densitometric profile. A location of the stenosis as close to the angiographic isocenter as possible can be easily achieved by proper manipulation of the table and gantry during the procedure. In this way, pincushion distortion,

which affects pixel size (d in the same formula) and occurs in a variable degree in all available X-ray systems, can be minimized, although it can be further corrected to a great extent during the analysis, using a pre-filmed grid and specific algorithms [45].

A major problem in videodensitometric analysis is derived from the presence of overlapping densities corresponding to other anatomical structures that can interfere during the calculation of luminal area. In order to correct for such *patient structure noise*, subtraction of the background has to be applied to obtain a net cross-sectional videodensitometric profile. Either information obtained from an identical image obtained prior to the injection of contrast (mask subtraction) or from the structures adjacent to the artery present in the same frame has to be used for this purpose. Both systems of background correction present weak points. The former is affected by patient motion, particularly respiration, while in the latter the structure-related variability cannot be fully replaced by the use of linear interpolation. Excessive background subtraction can occur when other vascular structures located close to the vessel contour are used by the subtraction algorithm or when the vessel is located in areas of rapid transition between dark and bright areas. In those cases, the subtraction can be so intense that the calculated cross-sectional area may even take a negative value. In 5100 angiographic frames analyzed with the videodensitometric algorithm of the CAAS system 287 (7%) yielded a negative area value. Several angiographic factors influence the appearance of this type of error: as shown in Figure 1, the prevalence of negative readings was significantly influenced by the anatomical location of the analyzed stenosis, presumably due to a higher prevalence of branch overlap. Lumen size was also a determinant in this type of error. Negative area values were more common in vessels of smaller diameter (2.40 versus 2.67 mm, $p = 0.0001$) and minimal luminal cross sectional area calculated from edge detection (0.79 versus 1.92 $mm^2$, $p = 0.0001$).

Although we have stated that the basic principle of videodensitometry is the relationship between density and lumen area, it is important to note that not all brightness observed at the end of the cinengiogram-video chain can be attributed to the attenuation of the X-ray beam by the opacified vessel and anatomical structures. X-ray scatter and light reverberation within the optical systems such as the image intensifier and videocameras (veiling glare) can contribute in up to 80% of the total light intensity [46]. When no correction is applied, these measured intensities are introduced in the calculation of luminal area (I and Io in the above mentioned formula) and may constitute an important source of error [46, 47]. The contribution of scatter and veiling glare varies with the location accross the thorax, reaching maximum values when the coronary arteries are projected in areas with a rapid transition between the cardiac silhouette and the lung field.This may provide a partial explanation for the influence that the angulation used has in the appearance of negative readings in the three epicardial vessels (Fig. 1 A–

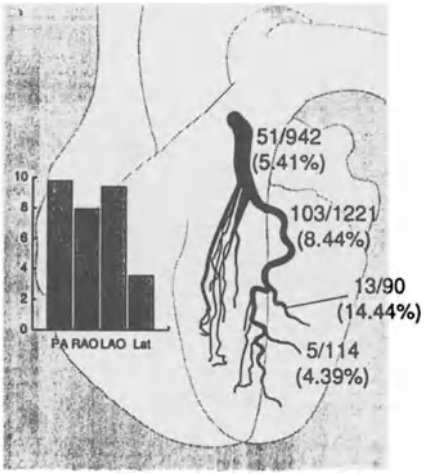


*Figure 1.A.*

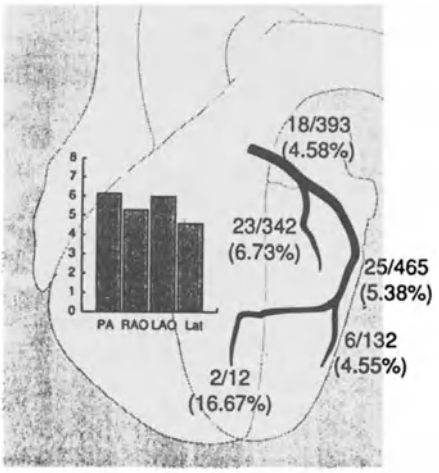


*Figure 1.B.*

C). The use of proper wedging during image acquisition is thus mandatory to minimise this source of error.

Finally, a critical point in the calculation of absolute area values with densitometry is that calibration of the system using a reference videodensitometric profile obtained in a segment of known dimensions is required. This reference profile is usually obtained in a user- or computer-defined disease-

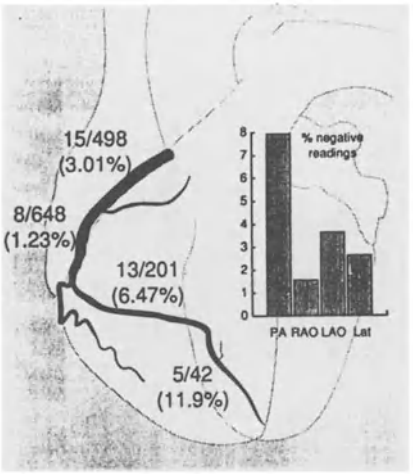


*Figure 1.* Prevalence of negative area measurements obtained during videodensitometric analysis in 5.100 angiographic frames. Negative area measurements result from excessive background subtraction when other opacified branches located close to the vessel contour are wrongly taken by the subtraction algorithm as background noise, or when the analysed vessel is located in areas of rapid transition between dark and bright areas. The results are shown separately for the 3 major epicardial vessel, showing the absolute and percentage prevalence of negative area measurements for each individual segment and for the 4 predominant angiographic angulations used (PA: postero-anterior; RAO: right anterior oblique; LAO: left anterior oblique; and Lat: lateral view).

free segment serving as a reference area and in which luminal area is calculated simultaneously from the luminal diameter, assuming that the lumen has a circular morphology (Fig. 2). When this is not the case, such as in diffusely diseased vessels, errors in area calculation can occur. Another potential source of error derived from the dependency of a reference segment for the calculation of absolute videodensitometric values can be found in the differences in the attenuating power of the opacified reference and stenotic segments. Since the column of contrast medium at this reference site is larger than at the stenotic site, the characteristics of the densitometric profile can be modified by the so-called beam hardening effect. This phenomenon consists in the selective attenuation of the less energetic fraction of the radiation produced by the X-ray tube by the contrast column, affecting brightness at the level of the image intensifier. The differences in the beam hardening due to the different attenuating power of the contrast column existing at the reference and stenotic segments can, when not corrected, affect all ulterior calculations of stenosis severity (Fig. 3).

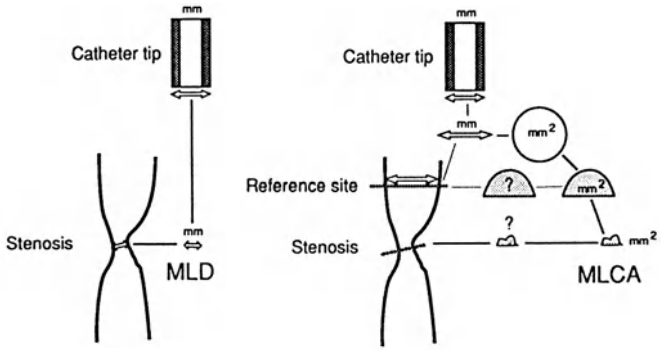


*Figure 2.* Calculation of absolute vessel dimensions by edge detection and videodensitometric analysis. In edge detection the calculation of minimal luminal diameter (MLD) is obtained by direct comparison with the diameter of the filmed catheter, which is used to calibrate the system. Videodensitometry yields a densitometric profile which has to be compared with a segment of known luminal area. This is achieved by automatic selection of a reference site where it is asumed that no occlusive atheromatous disease is present and that the lumen is circular. From the reference diameter (calculated from direct comparison with the coronary catheter as described above), geometric circular cross-sectional area at the reference site is calculated and compared with the densitometric profile at the same site. In this way, density units are transformed into area units ($mm^2$). By direct comparison of the densitometric area thus calculated at the reference site and the smallest densitometric profile in the stenotic segment, minimal luminal cross-sectional area (MLCA) is derived.

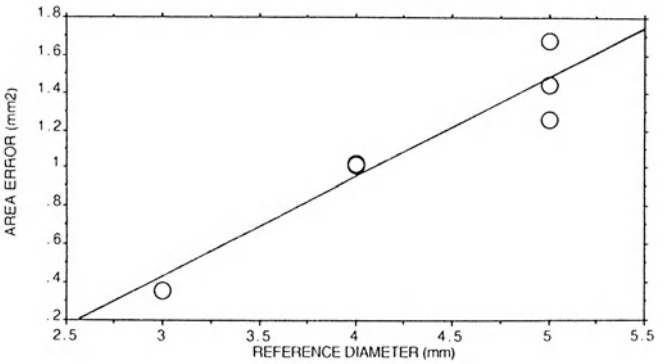


*Figure 3.* Area error in videodensitometric measurements obtained in precision-drilled circular phantoms with known dimensions, plotted against the reference diameter used. A significant relationship exists between these two parameters, suggesting that the "beam hardening" effect at the reference site influences the accuracy of videodensitometric measurements at the narrowest point.

**Changes in luminal morphology after coronary intervention**

How do the discussed advantages and limitations of videodensitometry translate to clinical practice and particularly to the field of coronary intervention? Videodensitometry has yielded good overall results in validation studies using engineered phantoms either in vitro [48–51] or after being inserted percutaneously in animal models [52, 53]. However, it has to be noted that in most cases phantoms with a circular lumen were used [48–50, 52, 53]. Given the characteristics of these studies (fixed luminal phantom morphology, absence of wall disruption), the reliability of videodensitometric measurements in circumstances similar to those found after angioplasty has not been clearly established in a experimental setting. This may explain the differences found with results obtained in clinical practice, where conflicting results suggesting a high variability in the obtained measurements has been reported [7–15].

We have discussed above that the ability to obtain reliable measurements from a single angiographic view would simplify enormously the use of online quantitative angiography. Although routinely applied in many laboratories, little information is available on the variability related with this approach. When geometric data is used, Lesperance et al. [41] has suggested that restricting the analysis to the angiographic view in which the stenoses appears most severe fulfills the degree of accuracy required in clinical practice. However, the conclusions of this study were strongly limited by the fact that the angiographic view used was not an independent variable but was also included in the calculating the averaged area used as an standard. Videodensitometry is an appealing alternative to edge detection since the obtained measurements should not be influenced by the angulation used, a principle supported by experimental in vitro studies [48–51]. Major controversy remains, however, as to the application of this principle in the clinical field. The correlation for individual measurements obtained in orthogonal views both before and after balloon angioplasty has been found by different authors to be high [11], moderate [9] or poor [8]. This correlation has also been found to be influenced by the stage of the intervention, deteriorating after balloon angioplasty to an unacceptable level [10].

To shed further light on these topics we have investigated the degree of agreement between measurements obtained in two orthogonal angiographic projections during the different stages of balloon angioplasty. Edge detection and videodensitometry analysis was performed separately in 47 vessels. Our objective was to test the basic premise of independence of the angulation used during the different stages of coronary intervention. We also wanted to compare whether in this regard videodensitometry proved superior to edge detection. For a fair comparison between both techniques, the study was restricted to a selected coronary segment with ideal characteristics for both types of quantitative analysis. The mid right coronary artery was chosen since in this segment the conditions of non-obliquity and absence of branch

overlap were easily and consistently achieved. In this regard, the mid right coronary artery represents an "in vivo phantom", which undergoes typical luminal changes as a result of balloon dilatation, and that provides an alternative to the limitations imposed by the use of artificial phantoms with fixed lumen morphology discussed above.

The correlation between pairs of orthogonal measurements obtained by using either videodensitometry or edge detection obtained in this work is shown in Fig. 4. The degree of agreement between these values is further illustrated with the mean difference between both measurements and its standard deviation (Fig. 5). Before angioplasty the accuracy of measurements obtained from a single view is similar using videodensitometry or edge detection (mean difference $-0.05$ and $-0.01$ respectively), although the precision of edge detection was significantly higher than that of videodensitometry (standard deviations 0.47 and.0.64 $mm^2$ for edge detection and videodensitometry respectively, $p = 0.023$). After balloon dilatation, the agreement between orthogonal measurements decreased for both videodensitometry and edge detection. The mean difference between orthogonal values was $-0.15 \pm 1.43$ $mm^2$ and $-0.56 \pm 1.53$ $mm^2$ for videodensitometry and edge detection respectively ($p < 0.05$). To investigate the contribution of vessel dissection to the observed loss of agreement between orthogonal measurements, the same analysis was applied separately to vessels with and without dissection (Fig. 6). No significant difference in the mean value or the standard deviation of the difference between orthogonal values was found between groups. Finally, at follow-up, the difference between orthogonal views was $0.17 \pm 1.16$ $mm^2$ and $-0.15 \pm 0.97$ $mm^2$ for videodensitometry and edge detection respectively. No significant difference in the precision of these measurements was found.

These results show that the agreement between single orthogonal measurements deteriorates significantly after balloon dilatation using either of the two techniques considered. Observations similar to ours have previously been attributed to the effect of histopathological changes secondary to the intervention on angiographic accuracy [5, 7, 8, 10, 54]. These include tearing of the intima and atherosclerotic plaque, dehiscence of plaque from the tunic media, and variable degrees of medial and adventitia disruption are known to be common after balloon dilatation [35].

We also investigated whether the presence of angiographically evident dissection was responsible for the increased variability between orthogonal measurements observed after balloon angioplasty. Figure 6 shows that a similar trend was observed in vessels with and without dissection. This suggest that lesser or occult changes in vessel morphology probably accounted for the loss of accuracy of quantitative angiography after balloon dilatation. At least two kinds of luminal changes may account for this phenomenon. First, the presence of intraluminal flaps and irregularities not actually identified angiographically but present after balloon dilatation, as reported in angioscopic [38, 55, 56], ultrasound [40, 56, 57] and pathological studies [40].

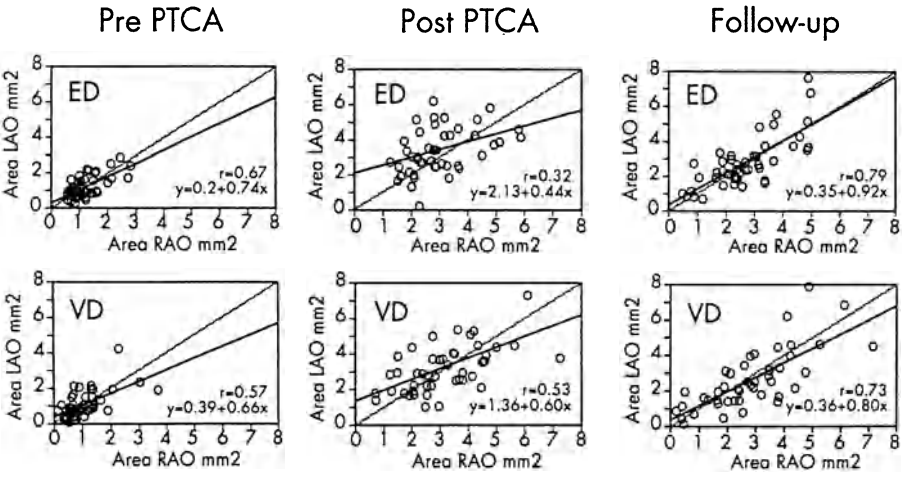


*Figure 4.* Correlation between minimal cross-sectional area measurements ($mm^2$) obtained in two orthogonal projections. The results obtained with automated edge detection and videodensitometric analysis are shown separately at the different stages of the study. Reprinted with permission from the American Heart Journal [65].

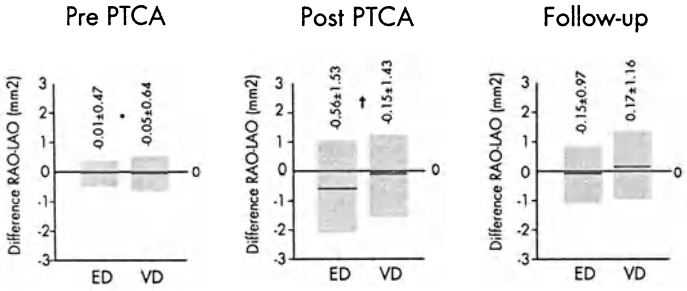


*Figure 5.* Differences between minimal cross-sectional area measurements ($mm^2$) obtained in two orthogonal projections with automated edge detection and videodensitometric analysis. All differences are plotted against the average of each pair of orthogonal readings. The mean difference is shown as a dotted line. The standard deviation is shown as a shadowed area. Reprinted with permission from the American Heart Journal [65].

When opacified during angiography, these irregularities may be wrongly identified as true luminal borders by edge detection algorithms, leading to a false estimation of luminal diameter. Secondly, the change to non-circular lumen geometry secondary to balloon dilatation [35]. Pathological studies have shown that slit-like or very irregular lumens are rarely seen in native vessels with non-complicated atherosclerotic plaques [34]. This fact may explain the excellent agreement between orthogonal measurements obtained with both edge detection and videodensitometry in a in vitro study using human coronary stenosis [51].

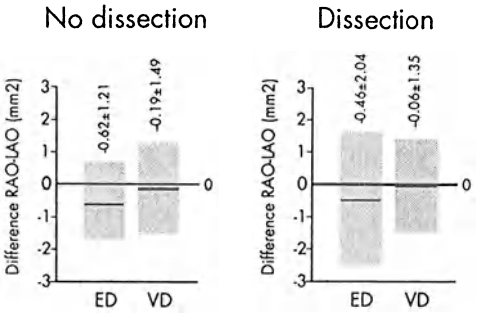


*Figure 6.* Differences between minimal cross-sectional area measurements ($mm^2$) obtained in two orthogonal projections immediately after balloon dilatation. The results obtained with automated edge detection and videodensitometric analysis are shown separately, as well as those cases with (+) and without (o) angiographically detectable dissection. All differences are plotted against the average of each pair of orthogonal readings. The mean difference is shown as a dotted line. The standard deviation is shown as a shadowed area. Reprinted with permission from the American Heart Journal [65].

Although the results shown suggest that the use of a single angiographic view for reliable quantitative analysis is precluded by the overall variability in orthogonal measurements, it can be observed that videodensitometry was less influenced by balloon dilatation than was edge detection. This observation may be related to the discussed theoretical independence from lumen morphology and to its relative insensitivity to imprecise border positioning [58]. Although its application may be currently hampered by the technical limitations discussed above, further progress to their solution may lead to a satisfactory application of the technique. In this direction, and as reported in a different chapter of this book, some of the modifications introduced in recent versions of videodensitometric algorithms show promising results (Chapter 3, J. Haase).

## Videodensitometry: an alternative or a complement of geometric analysis?

In a different chapter of this book (Chapter 3, J. Haase) we reported on the superiority of videodensitometry on edge detection in the assessment of very small lumina, while the opposite occurred in large vessels. Previous work has suggested that videodensitometry and edge detection have complementary advantages in measuring stented vessels [54, 59]. The question arises as to whether videodensitometry and edge detection constitute alternative methods of quantification of coronary dimensions or on the contrary constitute complementary techniques that can be harmonically integrated in a combined angiographic assessment.

We believe that the use of such combined analysis can offer valuable information, derived from the fact that both modalities of quantitative angio-

graphy use different principles in the calculation of luminal area. It has been discussed above that the pathological changes associated with intervention are likely to result in a loss of the circular luminal morphology of the treated vascular segment. It could be hypothesized, therefore, that the discrepancies between measurements obtained with edge detection (which represents the "ideal" or "expected" luminal area) and videodensitometry (which represents the "true" or "actual" luminal area) may be, in some way, related to the occurrence vessel wall disruption.

In a previous work from our group [54] coronary stenting with a mesh device was found to decrease the discrepancy between edge detection and videodensitometry found after balloon dilatation. This observation could be explained on the basis that coronary stenting produces a scaffolding effect on the disrupted vessel wall and restores circular lumen morphology. Discrepancies between edge detection and videodensitometry can be observed after stenting in areas where the scaffolding effect is not complete. Figure 7 shows the angiographic appearance of a vessel immediately after the deployment of a Palmar-Schatz stent. Although edge detection analysis suggest a complete absence of luminal narrowing, a clear discrepancy between edge detection and videodensitometric dimensions at the point where the two stent subunits are linked by a single strut is evident. Coronary angioscopy revealed that this mismatch was due to the protrusion of disrupted vessel wall in the area where the stent failed to provide complete scaffolding.

Using quantitative angiographic data obtained in 593 patients (710 lesions) from a multicenter study for pharmacological prevention of restenosis [60], we have found that the discrepancy between videodensitometric and geometrically derived areas increased dramatically after percutaneous intervention. Videodensitometry and edge detection analysis was performed in 4329 angiographic frames, corresponding to 1443 angiographic angulations obtained before and after PTCA, and at follow-up. The discrepancy between the two techniques found immediately after the procedure ($0.74 \pm 0.67$ mm$^2$) was significantly higher than that observed before ($0.36 \pm 0.35$ mm$^2$) or at follow-up ($0.58 \pm 0.55$ mm$^2$) ($p = 0.0001$).

Interestingly, the observed mismatch also supports some of the current views on the impact of vessel wall injury caused by coronary intervention on the degree of subsequent luminal loss during follow up. A direct relationshiphas found in a experimental models between these two variables [61] has also been shown in angiographic studies [62–64]. We have also studied whether the discrepancies observed between videodensitometry and edge detection after balloon dilatation also bore a relation with the subsequent degree of luminal loss, which might support its use as a surrogate of vessel wall injury. This is illustrated in Fig. 8, where the mismatch observed immediately after balloon dilatation is correlated with the degree of subsequent loss, assessed by edge detection analysis.

A graphic explanation of these results can be found in Fig. 9. The presence of dissections resulting from plaque splits and the formation of an eccentric

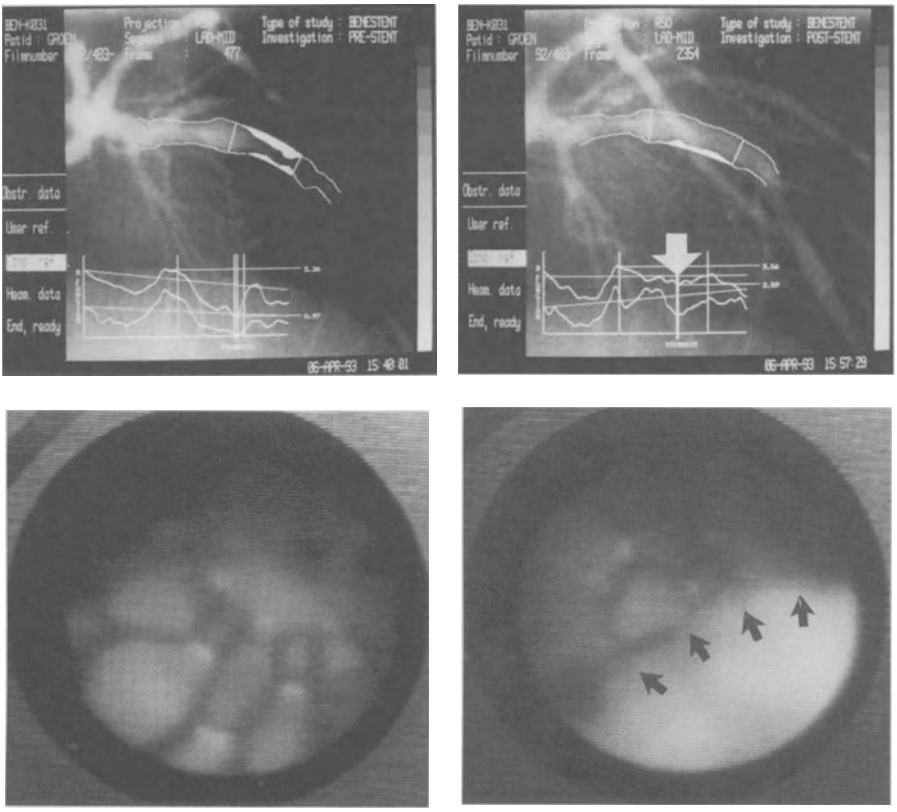


*Figure 7.* Combined quantitative analysis of a left anterior descending coronary artery lesion before and immediately after the deployment of a Palmar-Schatz stent. Prior to the procedure (A) the discrepancy between edge detection (upper diameter function curve) and videodensitometry-derived areas (lower curve) was 0.46 $mm^2$. Although after stent deployment (B) edge detection analysis suggests a complete absence of luminal narrowing, a threefold increase in the discrepancy between edge detection and videodensitometric dimensions is evident at the point where the two subunits of the stent are linked by a single strut (area discrepancy = 1.53 $mm^2$)(arrows). Coronary angioscopy revealed that although a regular circular lumen was achieved at the level of the proximal and distal (C) stent subunits a large flap of disrupted vessel wall (D, arrows) was present at the point where the stent articulation with a single strut failed to provide adequate scaffolding, corresponding with the discrepancy between edge detection and videodensitometric areas.

lumen are factors that contribute to a false appreciation of the results achieved by coronary intervention by using only the outmost opacified luminal edges. Pathological studies have shown how this component of luminal gain is invariably lost during the process of plaque healing. Figure 10A shows an intravascular ultrasound examination of a coronary segement immediately after balloon dilatation. A large circunferential dissection that allows opacification of the outmost recesses of the disected plaque yields a wrong

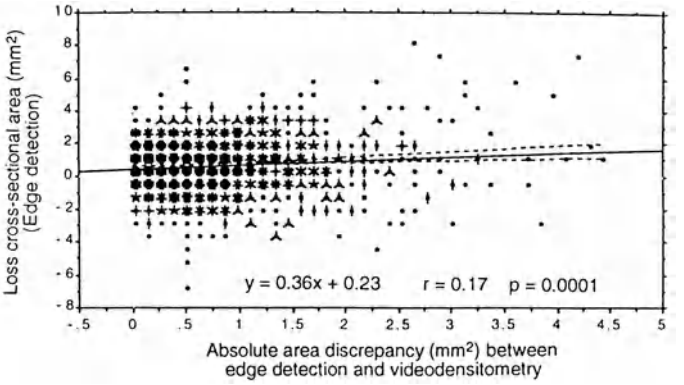


*Figure 8.* Regression analysis between the absolute discrepancy in luminal area measurements obtained with edge detection and videodensitometry after balloon dilatation and luminal loss developing at follow-up, calculated as the difference between minimal cross sectional area observed after angioplasty and at follow up.

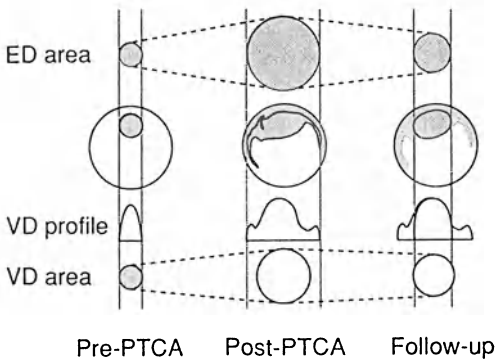


*Figure 9.* A graphic explanation of the pathological changes caused by coronary intervention that may account for the discrepancies between edge detection (ED) and videodensitometric (VD) area measurements. Prior to coronary intervention, the predominantly circular lumen yields a minor area discrepancy between both methods. However, after coronary intervention, the presence of dissections resulting from plaque splits and the formation of an eccentric lumen are factors that contribute to major discrepancies between luminal area measurements obtained by the two techniques, due to differences in the respective calculation methods (using the videodensitometric profile or assuming a circular cross-section). At follow-up, some of these features have dissappeared presumably as a consequence of the healing process, which restores a more circular morphology thus contributing to restoration of the agreement between edge detection and videodensitometric area measurements.

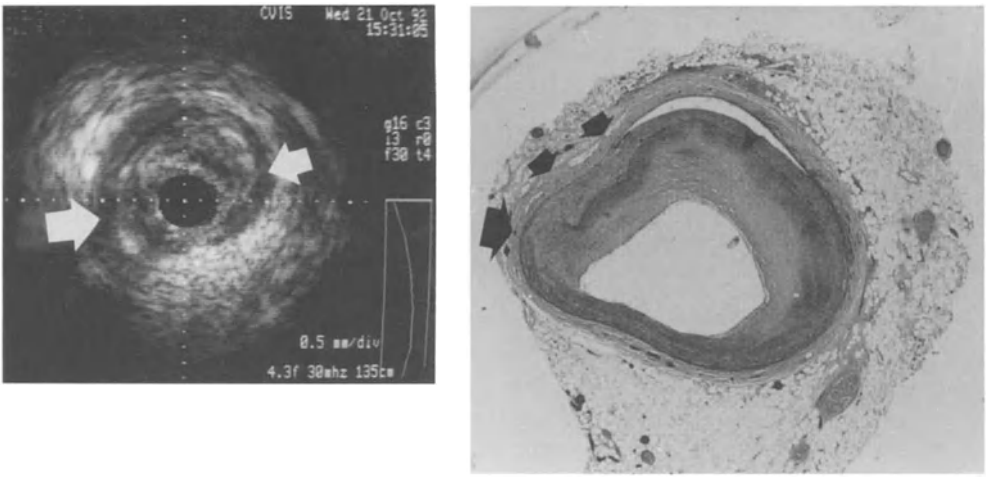


*Figure 10.* Circumferencial plaque dehiscence (white arrows) immediately after balloon dilatation as shown by intravascular ultrasound (10A). Opacification of the outmost borders of this dissection during angiography may lead to a wrong estimation of the true luminal area achieved by the procedure, which is still compromised by a large plaque in the lumen. Figure 10B illustrates how at follow-up such component of luminal gain has been lost due to the development of a relatively small volume of neointimal hyperplasia between the detached plaque and the arterial wall (black arrows) (patological specimen obtained in a patient with a previous coronary angioplasty diferent than that shown in 10A). The suboptimal result of angioplasy was not detected angiographically and the apparent but not actual loss of luminal dimensions during follow-up must be considered as *pseudorestenosis* rather than actual significant luminal narrowing.

estimate of lumen gain by edge detection and probably contitutes the substrate for its discrepancy with densitometric luminal area. On the long term, this type of dissections is filled by neointimal hyperplasia (Fig. 10B), leading to an overestimation of the actual luminal loss. It is foreseeable that such pitfalls in the detection of restenosis, or *pseudorestenosis*, will receive much attention in the near future as its correction will benefit the essay of different therapeutic approaches aimed to a preservation of the immediate results of angioplasty in the long term. In this regard, the combined use of videodensitometry and edge detection may constitute an alternative to more complex techniques of intracoronary imagig, such as intravascular ultrasound or angioscopy.

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*PART TWO: The QCA core laboratory: Practical lessons learned and application to clinical practice*

# 6. Post-angioplasty lesion measurement variability of the cardiovascular angiographic analysis system

DAVID P. FOLEY, JAAP DECKERS and PATRICK W. SERRUYS

## Introduction

Percutaneous transluminal coronary angioplasty is now a widely practised technique for coronary revascularization. Acute procedural success has been considerably improved by continuing development of adjunctive catheter and radiographic imaging technology so that approximately 95% of all lesions can be safely dilated without the consequential occurrence of major adverse per-procedural cardiac events [1, 2]. Restenosis, a fibroproliferative hyperplasic healing response to arterial wall injury imparted during intervention, continues to represent the most significant obstacle to maintained long term success after coronary balloon angioplasty, and has rightfully been called the Achilles' heel of the percutaneous approach to revascularization [3].

Multiple clinical studies of various prospective pharmaco-biological agents and alternative revascularization devices have already been completed with no effective approach for prevention or control of the restenosis process clearly emerging from the morass of data already accumulated [4–7]. Many further clinical studies are, thus, in the planning, recruitment, randomization or analytical stages. The approach to analysis and presentation of results of these studies has varied widely over the years with different clinical, physiological/functional or anatomic/angiographic end-points being employed [6, 8–10]. There is now a consensus that complete angiographic follow-up is required in clinical studies to assess the development of coronary luminal renarrowing in the months after intervention, since the sensitivity and specificity of clinical evaluation and non-invasive functional investigations are known to be give incomplete, ambiguous and unsatisfactory results [8, 9, 11–14]. Despite its shortcomings, angiography is the only widely available, objective and reproducible method by which to evaluate the outcome of interventions. Furthermore, quantitative computer assisted analytical techniques are now considered the gold standard for accurate and precise measurement of luminal dimensions recorded by the cine-angiogram [15–20]. Digital subtraction angiography provides high quality images for on-line



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analysis by recently adapted quantitative angiographic computer software packages [21, 22]. Developments in the approach to description of the angiographic immediate and long term outcome of percutaneous revascularization have been evolving at a rate complementary with these technological advances [14, 23, 24]. There is now a substantial body of opinion which holds that a continuous approach to presentation of the immediate and long term results of intervention is more meaningful and realistic than the traditional categorical approach of "restenosis rate" [6, 14, 20, 231. Furthermore, there is corroboratory evidence from a number of groups suggesting that the degree of long term luminal renarrowing during follow up after successful intervention is directly proportional to the degree of initial angiographic luminal improvement achieved at intervention [23–27]. This relationship is remarkably similar to the wall injury/intimal hyperplasia relationship which has been demonstrated in experimental studies [28].

The potential for lesion measurement inaccuracy due to the use of percent diameter stenosis has been highlighted by our group in the past and we have advocated the application of absolute luminal measurements [14, 15, 29]. Post-mortem [30, 31] and in vivo intravascular ultrasound [32] studies have confirmed that an arbitrarily selected "normal" or "reference" segment is frequently diseased and narrowed or ectatic, so that angiographic percent diameter stenosis values may significantly under- or over- estimate the degree of luminal obstruction. It is becoming more widely accepted that the use of absolute luminal measurements is thus more objective and reproducible than% diameter stenosis for the purposes of clinical interventional studies [9, 14].

The evolving spectacle of the "Achilles' Heel" of restenosis indicates that great care and attention must be paid to the accurate and precise measurement of coronary luminal dimensions, in the context of "restenosis prevention studies". This is particularly important post-intervention, when intimal dissection is only appreciated by angiography in one third of cases [33], whereas IVUS [34–37] and angioscopy [38] reveal its occurrence in the majority. In addition, the angiographic luminal contour post-PTCA is often described as being hazy and indistinct and the presence of intraluminal thrombus is sometimes noted. These features may interfere with accurate luminal measurement from the coronary angiogram, leading to misrepresentation of the true dimensions [39]. For these reasons the accuracy and precision of post-PTCA luminal measurements using the CAAS system has been called into question [39]. Since the initial studies investigating the short, medium and long term variability of this computer-based analysis system [40] were carried out in 1985, in larger coronary vessels and under different angiographic conditions than are routinely applied today [41, 42] and did not investigate the post-angioplasty measurement variability, the objective of this study was therefore to provide this information.

## Methods

### *Patients*

The study population was made up of 106 patients who underwent coronary angiography before, immediately after and 24 hr after coronary balloon angioplasty.

As shown in Table 1, the patient population is demographically representative of modern clinical experience with coronary balloon angioplasty. All patients had symptomatic obstructive coronary artery disease of one or more vessels, which was deemed suitable for treatment by PTCA. Full written informed consent was obtained by each patient prior to study entry. The PTCA procedure was carried out according to the routine practice of the individual interventionalist.

### *Special features of the study*

The particular precautions taken in this study which facilitate the investigation of the post-PTCA lesion measurement variability of the CAAS system were:

1. Performance of coronary arteriography in exactly the same projections post-angioplasty and at 24 hr ("multiple matched projections"),
2. Optimal vasomotion control pre-angiography using intracoronary bolus injections of isosorbide dinitrate or glycerol trinitrate,
3. Each patient was fully anticoagulated until after the 24 hr angiogram, so that any luminal changes occurring during the 24 hr period would be unlikely to be due to intracoronary thrombus formation and thus attributable to a morphological change.

### *Coronary angiographic procedures to facilitate qantitative analysis*

Angiograms were carefully recorded with the requirements of the computer analysis system in mind ie. avoidance of projections in which the spine or other structures, or closely parallel or overlapping side-branches, obscure the vessel segment of interest; filming of the lesion and segment of interest as close to field centre as possible, and in at least 2, preferably orthogonal, projections for the right coronary artery, and at least three projections for the left coronary artery, ideally at the end of a full inspiration; optimal contrast opacification of the coronary arteries for at least 3 complete cardiac cycles; optimal kilovoltage adjustment to avoid overexposure of the cinefilm; removal of guidewire and balloon catheter for the final post-PTCA angiogram; appropriate use of the metal indicators provided by the core laboratory to identify the administration (and timing) of various relevant medications (especially intracoronary nitrate); to enable accurate calibration, the contrast-empty angiographic catheter [43] (at least 7 french) is filmed prior to

*Table 1.* Patient demographics.

| | |
|---|---|
| *Clinical features*: | |
| Age | 58 (35–74) |
| Males | 83 (78%) |
| Previous MI | 39 (37%) |
| Diabetes mellitus | 5 (5%) |
| Hypertension | 32 (30%) |
| Current smokers | 25 (24%) |
| *Angiographic coronary disease pattern*: | |
| Single vessel disease | 87 (82%) |
| Two vessel disease | 17 (16%) |
| Triple vessel disease | 2 (2%) |
| *CCS functional classification*: | |
| I or II | 59 (56%) |
| III or IV | 47 (44%) |
| *Medication*: | |
| *Long acting nitrates* | 51 (48%) |
| Betablockers | 80 (75%) |
| Calcium antagonists | 72 (68%) |
| Acetyl salicylic acid | 88 (83%) |
| *Angiographic location of dilated segments*: | |
| Left anterior descending | 42 (40%) |
| Circumflex | 32 (30%) |
| Right coronary artery | 31 (29%) |
| Left main stem | 1 (1%) |

each contrast injection (ideally, but not necessarily, in the centre of the fluoroscopic field), and after the procedure, the distal 20 cm of each catheter used is severed and enclosed with the angiogram for micrometric measurement by the core laboratory.

In the core laboratory, angiographic analysis is carried out by independent analysts without any knowledge of clinical details on end-diastolic cine-frames selected for analysis by 2 experienced blinded cardiologists.

Comprehensive quantitative analysis is carried out on all angiograms, including minimal, mean and maximal luminal diameter, interpolated reference diameter, lesion length, plaque area, lesion symmetry, percent diameter stenosis and other measurements not employed in this study, viz. lesion entrance and exit angles, theoretical poiseuille and turbulence resistance, theoretical transstenotic pressure gradient, segment roughness. In addition videodensitometric measurements of minimal luminal cross sectional area, reference area and area stenosis are provided.

The theoretical basis of and methodological approaches to both the geometric and videodensitometric analyses has been extensively described in previous publications from our group [19, 40, 44].

**Statistical analysis**

Statistical analysis was carried out with the help of a standard commercially available statistical software package (BMDP, Berkely California). Quantitatively measured and derived values are given as mean ± standard deviation. Paired Student's t-tests are used to determine differences between angiographic measurements post-PTCA and at 24 hr and Pearson's product moment correlation coefficient is used to describe the correlation between these measurements. Accuracy and precision of measurements obtained from the immediately post-PTCA angiogram are defined according to the method suggested by Bland and Altman [45] i.e. the accuracy is the mean difference between the measurement immediately post-PTCA and that at 24 hr and the precision (or measurement variability) is the standard deviation of this mean difference, using the 24 hr measurement as the standard against which to compare the measurements obtained immediately post-PTCA.

Cumulative frequency curves are used to display the distribution of the angiographic measurements post-PTCA and at 24 hr.

**Results**

Among the 106 patients who underwent successful balloon dilatation and quantitative angiographic evaluation both post-PTCA and at 24 hr, the average reference vessel diameter (interpolated reference diameter was 2.67 mm pre-PTCA, the mean minimal luminal diameter was 1.03 mm and mean percent diameter stenosis 61%. Videodensitometry revealed the average reference area to be 5.95 $mm^2$, with a minimal cross sectional area of 0.92 $mm^2$ and an area stenosis of 85% (Table 2).

Balloon angioplasty effected an increase in minimal luminal diameter and cross sectional area to 1.72 mm and 2.57 $mm^2$ respectively, with a concomitant decrease in% diameter stenosis and area stenosis to 36% and 58% respectively. The dilatation process also caused a significant increase in measured reference diameter to 2.72 mm ($p < .01$) and in the reference area to 6.10($mm^2$) ($p = 0.04$).

No significant change was observed in minimal luminal diameter (Fig. 1b) or in minimal luminal cross sectional area (Fig. 1b) from post angioplasty to 24 hr (Table 2). Both reference diameter (Fig. 2a) and reference area (Fig. 2b) increased significantly during the 24 hr period, from 2.72 to 2.83 mm ($p < .0001$) and 6.1 to 6.61 $mm^2$ ($p < .0001$) respectively. Due to the increase in reference diameter, a significant increase was also observed in percent diameter stenosis (Fig. 3a), from 36% post angioplasty to 39% at 24 hr ($p = .0005$). The increase in reference diameter was also responsible for the observed increase in plaque area from 4.30 $mm^2$ to 4.92 $mm^2$ ($p < .0001$) (Table 2). Despite the significant increase in reference area, percent area

*Table 2.* Quantitative angiographic measurements pre, post and at 24 hr (means of multiple matched projections) given as mean ± sd.

| Pre | Post | 24hr | Mean diff. 24 hr - post. (paired student's t) | p Value of mean diff. | |
|---|---|---|---|---|---|
| Minimal luminal diameter (mm) | 1.03 ± .40 | 1.72 ± .36 | 1.72 ± .39 | 0.007 ± 0.20 | 0.74 |
| Minimal luminal cross sectional area ($mm^2$) | 0.92 ± .85 | 2.57 ± 1.51 | 2.64 ± 1.53 | 0.07 ± .85 | 0.42 |
| Percent area stenosis (%) | 84.9 ± 10.3 | 57.9 ± 12.8 | 59.8 ± 14.1 | 1.9 ± 14.1 | 0.17 |
| Lesion length (mm) | 5.91 ± 1.95 | 5.71 ± 1.78 | 5.75 ± 1.79 | 0.05 ± 1.3 | 0.72 |
| Lesion symmetry (ratio) | 0.57 ± 0.20 | 0.50 ± 0.20 | 0.49 ± 0.18 | −0.02 ± 0.20 | 0.37 |
| Vessel size (interpolated reference diameter)(mm) | 2.67 ± .64 | 2.72 ± .58 | 2.83 ± .59 | 0.11 ± 0.18 | < .0001 |
| Percent diameter stenosis (%) | 60.6 ± 12.9 | 36.3 ± 7.9 | 38.7 ± 8.7 | 2.4 ± 7.0 | .0005 |
| Reference area ($mm^2$) | 5.95 ± 3.02 | 6.10 ± 2.73 | 6.61 ± 2.93 | 0.51 ± .84 | < .0001 |
| Plaque area ($mm^2$) | 6.40 ± 3.39 | 4.30 ± 2.35 | 4.92 ± 2.82 | 0.62 ± 1.48 | < .0001 |

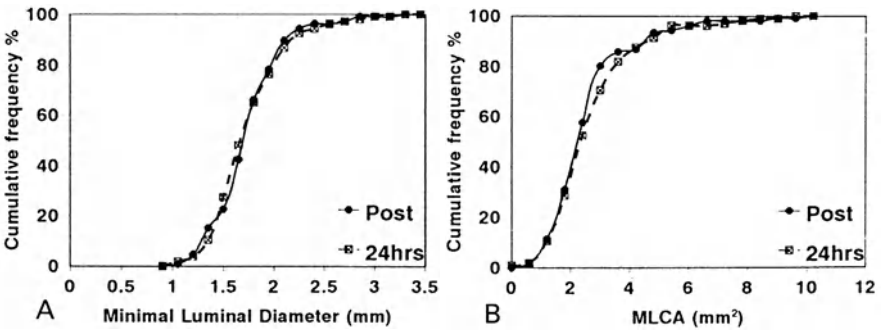


*Figure 1.* Cumulative distribution curves showing minimal luminal diameter (1a) and minimal luminal cross sectional area (1b) post aangioplasty and at 24 hr. It is clear that no significant difference exists between the curves.

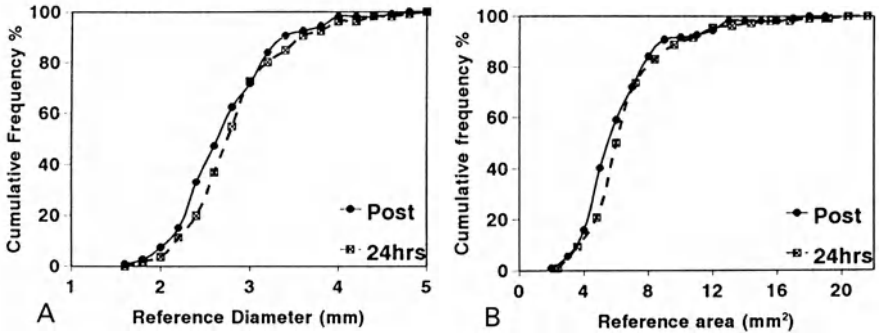


*Figure 2.* Reference diameter and area measurements post angioplasty and at 24 hr displayed as cumulative distribution curves. Clearly significant increase from post to 24 hr is evident for both paramaters (Table 2).

stenosis (Fig. 3b) did not change significantly during the 24 hr period (Table 2), nor did lesion length or lesion symmetry.

The accuracy of minimal luminal diameter measurement post angioplasty by the CAAS system was, thus, 0.007 mm and the precision ±0.20 mm (Table 3). Similarly, the accuracy and precision of reference diameter measurement were 0.11 mm and ±0.18 mm respectively. Minimal luminal cross sectional area was measured with an accuracy of .07 $mm^2$ and a precision of ±0.85 $mm^2$.

Considering quantitative measurements obtained from each individual projection post-PTCA and at 24 hr as separate measurements, there were a total of 308 matched views analyzed in the 106 patients (Table 4). The sub-segmental site of the lesion did not vary from post to 24 hr. As with the mean overall findings, there was no significant difference in minimal luminal diameter, minimal luminal cross sectional area, lesion length or symmetry

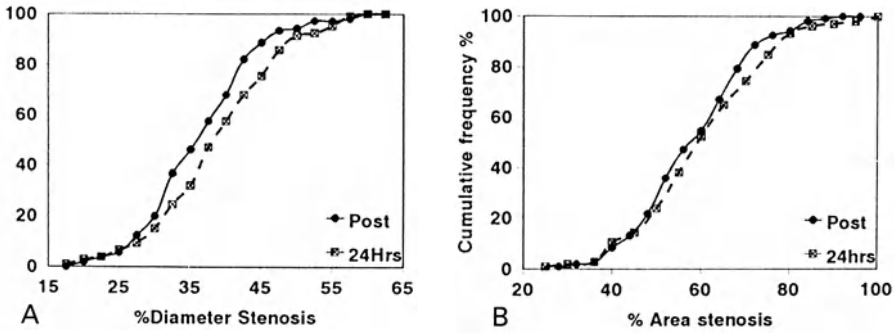


*Figure 3.* Cumulative distribution of percent diameter stenosis (2a) and percent area stenosis (2b) post angioplasty and at 24 hr. A significant increase in percent diameter stenosis is evident (Table 2) and a minor, insignificant increase in percent area stenosis.

*Table 3.* Accuracy and precision of luminal diameter measurements post angioplasty compared with 24 hr

| | Accuracy | Precision |
|---|---|---|
| Minimal luminal diameter (mm) | 0.007 | ±0.20 |
| Minimal luminal cross sectional area ($mm^2$) | 0.07 | ±0.85 |
| Reference diamater (mm) | 0.11 | ±0.18 |
| Reference area ($mm^2$) | 0.51 | ±0.84 |
| Percent diameter stenosis | 2.4% | 7% |
| Percent area stenosis | 1.9% | 14% |

*Table 4.* Quantitative angiographic measurements from individual matched projections post and at 24 hr (given as mean ± sd)

| | Post | 24 hr | Mean diff. (24 hr - post) | p Value of mean diff. |
|---|---|---|---|---|
| Lesion site (subsegment 1–6) | 2.44 ± 1.1 | 2.43 ± 1.2 | −0.01 ± .73 | 0.75 |
| Minimal luminal diameter (mm) | 1.70 ± .40 | 1.71 ± .41 | 0.008 ± 0.27 | 0.60 |
| Minimal luminal cross sectional area ($mm^2$) | 2.45 ± 1.63 | 2.50 ± 1.63 | 0.05 ± 1.3 | 0.50 |
| Percent area stenosis (%) | 59.0 ± 18.4 | 61.3 ± 19.6 | 2.2 ± 21.2 | 0.07 |
| Lesion length (mm) | 5.72 ± 2.35 | 5.81 ± 2.42 | 0.09 ± 2.07 | 0.45 |
| Lesion symmetry (ratio) | 0.50 ± 0.27 | 0.49 ± 0.26 | 0.01 ± 0.31 | 0.70 |
| Vessel size (interpolated reference diameter)(mm) | 2.70 ± .60 | 2.82 ± .59 | 0.12 ± 0.29 | < .0001 |
| Reference area ($mm^2$) | 6.01 ± 2.81 | 6.55 ± 2.95 | 0.54 ± 1.35 | < .0001 |
| Percent diameter stenosis (%) | 36.5 ± 10.4 | 39.0 ± 11.0 | 2.5 ± 10.0 | < .0001 |
| Plaque area ($mm^2$) | 4.29 ± 2.92 | 4.91 ± 3.55 | 0.62 ± 2.49 | < .0001 |

from post-PTCA to 24 hr angiography. Significant increase in reference diameter, reference area and percent diameter stenosis were observed, as well as a trend toward an increase in area stenosis, in agreement with the mean overall results.

## Discussion

The increasing use of intravascular ultrasound devices and coronary angioscopy has provided incontrovertible evidence that the coronary angiogram provides incomplete and frequently inaccurate and misleading information regarding coronary anatamo-pathology, most particularly in the context of diffuse multivessel atheromatous disease, as well as post angioplasty [32, 34, 35, 38]. Although percutaneous revascularization procedures are being increasingly applied to more complex clinical syndromes, the vast majority of balloon angioplasty procedures are still carried out for predominantly

single lesion disease [41,42]. Despite its limitations, contrast angiography is still the only universally available coronary imaging modality for clinical practice and indeed for large multicentre clinical studies [9]. Computer assisted quantitative analysis of angiographic images has provided an objective and reproducible approach to measurement of luminal obstructions and has properly replaced visual and user dependent techniques [16, 18, 46, 47]]. However the angiogram recorded immediately after balloon angioplasty presents theoretical and practical analytical difficulties due to the inherent mechanical properties and operational characteristics of the procedure with the creation of intimal tears and dissections of varying size, ranging from the angiographically indistinguishable, to the appearance of a false lumen distinct from and often obstructing the true lumen. Contour haziness, luminal irregularities and filling defects and the creation of eccentric asymmetrical lumen shapes may circumvent accurate measurements of luminal dimensions by the two dimensional angiogram [48]. Nevertheless, these difficulties may be at least partly adjusted for by using "multiple matched view angiography" to create a three dimensional impression of the coronary lumen [19, 49].

These characteristic features of the immediately-post PTCA angiogram have raised the question of the accuracy and reliability of quantitative angiographic measurements immediately after balloon angioplasty [39]. In this study we have addressed this problem by carrying out repeat angiography in multiple matched projections 24 hr after angioplasty, as well as immediately afterwards. We have attempted to perform the study under ideal angiographic conditions with a fixed angiographic table and repetition of exactly the same angiographic projections for each individual patient at 24 hr as carried out immediately post-PTCA, and to avoid the potentially confounding influence of vasomotion and thrombosis, intracoronary nitrate was administered pre-angiography and all patients were fully anticoagulated for the 24 hr period.

Regardless of whether either the mean of the multiple matched projections (as in standard clinical practice), or by considering each projection as a separate measurement, no change in minimal luminal diameter (measured by an edge detection approach), or in minimal luminal cross sectional area (measured by videodensitometry), was detected from immediately post balloon angioplasty to 24 hr later. Thus, the post balloon angioplasty lesion measurement accuracy of the CAAS system is less than 0.01 mm and the variability is $\pm 0.2$ mm, which in our estimation, is eminently acceptable. Twice this lesion measurement variability ($\pm 0.4$ mm) identifies, with 95% confidence, patients, or lesions, in whom a real, detectable ("significant") luminal decrease (or increase) occurs over time, and three times the variability ($\pm 0.6$ mm) will provide 99% confidence for the detection of a real change in luminal dimensions. While we do not advocate the application of a categorical approach to evaluation of the long term angiographic outcome of interventions, it may occasionally be desirable to stratify patients, or lesions, according to the degree of luminal change developing over time. To

this end, we suggest the application of the type of objective approach employed here, but not the actual measurement itself i.e. the use of lesion measurement variability of the particular measurement system involved, as the stratification method. The measurement variability may vary from system to system, and is a vital piece of information necessary for evaluation of measurement precision, for the purpose of objective comparison of the results of intervention trials employing different angiographic measurement systems.

The measurement variability observed in this study is considerably different from that previously found in patients undergoing diagnostic coronary angiography a mean of 90 days apart, without therapeutic intervention [40]. The reasons for this difference are many : in the original study published in 1985, mean vessel size was 3.7 mm, compared with 2.7 mm in this study, and the former study was performed under a self-proclaimed "worst-case scenario" i.e. unmatched angiographic projections, no particular care taken in recording angiograms suitable for quantitative analysis, no vasomotor control etc., whereas the current study was carried out under ideal angiographic conditions, as outlined previously. Since such procedures are nowadays routinely performed in all angiographic studies in which our core laboratory is involved [41, 42], the former study is now of historical and development interest only and the actual lesion measurement variability reported is no longer relevant. It is interesting to note that the medium term variability previously reported was 0.20 mm [40], exactly the same as found in this study. In the previous investigation, the medium term variability was investigated using vasomotion control and matched angiographic projections 1 hr after the index angiogram, which may explain the concurrence. It is also noteworthy that recent investigations of the accuracy and precision of off-line and on-line quantitative angiographic analysis (using insertion of intracoronary stenosis phantoms in a porcine model), revealed the CAAS system, used off-line, to have an average stenosis measurement accuracy of $-0.07$ mm and a precision of $\pm 0.21$ mm (measured dimension of the phantom stenoses versus actual phantom dimension) [22]. These findings are collectively indicative of the high level of accuracy and precision of minimal luminal diameter measurement by the CAAS system even in the aftermath of balloon angioplasty.

The significant increase in the interpolated reference diameter is responsible for the observed increase in measured percent diameter stenosis, which confirms previous reports from our group [29] and reiterates the potential for inaccuracy and misinformation by preferential use of this approach to the description of the severity of luminal obstructions. In addition the increase in plaque area (cross sectional area in $mm^2$) is due to the reference diameter increase since plaque area is calculated by the CAAS computer from the detected vessel contours and the diameter function curve (interpolated reference diameter). Plaque volume in $mm^3$ would be a more useful measurement but current technology cannot as yet provide this type of information. Technological improvements in the latest quantitative analysis systems may facili-

tate measurement of luminal volume over a coronary arterial segment using videodensitometry, but validation studies have yet to be performed.

It is interesting that although the cross sectional reference area (calculated by videodensitometry) increases significantly from post-PTCA to 24 hr, the increase in cross sectional percent area stenosis (1.9%), is not statistically significant. This is probably due to the minor (but statistically not significant) concomitant increase in minimal luminal cross sectional area (0.07 $mm^2$). The explanation for the increase in reference vessel dimensions (diameter and cross sectional area) may be greater effectiveness of intracoronary vasomotion control by the same dose of nitrate at 24 hr, relative to immediately post angioplasty, on the "normal" or relatively disease-free vessel segment. The vasoconstrictive stimulus caused by the dilatation procedure and the release of vasoactive substances from the damaged endothelium and platelets may prevent the immediate realisation of increase in dimension of relatively undiseased vessel adjacent to the target lesion.

## Limitations

The patients selected in this study may be considered, by some interventionalists, to be unrepresentative of routine clinical practice in many institutions, since patients with mainly single lesion single vessel disease were included. However, it must be remembered that this remains the only proven indication for coronary balloon angioplasty and that more than 80% of patients recruited in 2 recent major multicentre restenosis prevention trials had similar coronary disease patterns [41, 42].

Ultimately, comparison of quantitative angiographic with intravascular ultrasound findings post angioplasty would be the ideal test of accuracy and precision. Nevertheless, it must be recognised that intravascular ultrasound, for all its apparent advantages over quantitative angiography, cannot, as yet, be usefully applied to the evaluation of severe stenoses, or in extremely tortuous or small vessels, which makes complete pre-interventional assessment impossible in a considerable proportion of lesions treated in daily practice [34–37]. In addition IVUS is itself dependent on the acquisition of "good" quality images which may not be obtainable in certain clinical situations such as the presence of large intimal disruptions after angioplasty [50], and in the absence of an automated assessment system, is subject to varying degrees of inter-observer and intraobserver variability for various qualitative and quantitative morphological features [36, 37]. Until the images provided by intravascular ultrasound can be more clearly interpreted and the vessel wall and lumen areas are more objectively and reproducibly quantifiable, quantitative angiography must still be considered as the "gold standard".

## Final conclusions

The accuracy and precision of the post-PTCA angiogram, relative to angiography carried out 24 hr later are found to be eminently acceptable. Post balloon angioplasty lesion measurement variability of the CAAS system is found to be ±0.2 mm. Due to the observed potential for changes in dimensions of the reference segment, the use of percent diameter (or area) stenosis measurements, in important clinical studies, is discouraged and absolute luminal diameter (or area) measurements are recommended.

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# 7. Methodological problems with the quantitative angiographic assessment of elastic recoil, stretch and balloon-artery ratio

WALTER R.M. HERMANS, BENNO J. RENSING and PATRICK W. SERRUYS

## Introduction

Percutaneous transluminal coronary angioplasty (PTCA) is an accepted revascularization procedure for treatment of patients with stable and unstable angina pectoris and for patients with single and multi-vessel disease [1, 2]. Although earlier work has drawn attention to the process of in vivo inflation of the balloon, in vivo pressure-volume relationship [3] and in vivo pressure-diameter curves [4], the quantitative analysis of the inflated balloon at the site of the stenotic lesion has not been emphasized. Visual inspection of the inflated balloon led to the assumption that, with the use of a pressure as high as 20 atm, the balloon is fully and uniformly inflated to a diameter in accordance with the manufacturer's specification. With the introduction of computer-based quantitative analysis systems – edge detection and videodensitometry – it became possible to measure the exact diameter and area of normal and stenotic arterial segments pre- and post-PTCA as well as the balloon diameter during full inflation. However, conflicting data has been published about the correlation of post-angioplasty analysis between the two techniques [5–20]. The inflated balloon has important clinical implications since it affects the extent of 1) stretch (theoretical maximal gain in diameter or area during PTCA), 2) elastic recoil (influence the immediate post-PTCA result) [4, 21, 22] and 3) under- or over-sizing of the lesion (important factor in the incidence of dissections) [23–26]. In the assessment of these three parameters, the inflated balloon is used as scaling device and is presumed uniform along its entire length. However, this assumption has never been critically analyzed.

The objective of this study was to determine (using 2 quantitative methods) whether the balloon diameter is uniform along its entire length. In the event of non-uniformity of the inflated balloon, guidelines will be proposed for the selection of the balloon diameter for future quantitative studies.



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## Materials and methods

### *Study population and PTCA procedure*

The study population consisted of 453 patients (505 lesions) who had undergone a successful PTCA at the Thoraxcenter between June 1989 and December 1989, defined as a less than 50% diameter stenosis on visual inspection of the post-PTCA angiogram. Patients with stable and unstable angina were included; patients with acute myocardial infarction (<7 days) and patients with total occluded lesions pre-PTCA were excluded. Mean age of the patients was 56 ± 10 yr. Of the 505 lesions dilated, 146 were located in the right coronary artery (RCA), 238 in the left anterior descending (LAD) and 121 in the left circumflex artery (LC).

Medications at the time of the procedure were intravenous heparin and acetylsalicylic acid. Choice of balloon type (compliant vs non-compliant), inflation duration, total number of inflations and inflation pressure were left to the operator. Coronary angiograms were performed before and after angioplasty, and of the largest balloon size with the highest inflation pressure.

### *Quantitative coronary angiography*

The quantitative analysis of the stenotic coronary segments and the balloon at maximal inflation pressure was carried out by the Coronary Angiography Analysis System (CAAS) which has been validated and described in detail elsewhere [7, 12, 13]. Examples of analyses are shown in Fig. 1.

Single identical views pre-PTCA, post-PTCA and during balloon inflation were chosen for analysis. For this purpose, the largest balloon filled with contrast was filmed during the last inflation at maximum pressure. Contrast medium (Isopaque Cerebral 280 mg I/ml, Nycomed AS Oslo) that is routinely used for arteriography of the carotid arteries was selected for its high radiopacity, which enhances the automated edge detection and videodensitometric analysis. This contrast medium has a low-viscosity and therefore does not need to be diluted. Special attention was given to avoid air bubbles in the balloon when filling with contrast medium.

### *Edge detection*

Any area sized 6.9 × 6.9 mm in a select cine-frame (overall dimensions 18 × 24 mm) encompassing the desired arterial segment was digitized by a high-resolution CCD camera with a resolution of 512 × 512 pixels and 8 bits of gray level. Vessel and balloon contours are determined automatically based on the weighted sum of the first and second derivative functions applied to the digitized brightness information along scanlines perpendicular to the local centerline directions of an arterial segment or inflated balloon. A computer-derived estimation of the original arterial or inflated balloon di-

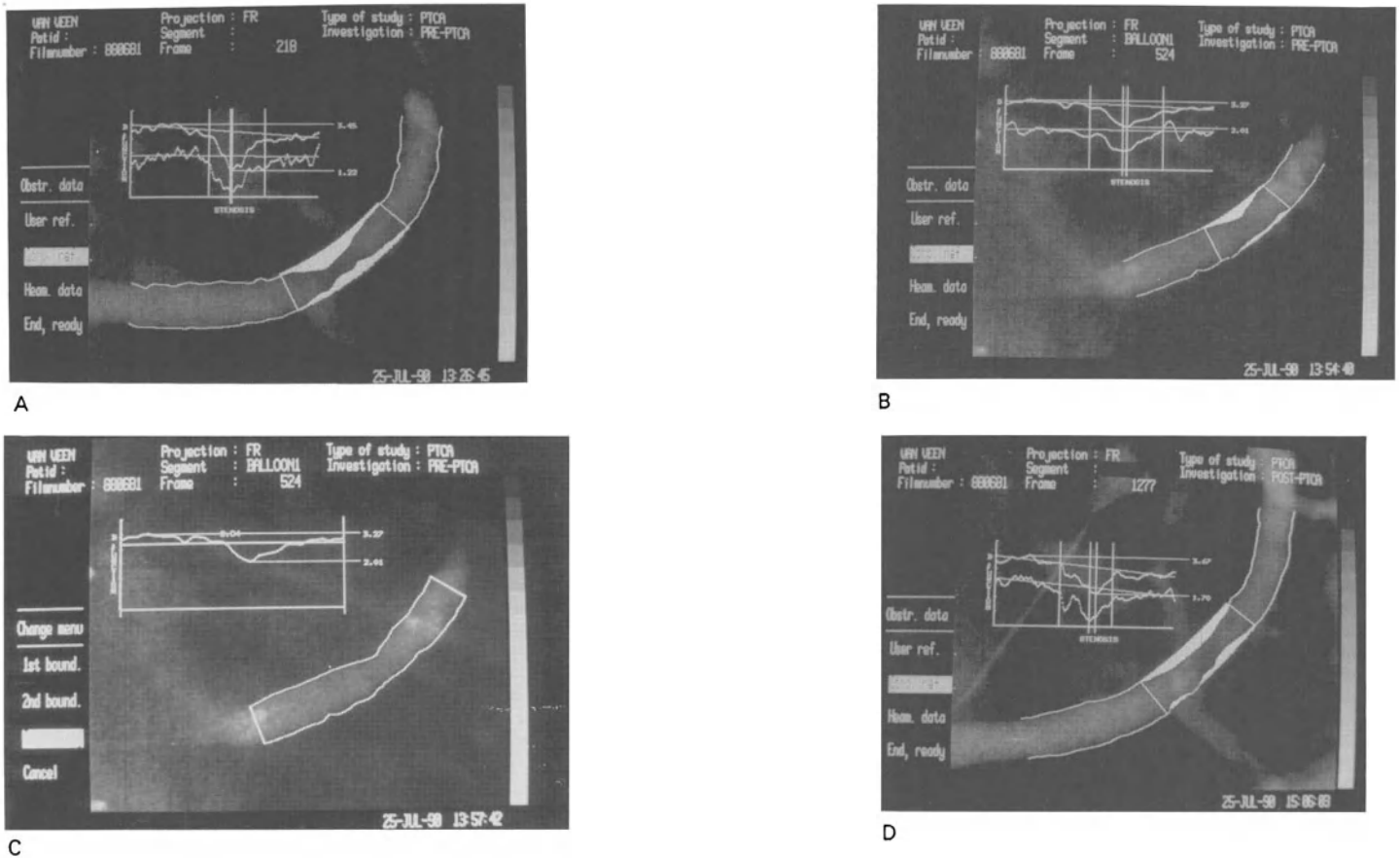


*Figure 1.* Single frame angiogram of a mid portion of a circumflex artery. Superimposed on the video image are the diameter function curve (measured by edge detection (upper curve)) and the area function curve (measured by videodensitometry (lower curve)) of the severity of the obstruction before and after balloon dilatation (A,D) as well as of the balloon during maximal inflation (B–C). The interpolated reference diameter line is computed from the contours proximal and distal of the lesion. The reference diameter value is taken at the point coincident with the point of maximal narrowing (white arrow). The white areas are a measure for the "atherosclerotic plaque". Figure 1B and 1C show the inflated balloon with an inflation pressure of 12 atmospheres. The computer measured a minimal balloon diameter of 2.01 mm, a mean diameter over the entire length of the balloon of 2.84, a maximal diameter of 3.27 and a reference diameter of 2.99 mm (value not shown in figure). The nominal size of this balloon was 3.25 mm and was inflated at a maximum pressure of 12 atmospheres. These figures clearly show the non-uniform inflation process.

ameter at the site of obstruction is used to define the interpolated reference diameter. This technique is based on a computer-derived estimation of the original diameter values over the analyzed region (assuming there was no disease present) according to the diameter function. The absolute minimal values as well as the reference diameter are measured by the computer, which uses the known contrast-empty guiding catheter diameter as scaling device. To achieve maximal vasodilatation, either nitroglycerin or isosorbide dinitrate was given intracoronary for each coronary artery involved pre-PTCA and post-PTCA [7]. All contour positions of the catheters, the arterial segments and the inflated balloon were corrected for pincushion distortion introduced by the individual image intensifiers.

*Densitometric analysis*

Densitometry is based on the approximate linear relation that exists between the optical density of a contrast-enhanced lumen and the absolute dimensions of the arterial segment. Constitution of the relation between the path length of the x-rays through the artery or balloon and the brightness values requires a detailed analysis of the complete x-ray/cine/video chain, including the film development process [12, 13, 27]. For the first part of the chain, from the x-ray tube to the output of the image intensifier, we use Lambert Beer's law for the x-ray absorption and apply certain models for the x-ray source and the image intensifier. From the output of the image intensifier up to the brightness values in the digital image, we use a linear transfer function. The cross-sectional area of a vessel or balloon is then obtained as follows. The contours of a selected arterial segment or balloon (in a non-foreshortening view) are detected by automated edge detection as described above. On each scanline perpendicular to the local centerline direction of the vessel, a profile of brightness values is measured. This profile is transformed into an absorption profile by means of a simple logarithmic transfer function. The background contribution is estimated by computing the linear regression line through the background points directly left and right of the detected contours. Subtraction of this background portion from the absorption profile within the arterial contours yields the net cross-sectional absorption profile. Integration of this function gives a measure for the cross-sectional area at the particular scanline. By repeating this procedure for all scanlines, the cross-sectional area function is obtained. A reference densitometric area is obtained following the same principles as described above for the diameter measurements. It is clear that homogeneous mixing of the contrast agent and the blood must be assumed for the measurements to be correct. The complete procedure has been evaluated with cinefilms of Plexiglass$^{R}$ of coronary obstructions [12, 27]. The in vivo validation of the densitometric analysis is described in a separate chapter (Di Mario et al.)

*Definitions of quantitative derived morphologic parameters*

The area ($mm^2$) between the actual and reconstructed contours at the obstruction site is a measure of the amount of "atherosclerotic plaque" [12, 28]. The length of the obstruction (mm) is determined from the diameter function on the basis of curvature analysis. Symmetry is defined as the coefficient of the left and right hand distance between the reconstructed interpolated reference diameter and actual vessel contours at the site of obstruction. In this equation the largest distance between actual and reconstructed contours becomes the denominator. A symmetrical location of the lesion has a value of 1 and a severely eccentric located lesion has a value of 0. To assess the extent of coronary bending, the curvature value at the obstruction site is computed as the average value of all the individual curvature values along the centerline of the coronary segment, with the curvature defined by the rate of change of the angle through which the tangent to a curve turns in moving along the curve and which for a circle is equal to the reciprocal of the radius.

*Assessment of stretch, elastic recoil and balloon-artery ratio*

Stretch was defined as the ratio between the inflated balloon diameter (mm) minus the minimal luminal diameter (MLD) of the vessel pre-PTCA and the reference diameter (RD)(mm) of the dilated segment and this represents the maximum diameter of the vessel at the time of balloon inflation:

$$\frac{\text{Balloon Diameter} - \text{MLD pre-PTCA}}{\text{RD pre-PTCA}}$$

As previously published [12, 13] elastic recoil of the stenosis is defined as the ratio between the balloon diameter (mm) minus the MLD post-PTCA (mm) and the reference diameter of the dilated segment and this represents the early loss in diameter immediately following balloon inflation:

$$\frac{\text{Balloon Diameter} - \text{MLD post-PTCA}}{\text{RD pre-PTCA}}$$

Balloon-artery ratio was defined as the ratio between the balloon diameter and the reference diameter pre-PTCA of the dilated segment and attempts to describe the extent of balloon under or over sizing of the normal segment of the vessel:

$$\frac{\text{Balloon Diameter}}{\text{RD pre-PTCA}}$$

Assessment of stretch, elastic recoil and balloon-artery ratio were derived from videodensitometry by substituting diameter measurements with densitometrically measured area measurements.

**Statistical analysis**

All continuous variables were expressed as mean values ± standard deviation (SD) (Tables 1, 2) and a t-test was applied to these variables (Table 1). A p-value of $<0.05$ was considered statistically significant. To measure the strength of the relation between the nominal size and the measured balloon diameter, the product-moment correlation coefficient (r) and its 95% confidence intervals (CI) were calculated. The agreement between the two measures was assessed by determining the mean and the standard deviation (SD) of the between-method difference as suggested by Bland and Altman [29]. This was done by computing the sum of the individual differences between the two measures to determine the mean difference and the standard deviation. The same statistical method was applied to assess the relationship between the minimal cross-sectional area derived from edge detection and videodensitometry as well as of the inflated balloon. To assess the relationship between several angiographic morphological variables (area plaque, curvature, length of the lesion, symmetry) and recoil, a univariate analysis was performed. To avoid arbitrary subdivision of data, cut off criteria for continuous variables were derived by dividing the data in three groups so that each group contained about one-third of the population. The group with the highest amount of recoil was then compared with the 2 other groups [30]. This method of subdivision has the advantage of being consistent for all variables and thus avoids any bias in selection of subgroups which might be undertaken to emphasize a particular point (Table 3). Analysis was carried out with a commercial statistical package (BMDP Statistical Software 1990).

**Results**

Quantitative angiographic lesion characteristics of the 505 lesions dilated and of the balloon at highest inflation pressure used, are shown in Table 1.

*Lesion.* minimal luminal diameter increased from 1.09 ± 0.31 mm to 1.83 ± 0.40 mm after PTCA with an increase in minimal cross sectional area from 0.81 ± 0.79 $mm^2$ to 2.63 ± 1.34 $mm^2$ ($p < 0.001$). There was a significant change in "interpolated" reference diameter after PTCA: 2.70 ± 0.55 mm pre-PTCA and 2.75 ± 0.51 mm post-PTCA and in reference area: 5.98 ± 2.19 $mm^2$ pre-PTCA and 6.13 ± 2.33 $mm^2$ post-PTCA ($p < 0.001$).

*Balloon.* The average length of the balloon analyzed was 16.2 ± 3.7 mm; the tapered proximal and the distal part of the balloon were not included in the analysis (Fig. 1). The average inflation pressure used was 8.3 ± 2.6 atm, the number of inflations varied between 1 and 17 (mean 3.1 times), and the average inflation time was 255 ± 217 seconds. As shown from table 1 the balloon is not uniformly inflated over its entire length at the highest pressure used. Quantitative analysis showed a mean difference of 0.59 ± 0.26 mm

*Table 1.* Quantitative analysis of 505 dilated coronary lesions and inflated balloons

| *Lesion* | | | |
|---|---|---|---|
| | Pre-PTCA | Post-PTCA | p Value |
| Edge detection | | | |
| Minimal diameter (mm) | 1.09 ± 0.31 | 1.83 ± 0.40 | 0.001 |
| Reference diameter (mm) | 2.70 ± 0.55 | 2.75 ± 0.51 | 0.001 |
| Length lesion (mm) | 6.5 ± 2.5 | 6.1 ± 2.6 | 0.001 |
| Plaque area ($mm^2$) | 7.09 ± 3.79 | 4.38 ± 3.32 | 0.001 |
| Symmetry value | 0.40 ± 0.24 | 0.35 ± 0.21 | 0.001 |
| Curvature (units) | 21.6 ± 10.9 | 20.4 ± 11.2 | NS |
| Videodensitometry | | | |
| Minimal area ($mm^2$) | 0.81 ± 0.79 | 2.63 ± 1.34 | 0.001 |
| Reference area ($mm^2$) | 5.98 ± 2.19 | 6.13 ± 2.33 | 0.001 |
| *Balloon* | | | |
| Edge detection | | Videodensitometry | |
| Minimal diameter (mm) | 2.37 ± 0.41 | Minimal area ($mm^2$) | 4.39 ± 1.61 |
| Mean diameter (mm) | 2.64 ± 0.40 | | |
| Maximal diameter (mm) | 2.96 ± 0.44 | | |
| Reference diameter (mm) | 2.75 ± 0.41 | Reference area ($mm^2$) | 6.09 ± 1.82 |
| Nominal size (mm) | 2.94 ± 0.39 | | |

NS = not significant.

*Table 2.* Variation in the extent of stretch, elastic recoil and balloon artery ratio in 505 dilated lesions.

| | Stretch | Elastic recoil | BAR |
|---|---|---|---|
| *Edge detection* | | | |
| Minimal balloon diameter (mm) | 0.49 ± 0.18 | 0.21 ± 0.15 | 0.90 ± 0.17 |
| Mean balloon diameter (mm) | 0.59 ± 0.18 | 0.31 ± 0.15 | 1.00 ± 0.17 |
| Reference diameter of balloon (mm) | 0.63 ± 0.18 | 0.35 ± 0.16 | 1.04 ± 0.18 |
| Maximal balloon diameter (mm) | 0.71 ± 0.20 | 0.43 ± 0.18 | 1.12 ± 0.20 |
| Nominal size of balloon (mm) | 0.71 ± 0.21 | 0.43 ± 0.18 | 1.12 ± 0.20 |
| *Videodensitometry* | | | |
| Minimal area of balloon ($mm^2$) | 0.67 ± 0.37 | 0.34 ± 0.32 | 0.81 ± 0.36 |
| Reference area of balloon ($mm^2$) | 0.98 ± 0.42 | 0.65 ± 0.36 | 1.12 ± 0.41 |
| Nominal area of balloon ($mm^2$) | 1.16 ± 0.54 | 0.82 ± 0.45 | 1.29 ± 0.51 |

BAR = Balloon-artery ratio.

between the maximal and minimal balloon diameter in case of edge detection and 1.70 ± 0.90 $mm^2$ between the reference area and minimal area by videodensitometry.

The manufacturer's size of the balloon used was 2.94 ± 0.39 mm (range 2.0 to 4.2 mm). The mean difference (±SD) in diameter (and the corresponding r

*Table 3.* Influence of the balloon diameter or area used in the univariate analysis of elastic recoil

| Balloon | Symmetry | | | Curvature | | | Area plaque | | | Length lesion | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | <0.24 #164 | >0.24 #341 | p | <16 #171 | >16 #334 | p | <5.1 #170 | >5.1 #335 | p | <5.2 #168 | >5.2 #337 | p |
| *Edge detection* | | | | | | | | | | | | |
| Minimal diameter | 0.23 | 0.20 | 0.08 | 0.23 | 0.20 | 0.03 | 0.22 | 0.20 | 0.14 | 0.22 | 0.21 | 0.56 |
| Mean diameter | 0.33 | 0.30 | 0.15 | 0.33 | 0.30 | 0.03 | 0.34 | 0.30 | 0.001 | 0.32 | 0.31 | 0.26 |
| Maximal diameter | 0.45 | 0.43 | 0.25 | 0.45 | 0.42 | 0.07 | 0.47 | 0.42 | 0.001 | 0.45 | 0.43 | 0.21 |
| Reference diameter | 0.37 | 0.35 | 0.15 | 0.38 | 0.34 | 0.02 | 0.38 | 0.34 | 0.001 | 0.37 | 0.35 | 0.25 |
| Nominal size | 0.44 | 0.43 | 0.34 | 0.44 | 0.42 | 0.24 | 0.48 | 0.41 | 0.001 | 0.45 | 0.42 | 0.10 |
| *Videodensitometry* | | | | | | | | | | | | |
| Obstruction area | 0.37 | 0.32 | 0.08 | 0.39 | 0.31 | 0.02 | 0.42 | 0.30 | 0.001 | 0.35 | 0.33 | 0.50 |
| Reference area | 0.69 | 0.63 | 0.11 | 0.72 | 0.61 | 0.001 | 0.77 | 0.59 | 0.001 | 0.70 | 0.62 | 0.04 |
| Nominal area | 0.85 | 0.81 | 0.40 | 0.88 | 0.79 | 0.05 | 1.01 | 0.72 | 0.001 | 0.89 | 0.79 | 0.02 |

and 95% CI) between the nominal diameter of the balloon and its in vivo measured diameter using edge detection were:

| | |
|---|---|
| 0.66 ± 0.32 for the minimal balloon diameter | (r = 0.67; 95% CI = 0.62 to 0.72), |
| 0.30 ± 0.29 for the mean balloon diameter | (r = 0.73; 95% CI = 0.69 to 0.77), |
| 0.19 ± 0.31 for the reference balloon diameter | (r = 0.71; 95% CI = 0.66 to 0.75), |
| −0.02 ± 0.33 for the maximal balloon diameter | (r = 0.68; 95% CI = 0.63 to 0.72) (Fig. 2 A–D). |

Although the nominal size of the balloon during inflation is reached at the maximal balloon diameter, it appears that the balloon is not inflated at the theoretical diameter along its entire length. The mean differences (±SD) in area (and the corresponding r and 95% CI) were calculated using the cross-sectional area of the balloon, derived from the nominal size assuming a circular model of the balloon and from videodensitometry measurements were:

| | |
|---|---|
| 2.53 ± 1.56 for the minimal balloon area | (r = 0.59; 95% CI = 0.53 to 0.64), |
| 0.83 ± 1.42 for the reference balloon area | (r = 0.70; 95% CI = 0.65 to 0.74) (Fig. 2 EF). |

Stretch measurement derived from edge detection varied between 0.49 ± 0.18 – when the minimal value of the balloon diameter was chosen – and 0.71 ± 0.21 if the nominal size of the balloon or the maximal value of the balloon diameter was used. When videodensitometry is applied, stretch measurement varied between 0.67 ± 0.37 – when the minimal value of the balloon area was chosen – and 1.16 ± 0.54 if the nominal area of the balloon (derived from the nominal balloon size) was used (Table 2).

Elastic recoil measurements derived from edge detection varied between 0.21 ± 0.15 – when the minimal value of the balloon diameter was chosen – and 0.44 ± 0.18 if the maximal value of the balloon diameter was used. With videodensitometry, elastic recoil measurement varied between 0.34 ± 0.32 using the minimal value of the balloon area and 0.82 ± 0.45 using the nominal area of the balloon (derived from the nominal size) was used (Table 2).

Table 3 shows the influence of the selected balloon diameter on the univariate analysis of elastic recoil. For each morphologic parameter, different levels of significance were observed. For instance, the degree of curvature was significantly related to the recoil phenomenon when the value of the minimal, mean or reference balloon diameter was selected. However, the relation is no longer significant if the maximal value of the balloon diameter or the nominal balloon size was considered. The amount of area plaque is significantly related to the recoil phenomenon with less plaque giving more

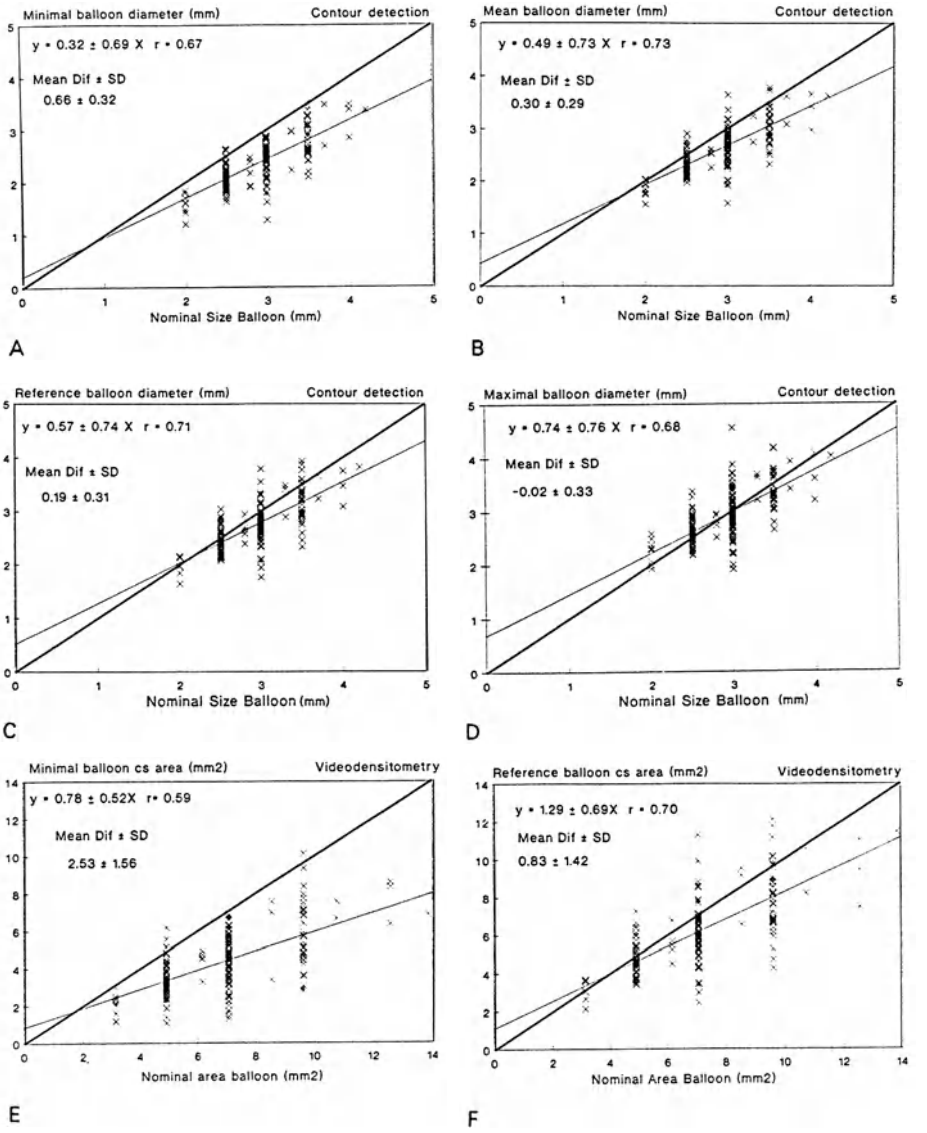


*Figure 2.* Four different balloon diameters measured by edge detection versus the nominal size of the balloon (A–D) and 2 different balloon area's measured by videodensitometry versus the nominal area of the balloon (EF).

Mean Dif ± SD = Mean Difference and Standard Deviation between the measured balloon diameter (area) and the nominal size (area) of the balloon.

r = correlation coefficient with regression line.

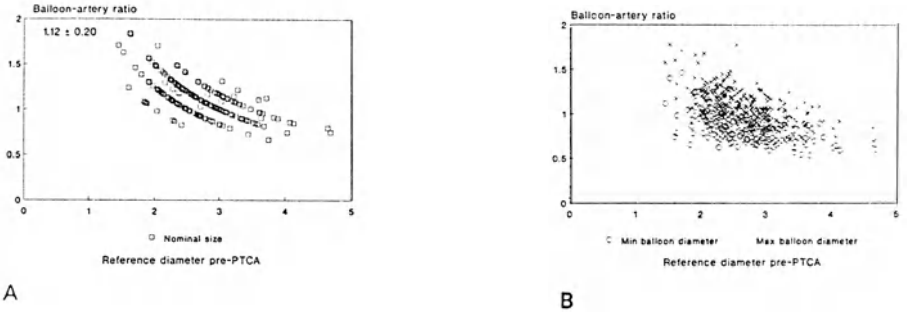


*Figure 3.* The balloon-artery ratio versus the reference diameter pre-PTCA. Depending on whether the minimal or the maximal balloon diameter is used, a single balloon inflation may be judged to be under sized (ratio <1) or over sized (ratio >1). Over sizing occurs more frequently in small vessels and under sizing more frequently in large ones.

elastic recoil. This is of significance for all selected balloon diameters or areas except when the minimal value of the balloon diameter was selected.

Balloon-artery ratio derived from edge detection varied between 0.90 ± 0.17 when the minimal value of the balloon diameter was chosen, and 1.13 ± 0.20 with the maximal value. With videodensitometry, the balloon-artery ratio varied between 0.81 ± 0.36 (with the minimal value of the balloon area) and 1.29 ± 0.51 when the nominal area of the balloon was selected (Fig. 3 A, B).

Comparison between edge detection and videodensitometry in the assessment of lesion severity pre- and post-PTCA, of the inflated balloon and of stretch and elastic recoil.

### *Lesion and balloon*

The mean difference (±SD) between the minimal luminal cross-sectional area pre-PTCA, post-PTCA and of the balloon derived from edge detection (assuming a circular cross-section) and measured by videodensitometry are 0.11 ± 0.50 $mm^2$ pre-PTCA, 0.11 ± 1.04 $mm^2$ post-PTCA and 0.16 ± 0.89 $mm^2$, respectively (Fig. 4). Figure 5 shows the relationship between stretch and elastic recoil assessed by edge detection and videodensitometry using the minimal luminal diameter or area of the balloon. The mean difference (±SD) between the 2 measurements are respectively 0.00 ± 0.19 for stretch and 0.00 ± 0.24 for elastic recoil.

## Discussion

This study showed that the balloon is not uniformly inflated at the highest pressure used. A maximal difference of 0.59 ± 0.26 mm in balloon diameter

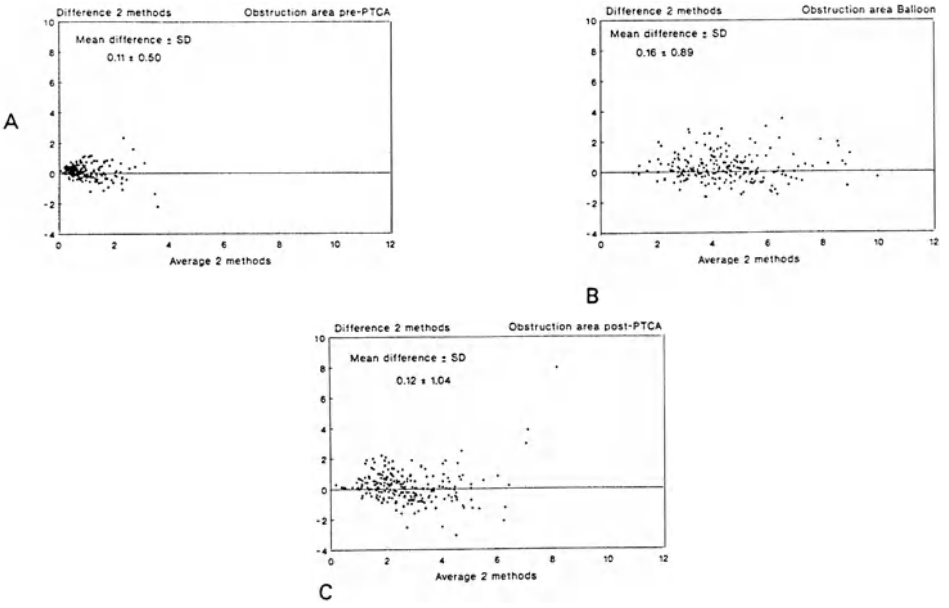


*Figure 4.* The mean difference (±SD) between the minimal luminal cross sectional area pre-PTCA (A), during balloon inflation (B) and post-PTCA (C) derived from edge detection and videodensitometry.

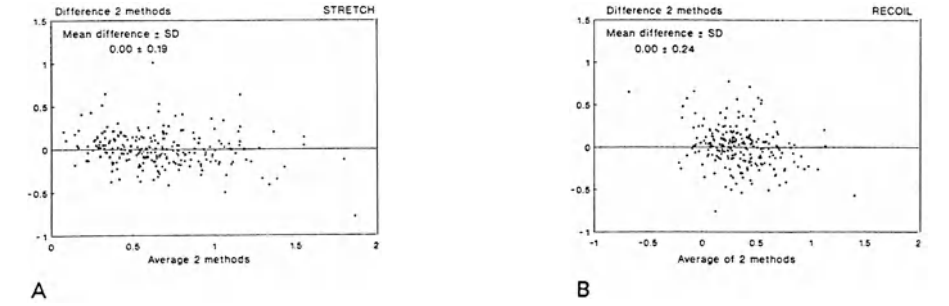


*Figure 5.* A: The relation between stretch using edge detection and videodensitometry (the minimal luminal diameter or area of the balloon).

B: The relation between elastic recoil using edge detection and videodensitometry (the minimal luminal diameter or area of the balloon).

was measured at an average inflation pressure of 8.3 atmospheres. Histologic studies have shown that the vast majority of atherosclerotic plaques in human coronary arteries are composed of dense fibrocollagenous tissue with varying amounts of calcific deposits and smaller amounts of intracellular and extracellular lipid ("hard plaques") [31]. Certain parts of plaques may restrict complete balloon expansion and explains the pattern of non-uniformity. It

has been the common clinical experience of many operators that some lesions will not yield even at inflation pressure up to 20 atmospheres. Recently intravascular ultrasound images have confirmed during coronary angioplasty this non-uniform inflation pattern (Personal communication, Dr Jeffrey Isner).

*Edge detection and videodensitometry*

Ideally in the assessment of stretch and elastic recoil, the measurement of interest is the precise relationship between the cross-sectional area of the vessel and the balloon at the site of the obstruction. It might be assumed that at each stage of the procedure, the luminal area of the vessel at the stenotic site is not circular so that the geometric evaluation (assuming a circular model) of stretch and the recoil phenomenon might be misleading particularly after the disruptive effect of balloon angioplasty. As earlier reported, the use of edge detection may be limited in the analysis of dilated lesions immediately following angioplasty [9, 13] because acute tears and dissections distort the anatomy. From a theoretical point of view, a videodensitometric approach seems to be the ultimate solution in measuring the vessel and balloon cross-sectional area in a single angiographic view. Although densitometry is independent of geometric shape, this technique seems to be more sensitive than edge detection to densitometric non-linearities (X-ray scatter, image intensifier veiling glare and beam hardening), oblique projection of the artery and overlap with other structures. Furthermore its application is limited in the presence of branch vessels that may cause errors in the background correction technique and in situations where the X-ray beam is not perpendicular to the long axis of the vessel [16]. In the present study it was felt that the videodensitometric approach was used in relative optimal condition since the inflated balloon was filmed in the least foreshortened view (for safety reasons), thereby avoiding large errors due to potential changes in background scatter and veiling glare. During inflation of the balloon, the surrounding coronary vessels were not opacified and in this way minimizing the problems related to the background correction. However, the analysis of the lesion remains subject to the well known pitfalls (mentioned in the previous paragraph) encountered with the videodensitometric technique. Despite the well known technical limitations, the assessment of stretch and elastic recoil by videodensitometry did not significantly differ from the assessment derived from edge detection and both techniques might be used in the future on-line in the catheterization laboratory during coronary angioplasty.

*Compliant versus non-compliant balloons*

In this study, the choice to use a compliant or non-compliant balloon during PTCA was left to the operator. In 241 lesions a non-compliant balloon (209 balloons were made from polyethylene terephthalate (PET) and 32 balloons

were made from hydracross) and in 264 lesion a compliant balloon (236 balloons were made from polyethylene (PE) and 19 balloons were made from polyvinylchloride (PVC) and 9 balloons were made from polyolefin copolymer (POC)) was used for dilatation. A significant difference was observed for the symmetry measurement ($0.42 \pm 0.25$ in the non-compliant balloon group versus $0.37 \pm 0.23$ in the compliant balloon group, $p < 0.03$) and for the highest balloon pressure used ($9.0 \pm 2.7$ in the non-compliant balloon group versus $7.6 \pm 2.2$ in the compliant balloon group, $p < 0.001$). Although no differences between the two groups in minimal lumen diameter or area pre-PTCA and post-PTCA, reference diameter or area pre-PTCA and post-PTCA, diameter stenosis or area stenosis pre-PTCA, nominal balloon size, calculated stretch, elastic recoil and the balloon-artery ratio was observed, there was a significant difference in post-PTCA diameter stenosis – with a better result in the group where lesions were dilated with a compliant balloon type (diameter stenosis of 32% versus 34% in the non-compliant balloon group). It is possible that this difference is caused by the type of lesions dilated (different symmetry) or due to the maximal balloon pressure used. A comparative study is warranted to investigate if this difference in post-PTCA result between the 2 groups is significant or that it reflects differences in selection.

Which measured balloon diameter should be used in the quantitative assessment of stretch, elastic recoil and balloon-artery ratio?

It is clear from our study that the nominal size of the balloon listed by the manufacturer should not be used in the assessment of stretch and elastic recoil of the stenotic lesion or in the assessment of the balloon-artery ratio because the nominal size is not reached at the stenotic site even at an average pressure of 8.3 atmospheres.

To determine the actual amount of stretch at the obstruction, we propose to use the minimal diameter or area in the balloon during inflation as this persistent encroachment of the balloon during inflation presumably localizes the non-distensible part of the stenosis that restricts the dilatation. Even more accurate would be a superimposition of the two diameter functions of the dilated vessel and inflated balloon to continuously assess stretch over the entire length of the dilated lesion (Fig. 6).

Recently Monson et al. [4] studied in 27 patients the angiographic patterns of balloon inflation during PTCA. Videodensitometry was used to measure the diameter of the inflated balloon and of the lesion pre-PTCA and post-PTCA. They defined recoil as the ratio between the balloon diameter at 6 atmospheres and the coronary diameter after angioplasty. They found that the nominal size of the balloon was almost never reached over the entire length of the balloon. Our data is in agreement with there observation (Table 1).

Any analysis of factors affecting the recoil phenomenon, will be greatly influenced by the selection of the value of the balloon diameter or area (minimal, mean, maximal, reference or nominal) used for the calculation of

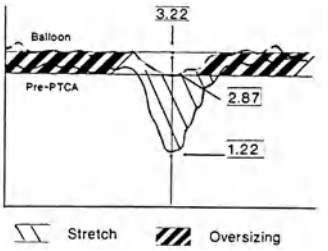


*Figure 6.* In this example the minimal luminal diameter of the lesion pre-PTCA and during balloon inflation are 1.22 mm and 2.87 mm respectively. The interpolated reference diameter for the lesion is 2.87 mm and for the balloon 3.22 mm. The nominal size of the balloon is 3.5 mm. Theoretically the maximal gain is 3.50–1.22 = 2.27 mm. However, due to the atherosclerotic plaque in the vessel wall, complete balloon expansion was not achieved. Stretch of the lesion was (2.87–1.22)/2.87 = 0.57. The upper line represents the diameter function curve of the balloon over the entire length of the balloon at maximum inflation pressure. The lower line represents the diameter curve pre-PTCA. The 2 interpolated reference diameter lines are also shown (see arrows). The difference between these 2 lines represents the balloon-artery ratio ///. It is clear that in this example oversizing took place: the interpolated reference diameter of the balloon is 3.22 mm and of the stenosis 2.87 mm; this results in a balloon-artery ratio of 1.12. In this case, the minimal diameter of the balloon and the lesion are localized at the exact same spot; however this is not always the case.

the elastic recoil. Our group earlier reported, that more elastic recoil was seen in asymmetric lesions (<0.37), lesions located in less angulated parts of the artery (<12.5 units) and in lesions with a small plaque content (<4.7 $mm^2$) [12]. In that latter study, the mean diameter (derived over the entire length) of the balloon was used. Table 3 shows the influence of the selected balloon diameter or area on the univariate analysis of factors affecting elastic recoil. From this table it is clear that small area plaque (<5.08 $mm^2$) and lesions located in less angulated parts of the vessel (curvature <16.3 units) are significantly or not significantly affecting the recoil phenomenon of the lesion depending on the balloon diameter chosen for analysis.

To accurately assess the extent of elastic recoil at the site of severest luminal narrowing we suggest to use the minimal value of the balloon diameter or area as this measurement presumably reflects the narrowing persisting at the site of the stenosis during dilatation. Even more accurate would be a superimposition of the two diameter functions of the dilated vessel and inflated balloon to continuously assess elastic recoil over the entire length of the dilated lesion (Fig. 7).

In the present study, the balloon-artery ratio derived from edge detection varied between 0.90 ± 0.17 (undersized) and 1.13 ± 0.20 (oversized) is selected (Fig. 3).

Roubin et al. [23] defined the balloon-artery ratio by estimating the so-called normal lumen of the coronary artery by direct visual comparison to the known diameter of the guiding catheter used. Then the patients were

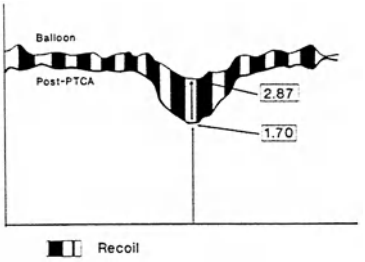


*Figure 7.* The upper line represents the diameter function curve of the balloon; this shows what maximally was achieved during PTCA. The lower line represents the diameter function curve post-PTCA. //// = elastic recoil; represents what is lost in diameter immediately post-PTCA. Post-PTCA the minimal luminal diameter is 1.70 mm. Immediately post-PTCA (2.87–1.70)/2.87 = 0.41 is lost due to elastic recoil. The ratio of elastic recoil is not necessarily at its maximum at the minimal obstruction site of the vessel.

randomized to a (nominal) balloon size smaller or larger than this so-called normal lumen. They found more acute complications with a balloon size greater than the so-called normal lumen. Nichols et al. [24] compared the diameter of the inflated balloon to a normal artery (in most cases proximal of the stenosis) adjacent to the stenosis (user-defined). In this study, balloon sizes provided by the manufacturer's were used. They concluded that the interventional cardiologist should approximate or slightly exceed the diameter of the normal arterial diameter in order to achieve optimal angiographic results with minimal dissections and minimal residual stenosis since oversized balloons (ratio >1.3) caused a higher incidence of dissections.

Over and under sizing of the balloon with respect to the vessel dilated always refers to the non-diseased part of the vessel as over sizing of the stenotic lesion itself always takes place (Fig. 6). So in theory, the nominal size of the balloon and the non-diseased diameter pre-PTCA should be used for the balloon-artery ratio. However, the present data shows that although the nominal size of the balloon is reached during inflation (Table 1) this maximal value represents only one point over the entire length of the balloon. The "reference diameter" of the balloon reflects the actual size of the balloon during inflation in the non-diseased part of the vessel. Therefore, we propose to use the reference diameter or area of the balloon in the quantitative assessment of the balloon-artery ratio.

## Conclusion

Irrespective of the quantitative analysis technique, the balloon during inflation is not uniform over its entire length. This observation has major impact on the calculated values of stretch, elastic recoil and balloon-artery ratio. As on-line quantification of the lesion before and during PTCA as well

as of the inflated balloon is technical feasible during routine PTCA, our observation is of clinical significance and it could help to determine whether higher balloon pressures should be applied or a greater balloon size should be used to achieve an optimal short-term and long-term result of the angioplastied lesion.

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# 8. Experiences of a quantitative coronary angiographic core laboratory in restenosis prevention trials

VICTOR A.W.M. UMANS, WALTER R.M. HERMANS, JEAN-PAUL R. HERRMAN, JAAP PAMEYER and PATRICK W. SERRUYS

## Introduction

Since its introduction more than 14 years ago [1], percutaneous transluminal coronary angioplasty (PTCA) has been attended by a 17% to 40% incidence of restenosis, typically developing within 6 months of the procedure [2–5]. Each year the number of patients undergoing PTCA has increased and now approaches the number treated with coronary artery bypass grafting (CABG). In the last 10 years, experimental models have given us more insight into the restenosis phenomenon and pharmacological agents have been developed aiming to prevent or reduce restenosis. Many of these agents have been investigated in clinical restenosis prevention trials [4–7] and although these agents were able to reduce restenosis in the animal model, most of the clinical trials failed to demonstrate a convincing reduction in the incidence of restenosis in man. In these clinical trials, the primary endpoint has been either angiographic (change in minimal luminal diameter at follow-up; >50% diameter stenosis at follow-up; loss >50% of the initial gain] and/or clinical [death; nonfatal myocardial infarction; coronary revascularization; recurrence of angina requiring medical therapy, exercise test, quality of life). The use of an angiographic parameter as a primary endpoint provides the necessary objectively whereby the patient population required for statistical analysis numbers between 500 and 700, whereas more than 2000 patients are necessary if a clinical endpoint is used [6].

Despite the widespread and long-standing use of coronary angiography in clinical practice, as well as the outstanding improvement in image acquisition, the interpretation of the angiogram has changed very little and is still reviewed visually. However, visual assessment is a subjective evaluation with a large inter- and intra observer variability and can therefore not be used in important scientific studies for example restenosis prevention trials [8, 9]. Quantitative coronary angiography has the advantage of being more accurate and reproducible in the assessment of lesion severity, than visual or hand-held caliper assessments. At the Thoraxcenter, the computer-assisted Cardiovascular Angiography Analysis System (CAAS) using an automated edge



*P.W. Serruys, D.P. Foley and P.J. de Feyter (eds.), Quantitative Coronary Angiography in Clinical Practice*, 121–135.

*Table 1.* Angiographic Core Laboratory in 4 restenosis prevention trials between 1988 and 1991.

| | |
|---|---|
| CARPORT | Coronary Artery Restenosis Prevention On Repeated Thromboxane antagonism. |
| | Intake and analysis complete, 707 patients, published: Circulation Oct 1991. |
| MERCATOR | Multicenter European Research Trial with Cilazapril after Angioplasty to prevent Transluminal coronary Obstruction and Restenosis. |
| | Intake and analysis complete, 735 patients, publication pending. |
| MARCATOR | Multicenter American Research Trial with Cilazapril after Angioplasty to prevent Transluminal coronary Obstruction and Restenosis. |
| | Intake complete, fup analysis pending, 1436 patients. |
| PARK | Post Angioplasty Restenosis Ketanserin trial. |
| | Intake complete, fup analysis pending, 703 patients. |

fup = follow-up.

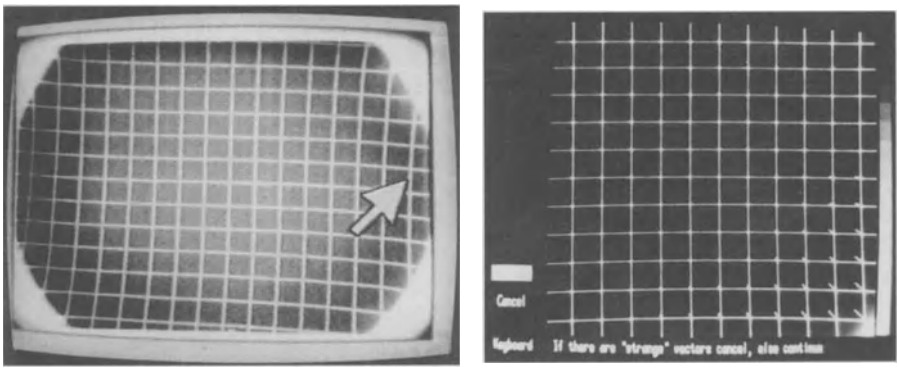
detection technique was developed and validated [8, 10]. Over the last 3 years, we have been the angiographic "core laboratory" (using the CAAS-system) in 4 restenosis prevention trials with recruitment of patients in Europe, United States and Canada (Table 1). In order to obtain reliable and reproducible quantitative measurements over time from coronary (cine)-angiograms, variations in data acquisition and analyses must be minimized.

In this chapter we present our experiences in the core laboratory with our approaches toward standardized angiographic data acquisition and analysis procedures as well as in qualitative or morphologic descriptions.

## Potential problems with angiographic data acquisition and analysis (Table 2)

### 1. *Pincushion distortion*

Pincushion distortion of the image intensifier introduces a selective magnification of an object near the edges of the image as compared with its size in the center (Fig. 1A). An inaccuracy in the measurement of the minimal lumen diameter of the stenosis over time could be introduced if, for example, the stenosis after the angioplasty procedure is filmed in the center and at follow-up near the edges of the image intensifier. To overcome this potential problem, a cm grid has to be filmed in each mode of the image intensifier in all the catheterization rooms to be used before the clinic can start to recruit and randomize patients for a restenosis prevention trial. With this cm grid film, the CAAS system calculates a correction factor for each intersection position of the grid wires so that the pincushion distortion can be corrected for (Fig. 2B). Fortunately, the newer generations of image intensifiers introduce significantly less distortion than the older ones from the early and mid 80's; the degree of distortion is even less when the lower magnification modes are used with multi-mode image intensifiers. At present time there are in




A B

*Figure 1.* Example of pincushion distortion introduced by the image intensifier (A, see arrow) and of the calculated correction factor with the use of the filmed cm-grid (B).

*Table 2.* Potential problems with angiographic data acquisition and analysis.

| | |
|---|---|
| 1 | Pincushion distortion of image intensifier |
| 2 | Differences in angles and height levels of x-ray system settings |
| 3 | Differences in vasomotor tone |
| 4 | Variation in quality of mixing of contrast agent with blood |
| 5 | Catheter used as scaling device (angiographic quality, influence of contrast in catheter tip on the calibration factor, size of catheter) |
| 6 | Deviations in size of catheter as listed by the manufacturer from its actual size |
| 7 | Variation in data analysis |

our database pincushion correction factors of 734 different modes of magnification (113 clinics with 285 angiorooms) from all over Europe, United States and Canada.

## 2. *Differences in angles and height levels of the X-ray gantry*

As it is absolute mandatory to repeat exactly the same (baseline) views of the coronary segments in studies to evaluate changes in lumen diameter over time, we have developed at the Thoraxcenter an on-line registration system of the x-ray system parameters such as parameters describing the geometry of the x-ray gantry for a particular cine-film run (rotation of U-arm and object, as well as distances from isocenter to focus, table height) and also selected x-ray exposure factors (kV, mA). When repeat angiography is scheduled, the geometry of the x-ray system is set on the basis of the available data, so that approximately the same angiographic conditions are obtained. In a clinical study with repositioning of the x-ray system, it was found that the angular variability, defined by the standard deviation of the absolute differences of angular settings, was <4.2 degrees and that the variability in the various positions of image intensifier and x-ray source was <3.0 cm [8,

11]. As on-line registration of the x-ray system settings is not available in all hospitals, we have developed a technician's worksheet that has to be completed during the PTCA procedure with detailed information of the procedure (view, catheter type, catheter size, balloon type, balloon size, balloon pressure, kV, mA, medication given) (Fig. 2). In this way minimization of differences in x-ray settings at follow-up angiography is ensured. Furthermore, each center intending to participate in one of the trials is required to provide 2 sample cine-angiograms from each of its catheterization rooms for verification of their ability to comply to our standards.

### 3. *Differences in vasomotor tone of the coronary arteries*

As the vasomotor tone may differ widely during consecutive coronary angiographic studies, it should be controlled at all times. An optimal vasodilatative drug for controlling the vasomotor tone of the epicardial vessel should produce a quick and maximal response without influencing the hemodynamic state of the patient. Only nitrates and calcium antagonists satisfy these requirements. On isolated human coronary arteries calcium antagonists are more vasoactive but they act more slowly; in the in vivo situation, however, the nitrates are more vasoactive than the calcium antagonists [12–15].

We have measured in 202 patients the mean diameter of a normal segment of a non-dilated vessel in a single view pre-PTCA, post-PTCA and at follow-up angiography 6 months later. In cases where a stenosis of the left anterior descending artery (LAD) had been dilated, a non-diseased segment in the left circumflex artery (LC) was analyzed and vice versa; where dilatation of a stenosis in the right coronary artery (RCA) was performed, a non-diseased segment proximal to the stenosis was used for analysis. All patients were given intracoronary (either 0.1 to 0.3 mg of nitroglycerin or 1 to 3 mg isosorbide dinitrate(ISDN)) before PTCA and before follow-up and all but 34 received similar dosage before the angiogram immediately after PTCA. Table 3 summarizes the results of the analyses; a decrease in mean diameter of $-0.11 \pm 0.27$ (mm) was observed in the segments of patients studied without intracoronary nitrates post-PTCA, whereas a small increase was seen of $+0.02 \pm 0.21$ (mm) in the group with intracoronary nitrates prior to post-PTCA angiography ($p < 0.001$). No difference in the mean diameter between pre-PTCA and follow-up angiography was measured.

In summary, the vasomotor tone should be controlled in quantitative coronary angiographic studies. This is only achieved by means of a vasodilator drug that produces fast and complete vasodilation without any peripheral effects. Therefore, we strongly advocate the use of 0.1 to 0.3 mg nitroglycerin or 1 to 3 mg of ISDN pre-PTCA, after the last balloon inflation before repeating the views used pre-PTCA and at follow-up angiography.

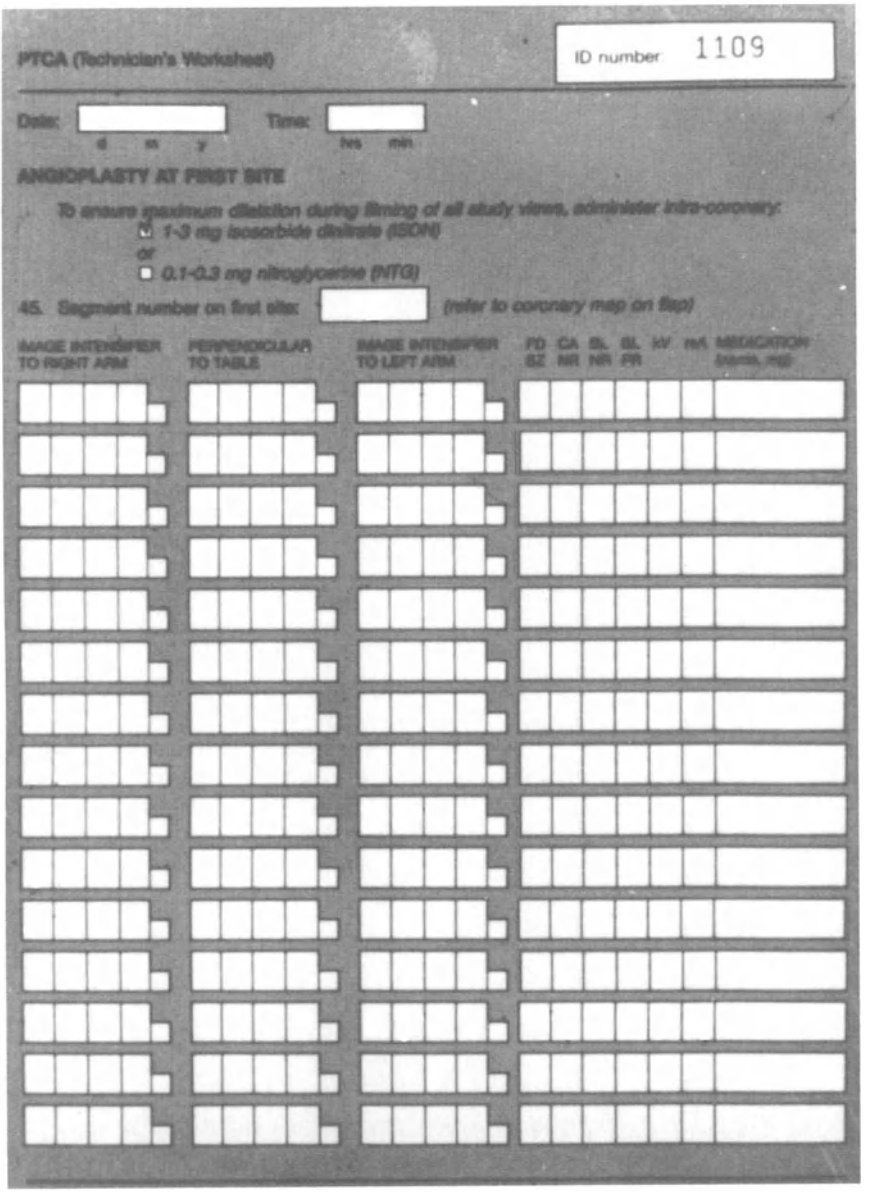



*Figure 2.* Example of a page of the technician's worksheet.

## 4. *Influence of contrast agent on vasomotor tone of epicardial coronary agents*

Jost and colleagues have clearly demonstrated that the vasodilative changes in vessel dimensions due to contrast medium administration are significantly

*Table 3.* Influence of nitroglycerin on the mean diameter of non diseased segments in 202 patients in single projection.

| Mean diameter (mm) | Without nitro post-PTCA N = 34 | With nitro post-PTCA N = 168 | t-test |
|---|---|---|---|
| Pre-PTCA | 3.12 ± 0.63 | 2.74 ± 0.63 | |
| Post-PTCA | 3.01 ± 0.64 | 2.75 ± 0.59 | |
| Follow-up | 3.18 ± 0.55 | 2.82 ± 0.63 | |
| Delta (Post - Pre) | −0.11 ± 0.27 | +0.02 ± 0.21 | $p < 0.001$ |
| Delta (Fup - Pre) | +0.06 ± 0.22 | +0.07 ± 0.22 | p = ns |

Ns = not statistically significant; p = probability value (t-test); fup = follow-up.

smaller with the use of a non ionic rather than ionic contrast medium [16]. Therefore, in quantitative coronary angiographic studies, non ionic contrast media with iso-osmolality should be applied.

It has been suggested to administer the contrast medium by an ECG triggered injection system. This is however not (yet) feasible during routine coronary angioplasty even in a setting of a clinical trial.

### 5. *Catheter used as scaling device for measurements of absolute diameters*

#### *A. Angiographic versus microcaliper measured size of catheter*

The image quality of the (x-ray radiated) catheter is dependent on the catheter material, concentration of the contrast agent in the catheter and kilovoltages of the x-ray source. Reiber et al. in 1985 showed that there was a difference of +9.8% in angiographically measured size as compared with the true size for catheters made from nylon. Smaller differences were measured for catheters made from woven dacron (+0.2%), polyvinylchloride (−3.2%) and polyurethane (−3.5%) [17]. It was concluded that nylon catheters could not be used for quantitative studies. Recently, our group have characterized the angiographic properties of newer generation catheters (Table 4). Also for these catheters small differences were found between the true size and the angiographically measured size (average difference: −1.16% to 6.77%). Therefore, it was concluded that these catheters may be used for qauntitative studies when the CAAS edge detection algorithm is applied.

#### *B. Influence of variation in contrast filling of the catheter on calibration*

It was also demonstrated that catheters made from woven dacron, polyvinylchloride and polyurethane when flushed with saline had, identical image contrast qualities whereas differences in image contrast at various fillings (air, contrast with 3 different concentrations [Urografin-76, Schering AG, Berlin, Germany; 100%–50%–25%) of the catheters acquired at different kilovoltages was seen [17].

In addition, we measured the calibration factor in 95 catheters from 15

*Table 4.* Comparison of the true sizes of the 7F, 8F, 9F, 9.5F, 10F and 11F catheter segments with angiographically measured dimensions (measurements were averaged over the two different fillings (water and contrast medium), each at two different kilovoltages (60 and 90 kV).

| | True size (mm) | Angiographically measured size (mm) | AVG dif (%) |
|---|---|---|---|
| *7F Catheters* | | | |
| Schneider | 2.26 | 2.23 ± 0.03 | −1.16 |
| Scimed | 2.21 | 2.36 ± 0.07 | 6.77 |
| USCI | 2.31 | 2.29 ± 0.18 | −1.03 |
| *8F Catheters* | | | |
| Medtronic | 2.58 | 2.61 ± 0.05 | 1.58 |
| Schneider | 2.63 | 2.67 ± 0.01 | 1.60 |
| Scimed | 2.58 | 2.66 ± 0.06 | 3.01 |
| USCI | 2.59 | 2.69 ± 0.03 | 3.76 |
| *9F Catheter* | | | |
| Schneider | 2.95 | 2.94 ± 0.03 | −0.06 |
| *9.5F Catheter* | | | |
| DVI | 3.17 | 3.21 ± 0.18 | 1.18 |
| *10F Catheter* | | | |
| Medtronic | 3.25 | 3.30 ± 0.04 | 1.42 |
| Schneider | 3.29 | 3.39 ± 0.07 | 3.15 |
| *11F Catheter* | | | |
| DVI | 3.66 | 3.52 ± 0.11 | −3.93 |

Mean value ± standard deviation.

different clinics to compare contrast with filled saline catheter. Figure 3 summarizes our results. In a considerable number of cases, a difference in calibration factor was present with an average calibration factor of 0.143 ± 0.020 (mm/pel) for the flushed (contrast empty) catheter versus 0.156 ± 0.030 (mm/pel) for the catheters filled with contrast ($p < 0.001$). This means that with the use of a contrast filled catheter instead of a flushed catheter, the minimal luminal diameter will have an apparent increase in diameter value of ±0.05 mm pre-PTCA, ±0.15 mm post-PTCA and ±0.20 mm for the reference diameter.

For this reason we strongly advise the clinics to flush the catheters before each cine-run to have an "identical flushed catheter" for calibration throughout the study period.

### *C. Size of the catheter*

Until recently only 7F and 8F catheters have been used for follow-up angiography and from earlier studies it is known which of the catheters are preferred for quantitative analysis [17, 18]. However, 5F and 6F catheters

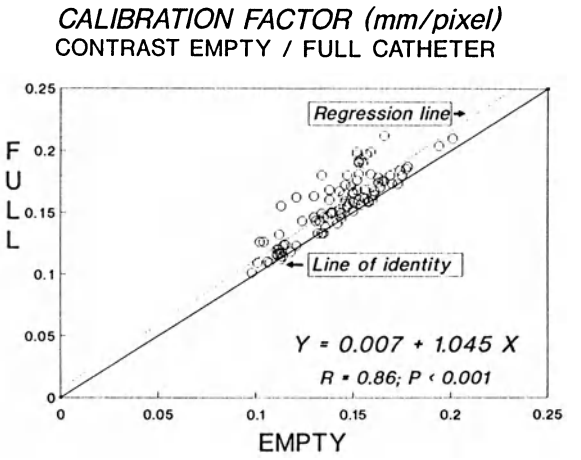



*Figure 3.* Relationship between the calibration factor calculated using an contrast empty (flushed) catheter versus a contrast filled catheter. A considerable number of measurements with the contrast filled catheter are above the line of identity.

are available and increasingly being used for follow-up angiography. Koning et al. have carried out a study to determine whether these catheters can be used for calibration purposes (Internal Report), (Table 5). They found that the differences between the true and angiographically measured diameters of the 5F and 6F catheters in all cases were lower for 6F than for the 5F catheters. Secondly, the Argon catheters showed the largest overall average difference, followed by the Edwards catheters and the 5F USCI catheter. The Cordis catheters, the 6F right Judkins Medicorp, the 6F Schneider and 6F USCI have the lowest average differences between the true and measured diameters. However, none of the catheters satisfy earlier established criteria [17], being that the average difference of the angiographically assessed and true diameter is lower than 3.5% and that the standard deviation of the measured diameters be smaller than 0.05 mm, under the following conditions: filled with 100% contrast concentration, filled with water, acquired at 60 kV and 90 kV. On the basis of these results, it was concluded that 5F or 6F catheters should not be used for QCA studies using the CAAS-system at the present time.

### 6. *Deviations in the size of the catheter as listed by the manufacturer*

In our experience, the size of the catheter as specified by the manufacturer often deviates from its actual size, especially disposable catheters. If the manufacturer cannot guarantee narrow ranges for the true size of the catheter, all catheters should be measured by a micrometer. Therefore, all catheters used during the angioplasty procedure and at follow-up are col-

*Table 5.* Comparison of the true sizes of the 5F and 6F catheter segments with angiographically measured dimensions (measurements were averaged over the three different fillings (water, contrast medium concentrations of 185 and 370 mg I/cc), each at two different kilovoltages (60 and 90 kV).

| | True size (mm) | Angiographically measured size (mm) | AVG dif (%) |
|---|---|---|---|
| *5F Catheters* | | | |
| Argon | 1.66 | 1.85 ± 0.09 | 11.3 |
| Cordis | 1.73 | 1.79 ± 0.15 | 3.2 |
| Edwards | 1.66 | 1.80 ± 0.08 | 8.5 |
| Mallinckrodt | 1.73 | 1.72 ± 0.14* | −0.8 |
| Schneider | 1.69 | 1.79 ± 0.07 | 6.1 |
| USCI | 1.61 | 1.75 ± 0.14 | 8.5 |
| *6F Catheters* | | | |
| Argon | 1.98 | 2.14 ± 0.07 | 8.1 |
| Cordis | 2.01 | 2.03 ± 0.11 | 1.1 |
| Edwards | 1.96 | 2.10 ± 0.07 | 7.1 |
| Medicorp (left) | 1.97 | 2.07 ± 0.04 | 5.1 |
| Medicorp (right) | 1.99 | 2.02 ± 0.10 | 1.6 |
| Mallinckrodt | 1.97 | 1.91 ± 0.15* | −2.9 |
| Schneider | 1.94 | 2.00 ± 0.09 | 3.0 |
| USCI | 1.99 | 2.06 ± 0.08 | 3.4 |

Mean value ± standard deviation, * measurements of the Softouch tip will be more favorable.

lected, labelled and sent to the angiographic core laboratory for actual measurement.

As the actual measurement can be hampered by individual variation, we have evaluated the inter- and intraobserver variability of catheter measurements at the Core Laboratory. A total of 96 catheters with different sizes (6F to 9F) were measured by 3 different analysts independent of each other. One month later, all three analysts measured the same catheters for a second time, unaware of the results from the first time (Table 6) . The intraobserver variability was excellent with a mean difference of less than 0.01 mm and a standard deviation of the difference of less than 0.03 mm for all catheter sizes. Similarly the interobserver variability between the 3 analysts showed a mean difference of less than 0.03 mm and a standard deviation dependening on the size between 0.00 and 0.04 mm. We conclude that the catheter can be measured with an excellent accuracy and precision.

## 7. *Variation in data analysis*

### *Minimal luminal diameter*

From the contours of the analyzed arterial segment, following pincushion correction and calibration, a diameter function can be determined by computing the distances between the left and right edges. From these data a number

*Table 6.* Intra- and inter-observer variability of 96 catheter diameter measurements with an electronic microcaliper.

Intra-observer variability

| | N | Overall mean | Mean of diff | P-value | S.d of diff |
|---|---|---|---|---|---|
| 9F | 30 | 2.75 | 0.008 | NS | 0.026 |
| 8F | 114 | 2.56 | 0.009 | NS | 0.028 |
| 7F | 132 | 2.25 | 0.001 | NS | 0.008 |
| 6F | 12 | 1.94 | −0.002 | NS | 0.006 |

Inter-observer variability

| | N | 1 vs 2 Mean dif | S.d. dif | 1 vs 3 Mean dif | S.d. dif | 2 vs 3 Mean dif | S.d. dif |
|---|---|---|---|---|---|---|---|
| 9F | 20 | 0.00 | 0.04 | 0.00 | 0.02 | 0.00 | 0.04 |
| 8F | 76 | 0.00 | 0.03 | 0.00 | 0.02 | 0.00 | 0.03 |
| 7F | 88 | 0.00 | 0.01 | −0.01 | 0.02 | 0.00 | 0.02 |
| 6F | 8 | −0.02 | 0.03 | −0.01 | 0.00 | 0.01 | 0.03 |

S.d = standard deviation; diff = difference.

of parameters can be obtained. *Direct measurements* include 1) minimal luminal diameter, 2) lesion length 3) obstruction and reference area. *Interpolated measurements* include the reference diameter while percent diameter stenosis and percent area stenosis are *derived measurements*.

Particularly, the minimal luminal diameter is of great importance as it presents to the inverse fourth power in the formulas describing the pressure loss over a coronary obstruction. Moreover to determine the effect of interventions on the severity of coronary obstructions, one should compute the changes in minimal luminal diameter and not those in percent diameter stenosis, as the reference position in general will also be affected by intervention.

A major limitation of edge detection (aside from the technical quality of the cinefilm) is the analysis of the post-angioplasty result. In particular, dissections are a frequent occurrence following PTCA and the resulting haziness, irregular borders or extravasation of contrast medium makes edge detection difficult. There is no ideal solution to this problem. If a dissection is present on the post-angioplasty angiogram, the computer "decides" whether the extraluminal defect is included or excluded in the analysis, thereby avoiding subjective bias.

To determine the accuracy and precision of the post-angioplasty luminal assessment by edge detection, a consecutive series of 117 end-diastolic post-PTCA cineframes were analyzed by two independent analysts. The agreement between the two analyses was 0.02 mm. The variability as determined by the standard deviation of the between-analysis difference was 0.21 mm. Therefore, quantitative coronary angiography shows that a small discrepancy

exists in the post-PTCA luminal assessment between two analyses. This observation suggests that edge detecion is an acceptable method for objectively assessing the result of coronary balloon angioplasty.

*Reference diameter*

Although the absolute minimal luminal diameter is one of the preferred parameters for describing changes in the severity of an obstruction as a result of an intervention, percent diameter stenosis is a convenient parameter to work with in individual cases. The conventional method of determining the percent diameter stenosis of a coronary obstruction requires the user to indicate a reference position. It is clear that this computed percent diameter stenosis of an obstruction depends heavily on the selected reference position. In arteries with a focal obstructive lesion and a clearly normal proximal arterial segment the reference region is straightforward and simple. However, in cases where the proximal part of the arterial segment shows combinations of stenotic and ectatic areas, the choice may be very difficult. To minimize these variations, we have implemented many years ago an *interpolated* technique, which is not user defined, to determine the reference diameter at the actual stenosis site without operater interference. The basic idea behind this 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. The interpolated percent diameter stenosis is then computed by comparing the minimal diameter value at the site of the obstruction with the corresponding value of the reference diameter function.

*Length of analyzed segment*

Anatomic landmarks such as bifurcations are used for the manual definition of start and end points of arterial segments so as to minimize the problem of non identical analyses. For that purpose, drawings are made by the investigator of all different views suitable for quantitative analysis, pre-PTCA, post-PTCA and at follow-up. In addition, a hard-copy is made of every drawing, to enable analysis of the exact same segments at follow-up angiography.

*Manual corrections*

For those parts along the detected arterial segment, where the observer does not agree with the automatically detected boundaries, manual correction by means of a writing tablet are possible. If the manual corrections are performed after the first iteration of the edge detection procedure, the system is allowed to find an optimal path within these limits during second iteration. It has been our experience that in almost all cases the contour will then follow the desired path at these locations. An advantage of this approach is that the final contour will still be based on the available edge information within the limitations set by the observer. This type of correction may be set

as "soft" correction. In those situations where the soft correction still does not result in the desired contour after the second iteration, the user may apply a final "hard" correction. The computer registers for both the left- and right- hand contours the length of the arterial segments that were manually corrected, expressed as percentages of the total length of the analyzed contour sides.

*Frame selection*

Usually, an end-diastolic cine-frame is selected for the quantitative analysis of a coronary obstruction to avoid blurring effect of motion. If the obstruction is not optimally visible in that particular frame (e.g. by overlap by another vessel) a neighboring frame in the sequence is selected. However, since a marker is not always present on the cine-film, the visually selected cine-frame may not be truly end-diastolic. Beside that, individual analysts may choose different frames even when the same selection criteria are followed. In addition, it is possible that the frames are selected from different cardiac cycles, in relation to the moment of contrast injection. Reiber et al have critically assessed this problem in 38 films whether selection of the frame (3 frames preceding, 3 frames immediately following the frame and the same frame as chosen by the senior cardiologist as the reference end-diastolic frame, but one cardiac cycle earlier or later) resulted in a significant differences in the measurements. They found no significant difference in the mean and the standard deviation of the differences for the obstruction diameter, interpolated reference diameter, percent diameter stenosis, extent of the obstruction and area of atherosclerotic plaque obtained in various frames with respect to the "select reference frame". Therefore, it is concluded that the selection of a true end-diastolic cineframe for quantitative analysis is not very critical and that in case of overlap it is possible to select a neighboring frame [19].

## Quality control in the mercator trial

In the MERCATOR-trial – a restenosis prevention trial with a new angiotensin converting enzyme inhibitor cilazapril – in which 26 clinics have participated, quantitative coronary angiography was used to determine the primary endpoint as defined by the rate and extent of restenosis. Before the clinics could start to recruit patients for the study, they had to supply 2 sample cinefilms for analysis to demonstrate that they could comply with the required standards. Of all participating clinics 1 or more cm-grid films of all modes of all image intensifiers were received at the core laboratory to allow correction for pincushion distortion of the image intensifiers. All clinics received a set of radiopaque plates to be able to make it clear on the film whether nitroglycerin or isosorbide dinitrate was given before the contrast injection, which field size of the image intensifier was used, the balloon pressure and balloon size used etc. In a period of 5 months (June 1989 –November 1989),

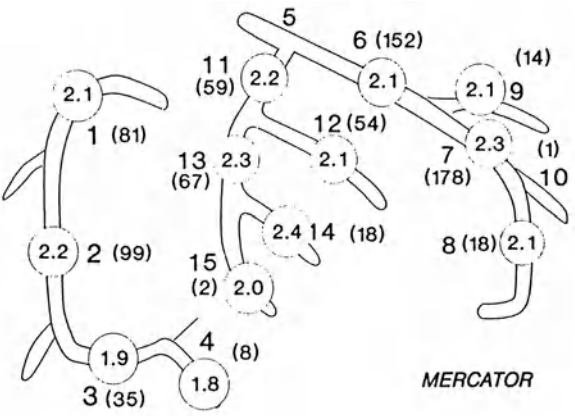



*Figure 4.* The average number of matched projections (pre-PTCA, post-PTCA and at follow-up) that were used for quantitative analysis in the MERCATOR trial per segment are given in the circles. The numbers between the brackets are the total number of stenoses for that particular segment.

a total of 735 patients were recruited with a minimum of 8 patients and a maximum of 56 patients per clinic. Five of the 735 patients were not included in the final analysis of the trial because their cinefilm could not be quantitative analyzed; in 1 patient the film developing machine broke down so that no post-PTCA film was available for analysis; in 2 patients analysis was not possible due to a large coronary artery dissection; in 1 patient no matching views were available and in 1 patient poor filling of the vessel had occurred (due to the use of a catheter with side holes) making comparison with the baseline film unreliable.

In 2 patients pre-PTCA, 34 patients post-PTCA and in 4 patients at follow-up angiography intracoronary nitroglycerin or isosorbide dinitrate had not been administered as assessed by the absence of the plate on the film and nothing had been recorded in the column "medication given during the procedure". In 26 patients, a 5 or 6 French catheter was used at the time of follow-up angiography. In 8% of the views pre-PTCA, 12% of the post-PTCA views and 12% of the follow-up views, the images had to be analyzed with a contrast-filled catheter because no flushed catheter was available. Figure 4 shows the average number of matched views available for QCA analysis per segment dilated.

## Qualitative assessment

In addition to quantitative measurements, an angiographic core laboratory can assess qualitative or morphologic factors, such as type of lesion (accord-

ing the AHA classification), description of the eccentricity of the lesion and type of dissection after the procedure, using modified NHLBI criteria, to establish the roles of these descriptors in the restenosis process. Recently, we have studied the interobserver variability for the description of the lesion and the type of dissection [20, 21]. Using the Ambrose classification there was an agreement of 80% between the two assessors of the core laboratory and for dissection there was an agreement of 87%. At the present time, no additional data is available but will become available in the near future.

## Conclusion

The use of quantitative coronary angiography is an objective and reliable method to evaluate changes in arterial dimensions over time. An angiographic core laboratory plays a crucial role in minimizing the problems of data acquisition and data analysis as well as the overall quality of the trial. Beside that an angiographic core laboratory may help demonstrating the reproducibility of qualitative factors and their role in the occurrence of acute and late complications of PTCA.

Furthermore, in our experience it has been possible to standardize angiographic data acquisition from 82 different clinics in Europe, United States and Canada.

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# 9. Visual versus quantitative analysis of coronary artery stenoses treated by coronary angioplasty: can the angiographer's eye be re-educated?

NICOLAS DANCHIN, YVES JUILLIERE, DAVID P. FOLEY and PATRICK W. SERRUYS

## Introduction

Visual interpretation of the degree of coronary artery stenoses may be grossly erroneous when compared with quantitative coronary angiography [1–7] : angiographers tend to overestimate the severity of tight stenoses and underestimate the degree of milder ones [4, 8, 9], a tendency which is particularly unfortunate when the results of interventional procedures such as coronary angioplasty must be "objectively" assessed [9–11]. Quantitative coronary angiography is now established as the "gold standard" for coronary stenosis assessment but its limitations have been recently emphasized [12] and it remains a time consuming technique, so that the use of digital calipers, an easier though less precise method, has been proposed for clinical purposes [5, 8].

The purpose of the present study was to test the hypothesis that experience in quantitative coronary angiography might improve the ability to accurately evaluate coronary artery stenoses visually, by a dual process of careful selection of the frames to be analyzed, and "re-education" of the angiographer's eye.

## Material and methods

### *Material*

One hundred and two consecutive coronary artery stenoses which had been analyzed using the Cardiovascular Angiographic Analysis System (CAAS) constituted the material for the present study, which was designed to compare visual estimates and quantitative measurements of the percent reduction of intraluminal diameter of a wide range of coronary stenoses. Of the segments analyzed, 26 were pre-PTCA, 24 were immediately post-PTCA and 52 were at 6–month follow-up in patients who had been enrolled in a European



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multicentre restenosis prevention trial, the results of which have already been reported [13].

For the CAAS analysis, 238 still-frames of the 102 segments had initially been selected but 11 were subsequently excluded from the present study because of obviously erroneous results due to the presence of total coronary artery occlusions or superimposition of side-branches on the narrowed segment. Therefore, 227 still-frames, corresponding to an average of 2.2 frames per stenosis, were reviewed by 2 observers (YJ, ND) extensively trained in quantitative coronary angiography (more than 100 analyses performed each).

*Angiographic methodology*

For the purposes of clinical studies, the coronary angiograms are recorded to facilitate quantitative analysis by the CAAS system, using fixed table systems and 35 mm cinefilms at a minimum speed of 25 frames per second [14]. Before recording the post-PTCA angiogram, radiopaque guidewires are necessarily removed, to avoid interference with the automated edge detection angiographic analysis method.

To standardize the method of data acquisition and to ensure exact reproducibility of the angiographic studies, cineframes to be analyzed are preferably selected at end-diastole, to minimize possible foreshortening and the blurring effect of motion, and superimposition of side-branches is avoided. In addition, to avoid the potential influence of vasomotion on vessel dimensions, the same dose of intracoronary nitrates, either nitroglycerin 0.1–0.3 mg or isosorbide dinitrate 1–3 mg, is administered before each angiographic study [13].

*Quantitative coronary angiography*

The CAAS has been extensively validated and described in detail elsewhere [3, 14, 15].

*Visual interpretation of the coronary angiograms*

For the present study, each frame that had been selected for CAAS analysis was placed on a Tagarno pojector and frozen. The observers, who were blinded to the results of the CAAS, were separately allocated 30 seconds in which to independently determine the degree of obstruction as a% diameter stenosis, with a 1% precision.

*"Per view" and "per stenosis" analysis*

For each of the 227 frames, the percent reduction of intraluminal diameter assessed by each of the observers was compared with the CAAS measurement ("per view" analyses).

In addition, in order to determine the percent reduction of intraluminal diameter for each of the 102 coronary artery segments, the average of the individual views was computed to derive a "per stenosis" analysis, both for CAAS analyses and visual assessment by each of the observers.

### *Statistical analysis*

The relationship between quantitative coronary angiography measurements and measurements of the same segments by each of the observers was assessed using linear regression analyses and Pearsons product moment correlation coefficient : r. In addition, as previously suggested [16, 17], paired t tests were used to compare the mean percent diameter stenosis as estimated by each method and the accuracy (mean difference between measurements obtained by the 2 methods) and precision (standard deviation of mean differences) were determined.

These statistical techniques were applied to both "per view" and "per stenosis" analyses. Comparisons were made between each observer-obtained set of measurements and CAAS.

To test the hypothesis that visual assessment overestimates tight stenoses and underestimates mild stenoses [9], paired t tests were used to compare measurements by each of the observers versus CAAS measurements, both for stenoses of 50% or higher and stenoses <50% by CAAS analysis, since historically 50% diameter stenosis was found to be the level of coronary narrowing at which reactive hyperemia became impaired [18] and is one of the most frequently used criteria for definition of restenosis following PTCA [19, 20].

Interobserver variability was tested using similar statistical tests, on all individual still-frames analyses made by each of the observers. Intraobserver variability was tested on the analysis of 21 still-frames from 10 patients, by one of the observers ; two analyses were made on two separate occasions, 6 weeks apart (study 1 and study 2).

All p values $<0.05$ were considered significant.

## Results

### *Intra- and inter-observer reproducibility*

Intraobserver reproducibility of diameter stenosis measurements from the 21 still-frames analyzed 6 weeks apart was excellent : mean percent stenosis was estimated at $46.1 \pm 26.1\%$ for study 1 and $45.4 \pm 25.4\%$ for study 2 (p : non significant) ; the accuracy and precision were 0.7% and 5.5%, respectively ; the correlation coefficient was $r = 0.98$.

For the 227 still-frames, interobserver reproducibility was also eminently

satisfactory : mean percent stenosis was 46.0 ± 19.0% for Observer 1 versus 46.2 ± 18.7% for Observer 2 (p : not significant) ; the accuracy and precision of measurements made by Observer 1 with respect to Observer 2 were −0.16 and 6.5% ; the correlation coefficient was r = 0.94.

*Individual still frames : "per view" analyses*

The correlations between Observer 1, Observer 2 and CAAS are listed in Table 1 and are plotted on Fig. 1. The correlation coefficients were r = 0.89 (Observer 1 vs CAAS) and r = 0.90 (Observer 2 vs CAAS). A greater than 10% discrepancy between visual analysis and CAAS measurements was noted in 55 of the 227 views analyzed (24%), both for Observer 1 and Observer 2 ; when measurements made by Observers 1 and 2 were averaged, 44 views were found to have a >10% discrepancy with the CAAS measurements (19%).

For the 124 still-frames with <50% stenosis by CAAS analysis, the accuracy of measurements made by Observers 1 and 2 compared with CAAS was −1.2% and −0.7% respectively and the corresponding measurement precision was 9.6% and 8.3%. For the 103 still-frames with stenoses 50% or higher according to CAAS analysis, the accuracy was −0.5% and −0.8% respectively for Observer 1 and Observer 2 measurements compared with CAAS, and the corresponding precision was 7.3% and 8.3%.

*"Per stenosis" analyses*

The correlations and mean differences (measurement accuracy) between each observer and CAAS are displayed in Table 2 and Fig. 2 for the 102 coronary segments analyzed and visually assessed. No significant differences were identified between per lesion measurements obtained visually by either observer and CAAS analysis and the correlation between each observer measurement estimates and CAAS were correspondingly excellent. When considering the site involved, the correlation coefficients ranged from r = 0.92 for the left circumflex (y = 8.6 + 0.8x) to r = 0.96 (y = 5.9 + 0.9x) for the right coronary arteries. Compared with the CAAS measurements, there were 11 segments with a >10% discrepancy for Observer 1 (11%), 13 segments for Observer 2 (13%) and 7 segments (7%) for the average of Observers 1 and 2.

*Detection of restenosis*

Nineteen of the 102 analyzed segments had a complete sequence of pre-, post- and 6 months post-PTCA. Using, as a definition of restenosis, the presence of a >50% stenosis at 6 months, 9 segments (47%) had restenosis according to CAAS analysis, versus 8 (42%) for the average of measurements estimated by Observers 1 and 2, yielding a sensitivity of 78%, specificity of

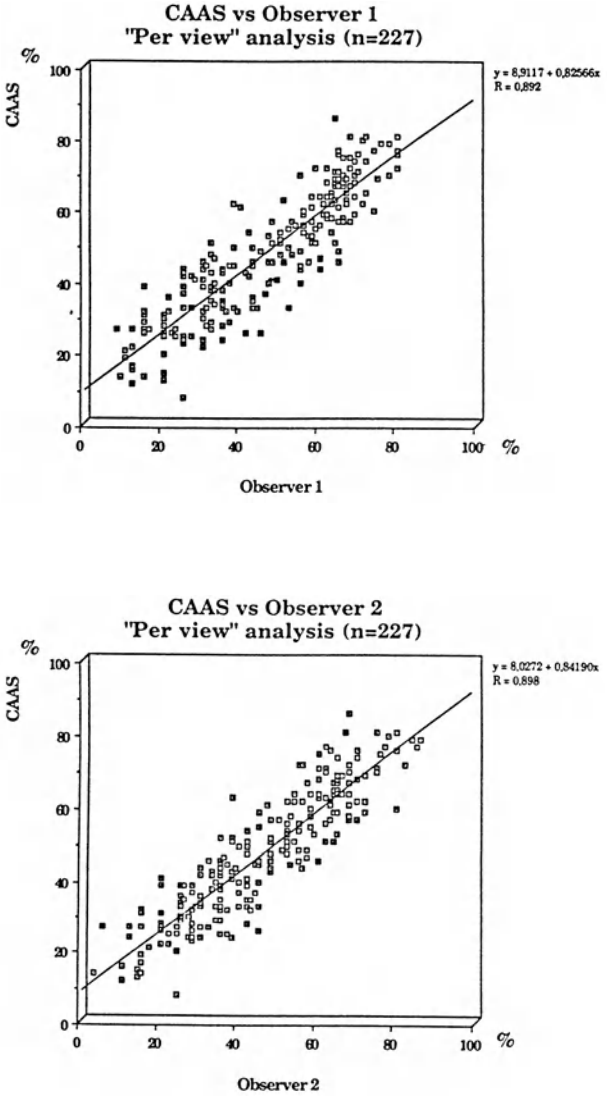


*Figure 1.* "Per view" analyses of the 227 still-frames. Correlations between Observer 1 and CAAS values (top) and Observer 2 and CAAS values (bottom).

90%, positive predictive value of 87% and negative predictive value of 82%. When restenosis was defined as a "loss of >50% of the initial gain", 7 segments had restenosis by CAAS analysis (37%) versus 9 segments for the average of Observers 1 and 2 (47%), with a sensitivity of 100%, specificity of 83%, positive predictive value of 78% and negative predictive value of 100%. Lastly, when restenosis was defined as progression of >20% from

*Table 1.* "Per view" analyses of the 227 frames selected for quantitative coronary angiography. Comparisons of Observers and CAAS measurements.

| | Slope | R value | P value | Accuracy | Precision | P value |
|---|---|---|---|---|---|---|
| Obs1 vs CAAS | $y = 8.9 + 0.83x$ | 0.89 | 0.0001 | −0.9% | 8.6% | NS |
| Obs2 vs CAAS | $y = 8.0 + 0.84x$ | 0.90 | 0.0001 | −0.7% | 8.3% | NS |
| Obs1 vs Obs 2 | $y = 3.4 + 0.93x$ | 0.94 | 0.0001 | −0.2% | 6.5% | NS |

Abbreviations: CAAS: Cardiovascular Angiographic Analysis; Obs1: Observer 1; Obs2: Observer 2.

post-PTCA to 6-months follow-up, 6 segments had restenosis by CAAS as well as by Observers measurements, yielding a sensitivity, specificity, positive and negative predictive value of 100%.

## Discussion

The findings of this study indicate that, provided observers have had extensive training in quantitative coronary angiography and a careful selection process of the frames to be analyzed is performed, visual estimates of the percent reduction of intraluminal diameter correlate well with CAAS measurements.

However, previous studies comparing visual and quantitative assessment of coronary artery stenoses, consistently showed that visual estimates were inaccurate or poorly reproducible [1, 2, 11], irrespective of the experience of the angiographers [7, 9], whereas quantitative coronary angiography measurements were both reliable and highly reproducible. It must be stressed, however, that reproducibility of quantitative angiography measurements was usually studied on previously selected still-frames, thereby only testing the reproducibility of the contour detection of the analyzed coronary segments [15]. Conversely, all of the studies assessing the reliability of visual assessment were carried out by the conventional practice, with the film running continuously on a projector. In the present study, the same still-frames analyzed by QCA were visually assessed by the observers. In such conditions, it appears that the eye of the observer with QCA experience can more easily integrate the relative diameters of the artery at the site of the stenosis, as well as at the level of its adjacent proximal and distal segments, taking into account the anatomic tapering of the vessel, in order to determine the percent stenosis in a similar fashion to QCA measurements relative to the "interpolated" reference diameter of the coronary artery. Our findings are in keeping with those of Scoblionko et al. [8], reporting a 7% intraobserver variability in visual analyses made on still-frames of 18 coronary stenoses of varying degree.

Using such a technique, the reproducibility of visual assessments by observers trained in QCA was satisfactory and was comparable with that pre-

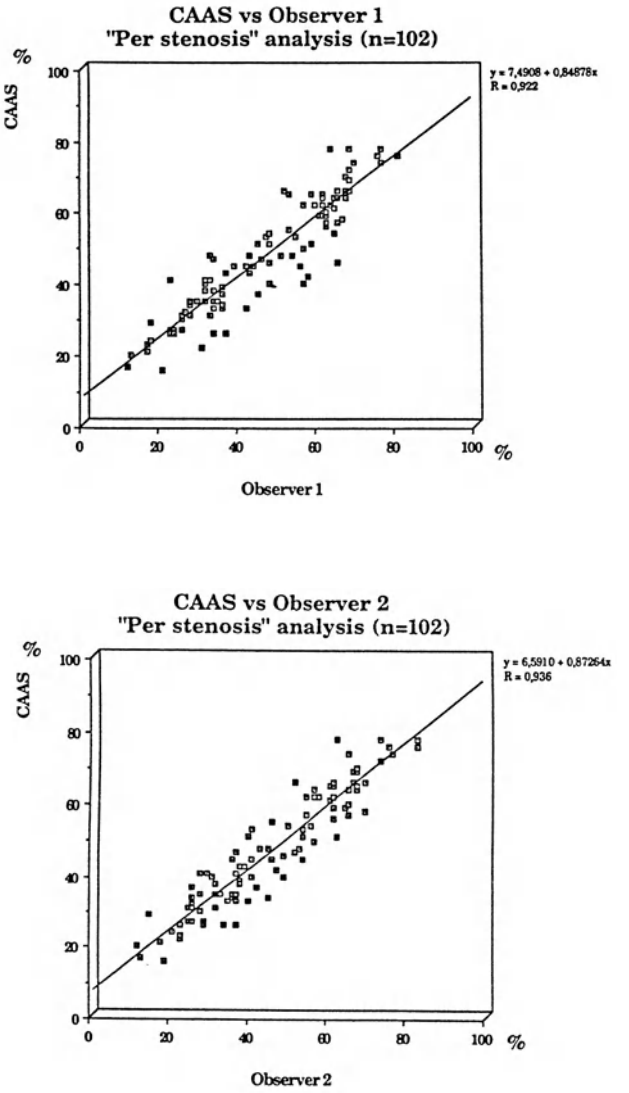


*Figure 2.* "Per stenosis" analyses of the 102 stenoses. Correlations between Observer 1 and CAAS values (top) and Observer 2 and CAAS values (bottom).

viously noted for quantitative analysis of coronary stenoses when the complete seqence of both frame selection (which remains a subjective observer-dependent step), and quantitative analysis (automatic contour detection) was repeated [7]. The importance of frame selection for QCA has very recently been emphasized and was shown to increase the variability of contour detection from 5% when QCA was repeated on the same previously selected still-

*Table 2.* "Per stenosis" analyses of the 102 coronary segments selected for quantitative coronary angiography. Comparisons of Observers and CAAS measurements.

| | Slope | R value | P value | Accuracy | Precision | P value |
|---|---|---|---|---|---|---|
| Obs1 vs CAAS | y = 7.5 + 0.85x | 0.92 | 0.0001 | −0.5% | 6.8 | NS |
| Obs2 vs CAAS | y = 6.6 + 0.87x | 0.94 | 0.0001 | −0.8% | 6.1% | NS |
| Obs1 vs Obs 2 | y = 2.2 + 0.95x | 0.96 | 0.0001 | +0.2% | 5.0% | NS |

Abbreviations: CAAS: Cardiovascular Angiographic Analysis System; Obs1: Observer 1; Obs2: Observer 2.

frames to 7% when a complete sequence of frame selection followed by QCA was repeated [12]. Furthermore, the variability of visual analysis in this study appeared only slightly higher than that previously noted for CAAS measurements made on 3 different frames preceding or following a given selected frame [21].

In addition, we did not find the usual bias of visual analysis made on running films, namely an overestimation of tight stenoses and underestimation of milder ones [4, 5, 9]. In particular, it is noteworthy that despite the fact that 24 lesions were undergoing angioplasty, neither observer reported a stenosis severity greater than 85%, whereas the 90% diameter stenosis is frequently reported by conventional visual coronary artery assessment. We have previously pointed out that 90% diameter stenosis probably does not exist in reality [22] and it has recently been clearly demonstrated that it would be physiologically impossible to maintain anterograde flow in lesions of this severity : in fact, among 1445 lesions treated by PTCA, the most severe lesion in a patent artery was 86% [23].

These results, however, should not be extrapolated to visual estimation of absolute measurements of minimum luminal diameter in mm, which would be a more hazardous task since the catheter used as a scaling device is distant from and never immediately contiguous to the stenosis site to facilitate its use as a calibration device for the observer. Also it is highly unlikely that visual analysis could provide a satisfactory level of accuracy or precision in mm comparable with QCA [14]. In this regard, it must be emphasized that for interpreting the results of pharmacological or instrumental interventions on restenosis or progression/regression of coronary artery disease, absolute measurements in mm as provided by quantitative analysis should preferentially be used [13, 24–26].

In conclusion, thus, it appears that, for angiographers accustomed to the results obtained with quantitative coronary angiography, and provided the analyses are made on still-frames which are as carefully selected as for quantitative analysis, visual assessment of coronary stenoses is reproducible, fairly accurate and may be sufficient for clinical purposes and indeed appropriate for certain clinical studies.

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*PART THREE: Physiological applications of QCA, correlation with intracoronary physiological measurements obtained by alternative methodology*

# 10. Intracoronary pressure measurements with a 0.015″ fluid-filled angioplasty guide wire

BERNARD DE BRUYNE, NICO H.J. PIJLS, PASCAL J. VANTRIMPONT, WALTER J. PAULUS, STANISLAS U. SYS, and GUY R. HEYNDRICKX

## Introduction

The usefulness of distal coronary pressure monitoring during percutaneous transluminal coronary angioplasty (PTCA) was recognized by the pioneers in balloon angioplasty as testified by the design of a fluid-filled lumen in the first generation of balloon catheters. However, the interest in measuring coronary pressure has oscillated between enthusiasm of having a simple index of coronary hemodynamics [1–4] and disillusion due to the inconsistency of the results [5–7]. Clinical practice learned that a marked reduction in coronary flow often accompanies the placement of the deflated balloon catheter across the stenosis. Accordingly, it was admitted that, even with the presently available ultra low profile balloon angioplasty catheters, a marked overestimation in gradient could occur. The development of monorail angioplasty catheters precluding pressure measurements, further prompted the trend away from measuring distal pressures during PTCA. Nevertheless, it still holds that the knowledge of the transstenotic pressure gradient can be of aid to estimate dilatation efficacy [8–10]. Accordingly, a fluid-filled pressure monitoring PTCA wire was developed. It is the smallest coronary pressure monitoring device ever built and, hence, it should not cause additional obstruction to coronary flow when positioned across the lesion. Furthermore, monorail balloon catheters are best suited to be used over this wire to perform angioplasty.

This chapter reports on the validation studies performed with this novel guide wire and describes the influence of different measuring equipments on stenosis hemodynamics.



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## Methods

### *Technical characteristics of the wire*

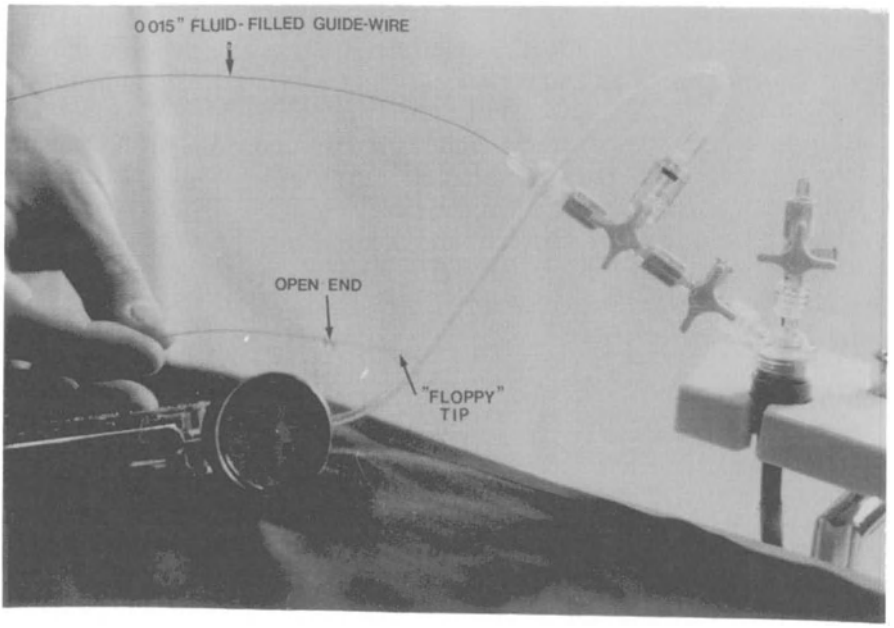
The pressure monitoring guide wire is a steerable angioplasty wire (Premo™ wire, Advanced Cardiovascular Systems, Santa Clara, CA). The pressure is transmitted through a fluid column. The proximal 129 cm section consists of a teflon coated hypotube with an external diameter of 0.015″. The next 45 cm are made of a second hypotube which is coaxial to a core wire. These two hypotubes communicate via ten 0.002″ diameter ports. A second series of ten 0.002″ diameter pressure monitoring ports are located 3 cm from the tip, at the junction of the non-radiopaque portion and the radiopaque tip of the wire. The 3 cm tip is radiopaque, flexible and shapable. The wire is to be connected to a conventional pressure transducer for pressure monitoring (Fig. 1).

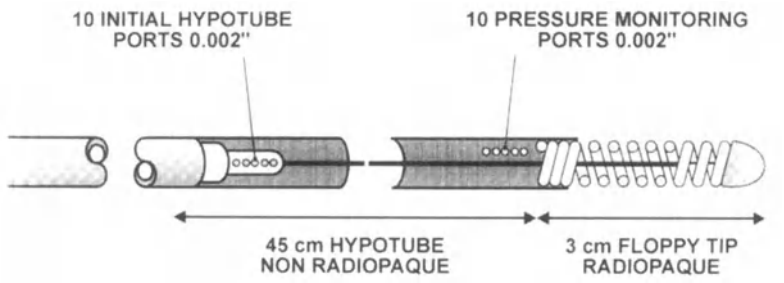
### *In vitro validation of the accuracy of the pressure measurements with the Premo™ wire*

Five pressure monitoring guide wires were tested in a hydrostatic model consisting of a water-filled barrel, connected to a silastic tube whom distal end was Y shaped. A tip micromanometer (Millar SP-780C) was introduced in one leg of the Y and the pressure monitoring guide wire to be tested as well as a 5F right Judkins coronary catheter were introduced in the other leg. By adjusting the height of the barrel, measurements at different pressures were performed. The 5 pressure-monitoring wires were tested consecutively in eight following steps : from 0 to 50 cm $H_2O$, from 50 to 100 cm $H_2O$, from 100 to 150 cm $H_2O$, from 150 to 0 cm $H_2O$, from 0 to 150 cm $H_2O$, from 150 to 100 cm $H_2O$, from 100 to 50 cm $H_2O$ and from 50 to 0 cm $H_2O$. At each level, pressure measured with the Millar manometer and the pressure-monitoring guide wire were simultaneously recorded until the wire pressure reached a plateau. The absolute pressures measured with both the microtip manometer and the fluid-filled guide wire were compared and the percent differences were calculated. The time constant of the pressure-monitoring wire was calculated for every step. It is defined as the time required for the signal to reach 63.2% of its final value.

### *In vitro experiments on the influence of PTCA wires on stenosis dynamics*

In rigid plastic tubes with an inner diameter of 4 mm, 6 narrowings were created ranging from 50 to 95% area reduction. The length of the narrowing was 10 mm. One extremity of the tube was attached to a connector with 3 side arms. A high-fidelity pressure-monitoring catheter (Model 110–4, Camino Laboratories, San Diego, CA) was advanced through one of the valves. The 0.015″ pressure-monitoring wire was passed through the second valve and




PREMO ™ GUIDE WIRE (Advanced Cardiovascular Systems)

*Figure 1.* Photography and schematic representation of the Premo™ angioplasty guide wire. (See text for details). The fluid-filled guide wire is connected to a pressure transducer via 2 three-way stopcocks. This allows to flush the wire with an "indeflator" during the procedure without disconnecting the wire from the pressure transducer.

the third arm was connected to a power injector (Mark IV, Medrad Inc, Pittsburgh, PE). The other extremity of the tube was attached to a conventional Y connector. A second high-fidelity pressure-monitoring catheter was introduced through the valve and the other arm was let open. Constant flow rates of 0.5, 1, 1.5, 2, 3, 4 and 5 ml/s were infused through the stenotic model by a power injector. The accuracy of the flow rates was controlled by means of a graduated cylinder placed under the distal opening of the system. For each stenosis severity, the pressures were recorded proximally and distally to the stenosis at different flow rates. Each of these pressure measurements were performed successively without and with the wire through the narrowing.

*Theoretical model*

The fluid dynamic equation was used to calculate the overestimation of the pressure gradient produced by the presence of the wire itself through the lesion. The percent overestimation in pressure gradient (pressure gradient with the wire through the lesion minus the true transstenotic pressure gradient divided by the true transstenotic pressure gradient) was calculated in 10 mm long lesions of increasing severity, in vessels of different reference diameters (2,3,and 4 mm) at flow rates of either 1 ml/s or 5 ml/s and for 2 different wire cross-sectional diameters (0.015″ and 0.018″).

*In vivo studies*

Thirty-seven patients undergoing PTCA for single vessel disease (14 left anterior descending, 15 right and 8 left circumflex coronary arteries) were studied. Total coronary occlusions were excluded from this study. The ability to perform quantitative coronary angiography in at least two projections was a prerequisite. An 8 French introduction sheath was inserted in the right femoral artery and a 7 or 8 French Judkins guiding catheter was used to cannulate the coronary ostium. Both the side arm of the sheath and the guiding catheter were connected to a pressure transducer (Spectranetics P 23 Statham). The Premo™ wire was flushed with heparinized saline and attached via two three way high-pressure stopcocks to the pressure transducer. The side arm of the distal stopcock was connected to an indeflator filled with heparinized saline for frequent flushing of the wire. The three pressure transducers were zeroed at mid-chest level. The pressure-monitoring guide wire was placed at the tip of the guiding catheter, where mean and phasic guiding pressure and guide wire pressure were simultaneously recorded. After administration of 2 mg of intracoronary isosorbide dinitrate, the wire was advanced through the stenosis while continuously recording the phasic pressures of the femoral sheath, of the guiding catheter and the pressure monitoring guide wire. Pressure recordings were performed at least 3 mins after the last contrast medium injection. In most cases the pressure

monitoring wire could crossed the lesion while remaining connected to the pressure transducer. When this was not possible, the wire was disconnected from the transducer for better torque control. Only the radiopaque tip was placed distally to the narrowing so that the side holes remained proximally to the stenosis. The proximal part of the wire was again connected to the pressure transducer. Under continuous pressure monitoring the guide wire was then advanced so that the side holes were positioned across the stenosis. After equilibration of the pressures, the mean pressure gradient was recorded between the guiding catheter and the pressure monitoring guide wire ($\Delta P_w$). A monorail type dilatation balloon catheter was mounted on the wire and advanced in the stenotic segments. After equilibration of the distal pressure, the mean pressures were again recorded through the guiding catheter and the pressure-monitoring guide wire. This allows to determine the pressure gradient measured with a deflated angioplasty balloon catheter across the stenosis ($\Delta P_b$). The percent overestimation induced by the presence of the deflated balloon catheter into the lesion was calculated as follows: $[(\Delta P_b/Pao_b - \Delta P_w/Pao_w)/(\Delta P_w/Pao_w)] * 100$ where $\Delta P_b$ is the pressure gradient measured with the balloon catheter, $Pao_b$ is the mean aortic pressure at the time of assessment of the pressure gradient with the balloon catheter, $\Delta P_w$ is the pressure gradient measured with the pressure monitoring guide wire and $Pao_w$ is the mean aortic pressure at the time of assessment of the pressure gradient with the pressure monitoring guide wire.

At least 5 min after the last balloon inflation and 2 min after 2 mg intracoronary isosorbide dinitrate administration the same measurements were repeated. Finally the guide wire was pulled back into the guiding catheter where the mean pressures of the guiding catheter and the pressure monitoring guide wire were again compared.

*Quantitative coronary angiography*

Measurements of the stenotic segment was performed with the Coronary Angiography Analysis System (CAAS) previously described and validated by Reiber et al. [11]. The percent area stenosis and the minimal luminal cross sectional area were calculated and averaged from at least two projections.

## Results

*In vitro studies*

The true hydrostatic pressure and the pressure recorded by the tip manometer were identical and therefore the latter was used as an equivalent of the true pressure.

An excellent correlation ($r = 0.98$) was found between the pressure mea-

surements performed with the tip manometer and the fluid-filled pressure-monitoring guide wire. However, the pressure recorded by the Premo™ wire slightly underestimated the true pressure in all cases. The percent difference between both measurements was $-3\% \pm 5\%$ ($n = 15$). The time constant for all steps was almost identical in a single pressure monitoring guide wire. However, there were wide variations in time constant between the 5 pressure-monitoring guide wires tested (from 9 to 27s, mean $16 \pm 5$s). Fig. 3 shows in vitro pressure gradient measured through lesions of increasing severity and at varying flow rates. All measurements were performed without and with a 0.015" wire in the stenosis. In mild lesions (50% area stenosis) the overestimation in pressure gradient measurement produced by the presence of the 0.015" wire through the lesion remained limited (<5 mmHg) even at high flow rates (5 ml/s). However in tight lesions ($\geq$90% area stenosis), the difference in pressure gradient measured without and with the wire through the lesion was large even at intermediate flow rates. In lesions of 80% area stenosis, the overestimation in pressure drop induced by the presence of the wire became significant only at high flow rates.

*Theoretical model*

These figures were confirmed by the calculations made on the basis of the fluid dynamic equation (Fig. 4) : the percent overestimation in pressure drop due to the presence of a 0.015" wire across a stenosis increased as an exponential function of percent area stenosis and as an inverse function of the reference diameter. By contrast, the influence of transstenotic flow on the relative overestimation in pressure drop was limited. The right panel of Fig. 4 demonstrates that the size of the wire is of crucial importance in assessing transstenotic pressure gradient. In a vessel with a reference diameter of 3 mm and presenting a 80% area stenosis, a 0.015" wire produced a 20% overestimation in pressure drop when the flow rate was 1cc/s. In the same lesion, a 0.018" guide wire produced a 30% overestimation in pressure drop at a flow rate of 1cc/s.

*In vivo studies*

The correlation between the mean pressures recorded by the guiding catheter and by the Premo™ wire advanced up to the tip of the guiding catheter is shown in Fig. 5. Both before and after PTCA a regression line close to the line of identity was found with only 3 patients showing a difference in mean pressure >5%.

The target vessel could be reached in all cases. All, except one lesion were crossed (97%) with the pressure monitoring guide wire without any particular difficulty and angioplasty could be successfully performed without need for another guide wire. There were no complications. The only lesion

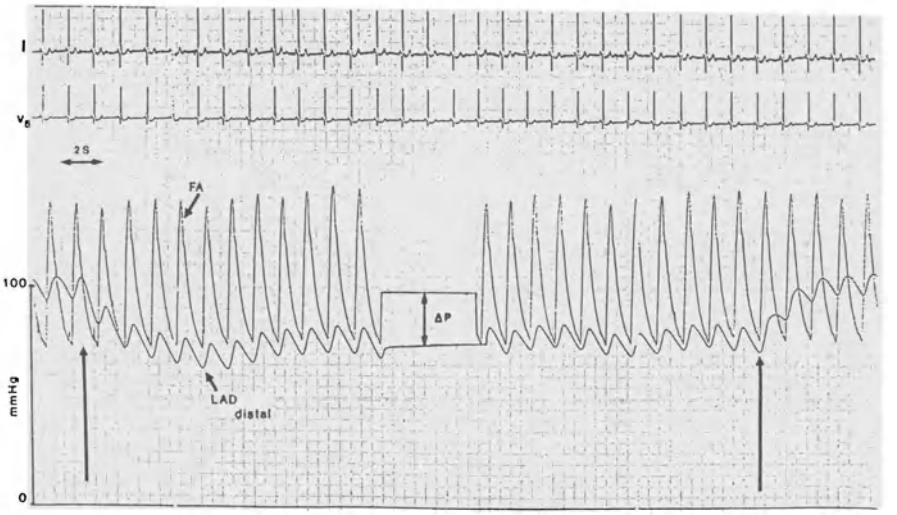



*Figure 2.* Example of coronary pressure gradient measurement with a 0.015" PTCA guide wire. From top to bottom: Two electrocardiographic leads (I and $V_5$), a pressure recording in the femoral artery (FA, through the side arm of the femoral sheath) and a pressure recording in the distal left anterior descending coronary artery (LAD, through the Premo™ guide wire). As compared to the pressure tracing recorded in the femoral artery, the pressure tracing recorded with the pressure monitoring guide wire is damped. When the distal pressure monitoring ports are advanced distally to the lesion (left arrow), a mean pressure gradient (ΔP) of 25 mmHg is observed.

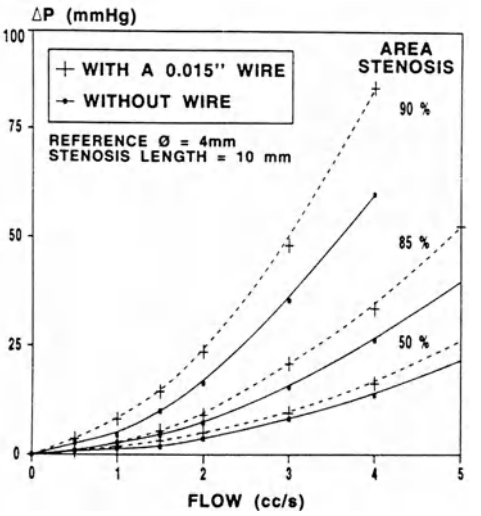



*Figure 3.* Plot of the pressure gradients measured in vitro for varying stenosis severity (50, 85 and 90% area stenosis) at incremental flow rates. Each measurement was obtained with (broken line) and without (continuous line) a 0.015" wire across the stenosis.

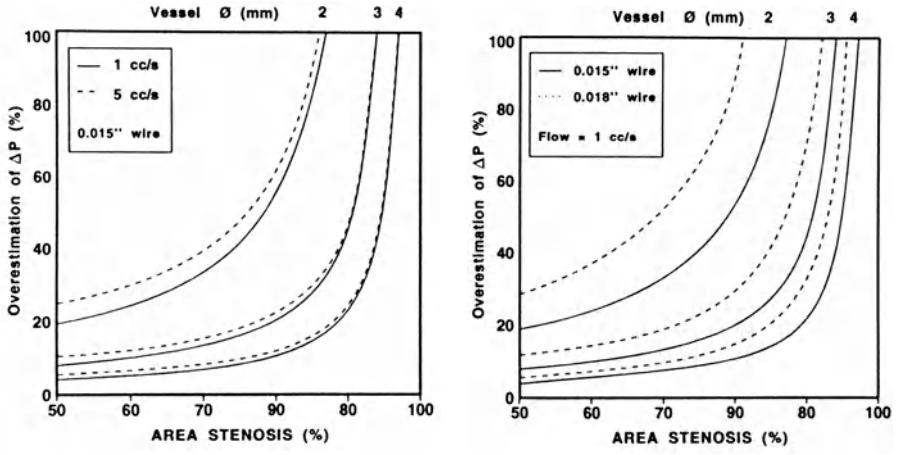



*Figure 4. Left panel*: Computer-derived calculation of the overestimation in pressure gradient measured with a 0.015" wire due to the presence of the wire itself in the stenosis.The overestimation was determined for incremental degrees of percent area stenosis (from 50 to 100%), for incremental reference diameters (from 2 to 4 mm) and for 2 different flow rates (1cc/s, continuous line and 5 cc/s, broken line). *Right panel*: Computer-derived calculation of the overestimation in pressure gradient due to the presence in a 10 mm long lesion of a 0.015" guide wire (continuous line) and of a 0.018" guide wire (broken line) for varying area stenoses and reference diameters at a constant flow rate of 1 cc/s.

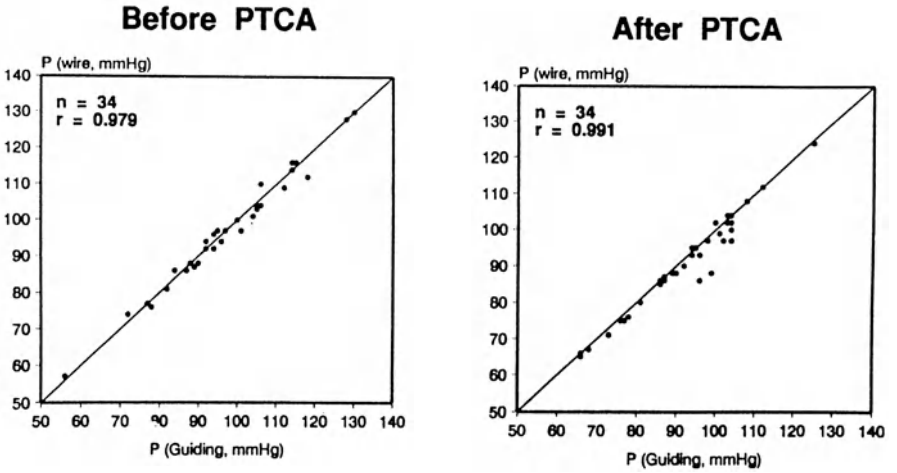



*Figure 5.* Correlation between the mean aortic pressure measured simultaneously with the guiding catheter and with the pressure monitoring guide wire when the latter is advanced up to the tip of the guiding catheter.

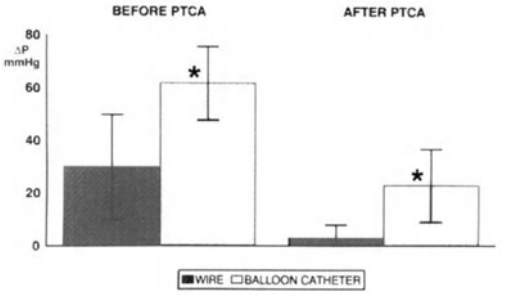



*Figure 6.* Transstenotic pressure gradient (ΔP) before and after coronary angioplasty measured either with the pressure monitoring guide wire or with the balloon catheter. (* = $p < 0.01$ vs ΔP measured with the Premo™ guide wire).

which could not be crossed with the Premo™ wire was an eccentric stenosis in the mid-LAD followed by a bend of approximately 80°.

The phasic pressure tracings were very damped as compared to those simultaneously obtained by the guiding catheter (Fig. 2). The mean transstenotic pressure gradient measured with the guide wire decreased from 30±19 mmHg before PTCA to 3±5 mmHg after PTCA ($p < 0.01$). Both before and after PTCA, the mean pressure gradient measured with the wire was significantly lower than the mean transstenotic pressure gradient measured with the balloon catheter (30±20 vs 62±14 mmHg before angioplasty, $p < 0.01$; and 3 ± 5 vs 23±14 mmHg, after angioplasty, $p < 0.01$). A weak correlation was found between the $\Delta P_w$ and $\Delta P_b$ before PTCA ($\Delta P_w = 0.53\Delta P_b - 2.9$; $r = 0.38$, $p = 0.026$). No significant correlation was found between both pressure gradient measurements after PTCA (Fig. 6).

### 2. *Comparisons of pressure gradient measurements and quantitative coronary angiography*

The relationship between the measured pressure gradient and the minimal obstruction area was best fitted by a quadratic equation as an inverse function of the obstruction area. This relation showed a steep decrease in gradient once the obstruction area exceeded 1.6 $mm^2$ (Fig. 7). Figure 8 shows the relationship between percent area stenosis as derived from coronary angiography and transstenotic pressure gradient measured either with the wire ($\Delta P_w$) or with the balloon catheter ($\Delta P_b$). A sharp increase in $\Delta P_w$ was observed once the area stenosis exceeded 80% ($r = 0.66$). Although statistically significant, the correlation between $\Delta P_b$ and the percent area stenosis was much weaker ($r = 0.53$), with a major scatter of the values around the fitted curve. Moreover, the inflection point of the curve was shifted toward much less pronounced stenosis severity. Figure 9 shows the relationship between the overestimation in pressure gradient induced by the balloon

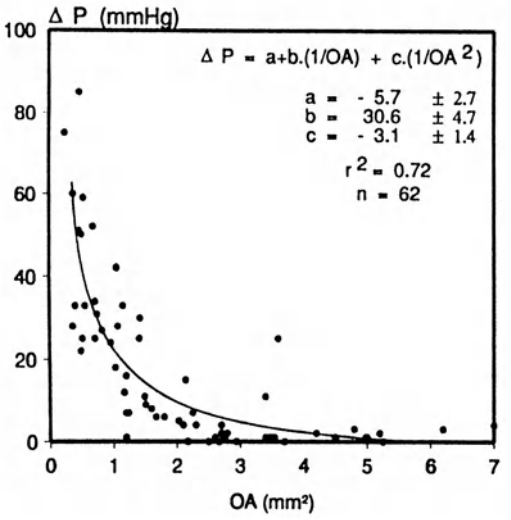



*Figure 7.* The relationship between the transstenotic pressure gradient (ΔP) and the minimal obstruction area (OA) is non linear and was best fitted by a quadratic equation.

catheter and the relative obstruction created by the catheter in the stenosis. Paradoxically, the smallest errors were found in severe lesions, when the catheter is totally occlusive since even without catheter these lesions induced a large pressure drop. In mild or intermediate lesions the overestimation due to the presence of the catheter was spread over a very large range of value, precluding any predictive value of the measurement.

## Discussion

### *Usefulness of the pressure gradient measurements during coronary angioplasty*

The physiological consequences of a stenosis in an epicardial artery are determined by its effects on coronary blood flow and distal coronary pressure, especially during exercise. Since regional coronary blood flow and perfusion pressure are difficult to assess during routine catheterization, the functional significance of a coronary lesion is mostly derived from their morphological appearance on coronary angiograms. It is, however, generally appreciated that coronary arteriography can underestimate as well as overestimate the true severity of a stenosis when compared with post-mortem examination [12, 13]. Moreover, interobserver and intraobserver variability in stenosis severity evaluation is a major concern, especially after PTCA [14]. Therefore, several computer aided methods quantitating all morphological character-

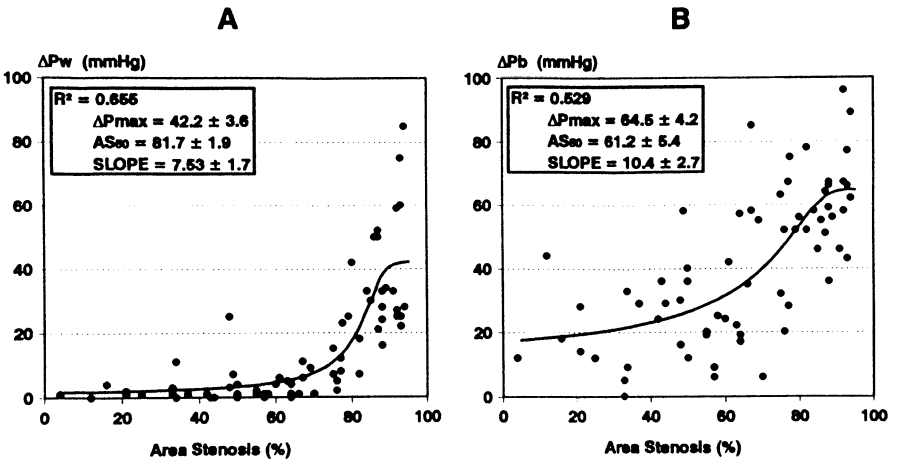



*Figure 8.* The relationship between percent area stenosis and transstenotic pressure gradient measured with a 0.015" fluid-filled pressure monitoring guide wire is shown in the left panel. The right panel shows the relationship between percent area stenosis and transstenotic pressure gradient measured with an angioplasty balloon catheter. A logistic function was fitted to the observed values: $\Delta P = \Delta P_{max}/(1 + \exp\ (4 * \text{slope} * (x_{0.5} - x)/\Delta P_{max}))$ where $x_{0.5}$ is equal to $100/(100 - AS_{50})$. The respective asymptotic error of the estimates are given in the figure.

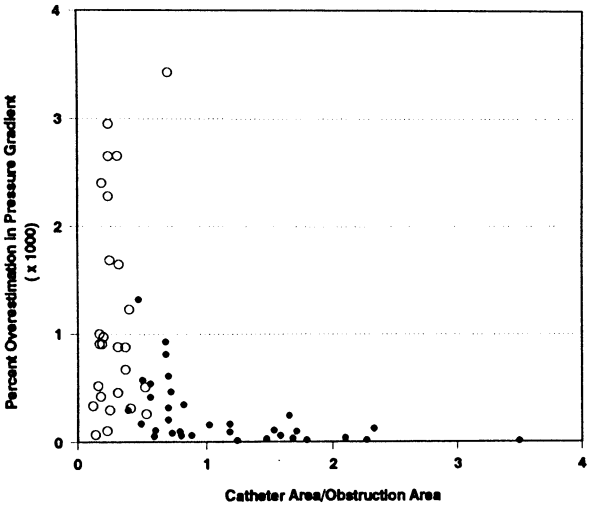



*Figure 9.* Relationship between the percent overestimation in pressure gradient due to the presence of the balloon catheter itself through the lesion, and the relative dimensions of the balloon catheter as compared to the stenotic cross sectional area. (Closed circles = before angioplasty, open circle = after angioplasty)

istics of coronary lesions have been developed [11, 15, 16]. Their main advantage is to be more objective therefore leading to more reproducible results. Furthermore, since quantitative coronary angiography is able to determine the length of the lesion, the reference diameter, the stenotic diameter and more recently the roughness of the stenotic boundaries [17], functional information can theoretically be derived from these morphological data. The link between the morphological and the functional approach has been clearly validated in an animal model instrumented with flow meters where a stenosis was created by external compression of a coronary artery. In these chronically instrumented dogs the percent area reduction correlated well with absolute and relative coronary flow reserve [18]. Moreover it was demonstrated that arteriographically measured stenosis flow reserve is a more specific functional measure of stenosis severity than direct measurement of absolute coronary flow reserve by flow meter because the effects of physiologic variables others than stenosis severity are eliminated [19]. However, in these studies the stenosis was induced by external compression of normal coronary arteries resulting in concentric lesions, whose smooth boundaries are easily detectable and which can be compared to nondiseased reference segments. This stenotic model is not necessarily equivalent to irregular atheromatous lesions as encountered in clinical practice, wherein thrombus material is often superimposed and whose reference segment is most often abnormal. Studies in man, indeed, suggested that coronary luminal stenosis, determined quantitatively, correlates closely with functional parameters when coronary obstruction is produced by discrete, limited coronary artery disease [20, 21]. In contrast, in patients with more diffuse coronary artery disease, coronary flow reserve poorly correlates with percent area and percent diameter stenosis probably because of the difficulty to angiographically determine the actual severity of the lesion and because of the limited value of the concept of coronary flow reserve in these situations [22, 23]. Furthermore, quantitative coronary angiography is not always applicable since overlapping with adjacent vessel tortuosities and side branches is difficult to avoid in two orthogonal planes and since the stenotic segment cannot always be placed perpendicular to the X-ray beam. After PTCA, the edges of the lumen are often hazy (as demonstrated by intravascular sonography) because of intimal tears and dissections rendering the edge detection difficult [24]. Hence, the need for a simple index providing information about the physiological consequences of coronary stenoses is evident. Several methods were developed to determine the coronary flow reserve [25,26] or maximal coronary flow [27, 28]. Although they were compared to other validated techniques, Doppler velocitometry assessment and myocardial densitometry cannot be performed routinely in the setting of coronary angioplasty to evaluate lesion severity or to control the immediate results after dilatation. These methods are time consuming and have inherent technical limitations : they need sophisticated and expensive equipment and they often need off-line analysis of the data. In an unselected patient population undergoing PTCA it has

recently been shown that coronary flow determination by densitometry was not reliable and therefore useless for correct decision making in the individual patient [29]. Newer videodensitometric techniques which compare maximal flow before and after PTCA, are more accurate for these purposes [28]. Nevertheless, videodensitometry remains laborious and sophisticated. In contrast, measuring transstenotic pressure gradient is basically very simple. For a given mean systemic pressure and a given coronary flow, it is a functional index of stenosis severity taking into account all morphological determinants of the lesions. Moreover, it has recently been shown that transstenotic pressure measurements alone during maximal arteriolar dilatation were sufficient to calculate relative maximal flow or fractional flow reserve of both the coronary artery and the myocardium including collateral flow [30]. The experimental basis of this concept is described in detail in a separate chapter hereinafter. Sofar, the distal coronary pressure has been measured through the angioplasty balloon catheter. As corroborated by the results of the present study, the presence of the catheter across the stenosis leads to an overestimation of the true pressure gradient since the stenotic lumen is further reduced by the balloon catheter. To correct for this overestimation Wijns et al. [20] subtracted the cross sectional area of the balloon catheter from the stenotic area measured from the coronary angiogram. However, in one third of patients, the catheter was completely occlusive in the stenosis. When antegrade flow is interrupted, the distal pressure, is mainly determined by collateral flow and no longer provides reliable information about the stenosis itself. This prompted Ganz et al. [31,32] to measure transstenotic pressure gradients in renal coronary arteries by means of 2 or 3 F catheters. However, even these thin catheters would have produced a complete or near complete occlusion in approximately 40% of lesions investigated in the present study.

### *Accuracy of pressure measurements with the* 0.015″ *fluid filled pressure monitoring guide wire*

As shown in the in vitro tests the pressure monitoring guide wire approximated real hydrostatic pressure reasonably well in most cases, once steady state pressure was reached. The mean underestimation of the real pressure reached 3±5% depending on the wire tested. In vivo, the mean pressure measured with the open-end wire advanced at the tip of the guiding catheter correlated very well with the mean pressure obtained by the guiding catheter advanced in the ostium of the coronary artery. This good concordance was present both before and after PTCA. In only 3 patients a difference larger than 5% was found. In contrast, the long time constant of the wire precluded phasic pressure tracings recording.

*Use of the Premo™ wire in man*

All but one angioplasty could be accomplished with the pressure monitoring guide wire without need for another wire (97%). No technical problems were encountered when crossing the lesion with the wire. The use of "monorail" angioplasty catheter systems facilitated the manipulation of the wire and the pressure recordings. Clotting of the lumen of the wire occurred in 2 patients and precluded further measurements of distal pressures. This emphasizes the need for frequent flushing of the wire.

*Comparison with pressure gradient measured with angioplasty catheters*

Comparative data of transstenotic pressure gradient measured with a pressure monitoring guide wire vs angioplasty balloon catheters confirm that a systematic overestimation is induced by the presence of the balloon catheter in the lesion. The same conclusions were drawn by Serruys et al. [6] using a theoretical pressure gradient calculation and by Sigwart et al. [33] who compared the mean pressure gradients measured with high-fidelity tip-transducers and with balloon catheters in 7 patients. Moreover, our results demonstrate that, even after angioplasty, when an angiographically satisfactory result was achieved, a significant overestimation of the pressure gradient was still present when measured with the angioplasty balloon catheter. This observation strongly suggests that after successful PTCA intraluminal defects, not appreciated by vessel edge detection, still diminish the cross sectional area of the dilated segment. In contrast to the theoretical model of Leiboff et al. [7] who found that the overestimation of the "true" transstenotic pressure gradient was predictable, our results suggest that the overestimation is not predictable in vivo. Hence, the pressure gradient measured by means of the balloon catheter is relatively accurate when this information is not needed (i.e. in critical lesions in which angiography most often suffices) but is inaccurate when this information is most desirable (i.e. in intermediate lesions and in post-PTCA segments were functional information can be clinically helpful).

*Correlation with quantitative coronary angiography*

The exponential relationship between transstenotic pressure gradient measured with the wire and both obstruction area (Fig. 7) and percent area stenosis (Fig. 8, left panel) evokes the relationship between coronary flow reserve and percent area reduction described by Gould et al. in the animal model [34]. This similarity further suggests the role of mean pressure gradient as a functional index of coronary stenosis severity. The role of other factors than area stenosis alone and the relative inaccuracy of quantitative angiography (especially after PTCA), can account for some marked differences in measured pressure gradients across stenosis of similar angiographic severity.

In contrast, when the gradient is assessed with the angioplasty balloon catheter, a major scatter of the data and a leftward shift of the fitted curve were observed suggesting that pressure gradients measured with angioplasty catheters poorly reflect stenosis physiology.

*Influence of the presence of the wire on stenosis dynamics*

The in vitro results showed that in mild to moderate stenoses the overestimation produced by the presence of the wire itself can be neglected because of the large ratio between obstruction area and cross sectional area of the wire (0.114 $mm^2$). According to the fluid dynamic equation, an inverse relation exists between the relative overestimation in pressure gradient due to the wire and the reference diameter of the vessel. This implies that in small coronary arteries the overestimation of the measured pressure gradient produced by the presence of the wire itself will be larger than in large coronary vessels for a given percent area stenosis. At low flow rates (equivalent to basal coronary flow) the absolute overestimation in pressure gradient due to the presence of the guide wire in the obstruction remained small. At high flow rates, these absolute values increased. The influence of a guide wire on coronary stenoses dynamics should be kept in mind when using recently developed Doppler [35] and micro manometer-tipped [36] guidewires. Nevertheless, from a clinical point of view, these figures are not relevant : no major increase in flow is to be expected once the stenosis exceeds 80% diameter reduction. The mean pressure necessary to increase the flow above 3 cc/s through a 90% area stenosis exceeds the physiological range (>190 mHg mean driving pressure). Furthermore, in clinical practice these lesions do not need sophisticated measurements to be considered as critical and to trigger adequate clinical decision making. In lesions of intermediate severity and in post angioplasty segments where angiography often fails to be conclusive, the wire should provide a true value of pressure gradient which can be helpful in clinical practice. Finally, since the relative overestimation of pressure drop produced by the wire across the lesion is very little influenced by the flow, the ratio of hyperemic on resting transstenotic gradient will not change significantly.

*Advantages and limitations of the fluid-filled wires as compared to micromanometer-tipped guide wires*

The main advantages of the Premo™ wire is its simplicity and its low cost. Since it has essentially the same technical characteristics of most of the currently available PTCA guide wires it could be routinely used to cross the majority of the lesions scheduled for angioplasty and could even be proposed to measure gradients across dubious lesions during diagnostic catheterization. Thanks to the small cross-sectional area of the wire only very limited hindrance on coronary hemodynamics is to be expected. The main limitation of

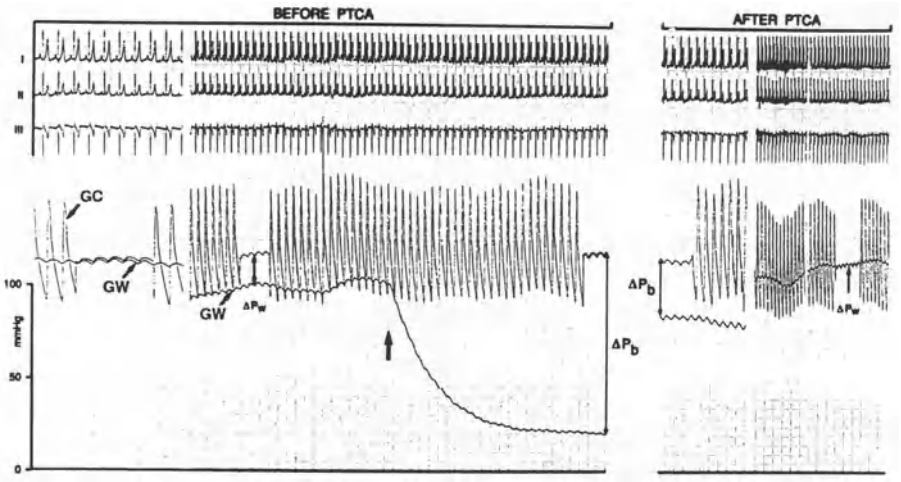



*Figure 10.* Example of pressure gradient measurements with either the Premo™ guide wire or with the angioplasty balloon catheter. *Left panel*: The mean aortic pressure recorded by the guiding catheter and by the Premo™ guide wire are first compared when the wire is advanced at the level of the coronary ostium. The distal holes of the wire are then advanced distally to the stenosis allowing to record the mean transstenotic pressure gradient ($\Delta P_w$). When the deflated balloon catheter is advanced into the stenotic segment (arrow), a marked increase in pressure gradient is observed ($\Delta P_b$). *Right panel*: After angiographically successful angioplasty, the gradient is measured again with the deflated balloon positioned across the dilated segment. When the balloon catheter is pulled back in the guiding catheter, the gradient measured across the lesion is virtual. (Abbreviations: FA = femoral artery, GC = guiding catheter, GW = pressure monitoring guide wire).

the fluid-filled pressure monitoring guide wire consists in the inability to measure phasic pressure tracings (Fig. 10). In contrast to micromanometer-tipped wires, systolic and diastolic components of the gradient cannot be distinguished with the fluid-filled pressure monitoring guide wire. Since coronary blood flow occurs predominantly during diastole, a gradient may exclusively occur during diastole in mild stenoses and in post PTCA segments (Fig. 11). However, this limitation should not have clinically relevant consequences and should be offset by several practical advantages.

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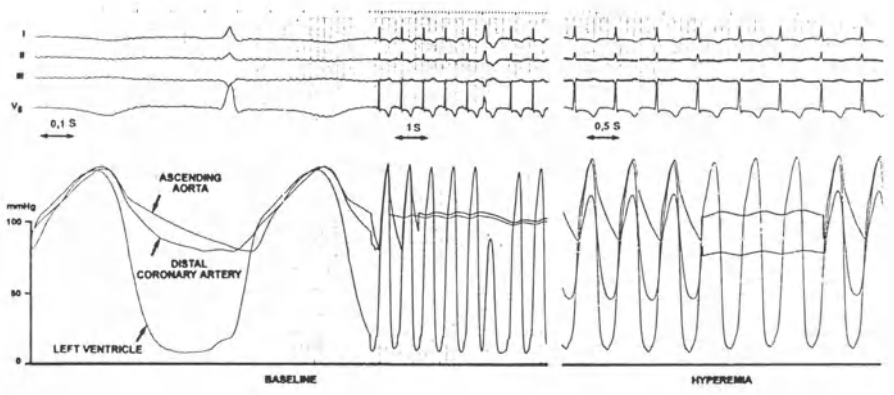


*Figure 11.* Example of pressure tracings recorded with high-fidelity micromanometers in the ascending aorta, in the left ventricle and in the distal left anterior descending coronary artery in a patient with a mild to moderate lesion in the proximal part of the vessel. Under baseline conditions, a pressure gradient between the ascending aorta and the distal part of the left anterior descending artery can be noted only during diastole (left panel). Therefore, the mean gradient (middle panel) reaches only 3 mmHg. When transstenotic flow increases (right panel), a pressure gradient is present during both systole and diastole. The mean gradient reaches approximately 30 mmHg.

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# 11. Measurement of coronary artery pressure and stenosis gradients – clinical applications

HÅKAN EMANUELSSON, MICHAL DOHNAL, CARL LAMM, CARLO DI MARIO and PATRICK W. SERRUYS

## Introduction

When considering a patient with ischemic heart disease for an invasive procedure such as coronary angioplasty (PTCA) or coronary artery bypass surgery (CABG), decision-making is heavily dependent on reliable tools to assess the physiological and clinical importance of the obstruction in the coronary artery. In spite of progressive refinements of computer-assisted analysis of the coronary angiogram during recent years, there are still some inherent limitations of the method that may render assessment of certain stenosis less reliable. In particular, diffuse atherosclerotic involvement, tortuous, long irregular lesions will be more difficult to evaluate. In addition, following PTCA the intimal layer of the vessel wall is frequently damaged, which may affect the angiographic picture considerably giving the appearance of haziness, intimal flaps or widespread dissection. This makes the interpretation of the angiographic picture even more difficult leaving an obvious need for complementary methods with a more physiological approach in these situations.

Certainly, exercise electrocardiography and echocardiography as well as perfusion scintigraphy may be helpful to assess a patient before PTCA or CABG. However, in the presence of multi-vessel disease, an isolated stenosis may be difficult to evaluate due to the relatively low spatial resolution of these methods. Furthermore, in the PTCA situation, a fast on-line method is required in order to decide whether the result of the procedure is satisfactory. Measurement of coronary artery pressure and/or coronary blood flow would seem to be suitable parameters to achieve this information. Unfortunately the techniques for measurement of these variables have been suboptimal with regard to feasibility or precision. However, devices with a high degree of accuracy have recently been developed [1, 2]. These will almost certainly facilitate the definition and understanding of the clinical consequences of disturbances in the coronary circulation. Most importantly, these methods can be practised without unduly increased risk for the patient, unnecessary time delay or excessive extra cost.



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In this study, measurement of transstenotic pressure gradients were performed before and after PTCA. These recordings were correlated with quantitative coronary angiography (QCA), which is currently the most widely applied parameter for assessing coronary lesion severity.

## Physiological considerations

The relationship between coronary blood flow (Q) and the pressure gradient ($\Delta P$) created across a stenosis in a coronary artery follows a quadratic equation:

$$\Delta P = fQ + sQ^2.$$

This relationship has been derived from basic fluid-dynamic principles and validated in in vitro as well as in vivo studies [3–5]. The pressure drop is the result of the sum of energy loss due to viscous friction and flow separation, where f in the equation above is the constant for viscous friction and s is a coefficient for flow separation. These constants are depending on fluid dynamics and stenosis morphology, since

$$f = \frac{8\pi\mu L}{A_s^2},$$

and

$$s = \frac{\rho}{2}\left(\frac{1}{A_s} + \frac{1}{A_n}\right)^2,$$

where $\mu$ is a coefficient for blood viscosity, $\rho$ is blood density, L stenosis length, $A_s$ minimal luminal cross-sectional area (MLCA) and $A_n$ the cross-sectional area of the normal segment of the vessel. From this equation it can be concluded that the length of the lesion is directly proportional to the pressure gradient, whereas changes in stenosis diameter will affect the pressure gradient by a fourth-power term. It can also be seen that it is MLCA which has the major influence on the gradient, not the normal segment area or percentage narrowing. However, if the equation is rewritten to include flow velocity (V), flow (Q) will be replaced by $V \cdot A_n$, which will change f to:

$$\frac{8\pi\mu L}{A_s}\left(\frac{A_n}{A_s}\right),$$

and s to

$$\frac{\rho}{2}\left(\frac{A_n}{A_s} - 1\right)^2.$$

In this velocity equation, it can be seen that the severity of the lesion is not only dependent on MLCA but also on the percentage narrowing. Consequently, vessels with similar degree of stenosis follow the same pressure-flow velocity curvilinear relationship independent of the size of the vessel. In the flow equation, on the other hand, a large and a small stenosed vessel follow the same curve only if MLCA is the same, irrespective of the physiologically equality of the lesions [6].

Obviously, pressure gradients and coronary flow during rest are of relatively little interest, since it is in the situation of maximal hyperaemia that the patient aquires symptoms and signs of myocardial ischemia. In the experimental situation therefore, papaverine or adenosine is often administered to achieve maximal arteriolar dilatation. The ideal agent for this purpose should exclusively cause arteriolar vasodilatation and not affect stenosis geometry in the epicardial coronary arteries. However, it has been shown in studies in dogs that there is some decrease in the minimal luminal diameter (MLD) at the time of peak hyperaemia with papaverine, due to passive collapse [5]. With a delay of 40–50 seconds, there is also a dilatation of the epicardial arteries. This results in an increase in relative per cent stenosis, which will cause an overestimation of the pressure gradient at hyperaemia.

Epicardial dilation of the normal vessel segment after papaverine has also been reported from human studies. Provided that the narrowed segment is compliant and not stiff and calcific, MLD will increase as well, resulting in a less pronounced percentage area stenosis contrary to the situation in dogs [7]. However, it was simultaneously shown that this potentially serious methodological problem could be circumvented by the intracoronary administration of nitrates causing maximal epicardial coronary vasodilatation with no further effect by papaverine and without affecting the severity of the lesion.

## Material and methods

### *Patients*

Forty-eight patients scheduled for a possible coronary angioplasty were included. There were 8 women and 40 men with a mean age of 62 years (47–78). Twelve patients had suffered a myocardial infarction prior to the study. The left descending artery was investigated in 23 patients, a diagonal branch in one patient, the circumflex artery in 6 patients, the right coronary artery in 15 patients and a vein graft in three. Patients with acute myocardial infarction, total vessel occlusion, valvular heart disease were excluded from the study. Likewise, only stenoses that were considered suitable for QCA analysis were included. Thus, extreme tortuosity as well as ostial or diffuse lesions were avoided.

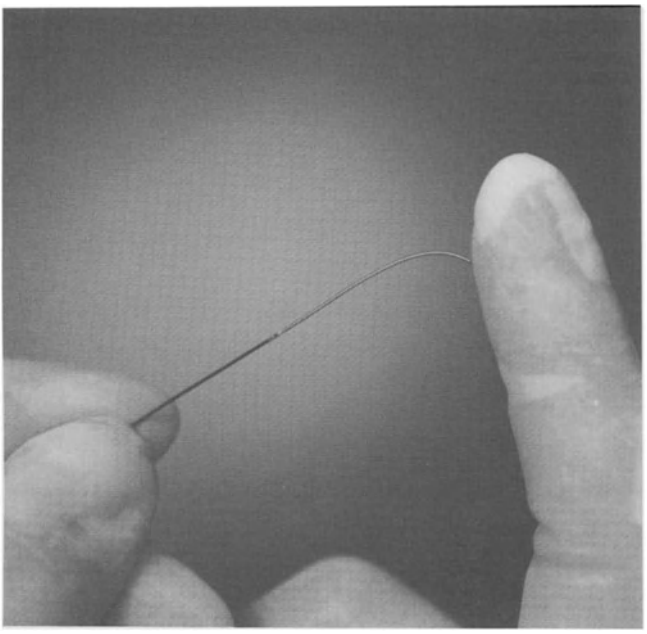

*Figure 1.* Picture of the distal part of the Pressure Guide. The sensor is located 3 cm proximal to the floppy guide wire tip.

*Intracoronary blood pressure measurement*

In order to obtain high fidelity pressure recordings, a fiberoptic tip-manometer device was used. The sensor, which has a diameter of 0.45 mm (0.17 $mm^2$), and the optic fiber are integrated into a 0.018″ guide wire (Pressure Guide, RadiMedical Systems, Uppsala, Sweden), which can be used in angioplasty balloons with a sufficient inner lumen. The sensor element is located 3 cm proximal to the floppy tip (Fig. 1). The principle of the fiber optic device is that light is emitted from a control unit through a beam-splitter and transmitted along the fiber to the sensor element, which consists of a silicon cantilever beam with a mirror integrated into its free end (Fig. 2). Deflection of the beam caused by pressure-induced elastic movement of the sensor modulates the reflected light. The signal is transmitted back through the same optic fiber and detected by a photo diode in the control unit.

The sensor is a relative sensor, comparing the recorded pressure with the ambient atmospheric pressure. For this purpose, the sensor has an air channel from the environment to the area of interest. The sensor has been validated in vitro with respect to signal characteristics, linearity, compliance and frequency response [8, 9].

The control unit is the interface between the sensor and the signal output.

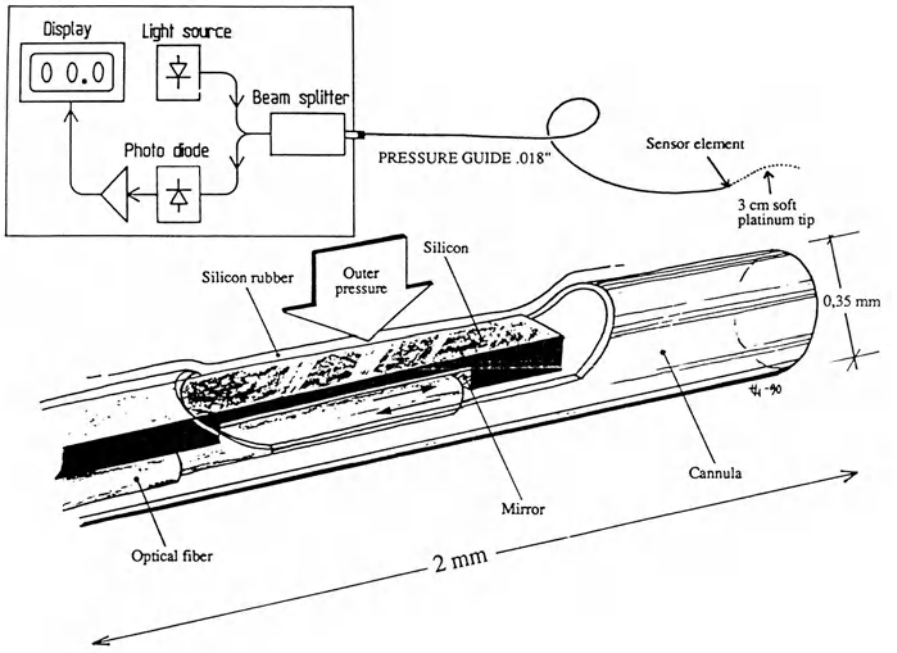


*Figure 2.* Schematic representation of the principal construction of the pressure sensor. The emitted light signal is transmitted back to the photodiode after modulation of outer pressure.

The unit can be connected to the ordinary pressure recording systems in the catheterization laboratory.

Acquisition of data was performed with a PC equipped with special hardware. The analogue ECG and pressure signals were continuously sampled with 1 KHz per channel and stored on hard disc for off-line analysis. The fidelity of the registered signals was verified by connected equipment with respective qualities and frequency response. The linear working range of the complete wire including the sensor and air channel is −20 mm Hg to +300 mm Hg and within 0 and 200 Hz. The upper frequency of the interface between the fiberoptic and electrical system is >1 KHz.

*Quantitative coronary angiography*

A Philips DCI monoplane angiography equipment was used in all patients. In 10 of the patients, the angiograms were analysed off-line by the computer-based Cardiovascular Angiography Analysis System (CAAS) as previously described [10]. In vivo validation of the CAAS system has been performed using precision drilled phantom stenoses implanted in porcine coronary arteries [11].

The remaining patients were analysed on-line in the catheterization labora-

tory with Philips Automated Coronary Analysis (ACA) program. The images are stored directly in digital form with a 512 × 512 matrix. This analysis, including the calibration procedure, is based on the same algorithms as the CAAS system, except that no correction for pin-cushion distortion is included [12]. The accuracy of ACA has recently been corroborated in comparison with the CAAS system and was found to provide highly reliable measurements [13].

*Procedure*

Initially, heparin 10.000 I.U. was given i.v. Thereafter, intracoronary nitroglycerin 125 g or isosorbide-dinitrate 2–3 mg was administered and coronary angiograms were performed in at least 2 orthogonal projections before and after PTCA and the same projections were repeated after the procedure. The Pressure Guide could usually be positioned without support of the balloon catheter. When not feasible, usually due to lack of adequate steerability of the wire, a regular PTCA guide wire (High Torque Floppy, Advanced Cardiovascular Systems) was used to cross the lesion. In that case, the balloon was positioned at the site of or distal to the stenosis, the guide wire was withdrawn and replaced by the Pressure Guide and the balloon was retracted into the guiding catheter. The mean transstenotic pressure gradient was measured by calculating the difference of mean proximal and mean distal coronary presure over 4–8 cardiac cycles. PTCA was then performed according to clinical practice. Upon the completion of the balloon procedure, new measurements were performed similarly to pre-treatment. In 34 patients pressure recordings were also done after intracoronary administration of 8–12 mg papaverine.

*Statistical analysis*

Multiple regressions were performed between pressure gradients on the one hand and MLD and MLCA on the other. Linear correlation coefficients were obtained by the least squares' method. A p value of $<0.05$ was considered as statistically significant.

## Results

1. *Pressure gradients at baseline and during peak hyperaemia*

The mean gradient at baseline was 15 ± 15 mm Hg, which increased after i.c. papaverine to 27 ± 17 mm Hg (Fig. 3). The change in gradient was most pronounced in patients with baseline gradients in the range of 5 to 20 mm

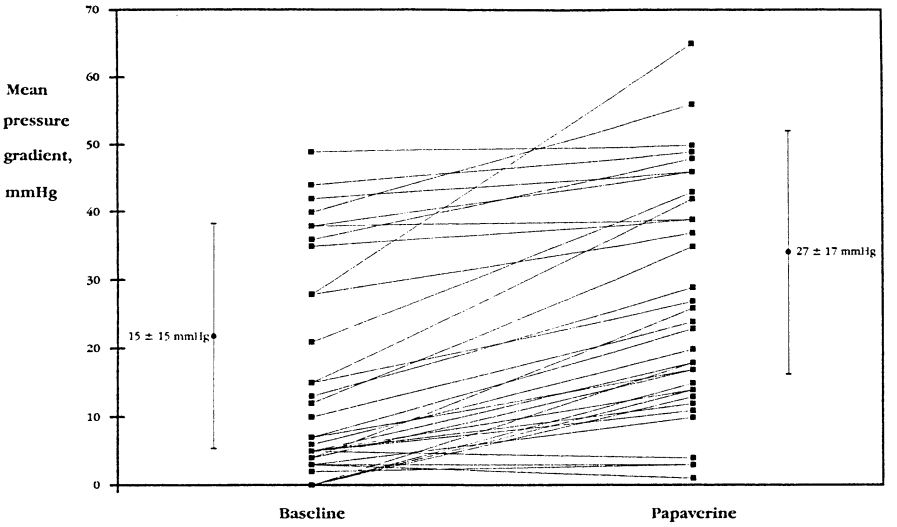


*Figure 3.* Transstenotic pressure gradients before and after intracoronary administra-tion of 8–12 mg papaverine.

Hg, whereas values in patients with gradients either close to zero or above 30 mm Hg tended to increase less.

2. *Pressure gradient vs QCA*

The relationship beetween the mean baseline pressure gradients and angiographic parameters, including the best fit curves, are shown in figs 4 and 5. The mean stenosis pressure gradient correlated significantly with MLD ($r = -0.65$ ; $p < 0.001$) and percent diameter stenosis ($r = 0.86$; $p < 0.001$), as well as with MLCA ($r = -0.61$; $p < 0.001$) and with percent area stenosis ($r = -0.65$; $p < 0.001$). The regression lines for the two latter relationships follow the equations and , respectively.

## Discussion

*Importance of the size of the pressure transducer*

The size of the pressure sensor is obviously of great importance when measurements are performed in small vessels like the coronary arteries. Even the smallest catheter or guide wire across a narrow stenosis will to some degree affect the pressure gradient. The various factors that influence the transstenotic gradients have been studied by Leiboff et al. [14], who reported that the ratio of the size of the exploring catheter across the lesion to the

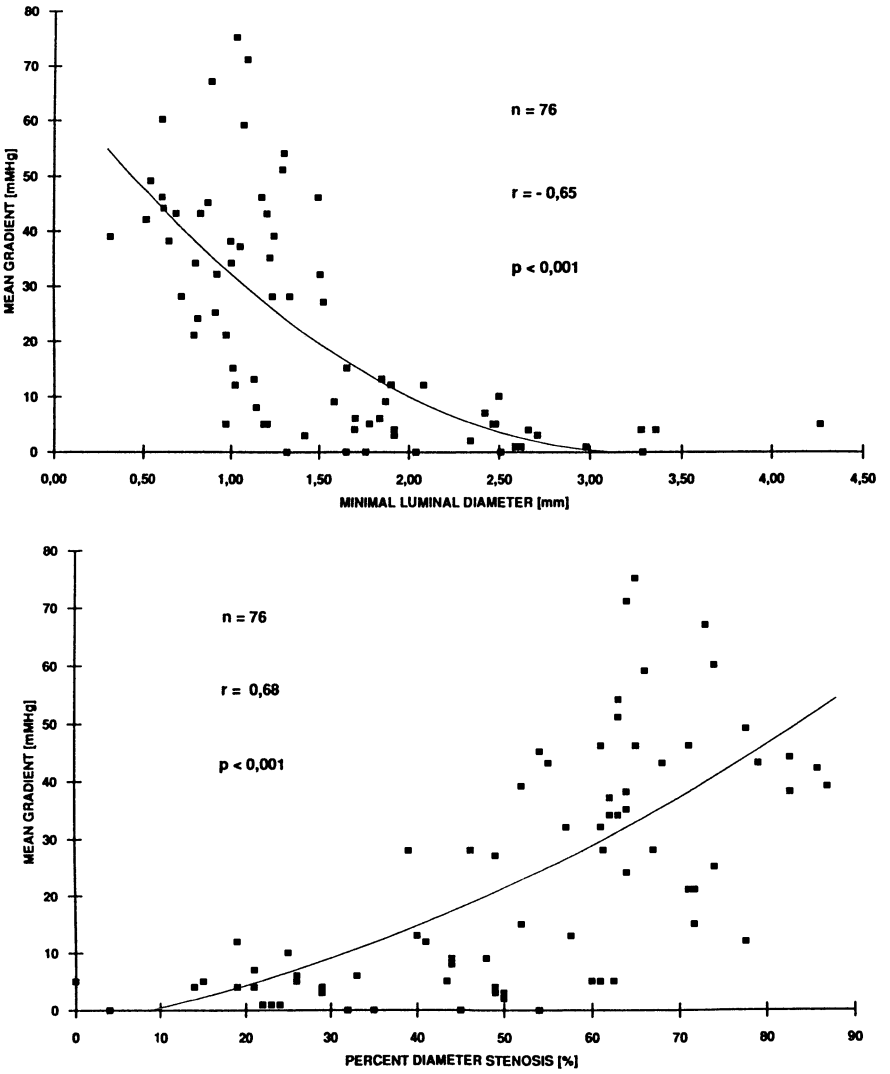


*Figure 4.* Relationship between the mean pressure gradient and MLD (4. A). Figure 4 B illustrates the correlation between the gradient and the percent diameter stenosis. The best fit curves are shown.

stenosis diameter had the greatest impact on the accuracy of the pressure gradient. Size of the normal segment of the vessel, length of the stenosis and magnitude of flow had lesser importance in this regard. According to this model, if the diameter of the sensor relative to the stenosis does not exceed 0.4, the overestimation of the gradient will be small, in fact, less than 10% if the stenosis diameter is 1.2 mm or more. After a successful PTCA, most

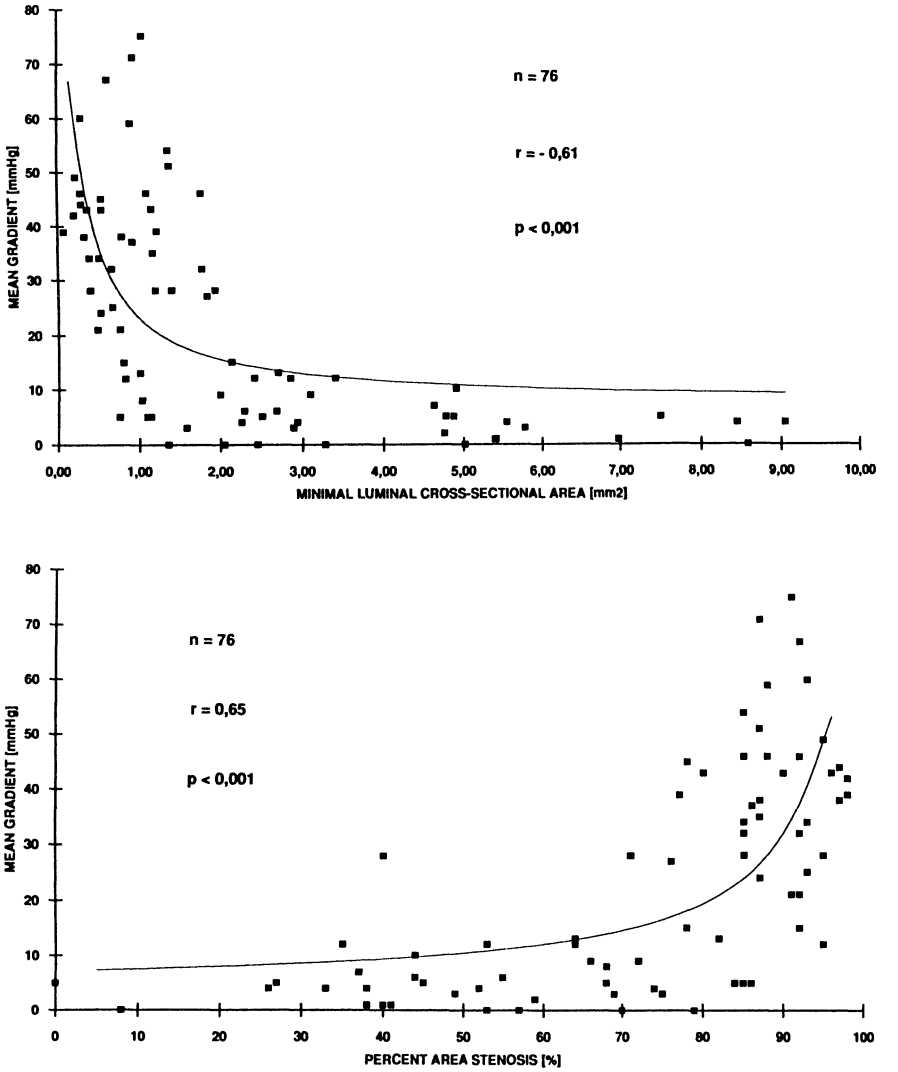


*Figure 5.* Relationship between mean transstenotic gradient and MLCA (5. A) and the percent area stenosis (5. B). Regression lines are indicated.

dilated segments will have a diameter that exceeds 1.2 mm, indicating that values obtained with the sensor may be considered reliable in most post-PTCA situations.

De Bruyne et al. [15] have recently reported their in vitro results from a model with a 4 mm reference diameter with varying flow levels and degrees of stenosis (10 mm length). They determined the change in pressure gradient produced by the presence of a 0.015″ guide wire through the stenosis and

found that overestimation was significant (>20%) only in case of tight stenosis (>85% area reduction).

The importance of the cross-sectional area of the sensor has been corroborated in the clinical situation. Serruys et al [16] noted that the transstenotic gradient systematically overestimated the theoretically gradient calculated from the laws of fluid dynamics. Moreover, Emanuelsson et al. [1], when reporting their initial experiences with the Pressure Guide, found that the gradient more than doubled when the balloon catheter was present in the stenotic segment compared to the situation with only the wire across the lesion.

*Which is the optimal measurement of stenosis severity?*

The concept that the coronary flow reserve (CFR) should provide an accurate and clinically useful measure of the physiological severity of a coronary stenosis was first suggested by Gould [17]. Although an attractive hypothesis, and also a frequent clinically practised method over the years [18, 19], several important limitations have been recognised [20]. Since CFR is the ratio of flow during hyperaemia and basal flow, all factors that influence basal and/or maximal perfusion will also affect CFR. This problem is clinically highly relevant, not least in the setting of coronary angioplasty. Therefore, several attempts have been made to find a denominator of flow reserve that is not dependent on the resting condition or a changing hemodynamic situation. This is particularly important if serial measurements are to be performed. Mancini et al have investigated the hemodynamic dependence of various indices of flow reserve, including the conventional CFR, and found that the slope of the instantaneous relation between diastolic hyperaemic flow versus pressure (i-HFVP) was least affected by changes in heart rate and blood pressure levels [21]. In addition, the slopes distinguished between various degrees of narrowings of the coronary arteries and the accuracy of the i-HFVP slope index has been further corroborated in studies using the micro sphere technique [22]. Since these experiments were carried out in anaesthetised dogs, applying the i-HFVP slope as a measure of coronary stenosis severity also in the clinical situation should be preceded by studies of its correlation to quantitative angiographic parameters in man.

The relationship between the transstenotic pressure gradient and coronary flow velocity has been extensively studied in the animal model by Gould and associates [4, 5, 23]. They found that phasic pressure gradient-flow velocity relationship in diastole during maximal hyperaemia characterized stenosis severity, with steeper curves for tighter lesions. Papaverine was used to induce vasodilatation, and a methodological problem was that the stenosis geometry changed during this intervention making the relative stenosis more severe and thus worsened the pressure gradient-flow velocity slope. However, as has been demonstrated in human studies, simultaneous administration of

nitroglycerin will prevent substantial changes of the relative percent stenosis and thus avoid this potential source of error.

As with all methods assessing CFR where flow measurements of epicardial coronary arteries are employed, the pressure-flow as well as the pressure gradient-flow relationships is limited by the fact that they do not take into account whether collaterals have been recruited to the compromised myocardium. Thus, two anatomically identical stenoses may have disparate i-HFVP loops, depending on the existence of substantial collateral flow.

It has recently been demonstrated in animal experiments [24], that the relative flow through the different parts of the coronary circulation can be calculated, provided the pressure proximal and distal to the stenosis are known, as well as the coronary wedge pressure (the distal coronary pressure when the balloon is inflated to occlude the vessel) and the central venous pressure. Consequently, if these pressures are measured at maximal hyperaemia, the relative coronary flow reserve and the contribution of collateral flow may easily be determined. This model clearly demonstrates that mere measurement of the transstenotic pressure gradient is inadequate to describe the hemodynamic consequences of the lesion. For example, identical reductions of the pressure gradient after coronary angioplasty may have different hemodynamic importance in different patients. However, additional valuable information regarding the magnitude of collateral flow can be achieved if the coronary wedge pressure is measured during the balloon inflation, which is feasible using a pressure monitoring guide wire.

## Conclusions

Since the introduction of coronary angioplasty, there has been a rapid development of the material used during the procedure, e.g. guiding catheters, balloon catheters and guide wires. In addition, investigational diagnostic devices have emerged (angioscopes, intravascular ultrasound and doppler, etc.), helping us to achieve additional information about the physiology of the diseased vessel. The accuracy and reliability of coronary artery pressure recordings are high with current pressure monitoring guide wires.

As was demonstrated in this study, there exists a fairly close relationship beetween measured translesional pressure gradients and angiographic parameters. The independent information obtained by pressure gradient recordings may be of particular value in intermediately severe lesions or in stenoses where the angiographic assessment otherwise is difficult.

Calculation of phasic pressure-flow velocity relationship, transstenotic pressure-flow velocity relationship and estimation of relative coronary flow reserve and collateral flow contribution by distal coronary pressure measurements all potentially provide deeper insight into the physiology of a coronary artery stenosis. However, further studies are required, and it is not clear at

the present time which of these methods will prove to be the clinically most useful.

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# 12. Application of coronary flow measurements to decision making in angioplasty

PATRICK W. SERRUYS, EDWARD S. MURPHY and NICO H.J. PIJLS

## 1. Introduction

Since its development in the early 1960s, coronary arteriography has been of great importance in the diagnosis and management of patients with ischemic heart disease [1–3]. Also for the next decade, it can be expected that, once the functional significance of a stenosis has been proven, anatomical data obtained at arteriography will remain necessary as a map for the cardiac surgeon or the interventional cardiologist to be informed about the correct sites where bypasses have to be placed or the balloon has to be inflated.

Despite this acknowledged pivotal role of coronary arteriography to locate a stenosis, the functional significance of an arteriographic lesion cannot always be settled from the arteriogram alone [3, 4].

Since the introduction of percutaneous transluminal coronary angioplasty (PTCA) in 1977 [5], the procedure has gained increasing importance in the treatment of coronary obstructions. So far, the immediate results of the procedure have been assessed by coronary angiography and occasionally by measurement of the residual pressure gradient.

In the setting of PTCA, the shortcomings of coronary arteriography to predict the functional result of the intervention are even more pronounced. The edges of the vessel after PTCA are often hazy because of intimal damage and therefore assessment of the degree of stenosis is more difficult and less reliable. Intravascular echocardiography has shown how severe overestimation of the result may occur and how small tears in the vessels wall may simulate considerable anatomic improvement. Because it is clear that accurate functional information about the PTCA result should be available on-line, cardiologists have searched for other methods to get this information. In the early eighties a number of studies were performed to relate decrease of transstenotic pressure gradient or final transstenotic pressure gradient to functional outcome of the PTCA. The measured residual pressure gradient may have short and long-term prognostic value, but it reflects only the hemodynamic state at rest [6–8]. Recent technical developments (pressure



*P.W. Serruys, D.P. Foley and P.J. de Feyter (eds.), Quantitative Coronary Angiography in Clinical Practice*, 181–230.

transducers on guidewire) might reintroduce the practice of translesional pressure measurement. In the meantime methods have been developed which tried to obtain direct information about improvement of coronary or myocardial blood flow by PTCA. The assessment of coronary flow reserve has been proposed as a better method to evaluate the functional results of dilatation of a coronary artery obstruction [4, 9–11]. Intracoronary blood flow velocity measurements with a Doppler probe, and the radiographic assessment of myocardial perfusion with contrast media have previously been used to investigate regional coronary flow reserve [12–17].

We have performed studies to evaluate the application of coronary flow reserve measurements in PTCA. We will describe the use of Doppler alone in PTCA, the relationship of Doppler to angiographic methods, the change of coronary flow reserve from acute to chronic as well as the role of coronary flow reserve measurements in unselected patients. In addition in this chapter we will propose a new method based on the assessment of flow during maximal hyperemia.

## 2. Methods of evaluation

### 2.1. *Intracoronary blood flow velocity measurements during and following transluminal occlusion*

Previously we have reported the use of a doppler tipped balloon angioplasty system. Briefly the system consists of a 20 mega Hz ultrasonic crystal mounted on the tip of the angioplasty catheter [10] (Fig. 1). The Doppler crystal has a 1.0 mm diameter annulus with a 0.5 mm central hole. Blood flow velocity was measured from the catheter tip transducer using a range-gated 20 MHz pulsed Doppler instrument. The master oscillator frequency of 20 MHz is pulsed at a frequency of 62.5 KHz. Each pulse is approximately 1 ms in width and therefore contains 20 cycles of the master oscillator frequency. The frequencies chosen allow velocities of up to 100 cm/s to be recorded at distances of up to 1 cm from the catheter tip. The sampling window is individually adjusted to obtain the optimal signal, which usually results in a sampling window of 1.8 mm (range: 1.5 to 2.2).

The output of the pulsed Doppler was displayed as a frequency shift (f, KHz) which can be related to blood flow velocity by the Doppler equation: $f = 2\ F\ (V/c) \cos a$, where F is the ultrasonic frequency (20 MHz), V is the velocity within the sample volume, c is the speed of sound in blood (1500 m/s), and a is the angle between the velocity vector and the sound beam. Using an end-mounted crystal with the catheter parallel ($\pm 20°$) to the vessel axis (cos a equals $1 \pm 6\%$), the relation between the Doppler shift and velocity is approximately 3.75 cm/s per KHz [10].

Sibley et al. [16] has validated clinically and experimentally the ability of a similar catheter with an end-mounted piezo-electric crystal to provide

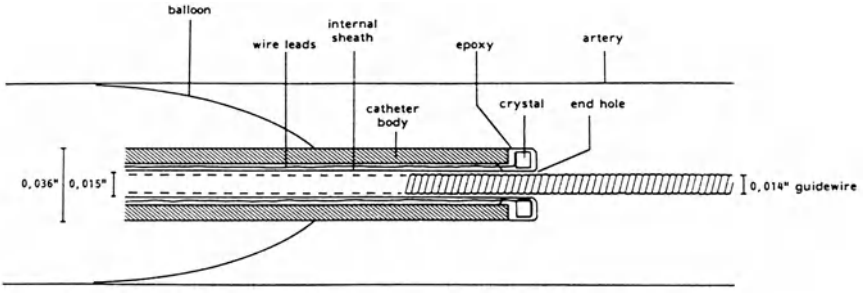


*Figure 1.* Schematic cross-sectional drawing of Doppler tip angioplasty catheter with inflated balloon in the artery.

accurate continuous on-line measurement of coronary blood flow velocity and vasodilator reserve. In our laboratory, we use to verify the accuracy of each velocity probe by correlating velocity recorded with the Doppler probe in a 9Fr femoral sheath with the volume flow measured by a timed collection of blood from the side branch of the same sheath. Graduated flow rates (range 12 to 165 ml/min) and the corresponding velocities (range 1.2 to 8.2 kHz) were obtained by incremental balloon inflation with the balloon positioned in the sheath. This simple model allows the assessment of the flow-velocity relation at different levels. As previously demonstrated, this relation is linear with correlation coefficients generally $\geq 0.95$, [17–19] but underestimates true volume flow for flows over 150 ml/min [16].

### 2.2. *Quantitative analysis of the coronary artery*

Coronary angiograms were performed in at least 2 orthogonal projections before and after PTCA and the same projections were repeated after the procedure. The determination of coronary arterial dimensions from 35 mm cinefilm was performed with the computer-based Cardiovascular Angiographic Analysis System (CAAS) [20–22].

### 2.3. *Exercise thallium scintigraphy*

As part of our routine evaluation, exercise testing is performed 1–2 days before and 7–10 days after the PTCA (and at 6 months at Thoraxcenter). In most patients this is combined with Thallium scintigraphy. Regular exercise testing was performed according to local routine, symptom-limited, and classified as negative or mildly, moderately, or strongly positive according to Selzer [23]. The procedure has been described extensively previously [24, 25]. In case of Thallium scintigraphy, one minute prior to maximal exercise, 1.5 mA Tl201 was administered. Planar imaging was started 3 min. later in 3 views: anterior, left anterior oblique 45° and 65°. These same static planar

images were repeated at rest 4 hr later (redistribution imaging). The exercise and redistribution images were processed on a DEC gamma-11 system with a quantification procedure developed at the Thoraxcenter [26, 27]. The exercise and redistribution images were spatially registered in the computer on the basis of the detected positions of point sources defined with a cobalt markerpen at two positions on the patients chest. Following automated left ventricular contour detection and interpolative background correction, exercise, redistribution and washout circumferential profiles were computed at 6° intervals (quantitative thallium perfusion analysis). The late circumferential profiles were normalized to a delay of 4 hr between the early and late images. The profiles of the early and late images were normalized to 100% and compared with normal values defined by the 10th and 90th percentiles of the profiles of a group of individuals without apparent heart disease. Semiquantitative thallium uptake in all regions was scored both in the immediate post exercise and late images on a 3-point scale. The scores of regions related to the diseased coronary artery were summed per patient and the difference between the post-exercise and late images was taken as a measure of the amount of redistribution between the post-exercise and late images. The analog Polaroid images from the gamma camera, the background corrected images and the circumferential profiles were interpreted prospectively on a routine basis by 3 experienced observers without knowledge of the angiographic data. Transient and persistent defects were considered abnormal [26, 27].

### 2.4. *Myocardial blood flow assessment by digital radiography*

#### 2.4.1. *Background theory*

Early studies about calculation of coronary blood flow by analysis of contrast agent passage in the coronary arteriogram were reported almost 25 years ago by Rutishauser [28, 29]. Analysis of these changes in contrast density, delineation of so-called time density curves (TDC's), and subsequent calculation of time parameters from these curves, was refered to as videodensitometry.

Shortly thereafter it was shown that visualisation of contrast agent through the myocardium could be enhanced by ECG-triggered subtraction imaging. If digital methods are used for this purpose, also the term digital radiography is applied [30].

According to the principles of indicator dilution theory [31], flow (F) can be calculated form these TDCs by equation 1:

$$F = V/T_{mn} \tag{1}$$

where V represents the volume of the vascular bed between injection site of contrast agent (i.e. the tip of the coronary catheter) and measuring site and

where $T_{mn}$ represents the mean transit time of the contrast particles which is calculated from the time density curve d(t) according to equation 2:

$$T_{mn} = \frac{\int_0^\infty t\, d(t)\, dt}{\int_0^\infty d(t)\, dt} \tag{2}$$

Calculation of flow in this way in the living organism is, however, seriously complicated by a number of problems. The most important problems are

1. The vascular volume V is unknown and not constant from one situation to another and
2. Flow F is not constant, even not during the acquisition of the TDC because of the hyperemic response to the contrast injection. In other words: the parameter to be measured is influenced by the indicator itself.
3. For reliable computation of $T_{mn}$, the major part of the TDC has to be known which requires high quality image acquisition without motion artifacts during approximately 15–20 heart beats.

Several solutions have been suggested to transform the principles of indicator dilution theory to a clinically useful method, applicable during routine coronary arteriography. One of these methods, which gained much popularity during the last 5 years, was the method, introduced by Vogel and co-workers [15]. This method is discussed in more detailed below.

2.4.2. *Coronary flow reserve measurements with digital subtraction cineangiography*

At the thoraxcenter we used the technique according to Vogel to assess the result of PTCA.

In this approach, mean transit time in equation (1) is replaced by the so-called myocardial contrast appearance time (MCAT, Tapp) and the vascular volume V is replaced by maximal contrast intensity

D max. These substitutions have served considerable advantages: the time parameter Tapp proceeds the hyperemic response to contrast agent and furthermore has the additional advantage that only the first part of the time density curve (corresponding with 5 or 6 heart beats) has to be obtained to determine this parameter.

Substitution of the vascular volume V by maximal contrast intensity is justified by assuming that all blood in the vascular compartment will be completely replaced by contrast agent at some moment during contrast passage. It should be emphasized that these substitutions are not supported by any physical or physiologic theory and in fact are not correct as will be demonstrated later. The coronary flow reserve measurement from 35 mm cinefilm according to this method has been implemented on the CAAS [14]. The heart was atrially paced at a rate just above the spontaneous heart rate. An ECG-triggered injection into the coronary artery was made with

Iopamidol at 37°C through a Medrad Mark IV (R) infusion pump. This nonionic contrast agent has a viscosity of 9.4 cP at 37°, an osmolarity of 0.796 osm.kg$^{-1}$ and an iodine content of 370 mg/ml. The angiogram was repeated 30 s after a bolus injection of 12.5 mg papaverine into the coronary artery by way of the guiding catheter [32, 33]. The injection rate of the contrast medium was judged to be adequate if back flow of contrast medium into the aorta occurred. When this was not observed on the hyperemic image, baseline and hyperemic image acquisition were repeated at a higher flow rate, necessitating flow rates of up to 6 ml/s in some patients . Five or six consecutive end-diastolic cineframes were selected for analysis. Logarithmic nonmagnified mask-mode background subtraction was applied to the image subset to eliminate noncontrast medium densities [34]. The last end-diastolic frame prior to the administration of contrast was chosen as the mask. From the sequence of background subtracted images, a contrast arrival time image was determined using an empirically derived fixed density threshold [14]. Each pixel was labeled with the sequence number of the cardiac cycle numbered from the cycle in which the pixel intensity level first exceeded the threshold. In addition to the contrast arrival time image, a density image was computed, with the intensity of each pixel being representative of the maximal local contrast medium accumulation. The coronary flow reserve was defined as the ratio of the regional flow computed from a hyperemic image divided by the regional flow of the corresponding baseline image.

Regional flow values were quantitatively determined using the following videodensitometric principle: regional blood flow (Q) = regional vascular volume/transit time [14]. Regional vascular volume was assessed from logarithmic mask-mode subtraction images, using the Lambert Beer relationship. Coronary flow reserve was then calculated as:

$$CFR = \frac{Qh}{Qb} = \frac{Dh}{Th} : \frac{Db}{Tb}$$

where D is the mean contrast density and T the mean appearance time at baseline (b) and hyperemia (h). Mean contrast medium appearance time and density were computed within a user-defined region of interest, which was chosen so that the epicardial coronary arteries visible on the angiogram, the coronary sinus, and the great cardiac vein were all excluded from the analysis [14]. Reproducibility data has been previously investigated and reported. Normal values for coronary flow reserve measured with this technique have previously been established [11, 14]. The coronary flow reserve of 12 angiographically normal coronary arteries was 5.0 ± 0.8. Therefore a flow reserve below 3.4 (2 SD below the mean) is taken to be abnormal.

2.4.3 *Maximal flow assessment by calculation of mean transit time at maximal hyperemia*

Despite reasonable results of the studies above mentioned, it has become more and more clear that the Vogel method is too inaccurate to predict small or moderate changes in coronary blood flow. In a recent study by Hess and Mancini [35], it was demonstrated that only changes in coronary flow reserve exceeding at least 40%, could be measured. This means that the method is not accurate enough to be informed on-line about the result of a coronary intervention. Therefore, more accurate methods have been searched for to assess improvement of myocardial perfusion by PTCA.

One of these is the method to assess maximal myocardial perfusion proposed by Pijls et al. [36, 37]. This method is described below.

2.4.4. *Prerequisites for myocardial flow assessment by digital radiography according to the physiology of indicator dilution*

From the former sections it can be concluded that calculation of coronary or myocardial blood flow by digital radiography in a theoretically sound way can only be performed if the following three conditions are fulfilled:

1. blood flow during image acquisition should not be influenced by the contrast agent,
2. the vascular volume should be known or remain at least constant if one wants to compare flow between different situations, such as is the case in PTCA,
3. image quality should be so good that a large part of the time density curve can be determined, enabling reliable determination of mean transit time.

Only if these three conditions are fulfilled, flow from one situation to another will be inversely proportional to changes in mean transit time. Recently, it was confirmed by Pijls et al. that in an animal model in which all these conditions were fulfilled, an excellent relation between inverse mean transit time and blood flow was present indeed. In that study all measurements were performed at maximal coronary and myocardial hyperemia, induced by intravenous administration of a high dose dypiridamole [36]. This means that no information about resting flow or CFR can be obtained anymore. Only the ratio between maximal flow at different degrees of stenosis (e.g. before and after PTCA) can be obtained. It will be discussed later, however, that this represents an excellent way to evaluate PTCA-results.

2.4.5. *Validation in animals*

Eight mongrel dogs were instrumented by an epicardial Doppler probe and a circular balloon occluder around the LCx artery and by pacing electrodes on the left atrium. Ten days later, the animals were brought to the catheterization laboratory, pressure catheters were placed in the ascending aorta and the left ventricle and a 6 F left Judkins catheter was advanced into the LCA. Thereafter, dipyridamole was administered intravenously to induce maximal

dilation of the myocardial vascular bed. Presence of maximal vasodilation was confirmed by the absence of any additional flow increase after a 20″ occlusion period. Thereafter, the balloon occluder was inflated in 12 small steps, corresponding with 12 degrees of stenosis, and at every step a contrast injection was performed (6 ml Iohexol-140, 4 ml/s).

Image acquisition was performed, one image per heart cycle using X-ray synchronous ECG-triggering. To prevent motion due to breathing the muscle relaxant drug norcuron was administered intravenously and artificial respiration was stopped during image acquisition. By means of these arrangements images without noticeable motion artifacts were acquired during 20 consecutive heart cycles.

Figure 2 shows a recording at low paper speed of such a step by step stenosis induction during maximal vasodilation: ECG, left ventricular pressure and its first derivative, aortic pressure, and phasic and mean Doppler shift are recorded. From left to right, step by step increase in stenosis severity corresponds with step by step decrease in flow velocity. A contrast injection is performed at every flow level and causes an artificial short dip due to lack of ultrasound reflection by the contrast agent. No increase in flow is observed following contrast injection and flow remains constant during image acquisition. Image acquisition can be recognized by the absence of breathing in the pressure signals. In the right part of the figure, presence of maximal vascular volume is confirmed by the absence of any additional flow increase after 20 seconds of CX occlusion . This maximal flow velocity equals the signal obtained in the left part of the figure where no stenosis is present.

Figure 3 shows some representative examples of the high image quality obtained in this study. The left series corresponds with the 3rd, 5th and 11th unsubtracted image after start of contrast injection. The right series represents the identical images using mask mode digital subtraction. After subtraction, not only the coronary arteries and the myocardial capillary bed are well delineated , but also the coronary veins are clearly visible.

Image acquisition and processing were performed using a Siemens Bicor X-ray equipment in connection with a Siemens Digitron 3 computer system. Images were digitized in a 512 square matrix with 1024 density levels. Regions of interest were chosen over the left main stem of the dog to record start of contrast injection, for definition of $t = 0$ (mean transit time of the injection signal) and over the myocardium supplied by the CX as well as the LAD artery. By performing a contrast injection during subtotal occlusion of the CX artery, the parts of the myocardium supplied by the CX and LAD artery could always be separately distinguished.

Close to the myocardial ROI's , background ROI's were chosen just outside the heart contour to detect changes in background density. Once defined ROI position was held constant in all studies belonging to one dog.

Time density curves were obtained by sampling the average pixel density within a ROI in the consecutive images. These curves were corrected by substraction of the sampled densities in the corresponding background ROI's.

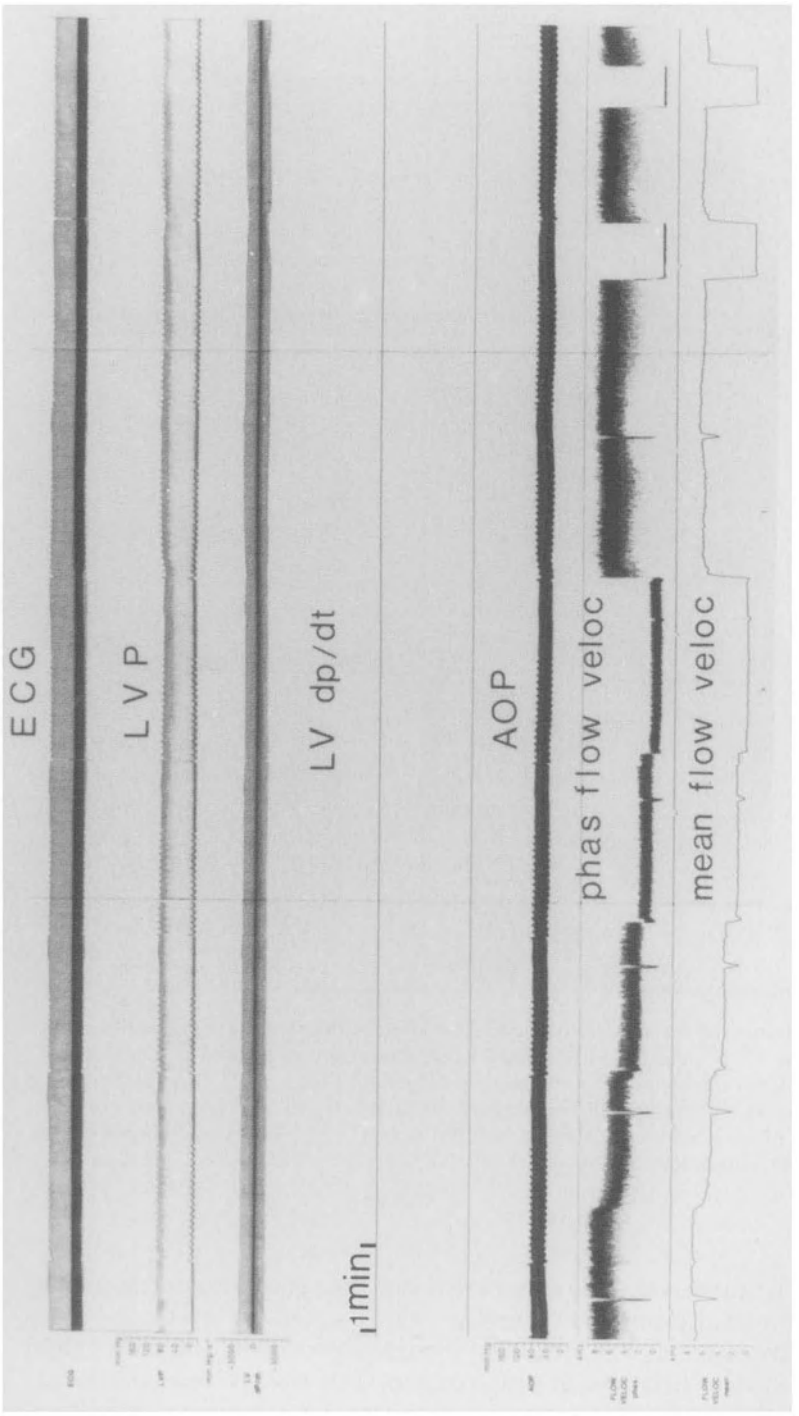


*Figure 2.* Example of step by step stenosis induction in the circumflex artery during maximally dilated myocardial vascular volume achieved by continuous dipyridamole infusion. ECG, left ventricular pressure (LVP), left ventricular dP/dt (LV dP/dt), aortic pressure (AoP), and phasic and mean Doppler shift are recorded. From left to right, step by step increases in stenosis correspond to the step by step decreases in flow velocity. A contrast injection is performed at every flow level and causes an artifactual short dip due to lack of ultrasound reflection by the contrast agent. No increase in flow is observed following contrast injection and flow remains constant during image acquisition. Absence of breathing shortly before and during image acquisition can be recognized in the pressure signals. Presence of maximal vascular volume is confirmed by the absence of any additional hyperemia after 20 seconds of CX occlusion (right part of the figure). This maximal flow velocity equals the signal obtained in the left part of the figure where no stenosis is present. Note that during steady-state drug infusion no changes in LVP and LV dP/dt are observed. (From Pijls et al. [36], with permission of the American Heart Association, Inc.)

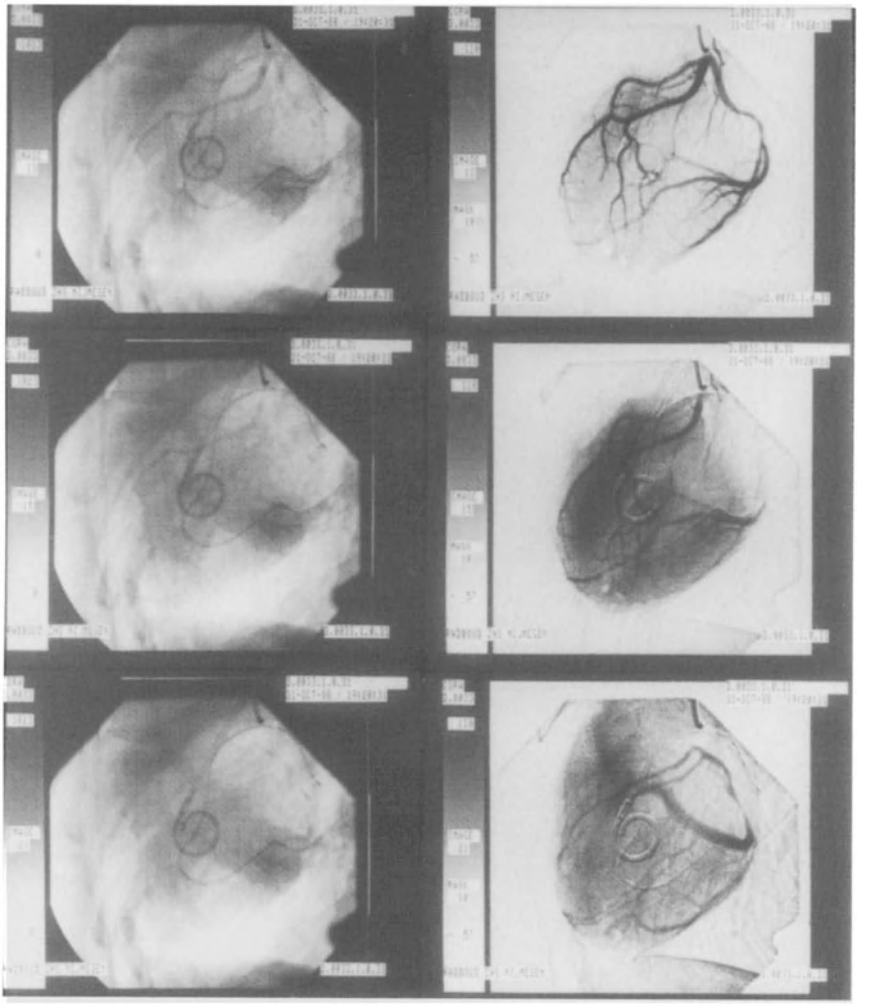

*Figure 3.* Illustration of the image enhancement achieved in this study. The left series corresponds with the 3rd, 5th and 11th unsubtracted image after contrast injection of 6 ml Iohexol-140. The right series represents the corresponding images using mask mode digital subtraction. Not only the coronary arteries and the myocardium itself are well delineated, but even the venous system of the heart is clearly delineated. (From Pijls et al. [36], with permission of the American Heart Association, Inc.)

The remaining curve was fitted to a gamma function whereafter mean transit time was calculated from the fit function.

The quality of the fit was judged by the relative error $E_r$ and only if this error was less than 10%, the fit was accepted. This was the case in 93% of

all studies. The average relative error was about 5%. Details about the fitting procedures have been described earlier [37].

In Fig. 4 the relation between CX flow velocity on the horizontal axis and inverse mean transit time on the vertical axis is shown for the eight individual dogs.

Inverse mean transit time obtained from the CX region of interest is indicated by the bold squares and in all dogs a good correlation with flow is found with correlation coefficients ranging from 0.92–0.99.

As a control, inverse mean transit time of the LAD region of interest is also displayed by the open circles. As should be the case this value almost remains constant during progressive flow reduction in the CX artery, which confirms the validity of the model.

To provide the opportunity to study the results of all dogs together, the data of every dog were normalized to the corresponding values without flow impairment. Figure 5 shows the results for an arbitrary ROI chosen over the CX myocardium and shows the excellent suitability of mean transit time to assess flow over a wide range. The correlation coefficient is 0.97 and 0.94 respectively.

Because in this animal model, vascular volume remained constant and flow was not influenced by contrast injection, this study also offered an ideal possibility to test the hypotheses as mentioned in the introduction about replacement of mean transit time by other time parameters and about maximal contrast intensity as an index of volume.

The results are summarized in Fig. 5. As can be seen in the left lower part, maximal contrast intensity $D_{max}$ does not remain constant but rather decreases with decreasing flow, which in fact can be predicted from theory.

In the right upper part it can be seen that the relation between inverse appearance time and flow is much worse than is the case for the physiologic time parameter mean transit time, displayed in the upper left corner.

Appearance time was defined in this slide as a 12.5% threshold crossing of the ascending limb of the curve. If the 1% threshold crossing or the time of maximal inclination were chosen, the results were even worse. We also tested the time of maximal contrast intensity. Results for this time parameter were only slightly, but significantly worse than was the case for mean transit time. The ratio $D_{max}/T_{app}$, which is often used in literature and described in paragraph 2.4.2, gives better results than appearance time alone for all 3 definitions of appearance time. It should be clearly recognized, however, that this improvement is not due to the suitability of $D_{max}$ to represent volume but should be explained by multiplication of two independent weaker correlations. Nevertheless the result is still inferior to mean transit time.

From this study it can be concluded that accurate comparison of maximal blood flow between different situations is possible by ECG-triggered, digital radiography in a theoretically sound way. The clinical implications will be discussed in paragraph 4.1.

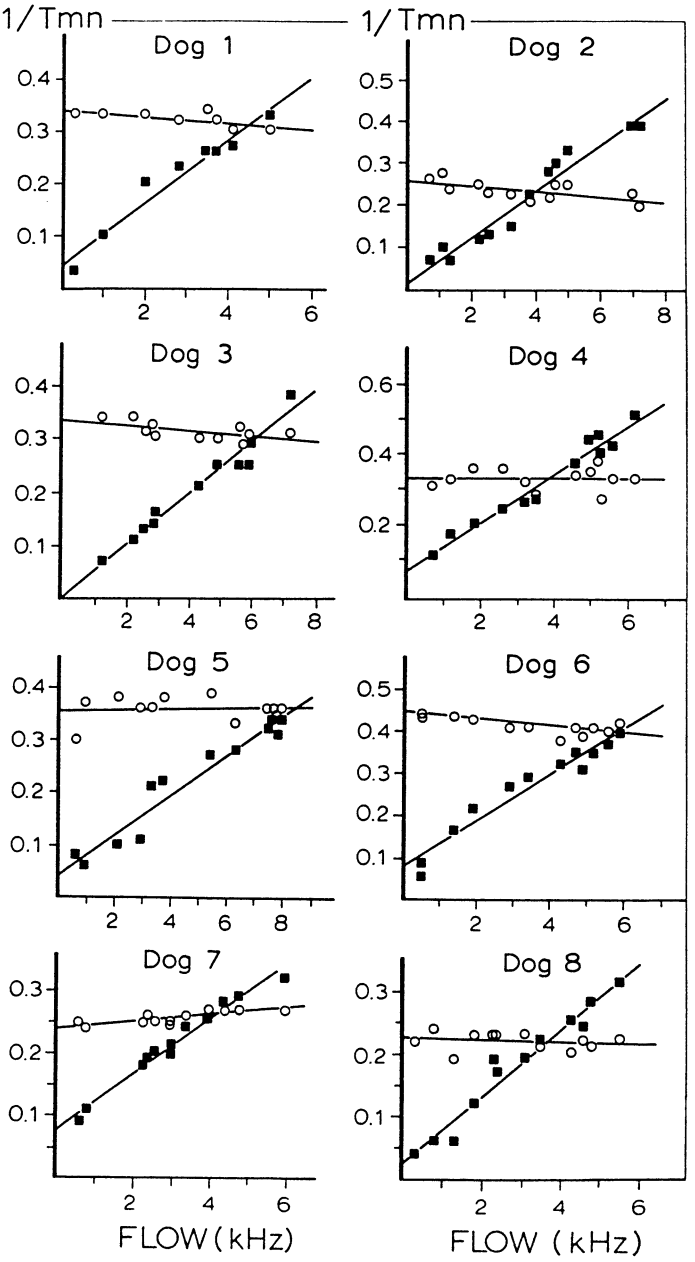


*Figure 4.* CX flow velocity vs. inverse mean transit time ($1/T_{mn}$) during different degrees of CX stenosis for the individual dogs for one ROI over the CX myocardium and one ROI over the LAD myocardium.
bold squares = CX myocardium
open circles = LAD myocardium
(From Pijls et al. [36], with permission of the American Heart Association, Inc.)

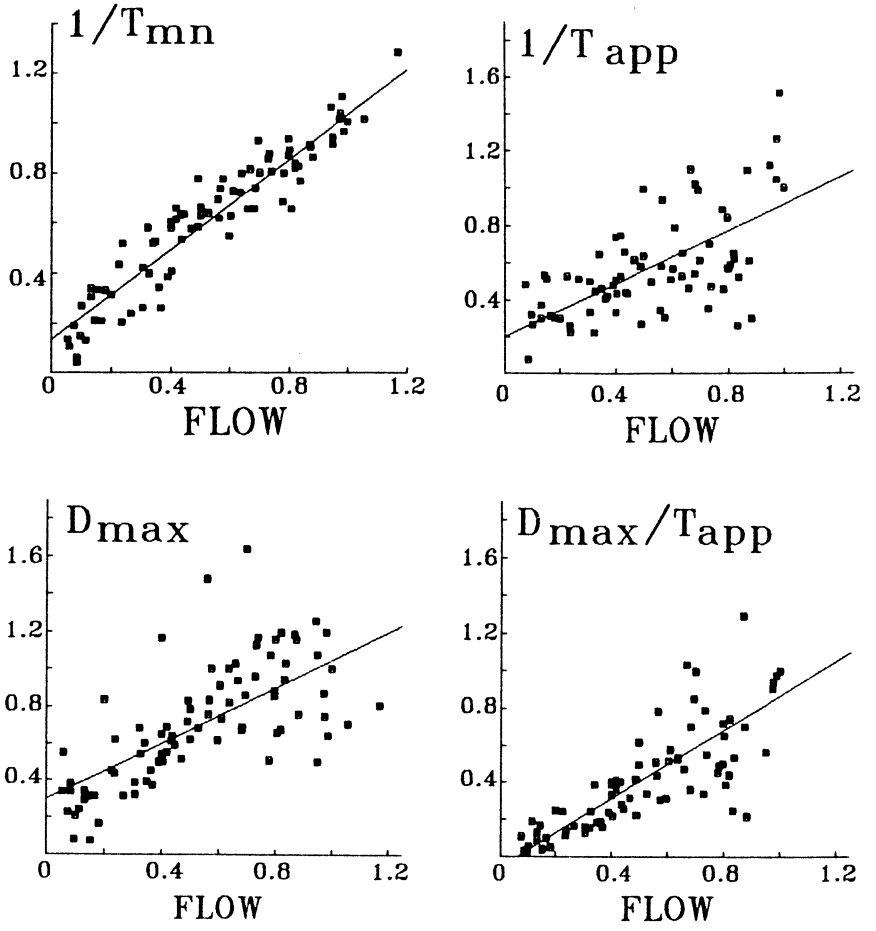


*Figure 5.* Normalized CX flow velocity vs. inverse mean transit time ($1/T_{mn}$), inverse appearance time ($1/T_{app}$), maximal contrast density ($D_{max}$) and $D_{max}/T_{app}$. Of all 3 definitions used for appearance time, $1/T_{app}$ was the least unfavourable and is used in this figure. (From Pijls et al. [36], with permission of the American Heart Association, Inc.)

## 3. Clinical experience at the thoraxcenter (1986–1990)

### 3.1. *Coronary blood flow velocity during PTCA as a guide for assessment of the functional result*

The balloon angioplasty catheter with a Doppler tip described above has been used in about seventy cases. In our experience after each of the first 3 dilatations, both resting and hyperemic velocities increase. On average the

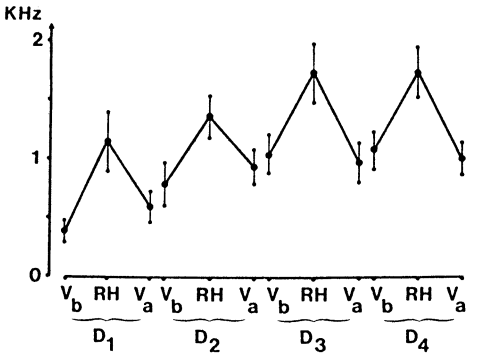


*Figure 6.* Doppler shift (kHz, mean ± standard error) during 4 sequential dilatations (D). Va = resting velocity after dilatation; Vb = resting velocity before dilatation; Vh = peak reactive hyperemia.

velocities of the last 2 dilatations did not differ statistically, suggesting that the end result was already achieved by the third dilatation (Fig. 6).

However, some patients still had a substantial increase after the fourth dilatation and might have well benefited from additional dilatations.

When calculating "coronary flow reserve" using the peak hyperemic velocity and the resting velocity recorded before the first 2 dilatations, we observed a paradoxical decrease of the ratio from 3.9 ± 0.6 to 1.9 ± 0.2. This is due to the major increase in resting velocity whose values were very low prior before the first inflation, with the catheter across the undilated lesion. When this ratio is based on the resting velocity recorded after dilatation, the coronary flow reserve differed little from 1 inflation to the next; values ranging between 1.7 and 2.1. This absence of change was confirmed statistically by variance analysis. *In other words, this ratio does not seem to be an useful functional guideline for PTCA, whereas the peak hyperemic velocity following successive balloon deflations shows a gradual and significant increase, levelling off in the most patients after the third dilatation.* This would tend to support the Nijmegen approach which asesses exclusively the hyperemic phase.

In these patients quantitative analysis of the coronary angiogram demonstrated that the minimal lumen cross-sectional area increased from 1.1 to 2.7 $mm^2$. Percent of area stenosis decreased from 83% to 57%. Percent of diameter stenosis decreased from 60% to 36%. The actual minimal lumen cross-sectional area before and after dilatation with the catheter across the lesion was estimated after subtraction of the area (0.68 $mm^2$) of the PTCA catheter. These results are similar to a large prospective study of restenosis [38].

Our original purpose was to use this information as an "on-line" assessment of the functional result of the dilatation, with the PTCA catheter

still across the stenosis. The technical innovation of this catheter was the combination of a diagnostic and therapeutic tool. Although the catheter was a prototype of first generation, it provides an unique opportunity to assess the reactive hyperemia in awake human beings. Furthermore the poststenotic velocities recorded with the catheter across the lesion were low when compared with the previously published data that document values recorded proximal to the stenotic lesion [12, 39]. It has recently been suggested [40] that the "zero crossing" method underestimates post-stenotic velocity possibly because of disturbance of laminar flow and this may also explain the discrepancy between our results and those previously published. The routine calibration of each Doppler probe by the timed blood volume collection from the femoral sheath (cross-sectional area : 6.9 $mm^2$) makes it unlikely that the intracoronary flow velocities recorded in this study with an end-mounted Doppler catheter were in error.

### 3.2. *Peak reactive hyperemia as a useful functional guide line during the procedure*

Intracoronary blood flow velocity measurements with a Doppler probe have previously been used to investigate regional coronary flow reserve, assessing the maximal reactive hyperemia induced by pharmacological vasodilation or ischemia [7–11]. However, because coronary flow reserve is a ratio between maximal and resting coronary blood flow, any increase in resting flow results in a decrease of this ratio.

This phenomenon was observed after the first 2 dilatations when the resting velocity preceding the inflation was used as the denominator of the ratio (peak hyperemic velocity/resting velocity). If the resting velocity after the deflation was used as denominator, the ratio remained unchanged during 4 dilatations; this alternative is therefore useless as a functional guide-line during the procedure. Because peak hyperemic velocity shows a gradual increase with successive dilatations which presumably reflects progressive enlargement of the lumen stenotis we attempted to correlate the cross-sectional area of the stenotic lesion "corrected" for the presence of the catheter across the stenosis, with the absolute value of the peak velocity during reactive hyperemia. Despite an orderly ranking of the 2 parameters, no close correlation ($r = 0.41$) could be established. Ideally cross-sectional areas measured after each stepwise enlargement of the lumen by the gradual inflation of the balloon should have been correlated with the peak hyperemic velocity after the transluminal occlusion. Unfortunately, the poor quality of the coronary angiography performed with the PTCA catheter in the guiding catheter precludes quantitative analysis.

In the setting of PTCA, the absence of precise mathematical relation between the peak hyperemic velocity measured after the last inflation and the post-PTCA "corrected" minimal lumen cross-sectional area is not so surprising. First, the changes in luminal size of an artery following the

mechanical disruption of its internal wall may be difficult to assess by angiographic means [41, 42]. The irregular shape with internal tears that fill with contrast medium to a variable extent will result in some overestimation of the true functional luminal size immediately following PTCA. Second, the extent of coronary atherosclerosis may be difficult to delineate angiographically. McPherson et al. [43] have documented substantial intimal atherosclerosis resulting in diffuse obstructive disease and involving the entire length of an epicardial artery, is often present, even when angiograms reveal only discrete lesions. As a consequence relative measurements of stenosis severity are an inadequate approach to assessing the severity of coronary obstructions. In addition, the calculated cross-sectional area of the stenotic lesion after the subtraction of the cross-sectional area of the catheter (mean $2.0 \pm 1.2$ mm$^2$, range : 0.5–4.6 mm$^2$) clearly suggests that *the catheter is not only impeding the flow through the stenotic lesion, even after dilatation, but might unpredictibly disturbe the velocity profile in the post-stenotic segment* [44]. *Further miniaturization of the catheter or doppler on a guidewire may improve this major draw-back. For all these reasons, the measurement of the peak velocity with this system does not permit, an on-line, accurate prediction of the morphological change of the stenotic lesion.* However, during sequential dilatations the plateau observed in the peak hyperemic and resting velocity signals still provides valuable information which indicates that no further improvement in flow velocity can be expected from additional dilatations.

After this initial experience and to confirm our preliminary results we decided to attempt a comparison between the intracoronary doppler measurements and the radiographic technique of measuring coronary flow reserve. We were expecting the radiographic technique to be easier to implement and to use as a clinical tool as it avoids use of any additional intracoronary hardware.

### 3.3. *A comparison of two methods to measure coronary flow reserve in the setting of coronary angioplasty: intracoronary blood flow velocity measurements with a doppler catheter, and digital subtraction cineangiography*

In the population studied for this comparison, the mean age of the 21 patients was 57 years [37–76], 17 were male. Eighteen patients had single vessel coronary artery disease and 3 patients two vessel disease. The investigated and dilated coronary artery was the left anterior descending artery in 14, the circumflex artery in 3 and the right coronary artery in 4 patients. In none of the patients a sidebranch was involved at the site of the lesion. The mean left ventricular ejection fraction was 67% and ranged from 38 to 81%. One patient had sustained a myocardial infarction in the anterior wall resulting in a large akinetic segment and an ejection fraction of 38%. None of the other patients had clinical evidence for a myocardial infarction and all had normal wall motion and an ejection fraction of more than 55%. In two

patients the coronary arteriogram showed grade III/IV collateral filling of the PTCA vessel [29]. A single patient had long standing arterial hypertension with left ventricular hypertrophy. None of the other patients had electrocardiographic, echocardiographic or angiographic evidence of left ventricular hypertrophy. The mean number of balloon inflations was 4.3/patient and ranged from 3 to 7. The dilation was successful in all patients, and none of the patients had a CPK-rise after the procedure. Seven patients had a dissection of the dilated coronary artery segment after the procedure. Five dissections were small, two dissections were of moderate severity. None of the dissections had clinical repercussions. The cross-sectional area at the site of obstruction was $1.1 \pm 0.6$ mm$^2$ before, and $3.2 \pm 1.1$ mm$^2$ after PTCA. Percentage diameter stenosis was $58 \pm 9\%$ before, and $32 \pm 10\%$ after PTCA. Percentage area stenosis was $82 \pm 8\%$ before, and $52 \pm 14\%$ after PTCA. The interpolated reference area was $6.6 \pm 1.6$ mm$^2$ and ranged from 3.9 to 9.8 mm$^2$. *During this part of the investigation the measurements were made with the Doppler catheter just proximal to the stenosis*, the tip of the catheter (1.2 mm$^2$) occupied $18 \pm 5\%$ (range 12 to 31%) of the cross-sectional area of the coronary artery. The reactive hyperemia following the last dilatation was measured with the balloon part of the Doppler catheter (0.65 mm$^2$) across the stenosis. In this situation the catheter occupied $20 \pm 5\%$, (range: 12–37%) of the luminal cross-sectional area at the site of the stenosis.

This implies that coronary flow reserve assessed with both techniques after PTCA was measured in the presence of an area stenosis of $52 \pm 14\%$, whereas reactive hyperemia was assessed in the presence of a residual area stenosis of $62 \pm 16\%$. In 14 patients a coronary flow reserve measurement with the angiographic technique was also obtained in a myocardial region supplied by a coronary artery which was not dilated and which had no significant stenosis (<50% diameter stenosis). The mean coronary flow reserve of these vessels was $3.4 \pm 0.8$ before PTCA and $3.3 \pm 0.9$ after PTCA.

The relationship between coronary flow reserve measured with digital substraction cineangiography (CFR-DSC) and the cross-sectional area at the site of obstruction (OA) is shown in Fig. 7. Patients 1, 4, 7, 9, 10, 11, 12, 17, 18 and 20 had conditions associated with a reduced coronary flow reserve, in addition to the presence of a coronary stenosis. In these patients only a weak relationship was found between these two parameters: CFR-DSC = 0.27 OA + 0.9, ($r = 0.55$, SEE = 0.57).

In the other patients in whom the epicardial narrowing was the sole factor determining the coronary flow reserve, a good relationship was found between these two parameters: CFR-DSC = 0.51 OA + 0.7, ($r = 0.88$, SEE = 0.36).

The relationship between coronary flow reserve measured with Doppler (CFR-DOP) and the cross-sectional area at the site of obstruction (OA) is shown in Fig. 8. The resting Doppler-shift before PTCA was $1.4 \pm 0.7$ kHz and after PTCA $1.5 \pm 0.7$ kHz. In the patients with conditions associated with a reduced coronary flow reserve aside from the presence of a coronary

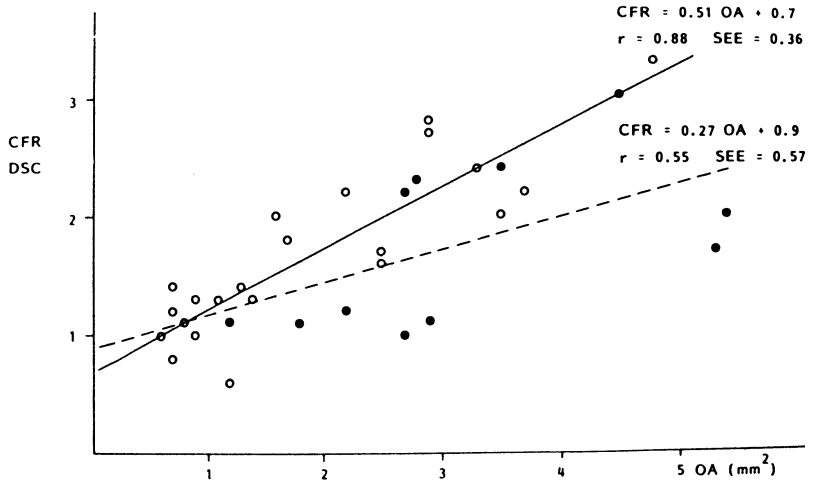


*Figure 7.* Relationship between coronary flow reserve measured with digital subtraction cine-angiography (CFR-DSC) and cross-sectional area at the site of obstruction (OA). The open symbols are the patients with any of the following characteristics: left ventricular hypertrophy, hypertension, previous myocardial infarction, collaterals or dissection after PTCA. The closed symbols are the patients without any of the above listed characteristics.

stenosis the relationship between these two parameters was weak: CFR-DOP = 0.27 OA + 1.0 (r = 0.59, SEE = 0.50). In the other patients a reasonably good relationship was found between these two parameters: CFR-DOP = 0.43 OA + 1.0 (r = 0.77, SEE = 0.45).

The relationship between the coronary flow reserve measured with the angiographic technique and the coronary flow reserve measured with Doppler probe is shown in Fig. 9. There is a good relationship between the measurements made with these two techniques, irrespective of whether the flow reserve is limited solely by the severity of the coronary stenosis (CFR-DSC = 0.88 CFR-DOP + 0.12, r = 0.85, SEE = 0.38) or whether there are additional patient characteristics present such as previous infarction, hypertrophy, collaterals or dissection after PTCA (CFR-DSC = 0.96 CFR-DOP + 0.01, r = 0.87, SEE = 0.34).

The relationships between the reactive hyperemia (RH) recorded after the final balloon inflation with the angioplasty catheter still across the lesion, and coronary flow reserve measured with the angiographic technique (CFR-DSC = 0.27 + 0.95RH, r = 0.85, SEE = 0.34) and with the Doppler catheter (CFR-DOP = 0.51 + 0.84RH, r = 0.83, SEE = 0.32) are shown in Figs 10 and 11 respectively. As expected the mean reactive hyperemia was somewhat lower than the coronary flow reserves measured with the angiographic technique or with the Doppler probe located proximal to the dilated stenosis. Reactive hyperemia was 1.9 ± 0.6, coronary flow reserve measured with the

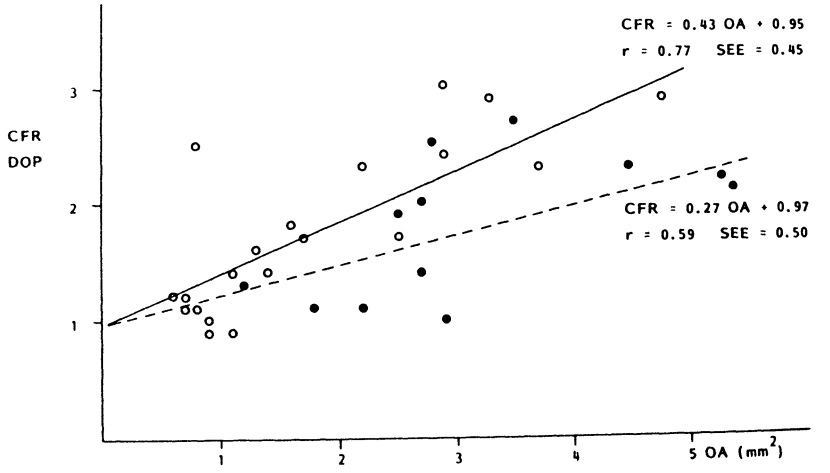


*Figure 8.* Relationship between coronary flow reserve measured with the Doppler probe (CFR-DOP) and cross-sectional area at the site of obstruction (OA). See for explanation of symbols Fig. 7.

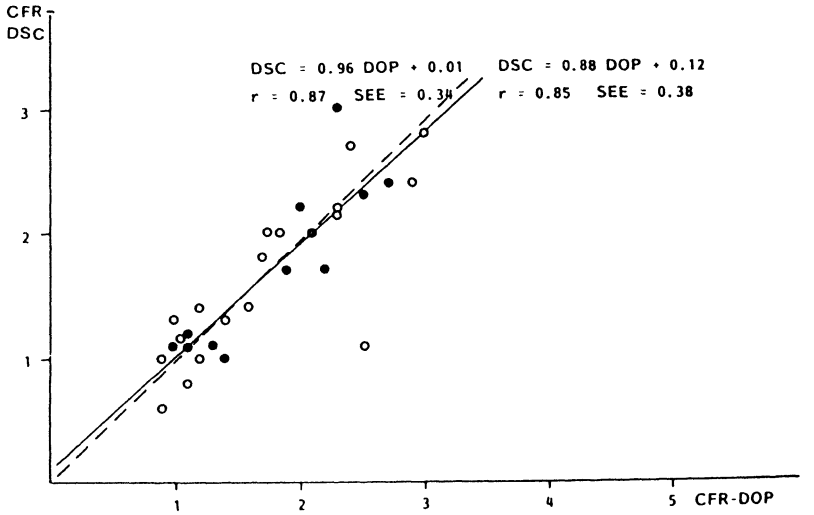


*Figure 9.* Relationship between coronary flow reserve measured with digital subtraction cine-angiography (CFR-DSC) and coronary flow reserve measured with the Doppler probe (CFR-DOP). See for explanation of symbols Fig. 7.

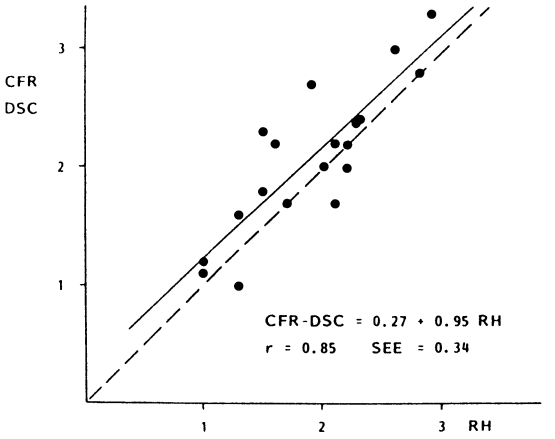


*Figure 10.* Relationship between coronary flow reserve measured with digital subtraction cine-angiography (CFR-DSC) and the reactive hyperemia recorded with the Doppler probe across the dilated lesion after the final balloon inflation (RH).

angiographic technique 2.1 ± 0.6 and coronary flow reserve measured with the Doppler catheter 2.1 ± 0.6.

### 3.4. *Discussion and limitation of the two techniques to measure coronary flow reserve*

Extensive validation studies with the Doppler technique have been performed in which the measured changes in velocity have been compared with changes in perfusion measured with timed-venous coronary sinus collection [12, 45], labeled microspheres [46], and electromagnetic flow probes [45]. These studies indicate that under a great variety of conditions, changes in coronary blood flow velocity measured by the Doppler technique accurately reflect changes in flow [47]. Recently, small sized Doppler catheters have been developed and validated. They are able to make selective measurements of flow velocity in the major proximal coronary arteries [10, 12, 16], without causing coronary obstruction [47]. For instance, in our experience the cross-sectional area of the Doppler balloon catheter was only 18 ± 5% of the cross-sectional area of the coronary artery in the segment proximal to the stenosis. However, two important limitations of the Doppler technique are, firstly: it measures flow velocity rather than volume flow – which may lead to inaccurate values for flow reserve if significant change occurs in cross-sectional areas between baseline and hyperemia [39] – and secondly: subselective coronary cannulation increases the risk during cardiac catheterization [12, 47]. Therefore less invasive approaches to determine the regional coronary flow reserve are urgently needed.

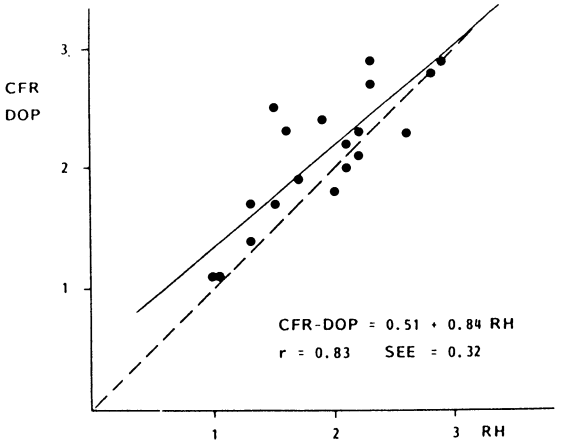


*Figure 11.* Relationship between coronary flow reserve measured with the Doppler probe (CFR-DOP) proximal to the dilated lesion and the reactive hyperemia recorded with the Doppler probe across the dilated lesion after the final balloon inflation (RH).

Selective coronary angiography is the standard means for obtaining anatomical information and is the most important tool for clinical decision making used by the clinician caring for patients with coronary artery disease. Recently, several attempts have been made to measure coronary blood flow parameters during cardiac catheterization using recent developments in radiographic technology [15]. However, radiographic contrast media cannot be used to measure coronary blood flow by the traditional methodological approaches [15]; an essential prerequisite of indicator-dilution (Stewart-Hamilton), inert substance washout (Kety-Schmidt), or firstpass distribution (Sapirstein) techniques is that the indicator substance does not affect the regional flow being measured [9]. Unfortunately, all radiographic media have substantial vascular effects [48], although nonionic media may disturb blood flow less than ionic agents [15]. Using ECG-gated power injection of a contrast agent at a rate that is presumed to be sufficiently rapid to achieve complete replacement of blood with contrast, Hodgson et al. [49] developed a mask mode subtraction technique that determines myocardial time-density curves before and during maximal hyperemia before the vascular effects of the contrast medium disturb the ratio between resting and hyperemic coronary blood flow. Since some of this techniques fundamental assumptions may not be met under clinical conditions, validation studies are of special interest [3]. *In this study we found a reasonable good correlation between radiographically determined coronary flow reserve and the coronary flow velocity reserve measured with a Doppler probe, despite the fact that the two approaches have methodologically nothing in common and that their respective regions of*

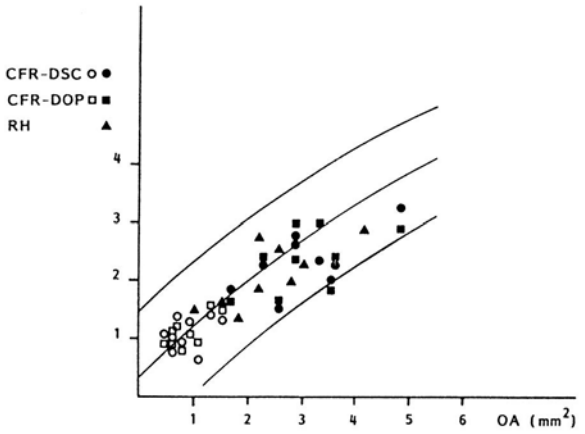


*Figure 12.* Relationship between flow reserve and cross-sectional area at the site of obstruction (OA) as described in a previous report of our laboratory [16]. The lines indicate the best fit curve and the 95% confidence limits. The data of the present study are superimposed. The open symbols are the measurements obtained before PTCA. The closed symbols are the measurements obtained after PTCA. CFR-DSC = coronary flow reserve measured with digital subtraction cineangiography, CFR-DOP = coronary flow reserve measured with the Doppler probe, RH = reactive hyperemia recorded following the final balloon inflation.

*interest (myocardium for the radiographic technique and intracoronary lumen for the Doppler technique) are basically different.*

When comparing these measures of the functional capacity of a coronary artery one has to bear in mind the potential sources of data scatter. Fortunately, the radiographic technique as well as the Doppler technique have a good reproducibility. Coronary flow reserve and reactive hyperemia are both ratios between maximal coronary blood flow and resting flow. Resting coronary blood flow is mainly determined by aortic pressure and heart rate and coronary blood flow during maximal vasodilation is linearly related to the prevailing perfusion pressure [4, 9]. These two hemodynamic parameters change little between the measurements of flow reserve and reactive hyperemia, although they certainly contribute to the scatter of the data.

Several studies have shown that in selected patients a close relationship exists between quantitatively determined stenosis geometry and measured coronary flow reserve [14, 50].

In a previous study from the Thoraxcenter we established the relationship between cross-sectional area at the site of obstruction and the measured coronary flow reserve in a patient population with single vessel coronary disease and the absence of other factors that might reduce flow reserve such as hypertrophy, infarction, hypertension, collaterals or dissection [14]. This relationship is shown in Fig. 12.

A coronary artery with an obstruction area of 2.4 $mm^2$ would be expected

to have a vascular reserve of 2.2 with confidence limits extending from 1.3 to 3.0, which corresponds almost exactly to the range found in our patients.

### 3.5. *Coronary flow reserve immediately after PTCA*

Several authors [11, 51, 52] have shown that the coronary flow reserve of the myocardial region supplied by the dilated vessel increases substantially after PTCA, but is not restored to normal values. The measurements obtained in the present study with two independant techniques confirm this fact. We also measured the coronary flow reserve of an adjacent myocardial region supplied by a not significantly diseased coronary artery, by the radiographic technique and found a marked difference in vasodilator response. For ethical reasons we did not obtain this measurement with the Doppler catheter as we felt that introduction of the Doppler probe into a second coronary artery might introduce additional risks to the investigational part of the procedure. Nevertheless, the results of the radiographic technique indicate that the abnormal vasodilatory response is restricted to the myocardium supplied by the dilated coronary artery. There are several potential explanations for this phenomenon.

1. *Since coronary flow reserve is a ratio between resting flow and maximal coronary blood flow, any increase in resting flow results in a decrease of this ratio.* Neither of the techniques we used, provided us with absolute measurements of volume flow. Therefore, we cannot make a definite conclusion regarding resting coronary volume flow after the PTCA. However, the resting Doppler shift was virtually the same before and after the PTCA procedure, $1.4 \pm 0.7$ kHz and $1.5 \pm 0.7$ kHz respectively. Furthermore, several authors using the thermodilution technique in the coronary sinus or the great cardiac vein have reported comparable resting volume flows before and after PTCA [53–55].

2. Metabolic, humoral or myogenic factors could potentially play a role in the limited restoration of coronary flow reserve after PTCA. However, the metabolic derangements due to the PTCA seem quickly reversible [53, 56, 57]. Although humoral factors may play a role in a specific subgroup of patients with complicated PTCA, sofar no evidence has been presented that implicates that humoral factors are important in this regard in the majority of patients [58]. The chronic reduction in perfusion pressure distal to the stenotic lesion may induce alterations in the complex mechanism of autoregulation and a prolonged period of time may be needed before these abnormalities subside [52].

3. *Finally, the impaired coronary flow reserve could be directly related to the residual stenosis* [9]. *Cross-sectional area measured immediately after PTCA* generally increases about threefold due to the procedure but *remains grossly*

*abnormal* [9, 59]. The relationship between cross-sectional area at the site of obstruction and coronary flow reserve as found in a previous study from our laboratory [14], is shown in Fig. 12 with the 95% confidence intervals.

The data of the present study for patients fulfilling the same exclusion criteria (group B) are superimposed: coronary flow reserve measured with both techniques and the reactive hyperemia following the final balloon inflation with residual obstruction area corrected for the presence of the Doppler balloon catheter. The large majority of measurements fall within the 95% confidence limits of this relation, suggesting that the *persisting reduction in cross-sectional area perse constitutes a sufficient explanation for the limited restoration of coronary flow reserve, although it does not exclude other contributing pathophysiological mechanisms.*

### 3.6. Coronary flow reserve immediately after *PTCA in an unselected patient population*

Recently a series of unselected clinical coronary angioplasty population (N = 15) were studied at the Thoraxcenter [60]. Although our intention was to study a consecutive series of patients, this could not be realized because of logistic restraints (e.g. emergency studies, patients refusal) and technical inadequate recordings (respiration artefacts, atrial frbrillation and frequent ectopic beats). Nevertheless, the patients group represented a random, unselected clinical coronary angioplasty population. Patients were not excluded for factors known to disturb coronary flow reserve. No patients showed electrocardiographic evidence of left ventricular hypertrophy but this could not be ruled out as no additional imaging techniques were performed to study this aspect. Seven patients (47%) had multivessel coronary artery disease. A previous myocardial infarction in the region under study was present in 4 patients (27%). Six patients (40%) had refractory unstable angina pectoris. In three cases (20%) the myocardial region under study was supplied by angiographically visible collaterals.

In each case the immediate result of angioplasty was thought successful by the operator. In six vessels angiographic evidence of dissection at the dilatation site was observed accompagnied by a "hazy" aspect in four cases and contrast staining in one. A filling defect without visible dissection was noted in one patient, while side branch occlusion occurred in another patient. These circumstances did not cause ischemic symptoms and creatine phosphokinase measurements after the procedure were in the normal range (less than 100 U/1).

Before coronary angioplasty the mean percentage diameter stenosis was $60.4 \pm 8.0\%$. Immediate after angioplasty this was $36.8 \pm 11.4\%$ ($p < 0.05$). After 24 hours the mean percentage diameter stenosis remained unchanged with a much smaller standard deviation ($37.6 \pm 5.3\%$; p = NS). In two cases,

the residual stenosis was more than 50% (51 and 56%) but 24 hours later the percentage diameter stenosis was less than 50% in all cases. On the other hand, the lowest percentage diameter stenosis (10%) immediately after angioplasty increased to an intermediate value (39%) after 24 hours. The mean minimal luminal diameter pre-angioplasty was $0.93 \pm 0.18$ mm and increased significantly to $1.53 \pm 0.28$ mm post-angioplasty ($p < 0.05$). At 24 hours follow-up the mean minimal luminal diameter was unchanged ($1.53 \pm 0.21$; p = NS) althought some individual variation was observed. The same trends were observed for the obstruction area measurements.

The mean coronary flow reserve before angioplasty was $1.26 \pm 0.59$ and remained at the same level ($1.30 \pm 0.42$; p = NS) after the intervention. Although coronary flow reserve improved in nine myocardial regions, a rather steep decrease in reserve was observed in three regions with the highest pre-angioplasty values. In one case this decrease could be explained by side branch occlusion. After 24 hours the mean coronary flow reserve showed a slight increase to $1.78 \pm 0.90$; $p < 0.05$) with an improvement in eight, decrease in four, and an unchanged situation in four myocardial regions compared to the immediate post-angioplasty measurements. No correlation between the anatomic parameters (percentage diameter stenosis, minimal lumen diameter and obstruction area) and the calculated coronary flow reserve could be found before, immediately after, and 24 hours after angioplasty, except for the minimal lumen diameter and the obstruction area immediately after the intervention.

### 3.7. A Word of caution

Coronary flow reserve can be influenced by many factors other than epicardial coronary stenosis, such as myocardial hypertrophy, tachycardia, hypertension, prior myocardial infarction, collaterals, dissection after PTCA [51, 61], changes in coronary vasomotor tone and changes in ventricular enddiastolic and intrathoracic pressures [4, 9]. Therefore, in order to relate the measured coronary flow reserve to quantitatively determined stenosis geometry, we have carefully divided our study population into a group of patients (A) with one or more of the above mentioned characteristics and a group of patients (B) without any of these characteristics. We tried to prevent changes in vasomotor tone which is relevant to both techniques [20] by inducing a constant maximal epicardial coronary vasodilation with repeated intracoronary administration of isosorbide dinitrate [62]. In accordance with previous reports [14, 50] we found a good correlation between cross-sectional area at the site of obstruction and measured coronary flow reserve in group B, in contrast to a poor correlation between these two parameters in group A.

In view of these results, we have drawn the following conclusions: Coronary flow reserve estimations in patients with clinical conditions known to

disturb coronary flow is hazardeous. It is particular problematic in these patients to use this functional measurement for assessing the result coronary angioplasty. The mean dimensions of the coronary artery after angioplasty do not change in the first 24 hours after the procedure, but there was a tendency for regression to the mean value for the best as well as for the worst immediate post-angioplasty results. *One day after the intervention only a gradual improvement can be observed. Whether this improvement in coronary flow reserve continues with time remains to be established and is discussed in paragraph* 3.8. *Thus, in spite of the promises of coronary flow reserve measurements in the setting of coronary angioplasty, application remains restricted to carefully selected patients.*

### 3.8. Evaluation of coronary flow reserve late after PTCA

In order to asses the long term change in flow reserve, the long term coronary flow reserve was measured in the myocardial region supplied by the dilated coronary artery before PTCA, immediately following PTCA as well as 5 months later. Consecutive measurements were also obtained in 12 adjacent myocardial regions supplied by a nondilated coronary artery. The coronary flow reserve of these adjacent myocardial regions remained unchanged immediately following PTCA as well as after 5 months follow-up. Coronary flow reserve (mean ± SD) in the myocardial region supplied by the dilated coronary artery increased from 1.0 ± 0.3 to 2.5 ± 0.6 immediately following PTCA ($p < 0.001$). In none of these patients was coronary flow reserve restored to a normal level immediately following PTCA. A substantial late improvement ($p < 0.01$) in coronary flow reserve had occurred 5 months later. Coronary flow reserve in the myocardial region supplied by the dilated coronary artery 5 months after PTCA was of the same magnitude as the coronary flow reserve in the myocardial region supplied by a nondilated and angiographically not diseased coronary artery (Fig. 13). In 11 of the 15 patients (73%) coronary flow reserve of the dilated coronary artery was restored to a normal level of $\geq 3.4$, whereas in 4 of 15 patients (27%) coronary flow reserve was still abnormal (Fig. 14). *Coronary flow reserve 5 months after PTCA was related to the change in minimal cross-sectional obstruction area occurring between immediately after PTCA and at follow-up* (*Fig.* 15). In 10 patients the minimal cross-sectional obstruction area 5 months after PTCA was larger than immediately following the procedure (late improvement). Only one of them had a coronary flow reserve of $<3.4$. In 5 patients the minimal cross-sectional obstruction area 5 months after PTCA was smaller than the area immediately following the procedure (late deterioration). The percentage of patients showing normalization of coronary flow reserve 5 months after PTCA is substantially higher ($p < 0.05$, chi-square test) in the group with late angiographic improvement (90%) compared to the group with late deterioration (40%). In an additional population of patients we have studied the relation-

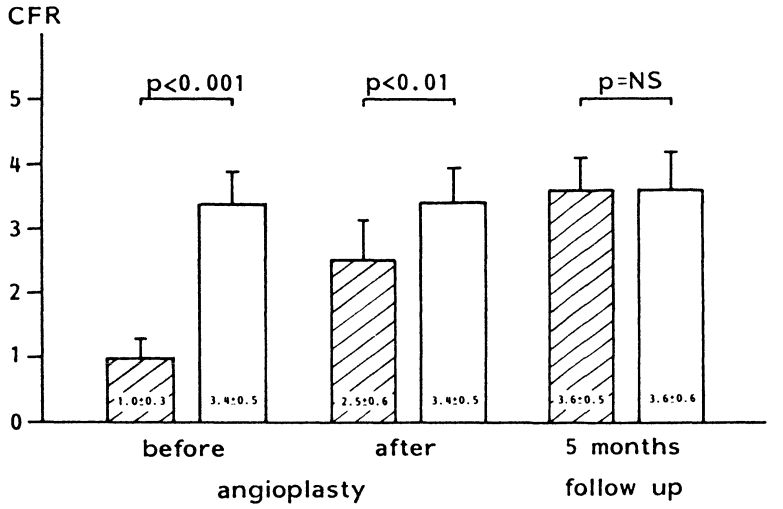


*Figure 13.* Coronary flow reserve (CFR) Measured with digital subtraction cineangiography before, immediately after and 5 months after PTCA. The shaded bars represent the CFR of the myocardial region supplied by the dilated coronary artery. The white bars represent the CFR of an adjacent myocardial region supplied by a nondilated and angiographically normal coronary artery.

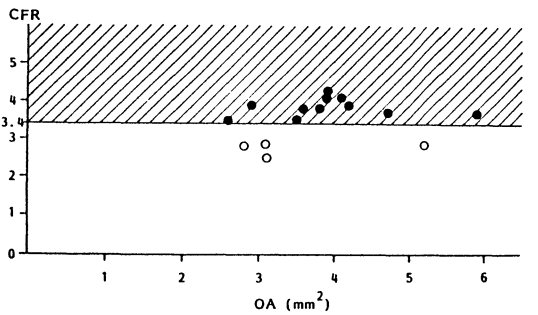


*Figure 14.* Coronary flow reserve (CFT) plotted against minimal cross-sectional obstruction area (OA) 5 months after PTCA. The lower limit of the normal value for CFR as measured with the digital subtraction cineangiographic technique is 3.4.

ship of late remodeling and coronary flow reserve which confirms these findings [63], Figs 16, 17, 18.

Wilson et al. [50] have shown in a human study that the impaired coronary flow reserve is directly related to the severity of the stenosis. Cross-sectional area measured immediately after PTCA generally increased approximately threefold as a result of the procedure, but remained grossly abnormal and

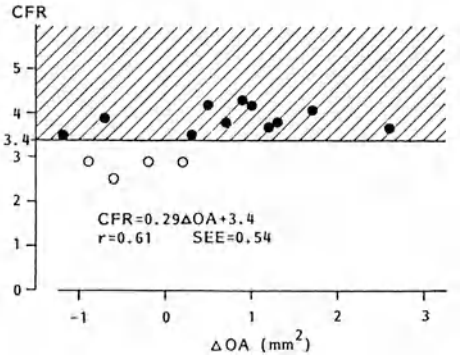


*Figure 15.* Relationship between coronary flow reserve (CFR) 5 months after PTCA and the change that occurred in minimal cross-sectional obstruction area (OA) between immediately after PTCA and 5 months later. The lower limit of the normal value for CFR as measured with the digital subtraction cineangiographic technique is 3.4.

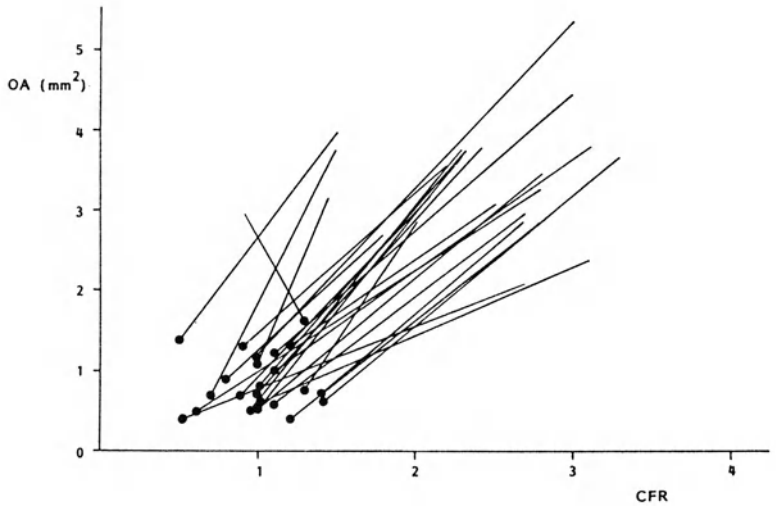


*Figure 16.* Cross-sectional area at the site of obstruction (OA) and coronary flow reserve (CFR) before and immediately after PTCA.

was generally less than half the diameter of the inflated dilating balloon [64]. In the 6 months after PTCA important morphological changes may take place. Johnson et al. [59] reported a late increase in cross-sectional obstruction area in about one third of their patients. In our selected group of patients with no angina and a normal exercise thallium scintigram, the percentage of patients with late angiographic improvement was even higher (66%). In a previous study in our laboratory the relationship between cross-sectional

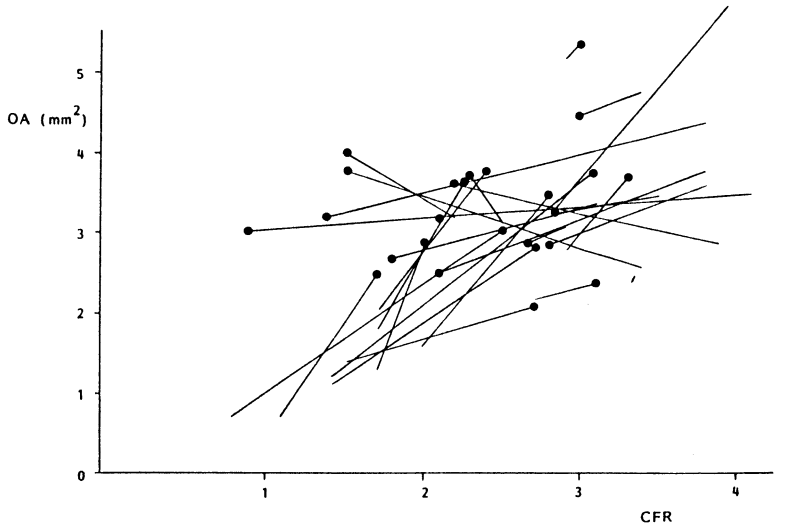


*Figure 17.* Cross-sectional area at the site of obstruction (OA) and coronary flow reserve (CFR) immediately after PTCA and 3 to 5 months later.

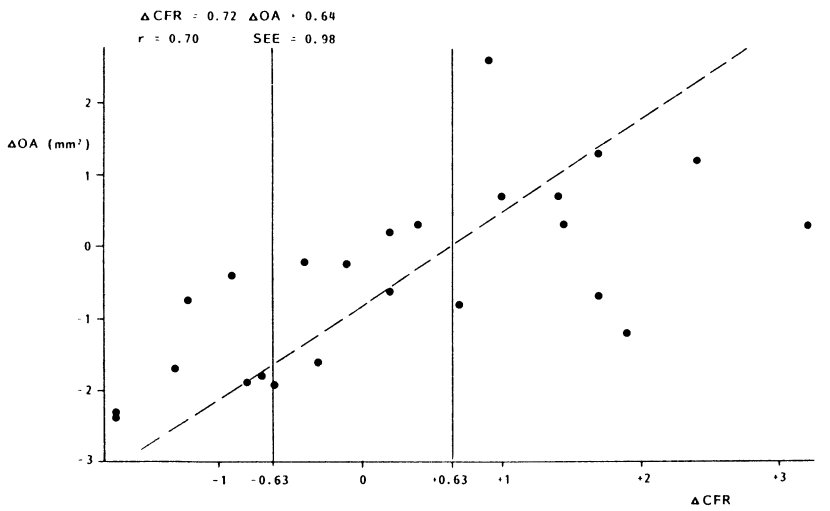


*Figure 18.* Relation between change in obstruction area (OA) and change in coronary flow reserve (CFR) occurring between immediately after PTCA and follow-up 3 to 5 months later. The verticle lines mark 1 SD of the long-term variability.

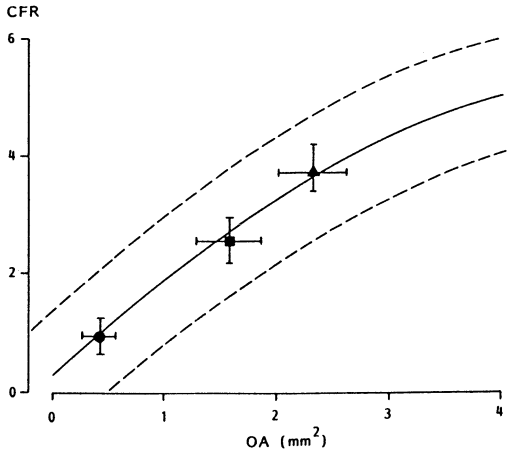


*Figure 19.* Relationship between coronary flow reserve (CFR) and cross-sectional obstruction area (OA) as previously reported. The solid line is the best-fit curve and the shaded area corresponds to the 95% confidence limits. The mean values and standard deviations of coronary flow reserve and obstruction area as obtained in the present study, before PTCA (●), immediately after PTCA (■) and 5 months after (▲), are plotted on this diagram.

obstruction area and coronary flow reserve in patients with stable angina and single-vessel coronary artery disease has been established [14]. In Fig. 19 this relation is shown with the results of the sequential coronary flow reserve and obstruction area measurements of the present study superimposed. The data of the present study are within the 95% confidence limits of the relation between flow reserve and obstruction area.

Therefore, *the persisting reduced obstruction area observed immediately after PTCA is by itself a sufficient explanation for the limited restoration of coronary flow reserve, although it does not rule out other contributing pathophysiological mechanisms. Conversely, at medium-term follow-up, the late improvement of the stenosis geometry is consistent with the increased coronary flow reserve measured at the time of the recent catheterization.*

## 4. Clinical experience at the university of nijmegen (1989–1991)

In this section the experimental method suggested by Pijls et al. as described paragraph 2.4.3 to 2.4.5, is applied in man for on-line evaluation of PTCA-results by comparison of maximal flow through the myocardium, supplied by the dilated artery before and after PTCA. As previously remarked and discussed in paragraph 2.4.4, it was hypothetized that the rate of increase of maximal flow is the best functional parameter to reflect success of the proce-

dure. The results are compared to other methods for on-line evaluation of PTCA-results, available at that time.

### 4.1. *The concept of maximal flow ratio for on-line evaluation of PTCA results*

We selected 50 consecutive patients with sinus rhythm who had single vessel disease at coronary arteriography less than 6 weeks before and had been accepted for elective PTCA. There were some exclusion criteria which will not be discussed extensively. The patients were seen at the outpatient department 24–48 hours before the intervention. At that time an exercise test was performed, if necessary combined with thalliumscintigraphy. The aim of the study was explained to the patient and thereafter breathholding at submaximal inspiration was thoroughly trained, using a nose clamp and preferably in the presence of the partner of the patient. Patients were asked to repeat this training at night and, if possible, the next day. Careful attention was paid to avoid motion of the head, neck, shoulders and thorax during breathholding.

Exercise testing was repeated 7–10 days after the PTCA procedure as described in paragraph 2.3.

At the time of the PTCA a 6F stimulation catheter was positioned into the right atrium and a protocol was followed as described below:

In case of a stenosis in the CX or LAD artery or one of its major branches, a diagnostic Judkins catheter was advanced into the right coronary artery and an ECG-triggered study was performed during maximal vasodilation in the RAO 30° projection. This was followed by a similar study of the LCA in the LAO 60° projection, sometimes with some cranial angulation depending on the patient's anatomy. Thereafter the regular PTCA procedure was performed, followed by another ECG-triggered study of the left coronary artery.

In case of a right coronary artery stenosis, RCA and LCA were interchanged in this protocol.

By following this protocol, not only maximal flow in the diseased artery could be compared before and after the intervention, but also reference data for apparently normal coronary arteries, could be collected.

For all studies 6 ml Iohexol was injected using a power injector with an injection speed of 4 ml/sec in analogy to the animal study.

Contrast injections started 30 sec after i.c. administration of 8 mg papaverine in the RCA and 12 mg papaverine in the LCA. It has been documented by the Iowa and Rotterdam groups that this dose of papaverine induces maximal vasodilation from about 25 to 60 seconds after its administration.

During image acquisition, mean arterial pressure was continuously recorded in the iliac artery.

Image quality was good enough to provide time density curves meeting

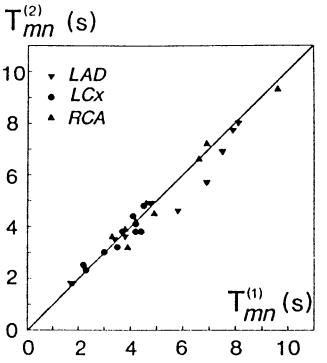


*Figure 20.* Mean transit time at maximal hyperemia, obtained in 2 identical studies with an interval of 10 minutes. Values derived from the myocardium of the left anterior descending (LAD) artery, left circumflex (LCx) artery and right coronary artery (RCA) are indicated by the inverse triangles, circles and upright triangles respectively. $T^{(2)}_{mn}$ is corrected for small pressure changes, if present, as outlined in the text. The line represents the line of identity.

the standards as set in the animal model in 90% of all studies, mostly at the first attempt.

To test reproducibility of calculation of $T_{mn}$ , in 2 × 10 patients one study of either the LCA or RCA was performed twice during maximal vasodilation under identical circumstances with an interval of 10 minutes. Image processing and ROI processing were automatically performed in exactly identical way in these paired studies. The absolute difference between the first and second measurement was always small and 8% at the average. The correlation coefficients were 0.98, 0.97 and 0.91 for the LAD, LCX and RCA respectively (Fig. 20).

Some examples of images and time density curves, which are representative for the image and curve quality in this study, are demonstrated in Figs 21 and 22.

Background corrected time density curves were obtained and fitted in an identical way as in the animal study, whereafter mean transit time was calculated according to theory.

Complete data were obtained in 42 patients. Reasons for incompletely evaluable patients are summarized in Table 1.

Table 2 summarizes the mean values of some of the relevant patient data and results.

Stenosis severity as judged by quantitative coronary arteriography, transstenotic pressure gradient and $T_{mn}$ at maximal hyperemia before and after the PTCA are mentioned. The ratio between $T_{mn}$ after and before PTCA was called Maximal Flow Ratio and constitutes a direct measure for improvement of maximal flow. This MFR averaged 2.1 after correction for changes in mean arterial pressure. If only successfull PTCA's according to exercise

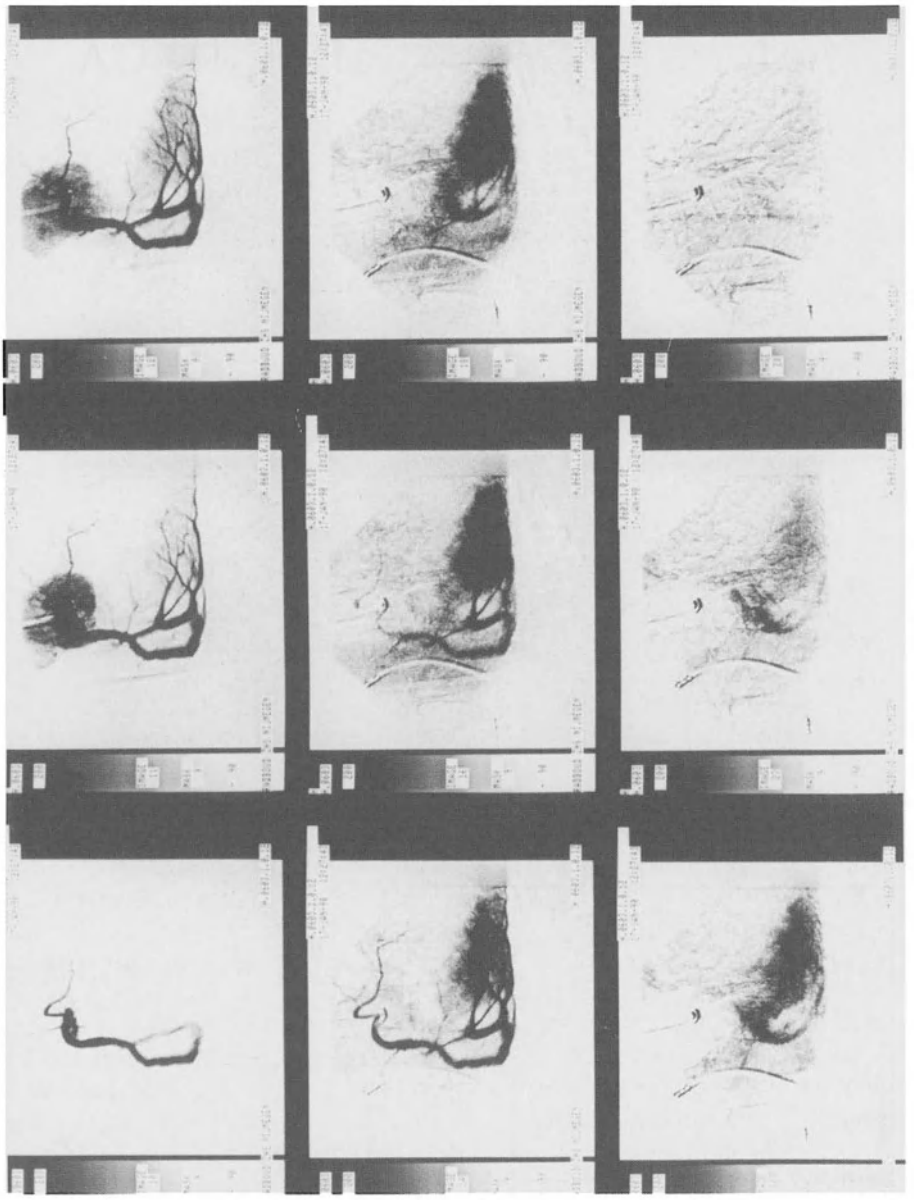

*Figure 21.* Example of a sequence of mask-mode subtracted images of the right coronary of a 63-year-old female. Contrast injection starts at the $10^{th}$ heart cycle after start of image acquisition. Image 9, therefore, has been chosen as mask. Filling of the capillary bed of the posterior septum by contrast agent and the subsequent washout can be clearly distinguished and even at the last image, corresponding with the $28^{th}$ heart cycle after start of image acquisition, motion artifacts are only mild. (From Pijls et al. [37], with permission of the American Heart Association, Inc.)

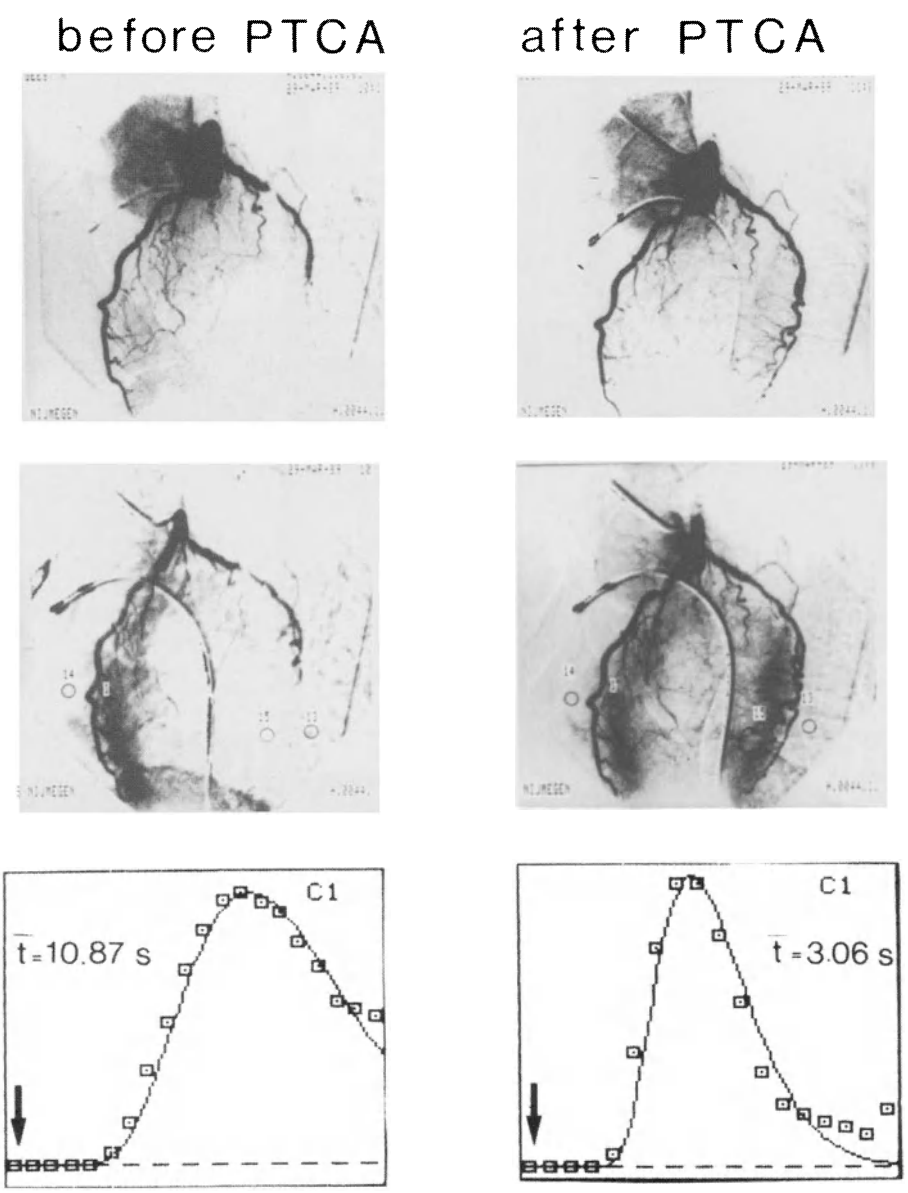


*Figure 22.* Mask mode subtracted images of a 69–year-old lady before (left) and after successful PTCA (right) of the left circumflex artery. The coronary artery itself, the filling of the myocardium by contrast agent, and the time-density curve over the indicated region of interest #15 are shown. The ratio between mean transit time at maximal hyperemia after and before PTCA was 10.87:3.06 which means that, as a result of the PTCA, maximally achievable flow through the LCx myocardium increased by 356%. The arrow indicates the start of contrast injection. The positions of the myocardial regions of interest and the corresponding background regions of interest are indicated by the small circles.

*Table 1.* Reasons for incomplete data acquisition or incomplete evaluation (n = 8)

| | | |
|---|---|---|
| * | Insufficient image quality for reliable determination of $T_{mn}$ (either before or after PTCA) | (4×) |
| * | Atrial fibrilation, due to stimulation catheter | (1×) |
| * | Total occlusion of LCx artery before PTCA | (1×) |
| * | Emergency surgery after occlusion of LAD artery | (1×) |
| * | Failure to pass an RCA artery stenosis | (1×) |

*Table 2.* Area stenosis severity (determined by quantitative densitometry), transstenotic pressure gradient (ΔP), mean transit time at maximal hyperemia ($T_{mn}$) and exercise time before and after PTCA (mean ± SD). The number of patients is mentioned in the last column

| | | | |
|---|---|---|---|
| % Area stenosis | 81 ± 12 | 39 ± 18 | 48 |
| Transstenotic ΔP (mm Hg) | 45 ± 10 | 14 ± 9 | 27 |
| $T_{mn}$ at max hyperemia (s) | 6.8 ± 2.0 | 3.4 ± 1.2 | 42 |
| Exercise time (s) | 370 ± 184 | 535 ± 86 | 48 |

test results were considered, this ratio averaged 2.4. Exercise time before and after the PTCA is also displayed and correlated well with the MFR. This MFR was at least 1.6 in all but one patients who had reversal of exercise test result from positive to negative. On the other hand, in 9 patients MFR was less than 1.6 and in 8 of these 9 patients no reversal of ET result was present. In 5 of these patients $T_{mn}$ at maximal hyperemia was already long before PTCA and remained so thereafter and in all these 5 patients a previously positive ET remained positive.

In the other 3 patients, severe anginal complaints had been present 2–6 weeks earlier, accompanied by a positive ET and significant single vessel disease at coronary arteriography. Remarkably these patients performed a normal exercise test 24–48 hours before the PTCA and if this test would have been the selection criterium they would not have been accepted for PTCA at all. Mean transit time during maximal hyperemia before the PTCA was already in what turned out to be the normal range and remained so after the PTCA. Although in all 3 of them an apparently severe stenosis was present and subsequently dilated, maximal flow did not change. MFR was 0.9, 1.1 and 1.2 respectively in these patients. This strongly suggests that between time of acceptance for PTCA and its actual performance, the functional significance of these lesions had diminished and the necessity of these 3 PTCA's can be considered doubtful.

The value of MFR for on-line assessment of the PTCA result is further evaluated in Table 3. In this table, pressure corrected MFR of more or less than 1.6 is correlated with presence or absence of reversal of ET result. It can be seen that $MFR_c$ more or less than 1.6, determined from studies immediately before and 10–15 minutes after PTCA, is highly predictive for functional success or failure as indicated by exercise testing.

*Table 3.* Relations between maximal flow ratio after correction for pressure changes ($MFR_c$), angiographic success, and baseline transstenotic pressure gradient as measured 5 minutes after the last balloon inflation (P), and presence or absence of reversal of exercise test (ET) result (+ indicates positive ET; − indicates negative ET). Angiographic success was defined as ≥20% area stenosis reduction and residual area stenosis <50% calculated by quantitative coronary arteriography

| $MFR_c$ ET | >1.6 | >1.6 | ET | Angio. succ. | Angio. unsucc. | ET | ΔP ≤15 mm HG | >15 mm Hg |
|---|---|---|---|---|---|---|---|---|
| + → − | 32 | 1 | + → − | 26 | 10 | + → − | 17 | 5 |
| + → + − → − | 1 | 8 | + → + − → − | 6 | 6 | + → + − → − | 2 | 3 |

It should be remarked in this context that in this particular group of patients the positive predictive value of a positive ET and the negative predictive value of a negative ET are almost 100% and therefore exercise testing can be used as the gold standard for functional evaluation of the PTCA result.

Despite their limitations, some other methods have been used until now for on-line evaluation of the PTCA, such as assessment of angiographic stenosis severity or measurement of resting trans-stenotic pressure gradients. Therefore we also investigated the relation between these on-line parameters and ET results 7–10 days after the procedure. As shown in table III, both relations were significantly less reliable than the use of MFR. At last we collected the values of mean transit time derived from the myocardium belonging to apparently normal coronary arteries.

These values were compared with the data of the corresponding diseased arteries before and after PTCA. The results are displayed in Fig. 23.

In the first place it can be seen that there is a definite range of what can be called a normal mean transit time during maximal hyperemia. For the RCA these values seem to be larger than for the LAD and CX. The dispersion is small as reflected by a small standard deviation.

In the second place, in the diseased arteries before PTCA a large range of values is found. After PTCA, however, the values return to normal with minimal scatter.

In those 30 patients with one diseased and one normal branch of the LCA, $T_{mn}$ at maximal hyperemia of the normal vessel could be compared before and after PTCA with $T_{mn}$ of the diseased branch.

$MFR_c$ for these control arteries was $1.0 \pm 0.2$ which confirms the intrinsic correctness of our method [24] (Fig. 24).

In conclusion we can state that the results of this clinical study indicate that reliable determination of mean transit time during maximal hyperemia is also possible in man, according to the original physiologic principles of indicator dilution theory. Therefore comparison of maximal flow before and after an intervention can be performed accurately. An appropriate means to

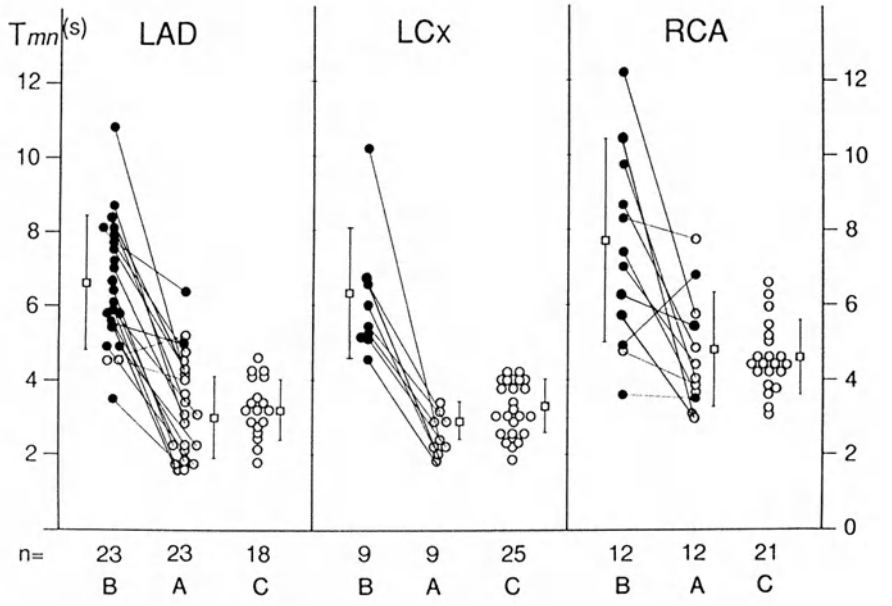


*Figure 23.* Values for mean transit time ($T_{mn}$) at maximal myocardial hyperemia belonging to stenotic vessels before (B) and after (A) successful PTCA and to normal control vessels (C). LAD = left anterior descending artery; LCx = left circumflex artery; RCA = right coronary artery. The closed points correspond with a positive exercise test and the open points with a negative exercise test. Mean values ± SD are also indicated. (From Pijls et al. [37], with permission of the American Heart Association, Inc.)

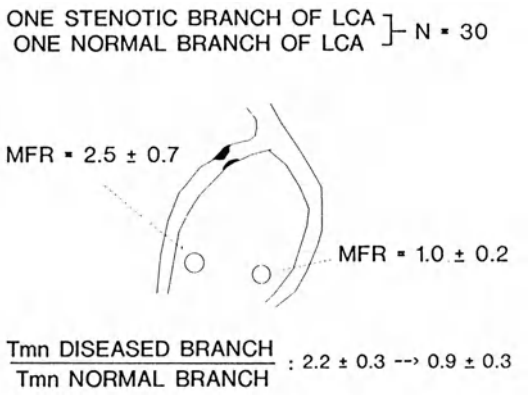


*Figure 24.* Maximal Flow Ratio of the dilated branch of the left coronary artery and of the normal branch which served as a control vessel (mean value ± SD).

evaluate the functional result of the intervention seems to be possible in this way. This evaluation can be performed on-line and can be used therefore for decision making while the procedure is still going on.

Moreover, we hope that even in diagnostic studies mean transit time during maximal hyperemia can help to decide about the functional significance of a coronary artery stenosis. More data of "normal" patients have to be gathered before conclusions on this last point can be drawn.

### 4.2. *Implications and limitations of the concept of the maximal flow ratio*

The videodensitometric approach for flow measurement as used in this clinical study, was very similar to the method validated in animal experiments as described in paragraph 2.4.5. In that validation study, it was proved, that comparison of maximal myocardial flow between situations with different degrees of stenosis can be accurately performed by calculating ratios of mean transit time.

In this clinical study, after extensive breath holding training and using synchronous X-ray pulses, image quality was so good that passage of contrast agent through the myocardium could be studied long enough to allow reliable determination of $T_{mn}$ in about 90% of the patients. Reproducibility of $T_{mn}$ in paired studies under identical circumstances was excellent.

Therefore, it can be concluded that this videodensitometric approach is applicable in clinical practice, at least in stable patients.

A difference between the previously mentioned experimental study and this clinical study is the different method to induce maximal hyperemia. In the validation study, continuous infusion of dipyridamole was applied for this purpose [36]. For practical reasons, such as short time of activity, intracoronary papaverine was used in the clinical study. It has been proved by former investigators that from approximately 25 to 60 seconds after i.c. administration of 8–12 mg of papaverine, maximal dilation of the myocardial vascular bed is achieved [32, 62]. Therefore we assumed that during acquisition of the time density curve, the vascular volume remained constant and flow was not influenced by contrast injection.

In this clinical study, exercise testing 24–48 hours before and 7–10 days after the PTCA was the method of choice for non-invasive functional evaluation of the result of the procedure. Because in all patients the combination of anginal complaints NYHA class III, a positive ET and proved single vessel disease had been present less than 6 weeks before the PTCA, exercise testing can discriminate accurately between presence or absence of (residual) ischemia in this particular group of patients [65–66]. Moreover, because of the presence of just single vessel disease, it is justified to assume that ischemia, if present at exercise testing, is actually caused by the affected artery [65]. Therefore, ET results could be used in this study as the gold standard for PTCA success. $MFR_c$, angiographic result and final transstenotic pressure gradient were correlated to this gold standard.

Because exercise testing after the PTCA was performed several days after the flow measurements, changes in coronary anatomy and physiology could have occurred in the meantime. The 94% agreement between $MFR_c$ and ET seems to be very high in this respect. If, however, PTCA result in this study was judged by classical anatomical criteria, a previously positive ET remained positive despite an angiographically successful intervention in 4 patients, leading to a clinical restenosis rate of 9.5% within one week which is in accordance with current literature [67, 68]. One may speculate if this finding merely reflects the fundamental hypothesis that insufficient increase in maximal flow after PTCA, is a better predictor for restenosis than coronary anatomy.

The approach used in this study for calculation of flow is only valid in situations of maximal vasodilation to guarantee constant vascular volume. It should be emphasized that no information about resting flow can be obtained and therefore no coronary flow reserve can be calculated. This approach, however, offers the possibility to compare maximal myocardial flow before and after an appropriate intervention, such as angioplasty in this study but possibly also long-lasting lipid lowering therapy. *Unlike coronary flow reserve, this maximal flow ratio is independent of resting flow which is in turn influenced by heart rate, left ventricular hypertrophy, previous infarction, prolonged ischemia and the PTCA procedure itself* [3, 4, 10, 69–72]. *At maximal vasodilation, flow is only dependent on pressure which can easily be measured and corrected for as was done in this study.*

In fact, $MFR_c$ as defined in this study can be considered as the improvement of relative coronary flow reserve as recently defined by Gould et al. [73]. It should be realized in this context that anginal complaints in the majority of patients are due to inadequate maximal flow. Therefore, *increase in maximal flow is a clinically relevant parameter and is expected to reflect improved exercise tolerance.*

In the practice of interventional cardiology, parameters for on-line evaluation of the result of the intervention are essential. Because $T_{mn}$ can be calculated within minutes after image acquisition and decrease of this value correlates well with the functional result of the PTCA, determination of $MFR_c$ can be used for this purpose.

Despite their limitations, some other methods have been used for on-line evaluation of the PTCA until now, such as assessment of angiographic stenosis severity or measurement of resting trans-stenotic pressure gradients [55, 74–76]. Therefore we also investigated the relation between these on-line parameters and ET results 7–10 days after the procedure. Both parameters were significantly less reliable than the use of $MFR_c$.

In most former videodensitometric approaches, eg. the method described in paragraph 2.4.2. flow has been represented by contrast density divided by a certain time parameter such as appearance time [13, 15, 76, 77] Because contrast density, expressed in arbitrary units, is dependent on many factors not related to flow, and differs more than thousand percents between differ-

ent patients, it has been regarded as impossible to indicate normal values in these studies. Because in the present study merely a time parameter is used as an index of flow, it makes sense to look if a range of normal values for $T_{mn}$ at maximal hyperemia does exist. Most of the patients in this study provided 2 apparently normal coronary arteries and indeed a definite range for $T_{mn}$ of these normal vessels during maximal hyperemia could be distinguished. Moreover, after successful PTCA according to exercise testing, $T_{mn}$ returned to the 'normal' range except in one case (Fig. 23).

In previous studies using digital radiography for evaluation of CFR improvement after PTCA, it was observed that CFR immediately after the intervention did not return to normal [11, 77]. *It has been hypothesized that this phenomenon could be caused by the fact that resting flow after PTCA would still be elevated due to prolonged ischemia and to the procedure itself* [11, 77, 78]. *Our results are in favour of this explanation because* $T_{mn}$ at maximal flow in the dilated vessel was not longer than $T_{mn}$ at maximal flow in apparently normal coronary arteries. Furthermore, in those 30 patients with one diseased and one normal branch of the left coronary artery, the ratio ($T_{mn}$ diseased artery) / ($T_{mn}$ normal artery) decreased from $2.2 \pm 0.3$ before PTCA to $0.9 \pm 0.3$ after PTCA, which gives further support to that explanation. This last observation also suggests that the ratio between $T_{mn}$ of a stenotic and of a normal branch can help to assess the functional significance of the stenosis. Finally, it was observed in this group that the $MFR_c$ of normal control vessels was $1.0 \pm 0.2$ which argues for the intrinsic correctness of this method (Fig. 24).

### 4.3. *Limitations*

For the time being, the approach suggested in this study only provides an index for the maximal flow achievable for a certain vascular bed prior to and following an intervention.

Although a certain range of normal values could be distinguished in this special group of patients, it is still to early to judge about its value for the diagnostic catheterization. More data about normal coronary arteries are necessary. It should be remarked in this context that inadequate MFR can either mean that the PTCA failed or that the situation before the PTCA was already (nearly) normal and that, in fact, PTCA had not been necessary as was probably the case in 3 of our patients.

*This ambiguity between an unsuccessful intervention and an anatomically successful intervention in a distribution without baseline flow abnormality, could restrict the clinical usefulness of this approach.* As can been observed in Fig. 23, however, knowledge of normal values for $T_{mn}$ during maximal hyperemia can help to discriminate between these possibilities. In case of the LAD and LCx arteries, an excellent partition between pathological and normal values is present. In case of the RCA there is some overlap. In

case of a stenosis in one branch of the LCA, also the ratio ($T_{mn}$ diseased branch)/($T_{mn}$ normal branch), can be helpful in this respect.

A further limitation is that acquisition of well-interpretable time density curves is highly dependent on sufficient image quality. In this study adequate image acquisition as well before as after PTCA was possible in about 90% of all patients but one can doubt on this point in case of emergency situations where no chance for previous breath holding training is present. In that case, motion artifacts serious enough to interfere with reliable image processing, will probably be present more often.

The population in this study consisted of a selected homogeneous group of patients with single vessel disease. Although from a theoretical point of view there is no reason why this approach would not be valid in multivessel disease, caution is warranted in extrapolation of these results to other groups of patients: It is well-known that a number of other methods for blood flow evaluation, although physiologically valid and validated in single vessel disease, are difficult to use in multivessel disease and more complex pathological states [4, 50, 73, 79]. The reason to confine this study to patients with single vessel disease, was to be sure of an unambiguous functional test to decide about success or failure of the intervention. As explained above, exercise testing could be used for this purpose in this particular group of patients. In multivessel disease, on the contrary, a positive ET even if combined with thallium scintigraphy, is hard to relate to one particular stenosis [70, 80].

Another factor which may restrict the clinical value of the MFR, is the presence of collateral circulation, excluded in this study. In that case, transport of contrast agent injected into the vessel itself can be slowed down by collateral blood supply. This also holds true for patients with bypass grafts in whom the native vessel is not completely occluded.

Next, it is necessary that overprojection of the myocardium supplied by the analyzed artery can be avoided while nevertheless its thickness in the chosen projection should be large enough to ensure sufficient staining after contrast injection. This can be hard to obtain for diagonal and intermediate branches of the LAD artery and for posterolateral branches of the LCx artery.

At last it should be remarked that, in case of serial lesions within one vessel, $T_{mn}$ at maximal hyperemia for the supplied vascular bed tells something about the summed effect of all abnormalities and nothing about the significance of the individual lesions. This last point, however, may be an advantage in the evaluation of long-term changes in diffusely diseased arteries in studies to determine the effects of lipid-lowering therapy.

Despite these limitations, this study shows that comparison of maximal flow before and after PTCA is possible in at least a large part of patients and enables reliable, on-line evaluation of the functional improvement achieved by the intervention.

## 5. Concluding remarks and future directions

### 5.1. *Concluding remarks*

Despite the inborn tendency of cardiologists, radiologists, and cardiac surgeons to overrate (overvalue) anatomical data from the coronary arteriogram as representative for the severity of coronary artery disease, it has became clear during the last decade that evaluation of coronary obstruction by quantitation of luminal narrowing from angiography has its pitfalls.

Although the coronary arteriogram will continue to play a pivotal role to locate a stenosis, data about coronary or myocardial blood flow are necessary to better understand its functional significance.

One of the new methods to collect data about flow or flow reserve, is to study contrast passage through the coronary arteries and the myocardium as a function of time, called videodensitometry or ECG-triggered digital radiography. During the last 10 years, this method has progressed from an experimental tool to a clinically feasible, but still more or less investigational, tool which is applied in a number of well equipped centers by well-motivated investigators

The appearance-time-contrast density approach, according to Vogel provides data about absolute coronary flow reserve, but, however, is only suitable to detect rather large changes in flow reserve. The more physiologic approach by Pijls is more demanding for investigator and patient and enables accurate comparison of relative coronary flow reserve between different situations, such as before and after an intervention. In the diagnostic catheterization, however, its value remains to be settled.

Other factors still limiting the widespread use of these methods are the absence of validation studies in heterogenous populations, the problems concerning overprojection (and more in particular the question if it will ever be possible to completely understand a three-dimensional problem from a limited number of scaler planes), and the problem of the collateral circulation, which is neglected in these approaches.

At last, one should realize that progression from an anatomic interpretation of coronary arterial lesions to measurement of blood flow is but one important step to understand ischemic heart disease, the relation between perfusion and contractile function is not yet answered. (Does sufficient flow always correlate with sufficient contractile capacity?)

Despite the tremendous efforts by a large number of outstanding investigators in the past 25 years a lot of work remains to be done.

### 5.2. *Back to the future*

Developments towards the three-dimensional reconstruction of the distribution of the contrast perfusion in the myocardial muscle from biplane angiographic views.

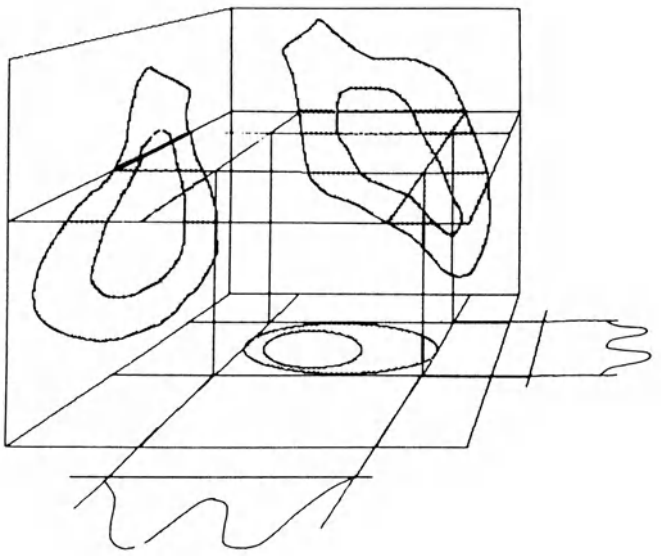

*Figure 25.* The purpose of three-dimensional reconstruction from biplane orthogonal angiographic views is to obtain a stack of slices selected approximately perpendicular the left ventricular long axis.

In theory, radiographic myocardial perfusion imaging allows a quantitative assessment of the functional significance of a coronary stenosis. All approaches published in the international literature are based on some kind of volume parameter and time parameter. These spatially related parameters, "volume of the myocardial region-of-interest" and "contrast medium transit time" however, should both be computed in three-dimensional space, rather than in a two-dimensional projection image.

In the conventional two-dimensional projection images there does not exist a one-two-one relationship between a selected myocardial region of interest (ROI) and one particular coronary segment perfusing that area due to over-projection of myocardial regions in front of and behind the selected ROI perfused by other arterial segments, which may result in measurements which are difficult to interpret or even unreliable. To overcome these problems, we have developed two algorithms to determine the spatial distribution of perfusion levels in slices of the heart, selected approximately perpendicular to the left ventricular long axis, from two orthogonal angiographic views: the Segmental Reconstruction Technique (SRT) and the Network Programming Reconstruction Technique (NPRT). Both techniques require a priori geometric information about the myocardium. Our basic approaches have been described in detail in [81]. A diagram of the basic reconstruction process is given in Fig. 25.

Two types of *a priori* information have been introduced: 1) endocardial and epicardial descriptions of the reconstructed myocardial geometry obtained from the corresponding left ventricular and coronary angiograms, respectively and; 2) the expected perfusion levels in the slice under reconstruction. The morphologic set of data will be used to restrict the set of feasible reconstructions, while the second set (expected perfusion levels) will be used to define an "optimal feasible solution" within the limited set of feasible solutions.

Using the SRT approach, pie-shaped segments are defined for each slice within the myocardial geometric constraints such that superimposition of these segments when projected in orthogonal biplane views is minimal. The reconstruction process uses a model with identical myocardial geometry and definition of segments. Each segment of the model is assigned a relative perfusion level with unit one if no other a priori information is available. In this case, the model contains geometric information only. In case a priori information about expected segmental perfusion levels is available, a level between zero and one is assigned to each segment. The a priori information on the myocardial perfusion levels can be extracted from either anatomic information about the location and severity of existing coronary arterial obstructions, or from a slice adjacent to the one under reconstruction.

Using the NPRT approach perfusion levels are computed for each volume picture element of a slice within the reconstructed myocardial geometry, thus resulting in an much higher spatial resolution than the SRT approach. A priori information of perfusion levels must be included in this approach again based upon anatomical information, or upon the slice adjacent to the one under reconstruction. The very first slice of a myocardial study is reconstructed by the SRT approach.

Both the SRT approach and the NPRT approach have been validated by computer-stimulated experiments [82].

A cardiologist defined model slices supposed to be distal to a coronary obstruction in cases of single vessel disease by assigning relative perfusion levels to the eight segments, which were geometrically defined by the SRT approach. The range of relative perfusion levels was from zero to one; zero indicates that no perfusion at all was expected, while one indicates normal perfusion. An example of such a perfusion model is shown in Fig. 26, for a slice distal to a coronary obstruction of 90% area-stenosis in the proximal part of the Left anterior descending artery. No perfusion is expected in segments which are supposed to be related to the Right Coronary Artery.

From this actual slice the density profiles were computed and reconstructed. The reconstruction result is shown in Fig. 26.

Though both the SRT and the NPRT are still under development and were only validated with computer-generated data, developments are directed toward a resolution of $128 \times 128 \times 32$ pixels, in order to obtain slices comparable to those obtained by Thallium-201 tomography.

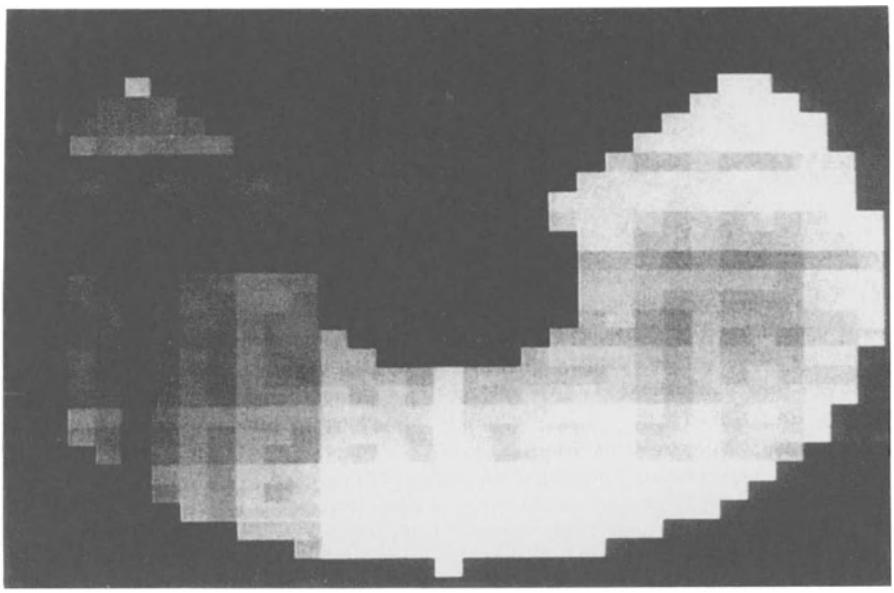

*Figure 26.* An example of expected myocardial perfusion levels in a slice supposed to be distal to a 90% area stenosis in the left anterior descending artery. The perfusion level of each voxel is reconstructed from the density profiles.

Computer-simulated experiments will be further extented with a sensitivity measure for deviations in myocardial geometry. Both reconstruction techniques will also be validated with patient studies of dual plane coronary flow reserve analysis and Thallium-201 tomography in the near future.

Extensive computer simulations for the SRT have proved that the mean difference between the actual and reconstructed segmental perfusion levels, on a scale from 0 to 1, is smaller than 0.45 (SEE = 0.0033, REE = 1.80) for various coronary artery disease states without the use of a priori information on expected perfusion levels. This error becomes smaller than 0.36 (SEE = 0.0026, REE = 1.42) if a priori information in the reconstruction technique is included. Similar computer simulations for the NPRT have proved that these mean differences, in geometric segments equal to those defined for the SRT, are smaller than 2.94 (SEE = 0.0308, REE = 0.77) on a scale from 0 to 16, without the use of a priori information on expected perfusion levels, and smaller than 1.72 (SEE = 0.0304, REE = 1.10) on the same scale when a priori information is included. Therefore, it may be concluded that slice-wise three-dimensional reconstruction of perfusion levels is feasible from biplane computer-simulated data, and that a similarity exists for mean per-

fusion levels in corresponding regions in the simulated and reconstructed slices, for various states of single coronary artery disease.

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# 13. On-line versus off-line assessment of coronary flow reserve

MARC M.J.M. VAN DER LINDEN, JÜRGEN HAASE and PATRICK W. SERRUYS

## Introduction

Since its introduction, coronary arteriography has been of great importance for the diagnosis and management of patients with ischemic heart disease [1]. Although location and morphology of coronary artery stenoses can sufficiently be assessed by this technique, information about their functional significance cannot always be obtained from the arteriogram alone [2–4].

The concept of coronary flow reserve (CFR) has been developed to describe the relationship between the angiographic severity of coronary artery disease and the resulting reduction or limitation of maximal coronary blood flow in the myocardium [3–7]. Even in the absence of focal atherosclerosis or other flow limiting factors in major epicardial vessels, CFR measurements can be used to evaluate dysfunction of the microcirculation. This is especially relevant in cardiac transplant recipients, where a diffuse arteriopathy can reach a flow limiting significance, without changes in the angiographic appearance [8, 9].

Different techniques of coronary flow reserve measurement have been described, and used in clinical practice. In general, these techniques are designed for application during the catheterization procedure, like venous blood flow measurements in the coronary sinus, or the assessment of phasic coronary blood flow velocities using ultrasonic Doppler catheters. The latter technique requires the insertion of hardware in the coronary artery tree, and is extremely "space dependent" [10]. Finally, the radiographic assessment of myocardial perfusion, using contrast media, combines the videodensitometric approach with digital subtraction angiography. Compared with the other invasive techniques to measure CFR, this approach has several advantages. First of all, the digital subtraction technique is more easily applicable during routine catheterization, because no additional catheter or intracoronary device has to be used, which makes this procedure safer, less time consuming and less expensive. Moreover, the analysis of multiple regions of interest (ROI) provides flow information from various subsegments of the coronary



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artery tree, which is not possible or more time consuming with other invasive techniques.

In the setting of pharmacological or mechanical interventions, where the results have to be estimated directly after the catheterization, these on-line assessment techniques of coronary flow reserve are very useful [5]. Off-line assessment of CFR, on the other hand, allows objective evaluation of multicenter trials in core laboratories, where the selection of ROI's can be carried out by an independent analyst, thereby non-biased by the investigator. However, only on-line assessments of CFR have been validated in animal experiments as well as in a clinical setting using flow calculations from simultaneously intravascular Doppler velocity measurements as a reference [11, 12].

## On-line and off-line assessment of coronary flow reserve

To assess coronary flow reserve by videodensitometry, a fixed amount of non-ionic contrast medium is injected at 37°C into the coronary artery using an ECG-triggered infusion pump. The injection rate of the contrast medium is judged to be adequate when back flow of contrast medium into the aorta occurs. The heart is atrially paced at a level approximately 10 beats/min above spontaneous heart rate. The X-ray exposure per frame is kept constant by selecting the lock-in mode on the X-ray generator. After intracoronary administration of 2 mg isosorbide-dinitrate, basal coronary angiography is performed. Thirty seconds after pharmacologically induced maximal hyperemia, using an intracoronary bolus injection of 12.5 mg papaverine, the angiogram is repeated.

### *Off-line*

Coronary flow reserve measurement with digital subtraction cineangiography from 35 mm cinefilm has been implemented in the Cardiovascular Angiography Analysis System (CAAS) [7]. Thereby, five end-diastolic cineframes are selected from successive cardiac cycles. Logarithmic non-magnified mask-mode background subtraction is applied to the image subset to eliminate non-contrast medium densities, using the last end-diastolic frame prior to contrast administration as a mask. The principle of mask mode subtraction techniques allows the determination of myocardial time-density curves before and during coronary vasodilatation. In the CAAS system at the Thoraxcenter, the appearance-time-contrast density approach, according to Vogel et al. [13], is used. From the sequence of background subtracted images, a contrast arrival time image is automatically determined, using an empirically derived fixed density threshold [7]. Each pixel is labelled with the sequence number of the cardiac cycle in which the pixel intensity level exceeds the threshold, starting from the beginning of the ECG-triggered contrast injec-

tion. Arrival time numbers are displayed color coded in the CAAS. In addition to the contrast arrival time image, a density image is computed, with each pixel intensity value being representative for the maximal local contrast medium accumulation.

On corresponding basal and hyperemic end-diastolic frame sequences, identical regions of interest (ROI) are selected in such a way that the epicardial coronary arteries visible on the angiogram, the coronary sinus and the great cardiac vein are excluded from the analysis.

For the calculation of relative blood flow within these regions of interest two parameters are required: the relative regional vascular volume and the mean contrast appearance time. The relative regional vascular volume can be calculated from the maximal density image, the intensity value being proportional to the transradiated amount of contrast medium within the vessel. Therefore, the regional vascular volume for a user-defined ROI is proportional to the mean radiographic density within the ROI. The mean contrast appearance time is derived from the contrast arrival time image.

Regional flow values are quantitatively determined using the following videodensitometric principle: $Q = V/T$ ($Q$ = regional blood flow, $V$ = regional volume and $T$ = mean appearance time).

The coronary flow reserve for one ROI is then calculated as follows:

$$CFR = \frac{Q_h}{Q_b} = \frac{V_h/T_h}{V_b/T_b} = \frac{V_h x T_b}{V_b x T_h} = \frac{D_h x T_b}{D_b x T_h}$$

($D$ = mean maximum contrast density; h = hyperemic; b = baseline)

*On-line*

The on-line method as implemented in the Phillips Digital Cardiac Imaging System (DCI) uses the same principle as the off-line method. After manual selection of the mask, the computer automatically determines the end-diastolic images. Interaction by the analyst is possible according to visual inspection and the ECG recording. After logarithmical transformation of the data, the mask image is subtracted from the subsequent images. Usually 5 to 8 of these images are necessary to perform the calculations. From these sequences 3 parametric images are constructed:

A contrast arrival time image ($T_{arr}$), where each pixel is related to the cardiac cycle in which the maximal change in density of contrast is achieved.

A contrast density image ($D_{max}$), where each pixel intensity value is representative for the maximal value for contrast density in the sequence of subtracted images.

Finally, a parametric flow image is constructed, in which the contrast density is divided by the arrival time.

When parametric images are obtained under baseline and hyperemic conditions, a fourth image, a CFR image, can be obtained by exactly super-

imposing both images, in which each pixel intensity value is representative for the calculated CFR. This is performed by the computer, but can also be corrected by the analyst, using anatomical landmarks. Gray scaling allows quick inspection of the CFR in different areas of the myocardium.

## The thoraxcenter experience

At the Thoraxcenter a study has been initiated to compare, in a clinical setting, off-line assessment of CFR, using the cinefilm based analysis system, which is implemented in the Cardiovascular Angiography Analysis System (CAAS, digital matrix 512 × 512), with the corresponding on-line software, which is implemented in the Phillips Digital Cardiac Imaging System (DCI, pixel matrix 512 × 512).

## Patients

Elective heart catheterization is performed in all cardiac transplant recipients as part of their annual follow-up protocol. This procedure consists of right ventricular biopsy, selective coronary angiography and off-line assessment of CFR. Since the DCI system has been installed at the Thoraxcenter, 18 patients (age 46±14, mean±SD) were included in this comparative study. The mean interval after transplantation was 3.2±1.1 year. All patients were free of acute rejection at the time of the procedure. They were investigated without premedication and their anti-hypertensive medication was discontinued the evening before the catheterization.

## Methods

On- and off-line measurements of CFR were performed as described. Simultaneous videocamera acquisition and cinefilm exposure was made possible by selecting the CINE-DCI mode, using a standard partially transmitting silver mirror. A print-out was made of the on-line CFR image with the selected regions of interest, to allow off-line assessment of CFR in the same areas, using anatomical landmarks (Fig. 1).

To assess left ventricular function, left ventricular angiography was performed in 60°C left anterior oblique and 30°C right anterior oblique projection. Left ventricular ejection fraction (EF) was calculated by the Dodge technique [14], and regional wall motion was assessed using the "Centerline-method", as described by Sheehan, using fractional shortening in 100 chords, perpendicular to a centerline drawn between the end-diastolic and end systolic contours of a ventriculogram [15].

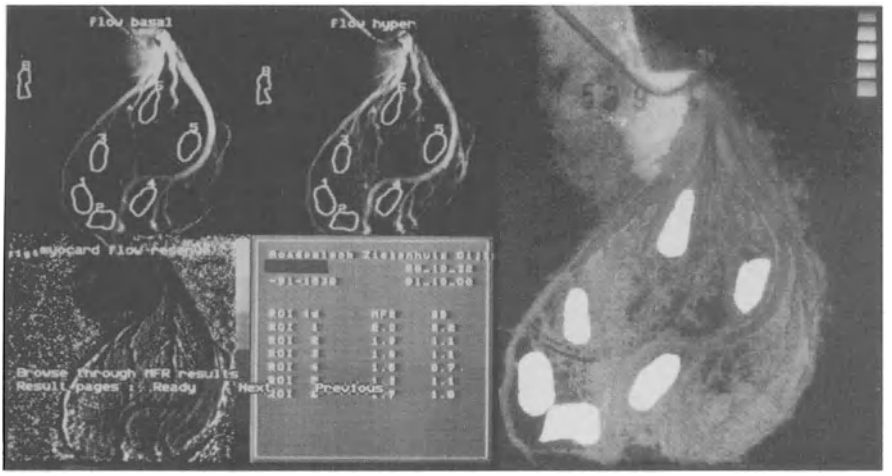


*Figure 1.* Illustration of the image acquisition in this study in a 58 year old male heart transplant recipient. Left: On-line assessment of CFR. Right: Off-line assessment of CFR.

## Statistical methods

Statistical analysis was performed using linear regression analysis. The Student's T test and Wilcoxon Matched-pairs Signed-ranks test were used for paired analysis. To assess the agreement between both measurements, the individual differences between CFR, measured by CAAS and DCI, were plotted against individual mean values, according to the statistical approach proposed by Altman and Bland [16]. Mean value and standard deviation of the signed differences in CFR between both methods were then calculated. Statistical significance was defined as a p value of 0.05 or less.

## Results

In 18 cardiac transplant recipients a total of 68 ROI's (3.7 per patient, range 3–6) were analyzed with both techniques. All patients had a normal left ventricular function with normal regional wall motion. Ejection fraction could be assessed in 17 patients and gave a mean value of 69±7%. Mean systolic blood pressure at the time of hyperaemia was 119±15 mmHg and mean diastolic blood pressure was 84 ± 11 mmHg.

Among the patients included in this study, there was no angiographic evidence of collateral circulation or flow limiting stenosis (>50% diameter reduction) by either visual assessment or quantitative analysis, using automated edge detection.

The linear regression analysis, as shown in figure 2, revealed a reasonable

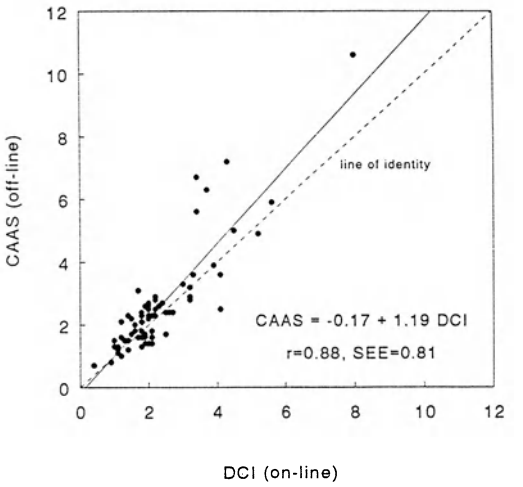


*Figure 2.* Results of comparison of digital and cinefilm measurements: The CFR results of the DCI are plotted against the results obtained by the CAAS system. The results of the linear regression analysis and the line of identity are included in the graph.

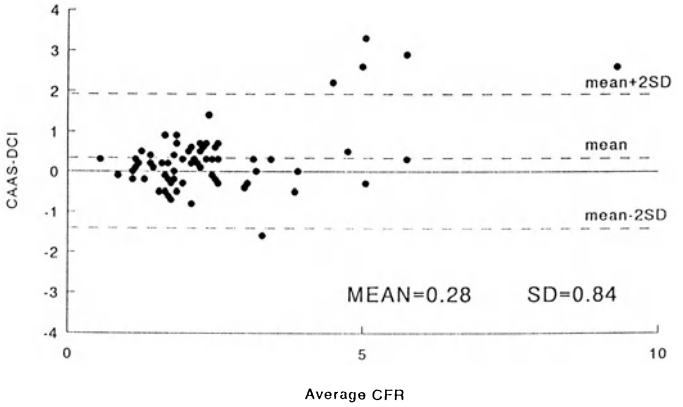


*Figure 3.* Comparison of digital and cinefilm measurements according to the method of Altman and Bland [16]: The differences between DCI and CAAS measurements are plotted against the mean values. The mean difference and 2–fold standard deviation are shown in the figure.

correlation between CFR measurements using the DCI and CAAS system ($r = 0.88$, $y = -0.17 + 1.19x$, $SEE = 0.81$). However, the CAAS measurements (mean $2.62 \pm 1.70$) were significantly higher than the DCI measurements (mean $2.33 \pm 1.25$) ($p = 0.01$, Wilcoxon Matched-pairs Signed-ranks test). According to the approach of Altman and Bland, as shown in Fig. 3, the mean difference between both methods was $0.28 \pm 0.84$.

As illustrated by Fig. 2, the difference between the results of on- and off-

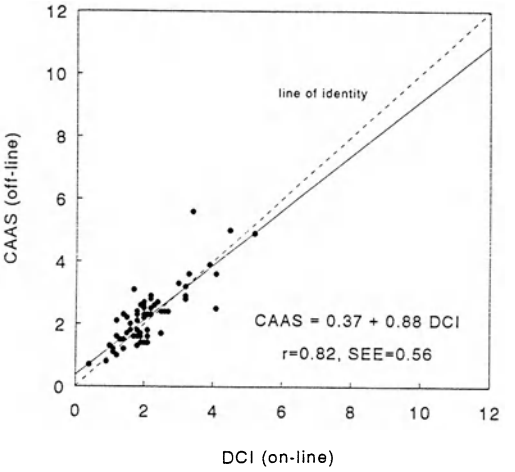


*Figure 4.* Results of comparison of digital and cinefilm measurements, excluding the 2 patients with high values for CFR as assessed by the off-line (CAAS) system.

line measurements is more pronounced for high values of CFR (>5,0 by CAAS; 6 ROI data points). These datapoints were derived from 2 patients only. In one of these patients the level of inspiration during the basal and hyperemic coronary angiogram was not identical. Therefore the position of the diaphragm could have influenced the result of CFR measurements. In the second patient the injection of contrast medium was performed selectively in de circumflex artery.

After exclusion of these 2 patients from the analysis, the relationship between off-line and on-line assessment of CFR improved ($r = 0.82$, $y = 0.37 + 0.88x$, $SEE = 0.56$), as shown in Fig. 4. There was no significant difference between the results of both measurements. The mean value for off-line measurements was $2.26 \pm 0.97$, for the DCI system $2.15 \pm 0.91$. The mean difference between both methods was $0.11 \pm 0.56$ (Fig. 5).

## Discussion

During the last decade several studies have demonstrated that the functional significance of a coronary obstruction cannot always completely be evaluated by visual interpretation of stenosis morphology or quantitative measurement of it's geometric dimension [17, 18]. As already stated in this book, additional assessment of myocardial blood flow provides better insight in the functional significance of a coronary stenosis.

Furthermore, assessment of CFR provides information concerning the specific characteristics of myocardial perfusion in patients with cardiomyo-

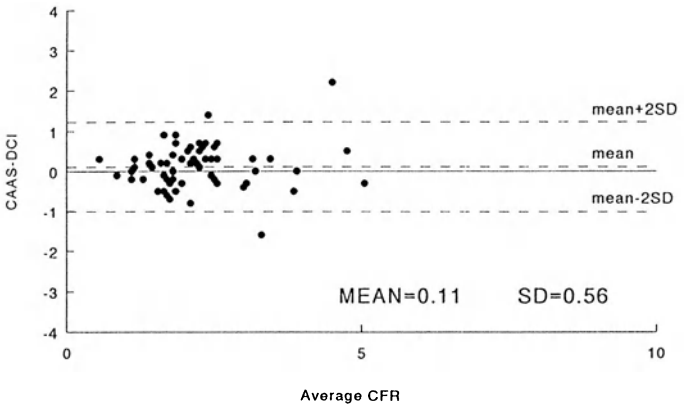


*Figure 5.* Comparison of digital and cinefilm measurements according to the method of Altman and Bland [16], excluding 2 patients with high values for CFR as assessed by the CAAS system.

pathy, syndrome × and diffuse coronary artery disease, as present in cardiac transplant recipients. The influence of different treatment strategies can be assessed by multicenter trials, where analyses are performed in an independent core laboratory, blinded for treatment and therapy.

The introduction of digitized facilities in the catheterization laboratories made it possible to perform on-line videodensitometric CFR measurements. However, since to date only 5% of the European catheterization laboratories (estimation by the industry) are equipped with digital angiographic facilities, there is a need for off-line analysis systems based on conventional cinefilm. Furthermore, the storage capacity for digital images, which is important for the transfer of the digital information to a core-laboratory, is still limited.

Animal experiments and in vivo validation studies of videodensitometric CFR measurements on myocardial regions of interest have shown excellent results [12, 19]. The validation using intravascular Doppler assessment of blood flow velocity is eminently relevant because the methodological approach of both techniques is completely different. In a study of 21 patients undergoing elective PTCA for angina pectoris [20], the CFR measurements using off-line digital subtraction cineangiography (OLDSC) were compared with CFR measurements using intracoronary blood flow velocity assessed by a Doppler balloon catheter (DOP). There was a good relationship between the measurements, irrespective whether the flow was only limited by the severity of the stenosis (OLDSC = 0.88 DOP + 0.12, r = 0.85, SEE + 0.38), or whether additional factors were present with potential influence on the outcome of CFR measurements, like left ventricular hypertrophy or coronary artery dissection (OLDSC = 0.96 DOP + 0.01, r = 0.87, SEE = 0.34).

Animal experiments using microspheres show that, despite the possible error sources, there is a good correlation between videodensitometric mea-

*Table 1.* Reproducibility of the digital subtraction technique [21]

| | Variability (mean ± SD) | |
|---|---|---|
| Intra-observer | −0.01 ± 0.07 | NS |
| Inter-observer | 0.08 ± 0.52 | NS |
| Short-term | −0.02 ± 0.26 | NS |
| Medium-term | −0.06 ± 0.52 | NS |
| Long-term | 0.11 ± 0.63 | NS |

surements of CFR and the application of microspheres (n = 86, r = 0.79, y = 0.58 + 0.81x, SEE = 0.80) [12].

Since the analysis of the cineangiogram includes the selection of ROI's in the end-diastolic images, and the boundaries are drawn by the observer using a writing tablet, interfaced with the computer, this procedure can introduce some interobserver variability. However, as shown in Table 1, both the inter- and intra-observer variabilities, as well as the short-, medium-, and long-term variabilities of CFR show a reasonable reproducibility of this technique [20]. Interobserver variability from 2 observers, measured in 12 regions of interest in 7 patients, was 0.08 ± 0.52 and intraobserver variability, measured in 11 regions of interest in 6 patients, was −0.01 ± 0.07. The short-term variability, based on the analysis of 2 coronary angiograms, made 5 min apart and including 13 regions of interest, was −0.02 ± 0.26, the medium-term variability, based on repeated coronary cineangiograms within 1–3 hr, was found to be −0.06 ± 0.52 and the long-term variability from repeated coronary cineangiograms within 3–5 months, was 0.11±0.63. In all these variability studies, no significant difference was found between both measurements.

To assess the relation between CFR, measured by digital subtraction technique, and the severity of coronary artery disease, assessed by quantitative coronary angiography, a precision study from the Thoraxcenter on 17 patients with single vessel coronary artery disease, and 12 patients with normal coronary artery dimensions, showed a good relation between CFR and the minimal luminal cross-sectional area (r = 0.92, SEE = 0.73) as well as between CFR and the percent area stenosis (r = 0.92, SEE = 0.74) [7]. In visually normal coronary arteries a CFR of 5.0±0.8 was calculated, which differed significantly from CFR of the coronary arteries with obstructive disease providing values between 0.5 and 3.9. In both this study as in later studies [19, 21] a normal CFR was defined as greater or equal to 3.4 (2 SD below the mean CFR of angiographically normal coronary arteries).

In this study the mean value of the measured CFR is 2.33±1.25 by DCI, and 2.62±1.70 by CAAS. The distribution of the ROI over the myocardium, using the coronary tree as a reference, is shown in figure 6. As can be appreciated from this scheme, only in a small percentage of ROI's a normal

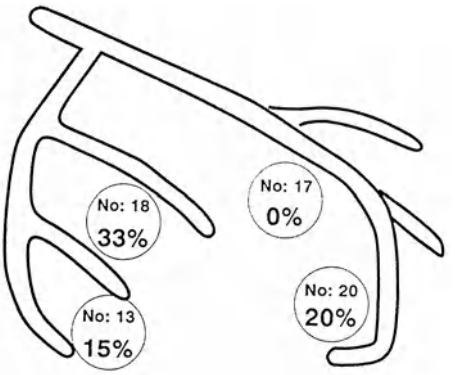


*Figure 6.* Distribution of the 68 ROI's over the myocardium with reference to the coronary artery tree. In bold the percentage of ROI's having a normal CFR is given.

CFR is measured, which is not an unexpected finding in such a group of patients [21].

The results of this study show that where estimated CFR was $\leq 5.0$, a good correlation was found between the CFR measurements using both systems. However, where estimated CFR was $>5.0$ by CAAS, the DCI yielded lower CFR values. There are a few possible reasons for discrepancy between the methods. First of all, the relation between the local amount of contrast and the resulting video brightness, has a different sign for both systems, i.e. negative for DCI and positive for CAAS. Despite the applied logarithmic substraction technique, non-linear terms may remain in the transfer function between contrast and videosignal level because of non-linear amplification stages in the DCI-chain and because of the non-linear relation between light exposure of the cine-film and its resulting optical transparency.

Moreover, the fixed density threshold, used in the contrast arrival time image to calculate contrast arrival time, is different for both systems. For the off-line system this threshold, expressed in percentage of the brightness scale, was empirically derived by analyzing the relationship between the baseline and the hyperemic myocardial contrast appearance times as well as the resulting CFR in 12 patients with visually normal coronary arteries [7]. With a low threshold of 4% above video black level and to a lesser extent with a threshold of 8%, background density was not eliminated, resulting in very short contrast medium appearance times. Therefore, a threshold of 12% was defined for the CAAS system to completely exclude the influence of background noise on the calculation of contrast medium appearance times. The DCI system uses a threshold of 50% of maximal pixel intensity for the calculations of contrast arrival time and maximal contrast density in a ROI.

*Limitations*

Comparing these methods, one has to realize the limitations of this technique. The videodensitometric method requires the use of contrast media, which have substantial vascular effects, although non-ionic media, like Iopamiro, which was used in this study, may disturb blood flow less than ionic agents [15, 22]. Furthermore, because the longterm variability is $0.11 \pm 0.63$, this approach is only suitable to detect rather large changes in flow reserve ($>1.37$, mean +2 SD) and should therefore be used in specific patients, in whom large changes of myocardial flow are expected.

For all techniques, the CFR is based on the ratio between maximal coronary blood flow and resting flow. The latter is mainly determined by the aortic pressure and heart rate, and therefore slight changes in these 2 parameters can influence CFR measurements. Flow during maximal hyperemia is linearly related to the perfusion pressure. This can result in a scatter of CFR data in a single patient. The recently described hyperemic versus perfusion pressure relationship [23] theoretically overcomes this problem, but is difficult to assess with angiography.

## Conclusion

The digital subtraction technique to measure CFR is a reliable method, which can be assessed on-line or off-line. This method is easily applicable, and less time consuming than other methods to assess CFR. In view of the good correlation between both the on- and off-line system it is reasonable to propose the use of the off-line technique to assess CFR in large multicenter trials where cinefilm is used. The design of the "REGRESS" study already included these measurements.

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# 14. Calculation of maximum coronory, myocardial, and collateral blood flow by pressure measurements in the coronary circulation

NICO H.J. PIJLS, K. LANCE GOULD, BERNARD DE BRUYNE, HANS J.R.M. BONNIER, G. JAN WILLEM BECH, WILLIAM WIJNS, GUY R. HEYNDRICKX, RICHARD L. KIRKEEIDE, and MAMDOUH I. EL GAMAL

## Introduction

Since many years it has been widely recognized that the functional significance of coronary artery disease cannot be completely understood from anatomic information obtained by the coronary arteriogram. The shortcomings of the angiogram are most pronounced in the evaluation of PTCA-results, where the edges of the lesion are often hazy and hard to determine, whereas especially in this situation on-line information about the impeding effect of the (dilated) stenosis on blood flow is of paramount importance. Also in diagnostic catheterization, especially in intermediate lesions, determination of the functional significance of the stenosis remains cumbersome. Therefore, may attempts have been made to measure coronary blood flow directly. Most approaches in this field, however, are either crude, inaccurate, laborious, expensive, require complex equipment or imply certain risks for the patient [1–4]. Of all those methods, only comparison of blood flow velocities by the Doppler wire and ECG-triggered digital subtraction angiography have gained some clinical application [5,6]. Both methods, however, only provide information about anterograde blood flow through the large epicardial coronary arteries. No information about the contribution of collateral flow to total myocardial perfusion can be obtained. In fact, no quantitative methods to assess collateral flow in conscious man are available at present. Both in diagnostic catheterization and in PTCA, it would be of great importance if a method would be available that enables measurement of myocardial perfusion by simple means and inexpensively, without extra instruction to the patient and without prolongation of the procedure. It would be of even more importance if the contribution of coronary blood flow (in the stenotic artery) and collateral blood flow to total myocardial perfusion could be separately quantified. In this chapter, the theoretical background and experimental validation of such a method will be discussed, which allows to achieve all information about flow simply from pressure measurements in the coronary circulation.



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*Theoretical background*

A direct relation between coronary pressure and flow or flow reserve may only be presumed if coronary resistances remain constant (and minimal) as theoretically is the case during maximum arteriolar vasolidation. In that case, pressure measurements alone theoretically can be used to predict flow and thereby functional stenosis severity. Under those circumstances, coronary pressure measurements in principle should also be able to quantify collateral flow without using radiolabelled microspheres suitable only for experimental preparations. The concept of coronary pressure measurements alone during maximum vasodilation to assess stenosis severity, flow reserve and collateral flow has not been previously reported although it is important to our understanding of the fluid dynamics of the stenotic coronary artery.

Therefore, the purpose of this study is to describe systematically the theoretical basis for calculation of flow in the different components of the coronary circulation, including collateral flow, by pressure measurements during maximum coronary vasolidation; to validate experimentally this theoretical model; and to show its potential clinical applications for assessing changes in functional stenosis severity before and after PTCA and during diagnostic catheterization. For this study, the maximally achievable coronary and myocardial flows in the presence of a stenosis are expressed as a fraction of their normal maximum values expected in the absence of a stenosis, defined as zero pressure gradient. Therefore, a normal coronary artery or normal reference distribution elsewhere in the heart is not necessary in this approach. Moreover, the separate contributions of coronary arterial and collateral flow to myocardial perfusion can be quantitated. The basic theory is developed by hemodynamic equations and validated experimentally in this report with potentially practical applications at PTCA.

Previous attempts to relate transstenotic pressure gradient ($\Delta P$) to the functional significance of a stenosis have been disappointing such that at present only a few centers still routinely perform these measurements [7]. Although decrease of $\Delta P$ after PTCA has been used to assess the success of the procedure, the correlation is poor and with little additional value over morphologic assessment of results [7–13].

There are three reasons why pressure measurements have not been useful for assessment of flow: *First*, the instrument used for pressure measurement in previous studies (in most cases the balloon catheter) is unsuitable because its size is too large compared with the size of the coronary artery. The cross-sectional area of an 80% area stenosis in a vessel with a diameter of 3.0 mm, is almost completely obstructed by a 3F balloon catheter, which is the thinnest catheter available now (Figure 1). Thus, with standard PTCA catheters severe overestimation of $\Delta P$ may occur [7,14].

*Second*, most previous measurements have been made in the basal state [9–11], in which $\Delta P$ is determined primarily by flow as affected by distal coronary autoregulation. Flow and pressure are related to each other by

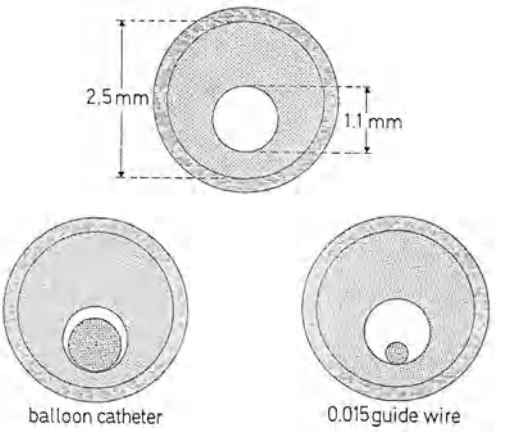



*Figure 1.* Severe overestimation of the transstenotic pressure gradient occurs with a regular 3F balloon catheter across an 80% area stenosis in a 2.5 mm Ø coronary artery. If, on the contrary, an 0.015″ guide wire is used for distal pressure recording, the influence on the gradient is negligable.

epicardial and myocardial vascular resistance. These resistances are continuously changing under the influence of myocardial oxygen demand, arterial pressure, contrast injections, and coronary vasomotion. Therefore, theoretically the relation between flow and pressure cannot be related to stenosis severity unless these resistances are known or at least remain constant. This condition can be met by obtaining pressure measurements during maximum vasodilation of the vascular bed when all resistances in the coronary circulation are close to minimal and presumably constant [2, 6]. As is true for coronary flow reserve, making functional measurements of stenosis severity from pressure measurements after maximum vasodilation is intuitively reasonable since the functional capacity of patients with ischemic heart disease is determined by the maximally achievable blood flow through the stenosis and its dependent myocardium [2–16]. Although the necessity of maximum vasodilation is generally recognized at present, it has not been applied to measurements of pressure gradients in a number of former studies [8–14].

*Third*, in previous studies for assessing stenosis severity by pressure measurements, coronary flow or improvement of flow has been related to transstenotic pressure gradient or decrease of that gradient or to transstenotic pressure gradient expressed as a percent of proximal arterial pressure [7–11]. This approach is fundamentally limited because it fails to recognize that the stenosis is only one part of a complex hydrodynamic system, other parts of which may also affect the influence of the stenosis on blood flow.

*Table 1.* Applications and limitations of absolute, relative, and fractional coronary flow reserve (CFR, RFR, and FFR, respectively)

| | Independent of pressure | Easy appl. in man | Appicable to 3-V dis | Assessment of collateral flow |
|---|---|---|---|---|
| CFR | − | − | + | − |
| RFR | + | +/− | − | − |
| FFR | + | + | + | + |

Gould and Kirkeeide first described a systematic analysis of flow-pressure relations that considered the coronary circulation as a system of serial resistances with the stenosis of the epicardial artery being one component [2, 4]. Their description, however, did not take into account the collateral circulation and as a result could not explain a number of experimental data. Therefore, we modeled the coronary circulation in flow-pressure terms after maximum vasodilation, including the contribution of flow through the epicardial coronary artery and the collateral flow to the total myocardial blood flow. In this specific model of maximum vasodilation, measurements of pressures alone enable calculation of relative maximum flow in the epicardial coronary artery and the myocardium, and the relative contribution of collateral flow. Therefore, this model theoretically provides a good measure of the functional significance of a coronary artery stenosis. Moreover, changes in maximum coronary flow, myocardial flow, and collateral flow as a result of an intervention, can be readily determined in this model by simple pressure measurements under conditions of maximum vasodilation.

### *Maximum vasodilation and fractional coronary flow reserve*

At this point it is necessary to spend some considerations to the choice of the flow parameter which is most relevant to reflect the influence of a coronary artery stenosis on coronary or myocardial blood flow. At a first glance, one should choose absolute blood flow, in ml/min. However, absolute flow is widely varying between different coronary arteries and from one person to another and therefore expressing flow as an absolute volume is meaningless unless the distribution supplied by the artery is known. For this reason other ways to express blood flow in the coronary circulation have been searched for an the concepts of absolute coronary flow reserve (CFR), relative coronary flow reserve (RFR) and fractional coronary flow reserve (FFR) will be shortly discussed (Table 1).

*Absolute coronary flow reserve* was defined by Gould in 1974 as the ratio between hyperemic flow in a coronary artery and resting flow in that same artery. It has been considered as the standard for the functional status of a coronary artery for many years [17].

In clinical practice, however, measuring CFR has limited applications

largely due to methodological limitations. In addition, because CFR is defined as a ratio, diminished CFR can either reflect decreased maximum flow, increased resting flow, or a combination of both. Because all methods proposed for CFR determination in man, except positron emission tomography, require invasive manipulations or intracoronary contrast injections, true resting conditions in clinical situations are difficult to obtain. Moreover, several physiologic and pathologic conditions unrelated to the stenosis itself, may result in altered CFR for a given fixed stenosis [15, 17]. Arterial pressure, heart rate, left ventricular hypertrophy, previous infarction, and a number of other confounding factors all affect absolute coronary flow reserve. To avoid some of these problems, *relative coronary flow reserve* (*RFR*) was introduced, stimulated by the rapid developments in imaging techniques [2, 16]. RFR is defined as maximum blood flow in a stenotic coronary artery, divided by maximum flow in an adjacent normal coronary artery. In a similar way, relative myocardial flow reserve can be defined. RFR has the big advantage to be independent from pressure changes because pressure affects the numerator and the denominator of the ratio in an identical way. RFR can be reliably assessed by positron emission tomography and by videodensitometry [2, 6, 15–17]. Clinical use of RFR, however, is limited because an adjacent normal distribution is necessary to compare with. Therefore, it can not be used in the presence of 3-vessel disease. Even in 1- or 2-vessel disease one can never be sure that an apparently normal coronary artery in an individual with ischemic heart disease is really normal.

Moreover, the imaging methods for reliable assessment of RFR are expensive and only available in a few research laboratories.

At last, both absolute and relative coronary flow reserve fail to provide information about the collateral circulation of the heart which, therefore, is mostly neglected.

At this point, *fractional coronary flow reserve* comes into perspective. Fractional coronary flow reserve (FFR *or* $FFR_{cor}$) is defined as the ratio between maximum flow in a stenotic coronary artery and normal maximum flow in that same artery, i.e., maximum flow in that artery in the hypothetical case that it would be completely normal. In other words, maximum blood flow in the presence of a stenosis is expressed as a *fraction* (or percentage) of its normal expected value in the absence of a stenosis. This parameter exactly describes to what degree the vessel's function is affected by disease. If this value is, for example, 0.44, one knows that the regarding coronary artery is stenotic to such a degree that the maximum volume of blood which can stream through that artery, is diminished to 44% of what would be normal. Fractional coronary flow reserve combines the information provided by absolute and relative coronary flow reserve and eliminates their disadvantages: it is independent of pressure changes and other confounding factors affecting absolute flow reserve and is applicable even in three vessel disease when no normal artery is present to compare with. *Fractional myocardial flow reserve* ($FFR_{myo}$) is defined in a similar way.

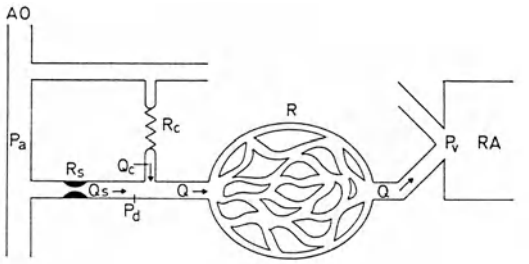



*Figure 2.* Schematic model representing the coronary circulation. Ao, aorta; $P_a$, arterial pressure; $P_d$, distal coronary pressure; $P_v$, venous pressure; Q, blood flow through the myocardial vascular bed; $Q_c$, collateral blood flow; $Q_s$, blood flow through the supplying epicardial coronary artery; R, resistance of the myocardial vascular bed; $R_c$, resistance of the collateral circulation; $R_s$, resistance of the stenosis in the supplying epicardial coronary artery; RA, right atrium. (From Pijls et al. [22], with permission of the American Heart Association, Inc.)

Recently we have developed a set of pressure-flow equations and demonstrated how both $FFR_{cor}$ and $FFR_{myo}$, as well as the separate contribution of coronary and collateral blood flow to myocardial perfusion, can be easily, rapidly, and reliably calculated from simultaneous pressure measurements in the ascending aorta, the distal coronary artery, and the right atrium under the condition of maximum vasodilation of the coronary arteriolar bed and using an ultrathin pressure-monitoring guide wire with a diameter of 0.015″. To derive, understand, and use these pressure-flow equations, a model of the coronary circulation is needed as explained below.

### *Description of the model*

The purpose of this model is to derive equations relating pressures to the regional distribution of maximum perfusion. Maximum flow through a stenotic artery is compared to what maximum flow would be in that same artery in the absence of that stenosis. Consequently, we express coronary flow reserve for a stenotic artery as a fraction of its normal expected value in that same artery in the absence of a stenosis. We therefore use the term fractional flow reserve (FFR) as defined in the former section. A unique strength of the model here is the theoretical capacity to determine fractional flow reserve even in the presence of three vessel disease when no normal adjacent coronary artery is present.

In Figure 2, the coronary circulation is schematically represented as an arrangement of variable resistances in parallel and in series. For maximum vasodilation, obtained by intracoronary administration of papaverine or adenosine [18–21], the resistances of the myocardial capillary bed (R) and the collateral circulation ($R_c$) are minimal and constant, and in that case the flow dependent stenosis resistance ($R_s$) is maximal and therefore also constant. $R_s$

may be changed by an intervention, such as a PTCA. Mean arterial pressure ($P_a$), central venous pressure ($P_v$), and coronary pressure distal to the stenosis ($P_d$), are defined in the usual way, whereas the coronary wedge pressure ($P_w$) is defined as the pressure distal to the stenosis during coronary artery occlusion. $\Delta P$ is defined as $P_a - P_d$. The total blood flow through the myocardial bed (Q) is the sum of the blood flow through the supplying, stenotic artery ($Q_s$, also called coronary artery flow) and collateral flow ($Q_c$). The normal values of all flow parameters are denoted by a superfix N. Therefore, $Q^N = Q_s^N$ and $Q_c^N = 0$. In other words: $Q^N$ and $Q_s^N$ represent maximum myocardial and coronary blood flow in the case that the supplying coronary artery would be completely normal. At total occlusion, $Q_s = 0$ and $Q_c = Q$.

As stated before, fractional flow reserve (FFR) is defined as the maximally achievable flow in the presence of a stenosis, divided by the maximum flow expected in the same distribution in the absence of a stenosis. In analogy to $Q_s$ and Q, fractional coronary artery flow reserve ($FFR_{cor}$) and fractional myocardial flow reserve ($FFR_{myo}$) are defined as $Q_s/Q_s^N$ and $Q/Q^N$, respectively.

By using this model of the coronary circulation, the relation between Q, $Q_s$, and $Q_c$ can be elucidated and both $FFR_{cor}$ and $FFR_{myo}$ can be calculated by performing pressure measurements under maximum vasodilated conditions using equations (1), (2), and (3) listed below. Different degrees of stenosis are indicated by the superfix "(1)" or "(2)", where "(1)" can be considered as an equivalent to the condition before PTCA and "(2)" thereafter.

The relation between $Q^{(1)}$, $Q^{(2)}$, $Q_s^{(1)}$, $Q_s^{(2)}$, $Q_c^{(1)}$ and $Q_c^{(2)}$ can be completely described by the equations (1b), (2b), and (3b) which theoretically means that maximum myocardial, coronary, and collateral flow can be compared before and after PTCA; that the contributions of coronary and collateral flow to myocardial flow can be quantified both before and after PTCA; and that all these parameters can be expressed as a percentage of normal maximally achievable myocardial blood flow. The respective formulas are listed below. The background, theoretical derivation, and validation of these pressure-flow equations have been extensively described by Pijls et al. in a recent issue of Circulation [22]. Some examples how to use the pressure-flow equations in the clinical catheterization laboratory, are given at the end of this chapter.

*Pressure-flow equations for fractional flow reserve and collateral blood flow*

$$FFR_{cor} = \frac{Q_s}{Q_s^N} = \frac{P_d - P_w}{P_a - P_w}$$

$$= 1 - \frac{\Delta P}{P_a - P_w} \qquad (1)$$

$$FFR_{myor} = \frac{Q}{Q^N} = \frac{P_d - P_v}{P_a - P_v}$$

$$= 1 - \frac{\Delta P}{P_a - P_v} \tag{2}$$

$Q = Q_s + Q_c$, or

$$Q_c = (FFR_{myo} - FFR_{cor}) \cdot Q^N \tag{3}$$

Equation (4), at last states the fundamental observation that the ratio $(P_a - P_v)/(P_w - P_v)$ is constant under conditions of maximum vasodilation:

$$\frac{P_a - P_v}{P_w - P_v} = 1 + \frac{R_c}{R} = \text{constant} \tag{4}$$

As explained later, equation (1) is used in connection with equation (1) and (3) in case $P_a$ is not constant.

*Pressure-flow equations for changes in fractional flow reserve and collateral blood flow after an intervention*:

The conditions for a stenosis before the intervention are indicated by the superfix "(1)" and the conditions thereafter by the superfix "(2)".

$$\frac{Q_s^{(2)}}{Q_s^{(1)}} = \frac{P_d^{(2)} - P_w^{(2)}}{p_d^{(1)} - P_w^{(1)}}, \text{ or}$$

$$\frac{FFR_{cor}^{(2)}}{FFR_{cor}^{(1)}} = \left(1 - \frac{\Delta^{(2)}P}{P_a^{(2)} - P_w^{(2)}}\right) : \left(1 - \frac{\Delta^{(1)}P}{P_a^{(1)} - P_w^{(1)}}\right) \tag{1b}$$

$$\frac{Q^{(2)}}{Q^{(1)}} = \frac{P_d^{(2)} - P_v^{(2)}}{P_d^{(1)} - P_v^{(1)}}, \text{ or}$$

$$\frac{FFR_{myo}^{(3)}}{FFR_{myo}^{(1)}} = \left(1 - \frac{\Delta^{(2)}P}{P_a^{(2)} - P_v^{(2)}}\right) : \left(1 - \frac{\Delta^{(1)}P}{P_a^{(1)} - P_v^{(1)}}\right) \tag{2b}$$

$$\frac{Q_c^{(2)}}{Q_c^{(1)}} = \left(\frac{\Delta^{(2)}P}{P_a^{(2)} - P_v^{(2)}}\right) : \left(\frac{\Delta^{(1)}P}{P_a^{(1)} - P_v^{(1)}}\right) \tag{3b}$$

The most important equations, abbreviations, and values of Q, $Q_c$, and $Q_s$ in special situations have been summarized in Table 2.

*Table 2.* Pressure flow equations.

(1) Coronary flow: $Q_s = \left(1 - \frac{\Delta P}{P_a - P_w}\right) \cdot Q^N$ or: $FFR_{cor} = 1 - \frac{\Delta P}{P_a - P_w}$

(2) Myocard. flow: $Q = \left(1 - \frac{\Delta P}{P_a - P_v}\right) \cdot Q^N$ or: $FFR_{myo} = 1 - \frac{\Delta P}{P_a - P_v}$

(3) Collateral flow: $Q_c = (FFR_{myo} - FFR_{cor}) \cdot Q^N$

(4) $\frac{P_a - P_v}{P_w - P_v} = 1 + \frac{R_c}{R} = \text{constant}$

*Abbreviations*:

$P_a$ = mean arterial pressure
$P_v$ = mean venous pressure
$P_d$ = distal coronary pressure
$P_w$ = coronary wedge pressure

$Q_s$ = max. *coronary* flow in the *presence* of a stenosis
$Q_c$ = max. *collateral* flow in the *presence* of a stenosis
$Q$ = max. *myocardial* flow in the *presence* of a stenosis
$Q^N$ = max. *myocardial* flow in the *absence* of a stenosis

$R_s$ = resisstance of the epicardial artery stenosis
$R_c$ = minimal resistance of the collateral bed
$R$ = minimal resistance of the myocardial bed

$FFR_{cor} = \frac{Q_s}{Q^N}$ $FFR_{myo} = \frac{Q}{Q^N}$ $Q = Q_c + Q_s$ $Q_c^N = 0$ $Q_s^N = Q^N$

At PTCA:

(1b) $\frac{Q_s^{(2)}}{Q_s^{(1)}} = \left(1 - \frac{\Delta^{(2)}P}{P_a^{(2)} - P_w^{(2)}}\right) : \left(1 - \frac{\Delta^{(1)}P}{P_a^{(1)} - P_w^{(1)}}\right)$

(2b) $\frac{Q^{(2)}}{Q^{(1)}} = \left(1 - \frac{\Delta^{(2)}P}{P_a^{(2)} - P_v^{(2)}}\right) : \left(1 - \frac{\Delta^{(1)}P}{P_a^{(1)} - P_v^{(1)}}\right)$

(3b) $\frac{Q_c^{(2)}}{Q_c^{(1)}} = \left(\frac{\Delta^{(2)}P}{P_a^{(2)} - P_v^{(2)}}\right) : \left(\frac{\Delta^{(1)}P}{P_a^{(1)} - P_v^{(1)}}\right)$

Note: These equations are already corrected for pressure changes which may have occurred during PTCA.

## Experimental methods

### *Animal instrumentation*

After premedication with 0.1 mg fentanyl, 5.0 mg droperidol and 0.5 mg atropine i.m., five mongrel dogs (weight 24–36 kg) were anesthetized with

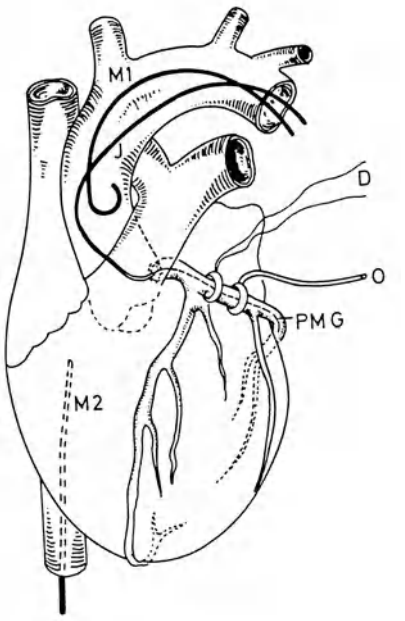



*Figure 3.* Animal instrumentation. D, Doppler probe; J, 6F left Judkins catheter; $M_1$, Millar catheter in ascending aorta: $M_2$, Millar catheter in right atrium; O, balloon occluder; PMG, pressure monitoring guide wire with its tip 3–5 cm distal to the balloon occluder. (From Pijls et al; with permission of the American Heart Association, Inc. [22])

sodium pentobarbital 25 mg/kg i.v. and ethrane. A left thoracotomy was performed and the proximal left circumflex artery (LCx) was dissected free. A perivascular ring-mounted 20-MHz pulsed Doppler transducer (Crystal Biotech Inc., Holliston, Massachusetts) was placed around the artery and a circular balloon occluder (R.E. Jones, Silver Spring, Maryland) was placed just distal to the Doppler probe. A femoral vein and two femoral arteries were dissected free. An 8F Millar manometer catheter (Millar microtipped-catheter transducer SPC-780 C) was introduced into the femoral vein and positioned into the right atrium for measurement of central venous pressure. Another 8F Millar manometer catheter was introduced into the left femoral artery and positioned into the ascending aorta, just above the aortic valve, for measurement of arterial pressure. A 6F left Judkins coronary arteriography catheter was introduced into the right femoral artery and advanced into the ostium of the left main coronary artery. Finally, a pressure monitoring device was advanced through the Judkins catheter into the LCx artery and positioned with its tip 3–5 cm distal to the balloon occluder (Figure 3). This pressure monitoring device consisted of a flexible synthetic tube with a length of 75 cm and an outer diameter of 0.028″, connected to the distal 15 cm of

an 0.015″ pressure monitoring guide wire (Advanced Cardiovascular System, Santa Clara, California). Only the distal part of this device, i.e. the guide wire, was allowed to enter the coronary artery. The time constant of this device was determined in advance according to a protocol described earlier and never exceeded 1 second [7]. Electrocardiogram, venous pressure ($P_v$), aortic pressure ($P_a$), distal coronary pressure ($P_d$), and phasic and mean coronary blood flow velocity in the LCx artery were continuously recorded on an eight-channel recorder (Hewlett-Packard).

*Experimental protocol*

In all dogs, experiments were performed at three different levels of mean arterial pressure, termed the normotensive, hypertensive, and hypotensive states. After stabilization of all hemodynamic parameters, maximum coronary blood flow velocity in the LCx artery was measured after intracoronary (i.c.) administration of 8 mg of papaverine through the guiding catheter into the left main coronary artery. This value was compared to maximum hyperemic blood flow velocity after a 20-second occlusion period to confirm that maximum arteriolar vasolidation was obtained by that dose of papaverine. Also, $P_w$ was recorded at the end of that 20 second occlusion of the LCx artery. Thereafter, 12 different degrees of stenosis were induced in the LCx artery by partial inflation of the balloon occluder [16]. Each stenosis was applied following an 8 mg i.c. papaverine injection through the guiding catheter. Next, $P_a$, $P_d$ and $P_v$ were measured at the moment of maximum transstenotic pressure gradient, corresponding to peak coronary hyperemia (Figure 4). Measurement of $P_w$ during occlusion of the coronary artery, was repeated halfway through and at the end of the series of stenoses.

Intravenous infusion of phenylephrine (0.05 mg/ml) was then started to achieve a steady state arterial pressure of approximately 25–50% above the normotensive state. After the desired steady hypertensive state was achieved, another series of 12 measurements at 12 different degrees of stenosis was performed, preceded and followed by registration of $P_w$ during total occlusion in an identical way as described before.

Finally, intravenous administration of sodium nitroprusside (1 mg/ml) was started to create hypotension at an arterial pressure of approximately 25–50% below the initial value and another series of measurements at 12 different degrees of stenosis was performed, again preceded and followed by determination of $P_w$, respectively.

*Data processing and statistical analysis*

With this experimental protocol, in each dog values for $P_a$, $P_d$, and $P_v$ during maximum vasodilation were determined for 36 different stenoses at 3 different pressure states. At first, $P_a$, $P_v$, and $P_w$ as measured during the different coronary artery occlusions, were substituted in equations (4) to

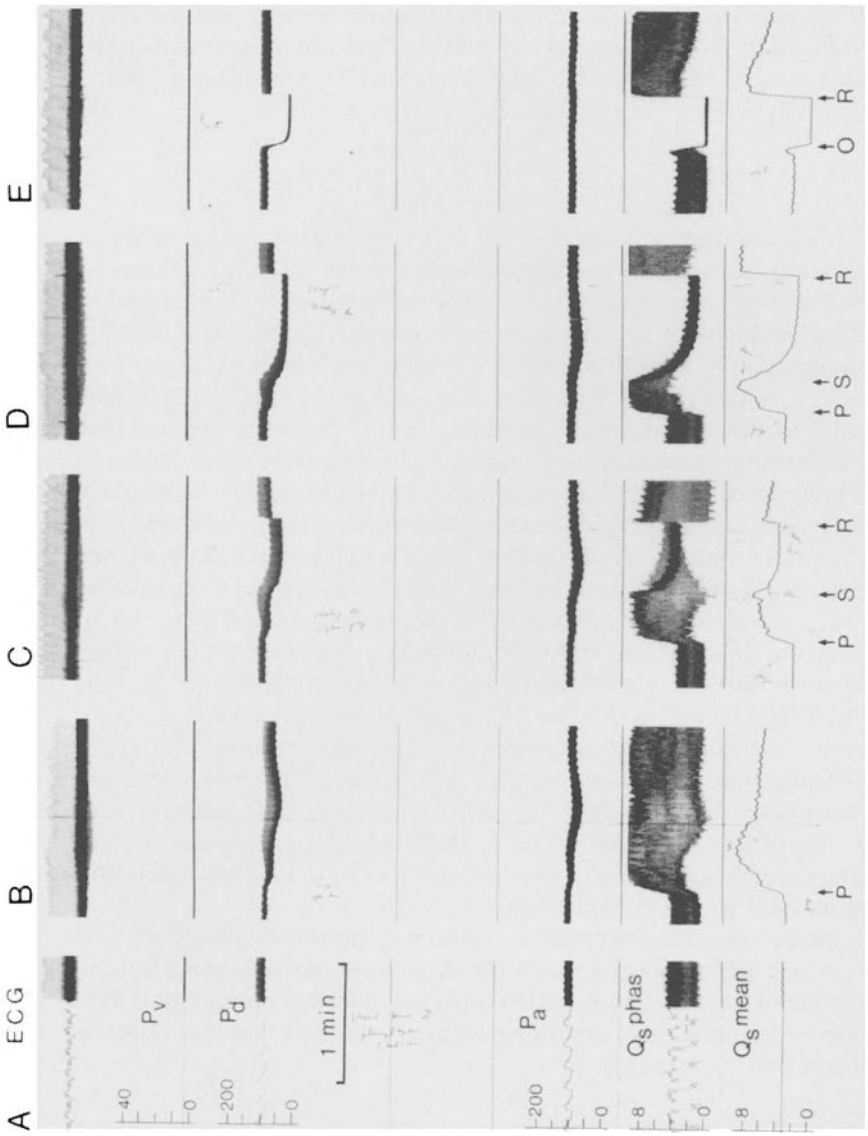



*Figure 4.* Example of hemodynamic recordings in one series of one dog. Electrocardiogram (ECG), central venous pressure ($P_v$), distal coronary pressure ($P_d$), mean aortic pressure ($P_a$), and phasic and mean blood flow velocity ($Q_s$) in the left circumflex artery are recorded before vasodilation (A), following i.c. papavarine administration (B), in the presence of a moderate (C) and a severe stenosis (D) induced at papaverine induced maximum hyperemia, and at coronary artery occlusion (E). O, occlusion of the coronary artery; P, intracoronary administration of 8 mg papaverine; R, release of stenosis; S, induction of stenosis. (From Pijls et al; with permission of the American Heart Association, Inc. [22])

*Table 3.* Mean arterial blood pressure ($P_a$) in the 5 experiments without medication (0), during infusion of phenylephrine (Ph), and nitroprusside (N), respectively, as well as the individual correlation coefficients (r), slope (sl), and intercepts (int) of the regression lines of the relation investigated in this study. $P_v$, venous pressure; $P_w$, coronary wedge pressure; $FFR_{cor}$, fractional coronary flow reserve calculated from pressure measurements; $FFR_{myo}$, fractional myocardial flow reserve calculated from pressure measurements; $Q_s$, blood flow through the coronary artery at maximum vasodilation in the presence of a stenosis; $Q_s^N$, blood flow through the coronary artery at maximum vasodilation in the absence of a stenosis. The ratios $Q_s/Q_s^N$ were measured directly by perivascular Doppler.

| | $P_a$ (mm Hg) | | | $FFR_{cor}$ vs $Q_s/Q_s^N$ | | | $FFR_{myo}$ vs $Q_s/Q_s^N$ | | | $P_a - P_v$ vs $P_w - P_v$ | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 0 | Ph | N | r | sl | int | r | sl | int | r | sl | int |
| #1 | 77 | 97 | 59 | 0.99 | 0.95 | 0.05 | 0.98 | 0.68 | 0.31 | 0.99 | 3.0 | 14.9 |
| #2 | 72 | 115 | 40 | 0.97 | 0.97 | 0.00 | 0.95 | 0.17 | 0.25 | 0.98 | 4.9 | 13.8 |
| #3 | 67 | 98 | 50 | 0.99 | 0.94 | 0.05 | 0.99 | 0.64 | 0.36 | 0.98 | 3.5 | −9.8 |
| #4 | 92 | 131 | 55 | 0.99 | 0.97 | 0.02 | 0.98 | 0.78 | 0.22 | 0.99 | 4.5 | 25.5 |
| #5 | 110 | 125 | 77 | 0.98 | 1.05 | −0.01 | 0.99 | 0.84 | 0.18 | 0.92 | 6.0 | 3.1 |

test the constancy of this expression. Thereafter, $FFR_{cor}$ and $FFR_{myo}$ were calculated according to equations (1) and (2) and these calculated values were compared to fractional coronary flow reserve ($Q_s/Q_s^N$) as measured directly by the epicardial Doppler probe. Correlation coefficients were calculated for each dog. Finally, at every degree of stenosis and at every pressure state, contribution of collateral blood flow was calculated according to equation (3). All hemodynamic data are expressed as mean ±SD.

## Results

### *Hemodynamic observations and the relation between mean arterial pressure and coronary wedge pressure*

There were no serious complications and no technical problems in performing the pressure measurements. In every dog, maximum coronary blood flow in the presence of the different degrees of stenosis, ranged from near zero to 100% of the initial control value in the absence of a stenosis, thereby indicating that the complete spectrum of stenosis severities was represented. The ratio between maximum blood flow velocity after i.c. papaverine injection (8 mg) and post-occlusional maximum blood flow velocity at the start of each series was 0.99 ± 0.03 (range 0.95–1.03), thereby confirming that presence of maximum arteriolar vasolidation was obtained by this dose of papaverine. In figure 4, examples of hemodynamic recordings at a number of steps in one series of stenoses for one dog are demonstrated. In all dogs, the three levels of arterial blood pressure were achieved (Table 3). In one dog, at the end of the hypertensive series, diffuse intrathoracic bleeding occurred and led spontaneously to arterial hypotension which was controlled thereafter by

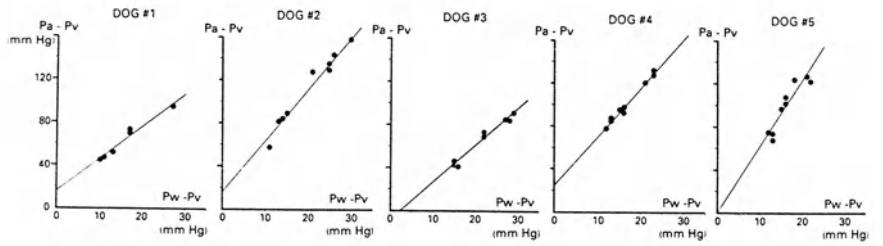



*Figure 5.* Relation between $(P_a - P_v)$ and $(P_w - P_v)$ in the 5 dogs. The solid line indicates the least squares best fit of the data. (From Pijls et al; with permission of the American Heart Association, Inc. [22])

fluid infusion to obtain a steady state hypotensive level for completion of the third series of stenoses. No sodium nitroprusside was administered in this case.

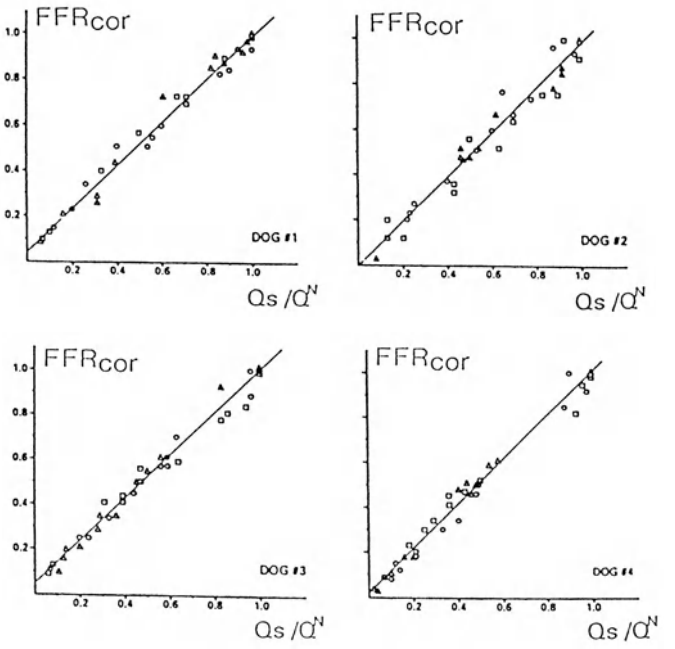
The relation between $(P_a - P_v)$ and $(P_w - P_v)$ is shown for the individual dogs in Figure 5. As expected from theory (equation (4)), the experimentally observed relation is constant. The correlation coefficient is $0.97 \pm 0.03$ with a slope of $4.4 \pm 1.2$ and an intercept of $9.5 \pm 13.3$ mm Hg (Table 3). This intercept is not significantly different from zero (Student's t-test). The slope of the regression line equals $1 + R_c/R$ and therefore can be considered to be a measure of the extent of collateral circulation. The resistance of the collateral circulation as a percentage of the resistance of the myocardial bed, can directly be calculated from this slope.

### *Calculated vs measured fractional flow reserve and contribution of collateral flow to total flow*

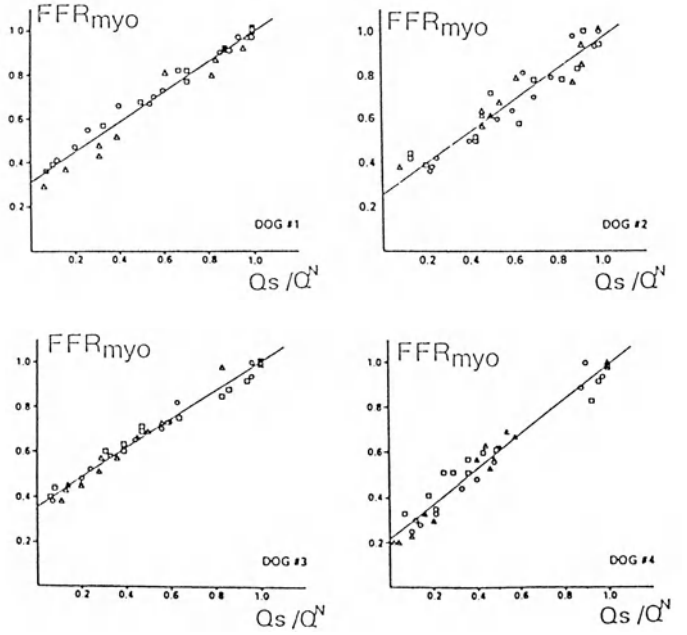
Fractional coronary flow reserve as directly measured by the Doppler transducer $(Q_s/Q_s^N)$ was compared to $FFR_{cor}$ as calculated from pressure measurements by $(P_d - P_w)/(P_a - P_w)$ at maximum hyperemia according to equation

*Figure 6.* Upper part of the figure: Relation between $(P_d - P_w)/(P_a - P_w)$ (pressure derived $FFR_{cor}$), and $Q_s/Q_s^N$ (directly measured $FFR_{cor}$) at different arterial pressures and different stenoses in 4 experiments. Also in the other dogs, or similar excellent correlation was found with a correlation coefficient of $0.98 \pm 0.01$; a slope of $0.98 \pm 0.04$; and an intercept of $0.02 \pm 0.03$.

Lower part of the figure: Relation between $(P_d - P_v)/(P_a - P_v)$ (pressure derived $FFR_{myo}$), and $Q_s/Q_s^N$ (directly measured $FFR_{cor}$) at different arterial pressures and different stenoses in 4 experiments. At increasing stenosis severity, corresponding with decreasing maximum blood flow through the supplying epicardial artery, $(P_d - P_v)/(P_a - P_v)$ increasingly exceeds $Q_s/Q_s^N$, indicating an increasing contribution of collateral blood flow to myocardial blood flow. The intercept of the regression line with the Y-axis theoretically represents the collateral flow achievable at total occlusion and expressed as a fraction of normal maximum myocardial flow.




o = no medic
Δ = phenylephr
□ = nipride



(1). This relation is shown in Figure 6, with excellent correlation in all dogs and a correlation coefficient of 0.98 ± 0.01, a slope of 0.98 ± 0.04 and an intercept of almost zero (0.02 ± 0.03; Table 3). If this data of all dogs and all pressure levels are lumped together, the correlation coefficient is 0.98, the slope 0.97 and the interception 0.03. This data validate the basic essential equations (1) and (1b), and prove the correctness of this part of the theoretical model experimentally.

The major goal of this study was to validate the basic concepts expressed in equations 1 and 2 using multiple Doppler and pressure measurements over a wide range of flows and pressures as shown in Figure 6. We did not use radiolabeled microspheres for myocardial perfusion since large number of flow measurements could not be made with that technique. Consequently, we could not validate directly the prediction of $FFR_{myo}$ from pressure measurements, i.e. equation 2. However, we obtained indirect support for the validity of equation 2 by comparing $FFR_{myo}$, predicted from pressure measurements by the expression $(P_d - P_v)/(P_a - P_v)$ according to equation 2, to $Q_s/Q_s^N$ measured directly by Doppler. This relation is shown in Figure 6. For mild or no stenosis, $Q_s/Q_s^N$ is equal to the calculated value $(P_d - P_v)/(P_a - P_v)$ since collateral flow is negligible in that case. With more severe stenoses, $FFR_{myo}$ and $FFR_{cor}$ are both reduced and $(P_d - P_v)/(P_a - P_v)$, representing calculated $FFR_{myo}$, is related to but larger than $Q_s/Q_s^N$, representing measured $FFR_{cor}$ to the extent that collateral flow contributes to myocardial perfusion. As shown in Figure 6, a good correlation is present between $Q_s/Q_s^N$, measured by Doppler, and $(P_d - P_v)/(P_a - P_v)$, representing $FFR_{myo}$ from pressure measurements ($r = 0.98 \pm 0.02$; slope = 0,73 ± 0.08; int = 0.26 ± 0.07). With total occlusion, $Q_s/Q_s^N$ is zero and the Y-intercept theoretically indicates the relative contribution of collateral flow to the myocardium, achievable during total occlusion. In Figure 6 this intercept ranges from 0.18 to 0.36, indicating that collateral flow achievable during coronary artery occlusion under conditions of maximum vasodilation was 18% to 36% of normal maximum perfusion in the absence of a stenosis (Table 3).

Finally, at every degree of stenosis, corresponding to the level of diminished maximum blood flow through the epicardial artery, the contribution of collateral flow can be determined from the regression lines of $FFR_{myo}$ and $FFR_{cor}$, or calculated by equation (3). For one of the dogs, this estimation of collateral flow is illustrated in Figure 7.

## Discussion

In our model of a stenotic arterial system at maximum arteriolar vasodilation, flow, expressed as a fraction of normal maximum flow in the absence of a stenosis, can be calculated from measurements of the relevant pressures, provided that vascular resistances are constant as is theoretically the case at

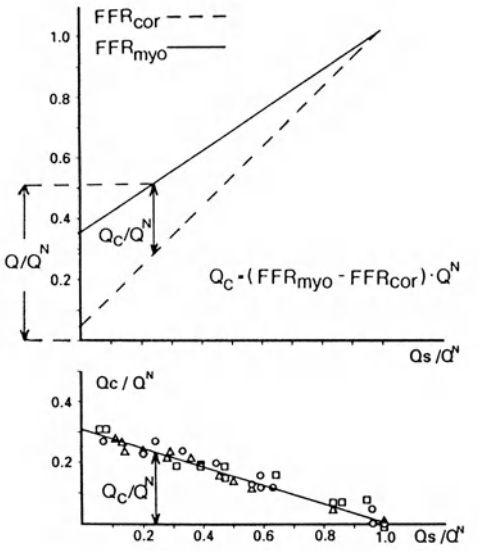



*Figure 7.* Diagram from one of the experiments, illustrating how at every arbitrary degree of stenosis the contribution of coronary ($Q_s$) and collateral blood flow ($Q_c$) to myocardial blood flow (Q) can be estimated from the regression lines of $FFR_{cor}$ and $FFR_{myo}$ (upper part of the figure). Pressure derived collateral blood flow, according to equation (4b), is presented in the lower part of the figure. In the absence of a stenosis, $Q_s$ equals Q, whereas $Q_c = 0$. At total occlusion $Q_s = 0$ and $Q_c$ equals Q. In the lower part of the figure, the intercept of the regression line with the Y-axis represents the collateral flow achievable at total occlusion, expressed as a fraction of normal maximum myocardial flow ($Q^N$). (From Pijls et al; with permission of the American Heart Association, Inc. [22]).

maximum vasodilation. These calculated values of fractional flow reserve correspond closely to those directly measured by Doppler velocitymeter, thereby confirming the validity of the concept that pressures alone under conditions of maximum vasodilation are related to maximum flow.

The basis for coronary flow reserve or maximum flow as a functional measure of stenosis severity has been well established [2–4, 6, 12, 16]. Since the concept of flow reserve was first introduced as a measure of stenosis severity, absolute coronary flow reserve (CFR), defined as maximum flow divided by resting flow, has been considered as the standard for the functional status of a coronary artery for many years [17]. In clinical practice, however, measuring CFR has limited applications largely due to methodological limitations [2, 16, 23–26]. In addition, because CFR is defined as a ratio, diminished CFR can either reflect decreased maximum flow, increased resting flow, or a combination of both. Because all methods proposed for CFR determination in man, except positron emission tomography, require invasive manipulations or intracoronary contrast injections, true resting conditions in clinical situations are difficult to obtain and invasive methodology is limited.

Moreover, several physiologic and pathologic conditions unrelated to the stenosis itself, may result in altered CFR for a given fixed stenosis [2–4, 6, 25, 26].

In contrast to CFR, determining maximum flow in a stenotic coronary artery as a fraction of normal maximum flow without a stenosis avoids the problem of variability in resting flow and is a complementary, independent measure of stenosis severity. Determining fractional flow reserve from pressure measurements alone has the additional advantage of theoretically being applicable to three vessel disease since, as shown in this experimental study, pressure measurements are made only in the stenotic artery, not in comparison to adjacent normal coronary arteries. In contrast to assessment of relative flow reserve by imaging techniques, no adjacent normally perfused reference distribution is necessary in the present approach. Finally, fractional flow reserve from pressure measurements in theory incorporates effects of collateral flow through its effects on $P_w$. The influence of other physiologic phenomena, such as compression, zero flow pressure, etc. are all accounted for through their effects on measured $P_d$ and $P_w$. Thus, assessing impairment of maximum flow or, in case of PTCA, assessing increase in maximum flow after the intervention, is a straightforward way to evaluate the functional significance of a stenosis or the improvement by PTCA. In a recent study we demonstrated an excellent correlation between increase in maximum blood flow after PTCA measured by videodensitometry and improved exercise test result [12], emphasizing the value of maximum flow as a clinically relevant endpoint.

For assessing functional significance of coronary artery disease by pressure measurements, most previous studies measured transstenotic pressure gradient or this gradient in relation to arterial pressure [2, 9–11, 22, 27]. Equations (1) to (4) indicate that measuring gradients only is an incomplete approach. Our model and results show that with increasing severity of stenosis, the contribution of collateral flow increases considerably even in acutely studied dogs. Corresponding fractional flow reserve of the coronary artery is overestimated when based on equations (2) or (2b) instead of the more complete equations (1) or (1b). Thus, fractional coronary flow reserve should be calculated using equations (1) or (1b) rather than (2) or (2b), initially proposed by Gould [2] but incomplete in failing to account for collateral flow. Fractional myocardial flow reserve on the other hand can be correctly addressed by equations (2) and (2b).

In the present study, the separate contributions of flow through the supplying coronary artery and collateral flow to myocardial blood flow can be differentially quantified. According to our calculations, the maximum recruitable collateral flow, as encountered during coronary artery occlusion, ranged from 18 to 36% of normal maximum myocardial blood flow. These data are compatible with a former study by Schaper in chronic instrumented dogs [28]. In that study, maximum collateral flow was approximately 30% of maximum myocardial blood flow.

Our model also shows that reduction of a transstenotic pressure gradient from e.g. 40 to 10 mm Hg by PTCA does not carry the same meaning in different patients, even when arterial pressure is identical in both patients. The extent of collateral flow represents a significant associated variable, where the effects of collaterals are not represented exclusively by $P_w$ at coronary occlusion, but also significantly depend on simultaneously measured $P_a$ and $P_v$. From equation (3), applied during complete coronary artery occlusion (in which case $FFR_{cor}$ equals zero), it can be shown that the collateral flow, expressed as a fraction of normal maximum myocardial flow, equals $Q_c/Q^N = (P_w - P_v)/(P_a - P_v)$. Therefore, according to our theory, $P_w$= 20 mm Hg in an individual with $P_a$ = 90 mm Hg and $P_v$ = 10 mm Hg, indicates a collateral contribution of only 12.5% of maximum myocardial perfusion, whereas the same $P_w$ in another individual with a simultaneously measured $P_a$ = 70 mm Hg and $P_v$ = 0 mm Hg, results in a collateral contribution of 29% of maximum myocardial perfusion. This example illustrates why $P_w$ alone does not reliably reflect the extent of collateral circulation as assumed in former studies [8, 13].

### *Limitations of the model*

Our model applies only to maximally dilated conditions when all resistances are constant and the derivation of flow reserve from pressure is possible. In this study, maximum arteriolar vasodilation and the resulting constant resistances were achieved by intracoronary administration of papaverine. Papaverine has been shown to induce maximum coronary and myocardial hyperemia within 30 seconds after intracoronary administration. The duration of maximum vasodilation, approximately 30 seconds, is long enough to permit reliable pressure measurements after which the effect completely vanishes within minutes so that repeated measurements may be made [19, 21]. Although polymorphous ventricular tachycardia associated with prolongation of the QT-interval has been described [29], in our experience with more than 600 patients, serious dysrythmias occurred in only 2 cases. Theoretically, other pharmacologic stimuli such as intravenous or intracoronary adenosine may also be used. [20]. However, the plateau phase after an intracoronary bolus of adenosine in a recommended dose of 16 μg is quite short (approximately 10 seconds) and no steady state distal coronary pressure may be reached, whereas very high doses of intracoronary adenosine of >60 μg will give longer lasting maximum hyperemia but are often accompanied by pronounced bradycardia. Intracoronary infusion of adenosine at a sufficient rate induces steady state maximum hyperemia [20], but this way of administration prevents recording of arterial pressure by the guiding catheter. Finally, intravenous adenosine will achieve maximum hyperemia in only 84% of the patients and is sometimes accompanied by various side effects [20]. Therefore, in our view papaverine remains the best coronary vasodilator for

this kind of studies in the human coronary circulation and is routinely used for this purpose in our laboratory.

In the present study, flow ratios were assessed by Doppler velocitymetry which could have been influenced by changes in luminal diameter of the coronary artery associated with the arteriolar vasolidation. However, as shown by Wilson et. al. in a previous study, no significant changes in epicardial luminal diameter occur after intracoronary papaverine injection [21]. Therefore, it is assumed that ratios of flow were accurately represented by ratios of flow velocity.

A prerequisite for correct pressure measurements is a small enough catheter or guide wire that has negligibly small effect on the transstenotic pressure gradient. Standard PTCA catheters do not meet this criterion and severe overestimation of $\Delta P$ may have occurred in former studies. Recently we demonstrated that for a wide range of stenosis severity, $\Delta P$ decreased significantly if pressure was measured by a small pressure monitoring guide wire with a cross-sectional area of only 0.11 $mm^2$ compared to measurements by a standard balloon catheter with a cross-sectional area of 0.72–1.0 $mm^2$ [7]. The device used for measuring distal coronary pressure in this study is of comparable small size and occupies only 25% of the area of a 90% area stenosis in a moderately sized coronary artery with a diameter of 2.5 mm. It consists of a main proximal part with a length of 75 cm and diameter of 0.71 mm (0.028 inches), connected to the distal 15 cm of the hollow pressure monitoring guide wire with a diameter of 0.38 mm (0.015 inches, Advanced Cardiovascular Systems, Santa Clara, California). Only the distal part of this device, the guide wire, entered the coronary artery in this study. The guide wire-tipped device is a prototype to test our concept as a basis for developing the complete wire.

An alternative instrument to record distal coronary pressure could be the so called Radiwire which is a microsensor tipped guide wire. It consists of a sensor element which modulates an optical reflection by pressure induced elastic movements and is integrated into a 0.018″ guide wire (Pressure Guide Radi Medical Systems, Uppsala, Sweden). The linear working range of this wire with the optical sensor is −20 mm Hg to +300 mm Hg. The sensor is located 3 cm proximal to a floppy guide wire tip. This pressure measurement device is able to record high fidelity phasic pressure tracings. Its disadvantages are the still relatively large diameter and the fact that its steering, push- and torque qualities are not comparable yet to regular guide wires. Moreover, because of a large plug at its proximal end, changing balloon catheters and other devices used in interventional cardiology, is still somewhat laborious and time-consuming. In the future, improvements in this microsensor tipped guide wire and further reduction of its diameter are expected.

Our model is not intended to address or separately account for a number of phenomenon affecting pressure and flow, such as extravascular compression and critical closing pressure since the model deals with flow and pressure as endpoints, affected by net accumulation of these phenomenon

lumped together [30–35]. Our results only give some indirect support to former observations that in maximum vasodilated beds critical closing pressure exceeds coronary venous pressure by a few mm Hg only [32]. To whatever extent these factors affect pressure and flow, they are accounted for through the pressure measurements at maximum vasodilation.

The capacitance characteristics of the coronary vascular bed may affect its instantaneaous, phasic pressure flow patterns [36, 37]. In this study, however, the endpoints measured are mean pressures at steady state maximum flow or at steady state levels after coronary occlusion. Therefore, since capacitance effects cancel out over diastole and systole, mean pressure measurements are theoretically not affected. Moreover, since pressures at coronary occlusion were measured only after reaching a steady state, venous capacitance effects are also avoided in our study. Consequently, we believe that potential effects of capacitance are not germane and do not have to be accounted for in our model nor in its potential clinical applications.

Our model assumes that maximally recruitable flow in collaterals remains constant throughout the procedure of a number of brief total occlusions for measuring $P_w$. The literature indicates different and sometimes longer time constants for opening collateral channels compared to our measurement period [27, 38–42], subject to further experimental validation. Therefore, it should be emphasized that changes in recruitable collateral flow during the procedure would invalidate the conceptional interpretation of our model. The excellent correlation between pressure derived fractional flow reserve and directly measured fractional flow reserve, provide strong indirect evidence for the correctness of our equations for measuring collateral flow. However, further confirmation of the details of our model for collateral flow is warranted and requires a different animal model in which arterial flow and separately collateral and myocardial perfusion are measured by radiolabeled microspheres. Since large numbers of flow measurements could not been made with that technique and because proof of equations (1) and (1b) was most essential to our concept, we used the simpler animal model described here to compare fractional flow reserve calculated from pressure measurements to direct measurements of relative maximum coronary flow, thereby validating the essential concept and the most complex equations (1) and (1b) directly.

Our results raise some conceptual questions which need further investigations in carefully controlled animal and human studies. Strictly speaking, we have validated the model in figure 1 by experimental single vessel disease with collateral flow that enters at the pre-arteriolar level. Although theoretically our equations are also true with repetitive units of the model in figure 1 that would be the equivalent of multivessel disease, further validation studies are warranted. Direct validation of equation (2) and (2b) in conscious man has been performed meanwhile by De Bruyne et al, who compared myocardial blood flow as calculated by these presssure-flow equations to myocardial blood flow as determined by position emission tomography [43].

Assessing relative flow reserve by imaging techniques becomes problematic in diffuse or balanced three vessel disease where relative flow reserve may erroneously appear normal despite extensive coronary artery disease [2]. Pressure, however, is a universal measure of the function of the coronary vascular system for different sizes of regional coronary vascular beds with and without coronary artery disease. Therefore, theoretically our approach should predict fractional flow reserve accurately even in the presence of balanced three vessel disease. This hypothesis, however, remains to be tested experimentally.

Another important qualification is necessary in the presence of small vessel disease distal of the location where $P_d$ and $P_w$ are measured, as occurs in diabetes. In that case, equations (1) and (2) represent maximum flow in the presence of an epicardial stenosis, expressed as a fraction of maximum flow in the absence of that epicardial stenosis but still not normal because of the distal small vessel disease. The value of this method for assessing the increase of maximum flow by PTCA would not be affected by that limitation. However, in that case ambiguity would remain about normal reference flow due to presence of small vessel disease.

A final issue that should be addressed in this context is coronary steal, a clearly recognized, well-documented phenomenon occurring in a number of patients with collateral circulation during maximum vasodilation [44, 45]. In our opinion, however, this phenomenon is already accounted for in our model because any decrease in $Q_c$ caused by increased conductance of the artery supplying the collaterals, is reflected by a lower coronary wedge pressure, $P_w$.

*Clinical implications*

The methods used in this animal study are applicable in man at PTCA provided that a pressure monitoring guide wire with a similar small size as the distal part of our device is used. No simplifications, adaptations, or additional hypotheses are necessary. The guide wire should be positioned across the stenosis as usual. Before crossing the lesion with the PTCA balloon, a maximum vasodilatory stimulus such as papaverine would be administered through the guiding catheter and $P_a$ and $P_d$ can be measured by the guiding catheter and the pressure sensitive guide wire tip, respectively. During balloon inflation, $P_a$ and $P_w$ are again recorded. After the last balloon inflation, when the balloon has been pulled back but the guide wire is still in situ, $P_a$ and $P_d$ are measured again after i.c. administration of papaverine. $P_v$ after papaverine can be measured directly by a Swan Ganz catheter or estimated from the neck veins. If venous pressure is not elevated and one is only interested in increase of $FFR_{cor}$ after the PTCA (which is most important from the view of the interventional cardiologist), the venous pressure may be neglected since its influence on equation (1) or (1b) is minimal in that case. The complete pressure measuring sequence can be

implemented during routine PTCA with prolongation of the procedure by only a few minutes. Other than a pressure monitoring guide wire, no special equipment is needed. No special instructions to the patient nor extra contrast injections or other manipulations are necessary. Therefore, fractional coronary flow reserve of the instrumented artery and its dependent myocardium, as well as the contribution of collateral flow would be readily obtainable before and after the intervention.

In case of diagnostic catheterization, it is necessary to enter the coronary artery with a wire, whereafter $FFR_{myo}$ can be determined. In that case, one should consider if this small but definite risk is counterbalanced by the extra information provided. Especially in case of an intermediate stenosis on the coronary arteriogram, a definite decision to dilate or not dilate can be made in that way. To assess maximum coronary flow and collateral contribution separately, knowledge of $P_w$ and therefore balloon inflation is necessary. Therefore, routine use of the pressure-flow equations will be most appropriate in PTCA for the time being.

Despite its importance for understanding coronary artery disease [46–51], a clinically feasible method for quantitative assessment of collateral blood flow has not been described previously. Our study provides the theory and experimental basis for a potential clinical method for assessing fractional flow reserve and collateral flow during PTCA.

Thus, despite some limitations, this model, based on pressure measurements at maximum vasodilation, provides a functional measure of stenosis severity and important insights into maximum coronary, collateral, and myocardial blood flow before and after PTCA with important clinical application.

## Examples

### *Example* 1

The first example is based on the simple hemodynamic case in which systemic pressures ($P_a$ and $P_v$) are unchanged during PTCA. Therefore, according to equation (4), wedge pressure $P_w$ is also constant.

Before and after a PTCA of one of the coronary arteries, pressure measurements are performed by the pressure monitoring guide wire at maximum coronary hyperemia, induced by intracoronary administration of papaverine or adenosine. Mean arterial pressure $P_a$ is 90 mm Hg both before and after the procedure, transstenotic pressure gradient $\Delta P$ is reduced from 50 mm Hg before to 10 mm Hg after the procedure, and venous pressure $P_v$ is 0 both before and after the procedure. Coronary wedge pressure, measured during balloon inflation, is 20 mm Hg. Therefore, $P_a^{(1)} = P_a^{(2)} = 90$ mm Hg, $P_d^{(1)} = 40$ mm Hg, $P_d^{(2)} = 80$ mm Hg, $P_v^{(1)} = P_v^{(2)} = 0$ mm Hg, and $P_w^{(1)} = P_w^{(2)} = 20$ mm Hg

Using equations (2b), (lb), and (3b):

$$FFR^{(2)}_{myo}/FFR^{(1)}_{myo} = (1 - 10/90):(1 - 50/90) = 2.0$$
$$FFR^{(2)}_{cor}/FFR^{(1)}_{cor} = (1 - 10/70):(1 - 50/70) = 3.0$$
$$Q^{(2)}_{c}/Q^{(1)}_{c} = 10/90:50/90 = 1:5.$$

In other words, maximally achievable blood flow through the myocardium increased by a factor 2, maximally achievable blood flow through the dilated artery increased by a factor 3, and collateral blood flow decreased by a factor 5.

By using the equations (1), (2), and (3) (both before and after PTCA), one obtains the values of all flow parameters, expressed as a fraction of normal maximum myocardial blood flow expected in the absence of a stenosis, normalized for pressure changes:

$$FFR^{(1)}_{myo} = 4/9 = 28/63 = 0.44$$
$$FFR^{(2)}_{myo} = 8/9 = 56/63 = 0.89$$
$$FFR^{(1)}_{cor} = 2/7 = 18/63 = 0.29$$
$$FFR^{(2)}_{cor} = 6/7 = 54/63 = 0.86$$
$$Q^{(1)}_{c} = 4/9 - 2/7 = 10/63 = 0.15$$
$$Q^{(2)}_{c} = 8/9 - 6/7 = 2/63 = 0.03$$

or in summary:

| | before PTCA | after PTCA |
|---|---|---|
| fractional myocardial flow | 0.44 | 0.89 |
| fractional coronary flow | 0.29 | 0.86 |
| fractional collateral flow | 0.15 | 0.03 |

Such a matrix completely describes the distribution of flow in the coronary circulation both before and after PTCA.

*Example* 2

The second example demonstrates the calculations when mean arterial and venous pressure do change during PTCA.

A PTCA of one of the coronary arteries is performed. At maximum coronary hyperemia, mean arterial pressure is 96 mm Hg before and 80 mm Hg after PTCA, $\Delta P$ is 45 mm Hg before and 15 mm Hg after the procedure, and venous pressure is 6 mm Hg before and 5 mm Hg after the procedure. Coronary wedge pressure is 23 mm Hg during balloon inflation. Mean arterial pressure during balloon inflation is 92 mm Hg and mean venous pressure during balloon inflation is 6 mm Hg.

In this case, with changing $P_a$ and $P_v$ at first $P^{(1)}_w$ and $P^{(2)}_w$ have to be

calculated, using the fact that $(P_a - P_v)/(P_w - P_v)$ is constant according to equation (4). Therefore, $P_w^{(1)} = 24$ mm Hg and $P_w^{(2)} = 20$ mm Hg. Thereafter, in an identical way as in example 1, equations (2b), (1b), and (3b) are used to calculate that:

$$FFR_{myo}^{(2)}/FFR_{myo}^{(1)} = (1 - 15/75):(1 - 45/90) = 1.6$$
$$FFR_{cor}^{(2)}/FFR_{cor}^{(1)} = (1 - 15/60):(1 - 45/72) = 2.0$$
$$Q_c^{(2)}/Q_c^{(1)} = 15/75:45/90 = 1:2.5.$$

In other words, maximally achievable blood flow through the myocardium increased by a factor 1.6, maximally achievable blood flow through the dilated artery by a factor 2, whereas collateral flow decreased by a factor 2.5. By using the equations (1), (2), and (3) (both before and after PTCA) one obtains the values of all flow parameters, expressed as a fraction of normal maximum myocardial blood flow expected in the absence of a stenosis, normalized for pressure changes:

| | before PTCA | after PTCA |
|---|---|---|
| fractional myocardial flow | 0.50 | 0.80 |
| fractional coronary flow | 0.375 | 0.75 |
| fractional collateral flow | 0.125 | 0.05 |

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# 15. Comparison between fractional flow reserve calculation and quantitative coronary arteriography in a non-selected patient population

BERNARD DE BRUYNE, NICO H.J. PIJLS and GUY R. HEYNDRICKX

## Introduction

In routine clinical practice, physiologic consequences of coronary stenoses are most often derived from their appearance on coronary arteriogram. In contrast to visual evaluation of coronary narrowings, quantitative coronary angiography allows more accurate and reproducible assessment of stenosis anatomy. Furthermore, it has been demonstrated in the animal model that functional evaluation of the lesion can be derived from its complete morphological description [1, 2].

So far, comparison between quantitative coronary angiography and functional indices of coronary stenosis severity has most often been restricted to selected cases with discrete, limited coronary atherosclerosis. In this selected patient population correlation between anatomical and functional approaches were satisfactory. However, in an unselected patient population, comparison between angiographic and physiologic assessment is scarce because both approaches are difficult.

The purpose of the present study is to investigate the relationship between indices derived from quantitative coronary angiography and fractional flow reserve as derived from coronary pressure measurements in a non-selected patient population with coronary artery disease.

## Methods

### *Patients*

The study population consisted of 56 patients (mean age 57±6 years) with one-vessel coronary artery disease and normal left ventricular systolic wall motion. There were 36 left anterior descending coronary arteries, 11 right coronary arteries and 9 left circumflex coronary arteries. Total coronary occlusions and "functional" coronary occlusions (i.e. with TIMI flow < grade 2) were excluded. The patients were scheduled for coronary angioplasty



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because of typical angina pectoris during exercise with positive stress test or because of unstable angina.

*Catheterization protocol*

Patients were brought to the catheterization laboratory in a fasting state. Diazepam 10 mg were given as premedication. A 8 French introduction sheath was inserted in the right femoral artery. A 7 or 8 French guiding catheter without side holes was used to cannulate the coronary ostium. Through the guiding catheter, a 0.015 inches fluid-filled pressure monitoring guide wire (Premo™ wire, Advanced Cardiovascular Systems, Temeluca, Ca.) was advanced up to the coronary ostium. The characteristics of the pressure monitoring guide wire have been described previously [3]. The side arm of the femoral sheath, the guiding catheter and the pressure monitoring guide wire were connected to pressure transducers (Spectranetics, Statham P23). The three pressure transducers were zeroed at mid-chest level. In 24 patients, right atrial pressure was monitored throughout the study. Therefore, a 7 French pigtail was advanced from the right femoral vein into the right atrium. Phasic and mean atrial pressure were measured continuously by a high-fidelity micromanometer advanced through the pigtail catheter.Before entering the coronary tree with the Premo™ wire, the mean pressures in the femoral artery (femoral sheath), and in the coronary ostium (guiding catheter and pressure monitoring guide wire) were compared to exclude any pressure difference. The guide wire was then advanced distally to the coronary narrowing under continuous pressure monitoring. Two mg of isosorbide dinitrate were injected into the coronary artery. At least 3 min after the last contrast medium injection, when baseline hemodynamics were restored, the resting transstenotic pressure gradient was measured. Eight mg (right coronary artery) to twelve mg (left coronary artery) of papaverine hydrochloride were then injected through the guiding catheter to induce a maximal arteriolar vasodilatation [4, 5]. The mean transstenotic pressure gradient during maximal hyperemia was measured 30 to 40 sec after injection of papaverine. Distal coronary pressure was allowed to return to baseline after injection of papaverine (Fig. 1).

Coronary angioplasty was performed using "monorail" type balloon catheters advanced over the pressure monitoring guide wire. After completion of the PTCA, resting and hyperemic transstenotic gradient were measured in the same fashion as before angioplasty. All measurements were performed after injection of another 2 mg of isosorbide dinitrate through the guiding catheter and at least 3 min after the last contrast medium injection and balloon coronary occlusion in order to avoid post occlusion hyperemia.

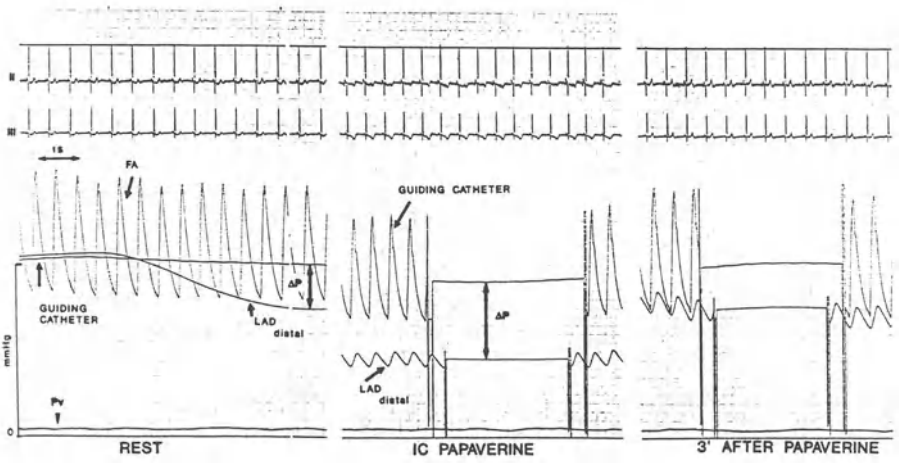


*Figure 1.* Example of simultaneous pressure recordings in the femoral artery (through the side arm of the sheath), in the coronary ostium (through the guiding catheter) in the distal coronary artery (through a 0.015 inches pressure monitoring guide wire) and in the right atrium. At rest (left panel), the translesional pressure gradient was 26 mmHg. During maximal hyperemia (middle panel), a slight decrease in mean aortic pressure occurred as well as an increase in translesional pressure gradient reaching 45 mmHg. Three minutes after intracoronary administration of papaverine (right panel), mean aortic and distal coronary pressures returned to their baseline values. No variations in right atrial pressure were noted (4 to 5 mmHg). Myocardial fractional flow reserve can be calculated by the equation: $FFR = 1 - \Delta P_{max}/(P_{ao} - P_v)$; where $\Delta P_{max}$ is the transstenotic pressure gradient, $P_{ao}$ is the mean aortic pressure, and $P_v$ is the mean right atrial pressure all recorded during maximal arteriolar vasodilation. (Abbreviations: FA = femoral artery; $LAD_{distal}$ = distal part of the left anterior descending coronary artery; $\Delta P$ = transstenotic pressure gradient.)

## *Calculation of fractional flow reserve*

As described in a previous chapter, the fractional flow reserve of both the coronary artery and the myocardium (including collateral flow) was calculated from pressure measurements only:

$$\text{Myocardial fractional flow reserve} = 1 - \Delta P/(P_{ao} - P_v)$$

$$\text{Coronary fractional flow reserve} = 1 - \Delta P/(P_{ao} - P_w)$$

where $\Delta P$ is the transstenotic pressure gradient during maximal arteriolar vasodilatation, $P_{ao}$ is the mean aortic pressure during maximal arteriolar dilatation, $P_v$ is the mean right atrial pressure during maximal vasodilatation, and $P_w$ is the distal coronary pressure during balloon inflation or coronary wedge pressure [6].

*Myocardial* fractional flow reserve is the ratio of the maximal achievable myocardial flow in a territory subtended by a stenotic coronary artery to the

maximal achievable flow in that same territory if the supplying vessel was normal. *Coronary* fractional flow reserve is the ratio of the maximal achievable blood flow in the stenotic coronary artery to the maximal achievable blood flow in that same artery if the latter was normal [7].

*Angiographic analysis*

Quantitative analysis of the stenotic segment was performed with an on line available ACA system (Automated Coronary Analysis, Philips Medical Systems, The Netherlands). It consists of the application to a digital imaging system of the CAAS program which was previously described and validated by Reiber [8].

## Results

Mean right atrial pressure, measured in 24 patients, reached 5±2 mmHg (range 1 to 7 mmHg) at rest and did not change (5±2 mmHg, range 1 to 8 mmHg) during maximal arteriolar dilatation. Therefore, in the remaining 32 patients in whom the mean right atrial pressure was not measured invasively, the value of 5 mmHg was introduced in the equation enabling to calculate myocardial fractional flow reserve.

*Relationship of myocardial flow reserve to coronary lesion geometry* (*Table* 1 *and Figs* 2 *and* 3)

Before angioplasty, **area stenosis** ranged from 57 to 96% (mean 85±10%), myocardial fractional flow reserve ranged from 0.27 to 0.93 (mean 0.52±0.12) and coronary fractional flow reserve from 0.09 to 0.97 (mean 0.41±0.17). A significant correlation was found between area stenosis and both myocardial fractional flow reserve ($r = 0.7$, $n = 56$) and coronary fractional flow reserve ($r = 0.67$, $n = 56$). After angioplasty, area stenosis ranged from 8 to 64% (mean 41±14%), myocardial fractional flow reserve ranged from 0.72 to 1 (mean 0.88±0.10) and coronary fractional flow reserve ranged from 0.61 to 1 (mean 0.84±0.14). Area stenosis was correlated neither with myocardial nor with fractional flow reserve ($n = 45$). When considering the pre- and post-angioplasty results together (Fig. 2), the relationship between area stenosis and myocardial fractional flow reserve was best fitted by a logistic function ($FFR_{myo} = 1/[1 + \exp(4.\text{slope}.(AS_{0.5} - AS))]$, where AS is percent area stenosis and $FFR_{myo}$ is myocardial fractional flow reserve, $r = 0.84$, $SEE = 0.12$). A similar relationship was found between area stenosis and coronary fractional flow reserve ($r = 0.81$, $SEE = 1.13$).

**Minimal Obstruction Area** ranged from 0.21 to 5.10 $mm^2$ (mean 0.82±0.46 $mm^2$) before angioplasty and from 2.13 to 7.00 $mm^2$ (mean 3.70 ±1.37 $mm^2$) after angioplasty. A significant correlation existed between minimal

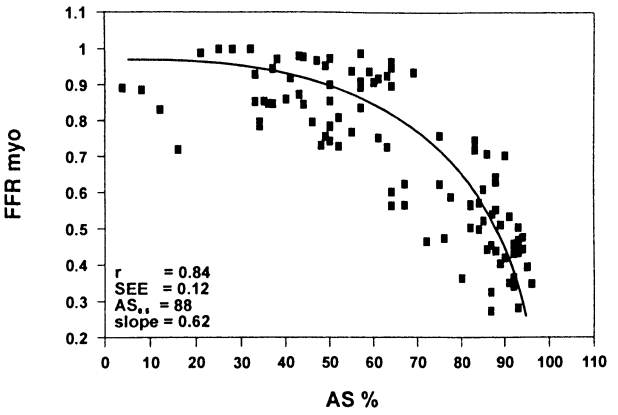


*Figure 2.* Relationship between the percent area stenosis and the myocardial fractional flow reserve. (Abbreviations: AS = percent area stenosis; $FFR_{myo}$ = myocardial fractional flow reserve)

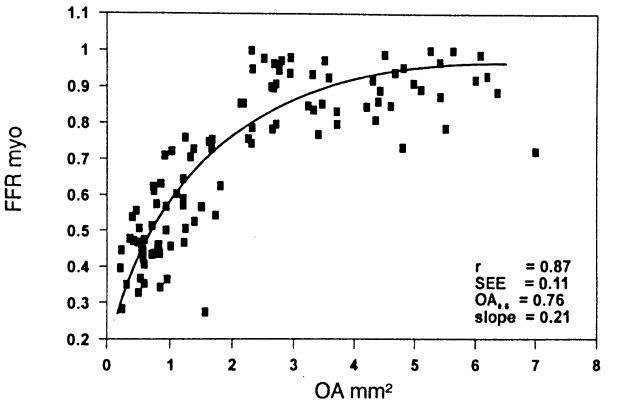


*Figure 3.* Relationship between minimal obstruction area and myocardial fractional flow reserve. (Abbreviations: $FFR_{myo}$ = myocardial fractional flow reserve; OA = minimal luminal obstruction area.)

obstruction area and both myocardial fractional flow reserve ($r = 0.72$, $n = 56$) and coronary fractional flow reserve ($r = 0.68$, $n = 56$) before angioplasty. No correlation was found between minimal obstruction area and myocardial or coronary fractional flow reserve after angioplasty. When pre- and post-angioplasty results were pooled, a statistically significant correlation was found between minimal obstruction area and both myocardial fractional flow reserve ($FFR_{myo} = 1/[1 + \exp(4.\text{slope}.(OA_{0.5} - OA))]$, where $FFR_{myo}$ is myocardial fractional flow reserve and OA is obstruction area, $r = 0.87$, $SEE = 0.11$) and coronary fractional flow reserve, $r = 0.82$, $SEE = 0.13$).

*Table 1.* Relationship of coronary artery stenosis geometry and transstenotic pressure gradient to fractional flow reserve before and after balloon angioplasty.

| | Myocardial Fractional Flow Reserve | | | Coronary Fractional Flow Reserve | |
|---|---|---|---|---|---|
| | n | Correlation Coefficient | p value | Correlation Coefficient | p value |
| Percent area stenosis | | | | | |
| before PTCA | 56 | 0.70 | <0.001 | 0.67 | <0.001 |
| after PTCA | 47 | 0.20 | NS | 0.16 | NS |
| Minimal obstruction area | | | | | |
| before PTCA | 56 | 0.72 | <0.001 | 0.68 | <0.001 |
| after PTCA | 47 | 0.24 | NS | 0.20 | NS |
| Stenosis flow reserve | | | | | |
| before PTCA | 39 | 0.69 | <0.001 | 0.67 | <0.001 |
| after PTCA | 30 | 0.15 | NS | 0.26 | NS |
| Transstenotic pressure gradient | | | | | |
| before PTCA | 56 | 0.81 | <0.001 | 0.71 | <0.001 |
| after PTCA | 47 | 0.21 | NS | 0.20 | NS |

**Stenosis flow reserve** derived from quantitative coronary angiography correlated significantly with fractional flow reserve and with coronary fractional flow reserve before ($r = 0.69$ and $r = 0.67$, respectively) but not after angioplasty. When pre- and post-angioplasty results were pooled, a linear relation was found between both myocardial ($FFR_{myo} = 0.24 + 0.13 * SFR$, $r = 0.86$, $SEE = 0.11$) and coronary fractional flow reserve ($r = 0.83$, $SEE = 0.14$).

*Relationship of transstenotic pressure gradient to myocardial fractional flow reserve*

Translesional pressure gradient was significantly correlated with measurements of fractional flow reserve before ($r = 0.81$) but not after angioplasty (table 1). This correlation was closer than, that between fractional flow reserve and morphologic parameters derived from quantitative coronary angiography.

## Discussion

The theoretical basis and the experimental validation of the concept of fractional flow reserve has been recently published [7]. Simultaneously, new developments in pressure monitoring guide wire technology have made it possible to calculate fractional flow reserve using only pressure measurements in the setting of PTCA and coronary angiography [3, 9]. The accuracy of fractional flow reserve in reflecting the physiological significance of a coron-

ary stenosis has been recently demonstrated by comparing the calculated values of fractional flow reserve with measurements of absolute myocardial perfusion as assessed by positron emission tomography [10].

In the present study, indices derived from quantitative coronary angiography are compared with values of myocardial and coronary fractional flow reserve as calculated from transstenotic pressure gradient measurements during hyperemia. These results are in agreement with previous studies performed both in the animal model [11] and in man [12–14] which showed an overall significant relationship of quantitatively assessed coronary artery dimensions to a physiologic measurement of coronary stenosis. In the present study, a curvilinear relationship was found between fractional flow reserve calculations from pressure measurements and both percent area stenosis and minimal obstruction area. A marked decrease in fractional flow reserve was seen once the percent area stenosis decreased below 70% or once the obstruction area decreased below 2 $mm^2$. In addition a linear relationship was found between stenosis flow reserve and fractional flow reserve. The correlations found between fractional flow reserve calculations and angiographic indices of stenosis severity are rather moderate and the dispersion of the individual values is very large, especially in the range of the lesions of "intermediate severity" (60 to 80% area stenosis). A closer correlation was found between transstenotic pressure gradient and fractional coronary flow reserve. This corroborates the study of Wilson et al. [12] who found an excellent correlation between the ratio of translesional pressure gradient to mean aortic pressure and coronary flow reserve derived from flow velocity measurements ($r = 0.91$) but weaker correlations between coronary flow reserve and either area stenosis or minimal cross-sectional area.

Most of the previous studies were performed in highly selected patients with discrete, limited coronary artery disease. In these lesions, the minimal luminal dimensions can be compared to normally appearing reference segments. In contrast, in this study quantitative coronary angiography and fractional flow reserve were compared in a non-selected stenoses both before and after PTCA. This difference in recruitment of patients and, hence, in angiographic characteristics of the lesions , probably explain the major scatter of the data presented in Figs 2 and 3 [15]. Overlapping side branches, the emergence of a side branche immediately before or after the stenosis, foreshortening of the stenotic segment, poststenotic dilatation, and marked irregularities of the coronary segments adjacent to the lesion are factors which are difficult to avoid in two orthogonal projections. These potential sources of errors in determining the precise dimensions of the stenotic segment are frequent in a non-selected patient population [16].

Before PTCA, minimal obstruction area was correlated more closely with fractional flow reserve than did percent area stenosis and stenosis flow reserve. This is probably due to the fact that obstruction area only depends on the measurements of the minimal diameter, whereas percent area stenosis depends on the measurements of minimal diameter and reference diameter

and stenosis flow reserve depends on the measurements of minimal diameter, reference diameter and lesion length. The increase in number of the measurements to obtain an angiographic index leads to an increased risk of inaccuracy in this non-selected patient population even though, theoretically, percent area stenosis and stenosis flow reserve more closely reflects lesion physiology than does the mere assessment of obstruction area.

Other factors might possibly have affected the relationship between quantitative measurements and fractional flow reserve. First, the administration of papaverine has been shown to increase minimal luminal diameter and percent area stenosis [13]. This can lead to changes in stenosis hemodynamics at the time of hyperemic transstenotic pressure gradient assessment. In this study, all vessels were predilated by nitroglycerine which has been shown to offset further dilation of the stenotic segment by papaverine [4]. Second, an edge-detection based method is theoretically not ideal to assess changes in luminal area produced by mechanical disruption of the arterial wall associated with balloon angioplasty [17]. Dimensions derived from the irregular angiographic vascular wall outlines will tend to overestimate the true luminal cross-sectional area. Nevertheless, recent studies have shown that both pre- and post-PTCA geometric measurements yielded a better reproducibility and a smaller variation between different views than videodensitometric measurements [18–20]. Third, myocardial fractional flow reserve includes, by definition, collateral flow which, in contrast, is not taken into account by quantitative measurements of stenosis geometry. This could partially explain the scatter of the results obtained when comparing stenosis dimensions with myocardial fractional flow reserve. However, when comparing stenosis dimensions to coronary fractional flow reserve (which does not take collateral flow into account) the correlation was not improved leaving a similar dispersion of the data. One possible explanation therefore is that the maximal transstenotic pressure gradient is recorded a few minutes before coronary occlusive pressure. This might lead to small changes in systemic driving pressure which, in turn, will influence differently both terms of the equation used to calculate coronary fractional flow reserve. In contrast, the terms of the equation used to calculate myocardial fractional flow reserve are all recorded at the same time during the procedure. Figure 4 shows an example of discrepancy between angiographic and functional approach after angioplasty.

In spite of the wide scatter of the individual values when comparing area stenosis and obstruction cross-sectional area with fractional flow reserve, some practical conclusions can be drawn from Figs 2 and 3. All lesions with an obstruction area exceeding 2 $mm^2$ were associated with a myocardial fractional flow reserve larger than 0.7 suggesting that they did not produce physiologically significant obstruction to coronary blood flow. In contrast, only 8 out of 54 lesions (15%) with an obstruction area smaller than 2 $mm^2$ were associated with a myocardial fractional flow reserve of more than 0.7. Similarly, 89% (42 of 47) of lesions with an area stenosis exceeding 70%

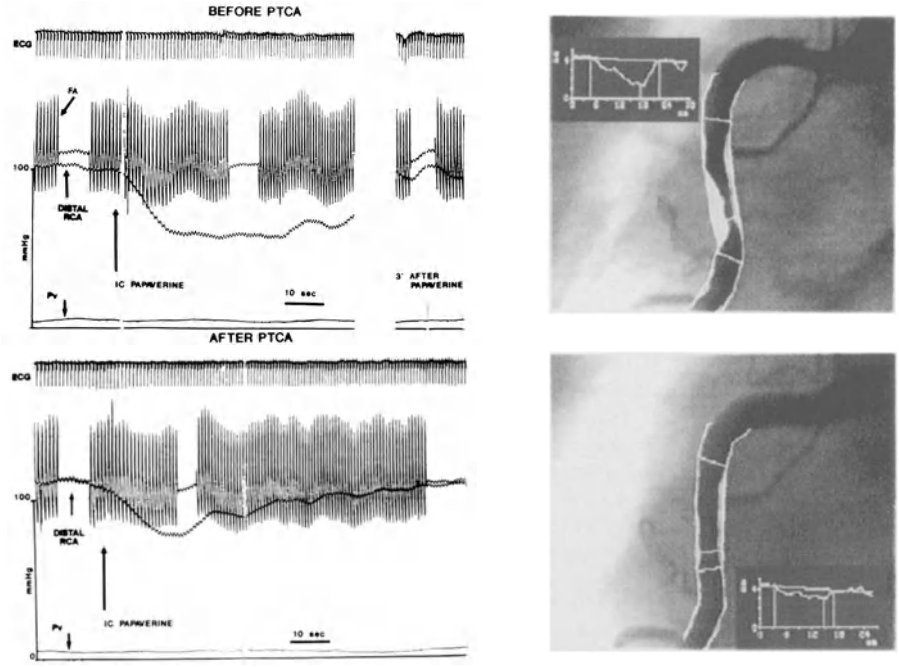


*Figure 4.* Simultaneous pressure tracings in the femoral artery (FA), in the distal part of the right coronary artery (RCA), and in the right atrium ($P_v$) illustrating some discrepancy between quantitative coronary angiographic measurements and information derived from pressure gradient measurements. Before PTCA (upper panel), the transstenotic gradient was 8 mmHg under basal conditions. Thirty seconds after intracoronary (IC) administration of papaverine (through the guiding catheter) an increase in pressure gradient was noted (44 mmHg). The calculated myocardial fractional flow reserve was 0.56. Quantitative coronary angiographic measurements revealed obstruction area of 1.57 $mm^2$, area stenosis of 87%, and stenosis flow reserve of 2.1 were calculated. After PTCA, under baseline conditions, no gradient was recorded. In contrast, during hyperemia, a transstenotic pressure drop of 29 mmHg was noted (calculated myocardial fractional flow reserve: 0.72) in spite of a very satisfactory angiographic result (obstruction area: 6.64 $mm^2$, area stenosis: 44%, and stenosis flow reserve: 4.77).

were associated with a myocardial fractional flow reserve of less than 0.7 although only 7% (4 of 56) of lesions with an area stenosis of less than 70% were associated with a myocardial fractional flow reserve of less than 0.7.

Therefore, it is concluded that quantitative coronary angiography performed in non-selected patients is not accurate enough to predict the absolute value of fractional flow reserve. Nevertheless, these data indicate that practical guide lines for clinical practice can be derived from quantitative angiographic assessment of coronary lesions in the setting of PTCA and coronary angiography in a non-selected patient population.

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# 16. Assessment of coronary stenosis severity from simultaneous measurement of transstenotic pressure gradient and flow. A comparison with quantitative coronary angiography

CARLO DI MARIO, PIM J. DE FEYTER, JOHAN C.H. SCHUURBIERS, PETER DE JAEGERE, ROBERT GIL, HÅKAN EMANUELSSON, CORNELIS J. SLAGER and PATRICK W. SERRUYS

## Introduction

Visual interpretation of the coronary angiogram is the method routinely used to assess the severity of a coronary stenosis and to plan, monitor and judge the results of coronary interventions. Quantitative arteriography allows accurate and reproducible measurements of absolute and relative vascular dimensions but, despite the progressive refinements of computer-assisted analysis in the last years, eccentricity, diffuse atherosclerotic involvement and vessel tortuosity remain major obstacles to a correct assessment. In addition, following interventions, the damage to the vessel wall greatly impairs the accuracy of quantitative angiography inducing haziness of the contours and intraluminal filling defects [1, 2]. Under these circumstances, videodensitometry was a promising alternative [3] but its application has been precluded so far by the presence of basic methodological limitations, requiring further refinement of the technique [4, 5]. Intracoronary ultrasound has the potential for a more accurate assessment of lumen dimensions in the presence of luminal cross-sectional area of complex geometry [6, 7]. The dimension of the currently available ultrasound catheters (diameter 1.0–1.45 mm), however, limits the application of intravascular ultrasound to the assessment of severe coronary stenoses. In addition, an accurate evaluation of all the geometric characteristics of a coronary stenosis (diameter of a normal reference segment, length of inlet-outlet segments and of the stenosis and minimal luminal cross-sectional area) can be obtained only with an automatic three-dimensional reconstruction of multiple ultrasonic cross-sections, a technology still in phase of development and requiring extensive clinical validation [8]. A method alternative to the morphologic study of the lesion is the use of the hemodynamic parameters which characterize the severity of a stenosis, blood flow velocity and transstenotic pressure gradient. A major technical development facilitating the acquisition of these measurements in the Catheterization Laboratory was the introduction of miniaturized pressure and Doppler sensors with guidewire technology, allowing a simultaneous measurement of post-stenotic flow velocity and pressure with only a



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moderate further obstruction to flow [9, 10]. Aim of this study is the assessment of the clinical applicability and usefulness of indexes of stenosis severity based on the simultaneous transstenotic pressure gradient and flow velocity measurements and in particular on the instantaneous relationship between pressure gradient and flow velocity.

## Methods

### *Patient population*

Twenty-one patients (age: 62±10 years, 17 males and 4 females) undergoing elective coronary angioplasty (n = 14) or scheduled for a possible angioplasty procedure but with a stenosis angiographically of intermediate severity ( > 40% and < 60% diameter stenosis; n = 7) were studied with a simultaneous measurement of flow velocity and post-stenotic coronary pressure. Patients with acute myocardial infarction, arterial occlusion/subocclusion {Thrombolysis in Myocardial Infarction (TIMI) flow class 0–1}, valvular heart disease, extreme tortuosity of the vessel to be dilated or the presence of an open aorto-coronary bypass graft on the vessel to be treated were not included in the study. Systemic arterial hypertension was present in 5 cases (23%). Previous myocardial infarction in the territory of distribution of the studied artery was present in 7 cases (33%). All patients were under antianginal treatment at the time of the study.

### *Catheterization procedure*

After intravenous administration of 10,000 I.U. of heparin and 250 mg of acetylsalicylic acid, an 8 French guiding catheter was advanced up to the coronary ostium. After isosorbide-dinitrate (2–3 mg intracoronary), cineangiograms suitable for quantitative assessment were obtained in one/three angiographic views.

The pressure guidewire was advanced into the artery to be dilated and the pressure sensor was positioned 1–3 cm distal to the stenosis (Fig. 1). The Doppler guidewire was maintained proximal to the stenosis, avoiding the presence of major side-branches between the site of the measurement and the stenosis and the segment of pre-stenotic acceleration of flow. In 5 patients, due to presence of side-branches immediately proximal to the stenosis, only the flow velocity recordings distal to the stenosis were used for analysis. The proximal coronary pressure, the post-stenotic pressure and the proximal flow velocity were recorded both in baseline conditions and after an intracoronary bolus injection of papaverine (8 mg: right coronary; 12.5 mg: left coronary, saphenous vein bypass graft) [11]. Intracoronary nitrates (isosorbide dinitrate 2–3 mg) were used before the injection of papaverine in order to induce a maximal coronary vasodilatation and avoid changes in cross-

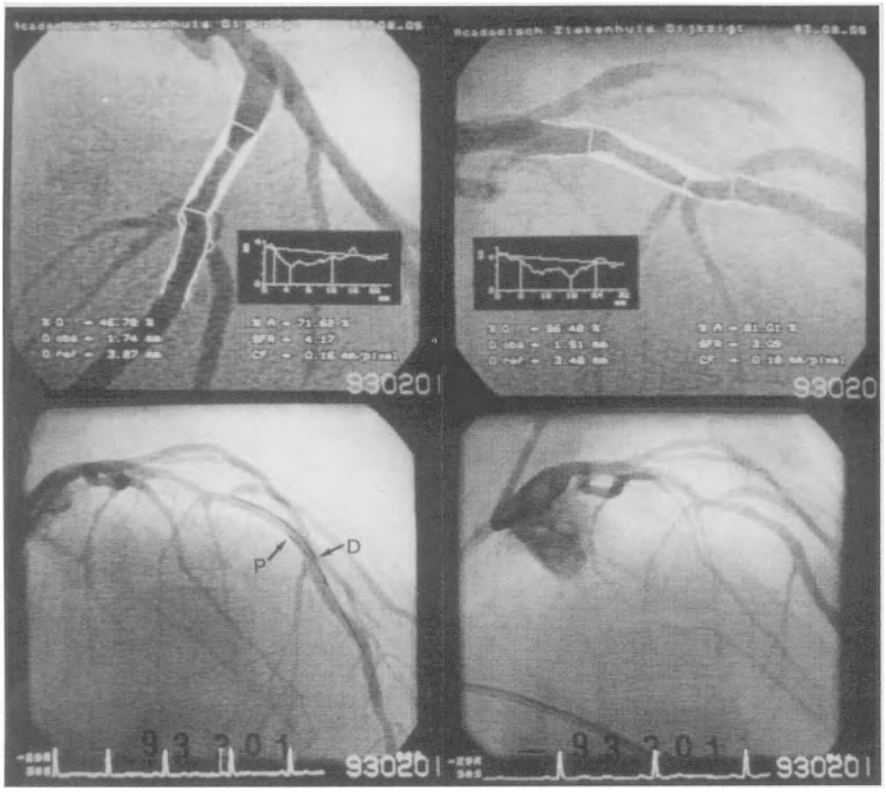


*Figure 1.* Upper panel: biplane orthogonal digital angiograms (left: LSO, right: RSO) of a left anterior descending coronary artery showing the presence of a significant concentric stenosis of the mid-segment. The diagrams show the diameter function of the examined segment after automatic contour detection. Bottom panels: the positions of the tip-mounted Doppler sensor (D) and of the sensor of the pressure guidewire (P) are indicated with arrows.

sectional area between baseline and post-papaverine assessment [12]. Care was taken to avoid impairment of flow during maximal hyperemia due to the presence of the guiding catheter in the coronary ostium. If damping occurred, the guiding catheter was withdrawn from the coronary ostium immediately after the injection of papaverine. The Doppler guidewire was then advanced distal to the stenosis and a new basal and post-papaverine acquisition was obtained (Fig. 1).

*Quantitative angiographic measurements*

The guiding catheter, filmed not filled with contrast medium, was used as a scaling device. A previously validated [13] on-line analysis system operating

on digital images (ACA-DCI, Philips, Eindhoven, The Netherlands) was used during the catheterization procedure. In this system, after automatic detection of the vessel centerline, a weighted first and second derivative function with predetermined continuity constraints is applied to the brightness profile on each scan line perpendicular to the vessel centerline [14]. From the measured minimal luminal diameter (MLD) the minimal luminal cross-sectional area was calculated assuming a circular cross-section (in 15 patients (71%) as the average of the measurements in multiple views). An interpolated technique was used to define the reference diameter. Percent diameter and cross-sectional area stenosis were also calculated. A user-defined diameter was measured at the site of the Doppler sample volume in order to calculate coronary blood flow as the product of mean blood flow velocity and cross-sectional area.

*Doppler guidewire and flow velocity measurements*

The Doppler angioplasty guidewire is a 0.018″ (diameter 0.45 mm, cross-sectional area 0.17 $mm^2$) 175 cm long flexible and steerable guidewire with a floppy shapable distal end mounting a 12 MHz piezoelectric transducer at the tip (Cardiometrics Inc., Mountain View, CA) [9]. The sample volume is positioned at a distance of 5.2 mm from the transducer in order to avoid the area of distortion of the flow profile due to the presence of the Doppler guidewire [15]. At this distance the sample volume has a width of approximately 2.25 mm due to the divergent ultrasound beam so that a large part of the flow velocity profile is included in the sample volume also in case of eccentric positions of the Doppler guidewire. The pulse repetition frequency (17 to 96 kHz) varies with the velocity range selected. After real-time processing of the quadrature audio signal a fast-Fourier transform algorithm is used to increase the reliability of the analysis [16], the Doppler system calculates and displays on-line several spectral variables including the instantaneous peak velocity and the time-averaged (mean of 2 beats) peak velocity. The flow velocity measurements obtained with this system have been validated in vitro and in an animal model using simultaneous electromagnetic flow measurements for comparison [9]. Mean flow velocity was calculated as time-averaged peak velocity/2, assuming a fully developed flow velocity profile [17]. Coronary flow reserve was defined as the ratio between maximal flow velocity at the peak effect of the papaverine injection and in baseline conditions.

*Pressure guidewire and transstenotic pressure gradient measurements*

The pressure sensor is located 3 cm proximal to the flexible tip of a 0.018″ guidewire (Radi Medical Systems, Uppsala, Sweden). Light is emitted from a control unit through a beam splitter and is transmitted to the sensor element along an optical fiber integrated in the guidewire. The sensor element consists

of a silicon cantilever with a mirror integrated into its free end. Deflection of the mirror induced by the elastic movement of the sensor in response to changes in the external pressure modulates the reflected light. The signal is then transmitted back through the same optical fiber and is detected by a photo diode in the control unit. The system has already been validated in vitro with regard to signal transfer characteristics, linearity and frequency response [10]. The pressure signal was calibrated immediately before insertion and the accuracy of the measurement was checked by superimposing the pre-stenotic coronary pressure measured with the pressure guidewire and the proximal coronary pressure measured with the guiding catheter. The mean transstenotic gradient was calculated as the difference of mean proximal and mean distal coronary pressure over 4 consecutive beats in baseline conditions and at peak papaverine effect (Fig. 2). The coronary flow measurements derived from the quantitative angiographic and Doppler measurements and the pressure measurements were used to calculate the hyperemic flow velocity-pressure gradient ratio and the delta flow-delta gradient ratio, calculated as the ratio of the differences of measurements of coronary flow and transstenotic gradient at the peak effect of papaverine and in baseline conditions.

*Comparison with physiological parameters derived from QCA measurements*

Stenosis flow reserve has been proposed by Kirkeeide et al. [18] as a single integrated index of stenosis severity and is based on the calculation derived from the measurements of stenosis geometry, of the transstenotic maximal pressure gradient and maximal flow increase under standardized conditions. These authors validated in vivo [19] flow dynamic equations developed in in vitro models by Young et al. [20, 21] and adapted for tapering stenoses and X-ray analysis by Brown et al. [22]. The algorithm, implemented also in the software package of the Philips DCI analysis system, uses the formula:

$$\Delta P = \frac{8\pi\mu L}{1.33\, A_s^2} Q + \frac{k_e \rho}{0.266} \left( \frac{1}{A_s} - \frac{1}{A_n} \right)^2 Q^2 \qquad (1)$$

where $\Delta P$ is the transstenotic pressure gradient in mmHg, $\mu$ is dynamic blood viscosity in Poise (assumed equal to 0.03), L is the length of the stenosis in mm, $A_n$ is the cross-sectional area of the reference normal segment in $mm^2$, $A_s$ is the minimal cross-sectional area of the stenotic segment in $mm^2$, Q is the mean coronary blood flow in ml/s, $\rho$ is blood density in g/ml (assumed equal to 1.05) and $k_e$ is the expansion coefficient used to correct for the entrance effect in order to apply the above equation in short stenoses as:

$$k_e = 1.21 + 0.08 \frac{\text{Lprox}}{\text{RefD}} \qquad (2)$$

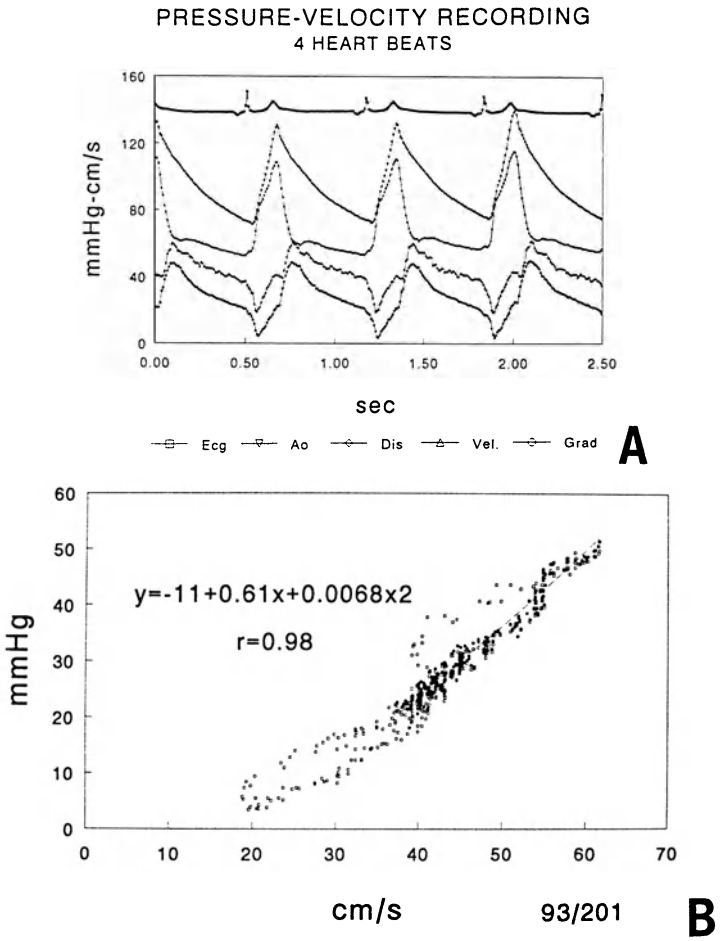


*Figure 2.* A) Simultaneous recording of electrocardiogram, proximal and distal (post-stenotic) coronary pressures, instantaneous peak flow velocity and transstenotic pressure gradient during four consecutive cardiac cycles at the peak effect of papaverine.

B) Pressure gradient and flow velocity relationship of the same 4 cardiac cycles. The data points corresponding to the phase of early diastolic relaxation and of early systolic contraction and the remaining systolic data-points (empty squares) are not considered for analysis. The dashed line is drawn from the exponential equation showing the best fitting for the mid-late diastolic data-points (filled squares).

where Lprox is the length of the entrance segment, approximated as lesion length divided by 2, and RefD is the diameter of the reference segment [23, 24]. Based on the post-stenotic pressure calculated from the above equations and the measurements of stenosis geometry, stenosis flow reserve was calculated assuming a maximal increase in coronary flow of 5 times at a mean

aortic pressure of 100 mmHg [25], a coronary venous pressure of 10 mmHg and a mean blood flow velocity of 15 cm/s [18, 19].

Stenosis flow reserve was compared both with the measured coronary flow reserve and, to allow a comparison under more standardized conditions, with the ratio between measured hyperemic mean velocity and basal mean velocity assumed in the above equation (15 cm/s).

Equation (1) was used to calculate the baseline and maximal hyperemic transstenotic pressure gradient using the real baseline and hyperemic flow velocities to calculate the corresponding coronary flow so that estimated and measured pressure gradient could be then compared at the same level of flow.

*Instantaneous assessment of the pressure gradient-flow velocity relation*

In 15 patients (71%) a continuous acquisition of the data was performed with a 12 bits analog-to-digital converter (DataQ Instr., Akron, OH) connected to a PC. Electrocardiogram, pre- and post-stenotic coronary pressure and peak coronary blood flow velocity were continuously sampled at 125 Hz per channel and stored on the hard-disk for off-line analysis (Fig. 2A). Positive or negative drifts of the 0–pressure level of the fiber optic pressure sensor, present in 7 patients (33%), and the phase delay of the pressure signal recorded through the fluid-filled guiding catheter were corrected by superimposing the pressure recorded through the guiding catheter and the prestenotic coronary pressure recorded through the pressure guidewire. Afterwards, the instantaneous transstenotic pressure gradient was calculated and plotted against the corresponding coronary flow velocity using dedicated software (AdvCodas, DataQ, Akron, Ohio), (Fig. 2B). Therefore, the transstenotic pressure gradient/flow velocity relation was analyzed from the digitized pressure and flow velocity during mid-diastole (start-point: maximal diastolic flow velocity, end-point: rapid deceleration of flow due to the begining of myocardial contraction). The phases of rapid acceleration/deceleration of flow were not considered for analysis, as suggested by Gould et al. [26], because the flow changes in these phases are dissociated from the transstenotic pressure gradient changes and are also conditioned by factors not related to the severity of the lesion (myocardial contractility, heart rate, etc.). The systolic phase of the cardiac cycle was not considered in order to avoid possible artifacts of the flow velocity signal, frequent during cardiac contraction (wall thumps, motion artifacts). Four consecutive beats were analyzed at the peak effect of the injection of papaverine.

*Statistical analysis*

Regression analysis was used to compare the measurements of pressure gradient and coronary flow and derived indexes with the minimal luminal cross-sectional area of the explored stenosis and with transstenotic pressure

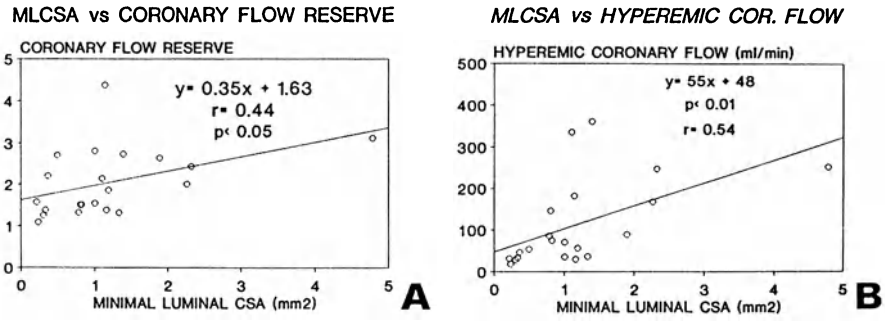


*Figure 3.* Linear regression analysis of coronary flow reserve (A) and hyperemic coronary flow (B) vs minimal cross-sectional area (MLCSA).

gradients and stenosis flow reserve. A best-fit analysis was used to assess the relationship between instantaneous pressure gradient and flow velocity (BmDP statistical package).Statistical significance was defined as $p < 0.05$. All data were expressed as mean±SD.

## Results

### *Flow velocity and transstenotic pressure gradient measurements*

The quantitative angiographic, flow velocity, pressure gradient and flow measurements of the 21 patients studied are reported in Table 1. Coronary flow reserve showed a partial but statistically significant correlation with minimal luminal cross-sectional area (Fig. 3A, $r = 0.44$, $p < 0.05$). Baseline coronary flow showed no significant correlation with the minimal luminal cross-sectional area ($r = 0.37$, NS). Coronary flow during maximal hyperemia, on the contrary, was significantly correlated with the minimal luminal cross-sectional area ($r = 0.54$, $p < 0.01$), (Fig. 3B). The baseline and hyperemic transstenotic pressure gradient showed a significant inverse correlation with the minimal luminal cross-sectional area ($r = -0.66$ and $r = -0.60$, respectively), (Fig. 4). An exponential increase in pressure gradient with the decrease in minimal luminal area was observed.

The maximal hyperemic transstenotic gradient showed a significant inverse correlation with the simultaneously measured hyperemic coronary flow, with a trend towards an exponential increase in transstenotic pressure gradient in the cases with the lowest maximal flow ($r = 0.61$, Fig. 5A). The non-significant stenoses were identified by the presence of hyperemic transstenotic gradients $< 20$ mmHg associated with a maximal coronary flow $> 150$ ml/min. At the other extreme, the presence of large transstenotic gradients during hyperemia associated with a low maximal hyperemic flow

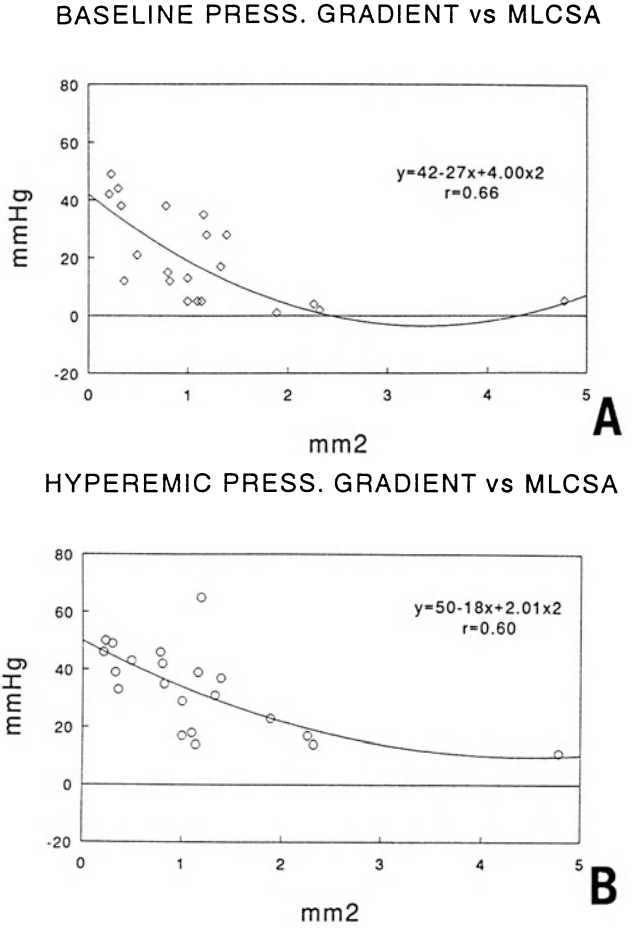


*Figure 4.* Baseline (A) and hyperemic (B) transstenotic pressure gradient plotted vs minimal luminal cross-sectional area (MLCSA). An exponential gradient increase is observed with decreasing cross-sectional areas.

identified the most severe stenoses. Similarly, when the pressure gradients from baseline to maximal hyperemia were plotted against coronary flow reserve, patients with moderate stenoses could be distinguished from patients with severe coronary stenoses (Fig. 5B).

*Combined flow velocity and pressure gradient measurements*

The hyperemic flow velocity-pressure gradient ratio and, in particular, the delta flow-delta gradient ratio, derived as previously described from the integration of flow and pressure gradient changes from baseline to hyperemia,

*Table 1.* Clinical and hemodynamic characteristics of the patients studied with a simultaneous recording of transstenotic pressure gradient and flow velocity.

| INIT | AGE (yrs) | SEX | VES | MLCSA $mm^2$ | CSA % | BAPV cm/s | HAPV cm/s | CFR | SFR | BAS GRAD mmHg | HYP GRAD mmHg | BAS FLOW ml/min | HYP FLOW ml/min | FLOW/ GRAD I ml/min/ mmHg |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| WA | 60 | m | rca | 0.49 | 0.92 | 10 | 27 | 2.70 | 1.25 | 21 | 43 | 20 | 53 | 1.53 |
| BJL | 73 | m | svbg | 0.21 | 0.98 | 7 | 11 | 1.57 | 0.30 | 42 | 46 | 20 | 31 | 2.85 |
| FB | 70 | f | rca | 2.26 | 0.74 | 31 | 62 | 2.00 | 3.13 | 4 | 17 | 84 | 167 | 6.44 |
| BKJ | 59 | m | rca | 0.82 | 0.95 | 10 | 15 | 1.50 | 1.0 | 12 | 35 | 50 | 74 | 1.08 |
| BJ | 62 | m | lad | 0.78 | 0.87 | 34 | 45 | 1.32 | 2.21 | 38 | 46 | 65 | 86 | 2.61 |
| RTR | 69 | m | rca | 0.33 | 0.97 | 8 | 11 | 1.37 | 0.49 | 38 | 39 | 24 | 33 | 9.00 |
| SA | 73 | m | svbg | 4.78 | 0.68 | 18 | 56 | 3.11 | 3.14 | 5 | 11 | 81 | 252 | 28.50 |
| WC | 59 | m | lad | 1.14 | 0.84 | 19 | 83 | 4.37 | 2.24 | 5 | 14 | 41 | 181 | 15.53 |
| BJ | 55 | m | lad | 1.10 | 0.86 | 66 | 141 | 2.14 | 2.66 | 5 | 18 | 157 | 336 | 13.74 |
| DHTA | 80 | m | rca | 0.30 | 0.97 | 8 | 10 | 1.25 | 0.46 | 44 | 49 | 23 | 28 | 1.13 |
| SEA | 74 | m | rca | 0.23 | 0.95 | 11 | 12 | 1.09 | 0.66 | 49 | 50 | 17 | 18 | 1.60 |
| OMV | 81 | f | rca | 1.39 | 0.85 | 48 | 131 | 2.73 | 2.89 | 28 | 37 | 132 | 361 | 25.39 |
| EC | 57 | m | rca | 0.80 | 0.92 | 30 | 45 | 1.50 | 1.92 | 15 | 42 | 97 | 146 | 1.80 |
| BW | 67 | m | svbg | 1.16 | 0.87 | 8 | 11 | 1.37 | 2.31 | 35 | 39 | 21 | 29 | 1.99 |
| JB | 63 | f | rca | 1.00 | 0.82 | 13 | 20 | 1.54 | 2.87 | 13 | 29 | 23 | 35 | 0.77 |
| LTW | 50 | m | lad | 1.19 | 0.71 | 21 | 39 | 1.86 | 4.24 | 28 | 65 | 33 | 56 | 2.05 |
| WHP | 41 | m | lcx | 1.89 | 0.77 | 14 | 37 | 2.64 | 3.92 | 1 | 23 | 34 | 89 | 2.50 |
| DAG | 52 | m | rca | 1.00 | 0.81 | 10 | 28 | 2.80 | 2.87 | 5 | 17 | 25 | 70 | 3.75 |
| JKF | 52 | m | lcx | 1.33 | 0.88 | 13 | 17 | 1.31 | 2.50 | 17 | 31 | 27 | 36 | 0.60 |
| GMJP | 60 | f | lad | 2.32 | 0.80 | 61 | 148 | 2.43 | 3.99 | 2 | 41 | 102 | 247 | 12.10 |
| JAK | 52 | m | rca | 0.36 | 0.93 | 15 | 33 | 2.20 | 1.31 | 12 | 33 | 21 | 46 | 1.19 |
| AVG | 62 | | | 1.18 | 0.86 | 22 | 47 | 2.04 | 2.21 | 20 | 33 | 52 | 113 | 6.48 |
| ± SD | 10 | | | 1.02 | 0.09 | 17 | 44 | 0.81 | 1.20 | 16 | 15 | 41 | 105 | 8.15 |

BAPV = Baseline time-averaged peak blood flow velocity; CSA = cross-sectional area; CFR = coronary flow reserve; FLOW/GRAD I = (hyperemic flow – baseline flow)/(hyperemic gradient – baseline gradient); HAPV = hyperemic time-averaged peak blood flow velocity; LAD = left anterior descending; LCX = left circumflex; MI = myocardial infarction; MLCSA = minimal luminal cross-sectional area (angiographic measurement minus cross-sectional area of the pressure and (5 cases) Doppler guidewire); NORM BASG = normalized baseline gradient; NORM HYPG = normalized hyperemic gradient; RCA = right coronary artery; SFR = stenosis flow reserve; SVBG = saphenous vein bypass graft.

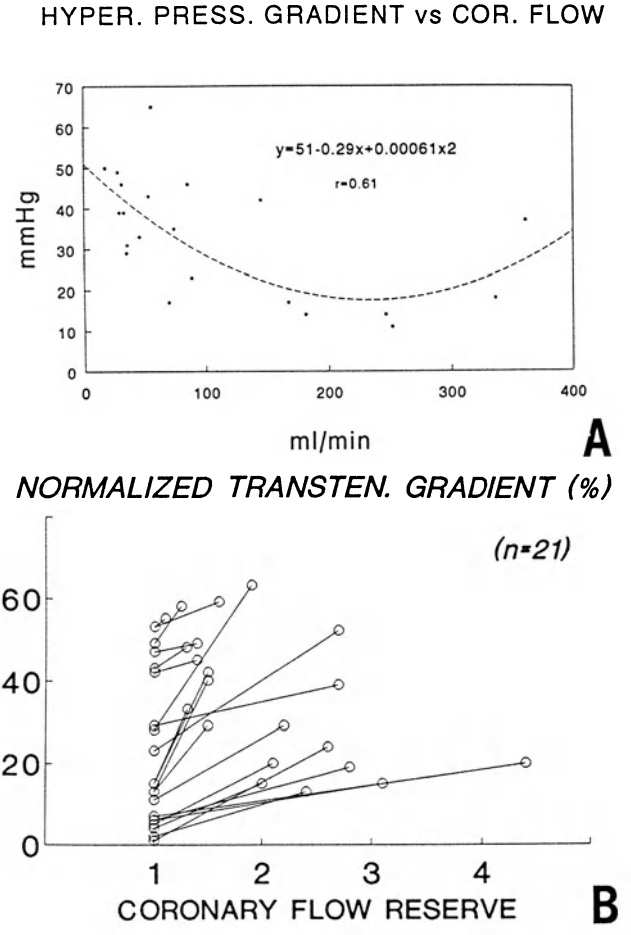


*Figure 5.* A) Relationship between hyperemic transstenotic pressure gradient and flow.
B) Baseline and hyperemic transstenotic pressure gradient, normalized for the corresponding aortic pressure, are plotted against coronary flow reserve. Higher hyperemic flow or flow reserve and low gradients indicate the least severe stenoses and viceversa.

showed a more strict correlation with minimal luminal cross-sectional area than the other flow velocity and pressure gradient measurements (Fig. 6, $r = 0.54$, $p < 0.02$ and $r = 0.66$, $p < 0.001$, respectively). In particular a delta flow-delta gradient ratio $< 3$ ml/min/mmHg identified 14 out of 17 cases with a minimal cross-sectional area $< 1.5$ mm$^2$.

*Measured and estimated flow reserve and transstenotic pressure gradients*

No correlation was present between coronary flow reserve and stenosis flow reserve (Fig. 7A). Despite a statistically significant correlation, measured and

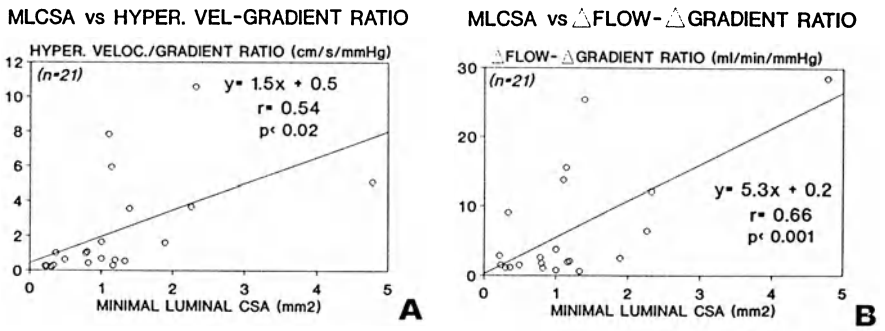


*Figure 6.* Linear regression analysis of the relationship between minimal luminal cross-sectional area (MLCSA) and (A) ratio between hyperemic flow velocity and pressure gradient and (B) ratio between the difference hyperemic-baseline coronary flow and pressure gradient. The latter index showed a higher correlation with MLCSA than all the other flow velocity and pressure gradient measurements.

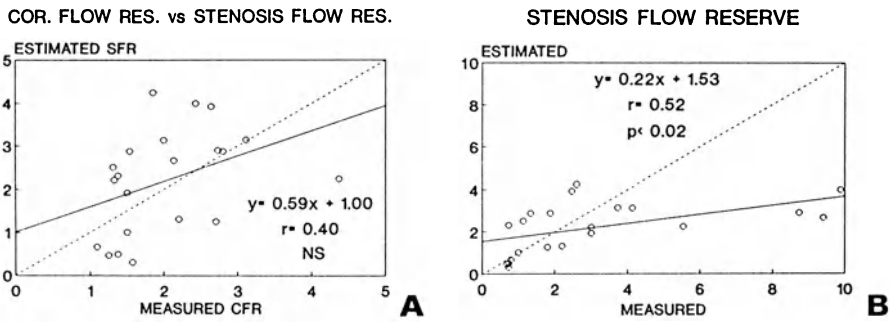


*Figure 7.* The stenosis flow reserve estimated from the angiographic stenosis geometry is plotted against the measured coronary flow reserve (A) and the ratio between measured maximal hyperemic flow velocity and mean velocity assumed for the calculation of stenosis flow reserve (15 mmHg). The dashed lines indicate the identity lines. The continuous lines indicate the regression lines.

estimated stenosis flow reserve showed a large dispersion of the individual measurements ($r = 0.52$, Fig. 7B). A better correlation was observed between estimated and measured transstenotic pressure gradient in baseline condition ($r = 0.65$, $p < 0.002$, Fig. 8A). During maximal hyperemia, however, no significant correlation was observed between estimated and measured transstenotic pressure gradients ($r = 0.13$, Fig. 8B).

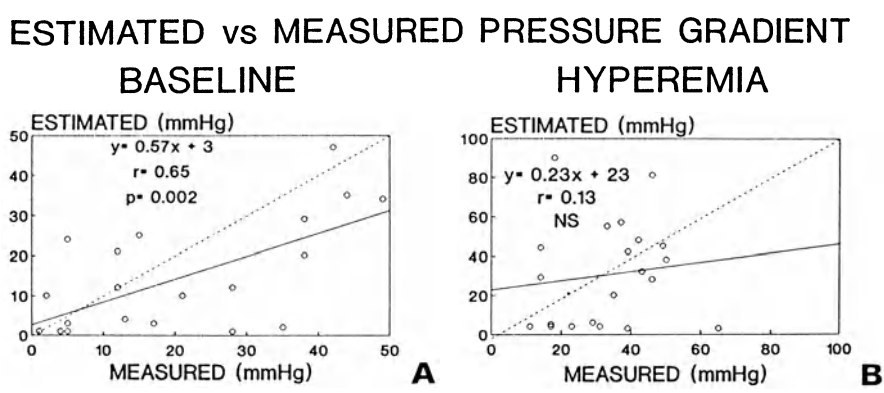


*Figure 8.* Estimated and measured transstenotic pressure gradients in baseline conditions (A) and at peak hyperemia (B). Dashed lines: identity lines; continuous lines: regression lines.

*Instantaneous assessment of the hyperemic coronary pressure/flow velocity relation*

A clear Doppler envelope allowing a reliable automatic detection of the hyperemic diastolic peak velocity during four consecutive beats was obtained in 12/15 cases (80%) (Fig. 9). A linear relationship between transstenotic gradient and flow velocity was observed in 5/12 patients (42%). In the remaining patients a quadratic equation had the best fitting for the data obtained (7/12, 58%). In all but 3 cases an intercept close to 0 (± 10 mmHg) was observed. Steeper increases of the transstenotic pressure gradient at a given flow increase were measured in the arteries with the most severe reduction in luminal cross-sectional area.

## Discussion

The identification of a single hemodynamic parameter, immediately measurable in the Catheterization Laboratory and predictive of the functional severity of a coronary stenosis would constitute an extraordinary diagnostic tool, especially for the assessment of the immediate results of coronary interventions.

*Coronary flow reserve*

Experimental reports have shown that a decrease in flow reserve may discriminantly detect a lesion of increasing severity [27]. Although the concept may be easily and accurately applied in an optimal physiological situation [28, 29], it must be recognized that coronary flow reserve is influenced by factors independent from the hydrodynamic characteristics of the stenotic lesion

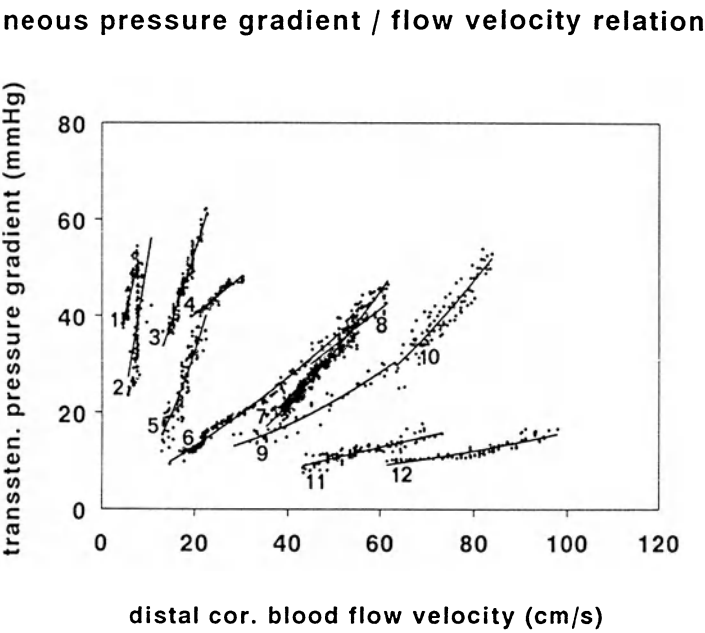


*Figure 9.* Instantaneous hyperemic diastolic pressure gradient/flow velocity relationship for 12 stenoses of increasing hemodynamic severity (from left to right and from bottom to top). The corresponding minimal luminal cross-sectional area (MLCSA) is reported after subtraction of the cross-sectional areas of the pressure and Doppler guidewires.

| Nb/INIT. | CATH.Nb | MLCSA($mm^2$) | EQUATION |
|---|---|---|---|
| 1 BJL | 92707 | 0.21 | $y = 21 + 2.72x$ |
| 2 RTR | 92999 | 0.33 | $y = -6 + 5.76x$ |
| 3 JKF | 921858 | 1.16 | $y = 2 + 2.01x + 0.0275x^2$ |
| 4 WA | 921132 | 0.49 | $y = 25 + 0.79x$ |
| 5 BKJ | 920922 | 0.82 | $y = 2 + 0.11x + 0.073x^2$ |
| 6 DAG | 922047 | 0.83 | $y = 1.6 + 0.50x + 0.0035x^2$ |
| 7 WHP | 930201 | 1.72 | $y = -4 + 0.28x + 0.009x^2$ |
| 8 JB | 920908 | 0.83 | $y = -4 + 0.76x$ |
| 9 JAK | 921502 | 0.36 | $y = 9 + 0.0055x^2$ |
| 10 LTW | 921504 | 1.19 | $y = -0.1 + 0.0074x^2$ |
| 11 SA | 921448 | 4.61 | $y = -1 + 0.23x$ |
| 12 FB | 921330 | 2.09 | $y = 5 + 0.0011x^2$ |

such as heart rate, aortic pressure, presence of collateral circulation, integrity of the distal resistance coronary vessels [30, 31]. Several pathological conditions (cardiac hypertrophy, myocardial scarring, hypercholesterolemia, systemic hypertension, etc) have been reported to alter the normal reactivity and impair the vasodilatory capacity of the distal coronary vasculature. In these conditions, therefore, the severity of the stenosis would be overesti-

mated if the low flow during maximal vasodilatation is attributed to the high resistance across the stenosis. Similarly, the presence of a well-developed collateral flow would lead to an overestimation of stenosis severity because of the decreased maximal flow through the stenosis. Coronary flow reserve is by definition a ratio, so that similar ratios may be obtained at very different levels of resting and maximal flow. Following coronary interventions, acute changes in resting blood flow together with changes in the anatomy of the stenotic lesion and concomitant persistent modifications of the hyperemic pressure-velocity relationship considerably hamper the clinical usefulness of coronary flow reserve for the assessment of the functional results. Our recently reported results with the use of a Doppler guidewire during coronary angioplasty [32] confirmed previous observations [33–36] that an increase in resting and maximal flow velocity occurs following angioplasty so that the usefulness of coronary flow reserve is limited in this clinical setting. Similar observations have been made by our group in the past, using Doppler tip balloon angioplasty catheters [37].

### *Stenosis flow reserve*

Stenosis flow reserve is an alternative approach, based only on quantitative angiographic measurements, to evaluate in standardized conditions the severity of a coronary stenosis, regardless of the individual variability of physiologic conditions [18, 19]. As clearly pointed out by the proposers of this index [18, 19], stenosis flow reserve can not be considered as an estimate of the real coronary flow reserve, determined also by the hemodynamic conditions at the time of assessment, the presence of collateral flow and the properties of the microcirculation. In this respect, the use of standardized conditions assumed in the calculation of this index has the advantage that only flow limitations induced by the stenosis studied are considered. The assumption of hemodynamic conditions not necessarily present in the studied patients is sufficient to explain the poor correlation observed in this study between estimated stenosis flow reserve and measured coronary flow reserve also when a baseline velocity equal to the velocity assumed for the calculation of stenosis flow reserve was used. A more consistent methodology to test whether hemodynamic parameters calculated from quantitative angiographic measurements reflect the real measurements is the comparison of the transstenotic pressure gradient, assuming a coronary flow velocity and an aortic pressure equal to the measured velocity and aortic pressure. This comparison, however, showed large individual differences between measured and estimated transstenotic pressure gradients, possibly as a consequence of the unavoidable inaccuracies in the measurement of the multiple geometric factors which determine stenosis severity and of the limitations to the applicability of the proposed equations, especially at high flows.

*Transstenotic pressure gradient*

The importance of the dimensions of the pressure sensor used for the measurement of the transstenotic pressure gradient has been reported and extensively studied in the years following the introduction of coronary angioplasty, when the pressure gradient recorded through the central lumen of the balloon catheter was used for the immediate assessment of the results of the procedure [38–40]. More recently, using a pressure guidewire as the angioplasty guidewire, the large increase in pressure gradient observed with the balloon catheter positioned in the lesion has been confirmed [10]. Despite these limitations, the clinical relevance of the residual transstenotic pressure gradient after coronary interventions has been confirmed by the presence of a significant correlation between residual pressure gradient $> 20$ mmHg after balloon angioplasty and development of restenosis [41]. The correlation observed in this study between transstenotic pressure gradient and angiographic lesion severity has been confirmed in a larger series of patients by Emanuelsson et al. [42]. The dependancy of the pressure gradient on flow, however, precludes a complete understanding of this parameter when the flow level is not simultaneously assessed.

*Simultaneous measurement of pressure gradient and flow velocity*

The simultaneous measurement of transstenotic pressure gradient and flow velocity avoids a possible misinterpretation of the changes of both these indexes during maximal vasodilatation. When a low maximal flow is present due to factors not dependent from the stenosis resistance, the measurement of a low transstenotic pressure gradient can be misleading, falsely suggesting the presence of a non-significant stenosis. Conversely, only the simultaneous measurement of the pressure gradient can discriminate a low flow increase during maximal vasodilatation due to a hemodynamically severe stenosis (high pressure gradient) from a reduction of the maximal transstenotic flow increase due to an impairment of the distal vasodilatory mechanisms or to competition of flow through a well-developed collateral circulation (low pressure gradient). Although the maximal flow and, consequently, the maximal transstenotic gradient are determined also by factors independent from the stenosis resistance, the transstenotic pressure gradient-flow relationship is intimately correlated with the stenosis hemodynamics. Two alternative approaches have been used to assess the slope of the pressure gradient-flow velocity relation. The first is based on the ratio of the differences of transstenotic pressure gradient and flow velocity from baseline conditions to maximal hyperemia. This index has the dimensions of flow conductance (ml/min/mmHg) and, in this study, showed a higher correlation with the angiographic minimal luminal cross-sectional area than all the single pressure gradient and flow velocity measurements. A technically more complex but promising approach is based on the assessment of the instantaneous pressure

gradient/flow velocity relationship during the progressive flow decrease in mid-late diastole. The advantage of an index based on instantaneous instead of mean gradient/flow changes during the cardiac cycle is that the phases of acceleration of flow in early diastole and deceleration of flow at the beginning of myocardial contraction can be excluded from analysis. In early systole, cardiac contraction induces an increase of the distal coronary pressure, with the possibility of a short reversed pressure gradient and a transient dissociation between transstenotic pressure gradient and flow [26]. An inverse phenomenon is observed in early diastole, when a sudden decrease of distal coronary pressure occurs during the phase of rapid cardiac relaxation, preceding the rapid increase in flow (Fig. 2). When only the passive, post-accelerative diastolic data-points are used for analysis, pressure gradient and flow velocity showed a high correlation in all cases, described by an exponential (58%) or linear (42%) relationship. This approach can also detect sudden changes in stenosis geometry from baseline to maximal hyperemia such as those due to a partial collapse of the vessel wall consequent to a critical reduction of the intrastenotic pressure [43]. In the presence of a fixed stenosis and when a premedication with nitrates intracoronary is used to negate diameter changes of the reference segments, the pressure gradient/flow velocity relationship is independent from the hemodynamic conditions of assessment (baseline or maximal hyperemia). In this study, however, the assessment was performed during maximal hyperemia so that the pressure gradient-flow relationship could be evaluated over a larger range of measurements. A possibility that we has been explored to evaluate the pressure gradient-flow velocity relationship over a large range of flow velocities and up to very low flow velocity levels is the induction of a prolonged cardiac arrest with the use of an extra-bolus of adenosine during post-papaverine maximal hyperemia (Fig. 10).

*Potential alternative analysis of the flow velocity-proximal and post-stenotic pressure relationship*

A more easily applicable method to assess the severity of a coronary stenosis, based only on the simultaneous assessment of aortic pressure and coronary flow (or flow velocity), has been proposed by Mancini et al. [44]. The slope of the instantaneous coronary flow and pressure relationship was measured during diastole in 43 dogs at 5 different levels of arterial pressure and inducing coronary stenoses of increasing severity. The measured instantaneous diastolic pressure/flow slopes were then compared with a microsphere derived index of myocardial conductance. The instantaneous hyperemic flow vs pressure index demonstrated no dependance on heart rate, left ventricular end-diastolic pressure, mean aortic pressure or inotropic changes [45, 46]. The decrease in flow/pressure slope with the presence of stenoses of increasing severity correlated well with the transmural and the subendocardial microsphere-derived measurements.

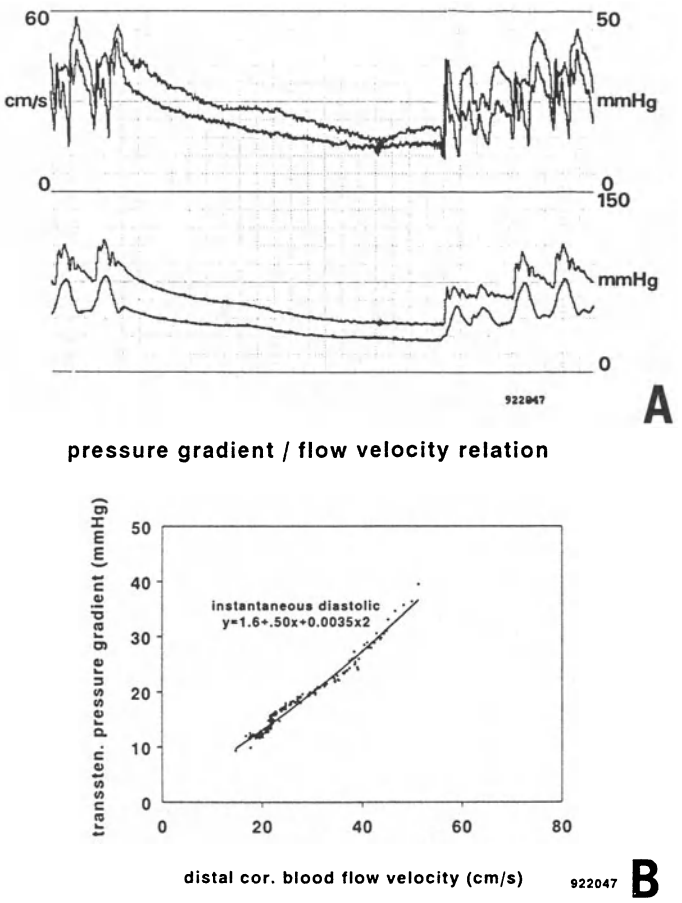


*Figure 10.* A) Long diastolic pause induced by the infusion of adenosine 3 mg intracoronary. From top to bottom peak flow velocity, instantaneous transstenotic pressure gradient and proximal and post-stenotic coronary pressure. B) Instantaneous hyperemic diastolic pressure gradient/flow velocity relationship of the previously shown diastolic pause.

Feasibility and beat-to-beat variability of the assessment of the instantaneous flow velocity-pressure relationship in humans was assessed in normal and stenotic coronary arteries using a Doppler guidewire [32, 47] (Fig. 11A). A significant difference was observed between velocity-pressure slopes measured in stenotic and normal coronary vessels, with the presence, however, of a partial overlap between the two groups. The measurement of a high fidelity post-stenotic pressure allows a direct assessment of the resistive properties of the distal coronary bed, not taking into account the resistance offered by the coronary stenosis. The integration of this approach with the assessment of the pressure gradient-flow velocity relationship has the poten-

tial for a complete characterization of the two resistances in series given by the epicardial stenosis and by the distal vasculature. After normalization with ballon dilatation or stent implantation of the epicardial arteries, the slope of the post-stenotic flow velocity-pressure relationship before the intervention can be compared with the flow velocity-proximal pressure slope after the interventions, to assess possible acute changes of the vasodilatory capacity of the distal coronary arteries. As evident from the example of Fig. 11B, however, the flow velocity/post-stenotic pressure relationship can be assessed only over a narrow pressure range in the presence of a severe coronary stenosis. An exponential decrease of pressure for any given flow velocity decrease seems to be present, possibly because of the rapid reduction in cross-sectional area in the low pressure range, resulting in an overestimation of flow using the corresponding flow velocity measurements. The consequent reduction of arterial cross-sectional area induces an underestimation of the true flow changes calculated only from the flow velocity measurements.

*Limitations of the pressure gradient-flow velocity relationship for assessment of stenosis severity*

The pressure gradient-velocity relationship has great advantages for the assessment of the hemodynamic severity of a stenosis but a precise characterization of stenosis hemodynamics does not necesserily provide sufficient elements to confirm or rule out the presence of myocardial ischemia in the territory of distribution of the examined artery. In particular, in the presence of stenoses of similar hemodynamic severity, the development of myocardial ischemia is influenced by the amount of recruitable collateral flow and by the mass of viable myocardium perfused.

The presence and development of the collateral circulation can not be determined based on conventional pressure-flow velocity measurements. Recently, Pijls et al. [48] has proposed a model using the post-stenotic pressure during occlusion (wedge pressure) to estimate maximal flow. This approach, experimentally validated, requires a balloon occlusion at the site of the stenosis so that its application is possible only during balloon dilatation.

Knowledge of the dimension of the perfused myocardial bed is essential to detect a possible mismatch between maximal flow achievable through the studied stenosis at a given aortic pressure and maximal blood flow requirement of the studied artery. The automatic measurement of the length of the angiographically visible coronary branches has been successfully used in animals to estimate the perfused myocardial mass [49]. This method, however, seems not easily applicable for routine diagnostic purposes. It must be noted that the pressure gradient-flow velocity relationship shows a steeper increase in smaller arteries than in larger arteries for a given severity of the coronary stenosis [50]. The use of velocity instead of flow can be considered a correction to this limitation because the characteristics of the coronary branching system result in a moderate reduction of flow velocity from proxi-

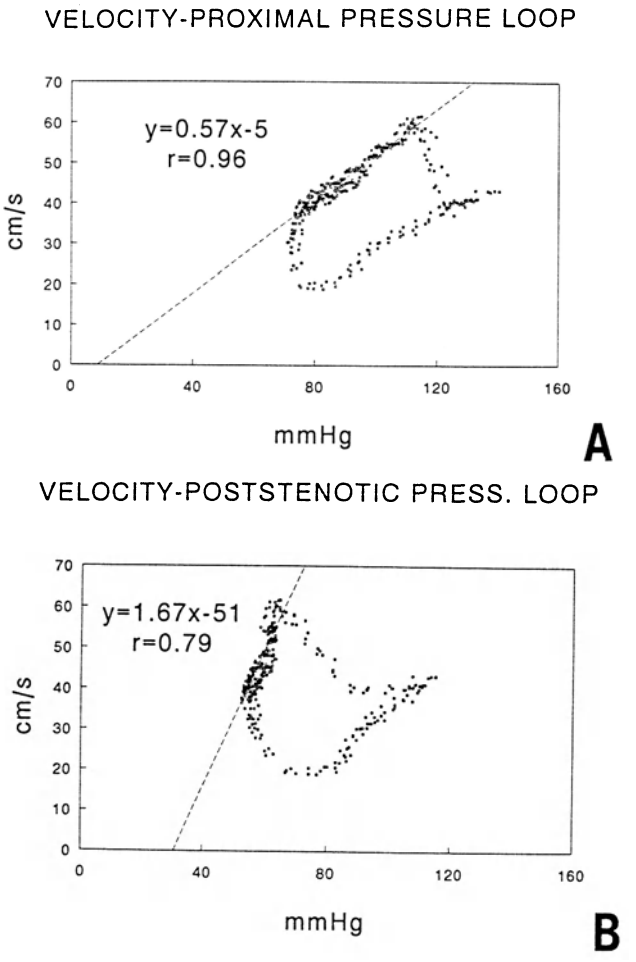


*Figure 11.* Flow velocity-pressure loop for the same cardiac cycles of Fig. 2. On the Y-axis proximal (pre-stenotic) and distal (post-stenotic) coronary pressure in A) and B), respectively. Linear regression analysis is used in both cases to analyze the flow velocity-pressure relationship in mid-late diastole.

mal to distal coronary segments despite the presence of large changes in coronary flow.

The most important limitation of the proposed approach, however, remains the complexity of the instrumentation required for the measurements. The passage of two separate guidewires with a cross-sectional area of 0.17 $mm^2$ can induce a significant additional obstruction in the presence of severe coronary stenoses [51]. Further, after coronary interventions the guidewires can prevent a complete collapse of the wall in the presence of large dissection

flaps, precluding a correct assessment of the obstruction to flow. Whenever possible, flow velocity was measured proximal to the stenosis to avoid the simultaneous presence of two guidewires across the lesion. This approach, however, precludes the possibility to take advantage of the availability, with the Doppler guidewire, of a flow velocity signal distal to the stenosis, certainly reflecting the flow limitations induced by the stenosis. Crossing of the lesion with the Doppler guidewire was required in the cases with large side-branches immediately proximal to the lesion and was felt to be mandatory for the recording of the velocity waveform used for the assessment of the instantaneous pressure gradient-flow velocity relationship. Prototypes of 0.014″ Doppler and pressure guidewires are available but a real solution can be obtained only with the combination of the two sensors in the same guidewire system. The ingenious system used to obtain a high fidelity pressure in the pressure guidewires has still practical limitations concerning the rigidity of the segment mounting the sensor and the possibility of a shift of the 0–pressure when this segment is positioned in a sharp vascular bend.

## Conclusion

Miniaturization of flow velocity and pressure sensors with guidewire technology now permits the application in conscious humans of a methodological approach to the assessment of stenosis severity previously limited to the animal laboratory. This initial experience suggests that the simultaneous measurement of pressure and flow velocity can reproducibly and accurately characterize the physiologic significance of coronary stenoses.

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*PART FOUR: QCA in the study of vasomotion*

# 17. Application of quantitative coronary angiography in the study of pharmacologically induced coronary vasomotion

HARRY SURYAPRANATA and PATRICK W. SERRUYS

## Introduction

Despite the widespread and long-standing use of coronary angiography in clinical practice, as well as the outstanding improvement in image acquisition, the interpretation of the angiogram has changed very little and is still reviewed visually. Visual assessment is a subjective evaluation with a large inter- and intra-observer variability and can not be implemented in scientific studies. Quantitative coronary angiography is therefore increasingly being used as the method of analysis in the evaluation of several pharmacological agents, as it is more accurate and reproducible as compared to visual or hand-held caliper assessments [1]. However, in order to obtain reliable and reproducible quantitative measurements from coronary angiograms, variations in data acquisition and analyses must be minimized.

In this chapter, we describe the application of quantitative coronary angiography in the study of pharmacologically induced coronary vasomotion. To this end, data on two drugs which have been studied [2, 3] are given as examples. The first one is nicorandil, a nitrate-like potassium-channel opener [2], and the second is elgodipine [3], a newly synthesized dihydropyridine calcium antagonist which is also supposed to have a potent coronary vasodilatory action.

## Protocol

In these two studies, a total of 37 patients who underwent cardiac catheterization for the investigation of suspected coronary artery disease were included. All patients were in sinus rhythm with no clinical signs of cardiac failure. Nicorandil 20 mg (n = 11) or 40 mg (n = 11) was given sublingually and elgodipine (n = 15) was administered intravenously at a rate of 1.5



*P.W. Serruys, D.P. Foley and P.J. de Feyter (eds.), Quantitative Coronary Angiography in Clinical Practice*, 307–316.

*Table 1.* Clinical and angiographic characteristics.

| | Nicorandil | Elgodipine |
|---|---|---|
| Number of patients | 22 | 15 |
| Mean Age (yr, range) | 54 (39–68) | 57 (40–69) |
| Male | 19 | 12 |
| Previous myocardial infarction | 5 | 9 |
| Multivessel disease | 12 | 7 |
| Mean ejection fraction (%, range) | 63 (58–79) | 61 (41–77) |

ug/kg/min over a period of 10 min. Clinical and angiographic data are summarized in Table 1.

Patients were studied after an overnight fast without premedication. All medication was discontinued at least 24 hr before the study. Cardiac catheterization was performed via the femoral route. No drug other than 50 mg of intravenous heparin was given during the study. Baseline coronary angiography was performed in standard views, including cranial and caudal angulations. The geometry of the x-ray gantry, and the kilovolts and milliamperes of the x-ray generator were acquired and recorded on-line for each angiogram. Electrocardiogram and intraaortic pressure were monitored continuously. Left coronary angiography was repeated 30 min after the drug administration in all projections, corresponding to those used during baseline angiography. All angiograms were obtained using the Judkins technique and recorded on Kodak® 35 mm cinefilm at a rate of 25 frames/second. A non-ionic contrast medium was injected manually.

### Systemic responses

Both drugs evoked similar systemic responses during spontaneous heart rate, in that aortic pressures decreased significantly in both groups, as shown in Table 2. Despite these marked decreases in blood pressures, the heart rate did not change significantly in either group.

### Quantitative coronary angiographic assessment

Quantitative analysis of selected coronary segments was performed using computer-assisted cardiovascular angiography analysis system that has been described in detail previously [1, 4, 5]. For non-obstructed coronary segments, the mean diameter of the analyzed segment was computed. For obstructed segments, the minimal obstruction diameter was assessed. Average values for baseline and 30–min angiograms, obtained from at least two orthogonal angiographic views, were compared.

This method of analysis was applied to two different drugs. The first

*Table 2.* Systemic responses.

| | Nicorandil 20 mg (N = 11) | | Nicorandil 40 mg (N = 11) | | Elgodipine i.v (N = 15) | |
|---|---|---|---|---|---|---|
| | Before | After | Before | After | Before | After |
| HR (beats/min) | 68 ± 4 | 66 ± 3 | 72 ± 5 | 75 ± 5 | 70 ± 4 | 75 ± 4 |
| SAP (mmHg) | 147 ± 5 | 122 ± 5* | 152 ± 6 | 110 ± 5* | 145 ± 5 | 123 ± 4* |
| MAP (mmHg) | 104 ± 4 | 90 ± 4* | 109 ± 3 | 86 ± 4* | 98 ± 3 | 86 ± 3* |
| DAP (mmHg) | 75 ± 2 | 68 ± 3* | 80 ± 3 | 68 ± 4* | 70 ± 2 | 61 ± 2* |

Values are expressed as mean±standard error of the mean. *$p < 0.05$. HR = heart rate; SAP = systolic aortic pressure; MAP = mean aortic pressure; DAP = diastolic aortic pressure.

one, nicorandil [N-(2–hydroxyethyl) nicotinamide nitrate (ester)], is a potent coronary vasodilator, and when administered sublingually, is rapidly absorbed from the mucosa of the oral cavity and gastro intestinal tract [6, 7]. The second drug, elgodipine, is a newly synthesized drug with calcium entry blocking properties belonging to the second generation of the phenyldihydropyridine group [8, 9].

A total of 172 coronary segments, including 30 stenotic segments, of the left coronary artery were selected from the study groups angiograms for quantitative analysis. The sequential changes in absolute diameter (mm) of all analyzed coronary segments, as measured during the two consecutive angiographies, are presented in Table 3. The mean coronary artery diameter increased significantly in almost all parts of left coronary artery, 30 min after sublingual administration of either 20 or 40 mg of nicorandil. These significant changes in mean coronary artery diameter were also observed to a similar extent after infusion of elgodipine (Table 3).

Among the 172 coronary segments analyzed, 30 stenotic segments were measured. The mean obstruction diameter increased respectively by 10% and 12% after 20 and 40 mg of nicorandil, and by 17% after intravenous elgodipine, as shown in Table 4.

## Theoretical pressure gradient across stenotic lesions

For obstructed coronary segments, the theoretical pressure gradients across the stenotic lesion at theoretical coronary flow rates of 1, 2 and 3 ml/s were calculated using the data obtained at quantitative angiographic analysis according to an accepted formula [10, 11]:

$$P_GRAD = Q.(R_P + Q.Rt)$$

where $P_{GRAD}$ is the theoretical pressure reduction (mmHg) across the

*Table 3.* Effects on absolute coronary artery diameter (mm) in all analyzed segments.

| | Nicorandil 20 mg | | | Nicorandil 40 mg | | | Elgodipine i.v | | |
|---|---|---|---|---|---|---|---|---|---|
| Segment | n | Before | After | n | Before | After | n | Before | After |
| LAD | | | | | | | | | |
| proximal | 11 | 2.42 ± 0.19 | 2.64 ± 0.21* | 11 | 2.53 ± 0.18 | 2.71 ± 0.20* | 15 | 2.46 ± 0.16 | 2.57 ± 0.18* |
| mid portion | 6 | 2.29 ± 0.21 | 2.51 ± 0.26 | 9 | 1.94 ± 0.12 | 2.16 ± 0.11* | 11 | 2.53 ± 0.18 | 2.67 ± 0.20 |
| distal | 11 | 1.84 ± 0.10 | 2.11 ± 0.12* | 11 | 1.64 ± 0.08 | 1.85 ± 0.07* | 14 | 1.81 ± 0.08 | 1.93 ± 0.10* |
| LCX | | | | | | | | | |
| proximal | 11 | 2.44 ± 0.16 | 2.75 ± 0.15* | 11 | 2.58 ± 0.18 | 2.85 ± 0.18* | 15 | 2.51 ± 0.16 | 2.64 ± 0.18* |
| distal | 11 | 2.09 ± 0.12 | 2.29 ± 0.15* | 11 | 1.97 ± 0.17 | 2.27 ± 0.19* | 14 | 2.06 ± 0.12 | 2.17 ± 0.15* |
| Total | 50 | 2.21 ± 0.15 | 2.47 ± 0.21* | 53 | 2.13 ± 0.13 | 2.36 ± 0.15* | 69 | 2.27 ± 0.17 | 2.39 ± 0.16* |

Values are expressed as mean±standard error of the mean. *$p < 0.05$.
LAD = left anterior descending coronary artery; LCX = left circumflex coronary artery.

*Table 4.* Effects on stenotic segments.

| | Nicorandil 20 mg (n = 7) | | Nicorandil 40 mg (n = 10) | | Elgodipine i.v (n = 13) | |
|---|---|---|---|---|---|---|
| Obstruction data | Before | After | Before | After | Before | After |
| Length (mm) | 6.46 ± 1.25 | 6.92 ± 1.35 | 5.03 ± 0.45 | 4.73 ± 0.41 | 5.09 ± 0.51 | 4.77 ± 0.43 |
| Obstr diam (mm) | 1.43 ± 0.10 | 1.58 ± 0.13 | 1.29 ± 0.14 | 1.44 ± 0.16* | 1.08 ± 0.10 | 1.26 ± 0.12* |
| Obstr area ($mm^2$) | 1.86 ± 0.45 | 2.20 ± 0.60 | 1.34 ± 0.27 | 1.78 ± 0.39* | 0.99 ± 0.11 | 1.24 ± 0.16 |
| Diam sten (%) | 43.1 ± 2.8 | 41.7 ± 3.1 | 48.9 ± 3.1 | 41.7 ± 4.5* | 58 ± 3 | 52 ± 2* |
| Area sten (%) | 70.3 ± 4.6 | 62.4 ± 7.3 | 73.4 ± 4.0 | 67.7 ± 5.0 | 85 ± 4 | 83 ± 5 |
| Symmetry index | 0.47 ± 0.10 | 0.49 ± 0.12 | 0.58 ± 0.10 | 0.58 ± 0.10 | 0.64 ± 0.10 | 0.56 ± 0.10 |
| Ref diam (mm) | 2.50 ± 0.18 | 2.83 ± 0.16* | 2.22 ± 0.11 | 2.39 ± 0.12* | 2.51 ± 0.18 | 2.63 ± 0.16* |
| Ref area ($mm^2$) | 5.09 ± 0.75 | 6.45 ± 0.75* | 3.95 ± 0.39 | 4.57 ± 0.43* | 5.13 ± 0.77 | 5.58 ± 0.75* |

Values are expressed as mean±standard error of the mean. *$p < 0.05$.
Obst = obstruction; Diam = diameter; Sten = stenosis; Ref = reference.

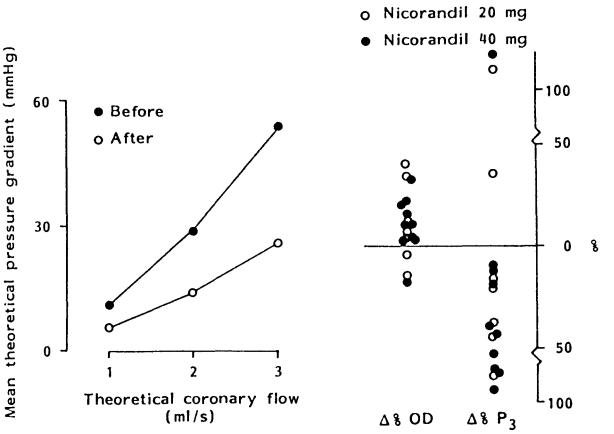


*Figure 1. Left panel*: changes in mean theoretical pressure gradients across the stenotic lesion following *nicorandil* at a theoretical coronary flow of 1, 2 and 3 ml/s.
*Right panel*: percentual changes (Δ%) in the obstruction diameter (OD) and the theoretical pressure gradient across the stenotic lesion at a theoretical coronary flow of 3 ml/s (P3). After *nicorandil*, an increase in obstruction diameter was observed in all but 3 of the analyzed stenotic lesions. The 3 stenotic segments, in which no increase in obstruction diameter was observed, showed an increase in theoretical pressure gradient.

stenosis, Q is the mean coronary blood flow (ml/s), Rp is the Poiseuille resistance, and Rt is the turbulent resistance. These resistances have been defined as follows

$$Rp = C1 \times (\text{obstruction length}) \times \pi/(\text{obstruction area})^2$$

where C1 = 8 × (blood viscosity), with blood viscosity = 0.03 (g/cm.s), and

$$Rt = C2 \times (1/\text{obstruction area} - 1/\text{normal distal area})^2$$

where C2 = blood density/0.266, with blood density = 1.0 ($g/cm^3$).

This assessment of pressure gradients has been used and described in our previous studies (12–14). Assuming theoretical coronary blood flows of 1, 2 and 3 ml/s, the theoretical pressure gradients across the stenotic segments decreased significantly after either nicorandil or elgodipine, as depicted in Figs 1 and 2.

## Discussion and conclusion

It has been validated that the use of quantitative coronary angiography is an objective and reliable method to evaluate changes in coronary artery dimensions over time [15]. The potential problems with quantitative angiographic data acquisition and analysis, such as: pincushion distortion of image

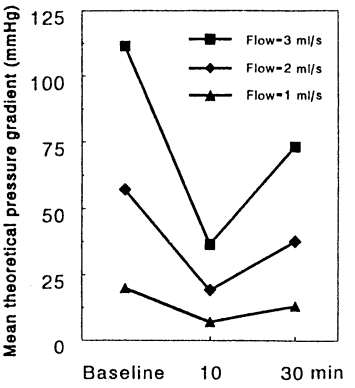


*Figure 2.* Changes in mean theoretical pressure gradients across the stenotic lesion after intravenous *elgodipine* at a theoretical coronary flow of 1, 2 and 3 ml/s.

intensifier, differences in angles and height levels of x-ray systems settings, influence of contrast agent on coronary vasomotor tone and catheter used as scaling device, as well as cine-frame selection, have been described previously [16] and intensively discussed in several chapters of this book.

When performing pharmacologic interventions during coronary angiography, 2 different approaches may be used: either repeat angiography in the same single view without altering the x-ray setting or the use of multiple angiographic views [5, 17, 18]. In the first case, if the coronary segment is non-axisymmetric, induced vasodilation may accentuate the asymmetry of the lumen by preferentially relaxing the non-atherosclerotic part of the arterial wall. Consequently, the use of a single angiographic view will then be misleading. It therefore follows that the effects of a vasodilatory agent will be better qualified if multiple projections are obtained. In order to increase the accuracy of diameter measurements and to better reflect the true luminal cross-sectional area, multiple (>2 orthogonal) angiographic views were therefore obtained in our studies.

The fact that a limited number of stenotic lesions were analyzed in these studies was attributed to the following reasons: (1) selection was based on the technical quality of the angiograms, with clear views of the pre- and poststenotic segments; (2) orthogonal projections of the stenotic lesions were required; and (3) only repeat angiography of the left coronary artery was performed. To insure exact reproducibility of the sequential angiographic studies, 4 measures were undertaken. First, as mentioned, the x-ray system was repositioned in the settings corresponding to the projections used during the baseline angiography. For this purpose, the angular settings of the x-ray gantry and the various height levels were readjusted according to the values previously documented with the on-line registration system. Second, for all studies, cineframes to be analyzed were selected at end-diastole to minimize

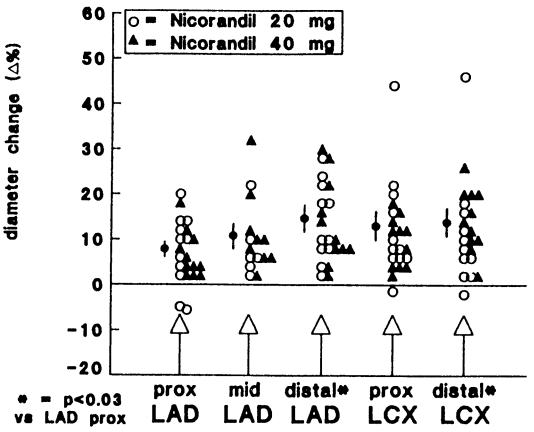


*Figure 3.* Percentual changes (Δ%) in coronary artery diameter following *nicorandil* in the proximal (prox), midportion (mid) and distal parts of the left anterior descending (LAD), and proximal and distal parts of the circumflex (LCX) coronary artery. The increase in coronary artery diameter was more pronounced in the distal segments when compared to the proximal segments. *$p < 0.03$ versus LAD prox.

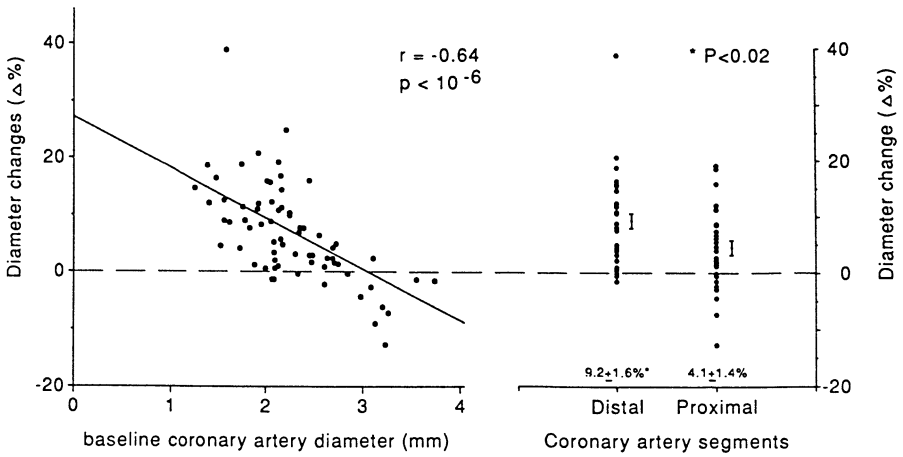


*Figure 4. Left panel*: correlation between baseline coronary artery diameter and diameter changes after intravenous infusion of *elgodipine*.
*Right panel*: diameter changes in proximal and distal parts of all analyzed coronary segments.

any possible foreshortening effect. Third, the user-determined beginning and end points of the major coronary segments between side branches were standardized according to the definitions of the American Heart Association [19]. Finally, Polaroid® pictures were taken of the video image with the

detected contours superimposed to ensure that the analyses were performed on the same coronary segment in the two consecutive angiograms.

The results demonstrate that, in the doses and routes used, both drugs induce significant vasodilatation not only in normal but also in stenotic coronary segments. In fact, the percentual increase in the diameter of the non-stenotic segments was more pronounced in the distal and smaller sized segments when compared to the larger proximal segments as shown in Figs 3 and 4. This more pronounced distal vasodilatation was also observed with other vasodilatory agents [20]. Furthermore, as far as the effects of the drugs on stenotic coronary segments are concerned, the theoretical pressure gradients across the stenotic lesions, computed from data derived from quantitative coronary angiography, showed a considerable decrease after either nicorandil or elgodipine.

Quantitative coronary angiography should be considered as an objective and reliable method to investigate the effects of a drug in a patient under relatively well-controlled circumstances.

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# 18. Long-term responsiveness to intracoronary ergonovine in variant angina

YUKIO OZAKI, DAVID KEANE*, JÜRGEN HAASE, FUMIMARO TAKATSU and PATRICK W. SERRUYS

## Introduction

While fixed coronary stenoses have traditionally been regarded as the principal determinant of myocardial perfusion, it has become increasingly apparent that vasomotor tone superimposed on a preexisting fixed stenosis plays an important pathophysiologic role in angina pectoris both at rest and on exercise [1–3]. Spasm plays an integral role in variant angina in particular [4–8]. MacAlpin proposed that the coronary spasm of variant angina is due to the amplification of normal vasoconstriction at sites of atheromatous luminal encroachments, the degree of vasoconstriction being related to the severity of encroachments (the geometric theory) [9]. The present study was performed to determine the applicability of the geometric theory to the coronary spasm of patients with variant angina and to assess the variability of coronary spasm over time, using a computer-based coronary angiography analysis system (CAAS). We assessed vasocontractility in 18 patients with variant angina by measuring the maximal changes in coronary arterial diameter induced by repeated ergonovine provocation tests. Using elementary geometric principles, we calculated the vasospastic changes that might be expected to occur at sites of fixed coronary stenosis on the basis of proportional vasomotion in normal proximal reference segments.

## Methods

### *Patient selection and vasomotor tone testing*

Eighteen male patients, admitted to Anjo Kosei Hospital (Anjo, Japan) who met the following criteria of variant angina were included in the present study: 1) chest pain at rest; 2) pain relief immediately following the adminis-

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tration of sublingual nitroglycerin; 3) no subsequent evidence of myocardial infarction and 4) coronary spasm associated with chest pain and ischemic ECG changes provoked by ergonovine during angiography [10–13]. The follow-up angiography and provocation test were performed to estimate progression of atherosclerosis as well as vasospastic activity and to provide information on the necessity to continue on long-term medication. After control angiograms of the right and left coronary arteries had been obtained, 0.2 mg ergonovine maleate was administrated intravenously by a rapid bolus injection. Heart rate and aortic pressure were monitored continuously, and 12-lead ECGs were recorded at 30-second intervals. Whenever chest pain or significant ST-segment changes were observed, selective coronary angiograms were immediately performed. Coronary vasospasm was relieved by the intracoronary administration of 2 mg to 5 mg isosorbide dinitrate (ISDN). Radiographic projections were identical during the sequential angiographic studies.

*Quantitative angiographic analysis system*

Arterial dimensions were measured at specific distances from identifiable branch points in end-diastolic frames at baseline (control), after the administration of ergonovine and after the administration of ISDN. The cinefilms obtained were analyzed off-line with the new version of the Coronary Angiography Analysis System (CAAS) which has recently been validated by in vitro and in vivo studies [14].

*Geometric considerations: dynamic vascular wall thickening*

Quantitation of vasomotion observed by angiography is limited to comparing the luminal diameter in two or more states of vasomotion. Because we cannot see the arterial wall itself, we do not always appreciate the changes which produce the variations in luminal dimensions which we call "vasomotion" [9, 15, 16]. The elementary geometric principle used to predict the narrowing expected at a site of fixed stenosis, given the severity of the fixed stenosis and the degree of vasoconstriction at the normal proximal reference segment, is shown in Figs 1 and 2.

For practical purposes, we assume the material of the arterial wall to be plastic can be moulded), but not compressible (of constant volume). If we exclude any change in the length of the artery as a result of varying diameter and any extrusion of tissue from the constricted area into nonconstricted adjacent parts of the artery, the cross sectional area of the arterial wall will be constant at any point of the artery regardless of the state of its contraction or dilation. The coronary artery is assumed to be circular in cross-section when distended by a normal blood pressure and its outer diameter is assigned to include the media but exclude the adventitia.

For each of the control (baseline) and vasoconstricted states, a set of values is assigned for the inner (luminal) and outer diameters of the normal

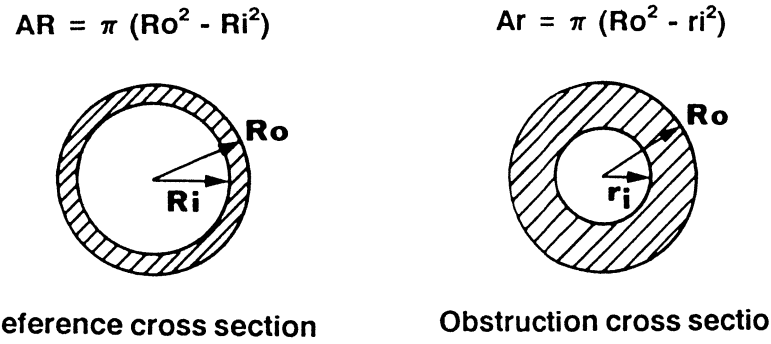


*Figure 1.* A coronary artery with circular cross sections (AR and Ar) at a prestenotic reference point and at the site of a fixed stenosis in the baseline state.

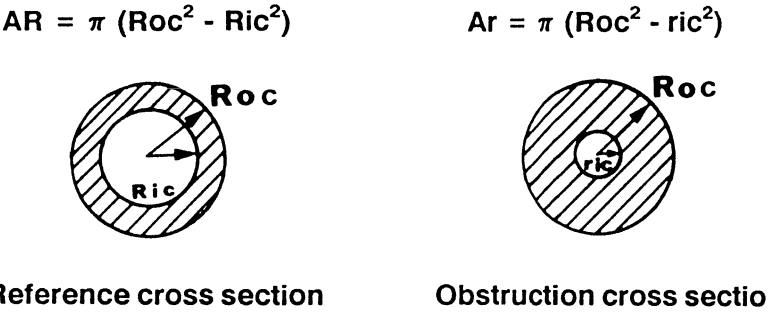


*Figure 2.* A coronary artery with circular cross sections (AR and Ar) at a prestenotic reference point and at the site of a fixed stenosis in the vasoconstricted state.

proximal (Reference) segment and the segment containing the fixed stenosis (obstruction): Thus, where

AR = Arterial wall Area at the Reference cross section
Ar = Arterial wall Area at the obstruction

2Ro = outer diameter of artery at baseline
2Ri = diameter at the Reference segment at baseline
2ri = inner diameter at the obstruction at baseline

2Roc = outer diameter of artery during vasoconstriction
2Ric = inner diameter at the Reference segment during vasoconstriction
2ric = inner diameter at the obstruction during vasoconstriction,

the following equation holds;

(i) $AR = \pi (Roc^2 - Ric^2) = \pi (Ro^2 - Ri^2)$

(ii) or $Ro^2 - Roc^2 = Ri^2 - Ric^2$

(iii) and $Ar = \pi (Roc^2 - ric^2) = \pi (Ro^2 - ri^2)$

(iv) or $Ro^2 - Roc^2 = ri^2 - ric^2$

Then equation (ii) and (iv) yield:

(v) $ric^2 = ri^2 - Ri^2 + Ric^2$

Therefore, if we know the reference diameter in the control state (2Ri) and after vasoconstriction (2Ric) and the obstruction diameter ri in the control state, we can then predict the obstruction diameter 2ric after vasoconstriction from Equation (v). Equations (i) to (v) are equally valid for the state of vasoconstriction as well as vasodilatation. Thus, for a given degree of vasoconstriction at any segment of a vessel, it should be possible to predict the decrease in the luminal diameter at any other site in the same vessel from simple geometric principles. On account of the greater arterial wall area due to the atherosclerotic plaque, the percentage reduction in luminal diameter should be greater at the site of fixed stenosis.

*Statistical methods*

Vasoconstriction at the spastic segment was considered to be correctly predicted if the minimal luminal diameter (MLD) measurement was within ±10% of the value derived by the geometric theory as described above. Changes in MLD and reference diameter (RD) induced by ergonovine and ISDN were compared by the Student's t test for paired data. Difference between characteristics of patient groups was compared by the Student's t test for unpaired data.

## Results

While, at the time of the initial study all 18 patients had classical symptoms of variant angina, at the time of follow-up only 10 patients had persistent symptoms of angina (group A) and in 8 patients symptoms had resolved (group B). There was no significant difference in age between the two groups (55 ± 8 versus 56 ± 8) and the interval between the initial and follow-up studies was 40 ± 12 months and 43 ± 12 months in groups A and B respectively (not significant). Twenty spastic coronary segments in 20 vessels in 18 patients were analyzed. Mean diameter of the normal proximal segment was used as the reference diameter. The results of quantitative analysis for the control, ergonovine and isosorbide dinitrate (ISDN) phases of the initial and follow-up studies for both groups are given in Tables 1 and 2.

In group A, ergonovine induced a significant reduction in the reference diameter (RD) and minimal luminal diameter (MLD) at spastic segments during both the initial and follow-up studies, and ISDN induced a significant increase in MLD as well as RD during both studies. The mean values of the initial and follow-up studies for group A are compared in Figs 3 and 4.

*Table 1.* Quantitative coronary analysis in three phases of vasomotion in patients with persistent angina at follow-up (group A).

| | | 1st Angiogram | | | 2nd Angiogram | | |
|---|---|---|---|---|---|---|---|
| Patient number | Vessel & phase | RD (mm) | MLD (mm) | % DS | RD (mm) | MLD (mm) | % DS |
| 1 | RCA-control | 2.8 | 2.38 | 15 | 2.53 | 2.22 | 12 |
| | RCA-erg | 2.41 | 0.83 | 66 | 2.16 | 0.87 | 60 |
| | RCA-ISDN | 3.41 | 2.72 | 20 | 3.67 | 2.86 | 22 |
| 2 | LAD-control | 2.33 | 1.47 | 37 | 2.18 | 1.2 | 45 |
| | LAD-erg | 2.19 | 0.69 | 68 | 2.1 | 0.67 | 68 |
| | LAD-ISDN | 2.54 | 1.62 | 36 | 2.59 | 2.17 | 16 |
| | RCA-control | 2.48 | 1.82 | 27 | 2.37 | 1.87 | 21 |
| | RCA-erg | 2.1 | 0.8 | 62 | 1.56 | 0 | 100 |
| | RCA-ISDN | 2.96 | 2.52 | 15 | 2.99 | 2.07 | 31 |
| 3 | RCA-control | 3 | 1.28 | 57 | 2.7 | 1.01 | 63 |
| | RCA-erg | 2.68 | 0.71 | 74 | 2.13 | 0 | 100 |
| | RCA-ISDN | 3.51 | 1.9 | 46 | 2.72 | 1.2 | 56 |
| 4 | RCA-control | 1.72 | 0.95 | 45 | 2.92 | 2.51 | 14 |
| | RCA-erg | 1.65 | 0.5 | 70 | 2.62 | 0 | 100 |
| | RCA-ISDN | 3.4 | 2.15 | 37 | 3.7 | 3.17 | 14 |
| 5 | RCA-control | 2.7 | 1.99 | 26 | 2.59 | 1.3 | 50 |
| | RCA-erg | 2.26 | 0.88 | 61 | 2.52 | 0.71 | 72 |
| | RCA-ISDN | 3.02 | 2.55 | 16 | 3.03 | 2.44 | 19 |
| 6 | LCX-control | 3.21 | 2.39 | 26 | 3.41 | 2.46 | 28 |
| | LCX-erg | 2.82 | 1.07 | 62 | 2.99 | 1.03 | 66 |
| | LCX-ISDN | 3.47 | 2.5 | 28 | 3.49 | 3.11 | 11 |
| 7 | LAD-control | 2.56 | 1.1 | 57 | 2.61 | 1.09 | 58 |
| | LAD-erg | 2.31 | 0.52 | 77 | 2.32 | 0.58 | 75 |
| | LAD-ISDN | 2.84 | 1.27 | 55 | 2.62 | 1.16 | 56 |
| | RCA-control | 2.82 | 1.32 | 53 | 2.77 | 1.58 | 43 |
| | RCA-erg | 2.76 | 1.11 | 60 | 2.42 | 1.08 | 55 |
| | RCA-ISDN | 3.1 | 1.37 | 56 | 3.27 | 1.81 | 45 |
| 8 | RCA-control | 2.49 | 1.78 | 29 | 2.33 | 1.36 | 42 |
| | RCA-erg | 2.32 | 0.81 | 65 | 2.14 | 0.77 | 64 |
| | RCA-ISDN | 3.18 | 2.37 | 25 | 2.76 | 1.96 | 29 |
| 9 | LCX-control | 1.93 | 1.13 | 41 | 1.62 | 1.26 | 22 |
| | LCX-erg | 2.05 | 0.34 | 83 | 1.23 | 0 | 100 |
| | LCX-ISDN | 2.58 | 1.49 | 42 | 2.46 | 1.8 | 27 |
| 10 | RCA-control | 2.63 | 1.93 | 27 | 2.59 | 1.77 | 32 |
| | RCA-erg | 1.9 | 0 | 100 | 2.07 | 0 | 100 |
| | RCA-ISDN | 3.17 | 2.64 | 17 | 3.49 | 2.83 | 19 |

RCA = right coronary artery; LAD = left anterior descending artery; LCX = left circumflex coronary artery; erg = after administration of ergonovine; ISDN = after administration of isosorbide dinitrate.

*Table 2.* Quantitative coronary analysis in three phases of vasomotion in patients with resolution of angina at follow-up (group B).

| | | 1st Angiogram | | | 2nd Angiogram | | |
|---|---|---|---|---|---|---|---|
| Patient number | Vessel & phase | RD (mm) | MLD (mm) | % DS | RD (mm) | MLD (mm) | % DS |
| 11 | RCA-control | 2.73 | 1.71 | 37 | 3.46 | 2.7 | 22 |
| | RCA-erg | 2.28 | 0 | 100 | 2.35 | 1.48 | 37 |
| | RCA-ISDN | 4.08 | 2.56 | 37 | 3.93 | 2.68 | 32 |
| 12 | LAD-control | 1.5 | 0.85 | 43 | 2.51 | 1.34 | 47 |
| | LAD-erg | 1.46 | 0.46 | 68 | 2.28 | 1.56 | 32 |
| | LAD-ISDN | 2.32 | 1.3 | 44 | 2.53 | 2.02 | 20 |
| 13 | LCX-control | 2.63 | 1.77 | 33 | 2.46 | 1.82 | 26 |
| | LCX-erg | 2.13 | 0 | 100 | 2.24 | 1.29 | 42 |
| | LCX-ISDN | 2.7 | 1.85 | 31 | 2.86 | 2.06 | 28 |
| 14 | LAD-control | 1.67 | 1.2 | 28 | 1.91 | 1.25 | 35 |
| | LAD-erg | 1.5 | 0.61 | 59 | 2.02 | 1.41 | 30 |
| | LAD-ISDN | 2.19 | 1.68 | 23 | 2.03 | 1.71 | 16 |
| 15 | LAD-control | 2.38 | 1.07 | 55 | 2.88 | 1.89 | 34 |
| | LAD-erg | 2.21 | 0.57 | 74 | 2.37 | 1.67 | 30 |
| | LAD-ISDN | 2.78 | 1.22 | 56 | 2.72 | 1.76 | 35 |
| 16 | RCA-control | 2.52 | 1.05 | 58 | 2.83 | 1.91 | 33 |
| | RCA-erg | 1.95 | 0 | 100 | 2.38 | 1.6 | 33 |
| | RCA-ISDN | 3.75 | 2.44 | 35 | 3.61 | 2.55 | 29 |
| 17 | RCA-control | 2.48 | 1.37 | 45 | 2.43 | 1.77 | 27 |
| | RCA-erg | 1.97 | 0 | 100 | 2.18 | 1.3 | 40 |
| | RCA-ISDN | 2.85 | 2.53 | 11 | 2.83 | 2.02 | 29 |
| 18 | LAD-control | 2.67 | 2.01 | 25 | 2.56 | 2.1 | 18 |
| | LAD-erg | 2.57 | 0.83 | 68 | 2.43 | 1.93 | 21 |
| | LAD-ISDN | 3 | 2.83 | 6 | 2.8 | 2.1 | 25 |

RCA = right coronary artery; LAD = left anterior descending artery; LCX = left circumflex coronary artery; erg = after administration of ergonovine; ISDN = after administration of isosorbide dinitrate.

In group B, significant reduction in both MLD at spastic segments and RD were observed during the initial study, while neither MLD nor RD changed significantly during the follow-up study; both MLD and RD increased following the administration of ISDN during both tests. The mean values of the initial and follow-up studies for group B are compared in Figs 5 and 6.

During the initial study, only 1 of 10 patients in group A developed total

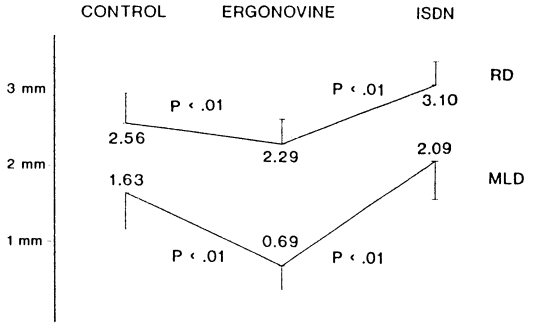


*Figure 3.* Mean values of reference diameter (RD) and minimal luminal diameter (MLD) at baseline (control), after administration of ergonovine and after administration of isosorbide dinitrate (ISDN) in Group A in the initial test.

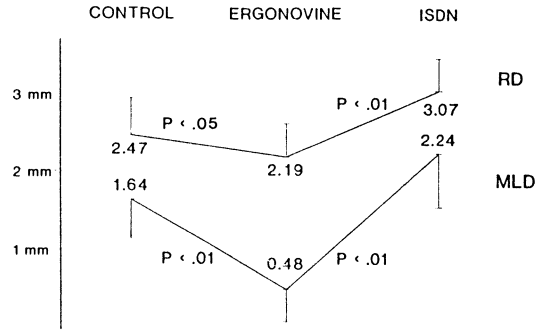


*Figure 4.* Mean values of reference diameter (RD) and minimal luminal diameter (MLD) at baseline (control), after administration of ergonovine and after administration of isosorbide dinitrate (ISDN) in Group A in the follow-up test.

transient spastic occlusion in response to ergonovine, while 4 out of 8 patients in group B demonstrated such an occlusive spastic response.

Using the elementary geometric principles described above, we calculated the changes that would be expected to occur at spastic sites if vasoconstriction throughout the coronary vessel was uniform. Figure 7 shows the behaviour of the 20 spastic segments during both provocation tests.

During the initial study, the decrease in MLD at the spastic site was proportional to the vasoconstriction in the RD in only 4 vessels, i.e. vasospasm at the site of fixed stenosis was correctly predicted. In 1 vessel, vasoconstriction at the site of fixed stenosis was less than predicted whereas in 15 vessels clear hypercontractility was exhibited at the sites of fixed stenosis.

During the follow-up study, only 1 of 4 segments which were correctly predicted at the initial test, developed the predicted value in MLD again,

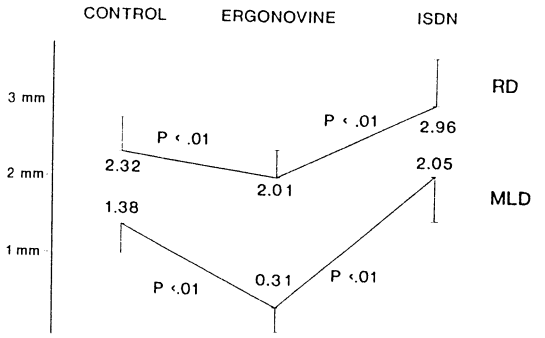


*Figure 5.* Mean values of reference diameter (RD) and minimal luminal diameter (MLD) at baseline (control), after administration of ergonovine and after administration of isosorbide dinitrate (ISDN) in Group B in the initial test.

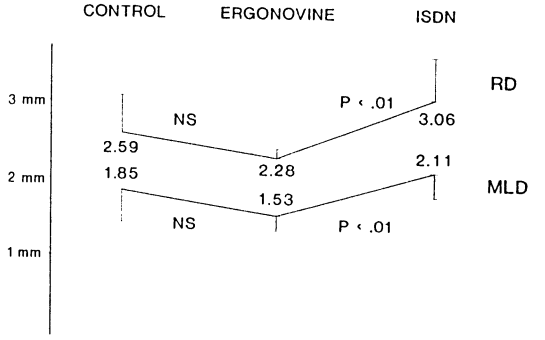


*Figure 6.* Mean values of reference diameter (RD) and minimal luminal diameter (MLD) at baseline (control), after administration of ergonovine and after administration of isosorbide dinitrate (ISDN) in Group B in the follow-up test.

while the other 3 segments showed hypocontractility. The 1 vessel in which hypocontractility was observed initially, again demonstrated hypocontractility at follow-up. Of the 15 segments which showed hypercontractility during the initial test, 11 exhibited hypercontractility again, 2 developed their predicted MLD values and the remaining 2 developed less contraction than predicted (hypocontractile).

Thus, the majority of spastic segments were hypercontractile during both tests while some segments changed from being hypercontractile initially to being hypocontractile at follow-up. In only one vessel could the behaviour of a fixed stenosis be correctly predicted by the geometric theory during both provocation tests.

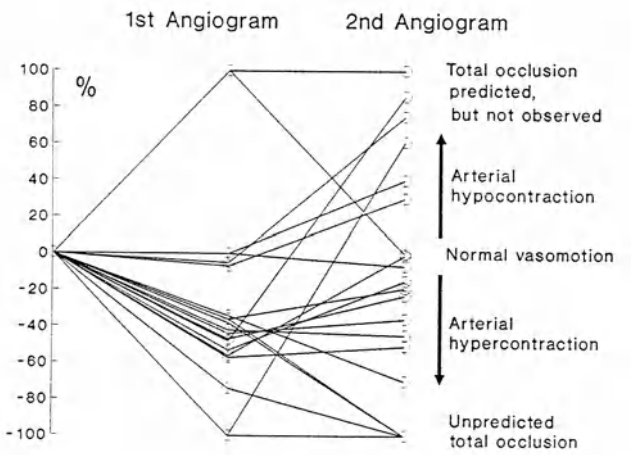


*Figure 7.* Percentage deviation of the obstruction diameter from predicted values after administration of ergonovine of all 20 spastic segments in the initial and follow-up tests.

## Discussion

During the past decade, clinical understanding of changes in vessel wall cross sectional area during coronary spasm was influenced by the geometric theory proposed by MacAlpin [9]. This theoretical model suggested that vascular hypersensitivity was due to the amplification of normal vasoconstriction at the sites of atheromatous luminal encroachment, the degree of vasoconstriction being related to the severity of encroachment. In the report by MacAlpin, arterial measurements were performed in three cases to support the geometric theory [9]. However, in at least one of the three cases, vasoconstriction induced by ergotamine was greater than that predicted by the geometric theory, so this theory could not completely explain occurrence of coronary spasm even in his cases. Our study, based on computerized quantitative analysis of coronary angiograms, further undermines the geometric theory. Our results support the hypothesis that coronary artery spasm results from hypersensitivity to vasoconstrictors at atherosclerotic sites as previously suggested by other investigators.

Coronary artery spasm in normal coronary arteries has also been reported by several authors [17–21]. In a study investigating the severity of fixed stenosis at the site of coronary spasm in 406 patients [22], 12% of the patients had no fixed stenosis in any coronary artery after administration of isosorbide dinitrate and only 30% of patients had severe fixed stenosis. It is clear from these results that the geometric theory alone cannot explain vasospasm in patients with angoiographically normal coronary arteries. Of interest, coronary spasm has been observed in a swine model in angiographically normal coronary arteries however subsequent histological studies revealed that early

atherosclerotic changes were already present [23]. Both clinical and experimental studies have demonstrated that hypercontractility of coronary arteries in response to a variety of vasoconstrictive agents is integrally related to the pathologic process of atherosclerosis; specifically, to the disruption of endothelial control of vascular smooth muscle tone [24–32] and to the release of vasoactive products by leucocytes and platelets [33, 34]. While such endothelial damage will usually progress it may occasionally heal over the course of several months [35, 36]. Other factors unrelated to advanced atherosclerosis such as mediation of autonomic nerve system might play a role in the genesis of coronary spasm [37].

A finding of particular interest in our present investigation was that while the majority of spastic segments showed arterial hypercontractility on both tests, some segments fluctuated from being hypercontractile to being hypocontractile between the two tests. This indicates the variability of vasoconstriction provoked at each spastic site of a coronary artery within a few years. Furthermore, we observed in a recent long-term study [38] that the location of coronary spasm shifts over a period of a few years in some patients with variant angina. This indicates that coronary spasm is not a permanent condition regulated by the severity of atherosclerosis but a dynamic process only partly influenced by geometric factors. The nature of the temporal and spatial variability of vasospastic angina remains to be elucidated.

It is concluded that the degree of coronary artery spasm cannot be directly derived from morphological changes at the site of the vasoconstriction. Alterations in the endothelium-dependent responsiveness of vascular smooth muscle seems to outweigh the predictive value of vessel wall geometry. Coronary vasospastic responsiveness is a dynamic process demonstrating both temporal and spatial variability.

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# 19. Response of conductance and resistance coronary vessels to scalar concentrations of acetylcholine. Assessment with quantitative angiography and intracoronary Doppler in 29 patients with coronary artery disease

CARLO DI MARIO, SIPKE STRIKWERDA, ROBERT GIL, PIM J. DE FEYTER, NICOLAS MENEVEAU and PATRICK W. SERRUYS

The in vitro observations of Furchgott and Zawadzki [1] and the in vitro and in vivo reports from the group of Moncada [2, 3] have shown that an endothelium-derived-relaxing-factor, identified as nitric oxide [2], modulates vascular tone in response to physiologic and pathologic stimuli (increase in wall shear stress, serotonin, bradykinin, histamine, thrombin, sympathetic stimulation, acetylcholine, endotoxins, etc.). Endothelial damage, leading to a decreased formation or release of nitric oxide from its precursor L-arginine, or reduced penetration due to the presence of subendothelial intimal thickening, are possible explanations of the impairment of endothelium-mediated vasodilatation observed in patients with systemic hypertension [4], hypercholesterolemia, diabetes mellitus [5], atherosclerosis [6].

The presence of paradoxical vasoconstriction induced by acetylcholine has been shown in coronary patients at sites of severe stenosis or moderate wall irregularities [7] and in angiographically normal segments [8–10]. Coronary spasm after acetylcholine infusion has also been demonstrated in patients with variant angina, with and without angiographically visible changes [11, 12]. The observed vasoconstriction or vasodilatation after acetylcholine is the net effect of the conflicting action of this substance on the endothelial cells (stimulation to the release of endothelium-derived relaxing factor) and on the smooth muscle cells (vasoconstriction due to the direct effect on the cholinergic receptors). With the use of intracoronary Doppler, an impairment of the endothelial derived vasodilatation was observed also after more physiologic stimuli such as the increase of blood flow [13–15]. The flow dependent vasodilatation is an essential mechanism of adjustment of coronary tone to prevent endothelial damage due to a pathologic increase in wall shear stress [12]. An abnormal vasoconstriction in response to sympathetic stimulation [16] or release of platelet-derived vasoconstrictors [17, 18] was observed if the direct effect of these substances on the muscular media was not antagonized by a preserved endothelium-mediated vasodilatation. Nitric oxide has also a powerful anti-aggregatory activity. Yao et al. [19] showed a protective effect of endogenous nitric oxide in the prevention of cyclic flow variations due to platelet aggregation at the site of endothelial injury. Endothelial



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dysfunction, therefore, is not only a potential mechanism of aggravation of ischemia in patients with coronary atherosclerosis but it increases the risk of endothelial injury and impairs the antithrombotic reaction, thus facilitating the development of acute coronary syndromes and the release of platelet-derived growth factors which may predispose to progression of atherosclerosis. An impairment of endothelium-mediated vasodilatation has been shown in patients with risk factors for coronary atherosclerosis but without angiographically visible atherosclerotic changes [9, 20]. A possible limitation of these studies is the poor sensitivity of angiography in the detection of early atherosclerotic changes. More recently, the presence of endothelial dysfunction also in patients with structurally normal coronary arteries but with hypertension, hyyperlipidemia, family history of coronary artery disease or smoking has been confirmed using two-dimensional intracoronary ultrasound [21]. A complete loss of endothelium-mediated vasodilatation was present in arteries with angiographically visible atherosclerotic changes. Angiographically normal arteries of patients with hypercholesterolemia showed a normal flow-mediated vasodilatation following papaverine but an abnormal vasoconstriction after acetylcholine [21].

The possible presence of opposite effects of acetylcholine infusion on epicardial and resistance coronary arteries have been reported by Hodgson et al. [22]. The observed increase of coronary flow after acetylcholine was prevented by the pretreatment with methylene blue, an inhibitor of endothelium-derived relaxing factor. Zeiher et al. [23] reported a significantly lower flow increase after acetylcholine in patients with coronary artery disease than in control subjects. These findings confirmed previous experimental results showing that the impairment of endothelial function in atherosclerotic arteries may extend into the coronary microcirculation [24–26]. The presence of an impaired endothelium-dependent vasodilatation of the resistance vessels may induce or facilitate the development of myocardial ischemia in response to neurohumoral stimulation or increased myocardial work [27]. The epicardial arteries and the arterioles have large structural differences and show a different involvement in the atherosclerotic process, mainly confined to the large epicardial coronary arteries. Both types of arteries, however, are likely to show a similar response to pathologic stimuli on the endothelial cells impairing the intracellular production and release of nitric oxide. The presence of an impaired diffusion or of an increased extracellular degradation of nitric oxide in the thickened intima is a phenomenon limited to the epicardial arteries and may explain an earlier and more severe impairment of the endothelium-mediated vasodilatation of these vessels.

Aim of this study is the simultaneous assessment of the endothelium-mediated vasodilatation of conductance and resistance vessels in coronary arteries without significant stenosis (<30% diameter stenosis). During selective infusion of scalar increasing concentrations of acetylcholine the changes of coronary cross-sectional area over a proximal/mid segment and a distal segment of the studied artery were measured with quantitative coronary

angiography and correlated with the changes in coronary flow, derived from the flow velocity measured with a Doppler guidewire and used as an index of vasodilatory response of the resistance vessels.

## Methods

### *Patient population*

Twenty-nine patients (age 57 ± 9 years, 24 men and 5 women) undergoing elective percutaneous transluminal angioplasty because of disabling stable angina pectoris were studied. Previous myocardial infarction was present in 8/29 patients (26%), in no cases involving the territory of distribution of the studied artery. Systemic hypertension was defined as a chronically elevated arterial blood pressure (≥150/90 mmHg) and was present in 9/29 patients (31%). Three patients were current smokers (10%). A previous history of smoking was present in 18 patients (62%). No patient had anemia (mean hemoglobin 8.8±0.57 mmol/l) or anamnestic/biohumoral signs of diabetes mellitus or hyperthyroidism. The angiographic selection criteria included absence of >30% diameter stenosis in one of the 3 major coronary arteries without visible collaterals originating from this vessel and with a normal left ventricular contraction of the segments of distribution of the studied artery. Angiographically visible wall irregularities were present in 19/29 patients (66%). The studied artery was the left anterior descending coronary artery in 7 patients (24%), the left circumflex in 13 (45%) and the right coronary artery in 9 (31%). Written informed consent was obtained in all cases. The protocol was approved by the Ethics Committee Erasmus University-Rotterdam Dijkzigt Hospital (protocol #MEC 114.542/1991/61). All vasoactive medication, with the exclusion of short-acting sublingual nitrates, was withheld at least 48 hr before the catheterization. No sublingual, intravenous or intracoronary nitrates were used in the 6 hr before or during the catheterization procedure.

### *Catheterization procedure*

After systemic anticoagulation with 10,000 I.U. of heparin and 250 mg of acetylsalicylic acid intravenously and sedation with 5–10 mg diazepam intravenously, the artery to be studied was instrumented using a 9F giant lumen (inner lumen = 0.084″) Amplatz or Judkins guiding catheter (left coronary artery) or a 7F Judkins diagnostic catheter (right coronary artery). A 0.018″ Doppler angioplasty guidewire was then advanced to a normal or near-normal straight proximal segment of the artery to be studied where a stable flow velocity signal could be obtained. A 3.6 F flexible infusion catheter (Tracker 25, Target Therapeutics, San Jose, CA) was then inserted over the Doppler wire into the proximal segment of the coronary artery in order to

obtain a selective injection into the left anterior descending or left circumflex artery [28]. Care was taken to avoid a too selective cannulation of the large guiding catheter into the left main coronary artery in order to avoid limitation of flow during maximal hyperemia. For the right coronary artery a selectively engaged 7 F diagnostic catheter was used for the infusion. Heart rate and mean aortic pressure were automatically measured using a previously described computer-assisted system [29] by averaging 16 consecutive seconds of recording. After the baseline acquisition of flow velocity, heart rate and blood pressure, the measurements were repeated 30 s after a bolus injection of 7 mg of papaverine diluted in 1.5 ml. After a recovery period of 8 min, new basal measurements were performed followed by a cineangiogram suitable for quantitation. Scalar concentrations of acetylcholine at 37°C (0.036, 0.36, 3.6 μg/ml) were infused at a flow rate of 2 ml/min using a precision pump-injector (Mark V, Medrad, Pittsburgh, PA). With these dilutions and flow rates and assuming a coronary blood flow of 80 ml/min in the studied artery, intracoronary blood concentrations of $10^{-8}$, $10^{-7}$ and $10^{-6}$ M were estimated. Five min after the beginning of the infusion of each concentration blood flow velocity and hemodynamic measurements were acquired and a new cineangiogram performed. Five min after the end of the series of acetylcholine infusions a new baseline flow velocity was acquired and, 1 min after a bolus injection of 3 mg of isosorbide dinitrate, a new cineangiogram was performed.

*Doppler guidewire and flow velocity measurements*

The Doppler angioplasty guidewire is a 0.018″ (diameter = 0.46 mm) 175 cm long flexible and steerable guidewire with a floppy shapable distal end mounting a 12 MHz piezoelectric transducer at the tip (FloWire, Cardiometrics Inc., Mountain View, CA). The sample volume was positioned at a distance of 5.2 mm from the transducer in order to avoid the area of distortion of flow profile due to the presence of the Doppler guidewire. At this distance the sample volume has approximately a diameter of 2.25 mm due to the divergent ultrasound beam so that a large part of the flow velocity profile is included in the sample volume even in case of eccentric position of the Doppler guidewire. In order to increase the reliability of the analysis of the Doppler signal [30] a real-time fast-Fourier transform algorithm was applied to the quadrature audio signal. The Doppler system used (FloMap, Cardiometrics, Mountain View, CA) performs a real-time spectral analysis of the Doppler signal and calculates and displays on-line several spectral variables including the instantaneous peak velocity and the time-averaged (mean of 2 beats) peak velocity (Fig. 1). The flow velocity measurements obtained with this system have been validated in vitro and in an animal model using simultaneous electromagnetic flow measurements for comparison [31]. Coronary flow reserve was defined as the ratio between maximal flow velocity at the peak effect of the papaverine injection and in baseline conditions.

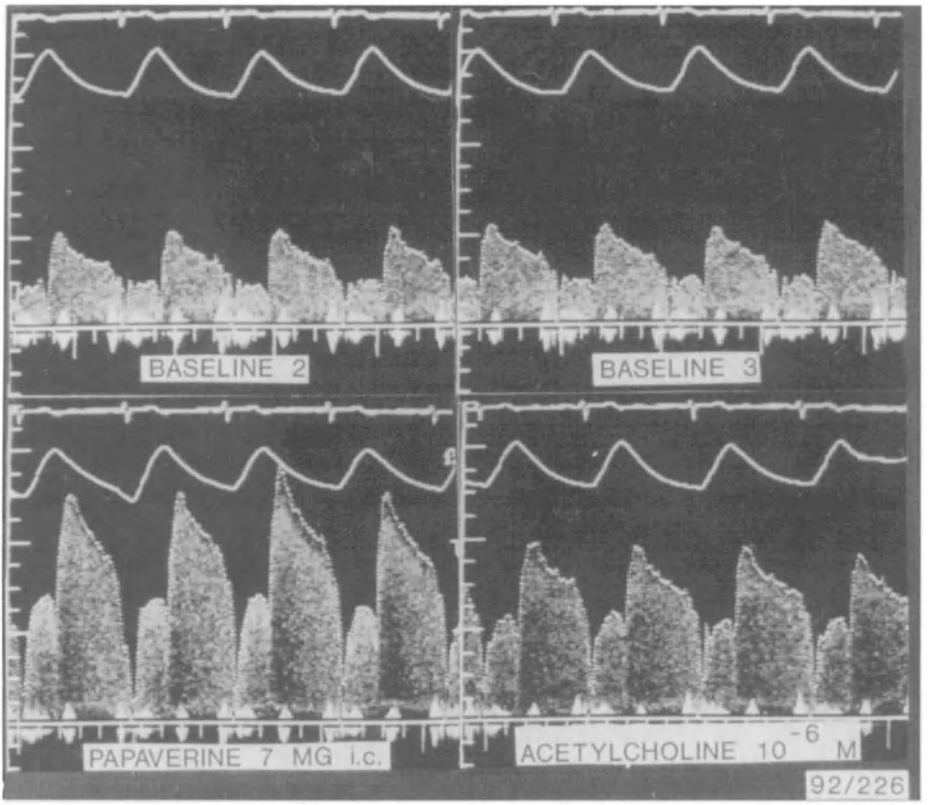


*Figure 1.* Flow velocity measurement in a proximal left circumflex artery before the injection of increasing concentrations of acetylcholine (Baseline 2), 5 min after the end of the infusion of acetylcholine (Baseline 3) and at the peak effect of papaverine and acetylcholine $10^{-6}$M. Note the stable flow velocity in baseline condition, the large velocity increase after papaverine and the moderate increase after the maximal concentration of acetylcholine. APV = time-averaged peak velocity.

Electrocardiogram, coronary pressure and peak coronary blood flow velocity were continuously sampled at 125 kHz per channel using a 12 bits analog-to-digital converter. The ACodas software package (DataQ Instr., Akron, OH) was used for off-line analysis.

*Quantitative angiographic measurements*

The preformed coronary catheter, filmed not filled with contrast medium, was used as a scaling device [32]. Before the study, when necessary, a previously validated on-line analysis system operating on digital images (ACA-DCI, Philips, Eindhoven, The Netherlands) [33] was used to exclude the presence of >30% diameter stenosis. Coronary angiography was per-

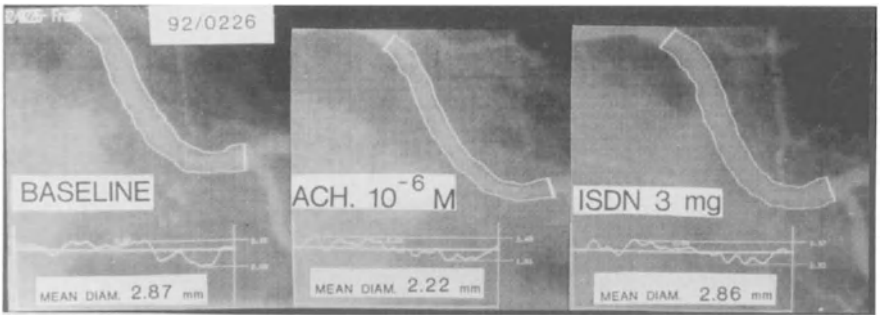


*Figure 2.* Quantitative angiographic measurements of the mean diameter of a proximal segment of the left circumflex artery. Two side branches are used as landmark to facilitate consistent repeated measurements of the same segment throughout the procedure. Note the severe decrease in mean coronary diameter (−22%) after the maximal concentration of acetylcholine (Ach $10^{-6}$ M). ISDN = isosorbide dinitrate.

formed with a manual injection of 6–10 ml of iopamidol (Iopamiro 370, Schering, Berlin, Germany). A 5″ or 7″ field-of-view of the image intensifier was used. No changes of the position of the patient or of the X-ray gantry were performed throughout the procedure. The same angiographic view was maintained during the study, avoiding foreshortening or vessel superimposition of the arterial segments of interest. A previously validated [34] cine-film based off-line system (CAAS System, Pie Medical Data, Maastricht, The Netherlands) was used to measure the mean diameter over a 2–3 cm long proximal/mid and distal coronary segment, using easily visible side-branches as anatomical landmarks to allow the analysis of the same segments in the successive cineangiograms (Fig. 2). In 14 cases (48%) a second order arterial branch (diagonal, obtuse marginal, postero-lateral, right ventricular branch) was analyzed as distal segment. In the remaining cases (15, 52%) the distal segment of one of the three major coronary arteries was used. After automatic detection of the vessel centerline, the system applies a weighted first and second derivative function with predetermined continuity constraints to the brightness profile of each scan line perpendicular to the vessel centerline [35]. A user-defined reference diameter was measured at the site of the Doppler sample volume [36]. Cross-sectional area was calculated from the corresponding diameter assuming a circular arterial cross-section. Coronary flow was calculated as:

$$\text{Coronary flow (ml/min)} = \text{CSA}(\text{mm}^2)\,\frac{\text{Time-Averaged Peak Vel (cm/s)}}{2}\,0.6$$

where CSA is the arterial cross-sectional area at the site of the Doppler sample volume. Coronary flow resistance was calculated as:

$$\text{Cor. flow resistance (mmHg·min·ml}^{-1}\text{)} = \frac{\text{Mean aortic pressure (mm Hg)}}{\text{Coronary flow (ml/min)}}$$

*Statistical analysis*

The significance of the differences between flow velocity and cross-sectional area measurements and derived indexes in baseline conditions and after papaverine, acetylcholine and isosorbide dinitrate was tested using a two-tailed Student's t test for paired data. A two-tailed Student's t test for unpaired data was used to compare the diameter and flow changes observed in patients with different clinical angiographic characteristics. Linear regression analysis was used to correlate the changes observed in cross-sectional area and in coronary flow and in coronary flow resistance. Analysis of variance for repeated measurements was used to test the time-response and the variability of the flow velocity changes after infusion of acetylcholine. Statistical significance was defined as $p < 0.05$. All data were expressed as mean±SD.

## Results

The heart rate was stable throughout the study, with a significant increase in heart rate only after the bolus injection of isosorbide-dinitrate (Fig. 3A). In two cases during the maximal infusion of acetylcholine short lasting epysodes of Mobitz I atrio-ventricular block, not requiring ventricular pacing, were observed.

Aortic pressure was stable in baseline conditions and during the infusion of the different concentrations of acetylcholine. A slight but significant decrease was observed at the peak effect of the papaverine and isosorbide-dinitrate infusions ( − 7 and − 5%, respectively) (Fig. 3B).

*Flow velocity changes*

Table 1 reports the individual changes in blood flow velocity in the studied patients.

In Fig. 4 the changes of time-averaged peak blood flow velocity were expressed as a percent of the baseline velocity (baseline 2). A moderate decrease of blood flow velocity was observed between the first baseline measurement (beginning of the study) and the second/third baseline measurement (5 min after papaverine and after the maximal concentration of acetylcholine, respectively, $p < 0.05$). On the contrary, a large increase was observed after papaverine injection, with a peak velocity 2.8±0.83 times higher than in basal conditions (baseline 2). The lowest concentration of

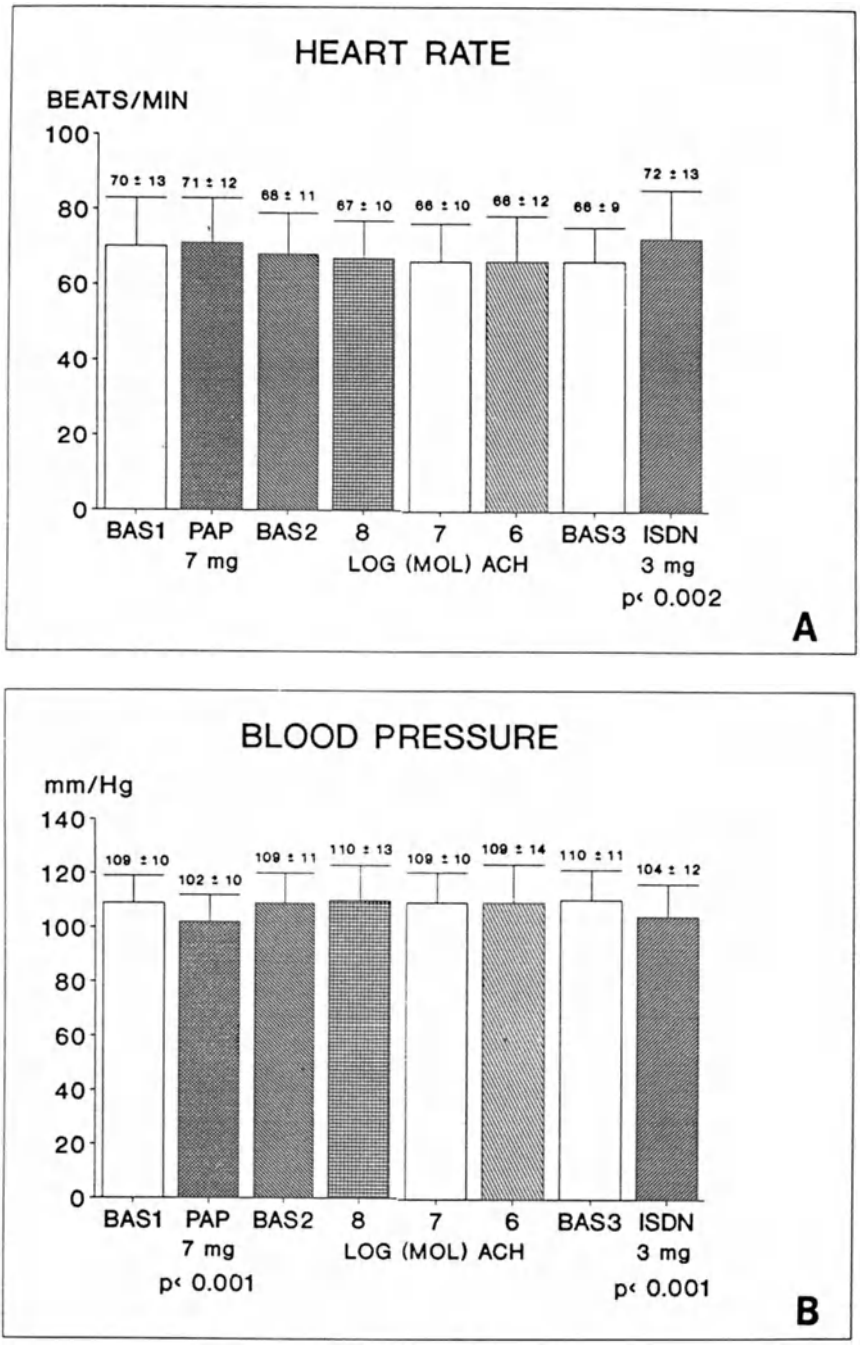


*Figure 3.* A) Heart rate and B) mean aortic blood pressure during the various phases of the study. ACH: acetylcholine; BAS: baseline; ISDN: isosorbide dinitrate.

*Table 1.* Clinical characteristics and flow velocity changes after papaverine and acetylcholine.

| Patient | Age yrs | Sex | Hypert. | Choles mmol/l | Vessel | Wall irreg. | BAS1 cm/s | PAV cm/s | BAS2 cm/s | Ach $10^{-8}$ cm/s | Ach $10^{-7}$ cm/s | Ach $10^{-6}$ cm/s | BAS3 cm/s | ISDN cm/s |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 70 | M | y | 5.5 | LAD | y | 22 | 44 | 22 | 21 | 18 | 20 | 21 | 30 |
| 2 | 63 | M | n | 5.7 | RCA | y | 20 | 48 | 19 | 16 | 22 | 33 | 22 | 35 |
| 3 | 68 | F | y | 7.3 | RCA | y | 19 | 40 | 20 | 20 | 21 | 32 | 24 | 22 |
| 4 | 58 | M | n | 4.9 | LCX | y | 33 | 60 | 26 | 29 | 24 | 50 | 26 | 24 |
| 5 | 49 | M | y | 5.8 | LCX | y | 44 | 79 | 26 | 25 | 25 | 23 | 23 | 28 |
| 6 | 59 | M | n | 6.5 | LCX | y | 32 | 89 | 22 | 29 | 30 | 49 | 25 | 33 |
| 7 | 50 | M | n | 6.4 | RCA | y | 11 | 41 | 14 | 19 | 19 | 26 | 15 | 24 |
| 8 | 53 | M | y | 5.6 | LCX | y | 23 | 70 | 21 | 23 | 35 | 53 | 23 | 65 |
| 9 | 48 | M | y | 7.2 | LAD | y | 17 | 39 | 17 | 22 | 41 | 66 | 20 | 32 |
| 10 | 53 | M | n | 5.5 | LAD | n | 38 | 56 | 32 | 29 | 30 | 32 | 26 | 42 |
| 11 | 66 | F | y | 7.7 | LCX | y | 27 | 65 | 20 | 19 | 20 | 37 | 16 | 26 |
| 12 | 52 | F | n | 7.4 | LCX | y | 25 | 80 | 19 | 19 | 35 | 44 | 17 | 25 |
| 13 | 59 | M | n | 6.6 | LCX | y | 22 | 52 | 24 | 26 | 28 | 46 | 24 | 38 |
| 14 | 42 | M | n | 5.2 | LCX | n | 33 | 53 | 24 | 24 | 23 | 24 | 22 | 36 |
| 15 | 54 | F | n | 5.9 | LCX | y | 28 | 71 | 28 | 28 | 27 | 43 | 28 | 43 |
| 16 | 45 | M | n | 7.1 | LCX | y | 42 | 120 | 39 | 39 | 41 | 65 | 39 | 66 |
| 17 | 45 | M | y | 6.1 | LAD | n | 27 | 77 | 25 | 25 | 32 | 48 | 26 | 29 |
| 18 | 44 | M | n | 7.7 | RCA | y | 32 | 68 | 23 | 21 | 22 | 67 | 23 | 43 |
| 19 | 67 | M | n | 5.8 | LAD | n | 27 | 70 | 17 | 19 | 25 | 31 | 19 | 22 |
| 20 | 67 | M | n | 6.9 | RCA | y | 25 | 66 | 27 | 27 | 36 | 72 | 30 | 39 |
| 21 | 71 | M | n | 4.7 | RCA | n | 25 | 57 | 21 | 19 | 34 | 69 | 23 | 23 |
| 22 | 45 | F | n | 7.0 | LAD | n | 36 | 90 | 55 | 40 | 35 | 120 | n.r. | n.r. |
| 23 | 46 | M | y | 6.8 | LAD | n | 23 | 44 | 21 | 16 | 24 | 17 | 17 | 18 |
| 24 | 58 | M | n | 5.4 | RCA | n | 26 | 66 | 24 | 20 | 20 | 18 | 21 | 30 |
| 25 | 66 | M | n | 4.9 | LCX | y | 15 | 52 | 11 | 14 | 42 | 89 | 17 | 26 |
| 26 | 69 | M | n | 5.4 | RCA | y | 28 | 65 | 28 | 28 | 27 | 29 | 25 | 40 |
| 27 | 65 | M | n | 5.9 | LCX | n | 21 | 34 | 15 | 15 | 22 | 39 | 21 | 24 |
| 28 | 54 | M | y | 5.3 | RCA | n | 12 | 43 | 9 | 19 | 9 | 15 | 9 | 21 |
| 29 | 56 | M | n | 7.1 | LCX | y | 32 | 65 | 23 | 17 | 19 | 18 | 23 | 19 |
| Mean | 57 | | | 6.2 | | | 26 | 62** | 23‡ | 23 | 27* | 44** | 22‡‡ | 32** |
| ±SD | 9 | | | 0.9 | | | 8 | 18 | 8 | 7 | 8 | 24 | 5 | 12 |

‡: $p < 0.02$ vs BAS1; ‡‡: $p < 0.005$ vs BAS1; *: $p < 0.05$ vs BAS2; **: $p < 0.002$ vs BAS2. Ach = acetylcholine; BAS = baseline; Choles = cholesterol;

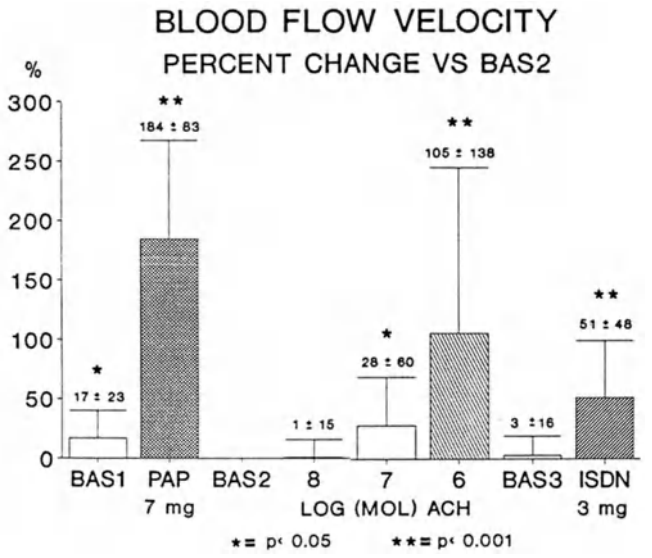


*Figure 4.* Flow velocity changes expressed as a percent of the baseline flow velocity. Legends as in Fig. 3.

acetylcholine did not induce significant changes in blood flow velocity. A 28±60% increase was observed after 5 min of infusion of acetylcholine $10^{-7}$ M ($p < 0.05$). At the end of the highest acetylcholine concentration ($10^{-6}$ M) a more than twofold increase in flow velocity was observed ( + 105±138%, $p < 0.001$).

*Time-response of the flow velocity change and flow velocity variability during acetylcholine infusion*

In Fig. 5 the time-response of the flow velocity changes during the infusion of the maximal concentration of acetylcholine is reported for the entire group (Fig. 5–A) and for all the individual cases. A significant increase of flow velocity was observed within 30" from the beginning of the infusion. Afterwards, during the remaining infusion period, no significant flow velocity changes were observed in the overall study population. However, if the individual response is considered, only in 10 patients (Fig. 5–B) a relatively stable flow velocity was observed during infusion. In the remaining patients, despite the constant rate of infusion and the stable hemodynamic conditions, a large variability was observed, with cases showing a progressive increase or decrease during the final phase of infusion (Fig. 5–C and D, respectively) or a bell-shaped or biphasic response (Fig. 5–E and F, respectively; example

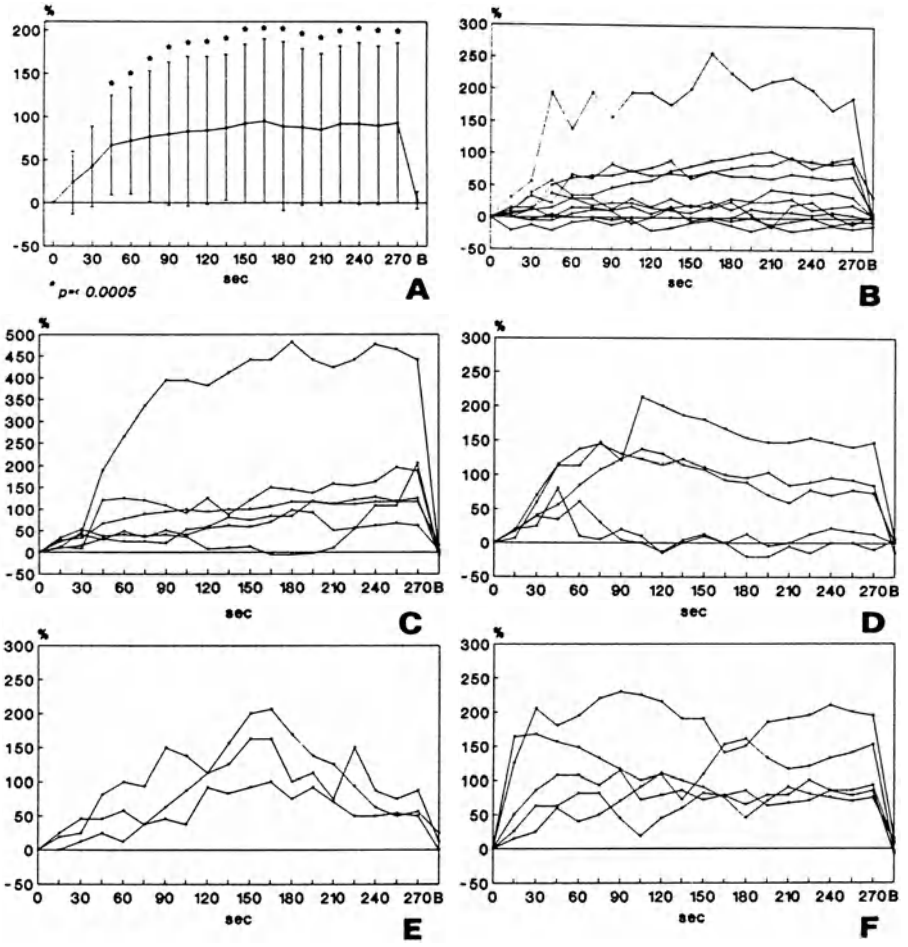


*Figure 5.* Temporal changes in flow velocity during infusion of the highest concentration of acetylcholine expressed as a percent of the value before infusion (time 0). A: mean±standard deviation; B: 10 individual curves showing a relatively stable flow velocity; C and D: 6 and 5 patients showing, respectively, a progressive increase and a progressive decrease from the beginning to the end of the infusion; E-F: 3 and 5 cases with a bell-shaped or a biphasic response during infusion. B: baseline 3 (5 min after the end of the acetylcholine infusion).

in Fig. 6). The variability was more evident in the patients with a large velocity increase after acetylcholine.

*Coronary artery cross-sectional area*

Table 2 indicates the individual measurements of the mean cross-sectional area of the proximal and distal coronary segments. In Fig. 7 the changes in

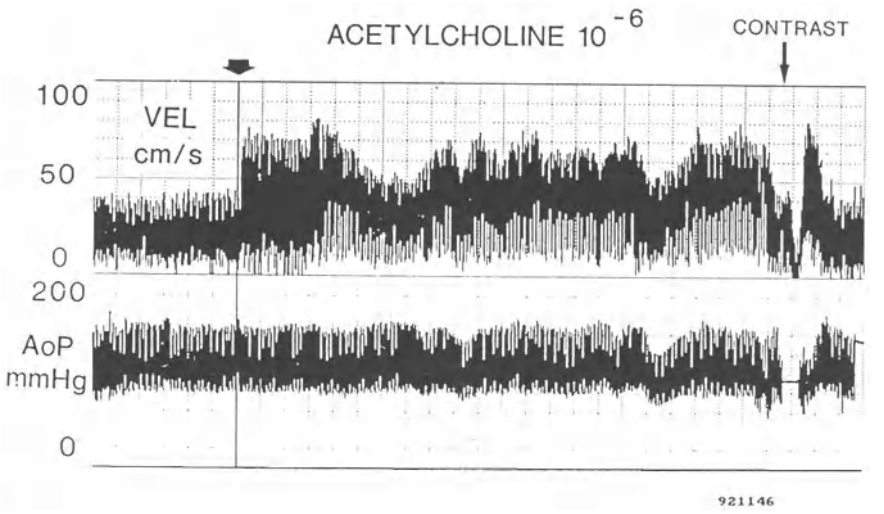


*Figure 6.* Continuous flow velocity (upper panel, VEL) and aortic pressure (lower panel, AoP) recorded continuously during the infusion of acetylcholine ($10^{-6}$ M). Note the rapid increase in flow velocity after the beginning of inflation (arrow), followed by a moderate decrease in spite of a stable aortic pressure. Flow velocity variations are present also in the following minutes of infusion, before contrast injection (5 min).

cross-sectional area after the three increasing concentrations of acetylcholine and the bolus of isosorbide dinitrate are expressed as a percent of the basal cross-sectional area. The injection of the two lowest concentrations of acetylcholine induced a moderate but significant reduction of the mean cross-sectional area both in the proximal segment and in the distal segment. A larger decrease was observed after the highest concentration of acetylcholine ($-24 \pm 20\%$ and $-22 \pm 20\%$ of the mean cross-sectional area of the proximal and distal coronary segments, respectively, $p < 0.00001$). At this concentration almost all the studied arteries showed a variable degree of vasoconstriction (26/29 arteries, 90%), (Fig. 8-A). In no cases a $> 75\%$ mean cross-sectional area reduction was observed. At the end of the infusion of the highest concentration of acetylcholine, focal vasoconstriction of the more distal branches of the studied artery was observed in 8 patients. In these cases also quantitative angiography showed a more severe vasoconstriction ($-32 \pm 25\%$ vs $-18 \pm 22\%$ cross-sectional area reduction of the analyzed segments with and without focal arterial spasm, respectively, NS).

The presence of a preserved vasodilatory capacity of the studied artery was confirmed by the diffuse cross-sectional area increase after bolus injection of a direct smooth muscle vasodilator such as isosorbide dinitrate ($+16 \pm 26\%$ and $+18 \pm 26\%$ cross-sectional area increase vs baseline for the proximal and distal coronary segments, respectively, $p < 0.002$).

*Table 2.* Quantitative angiographic changes after acetylcholine infusion.

| Patient | Mean diameter proximal segment (mm) | | | | | Mean diameter distal segment (mm) | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | BAS | Ach $10^{-8}$ | Ach $10^{-7}$ | Ach $10^{-6}$ | ISDN | BAS | Ach $10^{-8}$ | Ach $10^{-7}$ | Ach $10^{-6}$ | ISDN |
| 1 | 1.89 | 1.74 | 1.65 | 1.58 | 1.84 | 1.24 | 1.30 | 1.20 | 1.14 | 1.46 |
| 2 | 2.82 | 2.82 | 2.50 | 2.36 | 2.87 | 2.87 | 2.40 | 2.59 | 2.21 | 2.69 |
| 3 | 2.36 | 2.33 | 2.67 | 2.35 | 3.05 | 2.74 | 2.71 | 2.57 | 2.35 | 3.02 |
| 4 | 2.41 | 2.39 | 2.49 | 2.30 | 2.79 | 1.78 | 1.82 | 1.69 | 1.60 | 1.94 |
| 5 | 2.48 | 2.09 | 2.15 | 1.99 | 2.60 | 1.74 | 1.50 | 1.34 | 1.36 | 1.8 |
| 6 | 2.87 | 2.19 | 2.12 | 2.22 | 2.86 | 2.27 | 1.86 | 1 66 | 1.83 | 2.42 |
| 7 | 4.00 | 4.08 | 4.13 | 4.28 | 4.21 | 2.23 | 1.95 | 1.89 | 1.92 | 2.06 |
| 8 | 2.75 | 2.57 | 2.73 | 2.60 | 3.16 | 1.58 | 1.55 | 1.40 | 1.57 | 1.95 |
| 9 | 1.48 | 1.28 | 1.41 | 1.15 | 1.54 | 1.17 | 0.97 | 1.12 | 1.10 | 1.44 |
| 10 | 1.67 | 1.42 | 1.52 | 1.52 | 1.92 | 1.32 | 1.30 | 1.37 | 1.26 | 1.67 |
| 11 | 3.00 | 2.98 | 2.85 | 2.62 | 3.06 | 1.40 | 1.42 | 1.39 | 1.21 | 1.47 |
| 12 | 1.66 | 1.62 | 1.62 | 1.59 | 1.82 | 1.48 | 1.39 | 1.33 | 1.31 | 1.43 |
| 13 | 2.30 | n.a. | 1.97 | 1.38 | 2.02 | 2.15 | n.a. | 1.66 | 1.05 | 1.8 |
| 14 | 2.91 | 2.90 | 3.00 | 2.85 | 2.90 | 1.66 | 1.66 | 1.82 | 1.77 | 1.67 |
| 15 | 3.20 | 3.18 | 3.15 | 2.96 | 3.12 | 1.50 | 1.37 | 1.28 | 0.98 | 1.36 |
| 16 | 3.11 | 2.77 | 2.59 | 2.43 | 3.41 | 1.42 | 1.21 | 1.29 | 1.32 | 1.71 |
| 17 | 2.17 | 1.91 | 1.90 | 1.74 | 1.94 | 1.99 | 1.78 | 1.82 | n.a. | 1.77 |
| 18 | 2.69 | 2.51 | 2.54 | 2.41 | 2.96 | 1.33 | 1.21 | 1.26 | 1.40 | 1.52 |
| 19 | 2.59 | 2.28 | 2.23 | 2.07 | 2.62 | 1.60 | 1.32 | 1.31 | 1.30 | 1.76 |
| 20 | 3.13 | 2.52 | 2.72 | 2.42 | 3.16 | 1.78 | 1.57 | 1.67 | 1.69 | 1.83 |
| 21 | 2.96 | 3.27 | 3.14 | 3.15 | 3.57 | 1.71 | 1.73 | 1.54 | 1.60 | 2.08 |
| 22 | 1.52 | 1.43 | 1.62 | 1.49 | 2.21 | 1.36 | 1.46 | 1.42 | 1.09 | 1.99 |
| 23 | 2.22 | 2.24 | 2.06 | 2.12 | 2.26 | 1.76 | 1.76 | 1.74 | 1.88 | 2.12 |
| 24 | 3.03 | 2.70 | 2.91 | 2.41 | 3.23 | 2.35 | 2.23 | 2.35 | 2.31 | 2.62 |
| 25 | 2.28 | 1.90 | 1.77 | 1.39 | 2.37 | 1.66 | 1.55 | 1.48 | 1.18 | 1.94 |
| 26 | 2.72 | 2.72 | 2.71 | 2.41 | 3.20 | 1.74 | 1.74 | 1.67 | 1.42 | 2.11 |
| 27 | 2.47 | 2.40 | 1.96 | 1.91 | 2.63 | 1.11 | 1.17 | 0.95 | 1.09 | 1.23 |
| 28 | 3.16 | 3.22 | 3.28 | 3.28 | 3.09 | 1.90 | 1.77 | 1.73 | 1.67 | 1.75 |
| 29 | 2.47 | 2.26 | 2.18 | 1.81 | 2.68 | 1.46 | 1.31 | 1.29 | 1.29 | 1.56 |
| Mean | 2.56 | 2.42* | 2.39* | 2.23*** | 2.73** | 1.73 | 1.61* | 1.58** | 1.50*** | 1.85* |
| ±SD | 0.56 | 0.62 | 0.62 | 0.66 | 0.60 | 0.43 | 0.38 | 0.39 | 0.38 | 0.42 |

*: $p < 0.002$ vs baseline; **: $p < 0.0005$ vs baseline; ***: $p < 0.00001$ vs baseline; Ach = acetylcholine; BAS = baseline; ISDN = isosorbide dinitrate.

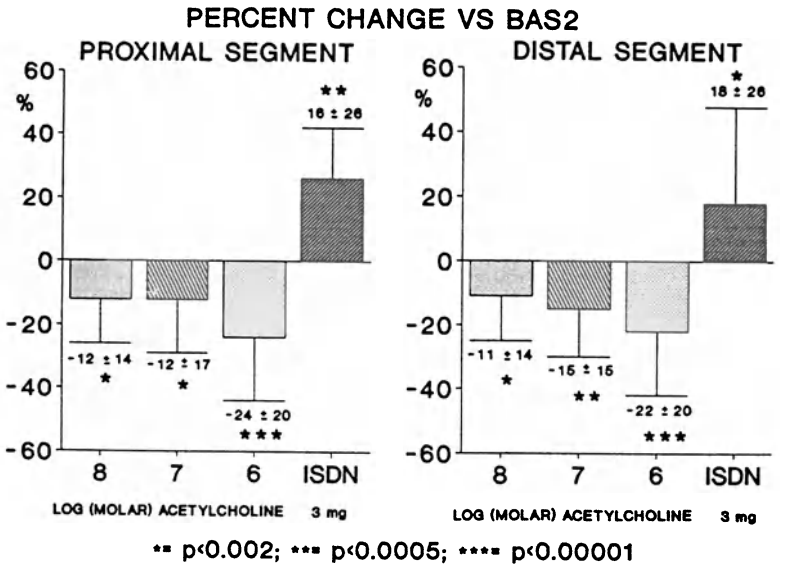


*Figure 7.* Mean cross-sectional area changes in the proximal and distal segment expressed as a percent of the baseline cross-sectional area. Legends as in Fig. 3.

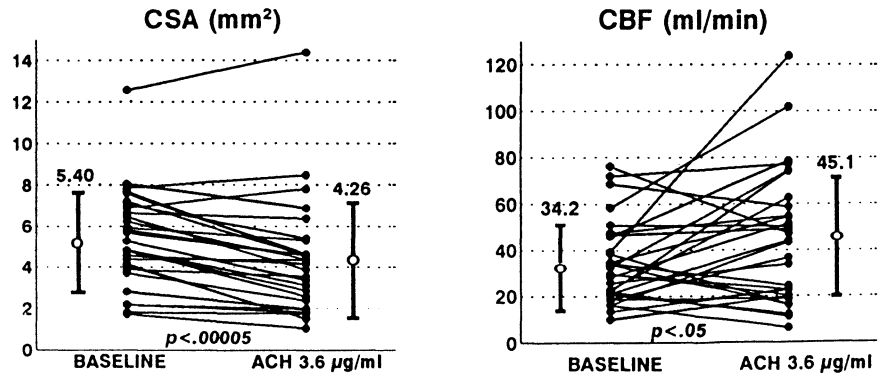


*Figure 8.* Cross sectional area (CSA) and coronary blood flow (CBF) in baseline conditions (baseline 2) and after infusion of the maximal concentration of acetylcholine (Ach $10^{-6}$ M). Note the almost uniform decrease in cross-sectional area and the large variability of the individual flow change.

## *Coronary flow changes*

A significant increase of coronary flow was observed only after the maximal concentration of acetylcholine (+43 ± 83%, $p < 0.001$). The large variability of the individual measurements for the highest concentrations of acetylcho-

line is shown in Fig. 8-B. Note that at the peak concentration of acetylcholine 10 patients showed a decrease of absolute flow and increase in coronary resistance.

*Correlation of the observed results with the clinical-angiographic characteristics*

The flow velocity, cross-sectional area and flow changes after acetylcholine showed no correlation with age, sex, presence of systemic hypertension, total cholesterol, HDL cholesterol, HDL cholesterol/total cholesterol ratio, plasma triglycerides, type of studied artery and basal coronary luminal diameter.

The presence of wall irregularities was associated with a larger decrease in luminal cross-sectional area ($-27 \pm 20\%$ change vs baseline in the 19 arteries with angiographically visible wall irregularities and $-16 \pm 20\%$ in the angiographically normal arteries). The difference, however, was not statistically significant. The arteries with wall irregularities showed also a smaller flow increase after the last concentration of acetylcholine ($+47 \pm 30\%$ vs $+68 \pm 56\%$ in the group with smooth arterial contours, NS).

A poor correlation was observed between flow velocity changes after acetylcholine and papaverine ($r^2 = 0.18$ for the maximal concentration of acetylcholine). Similarly, the percent increase of lumen diameter after isosorbide dinitrate was not correlated with the changes observed after acetylcholine infusion.

The flow changes and flow resistance changes after the maximal dose of acetylcholine infusion showed a poor correlation with the cross-sectional area changes observed in the proximal/distal coronary segments. Figure 9 shows the linear regression analysis performed using the cross-sectional area changes of the proximal segments. Also in the distal coronary segment analyzed a very poor correlation was observed, with a squared correlation coefficient of 0.01 and 0.05 for coronary flow and flow resistance.

## Discussion

Acetylcholine is the prototype and the most frequently used pharmacological stimulus with a primary endothelium-independent contractile action on the vascular smooth muscle cells and an opposite endothelium-mediated vasodilatory activity which is predominant in normal conditions and at physiologic concentrations [37, 38]. Acetylcholine was used in the in vitro experiments in which the role of intact endothelium in the regulation of vascular tone was established (1) and in the first in vivo study showing that acetylcholine induces severe vasospasm in human coronary arteries with significant stenoses [6]. The induction of an endothelium-dependent vasodilatation in canine femoral [39] and coronary [40] arteries after the application of acetylcholine

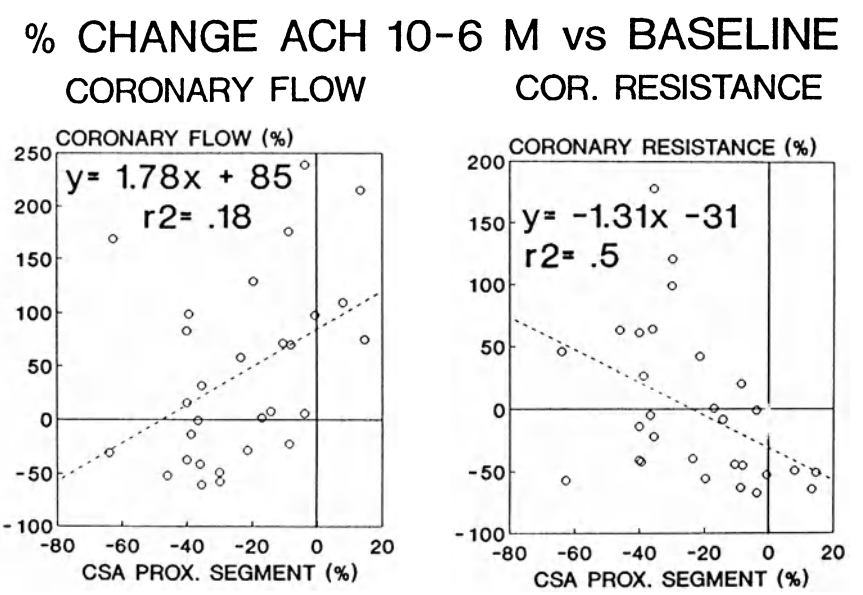


*Figure 9.* Linear regression analysis of the percent changes in mean cross-sectional area (CSA) of the proximal segment studied and of the percent changes of coronary flow and resistance. Note the poor correlation over the entire range of measurements.

on the arterial adventitia suggests a role of acetylcholine, the mediator of the parasympathetic stimulation, in the modulation of vascular tone. The circadian rhythm of the parasympathetic activity has been advocated to explain the higher incidence of acute coronary syndromes such as vasospastic angina and myocardial infarction in the early morning. Selective intracoronary infusion of acetylcholine elicited vascular responses comparable to those observed after serotonin [41], a substance that is released after platelet activation and may contribute to the development of myocardial ischemia in acute coronary syndromes [17, 42, 43].

In this study, concentrations and flow rate of acetylcholine were the same used in recent reports [14, 20, 23] in order to facilitate the comparison of the results. Papaverine and isosorbide dinitrate were infused selectively in doses sufficient to induce a maximal vasodilatation of the resistance and conductance coronary arteries with a limited systemic effect [44]. With these drugs, the presence of an aspecific impairment of vascular relaxation due to structural changes of the epicardial and resistance coronary vessels could be excluded.

*Cross-sectional area changes*

The arteries studied included both angiographically normal and minimally diseased arteries. In this latter group the severity of coronary vasoconstriction

was similar to that reported in two comparable series of patients by the group of Freiburg (−27% decrease in the present study vs −29% and −34% cross-sectional area decrease from baseline at the same concentration of acetylcholine) [16, 23]. The angiographically normal arteries showed a 16% decrease in cross-sectional area from baseline, similar to the 23% decrease reported by Vrints et al. [12] for normal segments of the left anterior descending coronary artery at this concentration. In the present study the arteries without angiographically visible lesions showed a less pronounced vasoconstriction after the maximal concentration of acetylcholine. No significant differences were present, however, between arteries with and without angiographically visible wall irregularities. A possible explanation is that the atherogenic factors that have already induced a severe symptomatic coronary stenosis in our study population can be sufficient to induce the development of a diffuse endothelial damage also in the absence of large atherosclerotic changes. An alternative explanation is that angiography is not sufficiently sensitive to detect initial atherosclerotic changes. Epicardial and intracoronary ultrasound imaging have shown that diffuse atherosclerotic changes are present in patients with coronary artery disease also in segments which have an angiographically normal lumen and smooth vascular contours [45–47]. Pathological reports have explained this phenomenon with the presence of an overall vascular enlargement able to preserve a normal vascular lumen despite large areas of wall encroachment [48]. In this study no patient showed a severe focal or diffuse spasm inducing a critical flow reduction and the development of symptoms and signs of myocardial ischemia. The characteristics of the studied population, including only patients with stable angina and, for the vast majority, single vessel coronary disease, may explain the different results observed in previous studies [7, 11, 22]. The absence of >75% cross-sectional area reduction from the basal measurement suggests that the impairment of flow after acetylcholine is not due to a critical vasoconstriction of the epicardial arteries. A flow limitation due to focal or diffuse vasoconstriction of small distal branches, not analyzable with quantitative angiography but visually detectable in 8 cases, is more difficult to be ruled out. In these patients, however, the flow changes after the maximal concentration of acetylcholine were similar to those observed in the remaining cases.

A diffuse vasoconstriction was present after the maximal concentration of acetylcholine in 90% of the patients studied (26/29). A progressive dose-response was observed with increasing concentrations of acetylcholine. The proximal and distal segments showed a similar decrease of lumen dimension. A moderate difference between proximal and distal segments was observed only after the intermediate concentration of acetylcholine (cross-sectional area decrease from baseline −12±17% in the proximal segment and −15±15% in the distal segment, $p < 0.05$). At the peak concentration of acetylcholine, however, no differences were observed between proximal and distal arterial segments. Vrints et al. [12] have confirmed the presence of similar changes of proximal and distal segments of the left anterior descending coronary artery. A more significant vasoconstriction after acetylcholine

of the distal coronary segments was reported by Rande' et al. [49] in a very limited patient population (5 cases). The variability of the response to acetylcholine of the proximal and distal segments observed in individual patients can explain this difference and probably reflects a different severity of atherosclerotic involvement of the two segments.

*Coronary flow and flow velocity changes*

Intracoronary Doppler was used to assess coronary flow velocity in this study. Technical improvements have recently increased the reliability of this technique for the assessment of coronary flow velocity. In particular the large Doppler sample volume and the use of peak blood flow velocity, allowed by the spectral analysis of the signal, avoid changes of the measured velocity in response to minor variations of the position of the Doppler probe inside the artery. It was so possible to minimize manipulation and repositioning of the Doppler probe and to avoid to exclude patients because of poor quality of the Doppler recordings. The accuracy in the calculation of absolute coronary flow from the corresponding mean flow velocity and cross-sectional area, however, is still limited by the difficulty of an exact measurement of the mean velocity and by the impossibility to acquire simultaneously the two measurements. In the presence of rapid changes of flow and cross-sectional area such as after the injection of a bolus of nitrates, papaverine or adenosine, the delay between flow velocity measurement and cineangiogram may result in a significant inaccuracy of the flow measurements. In this study no cineangiograms were performed at the maximal effect of the injection of papaverine. For this reason, absolute coronary flow after papaverine could not be calculated. The presence of a larger cross-sectional area at the peak effect of papaverine than in baseline conditions may explain the relatively low coronary flow reserve ($2.8 \pm 0.8$) observed in this study. Based on previously reported angiographic measurements after papaverine, a 15–20% underestimation of the true flow reserve is expected [50, 51]. In this study, however, papaverine was used only to confirm a normal response of the coronary resistance vessels to a direct smooth muscle vasodilator to exclude structural alterations of the microvasculature as the factor limiting the flow increase.

The lack of simultaneous flow velocity/cross-sectional area measurements is a serious limitation also to explain the changes observed during infusion of acetylcholine. Variations of flow velocity during infusion of acetylcholine have not been previously reported. With the previous generation of Doppler probes the Doppler signal was highly dependent from minor changes in the position of the the Doppler sample volume [52]. These changes, therefore, could have been misinterpreted as artifacts due to an unstable position of the catheter in the artery. The previously described characteristics of the Doppler guidewire and the modalities of signal analysis (fast Fourier transform, continuous automatic measurement of peak flow velocity) are ideal conditions for the assessment of these moderate flow velocity variations. Two

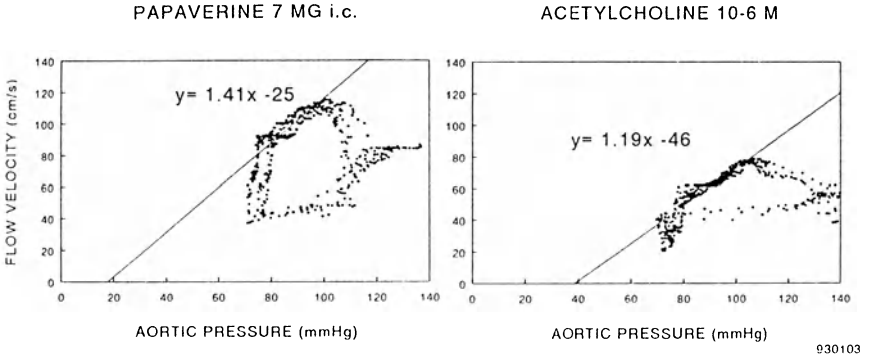


*Figure 10.* Pressure-flow velocity loop of 4 consecutive beats at the peak effect of the injection of papaverine and after 5 min of infusion of the highest concentration of acetylcholine. The regression line has been calculated from the mid-diastolic data-points. Note the steeper slope of the pressure-velocity relation after papaverine and the lower pressure-intercept.

causes can be suggested for these flow velocity variations: a true change in flow as the result of a variable vasodilatation of the resistance vessels over time, or a change of the cross-sectional area at the site of the Doppler sample volume (flow velocity changes but coronary flow remains the same). In the absence of a simultaneous continuous assessment of lumen cross-sectional area the mechanism of these flow velocity changes remains speculative. In the near future the combination of intravascular ultrasound imaging and Doppler may allow a continuous assessment of coronary cross-sectional area and flow velocity and facilitate the assessment of the dynamics of the flow/area changes after acute pharmacological interventions [53].

In this study the flow velocity changes after acetylcholine have been expressed as a percent change from baseline and not as a percent of the maximal flow increase (after papaverine) because a moderate (−7%) but significant aortic pressure reduction was observed at the peak effect of papaverine. A constant pressure is a prerequisite for a reliable comparison of a flow measured in autoregulatory conditions and during maximal vasodilatation [54]. Recently, the slope of the instantaneous hyperemic diastolic pressure-flow relation has been used in animal experiments as an index of coronary conductance and has been shown to be independent from changes in aortic pressure, heart rate and cardiac contractility [55, 56]. The instantaneous hyperemic diastolic pressure-flow velocity relation can be reproducibly assessed also in humans [57, 58]. The possibility to measure an index of coronary conductance independent from the hemodynamic conditions at the time of assessment during different pharmacologic interventions and during maximal vasodilatation is a of great potential interest (Fig. 10). This approach, however, still requires a more extensive clinical validation.

Experimental data have demonstrated that atherosclerotic animals show

an abnormal endothelium-dependent vasodilatation of the coronary resistance arteries, despite the absence of structural atherosclerotic lesions [24]. The comparison of the flow response to acetylcholine in patients with coronary artery disease and in control subjects has confirmed an impaired flow increase in the coronary patients, despite the absence of significant lesions of the epicardial coronary arteries [23]. In this study a large variability of the flow changes was observed after the highest doses of acetylcholine. A dose dependent vasodilatation after acetylcholine was present in most cases, with flow increase up to 3 times the baseline flow. In 10 patients, however, a flow decrease was observed after the maximal concentration of acetylcholine. The mean flow increase from baseline was $+44 \pm 24\%$ at the maximal concentration of acetylcholine, an increase much lower than the flow increase observed in normal controls at the same acetylcholine concentration [23, 59]. No clinical or angiographic predictors of these large individual differences could be observed.

A reduction of the endothelium-dependent relaxation is present in animals chronically maintained at an atherogenic diet with an high content of cholesterol [60, 61]. In hypercholesterolemic patients without angiographic evidence of coronary artery disease, an impaired endothelium-mediated vasodilatation of the epicardial coronary arteries and of the resistance coronary vessels have been demonstrated [16]. Thirteen of the study patients had a total cholesterol level $\geq 6.4$ mmol/l (250 mg/dl). This group, however, showed no significant differences in terms of flow increase and vascular diameter changes after acetylcholine. The importance of the relative amount of HDL and LDL cholesterol has recently been reported to correlate more closely than total cholesterol with the degree of impairment of the endothelium-mediated vasodilatation [62]. In the studied group, however, also the use of the HDL/total cholesterol ratio did not identify a subset of patients with a different response to acetylcholine.

*Correlation of coronary area/flow changes after acetylcholine*

In this study mean arterial cross-sectional area of the epicardial arteries and coronary flow have been considered as independent indices of response of conductance and resistance coronary vessels. This assumption has three potential limitations: the possibility that a flow-limiting vasoconstriction occurs in an epicardial artery; the development of a vasodilatation of the epicardial arteries secondary to the increase of flow; the use of a cross-sectional area measured along the analyzed segment to calculate coronary flow. In spite of all these potential reasons for interdependance, the flow or flow resistance changes after the maximal concentration of acetylcholine showed only a poor correlation with the corresponding cross-sectional area changes. The discrepancy between flow and cross-sectional area reflects a different response of the conductance and resistance arteries to acetylcholine. The large arteries are the preferential target of the atherosclerotic process.

At this level the presence of intimal thickening may constitute a barrier to the diffusion of nitric oxide from the endothelial cells to the muscular media [63]. A macrophagic infiltration or the presence of a lipidic component of the intimal plaque may also accelerate the degradation of nitric oxide and prevent its action on the underlying muscular layer [37]. The importance of these mechanisms in atherosclerotic human arteries is indirectly confirmed by the frequent development of focal vasoconstriction after acetylcholine. Myocardial perfusion is regulated predominantly by resistance arteries $< 200$ micron [64]. These arteries do not show signs of atherosclerotic involvement at histology, suggesting that biochemical or ultrastructural changes are the most likely mechanisms underlying the abnormal endothelium-dependent relaxation.

These observations have potential clinical implications. A prolonged treatment aimed at the regression of the atherosclerotic intimal changes may be required to restore an impaired endothelium-mediated response when the presence of an intimal barrier is the main operative mechanism [65]. On the contrary, acute pharmacologic interventions or a short lasting treatment may be sufficient to normalize the endothelial function when metabolic abnormalities are involved. The possibility to normalize the endothelial response in hypercholesterolemia with a short-term infusion of L-arginine has been shown in animal experiments [66] as well as in human coronary arteries [49, 67]. Similarly, different classes of drugs have shown the ability to restore a normal endothelium-mediated vascular reactivity in experimental animals [68–70].

## Conclusions

In angiographically normal or minimally diseased arteries of symptomatic patients with coronary artery disease, also very low doses of acetylcholine induced a significant coronary vasoconstriction of the epicardial coronary arteries. The resistance vessels showed a variable response, with a trend towards a moderate vasodilatation (flow increase in 2/3 of the patients after the highest concentration of acetylcholine). The presence of hypercholesterolemia or wall irregularities was not correlated with the diameter/flow changes after acetylcholine. The poor correlation observed between cross-sectional area and flow changes after acetylcholine suggests that different mechanisms induce impairment of endothelium-mediated vasodilatation in conductance and resistance coronary vessels.

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# 20. Angiographic evaluation of coronary bypass grafts vasomotion

CLAUDE HANET, ROBERT DION, and WILLIAM WIJNS

## Introduction

The internal mammary artery is considered the best available conduit for coronary artery bypass grafting. The high long-term patency rate of mammary artery grafts as opposed to saphenous vein grafts seems to result from favorable biologic properties that could protect this vessel against atherosclerosis. Recent studies have emphasized the role of endothelium in triggering or modulating mechanisms controlling the growth, metabolism and contractile status of smooth muscle cells. Endothelial cells produce several vasoconstrictor agents such as thromboxane and endothelin and vasodilators among which prostacyclin and endothelium-derived relaxing factor or nitric oxide. In addition to their effects on vasomotor tone, these agents influence platelet adhesion and aggregation that may be implicated in atherogenesis. Differences exist among different vessels in the amount of nitric oxide released in basal conditions, in the agents stimulating its production and in the sensitivity of vascular smooth muscle to that factor [1–4]. Similarly, various areas of the vascular system are different in their ability to produce prostacyclin [5].

The more prominent endothelium-dependent relaxation of vascular smooth muscle in mammary arteries when compared to saphenous veins has been demonstrated by several organ bath experiments evaluating the differential vasomotor response of arterial and venous grafts to vasoactive agents whose effect is modulated by the endothelium like acetylcholine, thrombin [1], histamine and serotonin [6]. Recent experimental data [7] showing similarities in endothelial control of vasomotor tone between rings of gastroepiploic and internal mammary arteries suggest that this concept of a protective role of the endothelium contributing to the higher long-term patency rate of mammary arteries is also applicable to gastroepiploic arteries. Major differences however exist between the conditions of these laboratory experiments on isolated vessel segments and those in which these vessels may be studied in vivo by quantitative angiography several months or years after their implantation as coronary bypass grafts. First, morphological [8,



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9] and functional [10–12] changes resulting both from surgical manipulations and from chronic adaptation to a different circulation and different local environmental factors are susceptible to affect the sensitivity and the reactivity of grafted vessels to vasoactive agents. Second, the basal level of circumferential tension which represents the starting point of any constrictor or dilator response differs in both types of experiments. In vitro, isolated vascular rings are studied after having been stretched and allowed to equilibrate at the optimal point of their length tension relation. In vivo, the basal level of circumferential tension of vascular smooth muscle is determined by the diameter of the vessel and transmural pressure. This basal level of tension to which the vascular smooth muscle is exposed in vivo may thus significantly differ from that of laboratory experiments. Third, the basal vasomotor tone is influenced by a large number of circulating neurohumoral agents and by vasoactive substances released locally in response to various stimuli like shear stress [13]. The magnitude of the changes in vessel diameter that may occur in vivo in response to interventions susceptible to modify the tone of contractile elements of the vessel wall can thus not be predicted from experimental studies performed in such controlled conditions.

This study was designed to compare in vivo the vasomotor response of chronically implanted internal mammary artery grafts, gastroepiploic artery grafts and saphenous vein grafts to pharmacological and physiological stimuli. Two pharmacological vasomotor stimuli have been studied: methylergometrine, a potent constrictor stimulus of coronary vessels [14] whose effect can be modulated by the endothelium and isosorbide dinitrate, a powerful endothelium-independent vasodilator agent. Pacing-induced tachycardia was used as a non-pharmacological stimulus to mimic the physiological increase in myocardial blood flow demand during exercise.

## Methods

### *Patients*

A total of fourty-nine patients (41 men, 8 women; mean age, 58 ± 6 years) were studied during cardiac catheterization, more than two days after interruption of all vasoactive medications. All patients had undergone coronary bypass surgery at least six months before the study and were either investigated in the context of postoperative functional and angiographic follow-up studies or referred for atypical chest pain. The characteristics of the patients have been reported previously [15–17]. In each case, one bypass graft was selected for the quantitative angiographic study. All grafts were angiographically smooth with a good runoff flow to the grafted arterial segments.

*Response to tachycardia*

The flow-induced vasomotor response to tachycardia was compared in 10 internal mammary artery and 7 saphenous vein grafts. Three angiograms were obtained at 3 min interval on 35-mm cinefilm, by manual injection of a nonionic contrast agent (Iohexol 350 mg/100 ml) through a 6F or 8F catheter. Baseline angiogram was obtained in sinus rhythm, in a projection selected to provide optimal view of the midportion of the selected graft near the center of the image intensifier field. One minute later, heart rate was increased by atrial pacing up to 135 beats/min for 2 min. When atrioventricular Wenckeback block developed, pacing rate was decreased until restoration of a 1/1 atrioventricular response and maintained below the Wenckeback point. No atropine was given in order not to influence vasomotion and blood flow. The second angiogram was obtained during the last seconds of the atrial pacing. Two minutes later, 1 mg of isosorbide dinitrate was injected directly into the graft and, 1 min later, the last angiogram was obtained.

*Response to ergometrine*

The vasomotor response to methylergometrine was studied in 14 internal mammary artery, 7 gastroepiploic artery and 11 saphenous vein grafts. The basal and the two subsequent angiograms were obtained on 35-mm cinefilm by manual injection of a nonionic contrast material (Iohexol). One minute after acquisition of the basal angiogram, 0.4 mg of methylergometrine was injected within the inferior vena cava and two minutes later, a second angiogram was obtained. Three minutes later, the last angiogram was obtained, 2 min after injection directly within the grafts of 1 mg of isosorbide dinitrate. In 16 cases, the selected angiographic projection allowed to include in the image intensifier field a segment of the grafted coronary artery (with saphenous vein grafts in 11 cases and with gastroepiploic artery grafts in 5 cases). Care was taken, in both protocols, to maintain the patient and the x-ray system in exactly the same position during the sequential angiographic studies.

*Data analysis*

The quantitative analysis of bypass and coronary angiograms was performed on the computer-based Cardiovascular Angiography Analysis System (CAAS, Pie Data Medical, Maastricht, The Netherlands) [18]. The mean luminal diameter of the same vascular segment, identified with the help of anatomic landmarks was measured by using automated contour detection algorithms, with reference to the measured size of the angiographic catheter. End-diastolic frames were selected for analysis. Changes in vessel diameter, expressed in absolute values and in percentage of basal diameter, were compared using a two-way analysis of variance for repeated measurements.

*Table 1.* Hemodynamic data.

| Group | Heart rate (beats/min) | | | Mean arterial pressure (mmHg) | | |
|---|---|---|---|---|---|---|
| | Control | Pacing | ISDN | Control | Pacing | ISDN |
| Internal mammary artery | 70 ± 13 | 129 ± 9* | 72 ± 14 | 88 ± 19 | 90 ± 18 | 86 ± 19 |
| Saphenous vein | 73 ± 16 | 129 ± 7* | 77 ± 8 | 96 ± 10 | 94 ± 15 | 91 ± 11 |

ISDN = isosorbide dinitrate; *$p < 0.0001$ vs control; all differences between groups are nonsignificant.

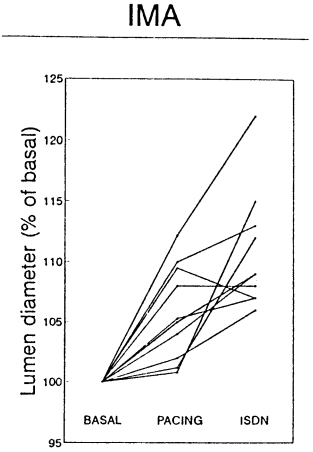


*Figure 1.* Individual changes in mean luminal diameter of internal mammary artery grafts (IMA) in response to atrial pacing and to intragraft infusion of isosorbide dinitrate (ISDN).

Differences between and within groups were assessed by unpaired and paired Student's *t* tests with Bonferroni correction.

## Results

### *Vasomotor response to tachycardia*

During atrial pacing, heart rate increased from 70 ± 13 to 129 ± 9 beats/min, the increase in heart rate exceeding 50% of basal sinus rhythm in all patients (Table 1). The individual changes in luminal diameter are represented in Figs 1 and 2. The vasomotor response of internal mammary artery grafts to pacing and to isosorbide dinitrate significantly ($p < 0.01$) differed from that of saphenous vein grafts. During tachycardia, a vasodilation of all internal mammary artery grafts was observed (mean: +6.4 ± 5.7% : $p < 0.005$ vs basal). In contrast, no consistent change in lumen diameter of saphenous

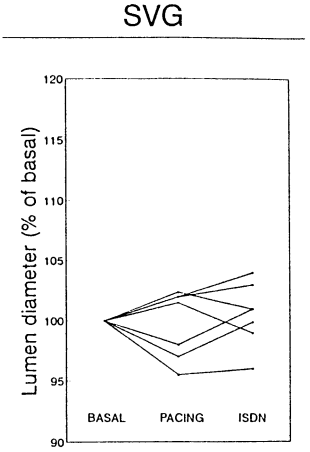


*Figure 2.* Individual changes in mean luminal diameter of saphenous vein grafts (SVG) in response to atrial pacing and to intragraft infusion of isosorbide dinitrate (ISDN).

vein grafts was observed, a slight increase in diameter being observed in 4 cases and a slight decrease in 3 cases (mean: $-0.3 \pm 3.0\%$). Infusion of isosorbide dinitrate resulted in a further dilation of internal mammary grafts, the gain in luminal diameter averaging $9.2 \pm 5.9\%$ of basal. No dilation of saphenous vein grafts was observed after isosorbide dinitrate ($+0.5 \pm 2.9\%$; NS).

*Vasomotor response to ergometrine*

Luminal diameter at baseline was significantly ($p < 0.001$) larger both in internal mammary artery ($3.27 \pm 0.42$ mm) and venous grafts ($3.26 \pm 0.71$ mm) than in grafted coronary arteries ($1.91 \pm 0.52$ mm) and gastroepiploic artery grafts ($1.63 \pm 0.32$ mm). After ergometrine infusion, a reduction in luminal diameter was observed in all grafted coronary arteries and gastroepiploic artery grafts (Fig. 3) and in all but one saphenous vein grafts. The vasoconstriction induced by ergometrine averaged $8.9 \pm 6.9\%$ ($p < 0.0005$) for grafted coronary arteries, $18.0 \pm 4.6\%$ ($p < 0.005$) for gastroepiploic artery grafts and $6.9 \pm 7.4\%$ of basal diameter ($p < 0.01$) for saphenous vein grafts. In contrast, no consistent change in the diameter of internal mammary artery grafts occurred after methylergometrine (mean reduction: $0.3 \pm 5.1\%$; NS), a dilation being observed in 7 of the 14 arterial grafts. Intragraft infusion of isosorbide dinitrate was followed by a dilation of all grafted coronary arteries and gastroepiploic artery grafts (up to $116.1 \pm 9.3$ and to $120.1 \pm 11.1\%$ of basal diameter; $p < 0.001$ and $p < 0.005$ respectively). The diameter of internal mammary artery grafts increased beyond basal values in 13 patients and to basal value in one patient (mean

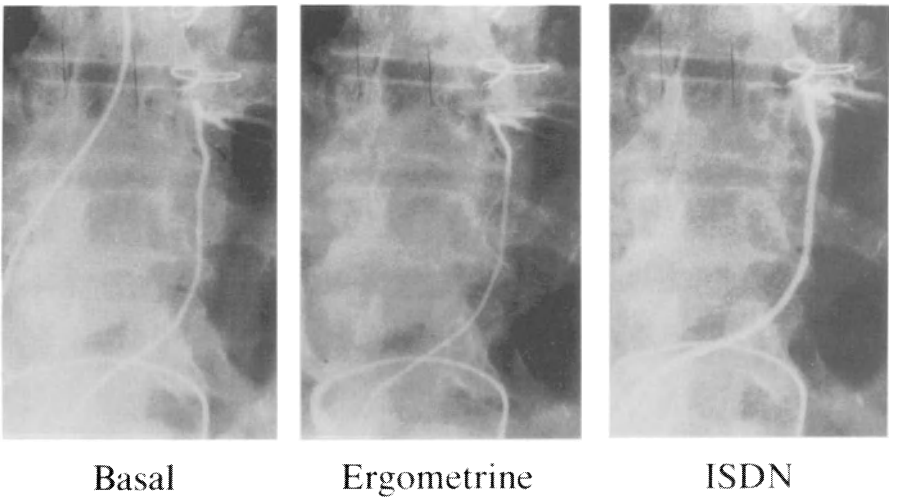


*Figure 3.* Angiograms of a gastroepiploic artery graft implanted to the distal right coronary artery in basal conditions, after intravenous ergometrine and after intragraft infusion of isosorbide dinitrate (ISDN).

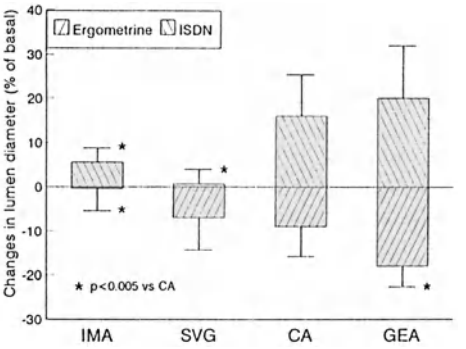


*Figure 4.* Changes in mean luminal diameter (mean ± SD) of internal mammary artery grafts (IMA), saphenous vein grafts (SVG), grafted coronary arteries (CA) and gastroepiploic artery grafts (GEA) in percent of basal diameter after intravenous injection of methylergometrine and after intragraft infusion of isosorbide dinitrate (ISDN).

increase : 5.5 ± 3.3% of basal diameter ; $p < 0.001$) while that of saphenous vein grafts returned to values within 5% above (6 patients) or below (5 patients) basal diameter (mean increase : 0.7 ± 3.1%; NS). The magnitude of vasomotor responses to ergometrine and nitrates of coronary arteries and bypass grafts is compared in Fig. 4. The constrictor responses to ergometrine of saphenous vein grafts and grafted coronary arteries were similar although the response of gastroepiploic grafts and internal mammary grafts were

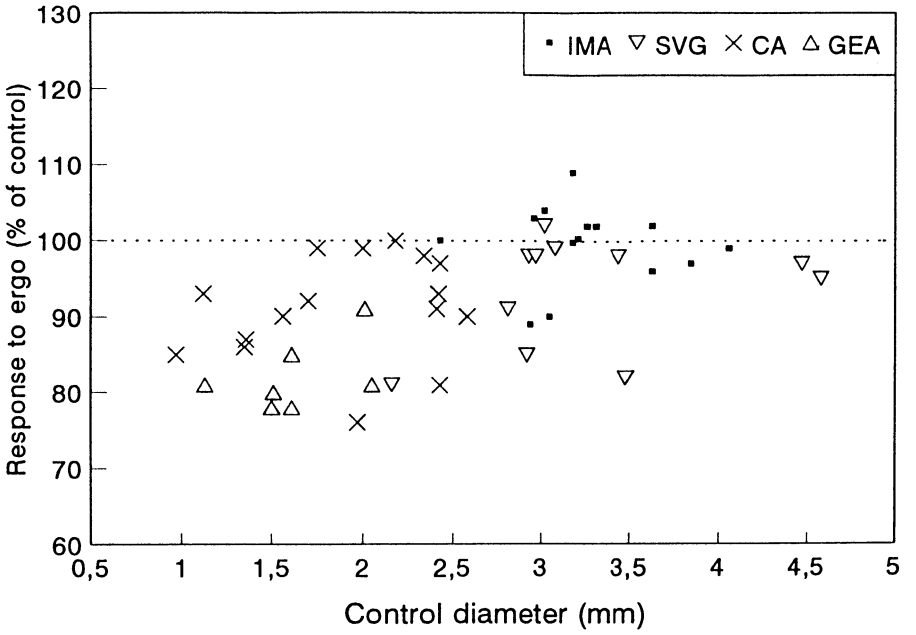


*Figure 5.* Changes in luminal diameter of internal mammary artery grafts (IMA), saphenous vein grafts (SVG), grafted coronary arteries (CA) and gastroepiploic artery grafts (GEA) in response to intravenous injection of methylergometrine (ergo) plotted against control diameter.

respectively larger ($p < 0.005$) and smaller ($p < 0.001$) than that of coronary arteries. The vasodilator response to isosorbide dinitrate was similar in gastroepiploic and coronary arteries, but significantly smaller in mammary arteries ($p < 0.002$ vs coronary arteries) and in saphenous vein grafts ($p < 0.001$ vs coronary arteries and $p < 0.01$ vs mammary grafts).

The relationships between basal diameter and the response to methylergometrine and nitrates of coronary arteries and bypass grafts are illustrated in Figs 5 and 6. Although an inverse correlation is observed between vasomotor response and vessel size when all types of vessels are considered together, such a correlation is not present for each type of vessel considered individually.

## Discussion

These results demonstrate that internal mammary arteries, gastroepiploic arteries and saphenous veins are capable of vasomotion, in vivo, several months after their implantation as coronary bypass grafts. Major differences however exist between grafts in the responsiveness to vasoactive stimuli.

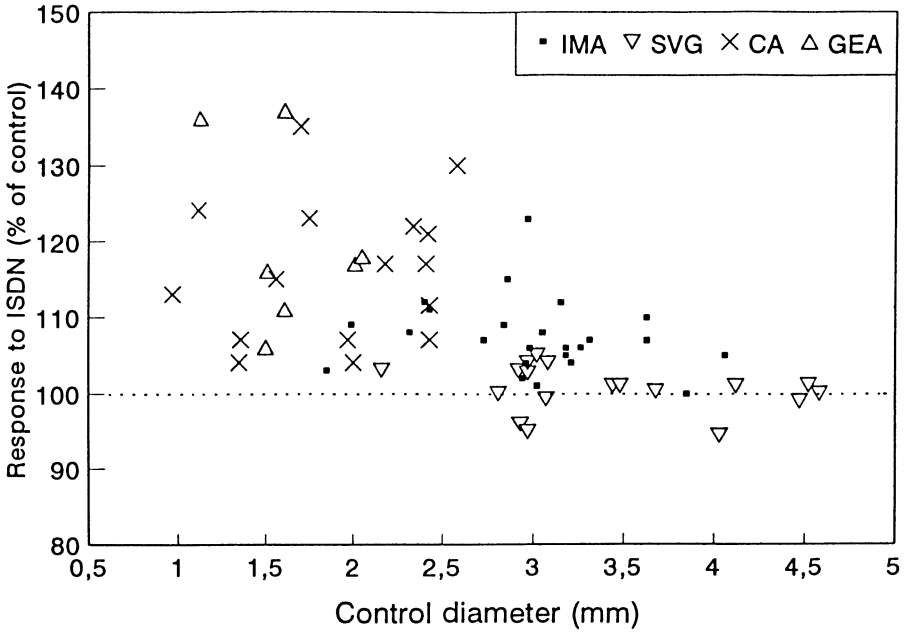


*Figure 6.* Changes in luminal diameter of internal mammary artery grafts (IMA), saphenous vein grafts (SVG), grafted coronary arteries (CA) and gastroepiploic artery grafts (GEA) in response to intragraft infusion of isosorbide dinitrate (ISDN) plotted against control diameter. Arterial and venous grafts previously exposed to ergometrine and to pacing have been pooled in this figure.

*Response to methylergometrine of arterial and venous grafts*

Although internal mammary artery grafts appear unresponsive to the vasoconstrictor effects of ergometrine but dilate in response to nitrates, gastroepiploic artery grafts are responsive both to ergometrine and to isosorbide dinitrate, and saphenous vein grafts constrict after ergometrine but do not dilate beyond basal diameter after local infusion of nitrates. Moreover, if the magnitude of the constrictor response to methylergometrine is similar in venous grafts and in grafted coronary arteries, the response of gastroepiploic artery grafts is greater than that of grafted coronary arteries and of other types of grafts.

Ergot alkaloids cause contraction of the smooth muscle mainly by activation of serotonergic receptors [19]. Angiographic studies have demonstrated that the intravenous infusion of the two structurally related alkaloids ergonovine and ergometrine was followed by a significant reduction in coronary artery diameter [14, 20]. This response was observed in patients with and without coronary artery disease. The magnitude of the constrictor response of

grafted coronary arteries observed in our study is similar to that reported to occur in proximal coronary segments after intracoronary ergonovine [21]. In different animal models, the endothelium has been shown to exert an inhibitory action against ergonovine-induced [19] and ergometrine-induced [22] vasoconstriction. This endothelium-dependent inhibition of the constrictor effects of ergot alkaloids is mediated by the release of nitric oxide triggered by the activation of endothelial serotonergic receptors [19]. The net response of vascular smooth muscle to ergometrine is thus the result of direct constrictor effects and indirect endothelium-mediated dilator effects. The capacity of vascular endothelium to modulate the tone of the underlying smooth muscle and to influence the vasomotor response to endothelium-dependent vasodilator agents may depend on species and, within species, on the specific vascular bed [2–4]. Endothelial function may also be altered by several disease states including atherosclerosis [23]. Differences in endothelial function could explain the different vasomotor responses of various vessels to the same vasoactive agent. The absence of vasoconstriction of internal mammary artery grafts in response to methylergometrine could thus reflect a more effective role of the endothelium in preventing the constrictor effects of the drug.

In contrast to mammary arteries, the vasoconstriction of gastroepiploic arteries is larger, and that of saphenous vein grafts is almost as pronounced as that of grafted coronary arteries. This suggests that, unlike that of mammary artery grafts, the endothelium-dependent relaxant activity of these vessels is insufficient to override the direct constrictor effect of ergometrine. The constriction of saphenous vein grafts in response to ergometrine has additional implications in terms of mechanical behavior of the vascular smooth muscle. Such a response indeed shows that the vascular smooth muscle is sensitive to this pharmacologic constrictor stimulus, but also demonstrates that smooth muscle is able to actively influence the diameter of venous grafts implanted to the arterial circulation. Although spontaneous spasms of venous grafts have been occasionally described [24], no angiographic study had shown changes in lumen diameter of venous grafts in response to vasoactive stimuli. Saphenous vein grafts, when implanted to the arterial circulation are thus commonly considered as rigid conduits incapable of any vasomotion. This concept is supported by the results of morphologic studies that demonstrated important changes in the wall of saphenous vein when used as an aortocoronary conduit. These changes include conversion of the medial wall containing large numbers of smooth muscle cells to a wall composed predominantly of fibrous tissue [9]. In addition, experimental studies have reported a decrease in maximal contractile response of venous segments several weeks after grafting into the arterial circulation [10]. This attenuation of contractile function together with a lower vessel wall/lumen diameter ratio than in arteries of similar size could be expected to result in a less effective control of vessel diameter by the contractile elements of the vessel wall. Our observation however demonstrates that the force-generating capacity of the

media of saphenous vein grafts remains sufficient to actively influence the lumen diameter of the graft when exposed to arterial blood pressure.

*Response to pacing of arterial and venous grafts*

Animal studies have shown that increasing blood flow through conduit arteries results in a vasodilation that may be abolished by removal of the endothelium [25, 26]. This flow-induced vasodilation is mediated by the release from endothelial cells of a relaxing substance that has many characteristics of nitric oxide [22, 27]. In humans, an increase in blood flow induced by rapid atrial pacing is associated with vasodilation of angiographically smooth but not of atherosclerotic coronary arteries [28]. This flow-mediated vasodilation of normal epicardial coronary arteries may have important physiological implications for maximizing flow rates during increased myocardial oxygen demand [29].

This study demonstrates in vivo that internal mammary artery but not saphenous vein bypass grafts chronically implanted to coronary vessels dilate during tachycardia induced by atrial pacing. Although our data do not provide direct evidence that the release of nitric oxide by the endothelium is responsible for the vasodilation of mammary artery grafts observed during tachycardia, this response is likely to be the angiographic manifestation of the flow-induced endothelium-dependent vasodilation phenomenon demonstrated by animal studies. These results, together with those of the ergometrine protocol, would confirm that the endothelial function of mammary arteries is preserved more than six months after their implantation as coronary grafts. The same conclusion was reached by Werner et al. [30] who used intracoronary infusion of acetylcholine to test endothelial function 3 to 35 months after surgery. These authors reported a marked difference in the vasomotor response, measured by quantitative angiography, of mammary artery graft and adjacent coronary segments. The absence of constriction of mammary grafts, contrasting with the constrictor response of coronary segments was interpreted as the reflect of the preserved functional integrity of the endothelium.

Tachycardia and the resulting increase in myocardial blood flow demand indeed represent physiological stimuli of endothelium-mediated vasodilation. During exercise, the vasodilation of mammary artery grafts may substantially reduce resistances through the graft and minimize the pressure drop at high flow rates. This may have important functional implications when a long internal mammary artery graft is implanted to a large coronary vascular bed. In addition to these favorable consequences on the adaptation of resistances to blood flow demand, the functional integrity of the endothelium of internal mammary grafts is probably one major factor responsible for its superior long-term patency rate. Indeed, production of nitric oxide by the endothelium in response to various stimuli including increased blood flow may prevent the development and progression of atherosclerosis. Dilation of the

vessel in response to increased blood flow will minimize the increase in shear stress and turbulent flow that promote endothelial injury and atherosclerosis progression. Moreover, nitric oxide potently inhibits the adhesion and aggregation of platelets, particularly if released together with prostacyclin with which it acts synergistically, preventing thrombus formation [2]. Finally, an antiproliferative action of nitric oxide could prevent the hypertrophy of smooth muscle that takes place during the development of atherosclerosis [31].

The response of saphenous vein grafts to atrial pacing and to isosorbide dinitrate infusion significantly differs from the response of internal mammary artery grafts. In contrast to mammary artery grafts, saphenous vein grafts seem unsensitive both to the endothelium-dependent vasodilator influence of increased flow secondary to tachycardia and to the endothelium-independent vasodilator effect of isosorbide dinitrate. This is in accordance with a recent study that demonstrated the absence of changes in diameter of chronically implanted saphenous vein grafts in response to local infusion of acetylcholine and nitrates [32]. Given this absence of vasodilator reserve of saphenous vein grafts in control conditions, the lack of vasodilator response of venous grafts to atrial pacing provides no evidence about whether or not endothelial function of saphenous veins is preserved more than six months after implantation as coronary artery bypass grafts.

*Response to nitrates of arterial and venous grafts*

Organic nitrates like isosorbide dinitrate are potent dilators of arterial and venous smooth muscle. Their vasodilator activity follows conversion to nitric oxide in vascular smooth muscle cells and is independent of the presence of the endothelium. The increase in diameter of grafted coronary arteries observed in our patients after intragraft infusion of nitrates is similar to that reported after intracoronary infusion of nitroglycerin [33] or isosorbide dinitrate [34]. This vasodilation confirms the existence of a basal vasomotor tone in grafted coronary arteries. The magnitude of the increase in diameter in response to a same dose of isosorbide dinitrate, similar in gastroepiploic and coronary arteries, is however significantly lower in mammary arteries, and no dilation beyond control values is observed in saphenous vein grafts. Nitrates however completely reversed the constrictor effects of methylergometrine, which demonstrates that venous smooth muscle is sensitive to the relaxant effect of isosorbide dinitrate infused locally. The absence of dilator response to nitrates of chronically implanted saphenous vein grafts is also observed in the pacing protocol, where no constrictor agents had been previously infused. Thus, this absence of dilation of venous grafts seems to reflect their inability to dilate beyond basal diameter rather than the balance of equipotent constrictor and dilator influences of ergometrine and nitrates.

Previous quantitative angiographic studies [14, 21] have shown a significant negative correlation between coronary size and responsiveness to dilator and

constrictor stimuli. Small and medium vessels appeared considerably more responsive than large epicardial vessels. In our patients, the magnitude of the vasomotor response to ergometrine and to nitrates (Figs 5 and 6) correlated with basal vessel diameter when all types of vessels were considered together. However, such a correlation was not observed when arterial grafts, venous grafts or grafted coronary artery segments were analyzed separately. This lack of significant correlation could result from the small size of each subgroup and from the relatively narrow range of luminal diameters in these subgroups. However, the analysis of the individual data reveals that differences in responsiveness between grafts remains evident when grafts of similar size are compared.

The mechanical properties of blood vessels are dependent on several factors including the relative amount and the contractile properties of smooth muscle cells, passive properties of other cellular components and of the extracellular connective tissue matrix, the anatomical arrangement of these various elements into a complex tissue and the loading conditions to which the contractile and elastic components are exposed in the conditions of the study. Structural and functional heterogeneity between vessels could thus explain important differences in the magnitude of changes in vessel diameter resulting from contraction or relaxation of their contractile elements for a given transmural pressure. Although it is unlikely that methylergometrine fully activated and that isosorbide dinitrate fully inactivated the contractile elements of the vessel wall, the larger vasomotor range observed in this study in coronary and gastroepiploic arteries that in other types of grafts in response to vasoactive stimuli could reflect such functional and structural differences.

In addition, vascular smooth muscle has some degree of basal contractile activity or tone which is regulated by a multitude of vasoactive agents. These agents may reach the vessel wall through the bloodstream, as do epinephrine, angiotensin II or arginine-vasopressin, may be released by adrenergic, cholinergic, or other nerve terminals in the vessel wall and may be generated by the vascular endothelium like prostacyclin or nitric oxide [4]. This basal level of vasomotor tone is thus susceptible to vary between vessels according to innervation, to differences in endothelial function or in the sensitivity to circulating or locally produced vasoactive agents. The absence of dilation of saphenous vein grafts in response to nitrates suggests that basal vasomotor tone of this vessel is too low to counteract the circumferential tensions resulting from the exposition to arterial pressure and to maintain some vasodilator reserve. The vascular smooth muscle of this graft, when stimulated, remains however able to influence its luminal diameter as demonstrated by the constrictor response to methylergometrine.

*Clinical implications*

Although clinical usage of internal mammary artery and saphenous vein as coronary bypass grafts began about the same time [35], the saphenous vein graft has preferentially been used until recently because it was feared that

the internal mammary artery would not provide enough blood flow to the coronary circulation. Follow-up studies however suggest the adequacy of blood flow through internal mammary artery grafts to meet resting and increased myocardial demands [36]. An increase in the diameter of internal mammary arteries grafted to severely stenotic or obstructed coronary arteries with good perfusion area has been demonstrated by several authors [37, 38]. Our studies show that, in addition to this known chronic adaptation of internal mammary artery grafts to increased blood flow requirements, this vessel is able to dynamically adapt its cross-sectional area to an acute increase in blood flow demand. This adaptability of internal mammary artery grafts to blood flow requirements of the coronary vascular bed resulting both from growth potential and from favorable vasomotor properties is probably a major factor contributing to the excellent long-term functional results of internal mammary artery grafts in coronary artery bypass surgery.

Differences exist in the responsiveness of arterial and venous coronary grafts to ergometrine and to nitrates. These differences could reflect heterogeneity in the sensitivity of the vascular smooth muscle to these agents due to a more or less effective modulatory role of the endothelium as well as differences in the basal level of vasomotor tone. A link between endothelial function and atherogenesis can be suspected on the basis of several experimental and clinical studies. Moreover, the endothelium is the principal regulator of the interactions between the platelets and the vessel wall and it plays a key role in the prevention of platelets adhesion and thrombus formation [1, 31]. The superior long-term patency rate of internal mammary artery graft, when compared to venous graft could thus be a clinical consequence of a superior endothelial function. Recently, gastroepiploic artery has been proposed as an alternative arterial conduit for coronary bypass grafting [39, 40]. The choice of this vessels is based, in part, on the assumption that this graft could share the same favorable biological properties as internal mammary arteries and thus be protected against vasospasm, thrombus formation and atherosclerosis. Although organ chamber experiments on vascular rings obtained from patients at the time of surgery support this hypothesis, the results of the present study clearly show that chronically implanted gastroepiploic and mammary artery grafts have different vasomotor properties. The strong vasoconstrictor response to ergometrine of gastroepiploic artery grafts, which contrasts with the lack of significant response of mammary arteries, suggests that the endothelium of both grafts differ in its ability to control the vasomotor response of the underlying smooth muscle and to prevent the direct constrictor effect of this drug. Further studies are needed to evaluate whether the important vasoreactivity of gastroepiploic artery grafts may have clinical consequences on blood supply to the revascularized myocardium.

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*PART FIVE: QCA in the setting of acute coronary syndromes, evaluation of the role of thrombolysis and balloon angioplasty*

# 21. Evaluation of thrombolytic and monoclonal platelet GPIIb/IIIa receptor antibody therapy in refractory unstable angina pectoris: correlation between quantitative assessment of coronary angiograms and clinical course

MARCEL VAN DEN BRAND, MAARTEN L. SIMOONS, ADDY VAN MILTENBURG, MENKO J. DE BOER, PIM J. DE FEYTER and the European Cooperative Study Group

## Introduction

Despite the effort of Braunwald [1] to provide a classification of unstable angina, definitions still vary widely. Therefore it can hardly be surprising that patients included in clinical studies on unstable angina, show different outcomes, despite comparable study designs. Another potentially confounding factor in studies aiming at a reduction of cardiac events in patients with unstable angina is the time delay between onset of the syndrome, classified according to Braunwald, and the institution of therapy because a temporal relation has been demonstrated between the frequency of thrombi and the interval between angina at rest and angiography [2, 3]. A third variable making comparison of studies in patients with unstable angina dubious, is the therapy installed before a study drug is added to the drug regimen already routinely administered. As both antiplatelet agents [4, 5] and heparin [6] are efficacious in changing the clinical outcome of patients with unstable angina, the effect of administration of newer antiplatelet or thrombolytic drugs, might be influenced by these previously administered medications.

The value of administration of thrombolytic therapy in recent myocardial infarction has clearly been demonstrated. It opens occluded coronary arteries, improves left ventricular function and reduces mortality by limiting infarct size [7, 8]. As unstable angina and myocardial infarction share a common pathogenetic substrate, it seems reasonable that thrombolytic therapy should ameliorate the syndrome of unstable angina pectoris [9]. Several



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studies have shown that thrombolytic therapy can reduce the incidence of sudden death, the number of ischemic episodes, and improve the threshold for ischemia during atrial pacing [10–18]. More recent randomized trials found an angiographic improvement after thrombolytic therapy in patients with unstable angina by opening occluded coronary arteries and reducing the incidence of intracoronary thrombi, however without decreasing in hospital cardiac events [19, 20].

We designed two studies in patients with ongoing unstable angina despite medical treatment, who were candidates for coronary angioplasty. In the first study patients were randomized to thrombolytic therapy with alteplase or placebo. In the second study another group of patients with the same syndrome was randomized to the GP IIb-IIIa blood platelet receptor antibody CentoRx$^{R}$ (c7E3) or placebo. Quantitative analysis of coronary angiograms was included in both studies, both before and after trial drug infusion.

## Patients and methods

### *Patients selection*

Included in both studies were patients between 21 and 75 years and

a) manifesting recurrent episodes of chest pain after hospital admission, occurring at rest and pending medical treatment, with at least one of these episodes with concomitant reversible ST-T segment changes or persistent negative T-waves on the electrocardiogram;
b) undergoing a diagnostic coronary arteriogram within 24 hr (alteplase) or 12 hr (c7E3) of the most recent episode of coronary ischemia (chest pain and/or ST-T segment changes);
c) exhibiting a "culprit" coronary lesion in a native vessel suitable for PTCA. A single vessel must be clearly indicated as ischemia related. Total occlusion of this vessel supposedly of recent origin, was considered acceptable for angioplasty;
d) ability to perform a second coronary angiogram followed by angioplasty within 24 hr after randomization;
e) providing informed consent after completion of the first diagnostic angiogram and prior to the initiation of protocol specific measures.

Excluded for both studies were patients exhibiting features of ongoing ischemia which required immediate intervention, prior PTCA of the same coronary segment within 6 months, recent major trauma including resuscitation, gastro intestinal or urinary tract bleeding within 3 months, persistent hypertension and known bleeding disorders. The c7E3 trial also excluded patients with prior Q-wave myocardial infarction within 7 days, and patients with a platelet count of less than 100,000/mm$^3$.

Reversible ST-T segment changes were classified in one of four categories: ST segment elevation or depression of at least 0.1 mV, persistent negative

or biphasic T waves with pseudonormalization during ischemic attacks, or minimal ST-T segment changes not fulfilling the criteria for the other categories.

*Medical treatment*

Patients were designated as refractory unstable angina if anginal attacks continued despite bed rest and medical treatment which required minimally i.v. heparin and oral or i.v. nitroglycerin. After randomization all patients were treated with the following combination of medication:

1) heparin 1,000 IU/hour, or a dose sufficient to prolong the activated partial thromboplastin time to twice the control value, after a bolus injection of 5,000 IU of heparin;
2) intravenous nitroglycerin ranging in dose from 50 to 300 μg/min;
3) metoprolol 50–200 mg, in order to reduce heart rate to 60 beats/min;
4) nifedipine in a dose of 40–120 mg/day;

After informed consent and randomization by a telephone answering service, study drug infusion was started as soon as possible, but at least within 4 hr after the first angiogram.

For the alteplase trial a bolus injection of 10 mg i.v. was followed by an infusion of 50 mg in the first hour and 20 mg/hour for the subsequent 2 hr. Thus a total amount of 100 mg of alteplase or placebo was administered in 3 hr.

For the c7E3 trial patients received a bolus dose of 0.25 mg/kg followed by a 10 μg/min. continuous infusion for at least 18 hr. Patients to receive placebo were administered a bolus of human serum albumin, likewise followed by continuous infusion. The infusion continued until one hour following the completion of PTCA.

Alteplase (Actilyse$^{R}$) was supplied by Boehringer Ingelheim International, and c7E3 (CentoRx$^{R}$) by Centocor, Malvern PA.

*Coronary arteriography and Angioplasty*

Coronary arteriography and left ventricular angiography were performed as soon as possible after the qualifying anginal attack using the Judkins technique. Heparin 2,500 to 5,000 IU was administered at the beginning of the procedure. A second angiogram was performed within 24 hr after the start of study medication followed by angioplasty. The coronary artery responsible for the ischemia was identified by means of electrocardiographic location of the reversible ST-T segment changes, and left ventricular wall contraction abnormalities. At least two orthogonal projections were made of the culprit coronary artery, after injection of 1–3 mg of isosorbide dinitrate. During the first and the second angiogram the same projections and X-ray gantry setting were employed to compare lesion severity. Low osmolar contrast medium (iopamidol) was used for all angiograms. All coronary and left ventricular

angiograms were scored by at least two observers who were blinded with respect to the treatment assignment. Qualitatively the following items were scored after the first contrast injection:

- TIMI flow grade [21] of the culprit artery;
- presence of intracoronary thrombus, defined as an intraluminal filling defect, visible during at least one complete cine-run, and surrounded on 3 sides by contrast medium [3]. A total ocluded coronary artery could contain a filling defect, but was not automatically scored as containing such a defect;
- stenosis severity as visually assessed in multiple projections.

The angiograms were analyzed in a quantitative manner with the help of the computer based Cardiovascular Angiography Analysis System (CAAS) [22]. "Plaque area" is the difference in area in $mm^2$ between the reference and detected contours over the length of the lesion [23].

The severity of the obstruction can be expressed as a percentage area reduction by videodensitometry, by comparing the minimal value at the obstruction site with the reference value obtained following an interpolative approach, as for diameter measurements [24].

The second angiogram to be followed by angioplasty was performed between 12 and 24 hr in the alteplase trial and between 18 and 24 hr in the c7E3 trial after the start of the drug administration. Angiograms of the culprit artery were obtained in the same projections as during the first angiogram, after intracoronary administration of isosorbide dinitrate. Before the start of the angioplasty procedure 10,000 IU of heparin and 250 mg of acetyl salicylic acid were administered. An extra dose of 5,000 IU of heparin was administered every hour after the start of the procedure. Monorail (Schneider-Shiley, Zürich) or Rapid Exchange (ACS, Billerica, MA) balloons were employed, introduced over 0.014″–0.018″ guide wires (ACS). Primary success was defined as a less than 50% residual diameter stenosis of the culprit vessel, without signs of myocardial infarction or recurrent ischemia and without urgent coronary bypass operation or death, within 24 hr. Analysis of angiograms was performed by the Core Laboratory at Cardialysis, Rotterdam, NL.

*Assessments*

The efficacy of treatment was assessed in several ways:

1. Frequency of recurrent ischemic events between the first and the second angiogram (maximal 24 hr).
2. Incidence of myocardial infarction during this observation period as assessed by serial serum enzyme measurements. For this purpose, serum CK was measured every 12 hr until at least 72 hr after the first angiogram, and 6 hr after each episode of chest pain. Myocardial necrosis was considered to be present when serum CK content was at any time more than twice the local upper limit for normal (i.e. $\geqslant$200 IU/l).

3. Quantitative angiographic differences between the first and the second coronary angiogram.
4. Presence or absence of intracoronary filling defects in both angiograms.
5. Procedural complications during angioplasty, such as death, myocardial infarction, and the need for emergency coronary bypass surgery.

### *Statistical analysis*

Differences between groups were analyzed with a two-tailed Student *t* test. Changes in quantitatively measured coronary artery stenosis in each group were compared with a two-tailed paired *t* test. Differences in incidence of recurrent ischemic attacks, myocardial infarction, presence of intracoronary clots were determined between groups treated with alteplase, $C_7E_3$ or respective placebo with Fisher's exact test. The agreement between the minimal luminal cross sectional area of the culprit artery measured with edge detection and videodensitometry was assessed by calculating the bias, estimated by the mean difference and the standard deviation of the differences [25].

## Results

### *Baseline characteristics*

The alteplase/placebo study was conducted between November 1987 and April 1989 in one hospital. The c7E3 Fab/placebo trial enrolled patients between September 1991 and July 1992 in five different hospitals. Baseline characteristics of the patients enrolled in both studies are summarized in Table 1. Medication at the time of the most recent episode of ischemia was intensive and similar in all groups (Table 2).During the study drug infusion all but 3 patients in the alteplase and one in the placebo group, and all patients in the c7E3 Fab/placebo study received intravenous heparin. One patient in each group from the alteplase placebo study and no patients from the other trial were not on intravenous nitroglycerin medication between both angiograms. More patients in both placebo groups had sustained a previous infarct compared with the treatment groups, but left ventricular ejection fraction was similar in the alteplase/placebo groups, while this parameter was not assessed int he c7E3 Fab/placebo study. Finally, significantly more patients in the placebo group from the last trial demonstrated multivessel disease, defined as a more than 50% diameter stenosis in one of the three main epicardial vessels. All other baseline parameters were similar between each treatment and respective placebo group.

*Table 1.* Baseline clinical electrocardiographic and angiographic characteristics of patient groups

| Group<br>N | Alteplase<br>19 | Placebo<br>17 | c7E3Fab<br>30 | Placebo<br>30 |
|---|---|---|---|---|
| Male/Female | 16/3 | 13/4 | 20/10 | 24/6 |
| Mean age (years) | 59 | 62 | 61 | 60 |
| Previous infarct | 7 | 10 | 9 | 16 |
| Previous CABG | 0 | 1 | 0 | 2 |
| Previous PTCA | | | 4 | 5 |
| ECG changes during ischemia | | | | |
| ST-T elevation ≥0.1 mV | 5 | 9 | 8 | 13 |
| ST-depression ≥0.1 mV | 5 | 4 | 11 | 8 |
| Persistent-negative T waves | 5 | 2 | 9 | 5 |
| Other ST-T changes | 4 | 2 | 2 | 4 |
| Ischemia related vessel | | | | |
| Left anterior descending artery | 11 | 6 | 16 | 14 |
| Left circumflex artery | 2 | 4 | 8 | 6 |
| Right coronary artery | 6 | 7 | 6 | 10 |
| Multivessel disease | 5 | 5 | 6* | 15* |
| Ejection fraction | | | | |
| <0.50 | 3 | 2 | n.a. | n.a. |
| ≥0.50 | 16 | 14 | | |
| Unknown | 0 | 1 | | |

CABG = coronary artery bypass grafting; PTCA = percutaneous transluminal coronary angioplasty; n.a. = not assessed, *p = 0.03.

*Table 2.* Medical treatment in all patient groups at time of qualifying anginal attack (Q) and at time of first angiogram before study drug administration (B)

| Group<br>N | Alteplase<br>19 | | Placebo<br>17 | | C7E3Fab<br>30 | | Placebo<br>30 | |
|---|---|---|---|---|---|---|---|---|
| | Q | B | Q | B | Q | B | Q | B |
| Heparin | 11 | 16 | 12 | 16 | 26 | 30 | 27 | 30 |
| Aspirin | 5 | 1 | 5 | 1 | 21 | 29 | 23 | 29 |
| Nitrates | | | | | | | | |
| * intravenous | 9 | 18 | 9 | 16 | 24 | 30 | 27 | 30 |
| * oral | 4 | 1 | 5 | 0 | 4 | 2 | 2 | 1 |
| β-blocker | 16 | 17 | 9 | 10 | 22 | 23 | 24 | 20 |
| Calcium channel blocker | 7 | 10 | 11 | 15 | 15 | 15 | 22 | 19 |

### *Recurrent ischemia*

Between the start of drug infusion and the second angiogram 5, 6, 3 and 7 patients from the alteplase, placebo, c7E3 Fab and placebo groups respectively, had one or more episodes of recurrent ischemia defined as chest pain, with or without ECG changes. Severe recurrent ischemia, not subsiding with medical measures, necessitated urgent coronary angioplasty in 4, 1, 0 and 3

*Table 3.* Major events in all 4 study groups

| N | Alteplase 19 | Placebo 17 | C7E3Fab 30 | Placebo 30 |
|---|---|---|---|---|
| Death | 1 | 0 | 0 | 1 |
| Myocardial infarction | 7 | 5 | 5 | 10 |
| Before PTCA | 4 | 3 | 4 | 7 |
| After PTCA | 3 | 2 | 1 | 3 |
| Urgent procedure | 5 | 1 | – | 7 |
| PTCA | 4 | 1 | – | 3 |
| CABG | 1 | – | – | 3 |
| Stent | – | – | – | 1 |
| Total nr of patients with one or more major events | 7 | 3 | 1 | 7 |

CABG = coronary artery bypass grafting; PTCA = percutaneous transluminal coronary angioplasty.

patients from the alteplase, placebo, c7E3 Fab and placebo groups respectively.

*Major events*

In the two studies a major event defined as death, myocardial infarction or urgent intervention occurred in 7, 3, 1 and 7 patients from the alteplase, placebo, c7E3 Fab and placebo groups respectively. The nature of these major events in all four groups is summarized in Table 3.

Death in the alteplase patient occurred after retroperitoneal hemorrhage caused by dissection of the right common iliac artery. This haematoma was drained, but 24 hr later the patient showed signs of occlusion of the right femoral artery. After embolectomy and a cross over operation from the left iliac artery, bleeding in the retroperitoneum progressed and bowel ischemia developed. This patient died 48 hr after the angioplasty procedure.

One other patient from the placebo group in the c7E3 Fab study died, 26 days after allocation after a complicated clinical course. Fifteen hours after the study drug (placebo) had been started, he developed severe recurrent ischemia, which was initially treated with alteplase followed by emergency PTCA of the culprit lesion in the left anterior descending artery, which was dilated successfully. Following the PTCA, myocardial infarction, heart failure and hypotension occurred, treated with an intra-aortic balloon pump, mechanical ventilation, and with a second PTCA for subsequent recurrent ischemia. He developed renal failure, skin rash, and bleeding at the IABP puncture site, gastric bleeding and pulmonary bleeding. A total of 17 units transfusions were given. He died from pseudomonas sepsis and multiple organ failure.

Myocardial infarction was already present at study entry in retrospect in

*Table 4.* Qualitative angiographic data

| Group | Alteplase | | Placebo | | C7E3Fab | | Placebo | |
|---|---|---|---|---|---|---|---|---|
| N | 19 | | 17 | | 30 | | 30 | |
| | B | A | B | A | B | A | B | A |
| TIMI flow | | | | | | | | |
| 0 | 2 | 3 | 1 | 1 | 1 | 1 | 4 | 3 |
| 1 | 0 | 0 | 0 | 0 | 2 | 1 | 0 | 1 |
| 2 | 3 | 3 | 3 | 2 | 10 | 5 | 7 | 6 |
| 3 | 14 | 13 | 13 | 14 | 17 | 23 | 19 | 20 |
| Improved | | 3 | | 2 | | 6 | | 4 |
| Worsened | | 4 | | 2 | | 0 | | 3 |
| Intracoronary filling defect | 1 | 4 | 2 | 2 | 5 | 2 | 1 | 1 |

B = before study drug infusion; A = after study drug infusion.

2 patients from the alteplase study (both placebo) and in 10 patients from the c7E3 Fab study, 6 in the placebo and 4 in the treatment group.

*Qualitative evaluation of coronary angiograms*

TIMI flow grade 3 in culprit arteries, assessed centrally by the Core Laboratory, was present in 57 to 76% of all patients at the first angiogram. Of all 4 groups studied, a substantial improvement in coronary blood flow occurred after treatment in the c7E3 Fab patient group only, while all three other groups showed both improvement and deterioration in TIMI flow score (Table 4).

Extensive filling defects in the coronary arteries were seldom encountered. Most filling defects were single, visible in more than one direction and located distally from the culprit lesion. The number of intracoronary clots, and total occlusions from both studies, in the pre and post treatment angiogram are shown in Fig. 1. In the alteplase study new occlusions of culprit arteries occurred in both groups, while other occluded coronary arteries became patent after study drug infusion. In the c7E3 Fab study a new occlusion was observed in the placebo group only, but also restored patency of a total occluded vessel in two cases with thrombotic remnants in one case. Three out of five coronary clots resolved in the treatment group of the c7E3 study.

*Quantitative coronary angiographic analysis*

Quantitative coronary angiographic data are summarized in Table 5. One patient from the c7E3 Fab study with a very proximal LAD lesion is missing in the calculated percentage diameter stenosis, because the reference diameter could not be ascertained. All videodensitometric area calculations of

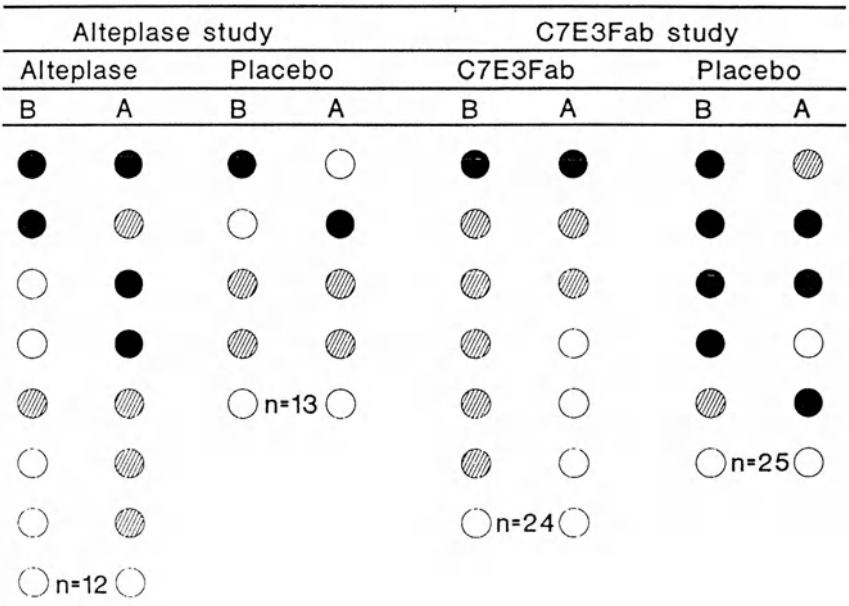


*Figure 1.* Qualitative coronary angiographic data of the ischemia related coronary artery before (B) and after (A) study drug infusion. ●, totally occluded coronary artery; ○, intracoronary filling defect; ○, patent coronary artery, without filling defect. Note: The number of non totally occluded vessels, without filling defects in both angiograms, are depictedin the bottomline.

more than 100% obstruction were left out, while plaque area and extent of obstruction could naturally only be calculated in patent coronary arteries.

In the alteplase study, no significant changes were observed in the quantitative parameters nor within nor between groups.

In the c7E3 Fab study significant decreases in percentage diameter stenosis, extent of obstruction and plaque area were observed in the c7E3 Fab patients.

In the placebo group the same changes were observed to a lesser extent, except for the extent of obstruction, which decreased in the c7E3 Fab patients, but increased in the placebo group patients. Differences between groups were not significant.

### *Agreement between videodensitometric and edge detected minimal luminal cross sctional area*

To measure the strength of the relation between the two methods to determine cross sectional area, the correlation coefficients for these two measurements were calculated for the c7E3 Fab and its concomitant placebo group before and after study drug infusion. The results are summarized in Table

*Table 5.* Quantitative angiographic data from the first angiogram (I) and after study drug infusion (II) and the difference between both measurements (II–I)

| Treatment | Alteplase (n = 19) | | Placebo (n = 17) | | c7E3Fab (n = 30) | | Placebo (n = 30) | |
|---|---|---|---|---|---|---|---|---|
| Variable | n | | n | | n | | n | |
| DS (%) | | | | | | | | |
| I | 19 | 66.7 (16.1) | 17 | 63.1 (13.1) | 30 | 65.7 (8.6) | 29 | 67.7 (16.1) |
| II | 19 | 67.0 (14.8) | 17 | 61.6 (13.5) | 30 | 62.3 (10.5) | 29 | 65.6 (15.8) |
| II–I | 19 | 0.3 (20.2) | 17 | −1.6 (16.2) | 30 | −3.4 (6.7)* | 29 | −2.1 (12.4) |
| MLD (mm) | | | | | | | | |
| I | 19 | 1.0 (0.4) | 17 | 1.1 (0.5) | 30 | 0.9 (0.3) | 30 | 0.9 (0.4) |
| II | 19 | 0.9 (0.4) | 17 | 1.1 (0.5) | 30 | 1.0 (0.3) | 30 | 0.9 (0.4) |
| II–I | 19 | −0.1 (0.6) | 17 | 0.0 (0.4) | 30 | 0.1 (0.2) | 30 | 0.0 (0.3) |
| Ext Ob (mm) | | | | | | | | |
| I | 17 | 7.1 (2.2) | 16 | 9.2 (4.0) | 29 | 7.3 (2.2) | 26 | 7.2 (3.4) |
| II | 17 | 7.0 (2.6) | 16 | 7.8 (3.3) | 29 | 6.9 (2.1) | 26 | 7.3 (2.9) |
| II–I | 16 | −0.1 (1.4) | 15 | −0.9 (2.0) | 29 | −0.5 (1.2)* | 26 | 0.3 (1.8) |
| Plq Area ($mm^2$) | | | | | | | | |
| I | 17 | 10.0 (5.3) | 16 | 12.0 (7.6) | 29 | 8.2 (3.4) | 26 | 9.1 (6.8) |
| II | 17 | 9.5 (6.8) | 16 | 8.9 (5.3) | 29 | 7.1 (2.5) | 27 | 8.6 (4.8) |
| II–I | 15 | −0.2 (3.0) | 15 | −2.1 (3.6)* | 29 | −1.1 (1.9)* | 25 | −0.5 (3.3) |
| AS (%) | | | | | | | | |
| I | 14 | 87.7 (9.6) | 15 | 84.6 (15.7) | 20 | 89.2 (6.7) | 21 | 90.7 (7.9) |
| II | 16 | 88.2 (8.4) | 14 | 85.5 (17.4) | 23 | 88.3 (8.4) | 22 | 89.6 (10.20) |
| II–I | 12 | −1.1 (10.4) | 14 | 1.1 (9.6) | 19 | 1.8 (8.1) | 19 | −1.3 (6.4) |

DS = diameter stenosis; MLD = minimal lumen diameter; AS = area stenosis; Ext Ob = Extent of the obstruction; Plq area = plaque area; *$p \leq 0.05$.
Data are given as mean values (standard deviation).

6. Also the mean between method difference was calculated as suggested by Bland and Altman, to determine the agreement between the two measures.

Although a fair to good correlation was found between the two methods, calculation of the between method difference showed poor agreement between the two methods. The absolute values for mean edge detected and videodensitometric minimal luminal cross sectional areas were of the same magnitude as two standard deviations of the between method difference (Fig. 2).

### *Angioplasty procedure*

Coronary angioplasty was performed in all 19 alteplase patients, in 16 of the placebo/alteplase patients, and all 60 patients from both groups in the c7E3 Fab study. The one placebo patient not undergoing angioplasty showed extensive clotting in the right coronary artery in the second angiogram prior to angioplasty. She was treated with streptokinase and alteplase, with resolution of the clots, leaving a virtually normal coronary artery.

*Table 6.* Correlation coefficients and mean between method differences for edge detected and videodensitometric measured minimal luminal cross sectional area

| | | Minimal luminal cross sectional area ($mm^2$) | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | Edge detection | | Videodensitometry | | Correlation coefficient | Between method difference ($mm^2$) | |
| | | Mean | SD | Mean | SD | | Mean | SD |
| C | b | 0.820 | 0.418 | 0.589 | 0.509 | 0.64 | 0.224 | 0.300 |
| | a | 0.916 | 0.371 | 0.641 | 0.520 | 0.40 | 0.314 | 0.390 |
| P | b | 0.861 | 0.572 | 0.648 | 0.784 | 0.78 | 0.274 | 0.398 |
| | a | 0.900 | 0.556 | 0.664 | 0.804 | 0.72 | 0.236 | 0.432 |

C = c7E3Fab group; P = placebo group; b = before study drug infusion; a = after study drug infusion.

Procedural success, defined as a residual stenosis of less than 50% in the culprit artery, without death, urgent bypass operation, re-PTCA or myocardial necrosis is summarized in Table 7.

## Discussion

Several studies have shown the efficacy of aspirin and or anticoagulants in patients with unstable angina to reduce the complications of this syndrome such as sudden death, myocardial infarction and recurrent ischemic episodes [4, 6, 18, 26, 27]. If, however, this medication adjunctive to beta-blockade, nitroglycerin and eventually calcium antagonists, and combined with bed rest and treatment of precipitating factors, does not prevent ongoing ischemia, other ways of treatment must be looked for. These treatment modalities have included intra aortic balloon pumping, bypass surgery, angioplasty and thrombolytic therapy. Generally speaking the number of complications with one of the revascularization options is high and related to the refractoriness of the syndrome to medical therapy.

When thrombolytic therapy revived for the treatment of acute myocardial infarction and showed beneficial effects, a logic next step was to add thrombolytics to the drug regimen of patients with ongoing unstable angina refractory to that regimen. Several studies have been conducted since using different thrombolytic agents in different classes of unstable angina [2, 11–13, 17, 20, 28–32]. Only the study of Gold, which included only 23 patients, showed a beneficial reduction in cardiac events from 55% to 9%. And although inclusion criteria varied in the interval between the last anginal attack and study drug infusion, in the classification according to Braunwald, and the presence of angiographically demonstrated significant coronary artery disease, all shared a common outcome of no clinical benefit. Only the study of Ardessino [29] showed a lower mortality in the group treated with alte-

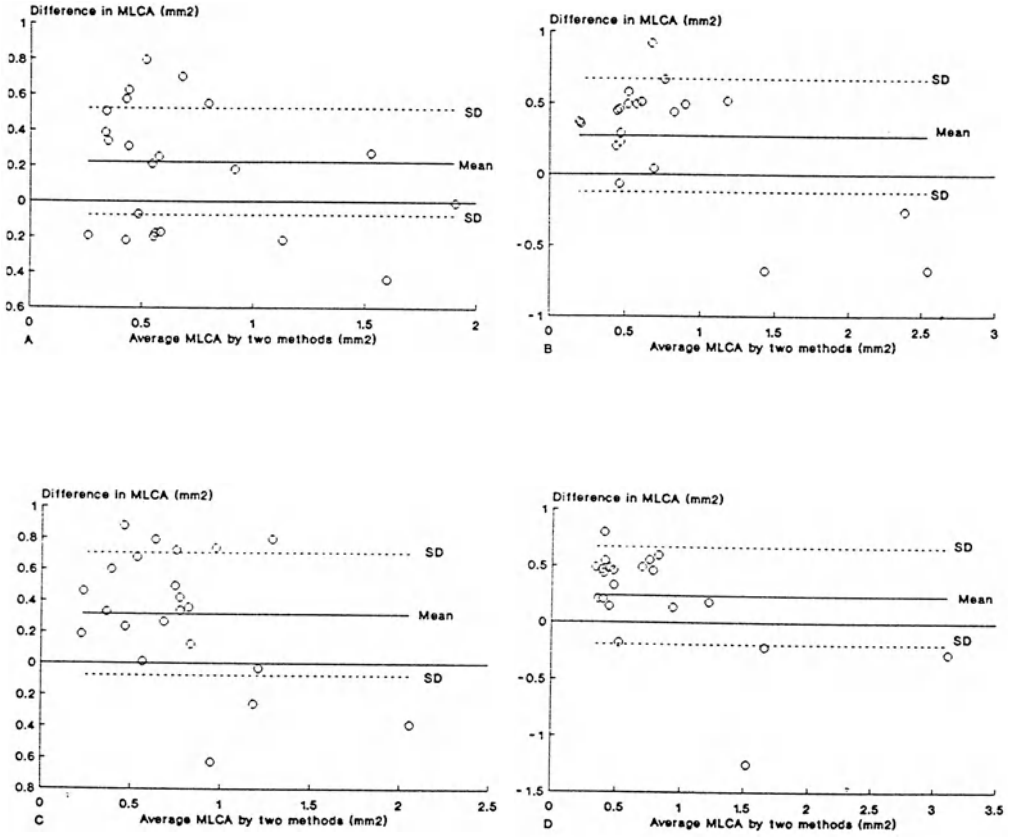


*Figure 2.* Comparison of the average minimal luminal cross sectional area (MLCA) by edge detection and videodensitometry versus between method difference in minimal luminal cross sectional area. SD = standard deviation. a) c7E3Fab group before drug infusion. b) Placebo group before drug infusion. c) c7E3Fab group after drug infusion. d) Placebo group after drug infusion.

plase, all other studies manifesting an equal [19] or higher mortality in the group treated with a thrombolytic agent [13, 18–20, 31, 32]. Also the incidence of myocardial infarction during and after treatment with thrombolytic agents was higher in the treated patients than in those receiving placebo, both groups receiving intravenous heparin as background therapy (29 of 270 and 15 of 289 patients respectively) [12, 13, 17–20, 30, 32, 33].

Some studies included quantitative analysis of coronary angiograms before and after study drug infusion, the angiography result being part of the inclusion process [12, 13, 17, 19, 20, 29, 32]. These studies all showed a minimal reduction in percentage diameter stenosis, both in the treatment and placebo groups, reaching only statistical significance in the treated group in two studies [17, 20]. Part of the problem of most studies was the small

*Table 7.* Complications and untoward events during and after coronary angioplasty in all four patient groups

| | Alteplase | Placebo | c7E3Fab | Placebo |
|---|---|---|---|---|
| N | 19 | 16 | 30 | 30 |
| Mortality | 1 | – | – | 1 |
| Myocardial necrosis | 2 | 2 | 1 | 3 |
| Urgent CABG | 1 | – | 0 | 3 |
| Re-PTCA | – | – | – | 2 |
| Residual stenosis > 50% | 2 | 0 | 4 | 6 |
| Number of patients with one or more untoward events | 5 | 2 | 5 | 9 |
| Procedural success (%) | 74 | 88 | 83 | 70 |

CABG = coronary artery bypass grafting; PTCA = percutaneous transluminal coronary angioplasty.

number of patients included, varying from 24 to 159 patients. It is remarkable that the two studies with a significant reduction in diameter stenosis in the treated groups included a relatively large number of patients 70 and 159 respectively.

In the thrombolytic study reported in this chapter on patients with refractory unstable angina, the incidence of cardiac events was high in both groups, possibly reflecting the severe nature of the syndrome in these patients, already treated with routine medication, including heparin and aspirin.

Two recent editorials addressed the relative inefficacy of thrombolytic agents in patients with unstable angina [9, 34]. They both explain the apparent discrepancy between the effects of thrombolytic agents in myocardial infarction and unstable angina pectoris by the difference in underlying disease and enhanced thrombosis formation. Opening of an occluded artery as in myocardial infarction, and keeping an artery open as in unstable angina require different approaches. In the Unasem study e.g. a significant reduction in diameter stenosis was only achieved by opening occluded arteries with anisoylated plasminogen streptokinase activator complex [20]. Several studies suggest that thrombolytic therapy might enhance thrombin formation and activate platelets to further coronary thrombosis [35–41]. These effects of tissue plasminogen activator can be countered by the monoclonal platelet GPIIb/IIIa receptor antibody as has been demonstrated in a canine model [42].

It is conceivable that this antibody alone prevents occlusion of coronary arteries in unstable angina and prevents platelet aggregation. In fact we demonstrated in the second pilot study described in this chapter that c7E3 Fab ameliorated the clinical course of patients with refractory unstable angina and facilitated the following angioplasty. These results look quite promising and might be confirmed in a larger trial which is now underway.

Also the modest but significant reduction in diameter stenosis of the culprit lesion corroborates these optimistic expectations. If these results can

be confirmed in the larger ongoing trial, quantitative assessment of coronary arteriograms could underline the clinical results, as the absence of clinical benefit in patients with unstable angina pectoris treated with thrombolytic agents has not been attended by quantitative improvement of coronary artery lesions.

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# 22. Clinical and quantitative angiographic results of a randomized trial comparing direct coronary angioplasty with intravenous streptokinase in acute myocardial infarction

FELIX ZIJLSTRA, MENKO J. DE BOER, JAN C.A. HOORNTJE, JOHAN H.C. REIBER and HARRY SURYAPRANATA

## Introduction

In 1980 De Wood et al. [1] showed that acute transmural myocardial infarction is usually caused by total coronary occlusion due to intraluminal coronary thrombus superimposed on an atherosclerotic lesion. Over the last 10 years the roles of thrombolytic therapy and coronary angioplasty, to restore patency of the infarct related coronary artery, have been studied extensively [2–9]. Although rescue angioplasty of infarct arteries that fail to reperfuse after thrombolytic therapy may be advantageous [10], in general there is no additional benefit of routine angioplasty after thrombolytic therapy [7, 8]. Recently published randomized trials indicate that the combination of streptokinase, aspirin and heparin is the generally accepted treatment of patients with acute myocardial infarction [11–13]. Direct coronary angioplasty without antecedent thrombolytic therapy avoids the potentially adverse effects of myocardial and intra-plaque hemorrhage that can be observed after the systemic pharmacologic approach to the obstructive coronary thrombus with thrombolytic agents [14]. Therefore the local mechanical approach is advocated by some authors as the preferred treatment of acute myocardial infarction [9, 15]. This has the additional advantage that it simultaneously reduces the hemodynamic importance of the underlying atherosclerotic lesion. One report however suggests that the incidence of complications of direct angioplasty is high [16]. Except for a small randomized study comparing intracoronary streptokinase and direct angioplasty [17] comparisons of these two approaches are lacking. For that reason we performed a prospective randomized trial comparing direct angioplasty with intravenous streptokinase in patients with acute myocardial infarction. The clinical results of this study have been reported [18]. In this chapter we will describe the differences between these two treatment strategies from a quantitative angiographic perspective.



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## Methods

The research protocol was reviewed and approved by the institutional review board. Enrollment began on August 20, 1990 and ended on February 10, 1992. Inclusion criteria were: 1. symptoms of acute myocardial infarction persisting for more than 30 min accompanied by an electrocardiogram with more than 1 mm (0,1 mV) ST segment elevation in two or more contiguous leads; 2. all patients presenting within 6 hr after symptom onset, as well as those presenting between 6 and 24 hr, if they had evidence of continuing ischemia; 3. age less than 76 years; 4. no contraindication to thrombolytic intervention, including prior stroke or other known intracranial diseases, recent trauma or surgery, refractory hypertension, active bleeding or prolonged cardiopulmonary resuscitation. Prior coronary artery bypass grafting, prior Q or non-Q wave infarction and cardiogenic shock were no reasons to exclude a patient. Before randomization : age, sex, Killip class on admission, electrocardiographic site of infarction, history of prior infarction, heart rate, arterial pressure, time of symptom onset and time of hospital admission were recorded.

### *Randomization*

After informed consent, patients were randomly assigned to one of the two treatment modalities by means of a closed envelope system.

### *Treatment*

All patients received aspirin, intravenous nitroglycerin and intravenous heparin. Drugs such as lidocaine, calcium-antagonist or ß-adrenergic blockers were only given on indication. Patients randomized to streptokinase received 1,5 million units intravenously in 1 hour. Patients randomized to coronary angioplasty were transported to the catheterization laboratory as quickly as possible and underwent coronary angiography. Both coronary arteries were visualized, left ventriculography was not performed. Time from admission to therapy was calculated as time from admission to start of the streptokinase infusion or to the first balloon inflation.

### *End points* (*see also ref.*18)

1. Recurrent ischemia before hospital discharge, which includes: stable angina, defined as chest pain and a positive exercise test; unstable angina defined as chest pain and ST-T segment changes at rest; and recurrent myocardial infarction, defined as chest pain, ST-T segment changes and a second Creatine Kinase rise of more than 2 times the upper limit of the normal range.
2. Left ventricular ejection fraction was measured with a radionuclide tech-

nique before discharge [19–21]. The technique used in our hospital has been described [22]. Essential characteristics are that it uses the multiple gated equilibrium method following the labeling of red blood cells of the patient with 99 m-Tc-pertechnetate. A General Electrics-300 gamma camera with a low energy all purpose parallel hole collimator was used. Global ejection fraction is calculated fully automatically by a General-Electrics Star View computer using the PAGE™ program.

3. Arterial patency, defined as a Thrombolysis In Myocardial Infarction grade 2 or 3 flow in the infarct related coronary artery [6] was assessed by coronary angiography. In angioplasty patients, repeat angiography was performed preferably 3 months later to assess the restenosis rate [23]. The angiographic data were generated at the Laboratory for Clinical and Experimental Image Processing, Department of Diagnostic Radiology and Nuclear Medicine, University Leiden. Only name, date of birth and electrocardiographic site of the infarction were known during assessments of the angiograms. All infarct related vessels were analyzed quantitatively with a computer based cardiovascular analysis system [24]: the CMS Cardiovascular Measurement System Medis Medical Imaging Systems, Nuenen, the Netherlands). The basic algorithms have been described [24–26].

*Statistical analysis*

All end points were examined according to the principle of intention to treat. Student's t-test was used to compare mean values. Comparisons of rates of recurrent ischemia, patency and complications were made with a conventional Chi-square test, but Fisher's exact test was used if an expected cell value was less than 5. All calculated P values are two-tailed. For descriptive presentation of data, continuous baseline and outcome variables were summarized using the mean and SD, whereas discrete variables were described in terms of absolute values as well as in percentages.

## Results

Baseline clinical and angiographic characteristics are presented in Table 1. Time from admission to start of the streptokinase infusion was 30 ± 15 min. All patients randomized to angioplasty underwent emergency angiography. The infarct related vessel showed a Thrombolysis In Myocardial Infarction grade 0 flow in 87% of patients. Two patients with open vessels were treated conservatively. Three patients with severe multivessel disease or left main stenosis had emergency coronary artery bypass grafting after insertion of an intra-aortic counterpulsation balloon. The remaining 65 patients had direct angioplasty of the infarct related vessel, with success in 64 patients (98%). The angioplasty was defined successful if a less than 50% residual stenosis

*Table 1.* Baseline clinical and angiographic characteristics.

| | Streptokinase (N = 72) | Angioplasty (N = 70) |
|---|---|---|
| Age (years) | 61±9 | 59±10 |
| Male gender | 59 (82%) | 62 (89%) |
| Anterior infarction | 30 (42%) | 31 (44%) |
| Previous infarction | 10 (14%) | 13 (19%) |
| Time onset-admission (min) | 162±145 | 167±165 |
| Killip class on admission: I. | 58 (80%) | 55 (78%) |
| II. | 9 (13%) | 11 (16%) |
| III. | 4 (6%) | 2 (3%) |
| IV. | 1 (1%) | 2 (3%) |
| Diseased vessels | | |
| None or one | 27 (37%) | 25 (36%) |
| Two | 18 (25%) | 20 (29%) |
| Three | 22 (31%) | 22 (31%) |
| Left main | 1 (1%) | 3 (4%) |
| Unknown | 4 (6%) | 0 (0%) |
| Infarct related artery | | |
| Left anterior descending | 23 (32%) | 26 (37%) |
| Left circumflex | 11 (15%) | 12 (17%) |
| Right coronary | 30 (41%) | 30 (43%) |
| Left main | 1 (1%) | 1 (1%) |
| Graft | 3 (4%) | 1 (1%) |
| Unknown | 4 (6%) | 0 (0%) |

(estimated visually) and a Thrombolysis In Myocardial Infarction grade 2 or 3 flow resulted at the end of the procedure. In one patient the infarct related vessel could not be reopened; this patient underwent immediate coronary artery bypass grafting. Time from admission to first balloon inflation was 61 ± 22 min.

The Creatine Kinase values rose to 1327 ± 1304 U/l and 1477 ± 1215 U/l in streptokinase and angioplasty patients respectively ($P = 0.49$). The normal value for Creatine Kinase is <100 U/l in our hospital. Complications are shown in Table 2. Intercerebral bleeding or bleeding necessitating a blood transfusion were considered a bleeding complication. There were less complications in patients randomized to direct angioplasty although statistically not significant. Especially death, bleeding and heart failure occurred less frequent in the angioplasty group. Recurrent ischemia (Table 3) occurred in 38% of streptokinase patients and in 9% of angioplasty patients ($P < 0.001$). Stable angina occurred in comparable frequencies, but the incidence of recurrent myocardial infarction and unstable angina was higher in streptokinase patients. Additional revascularization procedures were more often necessary in streptokinase patients (Table 3). Left ventricular ejection fraction at rest was measured in all 138 survivors, and was 45 ± 12% versus 51 ± 11% in streptokinase and angioplasty patients respectively ($P = 0.004$).

*Table 2.* Complications.

| | Streptokinase (N = 72) | Angioplasty (N = 70) | |
|---|---|---|---|
| Death | 4 (6%) | 0 (0%) | P = 0.13 |
| Stroke | 2 (3%) | 0 (0%) | P = 0.51 |
| Bleeding | 6 (8%) | 2 (3%) | P = 0.29 |
| Mechanical ventilation | 1 (1%) | 1 (1%) | P = 1.00 |
| Femoral artery repair | 0 (0%) | 1 (1%) | P = 0.49 |
| Heart failure | 8 (11%) | 4 (6%) | P = 0.25 |
| VT/VF | 6 (8%) | 5 (7%) | P = 0.79 |
| Emergency CABG | 2 (3%) | 4 (6%) | P = 0.44 |
| Any of the above | 19 (26%) | 10 (14%) | P = 0.07 |

VT = ventricular tachycardia, VF = ventricular fibrillation; CABG = coronary artery bypass grafting (within 24 hours after admission).

*Table 3.* Recurrent ischemia and additional procedures.

| | Streptokinase (N = 72) | Angioplasty (N = 70) | |
|---|---|---|---|
| Recurrent ischemia | 27 (38%) | 6 (9%) | P < 0.001 |
| Stable angina | 4 (6%) | 2 (3%) | P = 0.68 |
| Unstable angina | 14 (19%) | 4 (6%) | P = 0.02 |
| Recurrent MI | 9 (13%) | 0 (0%) | P = 0.003 |
| IABC | 9 (13%) | 8 (11%) | P = 0.84 |
| PTCA | 22 (31%) | 3 (4%) | P < 0.001 |
| CABG | 8 (11%) | 7 (10%) | P = 0.83 |

MI = myocardial infarction; IABC = intra-aortic balloon counterpulsation; PTCA = percutaneous transluminal coronary angioplasty; CABG = coronary artery bypass grafting.

Coronary angiography was performed in 68 out of 72 streptokinase patients after 21 ± 31 days. Repeat angiography was performed in 63 out of 65 patients that actually underwent angioplasty after 82 ± 67 days. Patency of the infarct related vessel was 68% (49/72) in streptokinase patients and 91% (64/70) in angioplasty patients (P = 0.001). In patients randomized to angioplasty patency at baseline angiography was only 7%, 60 min after admission patency was 47%, 90 min after admission 84%, and 120 min after admission as well as at follow-up 91%. Quantitative angiographic analysis of the infarct related vessels are given in Table 4, for all patients based on the principle of intention to treat. Restenosis defined as a lesion of > 50% in the dilated vessel was observed in 11/63 = 17% of our angioplasty patients. Although evidence has accumulated that restenosis peaks at 3 months [23], the clinical implications of restenosis in this setting, will only become clear after at least 6 months follow-up. Excluding all angiograms without restenosis made before 3 months after angioplasty, the restenosis rate is 11/46 = 24%. The result of a retrospective analysis of different subsets of patients are shown in table 5. Although there is a trend towards a less optimal result of angioplasty in patients with an occluded vessel at follow-up, this did not

*Table 4.* Quantitative angiographic data.

| | Angioplasty | | | | Streptokinase |
|---|---|---|---|---|---|
| | Before (N = 70) | After (N = 65) | F-U: 82 ± 67 days (N = 63) | | 21 ± 31 days (N = 68) |
| No of Proj | 2.0 ± 0.5 | 2.2 ± 0.6 | 2.2 ± 0.5 | | 2.1 ± 0.6 |
| DS (%) | 97 ± 10 | 29 ± 12 | 36 ± 20 | (P < 0.001) | 76 ± 19 |
| MLD (mm) | 0.11 ± 0.42 | 2.25 ± 0.62 | 2.04 ± 0.86 | (P < 0.001) | 0.70 ± 0.58 |
| Ref (mm) | – | 3.17 ± 0.66 | 3.15 ± 0.64 | (P = 0.244) | 3.02 ± 0.66 |
| Balloon (mm) | 2.98 ± 0.39 | | | | |

F-U = follow-up; No of Proj = number of projections analysed quantitatively; DS = diameter stenosis; MLD = minimal luminal diameter; Ref = reference diameter (interpolated method); Balloon = size of the largest balloon used during the angioplasty procedure.

reach statistical significance due to the small number of patients with reocclusion (5%). The results of the quantitative analysis of all patients as represented in Table 4 show a very marked difference in favor of the angioplasty patients. Even corrected for the relatively large proportion of patients with an occluded vessel in the streptokinase group (Table 5, compare A4 versus S2) there remains a very large difference between the two treatment groups as assessed by quantitative angiography.

## Discussion

Our study shows that direct coronary angioplasty in patients with an acute myocardial infarction is associated with a higher patency rate of the infarct related coronary artery, with a less severe residual stenotic lesion, a better left ventricular ejection fraction and a lower incidence of recurrent myocardial ischemia as compared to intravenous streptokinase. Several important issues should be considered to place these results into perspective.

Over the last decade, great efforts have been made to assess the optimal approach for patients with acute myocardial infarction with attention focussing on large scale trials with mortality as primary end point. However, the funds and patient numbers to support multiple "megatrials" are simply not available [28]. Left ventricular ejection fraction has been proposed [29] as well as rejected [28] as end point in trials in acute myocardial infarction. Long term survival after reperfusion therapy is strongly related to left ventricular ejection fraction [30], but one of the main objections against ejection fraction as end point has been the problem of "missing values" and the consequent debate about imputation of data due to failures to obtain the study or technically inadequate studies [28]. A second end point of our study is recurrent myocardial ischemia. As the mortality of acute myocardial infarction has steadily declined over the last decades and is less than 10% in

*Table 5.* Clinical and quantitative angiographic data of 6 subsets of patients.

| | | | | | | | | Before treatment | | | After treatment | | | At follow-up | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Age | Male | VD | Ant | Prev.inf | Time | EF | DS | MLD | Ref. | DS | MLD | Ref. | DS | MLD | Ref. |
| A 1 N = 2 | 65 | 100% | 2.5 | 0% | 0% | 192 | 53% | 49% | 2.1 | 4.1 | – | – | – | – | – | – |
| A 2 N = 4 | 65 | 75% | 3.5 | 25% | 50% | 120 | 47% | 92% | 0.2 | 2.9 | – | – | – | – | – | – |
| A 3 N = 3 | 57 | 67% | 2.3 | 67% | 33% | 157 | 38% | 100 | 0.0 | 2.7 | 32% | 1.8 | 2.7 | 100% | 0.0 | 2.7 |
| A 4 N = 61 | 58 | 90% | 2.0 | 46% | 16% | 171 | 51% | 98% | 0.0 | 3.2 | 28% | 2.3 | 3.2 | 32% | 2.2 | 3.2 |
| S 1 N = 23 | 63 | 87% | 2.4 | 43% | 26% | 201 | 42% | – | – | – | – | – | – | 100% | 0.0 | 2.9 |
| S 2 N = 49 | 60 | 80% | 1.7 | 41% | 8% | 144 | 46% | – | – | – | – | – | – | 67% | 1.0 | 3.0 |

A 1 = Patients randomized to angioplasty who were treated conservatively; A 2 = Patients randomized to angioplasty who were treated with immediate bypass surgery (this includes 1 patient with failed angioplasty); A 3 = Patients who did undergo angioplasty but had an occluded infarct related vessel at follow-up angiography; A 4 = Patients who did undergo angioplasty and had a patent vessel at follow-up angiography; S 1 = Patients randomized to streptokinase with an occluded vessel at angiography; S 2 = Patients randomized to streptokinase with a patent vessel at angiography.

All values reported are mean values; age = years; VD = number of diseased vessels whereby 4 is used for left main disease; ant = anterior infarct location; prev.inf = a clinically documented previous myocardial infarction; time = time from symptom onset to hospital admission (min); EF = left ventricular ejection fraction; DS = diameter stenosis; MLD = minimal luminal diameter(mm) and Ref = reference diameter (mm).

many recently published trials [8–11], morbidity in the survivors becomes the most relevant clinical end-point. Direct angioplasty as compared to streptokinase reduces the incidence of recurrent myocardial ischemia drastically.

The primary target of all reperfusion therapies is the reopening of acutely occluded coronary arteries. Two aspects of "patency" are important in this regard. Firstly, the time needed to establish reflow in the infarct related artery. Our angioplasty patients had acute patency rates that are not obtainable with currently available thrombolytic agents. Secondly, persistent patency of the infarct related artery is related to long-term survival [2]. The consequences of reocclusion after initially successful reperfusion are certainly a major concern [31]. However, the frequency of this phenomenon is low. Patency in the angioplasty group was 91%, two hours after admission, and still 91% at follow-up angiography after a mean of 82 days. So regardless of the timing of (repeat) angiography to assess patency, angioplasty patients have a higher patency rate.

The coronary angiographic findings of trials of acute myocardial infarction have so far been mostly assessed by visual interpretation of the angiograms, irrespective of whether stenoses grades or flow grades have been used [1–3, 6–11]. The well known limitations of visual assessment do not have to be emphasized here, but make it mandatory that more objective means should be developed to measure or assess the results of reperfusion therapies. Recently some doubt has been cast on whether the most widely used definition of patency, a TIMI grade 2 or 3 perfusion, is a proper way to assess the results of reperfusion therapies in acute myocardial infarction [32, 33], and this makes the introduction of more objective measurements, preferably not user dependent even more imperative. Methods that assess coronary flow parameters have in the setting of acute myocardial infarction the disadvantage that flow is not only dependent on coronary anatomy but probably even more related to myocardial function [34]. Quantitative analysis of the infarct related vessel is therefore currently the only objective means to compare the efficacy of different therapeutic strategies in patients with an acute myocardial infarction.

Our study demonstrates with quantitative analysis of the infarct related vessel a marked difference in the severity of the residual lesion after reperfusion. The fact that the mean left ventricular ejection fraction of patients treated with angioplasty is higher than the ejection fraction of streptokinase patients with patent vessels at the follow-up could very well be related to the superior coronary anatomy of patients treated with angioplasty. A recent study showed a close relation between the residual stenosis of the infarct related vessel and the degree of left ventricular dilatation after myocardial infarction [35]. The residual coronary artery obstruction may limit flow even after "successful" thrombolysis and result in continuing ischemia, delayed recovery and even ongoing necrosis of the myocardial tissue involved [32, 36]. Future studies combining quantitative assessment of both left ventricular function and coronary anatomy will increase our understanding of the thera-

peutic efficacy of different approaches to treat patients with an acute myocardial infarction.

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# 23. Merits of quantitative coronary angiography after thrombolytic therapy for evolving myocardial infarction

ALFRED E.R. ARNOLD and PATRICK W. SERRUYS

## Introduction

Acute myocardial infarction is caused by an acute occlusion of a coronary artery most often by a thrombus which is an attempt of nature to repair a sudden fissure in an atherosclerotic plaque in the vessel wall and is the net result of thrombogenic triggers and fibrinolytic plasminogen activators naturally occurring in the vessel endothelium. Whereas directly after the occurrence of the crack in a plaque thrombogenic triggers predominate, endogenous fibrinolysis often results in reopening of the occluded coronary artery in the days thereafter. This late reopening of the vessel may be important for the prognosis of the patient, but occurs often too late to limit infarct size. Therefore, administration with thrombolytic agents is needed to accelerate this process. Above pathophysiologic and therapeutic mechanisms are responsible for a rapid changing morphology in the infarct related coronary artery.

The extent of coronary artery disease and the residual left ventricular function are major determinants of prognosis after myocardial infarction [1]. Precision and accuracy of visual assessment of coronary artery narrowings are poor and, therefore, much effort is invested in the development of better techniques to measure coronary artery stenoses. In the early eighties a computer-based Coronary Angiography Analysis System (CAAS) was developed at the Thoraxcenter that allows an accurate assessment of the coronary artery narrowing by means of automated contour detection principles [2–3]. In the present survey, our experience with the CAAS system in patients with acute myocardial infarction is summarized.

## What can be measured in the infarct related coronary segment?

In the setting of acute myocardial infarction one can be a student of the hemodynamic effects of an infarct related coronary artery stenosis or one can be interested in the amount of atherosclerotic plaque ("plaque area"),



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which may partially consist of thrombus material and may be influenced by antithrombotic and thrombolytic therapy.

*Hemodynamic description of the stenosis*

*Minimal luminal diameter*

Historically coronary artery narrowings were measured in terms of luminal diameter (or area) stenosis. In clinical cardiology, a luminal diameter stenosis of 50% or more is considered clinically significant, since such diameter narrowings were found to decrease coronary flow reserve in the dog [4]. Resting blood flow did not change until coronary luminal diameter stenosis exceeded 90%. Although in animal experiences investigators could define the effects of progressive stenosis on resting and maximal coronary flow, in humans with atherosclerotic coronary artery disease there is a rather poor correlation between percent diameter stenosis and the physiological significance of a given obstruction [5]. This is due to asymmetry of the lesion and to the fact that often vascular segments immediately proximal and distal to the stenosis are abnormal due to atherosclerosis. Furthermore, the length of the coronary obstruction [5], especially at intermediate levels of stenoses, has impact on the physiological significance of coronary lesions. In addition, in the setting of acute myocardial infarction luminal diameter measurements have the disadvantage that lesions need to be symmetric in all directions [6]. But atherosclerotic infarct related narrowings are often not symmetric and very irregular [7–9]. In Fig. 1 some examples of the complex nature of infarct related stenoses are given. Geometric reconstruction of these asymmetric lesions is perhaps feasible from multiple different views, but certainly complicated and does not yield a single parameter for reporting. Furthermore, multiple matched angiographic projections are difficult to be obtained, especially if stenoses are assessed twice in time and paired data are required. For example, in the Reocclusion Trial of the European Cooperative Study Group in only 58% of the patients more than a single view could be obtained [10]. Therefore, effort has been invested to develop measures that do not have above disadvantages. With densitometric determined percentage area stenosis part of these problems are circumvented.

*Densitometric percentage area stenosis*

Using a known relation between the thickness of the irradiated object and the density level in the angiographic image, the true luminal cross sections of a contrast filled coronary artery can be computed, even from a single X-ray projection [6]. However, this feature came available only during the last years and many work is done without densitometry.

*Transstenotic pressure drop*

This parameter integrates length of the stenosis, minimal cross-sectional area, Poiseuille and turbulent resistance: the transstenotic pressure drop for

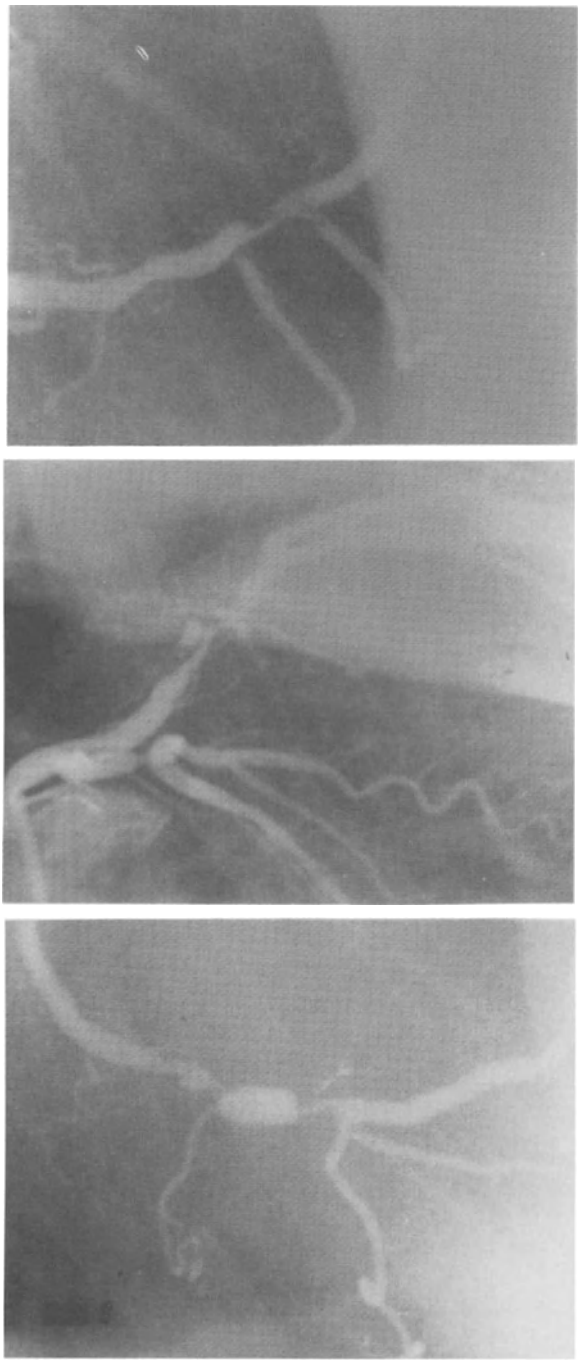

*Figure 1.* In the setting of acute myocardial infarction atherosclerotic narrowings are often not symmetric and very irregular. Some examples of the complex nature of infarct related stenoses are given.

assumed blood flows of 1, 2 and 3 ml/sec respectively. In a previously published study we showed a good correlation between the theoretical transstenotic pressure drop and the hemodynamic significance of the lesion in terms of coronary flow reserve, as determined with intracoronary papaverine in patients with stable angina pectoris and an isolated stenosis in the proximal left anterior descending artery [11]. No data are available to establish which coronary flow is optimal in the setting of an acute myocardial infarction. Animal experiments showed an earlier improvement in myocardial function after staged reperfusion in comparison with sudden and complete reperfusion, indicating that there is an optimal flow above which the benefits of reperfusion are diminished, rather than "the more, the better" [12]. Previously we reported a resting great cardiac vein blood flow of 1.3 ml/sec (median, range 1.0–2.1) in patients with stable angina before angioplasty of an isolated lesion in the left anterior descending artery [13]. Ganz found a mean coronary sinus flow of 2.0 ml/sec (range 1.4–2.7 ml/sec) for 14 normal subjects at rest and a mean great cardiac vein flow of 1.1 ml/sec (range 0.9–1.3 ml/sec) for 8 normal subjects at rest [14]. Therefore, we considered a flow of 2 ml/sec as optimal in the setting of acute myocardial infarction. The following formula was applied to calculate the transstenotic pressure drops across the stenoses [13, 15, 16]:

$$\text{Pgrad} = Q\ (\text{Rp} + Q^{*}\text{Rt}),$$

in which Q is the mean coronary blood flow (ml/sec), Rp is Poisseuille resistance and Rt is the turbulent resistance.

$$\text{Rp} = \text{C1} \times \frac{(\text{length obstruction})}{(\text{minimal cross sectional area})^2}$$

C1 = 8 pi (blood viscosity)
blood viscosity = 0.03 (g/cm/sec)

$$\text{Rp} = \text{C2} \times \left[\frac{1}{\text{min cross-sectional area}} - \frac{1}{\text{normal distal area}}\right]^2$$

$$\text{C2} = \frac{\text{blood density}}{0.266}$$

blood density = 1.0 ($g/cm^3$)

Transstenotic pressure drops were calculated for an assumed coronary blood flow of 1, 2, and 3 ml/sec. A transstenotic pressure drop exceeding 40 mmHg was considered to be flow-limiting, as it reduces a proximal pressure of 80 mmHg to a distal stop-flow perfusion-pressure of 40 mmHg [17]. Results from different angiographic projections were averaged.

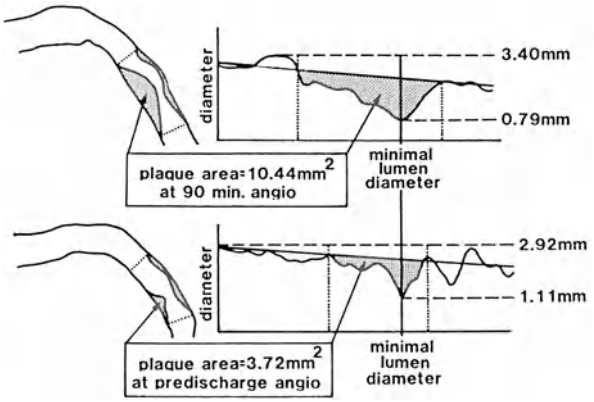


*Figure 2.* Thrombolytic therapy may result in a decrease of "plaque area" by cleaning-up of thrombolytic material without affecting the minimal lumen diameter. This is the case when thrombus material is mainly located both upstream and downstream to the site of maximal obstruction rather than at the site where the atherosclerotic lesion is maximally narrowing the vessel.

## *Description of the plaque*

### *Plaque area*

In contrast with diameter measurements, "plaque area" is an index of the thrombus associated with the stenosis. The "plaque area" measurement is based on a series of measurements along the length of the stenosis, rather than one single measurement at the site of the maximal stenosis as is the case for diameter stenosis or minimal lumen diameter measurements. "Plaque area" is therefore theoretically more accurate to describe cleaning-up by endogenous thrombolysis and administration of thrombolytic therapy than parameters of luminal diameter measurements like minimal luminal diameter or diameter stenosis. In fact, a decrease of "plaque area" by cleaning-up of thrombolytic material may occur without affecting the minimal lumen diameter or diameter stenosis if this thrombus material is mainly located both upstream and downstream to the site of maximal obstruction rather than at the site where the atherosclerotic lesion is maximally narrowing the vessel. This is illustrated in Fig. 2.

## Methods

### *Patients studied*

*Intracoronary streptokinase*
Patients with acute myocardial infarction at the Thoraxcenter were treated with intracoronary streptokinase between September 1980 and 1982. One hundred and five patients reported here were included in a multicenter trial of the Interuniversity Cardiology Institute of the Netherlands. Patients below 65 years of age were selected if ST-segment elevation was present and if the patient arrived within 4 hr after onset of symptoms. Intravenous nitrates and lignocaine 2 mg/min were administered to all. Heparin 5000 IU and 250 mg aspirin were administered intravenously after femoral arterial puncture. Non-ionic contrast was used to opacify the infarct related vessel. Subsequently, 0.2 mg nifedipine was administered intracoronarily before start of intracoronary streptokinase at a rate of 4000 units per min to a maximum of 250.000 units. If there were no signs of recanalization streptokinase was administered superselectively through a 2–3 French catheter. In 16 patients immediate angioplasty was performed in addition to intracoronary streptokinase.

*Recombinant tissue-type plasminogen activator*
One hundred twenty three patients were enroled in the Reocclusion Trial of the European Cooperative Study Group (ECSG). Consenting patients between 21 and 70 years, with chest pain for at least 30 min with ST-elevation of at least 0.2 mV in 2 limb leads or 0.3 mV in 2 precordial leads (60 msec after J-point) within 4 hr after start of symptoms, were treated with 40 mg of recombinant tissue-type plasminogen activator (rt-PA, G-11021, Genentech Inc., supplied by Boehringer Ingelheim GmbH) infused in 90 min after an intravenous bolus of 5000 IU heparin [18]. Patients with a patent infarct related vessel (locally assessed) were randomized to receive a second infusion of 6 hr duration, containing either 30 mg rt-PA or placebo. Recatheterization was performed at 6–24 hr after start of the 2nd infusion, and before discharge. A survey of patients with coronary angiography of sufficient quality to allow quantitative analysis is given in Fig. 3. Reasons for missing quantitative coronary angiography were published in detail previously [10]. In 18 out of 47 cases (38%) this was due to poor quality coronary angiography and in another 18 cases (38%) because registration was done in video format only.

### *Angiographic protocol*

For each series of angiograms following the initial angiogram the X-ray system was repositioned in projections corresponding as closely as possible to those obtained previously. Angiograms were obtained in multiple views, including hemi-axial views for the left coronary artery. The infarct related segment was identified for all films on the basis of electrocardiographic and

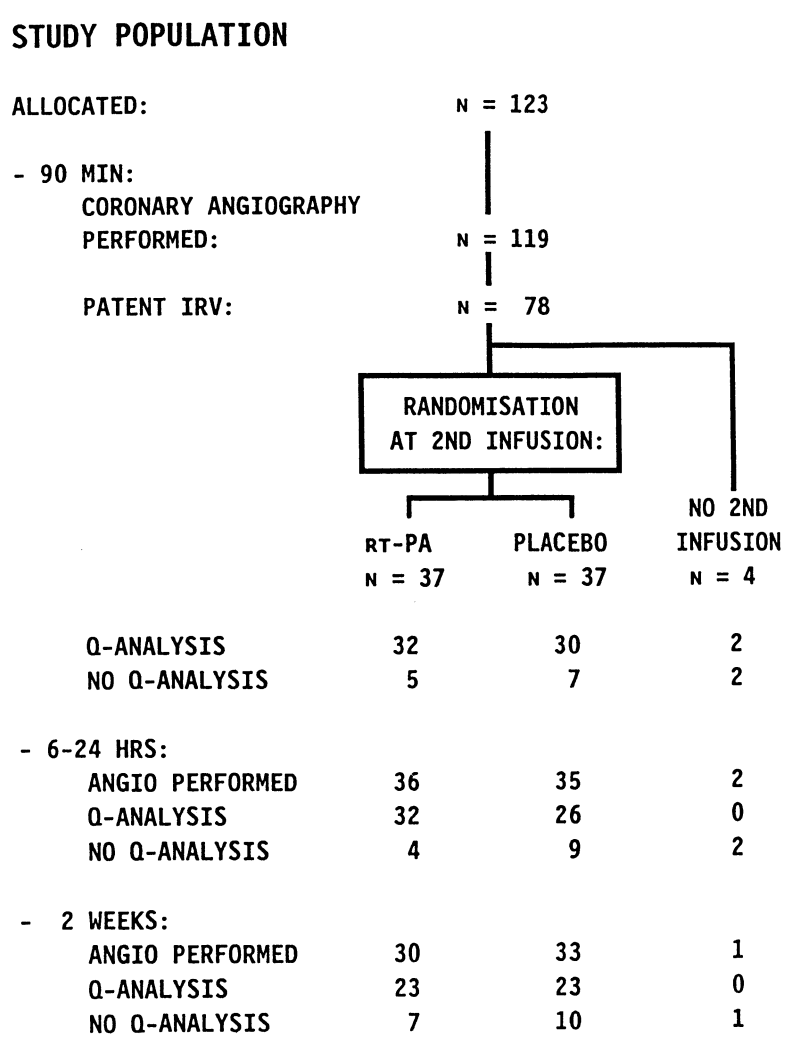


*Figure 3.* A survey of patients with coronary angiography of sufficient quality to allow quantitative analysis (Q-analysis). (Reproduced from reference nr. 10 with permission).

angiographic evidence. In those patients in whom the site of occlusion could not be established with certainty because of multiple lesions, the segment with the smallest minimal lumen diameter at the first film was assumed to be infarct related.

Qualitative assessment of patency was performed using a predetermined code: (0) normal vessel; (1) less than 50% diameter stenosis; (2) diameter stenosis between 50% and 90%; (3) more than 90% diameter stenosis with complete filling of distal vessels, not through collaterals, within three cardiac

cycles; (4) subtotal occlusion, no distal filling within three cardiac cycles; (5) total occlusion with or without collateral filling. End-diastolic cineframes were selected to avoid the blurring effect produced by the motion of the coronary artery during ejection and to limit the foreshortening often observed during systole [2]. Only those projections which were reproduced during sequential filming were selected and quantitatively analyzed. Average values of measurements obtained in multiple angiographic projections were determined for each segment. In the Reocclusion Trial of the ECSG, we excluded angiograms of patients with an occluded infarct related artery at 90 min, as well as the follow-up angiograms of patients in whom mechanical recanalization, angioplasty, or additional pharmacological agents such as streptokinase were applied before the follow-up angiograms were made.

*Analytic procedure*

The coronary cineangiograms were analyzed by CAAS (Pie Data Medical, Maastricht, The Netherlands), a computer-assisted Cardiovascular Angiography Analysis System. From the arterial contour data, a diameter-function was computed. The minimal lumen diameter and a reference diameter, computer-estimated by the interpolated diameter technique, were expressed in millimetres. On the basis of the proximal and distal centerline segments and the computed reference diameter function, the reference contours over the obstructed region was reconstructed. The extent of the obstruction was determined from the diameter function on the basis of curvature analysis and expressed in millimeters. The difference in area between the reference and the detected contours over the lesions is called "plaque area" and expressed in $mm^2$. The measurement error of repeated coronary angiography and quantitative analysis (2 standard deviations of the difference of duplicate measurements) in minimal lumen diameter and interpolated reference diameters were described previously [3]. The measurement error of the obstruction diameter is 0.72 mm, whereas the measurement error of the "plaque area" is 5.34 $mm^2$[19].

## Results

*Residual infarct related stenotic lesion*

*Intracoronary streptokinase*

Among 75 patients with successful recanalization by thrombolytic treatment the median lumen diameter was 1.32 mm and the 80% range was 0.78 and 1.88 mm (see Table 1). The median percentage diameter stenosis was 58%, with a 80% range of 37 to 74%. A percentage diameter stenosis of 50% or

*Table 1.* Parameters of quantitative coronary angiography in patients treated with intracoronary streptokinase a patent infarct related vessel at 90 min. Results are given as median and 80% range

| | All patients 90 min (n = 75) | |
|---|---|---|
| Minimal lumen diameter (mm) | 1.32 | (0.78–1.88) |
| Reference diameter (mm) | 2.98 | (2.22–4.20) |
| Length of stenosis (mm) | 9 | (2–16) |
| Diameter stenosis (%) | 58 | (37–74) |

more was found in 69% of patients. Only 19% of patients had a diameter stenosis of 70% or more.

*Recombinant tissue-type plasminogen activator*

Out of 123 patients enroled in the Reocclusion Trial of the European Cooperative Study Group, 119 underwent coronary angiography at the end of a 90 min infusion of 40 mg of rt-PA. Visual assessment revealed a patent infarct related vessel in 78 patients (66%, 95% confidence interval 57%–74%) and an occluded or minimally perfused infarct related vessel in 41 patients (34%). In patients with a patent coronary artery at 90 min after start of thrombolytic therapy the median value for the minimal lumen diameter was 1.19 mm with a 90% range of 0.69 mm to 2.55 mm (see Table 2). The median value for the percentage diameter stenosis was 56% with a 95% range of 17% to 80%. Thus only 5% had a diameter stenosis of 80% or more. As is illustrated in Fig. 4 a residual stenosis impeding coronary blood flow at rest (computed transstenotic pressure drop exceeding 40 mmHg for a flow of 2 ml/sec) was found in 13% percent of patients with a patent infarct related vessel. Out of 8 patients with a theoretical transstenotic pressure drop exceeding 40 mmHg at 2 ml/sec, only one patient had a percentage diameter stenosis of 80% or more at the 90 min angiogram. A residual lesion that impedes coronary blood flow at rest, was found more frequently in the left anterior descending artery than in the circumflex and the right coronary artery (22% vs 10%). Transstenotic pressure drops are not available for patients treated with intracoronary streptokinase.

*Evolution of the residual lesion after initial thrombolysis*

*Recombinant tissue-type plasminogen activator*

Patients with a patent infarct related vessel were randomized to a further 6-hour infusion with either 30 mg rt-PA or placebo, to establish the effect on the reocclusion rate. Coronary angiography was repeated at 6–24 hrs and before hospital discharge. The reocclusion rate at 6–24 hrs was 7% (95% confidence limits 2%–15%). Three of the 60 patients (5%, 95% confidence

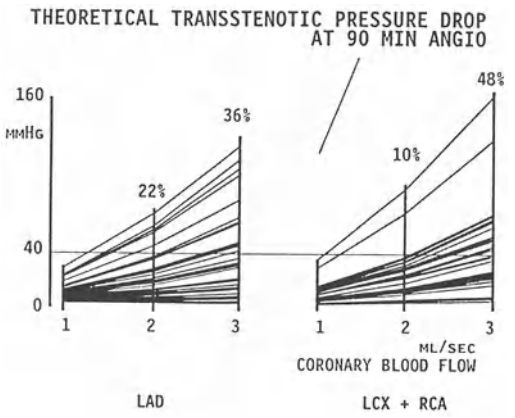


*Figure 4.* Theoretical transstenotic pressure drop across the infarct-related residual stenosis at 90 min after the start of rt-PA infusion in patients with a patent infarct related vessel at 90 min. Cases are subdivided in two groups: the 1st group consists of cases in which the left anterior descending artery (LAD) is infarct-related and the 2nd group combines cases with the circumflex (LCX) and the right coronary artery (RCA). The percentages refer to the fraction of patients with a transstenotic pressure drop exceeding 40 mmHg. (Reproduced from reference nr. 10 with permission).

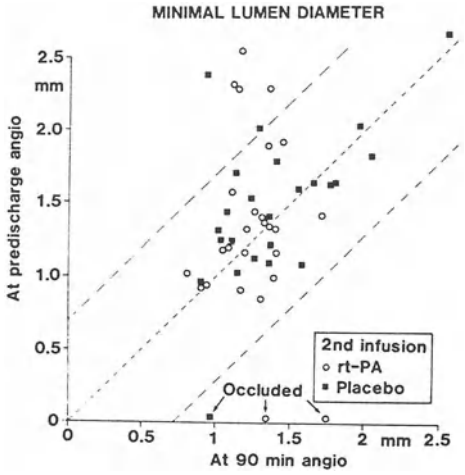


*Figure 5.* Scatterplot showing the minimal lumen diameter at 90 min angiography (x-axis) and at predischarge angiography (y-axis). The 2 lines parallel to the identity line indicate the measurement error band. (Modified from reference nr. 19 with permission).

*Table 2.* Parameters of quantitative coronary angiography 1n patients treated with tissue-type plasminogen activator with a patent infarct related vessel (4 patients with minimal perfusion are included) at 90 min. Results are given as median and 90% range

| | All pts | rt-PA at 2nd infusion | | Placebo at 2nd infusion | | | |
|---|---|---|---|---|---|---|---|
| | 90 min (n = 68) | 90 min (n = 35) | 6–12 hrs (n = 35) | predischarge (n = 27) | 90 min (n = 30) | 6–12 hrs (n = 28) | predischarge (n = 24) |
| Min lumen diam (mm) | 1.19 (0.69–2.55) | 1.19 (0.79–1.83) | 1.36 (0.86–2.49) | 1.40 (0.88–2.58) | 1.25 (0.89–2.55) | 1.40 (0.92–2.36) | 1.55 (0.98–2.70 |
| Reference diameter (mm) | 2.77 (1.40–4.78) | 2.66 (2.03–4.78) | 2.96 (1.92–4.17) | 2.81 (2.05–3.69) | 2.92 (1.4–3.86) | 2.90 (1.67–5.77) | 2.92 (1.66–4.25) |
| Length of stenosis (mm) | 6.8 (4.1–10.8) | 6.9 (4.7–10) | 6.8 (5.0–9.8) | 6.8 (5.2 –9.6) | 6.7 (3.6–10.8) | 6.7 (3.7–10.3) | 6.7 (4.0–11.8) |
| Diameter stenosis (%) | 55.7 (16.9–80.0) | 58.1 (16.9–73) | 54.1 (18.7–90.7) | 52.6 (15.3–66.3) | 53.4 (24.3–69.2) | 50.4 (21.1–78.3) | 44.3 (21.6–73.9) |
| Area-stenosis (%) | 80.3 (31.0–95.9) | 82.2 (31.0–92.7) | 78.6 (33.9–87.2) | 75.6 (27.4–88.5) | 78.2 (42.7–90.5) | 75.3 (37.7–95.3) | 68.3 (38.6–93.2) |
| Plaque area (mm2) | 6.85 (1.19–34.29) | 6.99 (2.25–18.42) | 6.66 (1.57–16.12) | 5.04 (1.18–17.25) | 6.73 (1.19–16.6) | 6.81 (1.26–19.57) | 5.78 (1.86–15.57) |
| Symmetry index | 0.43 (0.01–0.93) | 0.42 (0.01–0.93) | 0.45 (0.14–0.91) | 0.28 (0.04–0.67) | 0.43 (0.09–0.85) | 0.26 (0.06–0.98) | 0.36 (0.05–0.95) |

Diam: diameter.

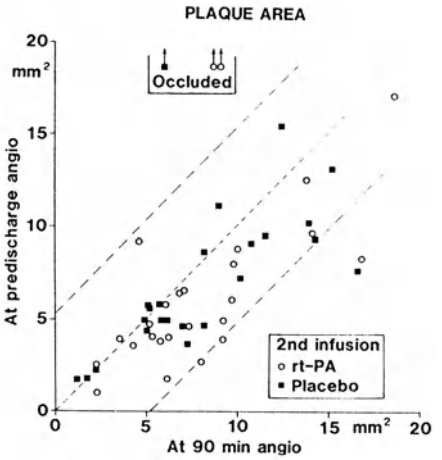


*Figure 6.* Scatterplot showing the "plaque area" at 90 min angiography (x-axis) and at predischarge (y-axis). The 2 lines parallel to the identity line indicate the measurements error band. (Modified from reference nr. 19 with permission).

limits 1% to 14%) with patent arteries at both previous angiograms had a later occlusion as judged on the angiogram made at hospital discharge. There was no difference between the two treatment groups in early or late reocclusion.

The degree of narrowing of the residual lesion, as quantified by minimal lumen diameter as well as plaque area, showed a decreasing trend from 90 min to 6–24 hrs angiography and from the 90 min angio to the predischarge angiogram in both treatment groups. However, this change was more pronounced for "plaque area". This is illustrated in Figs 5 and 6 where the minimal lumen diameter and the "plaque area" measured at predischarge are plotted against the measurements obtained from the 90 min angio with the measurement error bands imposed. Eighty-eight percent of the lesions (21 out of 24) in patients treated with a continued infusion of rt-PA were found to have a decrease in plaque area whereas only 57% of the lesions in the placebo group (13 out of 23) showed a reduction in plaque area ($p < 0.025$, chi square test).

Also the calculated transstenotic pressure drop changed from the 90 min angiography to the 6–24 hrs film and from the 90 min film to the predischarge angio, irrespectively whether a prolonged infusion of rt-PA was given. Whereas at 90 min 13% of patients with a patent infarct related coronary segment showed a transstenotic pressure drop exceeding 40 mmHg at a coronary flow of 2 ml/sec, at 6–24 hrs this was true for 6 of the 60 patients (10%) with an adequate coronary angio. At the time of the predischarge angio 5 out of 47 patients (11%) had a transstenotic pressure drop of more than 40 mmHg at a coronary flow of 2 ml/sec.

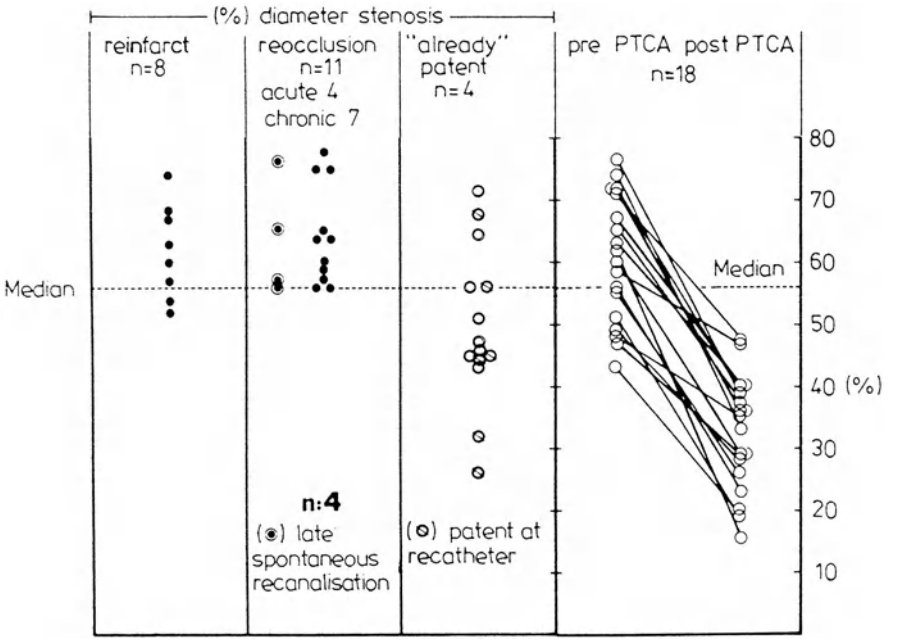


*Figure 7.* Percentage diameter stenosis in patients with reinfarction, angiographic reocclusion and those with a patent infarct related vessel at first angio in patients treated with intracoronary streptokinase. In the last column the effect of immediate angioplasty is illustrated. (Reproduced from reference nr. 20 with permission).

### *Value of quantitative coronary angiography for the prediction of reocclusion*

After intracoronary treatment with streptokinase, angiographically assessed reocclusion of the infarct related vessel occurred in 17% of patients during the first 2 weeks. In nearly all patients with reocclusion the infarct related segment was narrowed with a lumen diameter stenosis exceeding 58%. This is illustrated in Fig. 7. In the Reocclusion Trial of the European Cooperative Study Group reocclusion of the infarct related vessel was uncommon and therefore above relation could not be studied.

## Discussion

The quantitative coroanry angiography parameters of the residual infarct related lesion after successful thrombolytic recanalization were very similar in both patient populations. Furthermore, the diameter stenosis was identical to the post-mortem histological cross-sections of coronary arteries in patients

with transmural acute myocardial infarction with narrowings due to atherosclerotic plaque alone to 33–98% (mean 81%) obstructional area stenosis at the site of thrombosis [21]. Infarct related atherosclerotic lesions are usually of a complex nature [7–9]. A break or a tear could be identified in two thirds the cases [7]. It was postulated that exposure of material underlying the lesion to flowing blood was the probable cause of platelet aggregation and fibrin deposition [7]. In half of the patients a haemorrhagic dissection was found that resulted in an apparent reduction of the lumen. As the luminal cross section at the coronary obstruction is frequently irregular in shape, in particular in the setting of a myocardial infarction, the severity of the lesion should be quantified in as many angiographic projections as possible when the efficacy of the thrombolytic agent is to be assessed by diameter measurements [6, 22]. One of the limitations of quantitative coronary angiography in clinical practice lies in the limited number of matched angiographic projections available per patient (average 1.7). It should be pointed out that a selection bias may be introduced by the fact that in some cases, where complete occlusion occurred at a follow-up angio, serial quantitative analysis was not possible.

*Residual lesions after thrombolysis*

The values for minimal luminal diameter and percentage diameter stenosis in patients treated with intracoronary streptokinase and rt-PA are very similar. Gold and colleagues [23] have reported a greater degree of stenosis, but used a technique requiring visual interpretation of the arterial contours which may systematically overestimate the stenosis [24].

Assuming that a flow in the infarct related vessel of 2 ml/sec is optimal in patients with acute myocardial infarction, 13% of patients were identified with a flow-limiting transstenotic pressure drop at 90 min. This means that only in a minority of the patients with a successful recanalization with rt-PA, the residual stenosis impedes coronary blood flow at rest. It is therefore questionable on theoretical grounds wether routine coronary angioplasty in addition to thrombolytic therapy in the acute phase should be advocated. Immediate coronary angioplasty in the setting of acute myocardial infarction has been shown to have a lower success rate than in stable angina (65% [25] versus 90% [27, 28]). Furthermore, worsening of coronary flow in the infarct related vessel may occur [25]. Neither does routine coronary angioplasty prevent reocclusion of the infarct related vessel [25, 26, 29].

A trial of the TAMI study group [26], comparing immediate angioplasty with elective angioplasty at 7 days after successful recanalization showed no advantage of immediate angioplasty in terms of reocclusion or left ventricular function. Fifteen percent of the patients with successful recanalization allocated to angioplasty at 7 days needed cross-over to emergency angioplasty for definite recurrent ischemia. This is compatible with the finding in the present trial that 13% of the patients have residual stenoses that impede

coronary blood flow at rest. In patients treated with intracoronary streptokinase the severity of the residual infarct related coronary stenosis was related 3to subsequent reinfarction and reocclusion (Fig. 7). Angioplasty was suggested to be of value in these patients [22]. Such a strategy is however still not studied in a randomized trial. Also other preventive strategies, e.g. with aggressive antithrombotic regimen, are worthwhile to be studied.

*Evolution of residual lesions*

There was a consistent improvement between the first and second and first and third angiograms for all stenosis measurements except the symmetry index. This tendency to improve with time has been reported previously for both streptokinase induced and spontaneous reperfusion [25, 30–35]. In contrast with diameter measurements, the "plaque area", which under these conditions is probably an index of the thrombus associated with the stenosis, showed a significant difference between heparin alone and rt-PA plus heparin groups. The "plaque area" measurement is based on a series of measurements along the length of the stenosis, and may therefore be more sensitive than measurement of the minimal cross sectional area. It could be argued that thrombolytic therapy was helping to clear up thrombus both upstream and downstream to the site of obstruction rather than affecting the stenotic lesion itself. Qualitative assessment of the angiogram of the infarct related segment only describes secondary thrombus formation in terms of reocclusion, which is essentially an all or nothing phenomenon. Quantitative assessment, however, allows a more detailed and objective analysis of the gradual change, if any, of the morphology of the residual lesion which may partly consists of remnant thrombi.

There is a spontaneous trend to decreasing transstenotic pressure drops during the early days after the acute stage of the myocardial infarction. The improvement in transstenotic pressure drops during hospital stay is concomitant with a decrease in "plaque area", which in the setting of acute myocardial infarction probably consists partly of thrombus. This theory is in concordance with the finding that in the group that received a second infusion with rt-PA even more patients demonstrated a decrease in "plaque area" [19]. Because the obstruction length did not change during hospital stay the decrease in transstenotic pressure drop is caused by a decrease in minimal luminal diameter. The decrease in minimal luminal diameter is not due to vasomotor hyperactivity during the acute phase of the myocardial infarction, for, as demonstrated in Table 2, the reference area does not change during follow-up angiography.

## Conclusion

Quantitative coronary angiography with the CAAS system provides precise measures of the infarct related coronary segment. After successful recanalization in only a minority of patients have severe stenosis impeding blood flow at rest. The amount of atherosclerotic plaque and associated thrombus decrease further in the days after thrombolytic therapy.

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*PART SIX: QCA applied to the evaluation of immediate and long term outcome following coronary balloon angioplasty: experiences emerging from long multicentre restenosis prevention trials*

# 24. Elastic recoil after percutaneous transluminal coronary angioplasty. A quantitative angiographic approach

BENNO J. RENSING, WALTER R.M. HERMANS and PATRICK W. SERRUYS

## Introduction

Percutaneous transluminal coronary angioplasty (PTCA) is increasingly being used as an alternative to coronary artery bypass grafting in patients with acute and chronically obstructed vessels [1, 2]. Despite many publications on the mechanism of this treatment modality, little is known about the elastic behaviour of the vessel wall during and immediately after angioplasty. Castaneda-Zuniga et al. proposed an arterial paralysis model in which overstretching of the vessel wall beyond its limits of elasticity, was associated with histopathologic features of smooth muscle cell lysis [3]. According to Sanborn et al. part of the angioplasty mechanism consists of stretching the vessel wall resulting in a fusiform dilatation or localised aneurysm formation [4]. It is however a common clinical observation that in some lesions even the application of an oversized balloon leads to a poor angiographic result without a visible intimal tear or dissection. This phenomenon may be attributed to elastic recoil of the vessel wall after balloon angioplasty.

In this chapter chapter the influence of elastic recoil on the immediate, short term (24 hr) and long term (6 months) results of the balloon angioplasty procedure will be described.

## Methods

The quantitative angiographic methods (automated edge detection and densitometry) used in the studies described in this chapter were extensively discussed in the previous chapter.



*P.W. Serruys, D.P. Foley and P.J. de Feyter (eds.), Quantitative Coronary Angiography in Clinical Practice*, 415–431.

*Table 1.* Recoil in 151 coronary arterial narrowings.

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

CSA = cross-sectional area; MLCA = minimal luminal cross-sectional area; Recoil = balloon CSA - MLCA after PTCA.

## *I. Recoil and immediate angioplasty result*

### *Assessment of elastic recoil*

A successful PTCA was defined as a visually assessed diameter stenosis after PTCA of less than 50%. Single identical views pre PTCA, post PTCA and during complete expansion of the largest balloon at highest inflation pressure were chosen for densitometric analysis. Inflation pressure and duration of inflation were left to the discretion of the operator. Mean balloon cross-sectional areas were calculated from diameter values, assuming a circular cross-section at maximal inflation pressure. The same X-ray setting in terms of kilovoltage and milliamperes were used during the 3 cine recordings. In order to have the segment to be analysed as much perpendicular to the incoming x-rays as possible, a view was chosen with the coronary artery appearing least foreshortened. The same amount of nitrates, either nitroglycerine 0.1–0.3 mg or isosorbidedinitrate 1–3 mg, were given intra coronary before the pre- and post-angioplasty cinerecordings. This was done to maximally dilate the vessel and so to control the varying influence of vasomotor tone on luminal dimensions. Elastic recoil was then calculated as the difference between the minimal luminal cross-sectional area post-PTCA and the mean balloon cross-sectional area ($mm^2$).

### *Recoil and immediate angioplasty result*

The densitometric analysis of 151 dilated segments in 136 patients is listed in Table 1. Mean age of the 136 patients was 56.8 ± 8 years. There was no significant change in "interpolated" reference area after PTCA. Pre PTCA 6.0 ± 2.5 $mm^2$, post PTCA 6.2 ± 2.5 $mm^2$ (NS). The minimal luminal cross-sectional area increases from 1.1 ± 0.9 $mm^2$ to 2.8 ± 1.4 $mm^2$ ($p < 0.001$). The mean balloon cross sectional area was 5.2 ± 1.6 $mm^2$. Elastic recoil was 2.4 ± 1.4 $mm^2$. So nearly 50% of the theoretically achievable cross-section (i.e. balloon cross-sectional area) was lost immediately after the last balloon deflation. A subset of 16 patients (18 lesions) were angiographically reexamined 24 hr after PTCA as part of a study looking at changes in coronary flow reserve in the first 24 hr after balloon dilatation. Minimal luminal cross-secional area directly after PTCA in this group was 2.0 ± 0.8 $mm^2$ and 1.9 ± 0.5 at 24 hr (NS).

*Table 2.* Effect of balloon sizing on the amount of elastic recoil.

| Balloon-Artery Ratio | $\leq 1$ | $>1$ | $p$ value |
|---|---|---|---|
| $n$ | 87 | 64 | |
| Reference-diameter (mm) | 3.0 ± 0.5 | 2.3 ± 0.4 | $p < 0.001$ |
| Balloon-diameter (mm) | 2.5 ± 0.4 | 2.6 ± 0.4 | NS |
| Recoil (mm) | 0.6 ± 0.30 | 0.8 ± 0.3 | $p < 0.001$ |

Balloon-artery ratio = balloon diameter/reference diameter.

*Table 3.* Clinical charataristics and recoil in 136 patients.

| Variable present | Yes | No | $P$ value |
|---|---|---|---|
| Males (recoil) | 112 (0.45 ± 0.31) | 24 (0.42 ± 0.23) | NS |
| Smoking (recoil) | 106 (0.46 ± 0.29) | 30 (0.50 ± 0.23) | NS |
| Hypertension (recoil) | 61 (0.40 ± 0.28) | 75 (0.46 ± 0.29) | NS |
| Diabetes type 1 (recoil) | 1 | 135 | |
| Unstable angina (recoil) | 23 (0.39 ± 0.27) | 113 (0.44 ± 0.26) | NS |

Recoil corrected for reference area.

*Balloon oversizing and elastic recoil*

For each stenotic lesion the balloon-artery ratio was calculated. A ratio greater than 1 indicates oversizing of the balloon. The mean balloon-artery ratio in this study was 0.95 ± 0.18. This indicates a conservative balloon handling, considered to give optimal dilatation of the stenotic lesion with minimal residual stenosis and the smallest incidence of coronary dissection [5, 6]. Lesions with a ratio >1 (oversizing) were compared with lesions with a ratio ≤1. The comparative data are shown in Table 2. No difference was found in balloon diameter between the groups. As expected reference diameter was higher in the group with a ratio ≤1. Elastic recoil was more pronounced in the second group (0.84 ± 0.29 mm vs 0.66 ± 0.30 mm $p < 0.001$). So oversizing of the balloon leads to more elastic recoil. This is in concordance with elastic phenomena: more stretch leads to more recoil (within limits of elasticity).

*Clinical characteristics and recoil*

Clinical characteristics and risk factors of the 136 patients are summarized in Table 3. No differences in elastic recoil was observed for sex, the presence or absence of risk factors and the presence or absence of unstable angina.

Quantitative angiographic lesion characteristics and recoil. Quantitative data on lesion morphology before angioplasty are shown in Table 4. To avoid arbitrary subdivision of data, cut-off criteria for lesion length, symmetry, plaque area and curvature value were derived by dividing the data in 3 groups so that each group contained about one third of the population [7].

*Table 4.* Angiographic and procedural characteristics and recoil of 151 lesions.

| Variable present | Yes | No | *p* value | Mean |
|---|---|---|---|---|
| Lesion length >5.2 mm and <7 mm (recoil) | 50 (0.48 ± 0.25) | 101 (0.43 ± 0.33) | NS | 6.4 ± 2.4 mm |
| Calcified lesion (recoil) | 22 (0.43 ± 0.29) | 129 (0.45 ± 0.45) | NS | |
| Symmetry <0.37 (recoil) | 51 (0.48 ± 0.33) | 100 (0.41 ± 0.30) | $p = 0.07$ | 0.5 ± 0.3 |
| Plaque area <4.5 $mm^2$ (recoil) | 50 (0.53 ± 0.33) | 101 (0.41 ± 0.27) | $p < 0.01$ | 6.8 ± 3.9 $mm^2$ |
| Curvature <12.5 units (recoil) | 51 (0.53 ± 0.34) | 100 (0.43 ± 0.31) | $p < 0.01$ | 17.7 ± 10.4 |
| Max. infl. pres. <8 atm (recoil) | 49 (0.46 ± 0.24) | 102 (0.46 ± 0.35) | NS | 9.6 ± 2.5 atm |
| Inflation duration <220 seconds (recoil) | 50 (0.47 ± 0.30) | 101 (0.44 ± 0.29) | NS | 309 ± 170 seconds |

Atm = atmospheres; max. infl. pres. = maximal inflation pressure of the balloon; NS = difference not significant. Recoil corrected for reference area. See text for description of cut-off points.

The group with the highest amount of recoil was then compared with the 2 other groups. Lesions with a small plaque area and lesions with a shallow curvature showed significantly more recoil (Table 4).

*Procedural related variables and recoil*

In Table 4 total inflation duration and maximal balloon inflation pressure in relation to elastic recoil are summarized. No differences in elastic recoil were observed.

*II. Regional distribution of elastic recoil*

In a larger set of patients (526 patients, 607 lesions) the regional distribution of elastic recoil over the main branches of the coronary tree was studied. Data are summarized in Table 5. The beginning and end-points of the different coronary segments are shown in Fig. 1. The definitions are slightly modified from those of the American Heart Association [8]. Data on diagonal branches and the ramus descendens posterior in case of a left dominant system are omitted because of the small number of segments dilated in this series (5 and 0, respectively). Recoil, normalized for vessel size, increased from proximal to distal parts for all three major coronary branches. This increase in elastic recoil corresponds to a significant increase in the balloon-artery ratio from the proximal to distal parts of the coronary arteries (Table 5). Thus a tendency exists of balloon oversizing in distal parts of the coronary tree. Whether this tendency is caused by economic motives, an extra balloon for a second distal site nearly doubles the cost of angioplasty disposables, or

*Table 5.* Elastic recoil in different segments.

| | *n* | Recoil/reference | Balloon-artery ratio |
|---|---|---|---|
| LAD prox | 118 | 0.43 | 0.90 |
| LAD mid | 120 | 0.48 | 0.97 |
| LAD dist | 23 | 0.61 | 1.20 |
| CFX prox | 39 | 0.41 | 0.80 |
| CFX mid | 54 | 0.41 | 0.90 |
| Obtuse marginal | 29 | 0.47 | 0.93 |
| Posterolateral | 24 | 0.54 | 1.10 |
| RCA prox | 71 | 0.28 | 0.78 |
| RCA mid | 76 | 0.38 | 0.98 |
| RCA dist | 50 | 0.40 | 0.98 |

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

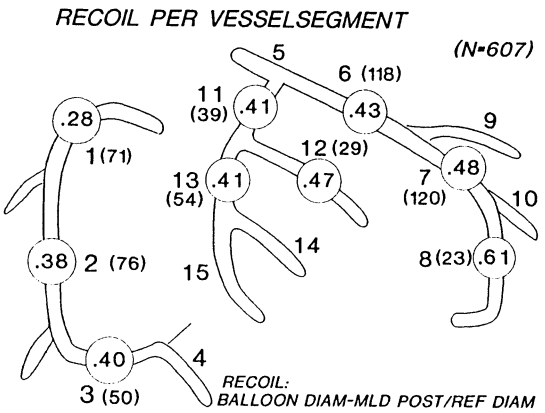


*Figure 1.* Coronary tree divided into 15 different segments with amount of recoil per segment shown in circles. Between brackets are number of lesions dilated for that segment. The amount of recoil was normalized for reference diameter.

is due to visual overestimation of smaller caliber vessels is difficult to discern from our data.

### *III. Recoil and angioplasty result at 24 hour.*

From pathologic and angiographic studies it is known that approximately 70% of atherosclerotic coronary lesions are eccentric [9, 10]. This implies that part of the vessel circumference is free of atherosclerotic plaque and that this disease free portion will be preferentially stretched during balloon angioplasty with little damage to the atherosclerotic plaque [11]. Waller

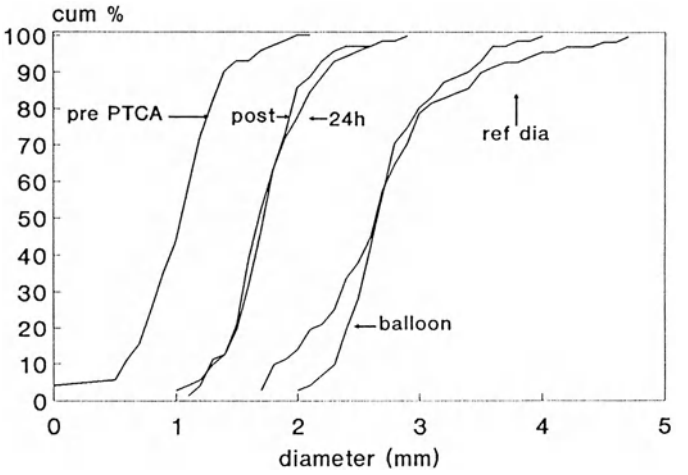


*Figure 2.* Cumulative distributions of minimal lumen diameter (MLD) pre angioplasty, mean balloon diameter, MLD post angioplasty, MLD at 24 hr angiography (fat line) and interpolated reference diameter (dotted line). for the total group of patients

suggested that stretching of the plaque free wall segment may result in an initial increase in luminal diameter but that gradual relaxation or restitution of tone of this overstretched segment reduces the coronary lumen towards its predilatation state in hours to weeks after the angioplasty [11]. This postulated "late recoil" was investigated in a group of patients that agreed to undergo repeat coronary angiography 1 day (range 17 to 29 hr) after a successful angioplasty procedure. The study group consisted of 71 patients, 55 male (77.5%) and 16 female. Mean age was 58 ± 8 years. The minimal lumen diameter pre angioplasty was 1.01 ± 0.37 mm and increased to 1.74 ± 0.32 mm ($p < 0.0001$, paired t-test) after angioplasty. At 24 hr, the average minimal lumen diameter was still 1.74 ± 0.37 mm. The interpolated reference diameter increased significantly from 2.68 ± 0.64 mm pre angioplasty to 2.76 ± 0.60 mm post angioplasty and 2.88 ± 0.61 mm at 24 hr follow-up angiography ($p < 0.005$, repeated-measures analysis of variance). Mean balloon diameter was 2.72 ± 0.41 mm. Figure 2 shows cumulative distribution curves of all individual data. The curves for the minimal lumen diameter post angioplasty and at 24 hr nearly completely overlap, suggesting that no further narrowing occurs in the first 24 hr after the procedure. This suggests that elastic recoil is an instantaneous phenomenon, occurring simultaneously with balloon deflation. Elastic recoil for the entire group was 0.38 ± 0.14. Mean aortic blood pressure was 98.4 ± 17.5 mmHg pre angioplasty and 98.3 ± 13.6 mmHg post angioplasty. At 24 hr follow-up angiography the mean aortic blood pressure had decreased to 93.0 ± 14.8 mmHg, probably due to the cumulative effect of vasodilatory drugs.

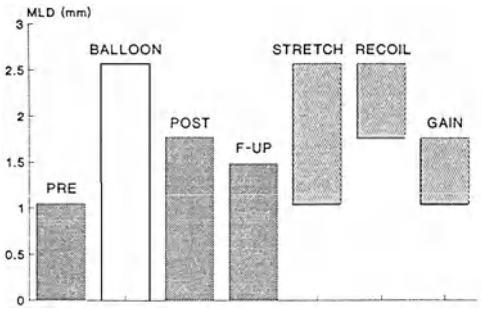


*Figure 3.* Graphical representation of the terms used. In this graph the mean absolute values of the variables is shown. Recoil and gain were normalized for vessel size (reference diameter) to correct for vessel size. pre = pre-angioplasty minimal lumen diameter, balloon = balloon mean diameter, post = post angioplasty minimal lumen diameter, F-up = follow-up minimal lumen diameter, MLD = minimal lumen diameter.

## *IV. Recoil and other angiographic risk factors for long term outcome of the angioplasty procedure*

Luminal narrowing in the first months after coronary angioplasty is a complex process that is only partially understood. Histologic studies of coronary arteries after dilation, obtained by either autopsy or atherectomy, have provided evidence that strongly supports the concept of intimal hyperplasia or proliferation of smooth muscle cells of medial or intimal origin as the underlying cause of luminal narrowing after angioplasty [12–14]. Pharmacological agents aimed at reducing the absolute amount of intimal hyperplasia are currently being investigated in many clinical trials. In these trials it is presumed that the clinical outcome is related to an anatomical substrate, i.e. the prevention or reduction of reactive intimal hyperplasia after angioplasty. If restenosis is viewed as an intraluminal growth process after a successful angioplasty, risk factors for restenosis should be risk factors for this growth process. The angiographically determined change in lumen diameter at follow-up is currently the only reliable indicator of the amount of reactive hyperplasia applicable to large study populations. In this study quantitative lesion measurements before angioplasty, after angioplasty, and at follow up were obtained in 575 patients (666 lesions) and correlated with loss in minimal luminal diameter at follow-up. To assess elastic changes (stretch, elastic recoil) of the vessel wall during and shortly after balloon deflation, balloon diameters were measured. Stretch was defined as the difference in mean balloon diameter and minimal lumen diameter pre-angioplasty and elastic recoil as the difference between mean balloon diameter and minimal lumen diameter post-angioplasty (Fig. 3). Both stretch and recoil were normalized for reference diameter to correct for the influence of vessel size.

*Significant luminal narrowing.*

To predict significant luminal narrowing after PTCA, we chose a cut-off point above which significant deterioration in MLD is likely. We have found a change in MLD of $\geq 0.72$ mm to be a reliable indicator of angiographic progression of vessel narrowing [15, 16]. This value takes into account the limitations of coronary angiographic measurements and represents twice the long-term variability for repeat measurements of a coronary obstruction using the CAAS system [16]. This variability reflects the long-term random variation in lesion measurements from coronary angiograms made at different catheterization sessions using the CAAS system. The use of 1 standard deviation would include 68.3% of the measurement variability, while the use of 2 standard deviations ($2 \times 0.36 = 0.72$ mm) includes 95.5% of the measurement variability. Therefore a difference in MLD of more than twice the long-term measurement variability can be considered indicative of significant luminal narrowing.

*Data analysis*

In a univariate analysis those variables that were related to restenosis were selected (Table 6). To allow risk stratification, logistic regression analysis using indicator variables was subsequently applied, with the loss in MLD (using a loss of $\geq 0.72$ mm as cut off value) as binary outcome variable because the logistic regression coefficients are easily related to adjusted rate ratios for the different variables. Continuous variables were therefore grouped into three equally sized subgroups (tertiles). Three subgroups were selected to enable assessment of trends in the incidence of $\geq 0.72$ mm loss and because more subgroups would weaken the strength of associations. The incidence of a $\geq 0.72$ mm loss was determined in each subgroup. If a trend for a higher incidence was present in each consecutive subgroup, then the subgroup with the lowest incidence was chosen as the reference group. If no trend for an increasing incidence of $\geq 0.72$ mm loss in MLD was present in each consecutive subgroup, the subgroup with the highest incidence was compared with the combined 2 other subgroups ( = reference group). Distortion of relation between different determinants of $\geq 0.72$ mm loss in MLD and the incidence of a loss $\geq 0.72$ mm (confounding) caused by an unequal distributions of these determinants among the tertiles was eliminated by multivariate logistic regression analysis and adjusted rate ratio's were obtained.

## Results

Mean age of the study population was $56 \pm 9$ years and mean time to follow up angiography was $172 \pm 41$ days. On average 1.16 lesion per patient was

*Table 6.* Univariate analysis of quantitative parameters and restenosis*.

| | No Restenosis (Mean ± SD) | Restenosis (Mean ± SD) | *P* |
|---|---|---|---|
| MLD pre-PTCA (mm) | 1.06 ± 0.36 (N = 549) | 0.94 ± 0.41 (N = 117) | 0.0025 |
| Reference diameter pre-PTCA (mm) | 2.64 ± 0.56 (N = 549) | 2.65 ± 0.56 (N = 117) | NS |
| Length obstruction pre-PTCA (mm) | 6.08 ± 2.24 (N = 533) | 6.94 ± 2.39 (N = 107) | <0.001 |
| MLD post-PTCA (mm) | 1.74 ± 0.36 (N = 549) | 1.89 ± 0.37 (N = 117) | <0.0001 |
| MLD f-up (mm) | 1.64 ± 0.44 (N = 549) | 0.72 ± 0.59 (N = 117) | <0.00001 |
| Balloon-artery ratio | 0.98 ± 0.19 (N = 490) | 1.02 ± 0.24 (N = 105) | 0.11 |
| Stretch | 0.58 ± 0.21 (N = 490) | 0.66 ± 0.26 (N = 105) | <0.001 |
| Recoil | 0.31 ± 0.15 (N = 490) | 0.30 ± 0.15 (N = 105) | 0.29 |
| Gain at angioplasty | 0.27 ± 0.15 (N = 549) | 0.37 ± 0.18 (N = 117) | <0.00001 |
| Loss in MLD at F-up (mm) | 0.10 ± 0.30 (N = 549) | 1.17 ± 0.42 (N = 117) | <0.00001 |

F-up = follow up; Gain = (MLD post PTCA – MLD pre PTCA) / reference diameter; MLD = minimal luminal diameter; PTCA = percutaneous transluminal coronary angioplasty; Recoil = (balloon diameter – MLD pre PTCA) / reference diameter; Stretch = (Balloon diameter – MLD pre-PTCA)/reference diameter.

*Restenosis according to the ⩾0.72 mm loss in minimal lumen diameter criterion.

dilated. Using the criterion of ⩾0.72 mm loss in minimal luminal diameter, restenosis occurred in 117 of 666 lesions (17.7%). Balloon measurements were available for 595 lesions. Twenty six lesions were totally occluded before angioplasty and therefore the length of the stenosis could not be measured. Mean minimal luminal diameter improved from 1.04 ± 0.37 mm to 1.76 ± 0.38 mm after angioplasty and deteriorated to 1.48 ± 0.59 mm at follow-up angiography. Reference diameter was not different pre-PTCA, post-PTCA and at follow up (2.64 ± 0.56 mm, 2.71 ± 0.54 mm and 2.71 ± 0.56 mm respectively), suggesting an accurate control of vasomotion during the three angiografic studies. With univariate analysis (Table 6) the following variables were significantly different in the restenosis and non restenosis group: pre angioplasty minimal luminal diameter, post angioplasty minimal luminal diameter, gain in minimal luminal diameter obtained at angioplasty, length of the obstruction, and stretch.

Logistic regression analysis. Lesions in the left anterior descending artery and totally occluded arteries are reported to have a higher risk for restenosis [17, 18], therefore lesion location and total occlusion were also entered in the logistic regression model. Balloon-artery ratio and recoil, although not significantly related to luminal narrowing in univariate were also entered in the logistic regression analysis. Since it is reported that thrombotic lesions are longer in length and that total occlusions frequently have a thrombotic component, angiographically determined thrombus at the dilatation site post-angioplasty was also included in the analysis (Table 7). A higher relative gain at PTCA, a lesion length of more than 6.8 mm, total occlusion pre-angioplasty and the presence of thrombus post-angioplasty all carried a sig-

*Table 7.* Univariate analysis of variables to be entered in logistic regression model (Loss ≥0.72 mm).

| Variate | | Incidence | Crude rate | 95% CI |
|---|---|---|---|---|
| Relative gain | <0.20 | 7.8% (18/232) | Reference | – |
| | 0.20–0.30 | 18.2% (38/209) | 2.34 | 1.38 to 3.98 |
| | ≥0.30 | 27.1% (61/225) | 3.49 | 2.13 to 5.72 |
| Length | <6.8 | 12.9% (55/428) | Reference | – |
| | ≥6.8 | 24.5% (52/212) | 1.91 | 1.36 to 2.69 |
| Stretch | <0.65 | 16.0% (62/388) | Reference | – |
| | ≥0.65 | 20.8% (43/207) | 1.30 | 0.92 to 1.85 |
| Balloon artery | <1.05 | 16.0% (65/405) | reference | – |
| Ratio | ≥1.05 | 21.1% (40/190) | 1.31 | 0.92 to 1.85 |
| Recoil | <0.24 | 20.8% (42/202) | 1.30 | 0.91 to 1.84 |
| | ≥0.24 | 16.0% (63/393) | Reference | – |
| Vessel | LAD | 15.9% (51/321) | 1.02 | 0.65 to 1.59 |
| | RCA | 22.0% (42/191) | 1.38 | 0.96 to 2.00 |
| | LC | 15.6% (24/154) | Reference | – |
| Thrombus post | present | 50.0% (8/16) | 2.98 | 1.77 to 5.00 |
| PTCA | absent | 16.8% (109/650) | reference | – |
| Total occlusion | patent | 16.7% (105/630) | Reference | – |
| pre PTCA | Occluded | 33.3% (12/36) | 2.30 | 1.37 to 3.85 |
| Trial | GR32191 | 18.6% (63/338) | 1.15 | 0.83 to 1.15 |
| Medication | Placebo | 16.5% (54/328) | reference | – |

LAD = left anterior descending artery; LC = Left circumflex artery; RCA = Right coronary artery; 95% CI = 95% confidence interval.

nificant unadjusted risk for developing a loss of at least 0.72 mm (i.e. 95% confidence intervals do not include 1). After logistic regression analysis (Table 8) higher relative gain at PTCA, a lesion length of more than 6.8 mm and a visible thrombus post-angioplasty were attended with a significant higher risk for developing restenosis (i.e. 95% confidence intervals do not include 1). A relative gain at angioplasty of more than 0.3 was attended with an adjusted rate ratio for developing restenosis of 2.90. This means that the risk for developing restenosis with at least this relative gain is 2.90 times as high as it is for lesions with a relative gain <0.2. Elastic recoil was not found to be related to significant luminal narrowing as determined by 6 month follow-up angiography.

*Table 8.* Multivariate logistic regression model for the assessment of risk of a loss in MLD ≥ 0.72 mm.

| Variate ($X_{i,j}$) | Coefficient ($b_{i,j}$) | Standard error | Adjusted ratio | rate95% CI |
|---|---|---|---|---|
| | | Gain at angioplasty | | |
| <0.2 | reference | – | – | – |
| 0.20 to 0.3 | 0.97 | 0.31 | 2.08 | 1.32 to 3.27 |
| ≥0.3 | 1.43 | 0.30 | 2.90 | 1.87 to 4.48 |
| | | Length of stenosis (mm) | | |
| <6.8 | reference | – | – | – |
| ≥6.8 | 0.67 | 0.22 | 1.67 | 1.19 to 2.33 |
| | | Thrombus post-angioplasty | | |
| Present | 1.20 | 0.54 | 2.63 | 1.11 to 6.20 |
| Absent | reference | – | – | – |
| | | Vessel patency pre-angioplasty | | |
| Patent | reference | – | – | – |
| Occluded | 0.52 | 0.43 | 1.51 | 0.77 to 2.96 |
| | | Trial medication | | |
| GR32191B | 0.15 | 0.21 | 1.12 | 0.81 to 1.53 |
| Placebo | reference | – | – | – |
| Intercept | − 2.98 | 0.31 | – | – |

95% CI = 95% confidence interval; MLD = Minimal lumen diameter; adjusted rate ratio after elimination of distortion of the relation between the determinants of restenosis found in this study, caused by unequal distribution of these determinants over the various subgroups.

## Discussion

### *Mechanisms of lesion dilation in balloon angioplasty*

Dotter and Judkins in 1964 envisioned that balloon angioplasty worked by remodelling and compression of the atheroma, because initial pathological studies revealed little intimal destruction and no evidence of dissection [19]. However the vast majority of atherosclerotic plaques in human coronary arteries are composed of incompressible, dense fibro collageneous tissue, and therefore it appears unlikely that plaque compression plays a major role in balloon angioplasty. However Kaltenbach showed, in an in vitro model, a reduction in weight and thickness of the atherosclerotic vessel wall after pressure application. This reduction was more pronounced in lipoidotic plaques, suggesting that fluid expression from atherosclerotic tissue could play

some role in the luminal widening achieved by angioplasty [20]. According to Sanborn, part of the angioplasty mechanism consists of stretching the vessel wall with a resulting fusiform dilatation or localised aneurysm formation [21]. If the lesion is eccentric then the least diseased portion of the vessel wall will stretch [22]. Castaneda Zuniga found angioplasty induced paralysis, by overstretching the vessel wall beyond its limits of elasticity, and suggested this to be the cause of permanent luminal widening after balloon angioplasty. This widening was associated with histopathological features of smooth muscle cell lysis and twisted nuclei [3] These correlates of severe medial damage were not found in human post mortem arteries after recent dilatation [23, 24].In in vitro models of balloon angioplasty in rabbit iliac artery, rabbit aorta and pig carotid artery, only severe oversizing of the balloon produced impairment of vasoconstrictor responsiveness [25]. Since it was becoming clear that oversizing of the balloon leads to an increased complication rate [6] and that satisfactory initial results can be obtained by conservative balloon sizing [5, 6], deliberate oversizing of the angioplasty balloon is not common practice in our institution. This is reflected by the mean balloon-artery ratio of 0.95 in our study. So arterial paralysis must be questioned as an explanation for the luminal widening achieved by angioplasty in human coronary arteries.

Relatively few studies have been performed, studying the mechanism of balloon angioplasty in vivo. Jain et al. [26] describe three patterns of plaque dilation by examining pressure volume curves created while the balloon was being inflated. The first pattern was stretching of the plaque. After dilation these vessels would recoil and required several dilatations to achieve adequate dilation. The second pattern showed small incremental jumps in the pressure-volume curve. This was believed to reflect progressive compaction of the lesion. The third pattern was sudden yielding of the balloon at a given pressure. This pattern was angiographically correlated with dissection of the artery at the angioplasty site. Finally, on-line analysis with an intravascular balloon ultrasound inflation catheter (BUIC) shows that plaque fracture is the major contributor to improved luminal patency by balloon angioplasty [27].

Thus the weight of evidence indicates that the mode of action of angioplasty is by "controlled injury" of the vessel wall, with intimal and sometimes medial disruption.

*Mechanism of early restenosis*

Vasoconstriction at the dilatation site is a common cause of early luminal narrowing. As has been shown elegantly by Fischell and co-workers this can be rapidly reversed by an intracoronary injection of nitrates [28]. Since we gave intracoronary nitrates before the pre- and post PTCA cine runs, it seems unlikely that the amount of recoil observed was caused by vasomotion. In Fig. 4 the difference between the post-PTCA and pre-PTCA reference

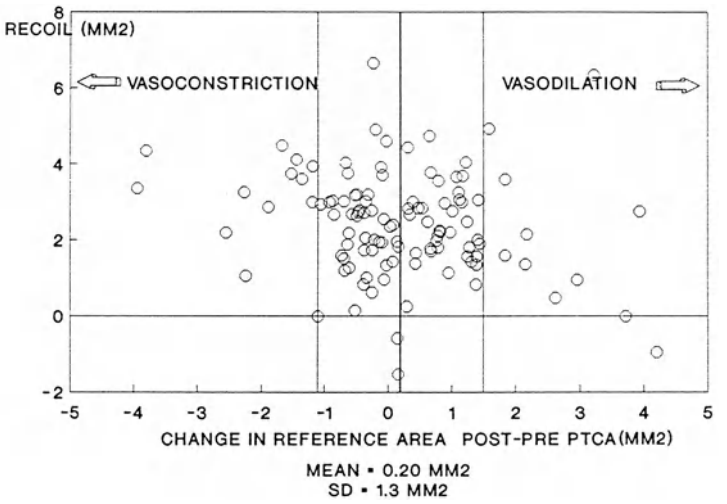


*Figure 4.* In this scatterplot the difference in interpolated reference area post and pre PTCA is plotted against the amount of recoil for each segment. The mean difference in reference area was $0.2 \pm 1.3$ mm$^2$ (vertical lines in graph). The values are randomly distributed around the mean value of 0.2 mm$^2$, suggesting that spasm was effectively eliminated.

area is plotted against the amount of recoil for each site. The values are randomly distributed around the mean value of 0.2 mm$^2$, suggesting the absence of vasoconstriction at the post-PTCA film.

Platelet deposition and the formation of a non occlusive mural thrombus despite full heparinization, is not an uncommon finding in post mortem hearts obtained from patients who die in the first hours after angioplasty [29]. This has also been confirmed by angioscopy 15–30 min after PTCA [30]. However our post PTCA angiograms were made within minutes of the last dilatation. Although we cannot rule out the possibility that mural thrombus formation is partly responsible for the observed phenomenon, we feel it cannot explain the 50% decrease in luminal area found. Subintimal hemorrhage is also a cause of severe early luminal narrowing or acute closure, a process which is usually impossible to reverse and nearly always resulting in a failed PTCA. In this study only successfully dilated lesions were analysed.

Relatively few studies have been performed, studying the mechanism of balloon angioplasty in vivo. Jain et al. found, using an in vivo technique for obtaining balloon pressure-volume loops, a pattern consistent with stretching of the arterial wall in 56% of lesions [26]. A pressure-volume loop consistent with stretching of the vessel was a far more common event than a cracking pattern (17%). Stretching within limits of elasticity implies its' counterpart elastic recoil. More stretching, should lead to more recoil. In our series oversizing of the balloon (i.e. a balloon-artery ratio >1) was associated with

more recoil, indicative of the elastic phenomenon. Hjemdahl-Monsen et al [31] found that at the same inflation pressure in eccentric lesions more distension of the vessel wall was achieved than in concentric lesions and that the former lesions showed more elastic recoil. Finally on-line analysis with an intravascular balloon ultrasound inflation catheter clearly showed the presence of recoil at balloon deflation [27]

The 71 lesions restudied 24 hr after PTCA showed no difference in luminal dimension with respect to the cross-sectional area immediately after PTCA. This suggests that elastic recoil is an instantaneous phenomenon, occurring simultaneously with balloon deflation. Similar findings have been reported by Hanet et al. [32]. This is not in concordance with the findings of Nobuyoshi, who found a significant deterioration of minimal luminal diameter 1 day after PTCA [33]. A trend towards more recoil was observed in asymmetric lesions. In these lesions the balloon will preferrably stretch the nondiseased part of the vessel circumference with a subsequent larger elastic recoil [11]. The fact that a small plaque area and a low curvature value are attended with a significant higher amount of elastic recoil might be due to the fact that dissections have been found most often in areas containing thick atherosclerotic plaques and a lesions with a high bending [34, 35]. It might be that gross disruption of the vessel wall prevents the recoil phenomenon. Procedural variables had no influence on the amount of recoil. Longer inflations and higher inflation pressures are often used after an initially poor angioplasty result. Only a randomized trial can really tell to what extend procedural factors influence procedural outcome.

Dobrin described pressure radius curves of KCN poisoned carotid arteries of Mongrel dogs. At low pressures, the vessel exhibited large changes in radius with each step in pressure, whereas at high pressure it showed very slight changes in radius. The curve described an elastic hysteresis loop, with the ascending and descending limb close to each other at all pressures, suggesting no active muscle contraction involvement in the retraction process [36].

Several experimental studies have suggested that dilation of the vessel wall is a stimulus for smooth muscle cell proliferation and later intimal hyperplasia [37, 38] either by stretch or direct injury to smooth muscle cells. In the present study, univariate analysis (table 6) showed that a significantly higher amount of stretch was induced on the vessel wall in the group with a $\geq$0.72 mm loss in MLD. These findings correlate with the observations by Fischell et al who showed a relationship between the degree of arterial stretching with subsequent recoil and the severity of smooth muscle injury as determined by loss of vasoconstrictor responsiveness and histopathological examination [39], and, more smooth muscle injury has been shown to enhance intimal hyperplasia in a more controlled animal model [38]. However after elimination of the unequal distribution of stretch over the various determinants of a significant loss in minimal lumen diameter by multivariate

analysis, stretch and elastic recoil were not found to be an independent predictor of luminal narrowing.

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# 25. The importance of coronary dissection during and after coronary balloon angioplasty as evaluated by quantitative coronary angiography

WALTER R.M. HERMANS, DAVID P. FOLEY and BENNO J. RENSING

## Introduction

In the initial "National Heart, Lung, Blood, Institute Percutaneous Transluminal Coronary Angioplasty Registry" publication, which describes the immediate results of patients treated with angioplasty, major adverse cardiac events – i.e. death, myocardial infarction, coronary artery bypass grafting, repeat dilatation, – were reported in 13.6% of patients [1]. Due to an increase in operator experience and improvement in radiographic equipment and balloon catheter design over the succeeding 5 years, this number dropped to 4 to 7%, despite extension of the indications for coronary balloon angioplasty to include patients older than 70 years, and those with multivessel disease or with poor left ventricular function, prior bypass surgery and more severe and complex lesions [2, 3].

Coronary angioplasty results in an angiographically visible dissection in 20% to 45% of the dilated lesions. This dissection could 1) result either in a complete or near complete total obstruction of the dilated vessel leading to an acute ischemic syndrome requiring urgent treatment with a further coronary re-vascularization procedure – the so called "*unwanted type of dissection*" – or 2) does not compromise the lumen significantly, so that there is neither reduction in blood flow, or impairment of clinical performance, and the patient will leave the hospital as scheduled, which is viewed by many clinicians as a "*therapeutic type of dissection*" [4–7].

This chapter addresses two issues: 1) whether evaluation of lesion morphology by quantitative coronary analysis [8], in addition to qualitative assessment and consideration of baseline clinical characteristics, can identify patients or lesions at particularly high risk of major procedural or in-hospital adverse cardiac events. The identification of certain risk factors might be of considerable importance in deciding whether certain patient or lesion may be more suitable for other devices than for balloon angioplasty; 2) whether there is a relationship between an angiographically visible dissection, restenosis and long term clinical outcome using a validated automated edge detection technique, on prospectively collected data, in a large series of



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patients undergoing successful balloon angioplasty with a high angiographic follow rate.

## Methods

### *Study population*

In total, 1442 patients were enrolled in 2 randomized double-blind placebo-controlled restenosis prevention trials (707 (CARPORT) and 735 (MERCATOR) patients respectively) between December 1987 and June 1990. Unfortunately, neither of these trials, which are described in detail elsewhere, demonstrated any clinical or angiographic benefit from the agent under investigation [9, 10].

To assess the predictability of major adverse cardiac events from clinical characteristics, procedural factors, angiographic quantitative and qualitative lesion morphological assessment, the study population was formed by those patients who experienced major procedural or in-hospital complications, (defined as death, myocardial infarction (at least 2 of the following: typical anginal pain, suggestive electrocardiographic changes for acute myocardial infarction, cardiac enzymes more than twice the upper limit of normal), the need for coronary artery bypass grafting or re-intervention) *after at least* 1 *balloon inflation*, regardless if the final result of the balloon angioplasty was considered successful or not (*Group I*, $n = 69$ *patients*). This patient group I was compared with a control group made up of patients having successful coronary angioplasty without any major adverse cardiac complications. Therefore, each patient in group I was randomly matched 1 : 3 with control patients by date of angioplasty (to the nearest week in the same hospital) (*Group II*, $n = 207$ *patients*). Where multilesion dilatation was performed, the most severe lesion was used for comparison [11].

To assess whether there exists a relationship between an angiographically visible dissection, restenosis and long term clinical outcome, the study population was formed by the 693 patients of the MERCATOR trial with a successful angioplasty procedure [4, 10].

### *Angioplasty procedure, follow-up and quantitative angiography*

Angioplasty procedure, follow-up and quantitative angiography was done as has been described elsewhere [8–10]. To standardize the method of data acquisition, data analysis and to ensure exact reproducibility of pre-coronary angioplasty, post-coronary angioplasty and follow-up angiograms, special precautions were taken, as previously described elsewhere [8–10].

*Definitions*

*Patient related variables*

The following patient related variables were recorded in the patient files: age, gender, duration of angina (days), cholesterol level (mmol/l), previous myocardial infarction, currently smoking, diabetes mellitus type I or II, extent of atheroslerotic disease (single or multivessel), Canadian Cardiovascular Society angina classification and unstable angina (defined as pain at rest requiring treatment with intravenous nitrates) [12].

*Lesion and procedural related variables*

*Qualitative lesion characteristics*

The following qualitative lesion parameters were assessed: *A*) Vessel dilated (right, left anterior descending or left circumflex), *B*) Location of the stenosis in the vessel dilated. Austen et al. divided the coronary tree in 15 different segments. This subdivision was used for location of the stenosis: *proximal*: corresponded with segments 1,6 and 11; *middle*: corresponded with segments 2,7,13 and 15; *distal*: corresponds with segment 8,9,10,12 and 14) [13], *C*) type of lesion, defined by a modified Ambrose classification 1) concentric, 2) eccentric (a stenosis asymmetrically positioned in the vessel in any non-foreshortened angiographic projection), 3) tandem lesion (2 discrete lesions in the same coronary segment), 4) multiple irregularities (2 or more serial diffuse irregularities in the same coronary segment), 5) totally occluded vessel [14], *D*) a bend was considered present, if in any non-foreshortened projection, the balloon, in position to dilate, appeared to be located in a portion of the vessel that had a 45°C or greater angulation, at end diastole [15], *E*) presence of a side branch in the lesion to be dilated, *F*) presence of a side branch, separate from the actual lesion but within the dilated segment, *G*) presence of intracoronary thrombus – a filling defect within the lumen, surrounded by contrast material seen in multiple projections, in the absence of calcium within the filling defect, or the persistence of contrast material within the lumen, or a visible embolization of intraluminal material "downstream" [16], *H*) presence of calcification: defined as fixed radiopaque densities in the area of the stenosis to be dilated, *I*) type of lesion (A, B, C) according the American College of Cardiology – American Heart Association Task Force [17]. *J*) Coronary artery dissections were defined according to modified National Heart, Lung, and Blood Institute criteria as the presence of angiographically evident intimal or medial damage [18, 19].If dissection is evident on the post angioplasty angiogram the quantification of a coronary lesion can be hampered by consequent indecision, i.e. the analysts may decide to include or exclude an extraluminal filling defect in the analysis (Figs 1–4). As advised by the mercator angiographic committee, the com-

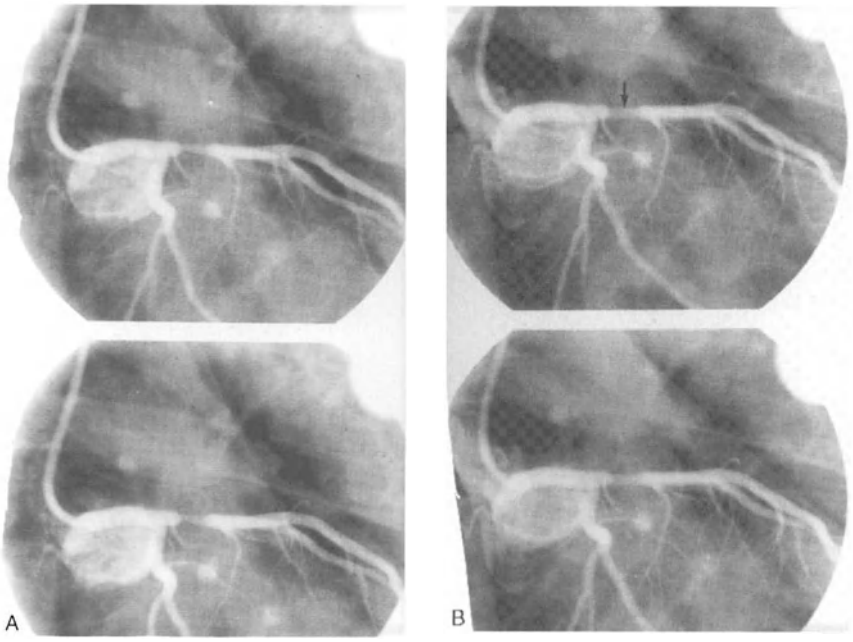


*Figure 1.* Stenosis in the proximal left anterior descending artery before (A) and after angioplasty (B), with a typical example of a type A dissection. The arrow indicates the presence of an intimal flap on the post-PTCA angiogram.

puter is allowed to "decide" whether the extraluminal defect is included or excluded in the analysis thereby avoiding subjective bias. If there is no clear separation between the lumen and the extravasation (large communicating channel), the computer will include the dissection in the analysis as the interpolated edge detection technique (making use of the weighted sum of first and second derivative difference functions applied to the brightness information using minimal cost criteria) will detect a small not significant difference in brightness. However, in cases where the extravasation is distinctly separate from the true vessel lumen, (small communicating channel), the computer will exclude the dissection from the analysis as there will be a steep difference in brightness between the extravasation and the true lumen (Fig. 5).

*Reproducibility of morphologic assessment*

Interobserver variability of the 2 reviewers for the qualitative lesion assessment was examined in an arbitrarily selected number of lesions. The coronary angioplasty films of 138 patients with 151 lesions (consecutive films reaching the core laboratory) were independently assessed for the diverse lesion morphologic characteristics by each observer on 2 separate occasions, 3

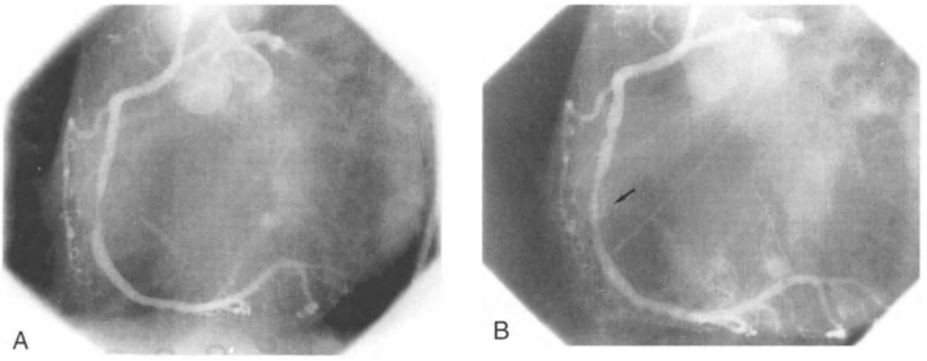


*Figure 2.* Stenosis in the mid right coronary artery before (A) and after angioplasty (B) with a typical type B dissection. The extravasation of contrast material is indicated by the arrow.

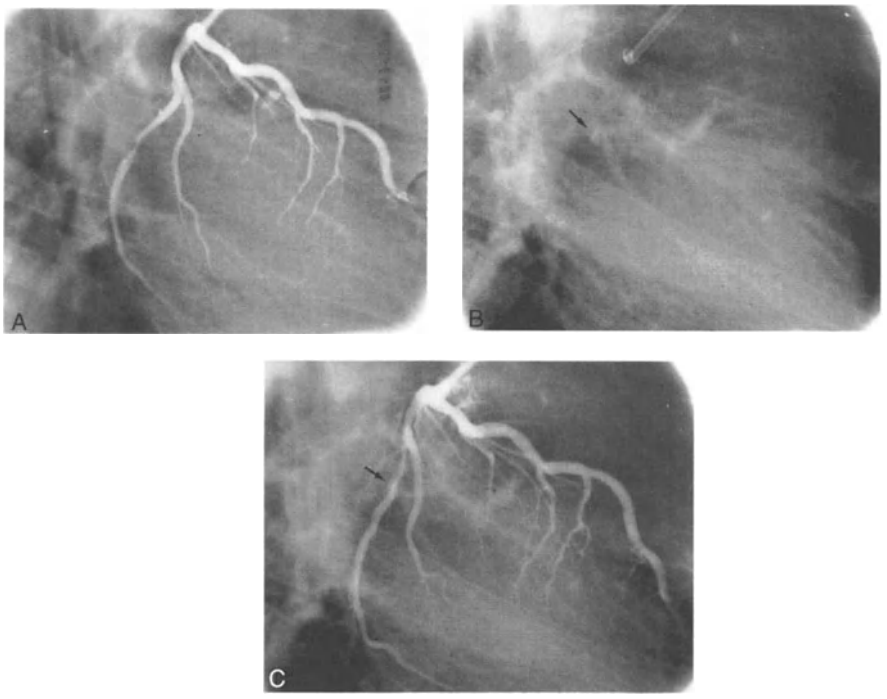


*Figure 3.* Stenosis in the left circumflex artery before angioplasty (A), after balloon inflation (B), and after angioplasty (C). This is a typical type C dissection, with persistence of contrast in the area of dilatation, indicated by the arrow.

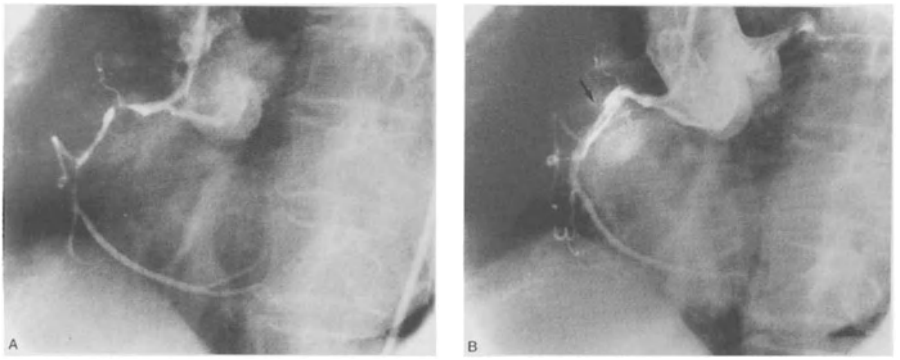


*Figure 4.* Stenosis in the proximal and mid right coronary artery before (A) and after angioplasty (B) with a typical type D spiral shaped dissection associated with decreased flow, indicated by the arrows.

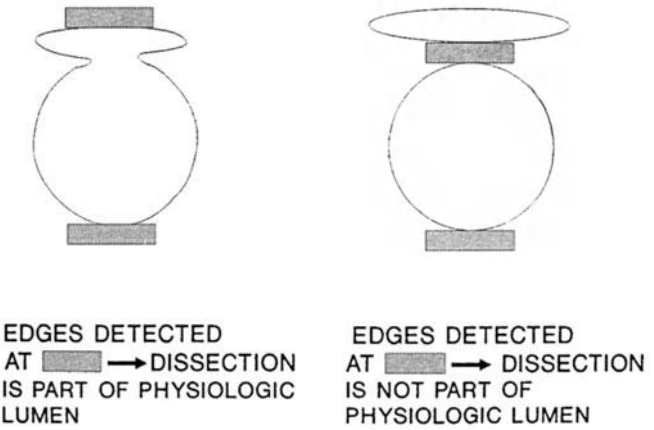


*Figure 5.* This figure explains how the quantitative analysis is done, in case a dissection is present on the post angioplasty angiogram. As a type A dissection is intraluminal, this type of dissection will be analyzed as seen on the left side (A). In contrast, type B to E dissection are extravasation outside the contrast filled lumen. In cases where the communicating channel between lumen and the extravasation is large (and of functional importance) – as can be seen in the brightness of contrast in the dissection – the computer will include the dissection in the analysis (right side) as only a small difference in brightness will be detected. However, in cases where this channel is small and not functional, the "computer" will exclude the dissection from the analysis as the difference in contrast density will be significant.

months apart with blinding for earlier assessment. Interobserver discordance was as follows: lesion eccentricity: 21%, branch point location 29%, branch point location in dilated segment 19%, bend point location 14%, presence of thrombus 2%, presence of calcification 10%, presence of dissection 11%,

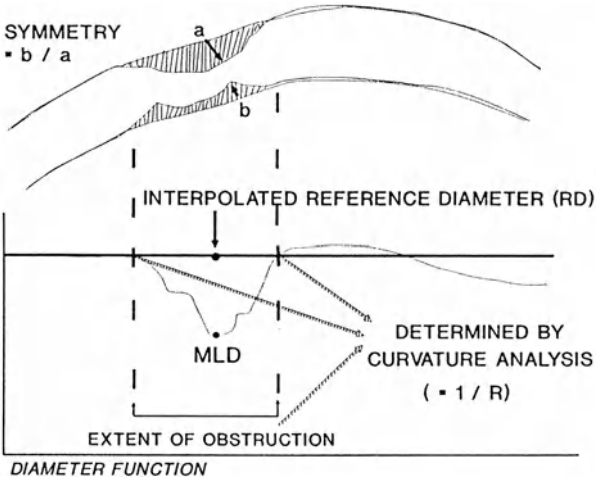


*Figure 6.* The area ($mm^2$) between the actual and reconstructed contours at the obstruction site is a measure of the amount of "*atherosclerotic plaque*". The *length of the obstruction* (mm) is determined from the diameter function on the basis of curvature analysis without interference of the technician. *Symmetry* is defined as the coefficient of the left hand distance and the right hand distance between the reconstructed interpolated reference diameter and actual vessel contours at the site of obstruction. In this equation the largest distance between actual and reconstructed contours becomes the denominator. A symmetrical lesion has a value of 1 and a severely eccentric lesion has a value of 0. To assess the extent of coronary bending, the *curvature* value at the obstruction site is computed as the average value of all the individual curvature values along the centerline of the coronary segment, with the curvature defined by the rate of change of the angle through which the tangent to a curve turns in moving along the curve and which for a circle is equal to the reciprocal of the radius. The curvature value was determined in the projection in the least foreshortened view (in which the analyzed segment appeared longest between 2 defined landmarks).

type lesion according American College of Cardiology – American Heart Association Task Force classification 25%.

*Quantitatively derived lesion characteristics*

The following quantitative measurements were obtained: minimal lumen diameter (mm), interpolated reference diameter (mm) and diameter stenosis (%), lesion length (mm), eccentricity index of the lesion, area of atherosclerotic plaque ($mm^2$) and the curvature value (Fig. 6). Balloon-artery ratio was defined as the ratio using the measured reference balloon size, divided by the vessel size. Relative loss was defined as the difference in minimal luminal diameter after coronary angioplasty and at follow-up, normalized for the vessel size [20–22].

**Restenosis clinical outcome**

Restenosis was defined per lesion. Two different approaches were used to look at the restenosis process. 1) *Categorical approach*: restenosis was considered to be present when the diameter stenosis was greater than 50% at follow-up angiography, since it is still common clinical practice to assess lesion severity in this manner. 2) *Continuous approach*: describes how the lesion "behaved" during follow-up: relative loss was defined as the absolute change in minimal luminal diameter, adjusted for vessel size, which allows comparison between vessels of different sizes [20, 22].

Clinical outcome was defined per patient, who was considered to have a dissection if in any one of the dilated segments (irrespective of procedural success) a dissection was visible on the post angioplasty angiogram. Full clinical follow-up was obtained in all 693 randomized patients during 6 month follow-up. Clinical status was ranked according to the most serious adverse clinical event which occurred, ranging from death (irrespective of cause), congestive heart failure class III or IV (New York Heart Association classification), non-fatal myocardial infarction (ECG-changes, Creatine Kinase (CK) enzymes above twice the upper limit of normal with MB-fraction >6% of total CK, with or without symptoms), need for coronary re-vascularization (CABG, repeat coronary angioplasty, stent implantation or atherectomy at the same site or other site), recurrent angina requiring initiation of or increase in medical therapy, or none of the above. Only re-vascularization procedures which were carried out before the study end-point (6 months ± 3 weeks) were included as clinical events.

*Statistical analysis*

Analyses were performed to test the hypothesis that clinical, qualitative and quantitative lesion morphologic and procedural characteristics are important determinants of major adverse cardiac event. The risk of major cardiac adverse events for each variable was expressed as an odds ratio:

$$\frac{\dfrac{\text{Probability of an event, variable present}}{\text{Probability of no event, variable present}}}{\dfrac{\text{Probability of an event, variable absent}}{\text{Probability of no event, variable absent}}}$$

Continuous variables were dichotomized, by cutpoints derived by dividing the data into 2 groups, each containing roughly 50% of the population. This method of subdivision has the advantage of being consistent for all variables and thus avoids any bias in selection of subgroups that might be undertaken to emphasize a particular point. An odds ratio of 1 for a particular variable implies that the presence of that variable poses no additional risk for major event; odds ratio >1 or <1 imply additional or reduced in risk, respectively.

The 95% confidence intervals were calculated to describe the statistical certainty. Multivariate analysis by multiple logistic regression was performed to identify variables independently correlated with the occurrence of major cardiac procedural or in-hospital adverse event, using only those variables significant at the $p < 0.10$ level in the univariate analysis. All these statistical analysis were carried out with a commercial statistical package (BMDP Statistical Software Package 1990).

In addition, analyses were performed to test the hypothesis that the occurrence of a dissection does not influence restenosis and clinical outcome by chi-square test and a one-way analysis of variance or student t- test. P-values less than 0.05 were considered statistically significant.

## Results

Of 1442 patients recruited, balloon angioplasty was not attempted in 9 patients because the lesion severity had changed or due to equipment failure. A further 43 patients had (sub)totally occluded lesions which either could not be reached or crossed with the guide wire or balloon catheter. Thus, of 1390 patients in whom balloon dilatation was actually performed, 69 experienced a major adverse cardiac events. Myocardial infarction occurred during or shortly after the procedure in 15 patients (or 1%) and in an additional 22 patients (or 1.5%) during the in-hospital stay. Emergency coronary bypass graft operation was necessary immediately after failed coronary balloon angioplasty in 18 patients (or 1.3%), and in a further 9 patients (1%), the indication for surgery arose after the patient had left the catheterization laboratory. In 5 patients, a redilatation was performed during the in-hospital stay. No patient died during the procedure or during the in-hospital stay.

### *Clinical characteristics, angiographic quantitative and qualitative lesion characteristics procedural factors as predictors of major adverse events*

The clinical characteristics as related univariate predictors of major procedural or in-hospital coronary events are listed in Table 1. Patients with unstable angina experienced more coronary events than patients without unstable angina (Odds ratio 3.11; $p < 0.0001$; 95% CI, 1.72 to 5.61). Age, gender, duration of angina, serum cholesterol, history of myocardial infarction, diabetes mellitus, multivessel disease and Canadian Cardiovascular Society angina class did not influence the risk for a major adverse cardiac event. Lesion morphology (as evaluated by quantitative coronary analysis and qualitative assessment) as univariate predictors of major adverse cardiac events are listed in Table 2. Location of the target lesion in the mid segment of the coronary artery dilated (Odds ratio 1.88; $p < 0.03$, 95% CI 1.08 to 3.26), lesion located at a bend of >45°C (Odds ratio 2.34; $p < 0.004$, 95% CI 1.31 to 4.15) and type C lesions (Odds ratio 2.53; $p < 0.004$, 95% CI 1.32

*Table 1.* Clinical related variables and the risk for a major procedural or hospital adverse cardiac event.

| Variable | Patient positive for the variable: event / total | Patient negative for the variable: event / total | Odds ratio (95% CI) |
|---|---|---|---|
| Myocardial infarction (history) | 23/107 | 46/169 | 0.73 (0.41 to 1.30) |
| Currently smoking | 10/45 | 59/231 | 0.83 (0.39 to 1.79) |
| Multivessel coronary narrowing | 29/117 | 39/146 | 0.89 (0.51 to 1.51) |
| Diabetes mellitus | 6/25 | 63/251 | 0.94 (0.36 to 2.46) |
| Age (<58 year) | 35/136 | 34/140 | 1.08 (0.63 to 1.86) |
| Duration of angina (>142 days) | 35/137 | 31/135 | 1.15 (0.66 to 2.01) |
| Total cholesterol (<6.2 mmol/l) | 34/129 | 27/132 | 1.39 (0.78 to 2.48) |
| Canadian cardiovascular society class III or IV | 47/169 | 21/100 | 1.45 (0.81 to 2.61) |
| Males | 59/221 | 10/55 | 1.64 (0.78 to 3.46) |
| Unstable angina | 29/69 | 39/206 | 3.11 (1.72 to 5.61) |

to 4.86) were significant associated with more major adverse cardiac events. No other lesion morphological characteristic, whether assessed qualitatively or by quantitative analysis, predicted the occurrence of major adverse cardiac events. The presence of any type of angiographically visible dissection after the procedure was strongly associated with the subsequent occurrence of a major adverse cardiac event (Odds ratio 5.39; $p < 0.0001$; 95% CI 2.90 to 10). Neither thrombus post dilatation or the balloon-artery ratio was found to be predictive of a major adverse cardiac event (Table 2).

*Logistic regression analysis*

Considering only baseline *pre-procedural* factors, the model entered unstable angina (Odds ratio 3.77; $p < 0.0003$, 95% CI 1.89 to 7.48), lesions located at a bend of >45°C (Odds ratio 2.87; $p < 0.0005$; 95% CI 1.47 to 5.59), and stenosis located in mid portion of artery dilated (Odds ratio 1.95; $p < 0.04$; 95 CI 1.01 to 2.74). If in addition post-procedural variables were added, then unstable angina (Odds ratio 3.46; $p < 0.002$; 95% CI 1.67 to 7.17), lesions located at a bend of >45°C (Odds ratio 2.54; $p < 0.006$; 95% CI 1.26 to 5.13) and angiographically visible dissection (Odds ratio 6.58; $p < 0.0001$; 95% CI 3.17 to 13.7) were independent predictors of major adverse cardiac events.

*Angiographicaly visible dissection after successful coronary angioplasty and restenosis*

In the MERCATOR, an angiographically visible dissection was identified in 247 (32%) of the 778 lesions which were successfully dilated and had angiographic follow-up (Table 3). In 242 lesions, the type of dissection was either

*Table 2.* Lesion and procedural related variables and the risk for a major procedural or in-hospital adverse cardiac event.

| Variable | Patient positive for the variable: event/total | Patient negative for the variable: event/total | Odds ratio (95% CI) |
|---|---|---|---|
| Coronary artery dilated | | | |
| Right | 15/67 | 54/209 | 0.83 (0.43 to 1.59) |
| Left circumflex | 17/72 | 52/204 | 0.90 (0.48 to 1.69) |
| Left anterior descending | 37/137 | 32/139 | 1.24 (0.72 to 2.14) |
| Multiple site dilated | 12/45 | 57/231 | 1.11 (0.54 to 2.29) |
| Total occlusion | 8/24 | 61/252 | 1.57 (0.64 to 3.84) |
| Mid portion of vessel dilated | 36/112 | 33/164 | 1.88 (1.08 to 3.26) |
| Lesion morphology quantitative derived pre-angioplasty | | | |
| Symmetry index (<0.34)[1)] | 30/121 | 32/131 | 1.00 (0.56 to 1.77) |
| Minimal lumen diameter (>0.98 mm) | 35/139 | 34/137 | 1.02 (0.59 to 1.76) |
| Diameter stenose (<62%) | 35/136 | 34/140 | 1.08 (0.63 to 1.86) |
| Length lesion (>5.8 mm)[1)] | 32/127 | 29/125 | 1.12 (0.63 to 1.99) |
| Vessel size (>2.53 mm) | 37/140 | 30/134 | 1.25 (0.72 to 2.17) |
| Atherosclerotic plaque (>6.1 $mm^2$)[1)] | 35/127 | 26/125 | 1.45 (0.81 to 2.59) |
| Curvature index (>19)[1)] | 37/128 | 24/124 | 1.69 (0.94 to 3.05) |
| Lesion morphology qualitative assessment | | | |
| Side branch in area of balloon | 46/186 | 20/80 | 0.99 (0.54 to 1.81) |
| Calcified lesion | 9/33 | 57/233 | 1.16 (0.51 to 2.63) |
| Side branch in stenosis | 38/144 | 28/122 | 1.20 (0.69 to 2.11) |
| Eccentric located stenosis | 36/130 | 30/136 | 1.31 (0.75 to 2.28) |
| Bend > 45° | 31/86 | 35/180 | 2.34 (1.31 to 4.15) |
| Type C lesion | 19/46 | 47/220 | 2.53 (1.32 to 4.86) |
| Procedural variables | | | |
| Balloon-artery ratio (>1.02) | 17/110 | 16/105 | 1.02 (0.48 to 2.14) |
| Thrombus post dilatation | 4/7 | 62/259 | 4.31 (0.94 to 19.80) |
| Intimal tear or dissection | 47/111 | 19/155 | 5.39 (2.90 to 10.00) |

Although 276 lesions were analyzed in total, some lesions could not be analyzed for certain variables.

A (# 82),B (# 132) or C (# 28). Only in 5 lesions, the dissection was assessed as type D (# 3) or E (# 2). When the restenosis cut-off criterion of ">50% diameter stenosis at follow-up" was used, then almost identical restenosis rates were seen for lesions with – 29% – or without dissections – 30%. Similar rates were found if the type of dissection was sub-categorized according the NHLBI classification with a restenosis rate of 33% for type A, 27% for type B and 32% for type C. When absolute change in minimal

luminal diameter during follow-up was used to define the restenosis process, the "relative loss" in lesions with $-0.10 \pm 0.22$ or without dissections $-0.10 \pm 0.19$. If the type of dissection was sub-categorized then the relative loss was 0.15 for type A, 0.08 for type B and 0.10 for type C.

*Angiographicaly visible dissection after successful coronary angioplasty and cclinical outcome*

In the MERCATOR, clinical outcome was obtained in all 693 patients at 6 month follow-up and was ranked according to the most serious adverse clinical event ranging from death (4 (0.9%) without, 1 (0.4%) with dissection), non-fatal myocardial infarction (4 (0.9%) without, 8 (3.2%) with dissection), coronary re-vascularization (73 (16.6%) without, 32 (12.7%) with dissection), recurrent angina requiring medical therapy (88 (20%) without, 47 (18.7%) with dissection) to none of the above (272 (61.7%) without, 164 (65.1%) with dissection) (Table 4). No significant differences in clinical outcome between patients with or without dissection was observed if clinical outcome was evaluated according to the occurrence or non-occurrence of "hard events" (death, non-fatal myocardial infarction, coronary re-vascularization) or "soft events" (recurrence of angina or no event) ($p = 0.22$).

## Discussion

*Predictability of major adverse cardiac events*

Despite the improvements in equipment and technique which have made it possible to dilate more than 90–95% of coronary obstructions, the occurrence of procedural and in-hospital cardiac adverse events, due to acute or subacute vessel closure, continues to be largely unpredictable. The reported frequency of so called major cardiac adverse events depends on the time window applied – *after* the patient left the catheterization laboratory 1 to 2% or *during and after* the procedure 4 to 7%. In the present study, major adverse cardiac events were observed in 33 of 1390 patients (2.4%) after at least one balloon inflation in the catheterization room and a further 36 (2.6%) during the hospitalization period.

The present results are in agreement with the earlier published studies showing that unstable angina, lesion located at a bendpoint of more than 45°C, and dissection were predictors of major procedural or in-hospital cardiac events [2, 3, 23]. It is noteworthy that lesion morphology, as assessed by quantitative coronary analysis, was not of any help for the prediction of major adverse cardiac events. Although inter and intraobserver variability potentially limits the qualitative assessment of lesion morphology, lesion located at a bend point of more than 45°C was identified as having a greater risk for major adverse cardiac event. The well described association of un-

*Table 3.* Dissection after successful coronary angioplasty and restenosis per lesion dilated: categorical and continuous approach.

| Restenosis | | | | Dissection | | | | |
|---|---|---|---|---|---|---|---|---|
| | None | Any | P | A | B | C | D | E |
| # | 531 | 247 | – | 82 | 132 | 28 | 3 | 2 |
| Continuous | | | | | | | | |
| Loss (mm) | 0.26 ± 0.48 | 0.28 ± 0.60 | 0.570.39 ± 0.65 | 0.23 ± 0.54 | 0.25 ± 0.55 | 0.41 ± 0.27 | −0.11 ± 0.50 | |
| R Loss | 0.10 ± 0.19 | 0.10 ± 0.22 | 0.88 | 0.15 ± 0.24 | 0.08 ± 0.21 | 0.10 ± 0.21 | 0.16 ± 0.11 | −0.04 ± 0.16 |
| Categorical | | | | | | | | |
| DS > 50% | 159 (30%) | 72(29%) | 0.82 | 27 (33%) | 36 (27%) | 9 (32%) | 0 | 0 |

Loss = difference in minimal luminal diameter between post-coronary angioplasty and follow-up; R Loss = Relative loss: loss, normalized for the vessel size); DS = Diameter stenosis at follow-up angiography.

*Table 4.* Dissection after coronary angioplasty per patient and clinical outcome at 6 months follow-up.

| Clinical outcome | | | Dissection | | | | | |
|---|---|---|---|---|---|---|---|---|
| | None | Any | A | B | C | D | E | F |
| # | 441 Pts | 252 Pts | 76 Pts | 136 Pts | 33 Pts | 3 | 3 | 1 |
| Death | 4 (0.9%) | 1 (0.4%) | 1 (1.3%) | 0 | 0 | 0 | 0 | 0 |
| NYHA III/IV | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Non-fatal MI | 4 (0.9%) | 8 (3.2%) | 4 (5.3%) | 4 (2.9%) | 0 | 0 | 0 | 0 |
| Coronary Revasc | 73 (16.6%) | 32 (12.7%) | 12 (15.8%) | 18 (13.2%) | 2 (6.1%) | 0 | 0 | 0 |
| Recurrent angina | 88 (20.0%) | 47 (18.7%) | 16 (21.1%) | 23 (16.9%) | 7 (21.2%) | 1 | 0 | 0 |
| No event | 272 (61.7%) | 164 (65.1%) | 43 (56.6%) | 91 (66.9%) | 24 (72.7%) | 2 | 3 | 1 |

NYHA = New York Heart Association classification for congestive heart failure; non-fatal MI = non-fatal Myocardial Infarction; Coronary Revasc = Coronary Revascularizations.

stable angina with the occurrence of major adverse cardiac events is confirmed in this study and the location of the target lesion in a bend >45°C has previously been identified by Ellis as a risk factor for acute vessel closure [23]. Their explanation was that the balloon must necessarily tear an atherosclerotic fixed and rigid bend lesion as it straightens and stretches it. In addition, the maximal stress is several times greater when there is a geometric discontinuity in the object to which this stress is applied [23]. Others have found that thrombus on the pre dilatation angiogram was predictive for a major adverse cardiac event [2, 3, 23]. However, thrombus was rarely seen on the pre dilatation angiogram in the present study, despite the fact that unstable angina, in which clinical syndrome the presence of intracoronary thrombus is frequently noted [24], was a risk factor for major adverse cardiac event. It could well be that intravenous heparin, which the majority of the patients with unstable angina, in this study design, received, effectively dissolves almost completely the clot and therefore no thrombus is seen on the pre dilatation angiogram. In contrast with Black et al., the balloon-artery ratio was not a factor for predicting major adverse cardiac events, although there is a difference in definition [25]. It is also possible that because of that publication, many investigators choice a smaller balloon size then they used to do, and therefore no significance could be found.

The most powerful predictor for major adverse cardiac events is the occurrence of an intimal tear or dissection, which is not surprising as all patients experiencing procedural events had dissection with flow limitation on their post dilatation angiogram.

There is no obvious explanation and could simply be due to chance finding, why location of the target lesion in the mid segment of the coronary vessel

was independently associated with a higher risk of major adverse cardiac events in univariate analysis.

From the literature, one would expect that dilation of "type C lesions" would be a risk factor for major adverse cardiac event as this is associated with a $< 60\%$ success according to the American College of Cardiology – American Heart Association Task Force [17]. However, a recent study in 1000 lesions by Myler et al. found an angioplasty success rate of 90% for type C lesions. This is only slightly below the% for type A and B [26]. In the present study type C lesions were predictive for major adverse cardiac events in univariate analysis but not in multivariate analysis.

*Relationship between an angiographically visible coronary dissection immediately after coronary angioplasty and restenosis and long-term clinical outcome*

Two major problems arise in the exploration of a possible relationship between an angiographically visible dissection following successful angioplasty and the long-term angiographic and clinical sequelae: 1) definition and assessment of dissection, and 2) definition and assessment of restenosis.

1. *Definition and assessment of dissection*

In the present study, the well-established National Heart, Lung, and Blood Institute classification for the assessment of dissection was used, as previously described by Dorros and Guiteras Val et al. [18, 19]. In earlier reports looking specifically at dissection and long-term follow-up, the assessment of dissection may well have been biased by knowledge of clinical parameters as assessment took place in a clinical setting by multiple assessors with unpublished inter and intra-observer variability [5–7]. As part of a multicenter study, we prospectively collected patient-lesion-procedural variables in order to analyze, as an ancillary study, the relationship of an angiographically visible dissection with restenosis and clinical outcome, in all randomized patients. All baseline and follow-up films were screened, processed and analyzed at an off-line angiographic core laboratory without knowledge of clinical data. Inter and intra-observer variability for dissection (irrespective of type) was defined for the 2 assessors in the core laboratory (WH, BR) with a kappa of 0.60 for assessor I, 0.58 for assessor II and 0.75 between the 2 assessors. These kappa values indicates a satisfactory agreement between the 2 assessors and for each assessor in time.

2. *Definition and assessment of restenosis*

In virtually all the reported studies on the relationship of dissection with restenosis, visual estimation or hand-held caliper measurements were used to assess restenosis [4]. Both of these methods are known to be hampered by relatively wide inter and intra-observer variability [8]. To avoid those pitfalls, in this study restenosis was assessed by quantitative coronary angio-

graphy using the CAAS-system, a well validated and extensively described method of analysis [8]. In addition, previous reports represent, in most cases, the early experience of an institution and describe the long-term follow-up of a group of patients, who were not angiographically re-studied at a predetermined time. The majority of these studies were retrospective analysis and involved small patient numbers [4].

The definition of choice for restenosis has been the subject of much debate [27]. Of the different restenosis criteria proposed, the "50% diameter stenosis at follow-up angiography" is the most frequently used to assess restenosis, since physiologic measurements demonstrate that this is the approximate value in animals with normal coronary arteries at which blunting of the hyperemic response occurred [28]. This definition was applied to our data. Earlier studies have shown that the reference diameter of a coronary artery is frequently involved in the restenosis process so that the use of % diameter stenosis may underestimate the change in the severity of a stenosis after coronary angioplasty. Therefore a criterium based on the absolute change in minimal luminal diameter represents more what is really going on, but may be limited because they make no attempt to relate the extent of the restenosis process to the size of the vessel. To circumvent this limitation, we used the change in minimal luminal diameter, from post-coronary angioplasty to follow-up, normalized for the reference diameter (*relative loss*) as earlier reported and published by our group and others [20–22]. This "sliding scale criterion", which adjusts for vessel size, allows the accurate regional assessment of the extent of the restenosis phenomenon in the entire coronary tree and also its relation to dissection.

*Dissection and clinical outcome*

Intimal tear or dissection has been reported as an important predictor of ischemic complications after coronary angioplasty, but only the minority of patients will develop an acute ischemic event. Huber et al. reported recently that patients with type B dissections have similar (low) complications rates to patients without dissection [7]. Patients with type C to F dissection had an significant increase in-hospital complications. The present study includes only patients with a successful coronary angioplasty, defined as a less than 50% diameter stenosis on the post angioplasty angiogram. If the clinical condition required re-coronary angioplasty, the angiogram immediately prior to re-intervention was used to obtain follow-up values, irrespective of the timing of re-intervention (hours, days or weeks). Although patients with dissection are considered to be at high risk for an ischemic complication during the in-hospital stay, similar or even slightly better clinical outcome was observed for patients with type B to F dissections in this study. Only 9 (or 1.5%) patients with a initially successful coronary angioplasty, had a re-intervention or emergency CABG during the in-hospital stay. Five of these patients had a dissection (3 patients with type A, 2 patients with type B)

visible on the post-coronary angioplasty angiogram. Apart from possible bias by participating centers in excluding patients with severe diffuse disease or requiring emergency coronary angioplasty or multi site dilatation, we have no explanation for this low in-hospital complication rate. Since type C to F dissections were detected in only 40 patients, strong conclusions regarding these types can not realistically be drawn regarding long-term clinical outcome in this setting.

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# 26A. Quantitative coronary angiography for the evaluation of pharmacolgical restenosis prevention trials after successful percutaneous transluminal coronary balloon angioplasty. The results of CARPORT and MERCATOR study

WALTER R.M. HERMANS, BENNO J. RENSING and PATRICK W. SERRUYS on behalf of the CARPORT [1] (Coronary Artery Restenosis Prevention On Repeated Thromboxane-antagonism) and MERCATOR [2] (Multicenter European Research trial with Cilazapril after Angioplasty to prevent Transluminal coronary Obstruction and Restenosis) study groups

## Introduction

Percutaneous transluminal coronary angioplasty (PTCA) was introduced by Andreas Gruentzig in 1977 as an alternative treatment for coronary artery bypass grafting (CABG) in patients with angina pectoris [1]. Increased experience and advances in technology have resulted in a high primary success rate (over 90%) and a low complication rate (death, non-fatal myocardial infarction; 4–5%) [2]. However, the late restenosis rate (17% to 40%) still limits the long term benefit of the procedure [3, 4]. It is well known that restenosis after balloon angioplasty is a time related phenomenon, occurring in the first months after balloon angioplasty [5, 6]. Only very rarely does restenosis present itself later than 6 months after coronary angioplasty [7, 8].

The cause of restenosis is unclear, but factors such as platelet aggregation, formation of mural thrombi, intimal proliferation of smooth muscle cells, elastic recoil and active vasoconstriction at the site of PTCA injury have all been implicated [3, 4, 9, 10–13]. A decade of intensive clinical and pharmacological research has not succeeded in altering the restenosis rate [3, 4]. Various treatments started shortly before or after PTCA and sometimes given for up to 6 months, such as intravenous administration of heparin, antiplatelet therapy (aspirin, dipyridamole, ticlopidine, prostacyclin, ciprostene), anticoagulants (coumadin), calcium channel blockers (nifedipine, diltiazem, verapamil) and other agents such as corticosteroids and colchicine, have failed to reduce the restenosis rate [14]. Fish oil and cholesterol-lowering agents have shown promises, although the published results are conflicting [3, 4, 15].

This chapter present the results of two multicenter, randomized, double-

[1,2] see for complete list of investigators reference 20 and 26.



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blind, placebo-controlled trials that were designed to test in man whether 1) thromboxane receptor blockade with GR32191B (*CARPORT*) or 2) angiotensin converting enzyme inhibition with cilazapril (*MERCATOR*) can prevent late restenosis after PTCA. The main and primary endpoint in both trials was the mean difference in coronary diameter between post angioplasty and follow up angiogram as all films were quantitatively analyzed using the Cardiovascular Angiographic Analysis System.

## Methods

### *Study Population*

All patients with angina and angiographically-proven coronary artery disease who were scheduled for angioplasty, were considered for inclusion in six (Carport) or twenty-six (Mercator) participating centers. Both trials were carried out according to the declaration of Helsinki. A screening log was maintained in respectively 2 (Carport) and 17 (Mercator) centers. In the Carport trial 81% and in the MERCATOR 72% of the screened patients were excluded (Table 1).

### *Randomization and treatment protocol*

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

One hour before angioplasty, patients allocated to GR32191B received 4 tablets of 20 mg GR32191B orally and an intravenous injection of a physiological salt solution. Patients allocated to control treatment received 250 mg acetyl salicylic acid intravenously and 4 placebo tablets.

In those cases in which angioplasty was successful, either 40 mg GR32191B twice daily or placebo was started in the evening and continued until the end of follow-up. The final dose of trial medication was taken one hour before the follow-up angiogram. In addition, all participants were provided with paracetamol in 500 mg tablets for use as analgesic and were asked to avoid acetyl salicylic acid or non-steroidal anti-inflammatory drugs while on trial medication. Randomization was stratified by center.

*Mercator trial*
Trial medication was given for the first time in the evening after successful PTCA and consisted of either capsules of cilazapril (first evening 2.5 mg, then 5 mg bid) or matching placebo for 6 months. In addition, all patients

*Table 1.* Screening results in respectively 2 (CARPORT) and 17 (MERCATOR) log keeping clinics.

| | CARPORT | | MERCATOR | |
|---|---|---|---|---|
| Total number of screened patients | 1614 | 100% | 1755 | 100% |
| Number of recruited patients | 296 | 18% | 478 | 27% |
| Excluded from the trial | 1318 | 82% | 1277 | 73% |
| *Reason for exclusion* | | | | |
| Insufficient lead-in time* | 235 | 18% | – | – |
| Use of platelet inhibiting drugs or NSAID's In 7 days preceding the study | 352 | 27% | – | – |
| Refusal to participate | 364 | 28% | 109 | 6.2% |
| Currently taking oral anticoagulant drugs | 119 | 9% | – | – |
| Angioplasty for restenosis | 105 | 8% | 268 | 15.3% |
| Acute M.I. 2 or 4 weeks preceding angioplasty | 52 | 4% | 174 | 9.9% |
| Bypass graft dilatation | 39 | 3% | – | – |
| History of obstructive airway disease | 26 | 2% | – | – |
| History of peptic disease or upper GI bleeding | 10 | 1% | – | – |
| Previous participation in the trial | 2 | 0.2% | – | – |
| Severe other disease | 6 | 0.5% | – | – |
| Participation in other trial | 6 | 0.4% | – | – |
| History of intolerance to aspirin | 1 | 0.1% | – | – |
| Under 21 years of age | 1 | 0.1% | – | – |
| History of sustained essential hypertension | – | – | 271 | 15% |
| Logistic reasons | – | – | 67 | 3.8% |
| Significant concomitant disease | – | – | 50 | 2.8% |
| Older than 75 years | – | – | 43 | 2.5% |
| Dilatation of bypass graft | – | – | 40 | 2.3% |
| Primary perfusion therapy | – | – | 39 | 2.2% |
| No informed consent given | – | – | 39 | 2.2% |
| Current evidence or prior history of heart failure | – | – | 28 | 1.6% |
| Other reasons [26] (less than 1% each) | | | 122 | 8.6% |

received 75 to 125 mg aspirin b.i.d. started before coronary PTCA until follow-up angiography. Randomization was stratified by center.

*Angioplasty procedure and quantitative angiography*

Angioplasty procedure, follow-up and quantitative angiography was done as has been described elsewhere [5, 16]. To standardize the method of data acquisition, data analysis and to ensure exact reproducibility of pre-coronary angioplasty, post-coronary angioplasty and follow-up angiograms, special precautions were taken, as previously described elsewhere [5, 16]. All angiograms were processed and analyzed in a central core-laboratory. At least 2 views of all lesions were analyzed, orthogonal if possible. A difference in angulation of at least 30 degrees was required for a view to be separately analyzed. The mean change in minimal lumen diameter from post-angioplasty angiography to follow-up angiography and from pre-angioplasty to post-angioplasty was derived from matched angiographic views. The follow-up coronary angiogram was performed at six months follow-up. If symptoms recurred within 6 months, coronary angiography was carried out earlier. Since the algorithm is not able to measure total occlusions and lesions with TIMI-1 perfusion, a value of 0 mm was used for the minimal lumen diameter and 100% for the percent diameter stenosis. In these cases, the post-PTCA reference diameter was used as the reference diameter pre-PTCA or at follow-up. All angiographic analyses including qualitative assessment of certain lesion characteristics were performed at a core laboratory which was blinded as regards treatment allocation and did not have access to clinical data [17–19].

*Follow-up evaluation*

After successful angioplasty, defined as at least one lesion successfully dilated (i.e. <50% diameter stenosis on visual inspection after the procedure) as judged by the investigator, patients returned to the outpatient clinic in the CARPORT trial after three weeks and three, six and seven months, and in the MERCATOR after one, two, four and six months for an interview, a cardiac examination, a physical examination, laboratory tests, a tablet count and except for the six and seven month visits new supply of trial medication. Patients with an unsuccessful angioplasty discontinued trial medication and received the standard medical care. Follow-up angiography was performed at the six month visit after the trial medication was discontinued. The follow up clinical status of all patients, irrespective of PTCA success, was assessed 6 months after the procedure. At six months follow-up, 1 to 4 days prior to angiography, a symptom limited exercise test was performed on a bicycle ergometer. Exercise was continued until anginal symptoms, a drop in systolic blood pressure, severe arrhythmia, or a ST depression of more than 1 mm occurred. A 12 lead ECG was recorded during exercise and recovery. ST

changes were measured 80 ms after the J point. Horizontal or downsloping ST segment depression associated with anginal symptoms was considered a positive response to the stress-test. The follow-up coronary angiogram was performed at the six month visit. If symptoms recurred within 6 months, coronary angiography was carried out earlier. If no definite restenosis was present and the follow-up time was less than 4 (CARPORT) or 3 (MERCATOR) months, the patient was asked to undergo another coronary arteriogram at 6 months.

*End points*

The primary end-point of both studies was the within-patient change in minimal lumen diameter as determined by quantitative angiography post-PTCA and at follow-up. Post-PTCA values were obtained from the last post-PTCA angiogram made before withdrawal of the guide catheter. The initial procedure was considered finished when the guide catheter were removed. In case evolution of the clinical condition required re-PTCA (with re-insertion of guide catheter), the angiogram made prior to repeat balloon inflation(s) was used to obtain follow-up values, irrespective of the timing of re-PTCA (hours, days or weeks). Otherwise, the follow-up angiogram made according to protocol was used. For each dilated segment, the post-PTCA and follow-up minimal lumen diameter was taken as the mean value from multiple matched projections. Within-patient change (i.e. the primary end-point) was defined as the follow-up minus the post-PTCA value. In case more than one segment was dilated (multivessel or multi site procedures), the change in minimal luminal diameter per patient was calculated as the average of the different lesions.

Secondary end-points were clinical events believed to be related to restenosis. These were: death (irrespective of cause), non-fatal myocardial infarction (at least two of the following: typical pain, ECG changes suggesting acute MI, cardiac enzymes above twice the upper limit of normal), coronary artery bypass grafting (CABG) and repeat angioplasty at the same site, presence and severity of angina pectoris as assessed by the Canadian Cardiovascular Society classification at last follow-up, or none of the above.

*Statistical methods and analysis*

The minimal sample size was estimated at the outset of the study to be 233 patients in each group, on the assumption of a change of $-0.40 \pm 0.50$ mm in mean minimal lumen diameter between post angioplasty and follow up angiogram in the control group [5] and $-0.25 \pm 50$ mm (i.e. a 30% difference) in the active drug group (two sided test with an alpha error of 0.05 and a power of 0.90).

For statistical evaluation, "intention-to-treat" and "per-protocol" populations were defined. The intention-to-treat population comprises patients who

fulfilled all in- and exclusion criteria and received at least one dose of test medication. The per-protocol population consists of all compliant patients of the intention-to-treat population who have an analyzable follow-up angiogram. A patient was judged compliant if at least 80% of the test medication was taken and the test medication was not stopped more than 5 days before follow-up angiography.

To test the hypothesis that the mean change in minimal lumen diameter is equal in the two treatment groups, an analysis of variance was done with treatment and center as main factors and treatment times center as interaction term. The treatment effect was defined as the difference in mean change in minimal lumen diameter between the two treatment groups. In addition, 95% confidence intervals of the treatment effect were obtained from the analysis of variance.

Comparison of the clinical outcome was done for the intention-to-treat population. Each patient was assigned at the time of follow-up to the most serious applicable event on the scale described above. For comparison of the clinical outcome between the two treatment groups, standard non-parametric statistical methods were used.

## Results

Selected demographic, clinical, and angiographic characteristics of the two trials for each study groups are shown in Tables 2 and 3.

In the *Carport* trial, a total of 707 patients were randomized. Of these patients 353 were randomized to receive GR32191B and 354 to the control group. No baseline differences were observed between the two groups. Figure 1A shows the patient flow and the reasons that subjects could not be evaluated with respect to quantitative angiographic restenosis. Thus 322 treated patients and 327 control patients underwent a successful angioplasty of at least one lesion and were eligible for follow up angiography. Quantitative angiographic follow-up was not available in 74 cases (35 treated, 39 control).

In the *Mercator* trial, 735 patients gave informed consent and subsequently 693 continued the trial and constituted the intention-to-treat population. Figure 1B shows the patient flow chart and 352 were randomized to receive placebo and 341 to receive cilazapril. In general, the baseline characteristics were evenly distributed in the two groups, except for patients with pain at rest and patients currently smoking, who were more frequently encountered in the control group. During follow-up, 40 patients stopped their treatment because of adverse experiences, 9 patients because they had a clinical event and 1 patient became a protocol violator. Thirty-nine patients did not fulfill compliance criteria (control 18, cilazapril 21), in 9 patients no angiogram suitable for quantitative analysis could be obtained due to either refusal (control 5, cilazapril 2) or to technical reasons (absence of matched views or

*Table 2.* Clinical characteristics of the intention to treat populations

| | Control 346 | GR32191B 251 | Control 352 | Cilazapril 341 |
|---|---|---|---|---|
| No. of Men | 276 (80%) | 279 (80%) | 292 (83%) | 282 (83%) |
| Age (years) | 56 ± 9 | 56 ± 9 | 56 ± 8 | 57 ± 9 |
| Ever smoked | 259 (75%) | 280 (80%) | 269 (76%) | 259 (76%) |
| Current smokers | 40 (12%) | 57 (16%) | 70 (20%) | 49 (14%) |
| Diabetes Mellitus | 28 (8%) | 29 (8%) | 20 (6%) | 21 (6%) |
| History of Hypertension | 111 (32%) | 120 (34%) | – | – |
| 1 Vessel Disease | – | – | 228 (65%) | 225 (66%) |
| 2 Vessel Disease | – | – | 106 (30%) | 99 (29%) |
| 3 Vessel Disease | – | – | 18 (5%) | 17 (5%) |
| Total cholesterol (mg/dl) | 239 ± 42 | 239 ± 46 | 228 ± 59 | 227 ± 54 |
| No angina present | – | – | 30 (9%) | 28 (8%) |
| – CCS class I | 37 (11%) | 42 (12%) | 46 (13%) | 53 (16%) |
| – CCS class II | 111 (32%) | 116 (33%) | 108 (31%) | 103 (30%) |
| – CCS class III | 141 (41%) | 140 (40%) | 102 (29%) | 100 (29%) |
| – CCS class IV | 57 (16%) | 52 (15%) | 66 (19%) | 57 (17%) |
| Pain rest iv nitrates | 43 (12%) | 48 (14%) | 28 | 15 |
| Duration of angina (mth) | 22 ± 44 | 24 ± 45 | 14 ± 30 | 14 ± 30 |
| Previous MI | 134 (39%) | 132 (38%) | 146 (41%) | 142 (42%) |
| Previous CABG | 7 (2%) | 12 (3%) | 6 | 7 |
| Previous angioplasty | 4 (1%) | 6 (2%) | 6 | 4 |
| No of patients on | | | | |
| – Nitrates | 235 (68%) | 225 (64%) | 246 (70%) | 236 (69%) |
| – Ca antagonists | 208 (60%) | 222 (63%) | 228 (65%) | 217 (64%) |
| – B-blockers | 175 (51%) | 191 (54%) | 182 (52%) | 180 (53%) |
| Mono therapy | 97 (28%) | 104 (30%) | 89 (25%) | 91 (27%) |
| Double therapy | 151 (44%) | 156 (44%) | 180 (51%) | 151 (44%) |
| Triple therapy | 73 (21%) | 74 (21%) | 69 (20%) | 80 (23%) |

CCS=Canadian Cardiovascular Society angina classification, iv=intravenous, MI=Myocardial Infarcation, Pts=Patients, Plus – minus values are means ± sd, p-value $< 0.05$.

poor quality of the follow-up film, control 0, cilazapril 2). Thus, the per-protocol population consisted of 309 control patients and 286 patients treated with cilazapril.

### *Result of the angiographic efficacy analysis*

Table 4 and Fig. 2 summarizes the quantitative angiographic findings of the efficacy analysis. In the *Carport* trial, the loss in minimal lumen diameter at follow-up was identical in both groups, −0.31 mm (treatment effect 0 mm, 95% CI: −0.09, 0.09). Figure 3a is a cumulative curve of the change in minimal lumen diameter observed in both groups. A loss of $\geq$0.72 mm [5, 20] corresponds to a restenosis rate of 19% in the control group and 21% in the treated group. The relative risk for restenosis in the treated group with

*Table 3.* Angiographic characteristics of the per protocol populations.

| | Control 261 pts 320 lesions | GR32191B 261 pts 316 lesions | Control 309 pts 367 lesions | Cilazapril 286 pts 342 lesions |
|---|---|---|---|---|
| *Vessel dilated* | | | | |
| RCA | 90 (28%) | 99 (31%) | 103 (28%) | 101 (30%) |
| LAD | 167 (52%) | 146 (46%) | 173 (47%) | 153 (45%) |
| LCx | 63 (20%) | 71 (23%) | 93 (25%) | 88 (25%) |
| *Type lesion* | | | | |
| Concentric lesions | – | – | 188 (51%) | 179 (52%) |
| Eccentric lesion | 133 (42%) | 135 (37%) | 108 (31%) | |
| Tandem lesion | 25 (8%) | 24 (8%) | 3 (1%) | 18 (5%) |
| Multiple irregularities | – | – | 31 (8%) | 25 (7%) |
| Total Occlusion | 12 (4%) | 10 (3%) | 10 (3%) | 12 (4%) |
| Calcified lesion | 19 (6%) | 32 (10%) | 45 (12%) | 46 (14%) |
| Side branch in stenosis | 99 (31%) | 78 (25%) | 213 (58%) | 197 (56%) |
| Lesion at bend point | – | – | 34 (9%) | 48 (13%) |
| Thrombus post-PTCA | 7 | 12 | 10 (3%) | 14 (4%) |
| Dissection | 49 (15%) | 46 (15%) | 105 (28%) | 107 (31%) |
| Maximal pressure (atm) | 9 ± 2 | 9 ± 2 | 8 ± 2 | 8 ± 3 |
| Total inflation (sec) | 138 ± 90 | 245 ± 226 | 247 ± 214 | |
| Balloon artery ratio | 1.10 ± 0.22 | 1.06 ± 0.22 | 1.14 ± 0.20 | 1.12 ± 0.18 |

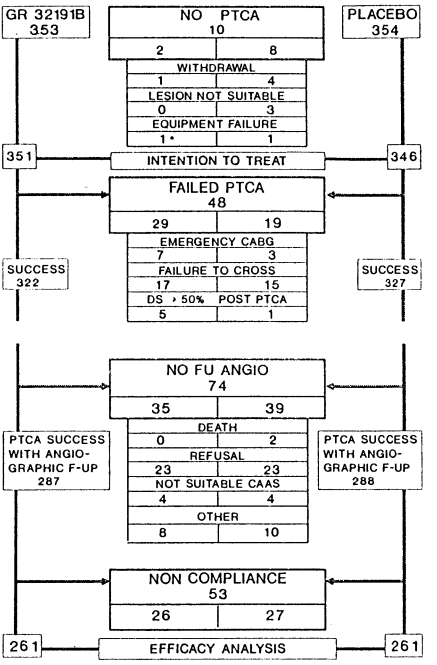
LAD=left antior descending coronary artery, LC=left circumflex artery, MLD=Minimal lumen diameter, PTCA=Percutaneous Transluminal Coronary Angioplasty, Pts=Patients, RCA=right coronary artery, Plus – minus values are means ± sd.

respect to the control group is then 1.15 (95% confidence intervals 0.82, 1.60).

For the *Mercator* trial, the loss at follow-up in minimal lumen diameter was $-0.29 \pm 0.49$ mm in the control group and $-0.27 \pm 0.51$ mm in the cilazapril treated group (treatment effect, 0.023 mm; 95% CI: $-0.06$ to 0.11 mm). Figure 3b represent a cumulative frequency curve of the minimal lumen diameter and of the change in minimal lumen diameter observed in both groups. Adjustment for current smoking and pain at rest did not affect the results. When participating clinics were analyzed separately, the results were consistent.

### *Results of bicycle ergometry*

Out of 649 patients who had a successful angioplasty in the *Carport* trial, 539 underwent exercise testing at follow-up. Reasons for not performing the test were death: 2 patients, unstable angina: 45 patients, inability to perform the test: 19 patients, refusal: 33 patients and other reasons: 11 patients. Table 5 summarizes results of exercise testing in both groups. No difference in any parameter was observed at submaximal and maximal exercise. ST deviation (depression or elevation) of more than 0.1 mV ( $>1$ mm) associated




A

*Figure 1a.* Patient flow in Carport trial and reasons why no follow-up angiogram and/or quantitative angiography was obtained. Angio = coronary angiography, CABG = aorto coronary bypass grafting, CAAS = Coronary artery analysis system, DS = diameter stenosis, FU = follow-up, angioplasty = percutaneous transluminal coronary angioplasty, * Patient twice randomized and excluded from trial.

with anginal symptoms (considered a positive was observed in 47 patients in the control group and 55 patients in the GR32191B group.

Out of 693 patients in the *Mercator* trial, 564 (81%) underwent exercise testing at follow-up. Reasons for not performing the test were: death in 5 patients (control 2, cilazapril 3), unstable angina in 58 patients (control 30, cilazapril 28), refusal in 18 patients (control 5, cilazapril 13), adverse event in 23 patients (control 11, cilazapril 12), logistic reasons in 6 patients (control 4, cilazapril 2), other reasons in 14 patients (control 5, cilazapril 9,). The X-test was not performed according to protocol in 5 patients (control 4, cilazapril 1). Table 5 summarizes results of exercise testing in both groups. No difference in objective parameters was observed. Chest pain during exercise was reported in 74 (25%) patients receiving placebo and 42 (15%) patients receiving cilazapril ($p = 0.03$). ST deviation (depression or elevation) of more than 0.1 mV associated with anginal symptoms was observed in 39 patients (13%) in the control group and 25 patients (9%) in the cilazapril group.

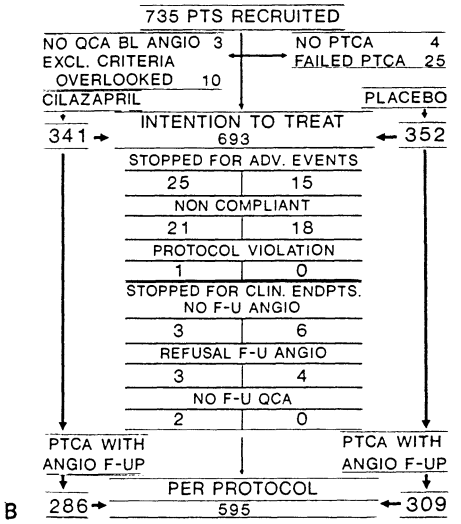



*Figure 1b.* Patient flowchart in MERCATOR trial. Pts = Patients, Bl = baseline, QCA = Quantitative Coronary Angiography, Fup = Follow-up, Ad = Adverse, Excl = Exclusion

*Table 4.* Quantitative analysis in the per-protocol populations.

| | Control 261 pts | GR32191B 261 pts | Control 309 pts | Cilazapril 286 pts |
|---|---|---|---|---|
| Obstruction diameter (mm) | | | | |
| Pre-angioplasty | 0.99 ± 0.35 | 1.06 ± 0.39 | 0.98 ± 0.35 | 1.05 ± 0.35 |
| Post-angioplasty | 1.77 ± 0.34 | 1.79 ± 0.33 | 1.77 ± 0.34 | 1.80 ± 0.36 |
| Follow-up | 1.46 ± 0.59 | 1.49 ± 0.58 | 1.48 ± 0.54 | 1.54 ± 0.54 |
| Reference diameter (mm) | | | | |
| Pre-angioplasty | 2.64 ± 0.57 | 2.70 ± 0.50 | 2.61 ± 0.54 | 2.66 ± 0.51 |
| Post-angioplasty | 2.71 ± 0.54 | 2.76 ± 0.48 | 2.67 ± 0.48 | 2.72 ± 0.49 |
| Follow-up | 2.72 ± 0.55 | 2.74 ± 0.52 | 2.68 ± 0.56 | 2.74 ± 0.52 |
| Difference in obstruction diameter (mm) | | | | |
| Post-pre-angioplasty | 0.78 ± 0.39 | 0.73 ± 0.38 | 0.79 ± 0.42 | 0.75 ± 0.37 |
| Follow-up-post-angioplasty | −0.31 ± 0.54 | −0.31 ± 0.55 | −0.29 ± 0.49 | −0.27 ± 0.51 |
| Percentage stenosis (%) | | | | |
| Pre-angioplasty | 62 ± 13 | 61 ± 12 | 61 ± 13 | 60 ± 12 |
| Post-angioplasty | 34 ± 9 | 34 ± 9 | 33 ± 9 | 33 ± 10 |
| Follow-up | 46 ± 19 | 45 ± 19 | 44 ± 18 | 44 ± 17 |
| Difference in percentage stenosis (%) | | | | |
| Post – pre-angioplasty | −28 ± 14 | −26 ± 14 | −29 ± 15 | −27 ± 14 |
| Follow-up – post-angioplasty | 12 ± 20 | 11 ± 19 | 11 ± 18 | 11 ± 18 |

Plus – minus values are means ± sd, Pts=Patients.

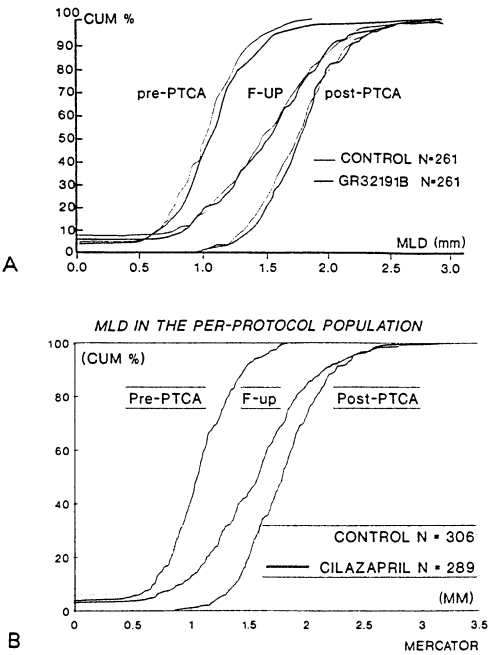



*Figure 2.* Cumulative distribution curve of the minimal lumen diameter pre-angioplasty, post-angioplasty and at 6 month follow-up in both treatment groups. (cum% = cumulative percentage of patients, MLD = minimal luminal diameter), respectively for Carport (A) and Mercator (B) groups.

## *Clinical follow-up*

Table 6 shows the clinical status 6 months after angioplasty.

In the *Carport* trial adjusted chi square test revealed no difference in ranking between the two groups. At 6 month follow up a comparable amount of patients in both treatment groups were in each Canadian Cardiovascular Society class. Finally 194 patients (56%) in the treated group and 197 (56%) in the control group were event- and symptom-free at 6 month follow-up.

In the *Mercator* trial, clinical follow-up was obtained for all 693 patients. During the course of the study, 5 patients died (control 2, cilazapril 3). The cause of death was in 4 cases cardiovascular and in 1 case of other origin. Non-fatal myocardial infarction was documented in 13 patients (control 8, cilazapril 5 ), 17 patients underwent bypass surgery (control 8, cilazapril 9), repeat PTCA, atherectomy or stent implantation was performed in 87 patients (control 43, cilazapril 44) and recurrent angina was observed in 135 patients (control 67, cilazapril 68). Finally 224 (64%) in the control group and 212 (62%) in the treated group were event free at 6 month follow-up. Adjusted chi square test revealed no difference in ranking between the two groups.

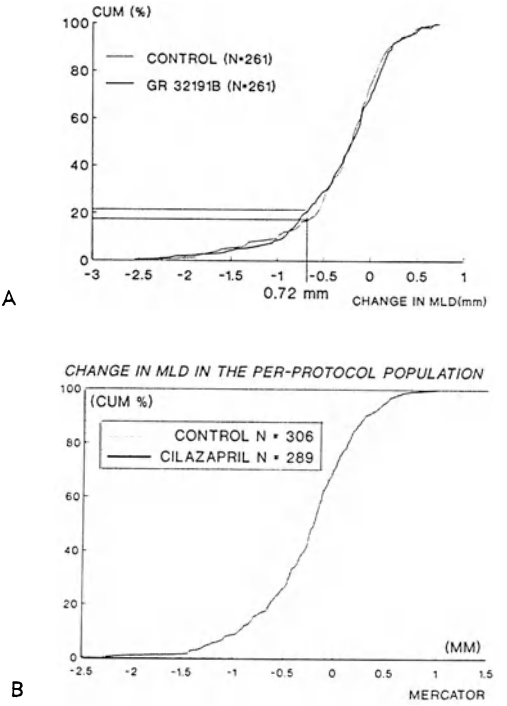



*Figure 3.* Cumulative distribution curve of the change in minimal lumen diameter from post-angioplasty to follow-up in both treatment groups. (cum% = cumulative percentage of patients, MLD = minimal luminal diameter) in Carport (A) and Mercator (B).

*Table 5.* Exercise test results

| | Control 262 pts | GR32191B 277 pts | Control 291 pts | Cilazapril 273 pts |
|---|---|---|---|---|
| Maximum workload (Watts) | 142 ± 41 | 144 ± 40 | 146 ± 39 | 151 ± 44 |
| Exercise time (sec) | 468 ± 178 | 468 ± 180 | 446 ± 124 | 454 ± 127 |
| Systolic blood pressure at peak exercise (mmHg) | 193 ± 33 | 196 ± 31 | 196 ± 27 | 192 ± 28 |
| Heart rate at peak exercise (bpm) | 133 ± 24 | 135 ± 22 | 142 ± 22 | 142 ± 21 |
| Double product (mmHg* 100/bpm) | | | 279 ± 65 | 275 ± 66 |
| ST-deviation>1 mm | 102 (39%) | 117 (42%) | 102 (36%) | 99 (37%) |
| Anginal symptoms during test | 76 (32%) | 73 (30%) | 74 (25%) | 42 (15%) |
| Combination of ST >1 mm and symptoms | 47 (18%) | 55 (20%) | 39 (13%) | 25 (9%) |

*Table 6.* Ranking per patient based on most serious clinical event during 6 months follow-up.

| | Control 346 pts | GR32191B 351 pts | Control 352 pts | Cilazapril 341 pts |
|---|---|---|---|---|
| Death | 6 (2%) | 4 (1%) | 2 (<1%) | 3 (<1%) |
| Non-fatal Myocardial infarcation | 22 (6%) | 18 (5%) | 8 (2.3%) | 5 (1.4%) |
| Coronary Revascularization | 71 (21%) | 71 (20%) | 51 (15%) | 53 (16%) |
| Angina recurrence | 63 (16%) | 61 (17%) | 67 (19%) | 68 (20%) |
| No Event | 194 (56%) | 197 (56%) | 224 (64%) | 212 (62%) |

## Discussion

### *Trial design: quantitative angiography as primary end-point*

The primary goal of a restenosis prevention trial is the improvement in short- and longterm clinical outcome of patients having undergone a PTCA procedure. It is assumed that the improvement in clinical outcome is related to an anatomical phenomenon, namely the prevention of the recurrence of the stenosis in the treated vessel. However in these type of trials testing pharmacological compound with possible anti-ischemic or anti-anginal effects, unrelated to the post-injury hyperplasia, the clinical outcome might be misleading and obscure the reason for the observed improvement. Quantification of luminal dimensions changes over time may provide insight in biological and mechanistic effect on the treatment following PTCA. The (re-)appearance of angina as a sole criterion of restenosis underestimates the angiographic rate of restenosis, and the value of recurrent anginal symptoms as a marker of restenosis is difficult to assess in many studies because the timing and completeness of angiographic follow-up often have been determined by symptomatic status [3]. In the present trials repeat catheterization with quantitative angiography was obtained in 88.5% of 649 patients (Carport) and 94% of 693 patients (Mercator) with a successful angioplasty.

The poor value of recurrent anginal symptoms as a marker of restenosis is confirmed by the low predictive value of symptoms found in many studies [3].

Similarly, the usefulness of ergometry to detect restenosis after PTCA has been questioned since several studies have found that the presence of exercise test induced angina or ST-segment depression/elevation or both are not highly predictive for restenosis if the test is performed early or late after PTCA [3]. A drug tested for its ability to prevent restenosis may be shown to be beneficial following PTCA by reducing angina during exercise-test and yet have no effect on intimal hyperplasia following balloon induced injury.

The prognostic value of the change in sequential coronary angiogram has been largely underestimated as a surrogate endpoint for clinical atherosclerotic events. In the phase II of pharmacological investigation, the main emphasizes should be put on the physiopathological mechanism of prevention of restenosis in the post-injury model and the improvement in clinical outcome

*Table 7.* Prognostic value of the minimal lumen diameter at follow-up in the per-protocol population divided in 5 equal groups. (Mercator study only)

| | Exercise test | | Clinical outcome | | | |
|---|---|---|---|---|---|---|
| MLD F-up (mm) | <1 mm STT-changes and no chest pain | ≥1 mm STT-changes and chest pain | MI | Re-intervention | Angina | None |
| <1.10 | 70 (75%) | 24 (26%) | 5 (4%) | 49 (41%) | 24 (20%) | 41 (35%) |
| 1.10 to 1.39 | 88 (88%) | 12 (12%) | 1 (1%) | 18 (15%) | 25 (21%) | 74 (63%) |
| 1.39 to 1.63 | 103 (90%) | 11 (10%) | 2 (2%) | 10 (8%) | 31 (26%) | 77 (64%) |
| 1.63 to 1.91 | 99 (93%) | 8 (7%) | 1 (1%) | 7 (6%) | 21 (15%) | 89 (75%) |
| 1.91 or more | 111 (98%) | 2 (2%) | 1 (1%) | 7 (6%) | 18 (15%) | 94 (78%) |
| | 471 Pts | 57 Pts | 10 Pts | 91 Pts | 119 Pts | 375 Pts |

MLD=Minimal Lumen Diameter, mm=millimeter, MI=Myocardial Infarcation, Pts=Patients.

should be viewed as a secondary benefit dependent on the anatomical status. When the patient population of the Mercator trial is stratified according to the minimal lumen values at follow-up then it appears that the percentage of patients having reached one of the predefined clinical endpoint is as high as 65% in the worst category (mld fup < 1.10 mm) while the percentage of the patients event free are ranging from 63% to 78% in the other categories (Table 7). It must be emphasized that 41% of the patients in the worst anatomical category had reintervention versus only 6% in the best anatomical category, irrespective of the initial dilatation site. Beside the prognostic value, the anatomical results has also a clear functional impact since only 2% of the patients had a positive exercise test in the best anatomical category versus 26% of the patients in the worst anatomical category [28].

### *Lack of effect on angiographic restenosis*

#### *Carport*

In this trial thromboxane A2 receptor blockade failed to demonstrate prevention of angiographic restenosis following angioplasty. Also, there was no apparent effect on overall clinical outcome. Several possible explanations for this can be put forward: 1) poor absorption 2) compliance could have been poor 3) it is possible that the substantial reduction in the aggregatory response of the platelet is still insufficient to prevent a substantial release of other factors involved in the initiation of the proliferative response. These explanations are discussed in the main publication [20].

More recently it has been advocated that inhibition of platelet adhesion is a more efficient means to prevent subsequent aggregation of platelets [21–24]. However it can be argued that complete inhibition of adhesion will cause untoward bleeding effects.

Finally, the pivotal role of the platelet in the initiation of the restenosis process might have been overestimated [25] and antiplatelet therapy as the sole modality of treatment is maybe intrinsically insufficient to control the restenosis phenomenon.

*Mercator*

Several explanations (which are not mutually exclusive) may account for the apparent failure of cilazapril to decrease the rate of coronary restenosis, which are discussed at length in the main publication [26]. Briefly, the following explanations: 1) *Dose related*; a possible explanation for the lack of effect in MERCATOR is that the dose used was to low, as the dose used in the rat model was 70 times higher (10 mg/kg/day) [27]. 2) *Time related*; in experimental studies the strongest inhibition of neointima formation was obtained when treatment was started 6 days before injury. It could be that a period of drug impregnation prior to injury might be required to obtain an inhibitory effect, although a significant, but slightly attenuated effect was observed when started 2 days after injury. 3) *Species related*; although quite attractive, the close parallel between the muscular response to experimental arterial injury and the development of restenosis in humans after therapeutic angioplasty remains a working hypothesis. The response of atherosclerotic human arteries may be modulated by cellular and molecular influences that are not exactly similar to those acting in non-diseased non-human arteries. 4) *Alternative pathways of angiotensin II production*; other enzymes as angiotensin converting enzyme are known for their ability to metabolize angiotensin I to angiotensin II (chymase, tonin and cathepsin). It could well be that these alternative pathways resulted in sufficient level of angiotensin II to activate or to stimulate the restenosis process. As no actual measurement was done of angiotensin I or II, it is difficult to say if these alternative pathways were active. However, we found a significant decrease in blood pressure immediately after the first drug intake, in patients randomized to cilazapril as compared to patients taking placebo. This effect was maintained during the whole 6 months follow-up period. Thus, clinically there was an effect of cilazapril by reducing blood pressure presumably by lowering the level of angiotensin II. The use of an angiotensin II receptor blocker might be worth exploring [28], as in this case all angiotensin II, irrespective of the metabolic pathway that is used, is blocked. 5) *Possible mitogenic effect of angiotensin I* Another explanation for failure of cilazapril to reduce restenosis, is that as a logical consequence by the use of ACE-inhibitors, the concentration of angiotensin I is increased, which has shown to be mitogenetic for arterial muscle cells [29]. This unavoidable side effect of ACE-inhibitors may, perhaps only in some species annihilate their favorable actions exerted through A II suppression.

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# 26B. Quantitative coronary angiography in the assessment of risk factors for luminal renarrowing

## *A study of clinical, procedural and lesional factors related to long term angiographic outcome in 2 restenosis prevention trials: CARPORT and MERCATOR*

WALTER R.M. HERMANS, BENNO J. RENSING and PATRICK W. SERRUYS, on behalf of the CARPORT (Coronary Artery Restenosis Prevention On Repeated Thromboxane antagonism) and MERCATOR (Multicenter European Research trial with Cilazapril after Angioplasty to prevent Transluminal coronary Obstruction and Restenosis) study groups

### Introduction

The major limitation of the long term success of percutaneous transluminal coronary angioplasty (PTCA) is still restenosis and is a complex process that is only partially understood [1, 2]. Histologic studies of coronary arteries after dilation, obtained by either autopsy or atherectomy, have provided evidence that strongly supports the concept of intimal hyperplasia or proliferation of smooth muscle cells, with abundant matrix production, of medial or intimal origin as the underlying cause of luminal narrowing after angioplasty [3–5]. Pharmacological agents aimed at reducing the absolute amount of intimal hyperplasia are currently being investigated in many clinical trials. In these trials it is presumed that the clinical outcome is related to an anatomical substrate, i.e. the prevention or reduction of reactive intimal hyperplasia after angioplasty. If restenosis is viewed as an intraluminal growth process after a successful angioplasty, risk factors for restenosis should be risk factors for this growth process. The angiographically determined change in lumen diameter at follow-up is currently the only reliable indicator of the amount of reactive hyperplasia applicable to large study populations. Quantitative coronary analysis is the most reliable available method of assessing coronary arterial luminal changes over time and has demonstrated that the change in minimal luminal diameter between post-PTCA and follow-up angiography is the most non-ambiguous measurement to describe the continuous process of restenosis at present time [6–9]. A model that accurately predicts the amount of luminal narrowing in the individual patient would be of value in several ways: First, it could be an aid in patient or lesion selection for the procedure because an accumulation of risk factors in the individual patient might indicate balloon angioplasty an



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unattractive means of revascularization; secondly, it could improve assessment of medium term (6 months) prognosis in the individual patient; third, modification or control of the identified risk factors could reduce overall restenosis rates; fourth, the model could assist in the selection of patients at risk for a large loss in lumen diameter. This population could then constitute the target population for pharmacological intervention studies because a larger mean loss in lumen diameter would permit the enrollment of a smaller number of patients in a study while maintaining an equal power. Therefore, in this chapter patient related factors, lesion related factors and procedural factors were correlated to the quantitative angiographic change in lumen diameter from post-angioplasty angiogram to follow-up angiogram in two recent restenose prevention trials, Carport trial with a thromboxane A2 receptor antagonist, and Mercator trial with a novel angiotensin converting enzyme inhibitor cilazapril [8, 9]. As these trials were similar in design and methodology, the results of both trials are described side by side.

## Methods

The orginal study population for the assessment of the effect of the novel drug on restenosis consisted of respectively 697 (Carport) and 735 (Mercator) patients, who were randomized in 6 and 26 European centers [8, 9]. The Carport trial investigated in a randomized, double blind, placebo controlled trial, a novel thromboxane $A_2$ receptor antagonist (GR32191B) and in the Mercator trial, a novel angiotensin converting enzyme inhibitor, cilazapril, was investigated for its ability to prevent restenosis after primary coronary angioplasty. Follow-up on these patients was done on a prospective basis and all patients agreed to undergo repeat angiography at 6 months.

All patients with both stable and unstable angina and angiographically-proven native coronary artery disease who were scheduled for primary angioplasty, were considered for inclusion. Exclusion criteria for trial participation and their relative frequencies have been published earlier [8, 9]. The results of both trials have been reported elsewhere [8, 9]. Clinical or angiographic benefit could not be demonstrated, so that the placebo and active treatment group could be pooled in each trial for the present study [8, 9].

Angioplasty success was defined as a less than 50% residual stenosis by visual inspection of the post-angioplasty angiogram and no occurrence of in-hospital complications (death, acute myocardial infarction, repeat angioplasty, aorto coronary bypass grafting or recurrence of symptoms), and was achieved in 649 patients (93.1%) in the Carport trial and 693 patients (94.2%) in the Mercator trial . Quantitative angiographic follow-up was available for 575 patients (88.6%) in the Carport trial and 653 patients (or 94%) in the Mercator trial and this forms the study population (Fig. 1).

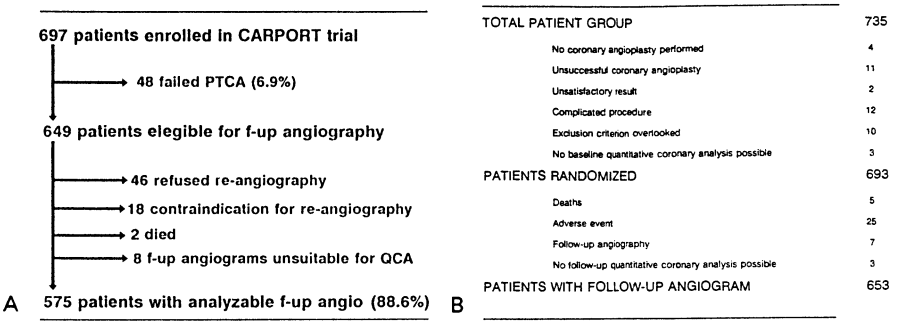


*Figure 1.* Patient flow chart of Carport (A) and Mercator trial (B).

### *Angioplasty procedure, follow-up and quantitative angiography*

Angioplasty procedure, follow-up and quantitative angiography was done as has been described elsewhere [6, 8, 9]. To standardize the method of data acquisition, data analysis and to ensure exact reproducibility of pre-coronary angioplasty, post-coronary angioplasty and follow-up angiograms, special precautions were taken, as previously described elsewhere [6, 8, 9]. All angiograms were processed and analyzed in a central core-laboratory. At least 2 views of all lesions were analyzed, orthogonal if possible. A difference in angulation of at least 30 degrees was required for a view to be separately analyzed.

The mean change in minimal lumen diameter from post-angioplasty angiography to follow-up angiography and from pre-angioplasty to post-angioplasty was derived from matched angiographic views. The follow-up coronary angiogram was performed at six months follow-up. If symptoms recurred within 6 months, coronary angiography was carried out earlier. If no definite restenosis was present and no revascularization procedure was performed and the follow-up time was less than 4 months, the patient was asked to undergo another coronary arteriogram at 6 months.

*Table 1.* Summary of studies using multivariate analysis techniques to find variables with increased risk for restenosis.

| | Pts | Angio fup (%) | Definition restenosis | Restenosis (%) | Patient | Risk factors/ Lesion | Procedural |
|---|---|---|---|---|---|---|---|
| Holmes | 665 | 84% | NHLBI I or IV | 34% pts | male, severity angina, no history of MI | bypass graft | – |
| Mata* | 63 | 96% | ↑ DS > 30% or DS > 70% | 23% lesion | – | LAD or LCX > RCA,% DS post-PTCA, (40% vs 20%), calcified lesion | bar (0.9 vs 1.1) |
| Leimgruber | 1758 | 57% | >50% DS | 30% pts | unstable angina | LAD, ↑ %DS post-PTCA, gradient >15 mmhg | absence of intimal dissection |
| Myler** | 286 | 57% | >50% DS | 57% pts, 43% lesion | diabetes, hypercholesterolaemie, new onset angina, current smoking | >95% DS pre-PTCA | ↑ max pressure |
| Guiteras Val | 181 | 98% | ↑ ⩾ 30% DS | 28% pts, 25% lesion | variant angina, multivessel | ↑ % DS post-PTCA, low% DS Pre - Post | – |
| Vandormael** | 209 | 62% | >50% DS | 50% pts | male, diabetes | prox LAD, longer lesions | – |
| de Feyter**** | 179 | 88% | >50% DS | 32% pts | worsening AP or post-MI AP | – | – |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Fleck | 110 | 86% | MLCA > 1 $mm^2$ (QCA) | 44% lesions | – | – | – |
| Halon**** | 84 | 56% | >70% DS | 25% | – | multiple irregularities, decrease coronary perfusion | – |
| Quigley*** | 114 | 88% | >50% DS | 32% pts | unstable angina, hypertension, diabetes | – | – |
| Renkin | 278 | 47%** | >50% DS | – | – | MLD post-PTCA | – |
| Rupprecht | 676 | 70% | >50% DS or loss > 50% of gain | 29% pts | unstable angina | ↑ %DS pre-PTCA, ↑ %DS post-PTCA | long single inflation |
| Bourassa | 376 | 66% | ≥50% DS + 10% ↑ post-fup | 36% pts, 35% lesion | severity angina | length >10 mm,% DS post-PTCA | – |
| Hirshfeld | 694 | 74% | ≥50% DS | 40% lesion | – | length >10 mm, vein graft, LAD,% DS pre-PTCA,% DS post-PTCA | optimal BAR (1.1–1.3) |

* = multivessel dilatation; ** = multilesion dilatation; *** = for restenosis; **** = unstable angina; ***** = review of patients with clinical recurrence; ** = angiography + exercise thallium scintigraphy.

Angio fup = % of successfully dilated patients with angiographic follow-up; AP = angina pectoris; bar = balloon artery ratio; DS = Diameter Stenosis; Fup = follow-up; LAD = Left Anterior Descending artery; LC = Left Circumflex; MI = Myocardial Infarction; MLCA = change in minimal cross sectional area; MLD = Minimal luminal Diameter; NHLBI = National Heart Lung Blood Institute classification; pts = patients; RCA = Right Coronary Artery, ↑ increase, ↓ decrease.

*Potential risk factors studied*

The loss in minimal lumen diameter was assessed for factors earlier reported to be predictive of luminal narrowing after successful PTCA (Table 1) [1, 2, 10–12]. Some of the lesional factors (type of lesion, branch involved in stenosis, lesion located in bend, calcification of lesion, thrombus post-PTCA, dissection post-PTCA) were assessed by the core laboratory blinded for the code and clinical data. For categorical variables the change in lumen diameter from post-angioplasty angiogram to follow-up angiogram was determined in each category. Continuous variables were grouped into three equally sized subgroups (tertiles) and the change in minimal lumen diameter assessed for each tertile.

*Patient related factors* are present systemically and thereby affect all dilated lesions in a single patient. These include age, gender, diabetes, unstable angina (defined as pain at rest requiring treatment with intravenous nitrates), extent of atherosclerotic disease (single or multivessel), history of smoking, previous myocardial infarction, duration of angina (months), total cholesterol level, Canadian Cardiovascular Society angina classification at baseline.

*Lesion related factors* are characteristics unique to each lesion. The following factors were assessed: minimal lumen diameter pre-PTCA and post-PTCA, relative gain (defined as the difference in obstruction diameter before and after angioplasty divided by the interpolated reference diameter (vessel size)), lesion length, atherosclerotic plaque area before PTCA, eccentricity of the lesion, percentage diameter stenosis pre-PTCA and post-PTCA, vesselsize before PTCA, total occlusion pre-PTCA, presence of thrombus before and after PTCA (defined as an intraluminal filling defect visible in all views, a visible embolization of intraluminal material downstream or dye staining at the site of a total occlusion (inter observer concordance rate for the assessment of intracoronary thrombus in the corelab 89%)), vessel dilated (either left anterior descending artery, circumflex artery or right coronary artery), calcification of the lesion, presence of dissection post-angioplasty [13], and presence of branch in stenosis.

*Procedure related factors* assessed were maximal or minimal measured balloon diameter, balloon-artery ratio (defined as the ratio of the quantitative angiographic diameter of the largest balloon at highest inflation pressure to the reference diameter), number of balloon inflations, maximal inflation pressure (atm.) and total duration of balloon inflation (sec.).

*Data analysis*

The unit of analysis reported here is the stenotic lesion, not the patient. The primary outcome variable was the change in lumen diameter from directly

post-angioplasty to follow-up angiogram. Data are presented as mean ±1 standard deviation. In univariate analysis continuous variables that were divided into 3 subgroups were compared with analysis of variance and for the discrete variables with Student's t-test. To obtain independent predictors for the loss in lumen diameter, variables were entered in a stepwise multiple linear regression analysis in which the loss in lumen diameter was the dependent variable. Stepwise multiple linear regression analysis was performed (BMDP statistical package, program 2R) to assess the relationship between the variables mentioned in the 'Methods' section (independent variables = $X_i$) and the loss in minimal lumen diameter from post-angioplasty angiogram to follow-up angiogram (dependent variable = Y): $Y = A + \Sigma_i B_i X_i$ where A is the intercept and $B_i$ is the $i^{th}$ regression coefficient. The standard BMDP 2R criteria of $F > 4$ for inclusion and $F < 3.9$ for elimination were applied. Continuous variables were entered as such in the multivariate analysis, except variables with 2 of 3 tertiles showing approximately the same amount of loss in lumen diameter for each tertile. These were entered as discrete variables.

To determine how well the regression model performs in predicting restenosis according to 2 frequently applied restenosis criteria and to illustrate the discrepancies between the 2 criteria, receiver operator characteristic (ROC) curves were constructed for each criterion. The criteria applied were: change in lumen diameter $\geq$0.72 mm at follow-up [14, 15] and the classic criterion of an increase in diameter stenosis from <50% post PTCA to $\geq$50% at follow up. The 0.72 mm value takes into account the limitations of coronary angiographic measurements and represents twice the long-term variability for repeat measurements of a coronary obstruction using the CAAS system [6, 14, 15]. The use of 1 standard deviation would include 68.3% of the measurement variability, while the use of 2 standard deviations ($2 \times 0.36 = 0.72$ mm) includes 95.5% of the measurement variability. The equivalent of the 0.72 mm value for diameter stenosis measurements is a change in diameter stenosis of 13%. In these ROC curves sensitivity (true positive%) at different cut off points of predicted change in minimal lumen diameter is graphed as a function of 100% – specificity (false positive%).

## Results

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

Of the 693 randomized patients in the Mercator trial, 653 (94%) with 778 lesions (1.2 lesion / patient) had a follow-up angiogram suitable for quantitative analysis. Using categorical criterion, restenosis rate was 30% according

*Table 2a.* Change in minimal lumen diameter per lesion for patient related variables in Carport (left) and Mercator (right).

| | | Change in MLD at fup (mm) | P value | | | Change in MLD at fup (mm) | P value |
|---|---|---|---|---|---|---|---|
| Age (years) | | | | | | | |
| <52 | (n = 211) | −0.26 ± 0.51 | | <55 | (n = 256) | −0.30 ± 0.58 | |
| 52–61 | (n = 213) | −0.31 ± 0.52 | 0.54 | 55–62 | (n = 263) | −0.25 ± 0.50 | 0.52 |
| ≥61 | (n = 242) | −0.31 ± 0.57 | | >62 | (n = 259) | −0.26 ± 0.48 | |
| Sex | | | | | | | |
| male | (n = 533) | −0.28 ± 0.50 | 0.11 | male | (n = 649) | −0.28 ± 0.53 | 0.21 |
| female | (n = 133) | −0.37 ± 0.65 | | female | (n = 129) | −0.22 ± 0.48 | |
| Diabetes I and II | | | | | | | |
| yes | (n = 56) | −0.56 ± 0.77 | <0.001 | yes | (n = 45) | −0.32 ± 0.53 | 0.52 |
| no | (n = 610) | −0.27 ± 0.50 | | no | (n = 733) | −0.27 ± 0.52 | |
| Unstable angina (pain at rest) | | | | | | | |
| yes | (n = 91) | −0.42 ± 0.73 | <0.05 | yes | (n = 72) | −0.29 ± 0.49 | 0.72 |
| no | (n = 575) | −0.27 ± 0.50 | | no | (n = 706) | −0.27 ± 0.52 | |
| Extent disease | | | | | | | |
| single vessel | (n = 401) | −0.31 ± 0.55 | 0.45 | single | (n = 424) | −0.30 ± 0.51 | 0.11 |
| multivessel | (n = 265) | −0.28 ± 0.52 | | multi | (n = 316) | −0.23 ± 0.54 | |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Ever smoked | | | | | | | |
| yes | (n = 515) | −0.28 ± 0.54 | 0.28 | yes | (n = 603) | −0.25 ± 0.49 | 0.08 |
| | (n = 151) | −0.34 ± 0.53 | | no | (n = 175) | −0.33 ± 0.59 | |
| Previous MI | | | | | | | |
| yes | (n = 253) | −0.33 ± 0.60 | 0.13 | yes | (n = 328) | −0.28 ± 0.54 | 0.70 |
| no | (n = 413) | −0.27 ± 0.50 | | no | (n = 450) | −0.26 ± 0.50 | |
| Duration of angina (months) | | | | | | | |
| <2.3 | (n = 210) | −0.37 ± 0.59 | | <86 | (n = 252) | −0.33 ± 0.55 | |
| 2.3–8.5 | (n = 227) | −0.26 ± 0.50 | 0.06 | 86–305 | (n = 258) | −0.29 ± 0.52 | 0.01 |
| ≥8.5 | (n = 229) | −0.26 ± 0.53 | | >305 | (n = 256) | −0.19 ± 0.48 | |
| Total cholesterol (mmol/l) | | | | | | | |
| <5.7 | (n = 225) | −0.32 ± 0.56 | | <5.7 | (n = 239) | −0.26 ± 0.53 | |
| 5.7–6.5 | (n = 217) | −0.34 ± 0.58 | 0.15 | 5.7–6.6 | (n = 254) | −0.26 ± 0.51 | 0.97 |
| ≥6.5 | (n = 216) | −0.26 ± 0.47 | | >6.6 | (n = 245) | −0.25 ± 0.51 | |
| AP class at baseline | | | | | | | |
| I,II | (n = 290) | −0.27 ± 0.49 | 0.25 | I,II | (n = 441) | −0.26 ± 0.52 | 0.68 |
| III,IV | (n = 376) | −0.32 ± 0.59 | | III, IV | (n = 365) | −0.28 ± 0.51 | |

to the >50% diameter stenosis criterion and 18% if the criterion of ≥0.72 mm loss in lumen diameter at follow-up was used.

*Variables predictive for change in minimal luminal diameter at follow-up (Table 2)*

*Patient related variables*

Table 2A summarizes the changes in minimal lumen diameter for all analyzed patient related variables. In the *Carport* trial, of the 10 patient related variables only 3, unstable angina, diabetes, and angina duration <2.3 months, showed a significantly larger loss in minimal lumen diameter at follow-up. The high loss in lumen diameter associated with the presence of these variables was probably caused by lesions that progressed towards total occlusion at follow-up. Indeed, if totally occluded lesions at follow-up (n = 42, 6.3%) were excluded from the analysis then a trend towards a higher loss in lumen diameter in the presence of one of these factors still existed, although not statistically significant: Diabetes: $-0.27 \pm 0.39$ vs $-0.20 \pm 0.39$ mm, $p = 0.18$, unstable angina: $-0.20 \pm 0.39$ mm vs $-0.18 \pm 0.39$ mm, $p = 0.66$, duration of angina <2.3 months $-0.24 \pm 0.37$ mm vs $-0.18 \pm 0.40$ mm, $p = 0.09$. In the *Mercator* trial, a greater loss in minimal luminal diameter was observed in association with duration of the angina, with a greater loss in minimal luminal diameter if symptoms are of recent origin.

*Lesion related variables*

The *pre-angioplasty* lesion related factors associated with a larger loss in the *Carport* trial at follow-up were: smaller minimal lumen diameter, lesion length ≥6.8 mm, higher percentage diameter stenosis, larger plaque area, and total occlusion (Table 2B). The *post-angioplasty* lesion related factors associated with a greater loss at follow-up were a larger post-angioplasty lumen diameter, lower percentage diameter stenosis post-angioplasty (ie a better angioplasty result), a higher relative gain achieved at angioplasty and thrombus post-angioplasty. Again, if total occlusions at follow-up were disregarded, the presence of total occlusions pre-angioplasty, and thrombus post-angioplasty were no longer associated with a significantly higher loss in minimal lumen diameter (total occlusion $-0.11 \pm 0.42$ mm vs $-0.20 \pm 0.39$ mm, $p = 0.25$, thrombus post − angioplasty $-0.25 \pm 0.39$ mm vs $-0.20 \pm 0.39$ mm, $p = 0.67$).

In the *Mercator* trial, a greater loss in minimal luminal diameter was observed in association with A) *pre-procedural variables*: 1) lower values of minimal luminal diameter, 2) higher values of diameter stenosis, 3) occluded vessel, 4) lesions in left anterior descending artery, 5) calcified lesion and B) *post-procedural variables* 1) higher values for minimal luminal diameter after

PTCA, 2) lower values for diameter stenosis after PTCA, 3) higher ratio of relative gain (Table 2B).

*Procedure related variables*

None of the procedural factors assessed was associated with a significantly greater loss in lumen diameter at follow-up in the *Carport* trial (Table 2C).

In the *Mercator* trial, a greater loss in minimal luminal diameter was observed in association with the total inflation time with a greater loss in minimal luminal diameter with longer total inflation time (Table 2C).

*Multiple linear regression analysis*

The stepwise multiple linear regression analysis of the Carport trial showed 2 pre-angioplasty angiographic characteristics as predictive of luminal narrowing at follow-up, namely length of the stenosis and the minimal lumen diameter pre-angioplasty (Table 3). Only 2 clinical variables and 2 post-angioplasty variables, namely diabetes, duration of angina, the relative gain in lumen diameter achieved at angioplasty, and thrombus post angioplasty were found to be independently predictive for luminal narrowing following balloon angioplasty. To rule out any influence of the investigational drug on our findings, the use of either the thromboxane A2 receptor blocker GR32191 or placebo was forced into model. Trial medication had only a very small, statistically unsignificant, contribution to the fit of the model (Table 3).

The stepwise multiple linear regression analysis of the Mercator trial showed that 1) relative gain, 2) minimal luminal diameter post-PTCA, and 3) dilatation of another vessel than right coronary artery were independently predictive for luminal narrowing at follow-up. Trial medication, which was forced into the model, had only a very small statistically insignificant contribution to the fit of the model (Table 3).

In an attempt to assess how well the model predicted the amount of luminal narrowing at follow-up, the percentage of correct classified lesions was calculated for 5 intervals of predicted change in lumen diameter in each trial (Table 4). In the Carport trial, correct prediction by the model was poor, particularly in the range of predicted change from $-0.1$ to $-0.4$ mm. In fact only 10% of lesions in the middle 3 categories were correctly classified by the model. On the other hand lesions showing no change or regression and lesions showing large progression were more predictable. The information content of the model according to the ROC curves (Fig. 2) was optimal for the "loss of $\geq 0.72$ mm" restenosis criterion. For the ">50% diameter stenosis" criterion the curve was very close to the line of "no prognostic value". If in addition to >50% diameter stenosis at follow-up also a loss of at least 13% in percent diameter stenosis (= twice the long term variability for diameter stenosis measurements, using the our analysis system) was required for a lesion to be classified as restenosis, a shift of the ROC curve to the left upper corner was apparent.

In addition, correct prediction by the model in the Mercator was poor,

*Table 2b.* Change in minimal lumen diameter per lesion at follow-up for lesion related variables in Carport (left) and Mercator (right).

| | | Change in MLD at fup (mm) | P value | | | Change in MLD at fup (mm) | P value |
|---|---|---|---|---|---|---|---|
| <0.9 | (n = 219) | −0.37 ± 0.58 | | <0.92 | (n = 260) | −0.36 ± 0.55 | |
| 0.9–1.15 | (n = 216) | −0.31 ± 0.51 | <0.02 | 0.92–1.14 | (n = 258) | −0.27 ± 0.51 | 0.0001 |
| ≥1.15 | (n = 228) | −0.22 ± 0.51 | | >1.14 | (n = 260) | −0.17 ± 0.47 | |
| MLD post PTCA (mm) | | | | | | | |
| <1.65 | (n = 220) | −0.16 ± 0.48 | | <1.60 | (n = 256) | −0.16 ± 0.49 | |
| 1.65–1.9 | (n = 221) | −0.33 ± 0.50 | <0.001 | 1.60–1.90 | (n = 263) | −0.25 ± 0.47 | 0.0001 |
| ≥1.90 | (n = 225) | −0.39 ± 0.55 | | >1.90 | (n = 259) | −0.40 ± 0.57 | |
| Relative gain at PTCA | | | | | | | |
| <0.2 | (n = 230) | −0.13 ± 0.45 | | <0.22 | (n = 258) | −0.09 ± 0.43 | |
| 0.2–0.3 | (n = 209) | −0.33 ± 0.49 | <0.001 | 0.22–0.33 | (n = 259) | −0.20 ± 0.48 | 0.0001 |
| ≥0.3 | (n = 224) | −0.46 ± 0.58 | | >0.33 | (n = 261) | −0.51 ± 0.55 | |
| Length obstruction (mm) | | | | | | | |
| <5.25 | (n = 229) | −0.23 ± 0.46 | | <5 | (n = 241) | −0.27 ± 0.47 | |
| 5.25–6.8 | (n = 195) | −0.24 ± 0.51 | <0.01 | 5–6.7 | (n = 243) | −0.22 ± 0.48 | 0.41 |
| ≥6.8 | (n = 203) | −0.38 ± 0.55 | | >6.7 | (n = 243) | −0.26 ± 0.55 | |
| Plaque area (mm2) | | | | | | | |
| <4.7 | (n = 208) | −0.21 ± 0.45 | | <4.7 | (n = 240) | −0.24 ± 0.46 | |
| 4.7–7.6 | (n = 212) | −0.29 ± 0.53 | <0.03 | 4.7–7.3 | (n = 244) | −0.23 ± 0.45 | 0.57 |
| ≥7.6 | (n = 207) | −0.34 ± 0.53 | | >7.3 | (n = 243) | −0.28 ± 0.58 | |
| Eccentricity | | | | | | | |
| <0.2 | (n = 210) | −0.31 ± 0.52 | | <0.24 | (n = 232) | −0.22 ± 0.46 | |
| 0.2–0.45 | (n = 205) | −0.26 ± 0.50 | 0.42 | 0.24–0.45 | (n = 250) | −0.26 ± 0.50 | 0.55 |
| ≥0.45 | (n = 212) | −0.27 ± 0.50 | | >0.45 | (n = 245) | −0.27 ± 0.53 | |
| % Diameter stenosis pre-PTCA | | | | | | | |
| <56.5 | (n = 244) | −0.20 ± 0.48 | | <55 | (n = 252) | −0.19 ± 0.45 | |
| 56.5–64.5 | (n = 210) | −0.35 ± 0.54 | <0.001 | 55–64 | (n = 276) | −0.24 ± 0.48 | 0.0001 |
| ≥64.5 | (n = 209) | −0.35 ± 0.58 | | >64 | (n = 250) | −0.38 ± 0.61 | |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| % Diameter stenosis post-PTCA | | | | | | | |
| <29.5 | (n = 217) | −0.40 ± 0.57 | | <29 | (n = 258) | −0.40 ± 0.50 | |
| 29.5–38 | (n = 225) | −0.32 ± 0.53 | <0.001 | 29–37 | (n = 258) | −0.29 ± 0.48 | 0.0001 |
| ⩾38 | (n = 224) | − 0.17 ± 0.49 | | >37 | (n = 262) | −0.12 ± 0.54 | |
| Vessel size (mm) | | | | | | | |
| <2.4 | (n = 240) | −0.30 ± 0.53 | | <2.35 | (n = 247) | −0.26 ± 0.45 | |
| 2.4–2.85 | (n = 214) | −0.30 ± 0.51 | 0.91 | 2.35–2.80 | (n = 262) | −0.30 ± 0.54 | 0.59 |
| ⩾2.85 | (n = 212) | −0.28 ± 0.57 | | >2.80 | (n = 269) | −0.25 ± 0.56 | |
| Patency pre-PTCA | | | | | | | |
| occluded | (n = 36) | −0.54 ± 0.87 | <0.01 | occluded | (n = 51) | −0.54 ± 0.68 | 0.0001 |
| patent | (n = 630) | −0.28 ± 0.50 | | patent | (n = 727) | −0.25 ± 0.50 | |
| Thrombus pre PTCA | | | | | | | |
| yes | (n = 32) | −0.32 ± 0.51 | 0.65 | – | – | – | – |
| no | (n = 634) | −0.29 ± 0.52 | | – | – | – | – |
| Thrombus post PTCA | | | | | | | |
| yes | (n = 16) | −0.71 ± 0.90 | <0.01 | yes | (n = 29) | −0.34 ± 0.73 | 0.48 |
| no | (n = 650) | −0.28 ± 0.52 | | no | (n = 749) | −0.27 ± 0.51 | |
| Vessel dilated | | | | | | | |
| LAD | (n = 321) | −0.27 ± 0.46 | | LAD | (n = 360) | −0.32 ± 0.49 | |
| LCX | (n = 154) | −0.28 ± 0.55 | 0.36 | LCx | (n = 196) | −0.24 ± 0.47 | 0.05 |
| RCA | (n = 191) | −0.34 ± 0.63 | | RCA | (n = 222) | −0.21 ± 0.59 | |
| Calcified lesion | | | | | | | |
| yes | (n = 233) | −0.29 ± 0.50 | 0.61 | yes | (n = 80) | −0.16 ± 0.47 | 0.04 |
| no | (n = 433) | −0.31 ± 0.56 | ntno | (n = 698) | −0.28 ± 0.52 | | |
| Dissection post PTCA | | | | | | | |
| yes | (n = 125) | −0.32 ± 0.59 | 0.60 | yes | (n = 247) | −0.28 ± 0.60 | 0.57 |
| no | (n = 541) | −0.29 ± 0.52 | | no | (n = 531) | −0.26 ± 0.48 | |
| Branch in stenosis | | | | | | | |
| yes | (n = 194) | −0.31 ± 0.49 | 0.69 | yes | (n = 413) | −0.27 ± 0.51 | 0.94 |
| no | (n = 472) | −0.29 ± 0.56 | | no | (n = 364) | −0.27 ± 0.53 | |

*Table 2c.* Change in minimal lumen diameter per lesion at follow-up for procedural related variables in Carport (left) and Mercator (right).

| | | Change in MLD at fup (mm) | P value | | | Change in MLD at fup (mm) | P value |
|---|---|---|---|---|---|---|---|
| Maximal balloon diameter (mm) | | | | Minimal balloon diameter | | | |
| <2.35 | (n = 189) | −0.26 ± 0.50 | | <2.15 | (n = 209) | −0.23 ± 0.46 | |
| 2.35–2.7 | (n = 214) | −0.30 ± 0.50 | 0.11 | 2.15–2.51 | (n = 213) | −0.30 ± 0.50 | 0.22 |
| ≥2.7 | (n = 192) | −0.35 ± 0.55 | | >2.51 | (n = 209) | −0.30 ± 0.52 | |
| Balloon artery ratio | | | | | | | |
| <0.9 | (n = 201) | −0.27 ± 0.55 | | <0.98 | (n = 169) | −0.22 ± 0.49 | |
| 0.9–1.05 | (n = 201) | −0.29 ± 0.53 | 0.17 | 0.98–1.11 | (n = 245) | −0.30 ± 0.56 | 0.20 |
| >1.05 | (n = 193) | −0.36 ± 0.54 | | >1.11 | (n = 217) | −0.30 ± 0.49 | |
| No. of inflations | | | | | | | |
| 1 | (n = 178) | −0.29 ± 0.47 | | 1 | (n = 94) | −0.24 ± 0.43 | |
| 2–4 | (n = 254) | −0.30 ± 0.51 | 0.55 | 2–4 | (n = 544) | −0.27 ± 0.53 | 0.88 |
| >4 | (n = 234) | −0.35 ± 0.57 | | >4 | (n = 140) | −0.27 ± 0.53 | |
| Maximal inflation pressure (atm) | | | | | | | |
| <8 | (n = 261) | −0.31 ± 0.58 | | <7 | (n = 219) | −0.20 ± 0.51 | |
| 8–10 | (n = 264) | −0.30 ± 0.52 | 0.43 | 7–9 | (n = 285) | −0.29 ± 0.52 | 0.09 |
| ≥10 | (n = 141) | −0.24 ± 0.50 | | >9 | (n = 274) | −0.30 ± 0.50 | |
| Total inflation duration (sec) | | | | | | | |
| <220 | (n = 202) | −0.30 ± 0.54 | | <145 | (n = 245) | −0.24 ± 0.43 | |
| 220–470 | (n = 230) | −0.28 ± 0.52 | 0.69 | 150–240 | (n = 285) | −0.29 ± 0.52 | 0.05 |
| >470 | (n = 224) | −0.27 ± 0.48 | | >240 | (n = 248) | −0.31 ± 0.55 | |

*Table 3.* Multivariate linear regression model for the prediction of change in lumen diameter (per lesion analysis, n = 666 (Carport) and n = 778 (Mercator)).

| Carport | | | | Mercator | | | |
|---|---|---|---|---|---|---|---|
| Model | Coefficient | SE of coefficient | F to remove | Model | Coefficient | SE of coefficient | F |
| Intercept | 0.40 | | | Intercept | 0.33 | | |
| Relative gain at PTCA | −1.36 | 0.18 | 57.5 | Code | 0.04 | 0.04 | 1.73 |
| MLD pre PTCA | −0.19 | 0.07 | 6.7 | Relative Gain | −0.95 | 0.12 | 65.73 |
| Lesion length ⩾6.8 mm | −0.19 | 0.04 | 19.7 | MLD post-PTCA | −0.21 | 0.05 | 14.95 |
| Diabetes | −0.34 | 0.07 | 20.7 | Vessel dilated (rca vs other) | 0.11 | 0.04 | 7.80 |
| Duration of angina <2.3 months | −0.11 | 0.04 | 6.2 | | | | |
| Thrombus post angioplasty | −0.31 | 0.14 | 5.2 | | | | |
| Allocation to GR32191B | 0.03 | 0.04 | 0.5 | | | | |

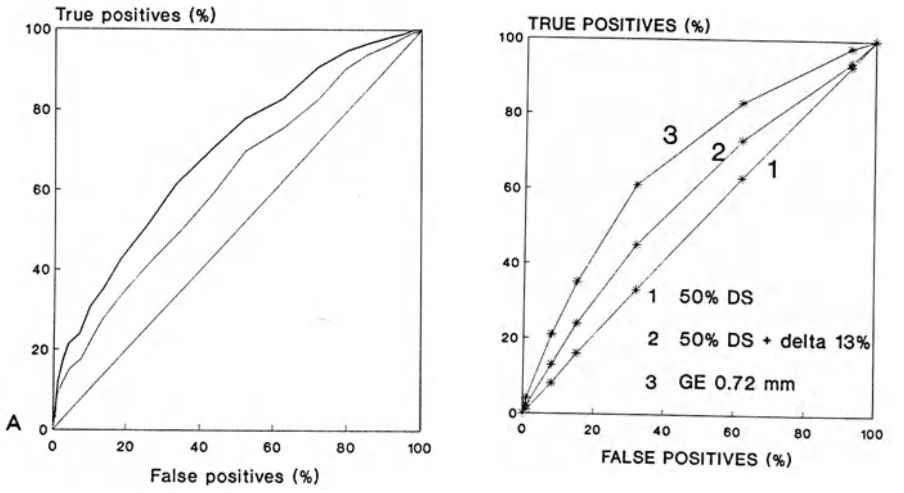


*Figure 2.* Receiver operator characteristic curves (ROC curves) for comparison of restenosis criteria at different cut off points of predicted change in lumen diameter. The diagonal line is the line of identity or line of "no prognostic value". ROC curves on the line of identity have no prognostic value, those in the left upper corner are most informative. Solid curve 3: 0.72 mm criterium, normal curve 2: 50% diameter stenosis criterium with a change in diameter stenosis at follow-up of at least 13%, dotted curve 1: 50% diameter stenosis criterion. Carport trial (A), Mercator trial (B).

especially in the lower range. On average only 30% of lesions were correctly classified. On the other hand, lesions that showed moderate or more sever change were more predictable, although the percentage is still low (Table 4). The information content of the model according to the ROC curves was best for $\geqslant 0.72$ mm cut-off criterion (Fig. 2].

These findings underscore the very poor predictability of luminal renar-

*Table 4.* Percentages of correct classification.

| | Carport | | Mercator | |
|---|---|---|---|---|
| Interval of predicted change in MLD | Percentage correct classification * | | Percentage correct classification * | |
| ≤−0.4 mm | 98/197 | 50% | 97/260 | 37% |
| −0.3 to −0.4 mm | 9/116 | 8% | 7/64 | 11% |
| −0.2 to −0.3 mm | 13/123 | 11% | 19/72 | 26% |
| −0.1 to −0.2 mm | 12/106 | 11% | 20/82 | 24% |
| >−0.1 mm | 72/121 | 60% | 91/300 | 30% |

rowing after balloon coronary angioplasty and explains the discrepancies between the 2 restenosis criteria with >0.72 mm decrease in minimal luminal diameter as an "active criterion" and the 50% diameter stenosis as a "static criterion".

## Discussion

During 15 years of percutaneous transluminal coronary balloon angioplasty an abundance of clinical and experimental studies have been carried out in an attempt to elucidate factors that can predict the "Achilles' heel" of coronary angioplasty, namely progressive luminal narrowing after a successful procedure. Although many clinical, procedural and lesion related factors have been linked with a higher angiographic restenosis rate, results of these studies are sometimes conflicting. As pointed out by Beatt et al. [16], most of the discrepancies can be attributed to 1) patient selection, 2) the method of analysis and 3) the definition of angiographic restenosis employed.

*Patient selection*

To obtain objective, unbiased results, all patients should be recatheterized after a predetermined follow-up period regardless of their symptomatic status. Failure to perform angiographic follow-up in a majority of patients will introduce bias in the assessment of the true change in minimal lumen diameter at follow-up. The restenosis rate according to a more or less arbitrary cut-off point will be biased towards higher values if symptomatic patients or patients with unfavorable anatomy post-angioplasty are preferentially recatheterized. In these studies 88.6% and respectively 94% of all patients with a successful angioplasty had a follow-up angiogram performed within a predetermined time frame of 6 months.

*Method of analysis*

A well validated quantitative angiographic analysis system should be employed. Computer assisted automated edge detection techniques enhance objectivity and reproducibility and reduce the high inter- and intra-observer

variability inherent to visual interpretation of the coronary angiogram [17, 18]. The quantitative analysis system we applied for the analysis of the angiograms meets these requirements [16]. Recently we performed a study [19] comparing luminal dimensions 24 hr after angioplasty with those on the immediatel post angioplasty angiogram using the same methodology as in the present study. Mean difference in minimal lumen diameter (accuracy) of 119 lesions was 0.00 mm with a standard deviation (precision) of 0.20 mm. It was concluded that a) in the first 24 hr after angioplasty no major renarrowing takes place and b) that variability of the CAAS measurements immediately after balloon dilatation is less than the long term variability of the method [6]. It should be noted that this long term variability was measured 8 years ago on stenoses not submitted to angioplasty and with a reference diameter of 3.6 mm (present study 2.6 mm). Also standardization of angiofilm recording was far less standardized in the CAAS variability study [6] than in the present study. Another point of concern with quantitative analysis of a lesion immediately post angioplasty is the amount of analyst interference with the automated edge detection technique. In our population the amount of editing performed by the analysts was 3.7% pre angioplasty, 4.2% post angioplasty and 3.7% at follow-up angiography. That is 4.2% of the automatically detected vessel contours were corrected by the analysts. The inter- and intra-observer variability of the analysis of the post angioplasty angiogram is subject of ongoing investigation. A post angioplasty frame of a right coronary artery was analyzed 10 times by 2 different analysts. The mean value of the minimal lumen diameter was $2.22 \pm 0.02$ mm for analyst 1 and $2.22 \pm 0.03$ for analyst 2. Mean difference was $0.00 \pm 0.04$ mm. We can therefore conclude that for quantitative analysis of the immediate post angioplasty angiogram most likely the same variability values apply as for quantitative analysis of non-dilated vessel segments.

*Restenosis criteria*

The third factor influencing the restenosis rates is the restenosis criterion. The most frequently applied criterion in the literature is the >50% diameter stenosis at follow-up criterion. This criterion is historically based on the physiological concept of coronary flow reserve introduced by Gould and others in 1974 and is taken because it represents the approximate value in animals with normal coronary arteries at which blunting of the hyperemic response occurs [20]. Although this criterion may be of some relevance in determining a clinically significant stenosis in human atherosclerotic vessels, it is a static measurement of lesion severity and tells us nothing about the dynamic behavior of the restenosis process. If the "50% diameter stenosis at follow up" criterion is applied, lesions with a suboptimal angioplasty result will preferentially be selected (ie have to undergo a small loss in lumen diameter to be classified as restenosed). Bourassa et al. [10] have recognized this shortcoming and thus considered lesions with ⩾50% diameter stenosis

at follow-up that did not show a change of at least 10% at follow-up as not "restenosed".

The predictive accuracy of the multivariate model for restenosis of both trials according to the 50% diameter stenosis criterion was very poor (Fig. 2). If in addition a change in percent diameter stenosis of at least 13% (twice the long term variability for percent diameter stenosis measurements) was required, then predictive accuracy of the model improved markedly, since lesions with a suboptimal angioplasty result did no longer unduly influence the restenosis rate. This requirement shifts the ROC curve to the left upper corner. A criterion that better reflects the dynamic behavior of the lesion after PTCA is the $\geqslant$0.72 mm loss in lumen diameter criterion as proposed by our group [6, 14, 15]. This criterion is not meant to be a restenosis criterion strictu sensu, since that implies also some sort of functional measure of lesion severity at follow up, but rather an indicator of significant intraluminal growth as monitored angiographically.

**Predictive factors for luminal narrowing after balloon angioplasty.**

*Patient related factors*

In the *Carport* trial, diabetes, unstable angina and duration of angina shorter than 2.3 months were associated with more luminal narrowing at follow-up. If total occlusions at follow-up were disregarded, none of these variables showed significantly more narrowing. In multivariate analysis however, diabetes was independently predictive of luminal narrowing. The assumption that risk factors for restenosis are similar to risk factors for atherosclerosis was not confirmed in the present study. Only diabetes was found to be independently related to the amount of luminal narrowing at follow-up. This finding has also been recognized by others [1, 2]. In a recent study by Bourassa et al. [10] using the same quantitative angiographic analysis system, diabetes was not found to be predictive of restenosis. Other classic risk factors for atherosclerosis such as male gender, systemic hypertension, high cholesterol level and continued smoking after the PTCA, were not found to be related to luminal narrowing in the present study. The controversy regarding these risk factors is considerable, with many studies being positive for one or more patient related factors and many studies being negative [1, 2].

In the *Mercator* trial, patients undergoing PTCA for recent onset angina exhibited greater mean loss in minimal luminal diameter during follow-up. Perhaps this is related to the tendency of lesions associated with new onset angina to be biologically more active ("softer") and more compliant and therefore more amenable to the dilating forces of the balloon. Consequently, a better initial result is obtained with a greater " relative gain". Long presence of stable angina pectoris is associated with more calcification in the lesion and therefore less gain in minimal diameter can be achieved. Beside

that less cells that can growth are present and therefore less intimal hyperplasia is presumably seen.

*Lesion related factors*

*Pre-angioplasty variables*. In univariate analysis 5 pre-angioplasty variables were associated with more luminal narrowing at follow-up: minimal lumen diameter pre- angioplasty, percent diameter stenosis pre-angioplasty, length of stenosis, total occlusion pre-angioplasty, and collateral circulation to dilatation site. A relation between stenosis severity and restenosis rate has been shown previously [1, 2, 10]. It is conceivable that more severe lesions undergo more severe vessel wall damage during the procedure, a known trigger for the hyperplastic reaction [21–23]. In our multivariate analysis the pre-angioplasty minimal lumen diameter was found to be an independent determinant of subsequent loss in lumen diameter. In longer lesions more smooth muscle is possibly exposed to injury and platelet adhesion, which probably enhances the intimal hyperplastic reaction. A relation between stenosis length and restenosis has also been described by others [1, 2]. Total occlusion pre-angioplasty is a well known factor connected with total occlusion at follow-up [1, 2] and thus a large loss in lumen diameter at follow-up. Because total occlusion pre-angioplasty is part of the continuous variables minimal lumen diameter and diameter stenosis pre PTCA, total occlusion pre-angioplasty was not found to be an independent predictor of loss in lumen diameter. No differences in luminal narrowing was observed for the 3 coronary arteries. Others [1, 2] have reported a higher incidence of restenosis for the left anterior descending artery, a finding recently challenged by Hermans et al. [24].

*Post-angioplasty variables*. Relative gain achieved at PTCA was both in univariate and multivariate analysis the strongest predictor (largest F to remove in final model) of luminal narrowing at follow-up. This variable probably best reflects the amount of damage inflicted upon the vessel wall by the angioplasty balloon. It is conceivable that more damage to the vessel wall with more deep arterial injury will result in a more aggressive repair process [3, 21–23]. Other post-angioplasty variables that were related to more luminal narrowing at follow-up in univariate analysis were: higher minimal lumen diameter post-angioplasty, diameter stenosis post-angioplasty $<29.5\%$ and visible thrombus post-angioplasty. Thus a better post-angioplasty result leads to more luminal narrowing or intimal hyperplasia at follow-up. Others have reported that a poorer post-angioplasty result was predictive of restenosis [1, 2]. In general they applied the 50% diameter stenosis cut off point and, as discussed above, lesions with a poor post-angioplasty result will exceed this cut-off point with only minimal additional deterioration. Because lesions with a low percent diameter stenosis and a large lumen diameter post- angioplasty were also the lesions that underwent a high relative gain at angioplasty and since this variable was the strongest independent predictor of the absolute amount of luminal narrowing at follow-up, percent

diameter stenosis post-angioplasty and lumen diameter post-angioplasty were not retained in the multivariate analysis. Thrombus post-angioplasty was retained in the multivariate model. Five of 16 lesions (31%) with a visible thrombus post-angioplasty were totally occluded at follow-up and therefore showed a greater overall loss in lumen diameter. We did not find an association between coronary dissection immediately post-angioplasty and subsequent luminal renarrowing. Conflicting data have been reported concerning dissection and restenosis [1, 2]. It is however clear that severe dissections are associated with a higher acute complication [25] and restenosis rate, the latter probably due to a poorer angioplasty result in combination with the 50% diameter stenosis criterion.

In the *Mercator* trial, the one factor most strongly associated with luminal renarrowing after angioplasty was "relative gain" achieved by the angioplasty procedure. This is the ultimate paradox of treatment with coronary balloon angioplasty; the greater the initial "relative gain", the greater the subsequent loss. The final result or "relative gain" of an angioplasty procedure is the combination of permanent plastic and reversible elastic changes i.e. a combination of deep arterial injury and reversible stretch imposed on the diseased vessel wall. The more severe the stenosis is, the more deep arterial damage will occur, resulting in a more aggressive repair process. This phenomenon has been observed in animal models of arterial injury and is a perfectly logical consequence of the healing process [26, 27].

In univariate analysis the separate variables were also highly significant: minimal luminal diameter before and after PTCA, diameter stenosis before and after PTCA, and the presence of totally occluded vessels, but only minimal luminal diameter post-PTCA, beside relative gain, was retained in the multivariate linear regression model. High values of post-PTCA diameter stenosis has been reported to be associated with higher restenosis rates (Table 1), although confusion could be caused by suboptimal dilatation (i.e. 49% diameter stenosis) in which case only a small loss (i.e. 2% increase in diameter stenosis) is required to exceed this categorical cut-off point of 50%. However, in our study *low* values of diameter stenosis post-PTCA is associated with more loss. Totally occluded vessels have been reported to be associated with higher restenosis rates using "traditional" restenosis criteria [1, 2], but was not retained as a separate factor in our analysis. This is due to the fact that total occlusions are part of the continuous variables minimal luminal diameter which is by means of the relative gain the most important predictor.

There has been many conflicting studies whether the vessel dilated is a risk factor for restenosis (Table 1). In present study, univariate analysis shows a greater loss in minimal luminal diameter in the left anterior descending artery as compared to the right coronary or left circumflex artery (Table 2B). In stepwise linear regression analysis, dilatation of another vessel than the right coronary artery consistuted an independent riskfactor predictive for loss. This is somewhat surprising, as recently our group has found no statisti-

cal significant difference in loss between the 3 major coronary arteries in 1452 dilated lesions, although a trend towards more (relative) loss in left anterior descending artery was observed [8, 9, 24]. Those 1452 lesions were derived from two identical executed restenosis prevention trials using a similar methodologic approach. The observed loss in lumen diameter for respectively the CARPORT and MERCATOR trial were: $0.34 \pm 0.63$ and $0.21 \pm 0.59$ for RCA (vessel size 2.85 mm), $0.27 \pm 0.46$ and $0.32 \pm 0.49$ for LAD (vessel size 2.53 mm) and $0.28 \pm 0.55$ and $0.24 \pm 0.47$ for the LCX (vessel size 2.53 mm). Although similar loss during follow-up was observed for the LAD and LCX, the loss in the RCA was low in the MERCATOR trial and high in the CARPORT trial. We have no explanation for this contradictory observation. In addition, the coefficient is 0.11, which means that 0.11 mm of what is lost can be explained by dilatation of the vessel and therefore is of limited value for the prediction of loss in the individual patient.Calcified lesions are associated with less loss during follow-up. A possible explanation is that in these lesions less gain is achieved, as calcified lesions are difficult to dilate successfully.

*Procedure related variables*

In the *Carport* trial, balloon oversizing (balloon-artery ratio >1.05) was not related to more luminal narrowing at follow-up. Some investigators found a positive effect of balloon oversizing on restenosis others have not [1, 2], however in a prospective randomized study, Roubin et al. found a higher incidence of acute complications in case of oversizing but no difference in restenosis rate [25].

In the *Mercator* trial, higher total inflation times was associated with more loss during follow-up. This reflects an initial poor result after 1 to 3 dilatations and consequently more extensive deep arterial injury with perhaps prolonged sub-intimal ischemia due to pressure occlusion of vasa vasorum. This has been the observation in animal experiments [22].

## Limitations

Although this study suggests several factors that may be determinants of luminal narrowing after coronary balloon angioplasty it does not address the actual mechanism of restenosis. Vasomotion at follow-up angiography cannot be ruled out as a possible cause of the observed luminal renarrowing in individual lesions, although intracoronary nitrates in appropriate doses were administered before each angiography. Mean reference diameter was not different before PTCA, after PTCA and at follow-up in the Carport trial $2.64 \pm 0.56$ mm, $2.70 \pm 0.53$ mm and $2.70 \pm 0.56$ mm respectively, suggestive of accurate control of vasomotion. Due to the relatively small sample sizes of some variables, ß error cannot be ruled out in this study. Furthermore,

in performing multiple statistical comparisons, there is a risk that some of them may reach significance by chance alone. The multivariate model was developed and tested in the same population. Generally a model will be less accurate if assessment of fit is carried out in a different population. However, the poor fit of the model even when tested in the same population underscores the poor predictability of the restenosis process.

The analyses described in this study were based on data from 2 restenosis prevention trials [8, 9] These trials were designed to investigate whether a certain drug was capable of reducing the amount of intimal hyperplasia relative to placebo treatment and not specifically to determine risk factors for this event. The post hoc nature of the present analyses might therefore have influenced the outcome of the analyses. In both trials, only patients with a scheduled angioplasty for a primary lesion of the native coronary system could be entered. Therefore several variables that have been found important in other analyses, such as saphenous vein graft location and restenosed lesions could not be analyzed. At the time of the design of the trials, the risk factor ostial lesion was not known and therefore could not be included in the analysis.

According to the protocol patients were to undergo repeat catheterisation within the time window of 6 months ± 2 weeks. However, if symptoms reappeared before this predetermined time of follow-up early angiography was performed. If no serious restenosis was found and/or no reintervention followed and the follow-up period was less than 4 months the patient was asked to undergo another angiography 6 months after the balloon angioplasty. This 4 months cut-off point was derived from the studies by Nobuyoshi [28] and Serruys [14] who showed the time relation of the restenosis process. In both studies luminal narrowing continued upto 4 months after balloon dilatation and came to a halt afterwards. In our population 88 (13.1%) of the lesion were re-filmed before 4 months of follow-up. It might be possible that these lesions would have further deteriorated if catherisation had been performed at 6 months thereby influencing the analysis. Most of these patients underwent re-intervention (PTCA, bypass grafting) and a minority refused repeat angiography. Early repeat angiography is an unavoidable aspect of these type of studies. It was considered unethical to delay angiography in patients with symptom recurrence. In the Carport trial, minimal luminal diameter before angioplasty was 1.04 mm in both groups, after angioplasty this was 1.67 mm post angioplasty in the <4 months catheterisation group and 1.78 mm in the 6 months catheterisation group. At follow-up angiography minimal lumen diameter was 1.06 mm in the <4 months catheterisation group and 1.54 mm in the 6 months catheterisation group. Mean loss in lumen diameter was 0.61 mm with early catheterisation and 0.25 mm in the 6 months catheterisation group. A mean lumen diameter of 1.06 mm at follow-up angiography in the early angiography group represents a recurrence to the pre angioplasty state.

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# 27. Restenosis assessed by quantitative angiography. Lessons learned from two european multicenter trials

BENNO J. RENSING, WALTER R.M. HERMANS and PATRICK W. SERRUYS

## Introduction

Over the past years several large randomized restenosis prevention trials have been carried out in Europe [1, 2]. These well organized and meticulously executed trials yielded an enormous amount of high quality clinical and quantitative angiographic data. This allowed us to perform additional analyses with the purpose of gaining more insight in the enigmatic restenosis process, which is still surrounded by conclusions drawn from retrospective trials with non-standardized angiography protocols, incomplete angiographic follow-up and qualitative analysis of the angiograms. In this chapter the spin-off of the Carport and Mercator trials will be described. The Carport and Mercator trials were the first multicenter European restenosis prevention trials with a standardized angiography protocol and an almost complete quantitative angiographic follow up. In both trials quantitative angiographic and clinical outcome were similar in both the active treatment group and the placebo group, so for the secondary analyses both groups could be pooled. The results of these trials will be discussed in chapter 26. The extensive experience with restenosis and quantitative angiography [3] at the Thoraxcenter allowed us to develop a standardized protocol for the acquisition of the angiographic data which was easily implemented in the day to day practice of 32 catheterization laboratories in Europe. Furthermore the analysis of both baseline and follow-up coronary angiogram was done in a central core laboratory with strict guidelines for the analysts.

In the studies described in part I and III the complete quantitative angiographic databases of both the Carport and Mercator trials were combined. In part II a selection of Carport patients with single site coronary artery disease and a single site dilatation were studied to investigate the correlation between quantitative angiographic variables and clinical variables 6 months after a successful coronary balloon angioplasty.



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## Part I. Gaussian distribution of luminal narrowing after percutaneous transluminal coronary angioplasty

### *Introduction*

For more than a decade investigators in the field in of coronary balloon angioplasty have assumed a Gaussian distribution of continuous (quantitative) angiographic parameters used to describe the severity of the coronary lesion before angioplasty, after angioplasty and at follow-up angiography. Therefore they used parametric statistical tests for comparisons in their studies [3–9]. In a recent study [10] it was reported that the percentage diameter stenosis at follow-up angiography follows a bimodal distribution. This finding seems to support the clinical observation that the restenosis process is a yes or no event occurring in some patients or lesions but not in others.

In the present study we assessed the distributions of angiographic parameters of lesion severity, before angioplasty, after angioplasty, and at 6 months follow up in a large population. Quantitative analysis was performed off-line in a central core-lab with an objective, off-line, automated edge detection technique [11] by analysts not involved in the treatment of the patients.

### *Patients and methods*

The original study cohort consisted of 1427 patients in whom primary coronary balloon angioplasty was attempted between December 1987 and June 1990 and agreed to undergo a follow-up angiogram at 6 months. All patients signed informed consent and the study protocol was approved by the Institutional Review Board.

The procedure was successful in 1353 patients (primary success rate 94.8%), defined as a less than 50% residual stenosis by visual inspection of the post angioplasty angiogram of at least 1 lesion and no occurrence of in-hospital complications (death, acute myocardial infarction, bypass grafting, repeat angioplasty or symptom recurrence). Patients with stable as well as unstable [12] angina were included. Patients with evolving myocardial infarction were excluded. In 2 patients the angioplasty angiogram could not be analyzed due to technical deficiencies. A total of 1232 patients (91.1%) had a follow-up angiogram suitable for quantitative angiography and this forms the study population. Reasons for not completing the study were: late death (n = 8), contraindication for repeat catheterization (n = 24), refusal (n = 76), while 11 follow-up angiograms were unsuitable for quantitative analysis.

#### *Angioplasty procedure and follow-up angiography*

Coronary angioplasty was performed with a steerable, movable guide wire system via the femoral route. Standard available balloon catheters were used.

Choice of balloon type and brand as well as inflation duration and inflation pressure were left to the discretion of the angioplasty operator. At the beginning of the angioplasty procedure all patients received 10000 IU of intravenous heparin for the first two hours, afterwards 5000 IU/hour for as long the procedure continued. All patients received 10 mg nifedipine every two hours for the first 12 hr after angioplasty. Thereafter they received 20 mg slow release nifedipine tablets 3 times during the second day after angioplasty.

Three coronary angiograms were obtained in each patient, one just before PTCA, one immediately after angioplasty, and an angiogram at follow-up. The angiograms were recorded in such a way that they were suited for quantitative analysis by the Cardiovascular Angiography Analysis System (CAAS). For calibration purposes the cathetertips were cut off for later measurement with a microcaliper.

To standardize the method of data acquisition and to ensure exact reproducibility of the angiographic studies, measures were taken as described previously [3, 13, 14]. All angiograms were processed and analyzed in a central core-lab.

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

*Quantitative angiography*

All cineangiograms were analyzed using the cardiovascular angiography analysis system (CAAS) which has been described and validated earlier [11, 15]. A description of a typical analysis can be found elsewhere in the book. Since the algorithm is not able to measure total occlusions, a value of 0 mm was substituted for the minimal lumen diameter and a value of 100% for the% diameter stenosis and% area stenosis. In these cases the post angioplasty reference diameter was substituted for the reference diameter pre angioplasty or at follow-up angiography. The mean change in minimal lumen diameter from post angioplasty to follow up angiography and from pre angioplasty to post angioplasty was derived from matched angiographic projections. The percentage area stenosis was calculated using the measured minimal lumen diameter and interpolated reference diameter assuming a circular cross-section at the stenosis site.

*Results*

*Baseline characteristics*

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

*Table 1.* Baseline patient and lesion characteristics.

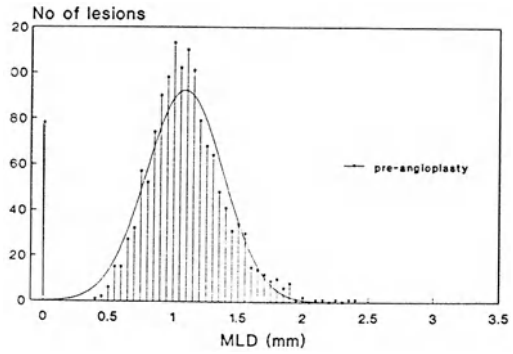
| | |
|---|---|
| Patients | 1232 |
| Lesions | 1445 |
| Male sex | 1002 (81%) |
| Age (years) | 56 ± 9 |
| Time to follow-up angiography (days) | 165 ± 41 |
| Dilated artery | |
| LAD | 681 |
| LCX | 352 |
| RCA | 412 |
| Extent of coronary artery disease | |
| 1 vessel | 755 (61.3%) |
| 2 vessel | 399 (32.4%) |
| 3 vessel | 78 (6.3%) |

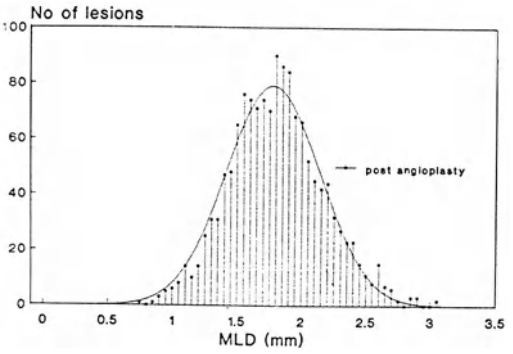
Extent of coronary artery disease was visually assessed, >50% diameter stenosis was considered significant; LAD = left anterior descending artery; LCX = left circumflex artery; RCA = right coronary artery. Reproduced with permission [39].

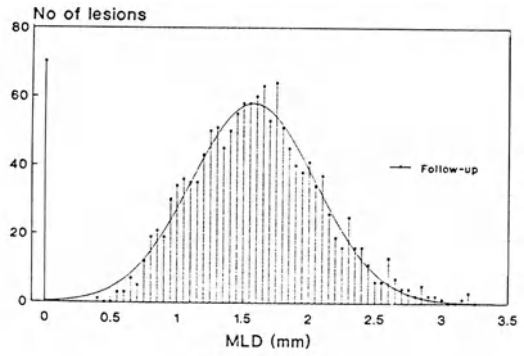
fully dilated (1.17 lesions/patient). Seventy eight totally occluded lesions were successfully dilated. At follow-up 70 lesions had progressed to total occlusion. Four hundred ninety one patients (39.9%) had a history of myocardial infarction.

*Quantitative angiographic findings and distributions*

Table 2 summarizes the quantitative angiographic data. Reference diameter was not significantly different pre-angioplasty, post-angioplasty and at follow-up, suggesting that vasomotion was accurately controlled during the 3 angiographic studies. Distribution plots of the minimal lumen diameter data are given in Figs 1a to 1c. The distribution of the change in minimal lumen diameter from post angioplasty angiogram to follow up angiogram (loss in minimal luminal diameter) is depicted as well (Fig. 1d). A positive change corresponds to a decrease in minimal luminal diameter. If the restenosis criterion of $\geq$0.72 mm loss in lumen diameter is applied [3], 244 lesions (16.9%) were restenosed at follow-up. All distributions are more or less bell-shaped and follow the theoretical normal or Gaussian distribution (curve superimposed on the distributions) for the given mean and standard deviation values after if the totally occluded lesions are not taken into account. The distribution of the loss in minimal luminal diameter, excluding lesions that were totally occluded at follow-up (bars, Fig. 1d) is almost identical to the distribution including totally occluded lesions at follow up (asterisks, Fig. 1d) with the latter lesions showing a greater loss in minimal lumen diameter. This suggests that lesions progressing to total occlusion are not necessarily lesions with a poor or marginal angioplasty result and that a different mechanism of luminal narrowing may also be involved. Figure 2 shows this more clearly. In this normal probability plot of change in minimal lumen diameter, slashes denote the expected Gaussian distribution based on the rank of the




*Figures 1.*a–c.

observations and the squares denote the actual observed values. It appears that if the lesions that progress to total occlusion are excluded, the observed values closely follow the expected Gaussian distribution.

The distribution of percent diameter stenosis at follow-up was found to be unimodal and almost symmetrical and bell-shaped if lesions that progressed towards total occlusion were disregarded (Fig. 3). Disregarding these total

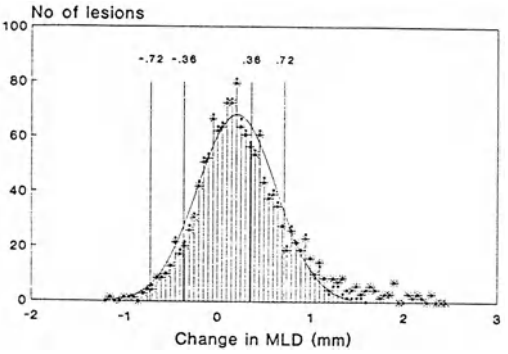



*Figure 1.* Histograms of minimal lumen diameter (MLD) measurements of 1445 lesions pre-angioplasty, post angioplasty and at 6 months follow-up angiography. The curves superimposed on the histograms represent the theoretical Gaussian distribution curves given the mean and standard deviation of the population under study, excluding total occlusions.
Fig. 1a: histogram of MLD pre angioplasty,
Fig. 1b: histogram of MLD post angioplasty,
Fig. 1c: histogram of MLD at follow-up angiography,
Fig. 1d: histogram of change in MLD from post angioplasty angiogram to follow-up angiogram. The asterisks denote the distribution of the change in minimal lumen diameter including those lesions that had progressed towards total occlusion. A positive change denotes a loss in minimal lumen diameter. The long term variability cut-off points are drawn in the histogram (see text for explanation). Reproduced with permission [39].

occlusions, mean% diameter stenosis at follow-up was 41.3 ± 16.1. The mean 60.5% diameter stenosis *pre-angioplasty* marks 1.2 standard deviations to the right on the bell shaped curve and thus the area under the curve located to the right of the 60.5% limit comprises 11.5% of all observations. Together with the 4.8% of lesions that were totally occluded at follow up 16.3% of all lesions demonstrate restenosis to at least the same severity as the mean stenosis severity prior to angioplasty. If the >50% diameter stenosis at follow up criterion is applied, 444 lesions (30.7%) were restenosed.

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

*Regression in lesion severity at follow-up angiography*
Among the 1445 lesions analyzed, 429 showed an increase in minimal lumen diameter at follow-up (29.6%) (change <0 mm, Fig. 1d). The long term variability of minimal lumen diameter measurements (i.e. 1 standard deviation of the difference of the means of 2 measurements of the same lesion

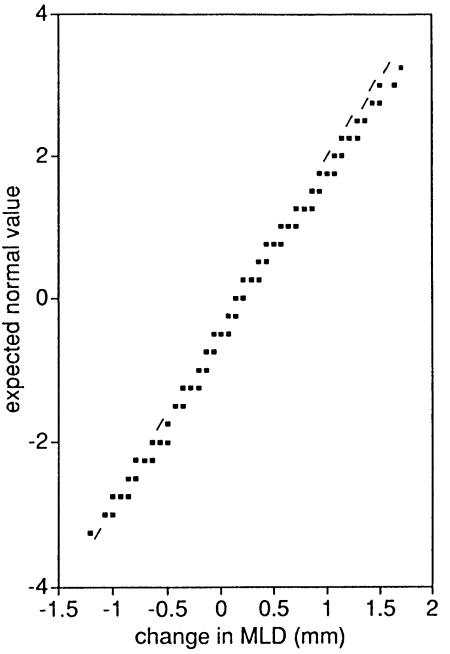



*Figure 2.* Normal probability plot of the change in minimal lumen diameter (MLD) from post angioplasty angiogram to follow-up angiogram, excluding lesions that had progressed towards total occlusion. The slashes depict the theoretical Gaussian distribution. The squares are the actually observed values. A change greater than 0 corresponds to a loss in minimal lumen diameter. Reproduced with permission [39].

*Table 2.* Quantitative angiographic data of 1445 lesions.

| | Mean ± 1 SD |
|---|---|
| Minimal lumen diameter (mm) | |
| Pre-angioplasty | 1.03 ± 0.37 |
| Post-angioplasty | 1.78 ± 0.36 |
| Follow-up | 1.50 ± 0.57 |
| Reference diameter (mm) | |
| Pre-angioplasty | 2.63 ± 0.54 |
| Post-angioplasty | 2.69 ± 0.52 |
| Follow-up | 2.70 ± 0.56 |
| Difference in Minimal Lumen Diameter (mm) | |
| Post-angioplasty – pre-angioplasty | 0.75 ± 0.41 |
| Post angioplasty – follow up | 0.28 ± 0.52 |
| Diameter stenosis (%) | |
| Pre-angioplasty | 60.5 ± 13.6 |
| Post-angioplasty | 33.6 ± 9.8 |
| Follow-up | 44.2 ± 18.7 |

SD = standard deviation.

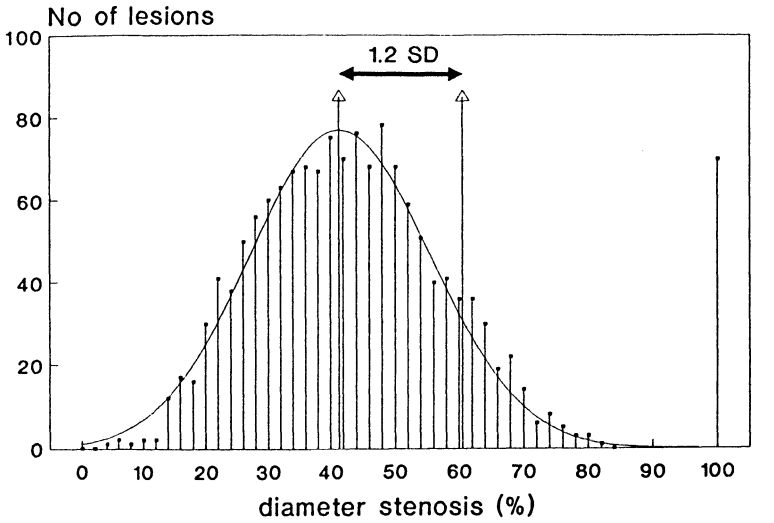



*Figure 3.* Histogram of percent diameter stenosis at follow-up angiography of 1445 lesions. The curve superimposed on the histogram represents the theoretical Gaussian distribution curves given the mean and standard deviation of the population under study, excluding total occlusions. Mean percent diameter stenosis excluding total occlusions is 41.3 ± 14.5. Also indicated is the mean 60.5% diameter stenosis pre angioplasty. This limit marks 1.2 standard deviations to the right of the 41.3% value, indicating that 11.5% of the observations under the curve are located to the right of the 60.5% limit. If the 4.8% of totally occluded lesions are added, 16.3% of all lesions demonstrate restenosis to the same severity as the mean stenosis severity prior to angioplasty. SD = standard deviation. Reproduced with permission [39].

at different catheterizations, 90 days apart) was earlier found to be 0.36 mm [11]. The mean difference in minimal lumen diameter in that same period was found to be 0 mm [11]. This implies that no detectable progression or regression occurred over the 90 days period. Therefore the long term variability reflects the long-term random variation in lesion measurements from coronary angiograms made at different catheterization sessions using the CAAS system. The use of 1 standard deviation would include 68.3% of the variability, while the use of 2 standard deviations ($2 \times 0.36 = 0.72$ mm) includes 95.5% of the variability. Therefore an increase of more than twice the long-term measurement variability ($\geq 0.72$ mm) can be considered significant and indicative of regression. If this definition is applied, only 16 lesions showed a definite increase in lumen diameter (1.1%) over the 6 months follow-up period (Fig. 1d).

## *Discussion*

There is increasing evidence that reactive intimal hyperplasia is the underlying cause of luminal narrowing after successful balloon angioplasty. Post

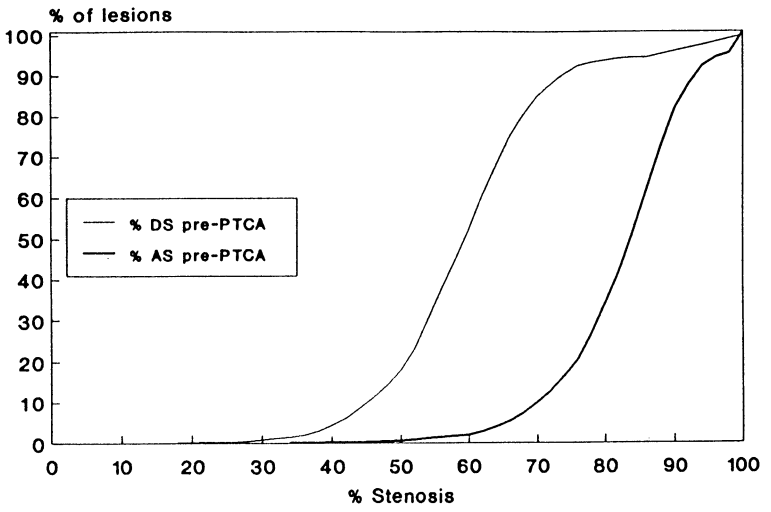



*Figure 4.* Cumulative distribution of percent diameter reduction (percent diameter stenosis (%DS) thin curve) and of percent area reduction (percent area stenosis (%AS), fat curve) for 1445 lesions pre angioplasty. Ninety percent of all lesions show a% DS of less then 74%, which corresponds to 93% AS. Reproduced with permission [39].

mortem studies and atherectomy specimen have revealed that medial smooth muscle cell migration and proliferation with the production of abundant extracellular matrix probably are the key factors in the luminal narrowing process after angioplasty [16–18]. Like most physical and biological phenomena this angiographically observed natural 'healing' process was found to be approximately Gaussian distributed.

*Method of quantitative and distribution of variables of lesion severity*

In clinical medicine continuously distributed parameters of disease severity pose a problem because the decision on when or how to intervene has to be based on a more or less arbitrary cut-off point. For coronary stenosis severity, the 50% diameter stenosis value has emerged as a cut-off point, because it represents the approximate value in animals with normal coronary arteries at which a blunting of the coronary flow reserve occurs [19]. In a recently presented study [10] it was reported that the percentage diameter stenosis of lesions 4 months to 1 year after balloon angioplasty followed a bimodal distribution with the nadir between the 2 peaks at 50% diameter stenosis. This suggests that after balloon angioplasty 2 types of lesion behavior can occur, a restenosing- and a non restenosing reaction. If 2 different populations are present from the start, then it must be possible to isolate the restenosing patients before angioplasty. However, the prediction of restenosis with both invasive and non invasive tools is at most not very effective

[20, 21]. This finding has also far reaching consequences for the statistical analysis of angiographic restenosis data. The use of parametric statistical tests (eg t-test, analysis of variance) might no longer be appropriate.

In our population the distribution of percentage diameter stenosis was found to be unimodal and almost symmetrical and bell-shaped (Fig. 3). This discrepancy might be explained by the fact that quantitative angiography in the study of King et al. was carried out on-line in the catheterization laboratory with a non automated analysis technique and before clinical decision making was carried out. In this setting a percentage diameter stenosis around 50 is unwanted since it does not add information for the decision making process. Therefore a bias away from the 50% value is likely to occur. This type of bias was proposed by King et al. at the 40th annual scientific session of American College of Cardiology as an explanation for the bimodal distribution found in their series [10]. In the present study quantitative angiography was carried out off-line in a central core laboratory using an objective automated quantitative analysis technique with minimal interference of the analysts who were not involved in clinical decision making. We therefore believe that the present values have been less biased.

*Values of quantitative angiographic masurements*

The leptokurtic distribution of the minimal lumen diameter pre angioplasty with a higher peak than expected (Fig. 1a) can be explained by lesion selection. Values around 1 mm correspond with diameter stenosis values in the range of 60 to 70%. These are generally the type of lesions selected for balloon angioplasty.

Minimal lumen diameters smaller than 0.5 mm were not encountered. Figure 5 shows the theoretical pressure drop over a stenosis with a length of 6.5 mm (mean stenosis length in study) and an interpolated reference diameter of 2.6 mm (mean value in this study) at assumed flows ranging from 1 ml/second (rest) to 5 ml/second (maximal hyperemic flow). Pressure drops were calculated using the fluid dynamic equation derived by Gould and Kirkeeide [22, 23]. Luminal diameters less than 0.5 mm are unrealistic from a fluid dynamics point of view since the pressure gradient over the stenosis necessary to maintain rest flow will be far beyond the physiological range (Fig. 5). Lesions that are approaching this severity will therefore show a severely reduced flow, become unstable and will eventually thrombose and occlude. For the same reason are diameter stenosis measurements of more than 75% very rarely encountered. Only 10% of all lesions had a percentage diameter reduction pre angioplasty of more than 74% (Fig. 4). The highest pre angioplasty% diameter stenosis value encountered in this study (excluding total occlusions) was 86%. These at first glance low values of quantitatively measured diameter stenosis values correspond however with percentage area reduction values of more than 93! (Fig. 4). Therefore, visual stenosis severity scoring systems that allow classification of over 90% diameter reduction do not reflect the actual lesion severity and will describe

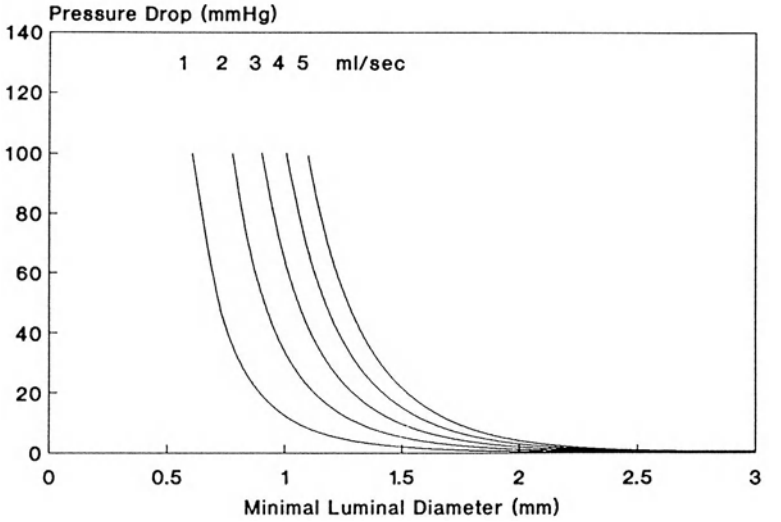



*Figure 5.* Theoretical pressure drops calculated with the fluid dynamics equation derived by Gould and Kirkeeide [19, 23] at assumed flows of 1, 2, 3, 4 and 5 ml/sec respectively. Reference diameter was assumed 2.6 mm and lesion length 6.5 mm. Reproduced with permission [39].

lesions which are physiologically impossible. Furthermore, for accurate interpretation of studies using quantitative coronary angiography this discrepancy should be kept in mind.

*Lesion progression towards total occlusion*

From Fig. 1d and Fig. 2 it can be inferred that lesion progression towards total occlusion involves not only the near normally distributed luminal narrowing process, but that a part of the narrowing in lesions progressing towards total occlusion must be ascribed to a different process. Since lesions with a minimal lumen diameter of less than 0.5 mm are impossible because of the unphysiological high pressure drops necessary to maintain blood flow (Fig. 5), it is likely that the last step in lesion progression towards total occlusion is due to thrombosis. Delivery and activation of platelets is dependent on shear rate, which is a measure of the difference in blood velocity between the center and the periphery of the vessel. A tightening stenosis causes progressively higher shear rates to occur which favors platelet activation and deposition [24, 25]. Animal experiments by Folts et al. showed that platelet aggregation spontaneously occurs in partially obstructed coronary arteries [26]. Another explanation might be that a 'silent' thrombotic occlusion occurs early after an angiographic successful angioplasty. In the absence of an important collateral circulation one would expect a high amount of myocardial infarctions in patients with a total occlusion at follow-up. Sixteen of the 70 totally occluded lesions at follow up were also totally occluded before

*Table 3.* Total occlusions at follow up angiography ($n = 70$).

| | |
|---|---|
| Number of these lesions that were totally occluded pre angioplasty | 16 (23%) |
| Presence of collaterals pre angioplasty in the absence of total occlusion | 8 of 54 (14.8%) |
| Myocardial infarctions during follow-up | 5 (7%) |
| MLD pre angioplasty (mm) | 0.73 ± 0.43 |
| MLD post angioplasty (mm) | 1.62 ± 0.36 |

MLD = minimal lumen diameter. Values of MLD as mean ± 1 standard deviation.

angioplasty and were collaterally circulated. Of the 54 patent arteries pre angioplasty only 4 were infarct related during follow-up (enzyme elevation to twice normal and/or presence of new Q waves). Visible collateral circulation before angioplasty was present in 8 of these 54 lesions (Table 3). A slowly progressing lesion on the other hand could allow for a gradual build up of collateral circulation enabling a total occlusion to develop without myocardial necrosis.

*Lesion regression*

A definite increase in minimal lumen diameter (regression) was observed in 16 patients only (1.1%) (Fig. 1d). This finding is in concordance with earlier reported data [3]. True angiographic regression in the first months after angioplasty thus appears to be a rare phenomenon. On the other hand, Rosing et al. [27] described regression of the dilated lesion in 46 patients 3 years after successful angioplasty as compared to a 6 months angiogram. This finding can be ascribed to a late resorption of the extracellular matrix in the neointima [17].

## *Conclusion*

The process of luminal narrowing after coronary balloon angioplasty is approximately normally distributed, with few lesions showing regression, most of the lesions showing no change and a considerable amount of the lesions showing progression. Restenosis can thus be viewed as the tail end of a near Gaussian distribution, with some lesions crossing a more or less arbitrary angiographic cut-off point, rather than a separate disease entity that occurs in some lesions but not in others. For comparison of the angiographic efficacy of pharmacological agents and new interventional devices, the use of change in minimal luminal diameter as end-point rather than restenosis rate is therefore recommended.

## Part II. Which angiographic parameter best describes functional status 6 months after balloon angioplasty?

### *Introduction*

Soon after the introduction of percutaneous transluminal coronary balloon angioplasty the vexing problem of restenosis became apparent. Approximately 30–40% of patients will show functional and/or angiographic signs of restenosis in the first months after a successful angioplasty procedure. A multitude of angiographic restenosis criteria have been developed over the last 12 years [28]. Restenosis criteria currently in use can be divided in those that describe the change in lesion severity from the post angioplasty situation up to the follow-up angiogram and those that merely describe lesion severity at follow-up angiography. An example of the first category is the loss in lumen diameter of more than 0.72 mm as proposed by Serruys [3], and an example of the latter category is the criterion of >50% diameter stenosis at follow-up. Criteria that describe a change in lumen diameter may ignore the functional significance of the lesion at follow-up, especially in large vessels [29], whilst criteria that only describe the situation at follow-up will preselect lesions with a suboptimal result after angioplasty and thereby disregard the magnitude of the reactive intimal hyperplasia [28]. Recurrence of a flow-limiting stenosis can usually be identified by symptoms of chest pain similar to those that occurred before angioplasty. In addition to the medical history, exercise electrocardiographic testing is generally performed as a non invasive approach to confirm the recurrence of a coronary artery obstruction because it is a relatively simple, safe and inexpensive test. To determine which quantitative angiographic variable best predicts the functional status of the individual patient, we studied the recurrence of anginal complaints and positive electrocardiographic exercise testing 6 months after a successful angioplasty of a selected patient group with single vessel disease and single site dilatation. The functional parameters (recurrence of angina and positive exercise testing) were correlated with quantitative angiographic variables of change in lesion severity (change in minimal lumen diameter, change in percent diameter stenosis) and variables that merely describe lesion severity at follow-up angiography (minimal lumen diameter and percent diameter stenosis).

### *Methods*

#### *Study population.*

The original patient group consisted of 697 patients that were enrolled in the multicenter CARPORT trial. A list of participating centers and investigators has been published previously [1]. In this randomized trial a thromboxane A2 receptor antagonist (GR32191B) was clinically tested against placebo for

its ability to prevent restenosis after primary coronary angioplasty. Identical angiographic, clinical and exercise test outcomes were observed in both randomization groups, so that the placebo- and active treatment group were pooled for the present study [1]. Antianginal medication during follow-up was not standardized after the procedure, but was also comparable in the 2 treatment groups. Selection criteria for this trial have been published previously [1]. Of the 697 patients, 649 had a successful procedure, defined as a less than 50% residual stenosis by visual inspection of the post angioplasty angiogram and no occurrence of in-hospital complications (death, acute myocardial infarction, bypass grafting, repeat angioplasty or symptom recurrence). Five hundred seventy five patients underwent subsequent follow-up angiography that was suitable for quantitative analysis (follow-up rate 88.6%). Of these 575 patients, 350 had single vessel coronary artery disease and underwent a single site dilatation and therefore it was presumed that complete revascularization was achieved in this group of patients. All patients signed informed consent and the study protocol was approved by the institutional review boards of the participating centers.

The angioplasty procedure and follow-up angiography protocol have been described in part I of this chapter. All cineangiograms were analyzed using the cardiovascular angiography analysis system (CAAS) which has been described and validated earlier [11, 15]. A description of a typical analysis can be found elsewhere in the book.

*Follow-up evaluation and bicycle ergometry*

One to four days prior to follow-up catheterization each patient was seen in the outpatient clinic for an interview, physical examination and a symptom limited exercise test. Assessment of anginal complaints and test evaluation was documented at the individual centers prior to repeat angiography and thus without knowledge of the coronary anatomy. Typical anginal complaints were classified according to the Canadian Cardiovascular Society angina classification. The exercise test was performed on a bicycle ergometer according to two different protocols. In Berlin the test was performed in a supine position, starting with a workload of 25 watts which increased by 25 watts every 2 min. In the other 5 participating clinics the test was performed in a sitting position, starting with a workload of 20 watts which was increased by 20 watts every minute. Exercise was continued until anginal symptoms, a drop in systolic blood pressure, severe arrhythmia, or a horizontal or downsloping ST segment depression of more than 1 mm developed. A 12 lead ECG was recorded during exercise and recovery. ST changes were measured 80 ms after the J point. Horizontal or downsloping ST segment depression in any lead of at least 1 mm, as measured with calipers, was considered a positive response to the stress-test.

Of the 350 study patients, 330 performed an exercise test at follow-up. Reasons for not performing the exercise test were: unstable angina: 14 patients, orthopedic problems: 5 patients and refusal: 1 patient. None of the

patients used digitalis or showed a bundle branch block on the ECG, rendering the exercise ECG uninterpretable. In case of an abnormal baseline angiogram, an additional ST segment depression of at least 1 mm was considered a positive test response.

*Restenosis criteria*

Sensitivity and specificity for anginal status at follow-up and exercise testing at different cut-off points of continuous quantitative angiographic variables were determined. The angiographic variables were classified as describing the lesion severity at follow-up angiography, "static variables": percent diameter stenosis and minimal lumen diameter, or as describing the change in lesion severity at follow-up angiography, "dynamic variables": change in percent diameter stenosis and change in minimal lumen diameter. In addition, diagnostic accuracy of six previously proposed definitions of restenosis was determined; (1) an increase in diameter stenosis of at least 30% by the time of follow-up angiography (National Heart, Lung and Blood Institute criterion 1 [NHLBI 1]), (2) an immediate post-angioplasty diameter stenosis of less than 50% increasing to greater than or equal to 70% at follow up (NHLBI 2), (3) an increase in stenosis severity to within 10% or less of the predilatation diameter stenosis at the time of follow-up angiography (NHLBI 3), (4) a loss of at least 50% of the gain achieved at angioplasty (NHLBI 4), (5) increase of lesion severity to more than 50% diameter stenosis at follow-up, (6) deterioration in minimal lumen diameter of at least 0.72 mm from immediately post-angioplasty to follow-up. The latter criterion is based on the long-term variability of minimal lumen diameter measurements using the CAAS system (0.36 mm). This variability is 1 standard deviation of the mean difference of 2 measurements of the same lesion filmed at 2 catheterization sessions on average 90 days apart [11]. This long term variability reflects the long-term random variation in lesion measurements from coronary angiograms made at different catheterization sessions using the CAAS system [11]. The use of 1 standard deviation would include 68.3% of the variability, while the use of 2 standard deviations ($2 \times 0.36 = 0.72$ mm) includes 95.5% of the variability.

*Results*

Table 4 summarizes the baseline characteristics of the 350 study patients. No differences were found in the proportion of patients with recurrent angina and ST depression at exercise with respect to the vessel dilated (Table 5). The occurrence of Q waves in the area supplied by the dilated artery as an indicator of prior transmural infarction (Table 5) was low.

*Recurrent angina and quantitative angiography*

At follow-up 102 of 350 patients (29%) had recurrent angina. Percentage correct classification of recurrence of angina (sensitivity) and percentage

*Table 4.* Baseline characteristics of the study population.

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

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

*Table 5.* Ischemia at follow-up and prior Q wave infarction by vessel type.

| | |
|---|---|
| Proportion of patients with recurrent angina and | |
| LAD dilatation | 28.9% (56 of 194 patients) |
| RCA dilatation | 28.3% (26 of 92 patients) p = 0.33* |
| LCX dilatation | 31.3% (20 of 64 patients) |
| Proportion of patients with ST depression of ⩾1 mm at exercise and | |
| LAD dilatation | 37.0% (67 of 181 patients) |
| RCA dilatation | 28.7% (25 of 87 patients) p = 0.91* |
| LCX dilatation | 38.7% (24 of 62 patients) |
| Proportion of patients with LAD dilatation and | |
| Q wave in ECG leads V1 to V5 | 10.3% (20 of 194 patients) |
| Q wave in ECG leads II,III,aVF | 17.0% (33 of 194 patients) |
| Q wave in ECG leads V6,aVL | 18.6% (36 of 194 patients) |
| Proportion of patients with RCA dilatation and | |
| Q wave in ECG leads II,III,aVF | 3.3% (3 of 92 patients) |
| Q wave in ECG leads V1 to V5 | 32.6% (30 of 92 patients) |
| Q wave in ECG leads V6,aVL | 28.3% (26 of 92 patients) |
| Proportion of patients with LCX dilatation and | |
| Q wave in ECG leads V6, aVL | 20.3% (13 of 64 patients) |
| Q wave in ECG leads V1 to V5 | 23.4% (15 of 64 patients) |
| Q wave in ECG leads II,III,aVF | 3.1% (2 of 64 patients) |

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

correct classification of absence of angina at follow up (specificity) as a function of cut-off points for the different quantitative angiographic variables are given in Fig. 6. The point of intersection of the sensitivity and specificity curves represents the cut-off point for which diagnostic accuracy was best. The "static" variables minimal lumen diameter at follow-up and percent diameter stenosis at follow-up, performed equally well with a sensitivity and specificity slightly above 70% at cut-off points of 1.45 mm and 46.5%

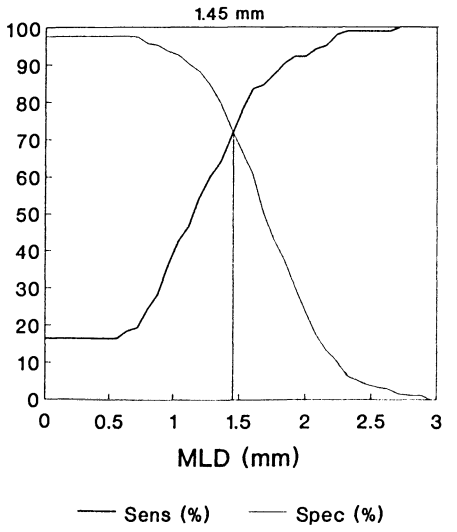
respectively. Parameters that reflect the change in lesion severity from directly post angioplasty to follow-up performed only slightly less favorable, with a sensitivity and specificity of just below 70% at cut-off points of −0.30 mm for the change in minimal lumen diameter and −10% for the change in percent diameter stenosis. In order to compare the diagnostic accuracy of the different variables, receiver operator characteristic (ROC) curves were constructed (Fig. 7). Quantitative angiographic parameters denoting a change in lesion severity are only slightly less accurate than those that denote a static measurement of lesion severity at follow-up.

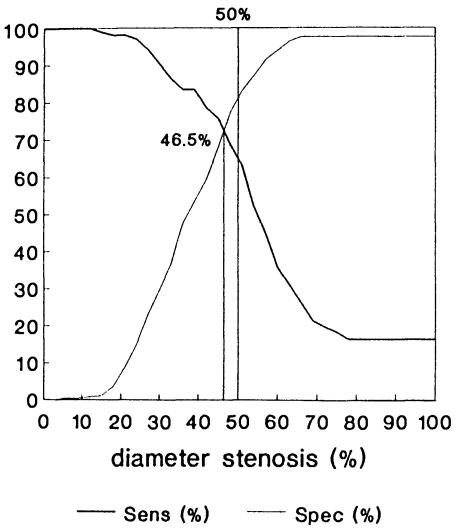
*Positive exercise test and quantitative angiography*

The exercise test result was abnormal in 116 patients (35%). Percentage correct classification for an abnormal test (sensitivity) and percentage correct classification for a normal test (specificity) as a function of cut-of points for the different quantitative angiographic variables are given in Table 6. It is clear that the diagnostic accuracy of exercise testing was lower than for anginal status at follow-up. The optimal combination of sensitivity and specificity was around 60% for all angiographic variables, with the "static" variables performing slightly better than the "variables of change" (Table 6). However, the cut-off points associated with the point of intersection of the sensitivity and specificity curves were similar to those obtained with anginal status. This was 45.5% diameter stenosis at follow-up, 1.46 mm minimal lumen diameter at follow-up, a change of 10% in diameter stenosis and a change of 0.32 mm in minimal lumen diameter. ROC curves for the different quantitative angiographic variables are shown in Fig. 8.

*Recurrent angina, positive exercice test and restenosis criteria in current use*

Table 7 and 8 list the sensitivity, specificity and predictive values for recurrent angina and a positive exercise test of different previously proposed restenosis criteria. None of the criteria predicted recurrent angina and positive exercise testing with great accuracy. In particular a positive exercise test was very hard to predict with all angiographic restenosis criteria. Criteria that require a large change (NHLBI 1 and the ≥0.72 mm criterion), and the NHLBI 2 criterium that requires an extraordinary high diameter stenosis at follow-up, had a low sensitivity. In fact the NHLBI 2 criterion is more a predictor of total occlusions since 22 of 26 lesions that fulfilled this criterion were totally occluded at follow-up. For the 330 patients that underwent exercise testing 19 of the 22 lesions that fulfilled the NHLBI 2 criterium were totally occluded at follow-up. The NHLBI 3 and 4 criteria and the ≥50% diameter stenosis criterion performed better. The 50% diameter stenosis cut-off point lies close to the optimal cut-off point of 46.5% and is therefore one of the best predictors of recurrent angina or positive exercise testing, whereas the NHLBI 1 criterion (change in diameter stenosis ≥30%) and the ≥0.72 mm criterion are clearly remote from the optimal cut-off points of −10% and −0.32 mm respectively (Figs 6c, 6d and Table 6).




*Figures* 6a,b.

*Diagnostic Accuracy of Quantitative Angiography in Large Versus Small Vessels*

Coronary arteries taper from proximal to distal. The comparison of proximal with distal coronary vessels carries the disadvantage of grouping together vessels of different diameter. To study whether the quantitative angiographic values found apply to both large and small vessels we determined the points

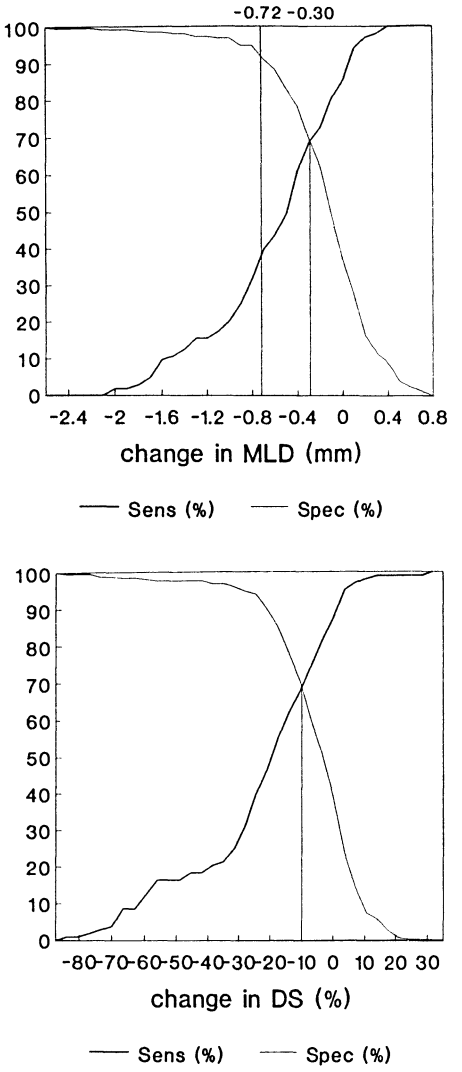



*Figure 6.* Percentage correct classification of recurrence of angina (sensitivity) and percentage correct classification of absence of angina at follow up (specificity) as a function of cut-off points for the different quantitative angiographic parameters. The point of intersection of the 2 curves denotes the cut-off point with the highest diagnostic accuracy. Where appropriate the 50% diameter stenosis and the $\geq$0.72 mm loss in minimal lumen diameter restenosis criteria were drawn in the figure. Fig. 6a: curves for minimal lumen diameter at follow-up.
Fig. 6b: curves for percent diameter stenosis at follow-up.
Fig. 6c: curves for change in minimal lumen diameter at follow-up.
Fig. 6d: curves for change in percent diameter stenosis at follow-up.
DS = diameter stenosis, MLD = minimal lumen diameter, Sens = sensitivity, Spec = Specificity.
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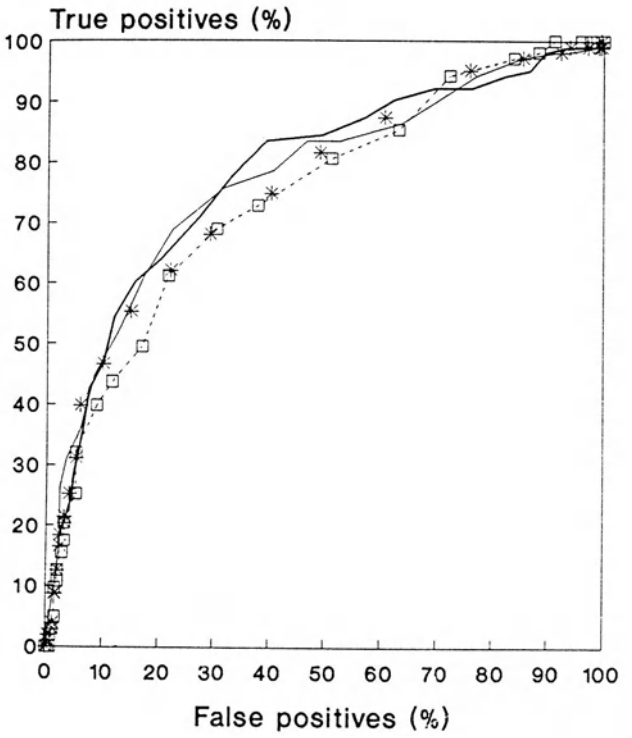


*Figure 7.* Receiver-Operator Characteristic (ROC) curves for comparison of the diagnostic accuracy of anginal status at follow-up for minimal lumen diameter at follow-up (solid line), percent diameter stenosis at follow-up (normal line), change in minimal lumen diameter (dotted line with squares) and change in percent diameter stenosis (dotted line with asterisks) Reproduced with permission [61].

of intersection of the sensitivity and specificity curves for all four measurements of restenosis. Therefore the vessels were divided in 2 equally large groups according to the reference diameter so that each group contained 50% of the population. Large vessels had a reference diameter of $\geq$2.63 mm (n = 176) and small vessels had a reference diameter of $<$2.63 mm. Results are shown in Table 9. The point of intersection of the sensitivity and specificity curves of the absolute diameter at follow-up was the only quantitative angiographic cut-off point that was different in large vessels as compared to smaller vessels.

## *Discussion*

### *Patient selection and methodological considerations*

In this study we preferentially studied patients with single vessel disease and with a single lesion which was successfully dilated. In these patients only

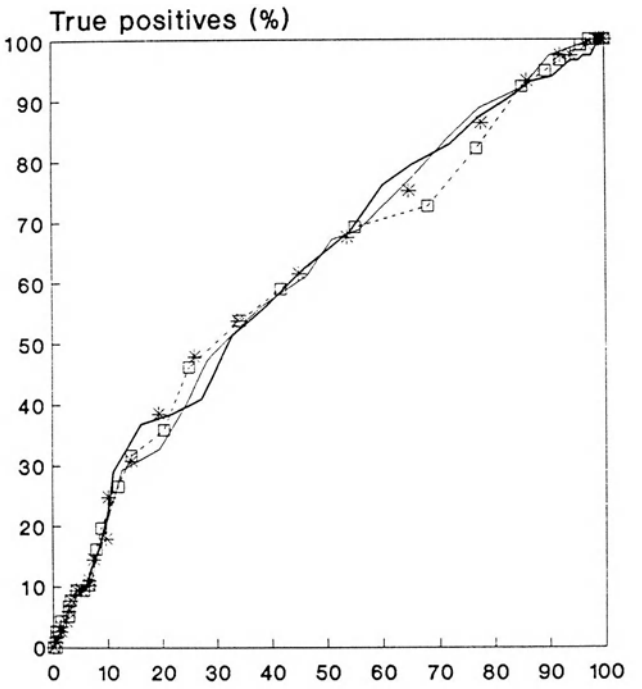


*Figure 8.* Receiver-Operator Characteristic (ROC) curves for comparison of the diagnostic accuracy of exercise electrocardiography for minimal lumen diameter at follow-up (solid line), percent diameter stenosis at follow-up (normal line), change in minimal lumen diameter (dotted line with squares) and change in percent diameter stenosis (dotted line with asterisks). Reproduced with permission [61].

*Table 6.* Points of intersection of the sensitivity and specificity curves for the prediction of exercise test result.

| Quantitative angiographic variable | Intersection point | Diagnostic accuracy at intersection point* |
|---|---|---|
| MLD (mm) | 1.46 | 58% |
| Diameter stenosis (%) | 45.5 | 58% |
| Change in MLD (mm) | −0.32 | 58% |
| Change in diameter stenosis (%) | −10 | 59% |

MLD = minimal lumen diameter. At point of intersection diagnostic accuracy is maximal and sensitivity = specificity *point at which sensitivity equals specificity.

restenosis of this lesion can be held responsible for an abnormal ECG response at follow-up exercise testing or recurrent angina, whereas in multivessel disease the responsible lesion is not always easy identifiable. Moreover coronary angioplasty in multivessel disease will not result in complete revascularization in a considerable number of cases [30].

*Table 7.* Diagnostic accuracy of different angiographic restenosis criteria for patients with recurrent angina.

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

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

*Table 8.* Diagnostic accuracy of different angiographic restenosis criteria for patients with positive bicycle ergometry at follow-up.

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

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

*Table 9.* Point of intersection for small and large vessels.

| Reference diameter | Intersection for anginal status | Intersection for exercise test result |
|---|---|---|
| | MLD at follow-up | |
| <2.63 mm | 1.38 mm ($n$ = 176) | 1.37 mm ($n$ = 161) |
| ≥2.63 mm | 1.58 mm (n = 174) | 1.57 mm (n = 169) |
| | Diameter stenosis at follow-up | |
| <2.63 mm | 47.5% (n = 176) | 44.5% (n = 169) |
| ≥2.63 mm | 46% ($n$ = 174) | 44% ($n$ = 161) |
| | Change in MLD | |
| <2.63 mm | −0.33 mm ($n$ = 176) | −0.34 ($n$ = 169) |
| ≥2.63 mm | −0.27 mm ($n$ = 174) | −0.30 ($n$ = 161) |
| | Change in diameter stenosis | |
| <2.63 mm | −11% ($n$ = 176) | −11% ($n$ = 169) |
| ≥2.63 mm | −9% ($n$ = 174) | −9% ($n$ = 161) |

MLD = minimal lumen diameter.

With conventional exercise protocols, ECG leads and ECG criteria, exercise testing is characterized by a high specificity and a moderate sensitivity [31]. Furthermore, its sensitivity increases with the extent of coronary artery disease, which implies a low sensitivity in patients with single vessel disease [32–34]. This explains the low predictive accuracy found in our population of patients with single vessel disease for the different restenosis criteria. These findings are comparable with the findings of Bengtson et al. [35] who found a sensitivity of 32% and a specificity of 79% for a positive exercise ECG.

It is known that diagnostic accuracy for restenosis of recurrent angina is better than for ST segment change [35, 36]. From the data of Bengtson et al. [35] a sensitivity for recurrent angina of 59% and a specificity of 73% can be calculated. They applied the 50% diameter criterion for restenosis. Zaidi et al. [37] reported a sensitivity of 70% and a specificity of 66% for recurrence angina as a test for restenosis. Although the predictive accuracy of quantitative angiographic parameters was generally poor in the present study, it is remarkable that the points of intersection of the sensitivity and specificity curves were similar for 2 different markers of myocardial ischemia.

Angioplasty of the left anterior descending artery made up 55.4% of all procedures in this study. It might be argued that the large mass of myocardium supplied by this artery which is potentially ischemic in case of severe renarrowing, would render the findings of this study only applicable to LAD lesions. However no differences were found in the proportion of patients with recurrent angina and ST depression at exercise with respect to the vessel dilated (Table 5). Prior myocardial infarction is known to falsely increase the accuracy of exercise testing [38]. However the occurrence of Q waves in

the area supplied by the dilated artery (Table 5) was low, indicating an only small possible influence on our findings.

*Angiographic restenosis and functional status*

Restenosis after a successful angioplasty procedure is now viewed as an fibroproliferative repair process in response to traumatic injury to the vessel wall [16, 17]. We recently showed that luminal narrowing after angioplasty occurs to a certain extent in all dilated lesions [39] and that angiographic restenosis is the tail end of a normally distributed phenomenon. The restenosis rate is then dependent on the cut-off criterion applied. Generally 2 types of angiographic restenosis criteria have been developed: criteria that denote the change in stenosis severity at follow-up angiography (e.g. the $\geq$0.72 mm change criterion) and criteria that assess stenosis severity at follow-up angiography (e.g. the >50% diameter stenosis at follow-up criterion). From a functional point of view restenosis can be detected by recurrence of angina and by several noninvasive tests. These tests are aimed at detecting myocardial ischemia due to a flow limiting stenosis in an epicardial artery and give no information on the magnitude of the luminal narrowing process in the individual lesion. Angiographic restenosis criteria that give a static assessment of lesion severity at follow-up have the disadvantage of preselecting lesions with a marginal angioplasty result [28]. This means that these lesions have to undergo only a small deterioration to cross the cut-off point and be classified as "restenosed". Classically the 50% diameter stenosis criterion is applied to classify lesions or patients as "restenosed" at follow-up angiography after angioplasty. This definition is historically based on the physiological concept of coronary flow reserve introduced by Gould and others in 1974 and is taken because it represents the approximate value in animals with normal coronary arteries at which blunting of the hyperemic response occurs [19]. Although the 50% diameter stenosis criterion is attractive because it links the angiographic appearance of a lesion with the clinical situation of the patient, it tells us nothing about the dynamic behavior of the restenosis process. Our findings underscore the significance of the 50% diameter stenosis criterion because the optimal cut-off point for prediction of functional status 6 months after coronary angioplasty was found to be close to this value (46.5% diameter stenosis). Diagnostic accuracy of the *absolute* stenosis diameter at 6 months follow-up however, was similar to percent diameter stenosis (Fig. 7 and Fig. 8) with a point of intersection of the sensitivity and specificity curves for both anginal status and exercise testing at approximately 1.45 mm. This indicates that an absolute measure of stenosis severity is equally predictive of clinical status after angioplasty as a relative measurement. These values correspond well with the findings of Wilson et al. [40]. They found that coronary flow reserve dropped below 3.5 (the lower threshold of normal) at a minimal cross sectional area of 1.5 $mm^2$ and a percent area stenosis of 75 which corresponds to a minimal lumen diameter of 1.4 mm and a percent diameter stenosis of 50% respectively.

Wijns et al. demonstrated a steep increase in pressure drop over left anterior descending artery stenoses once a critical value of minimal cross-sectional area of 2.5 $mm^2$ was reached. This corresponds to a minimal lumen diameter of 1.78 mm [41]. The pressure measurements were made with a dilatation catheter across the stenosis (cross-sectional area of catheter: 0.64 $mm^2$). If this value is subtracted from the 2.5 $mm^2$ value, a minimal lumen diameter value of 1.54 mm emerges, which is close to the 1.45 mm found in the present study.

An approach that more closely reflects the magnitude of the reactive intimal hyperplasia after angioplasty is applying criteria that describe the change in lesion severity at follow-up angiography. The major critique on this type of criterion is that they might disregard the functional significance of a lesion at follow-up. For instance a lesion with a post angioplasty percent diameter stenosis in the range of 0–15% can undergo a large deterioration and still not be flow limiting. Our study however, not only shows that the static parameters of minimal lumen diameter and percent diameter stenosis perform equally well in predicting clinical significance of a lesion 6 months after successful coronary angioplasty but also that the parameters of change in lumen diameter and change in percent diameter stenosis were only slightly less accurate in predicting the clinical significance of the lesions (Figs 7 and 8). Therefore, parameters of change, apart from their usefulness in reflecting the magnitude of the reactive hyperplasia, also reflect nearly to the same extent as the "static" parameters, the clinical significance of the lesion at follow-up. The optimal cut-off point for the parameters of change was −0.30 mm for the change in lumen diameter and −12% for change in percent diameter stenosis with nearly equal diagnostic accuracies showing that absolute change in lesion severity (in mm) and relative change in lesion severity (in percentage) perform equally well in the prediction of recurrent angina or positive exercise ECG 6 months after coronary angioplasty.

*Limitations*

First of all more sophisticated invasive and non invasive methods are available for the assessment of the functional significance of a coronary stenosis. It is known that exercise thallium scintigraphy has a higher diagnostic accuracy than electrocardiographic exercise testing [20]. The present data originate from a multicenter trial and therefore it is logistically difficult to standardize the methodology of radionuclide exercise tests or flow-reserve measurements in all participating centers. Exercise electrocardiographic testing on the other hand is inexpensive, safe and identical exercise protocols can be easily implemented in the participating centers. As proposed by Popma et al. [42], paired stress tests, (shortly after angioplasty and at 6 months follow up) should ideally be obtained, otherwise the interpretation of an ischemic exercise test at follow-up may be more difficult, especially in patients with multivessel coronary artery disease. Our study population consisted of patients

with single vessel disease in whom complete revascularization was achieved. The absence of myocardial ischemia at hospital discharge after angioplasty, however, was not objectively confirmed by exercise testing. The diagnostic accuracy of quantitative angiographic parameters for the prediction of recurrent angina and an abnormal ECG response at exercise was not very high. However, the *absolute* values of sensitivity and specificity were not crucial to this study, but rather the point of intersection of the sensitivity and specificity curves. Anginal medication was not standardized in this study. This might have influenced the assessment of functional status. An attempt was made however to withdraw antianginal medication at least 24 hr before exercise testing. Finally all angiograms were preceded by an intracoronary dose of nitrates and not all patients were using vasodilatory drugs at the time of exercise testing. This might have shifted the points of intersection towards a higher minimal lumen diameter and lower percent diameter stenosis.

*Conclusion*

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

## Part III. Restenosis rates in different coronary arteries

*Introduction*

Ever since the introduction of percutaneous transluminal coronary angioplasty (PTCA) [4] as an alternative to coronary artery bypass grafting, this means of treatment has been plagued by the problem of restenosis which has become an important field of investigation in interventional cardiology. Over the last 14 years, clinicians have sought extensively for factors increasing the risk of restenosis and many patient-lesion-procedure related factors have been put forward [20, 21]. However, the cause and effect relationship of these factors can be questioned because these early studies were, in general,

retrospective analyses with relatively small numbers of patients. In addition, these studies were fraught with methodologic problems: angiographic follow-up was incomplete, the incidence of restenosis was influenced by the recurrence of symptoms and the time for restudy was not predetermined. Furthermore, the definition of restenosis varied between the different studies and the presence or absence of restenosis was assessed visually, a method known to be limited by inter and intra-observer variability [15, 28]. One risk factor for restenosis that led to controversy is the site of dilatation, with in some studies a higher incidence of restenosis in the proximal left anterior descending (LAD) as compared to narrowing in the right or in the left circumflex coronary artery (LC) (Table 10) [7, 8, 43–54]. Recently, 2 multicenter restenosis prevention trials have enrolled more than 1400 patients and have been analyzed at the same angiographic core laboratory. In 91% of the enrolled patients, follow-up angiography was performed and the same quantitative coronary angiographic method of analysis was used [11, 15]. The present study investigates whether the previously reported differences in restenosis rates in the 3 major coronary arteries could be confirmed in this large study group.

*Patients and methods*

The study population consisted of 1442 patients with significant primary stenoses in native coronary arteries who were prospectively enrolled in 2 restenosis trials in Europe. As no angiographic or clinical benefit of the 2 tested compounds could be demonstrated, the control and the active treatment groups were pooled for the present study. The PTCA and follow-up films of all successfully dilated patients were analyzed at the thoraxcenter core laboratory. Informed consent was obtained in all cases before the PTCA procedure and all patients were asked to return to the hospital for follow-up angiography.

Patients with stable and unstable angina pectoris and patients with totally occluded vessel segments were included. Patients with an evolving myocardial infarction and with significant left main disease were excluded. The PTCA procedure was successful if the final diameter stenosis was <50% on visual inspection of the post-PTCA angiogram. The PTCA procedure was considered complete as soon as the guiding catheter was removed from the groin. When recurrence of chest pain during the hospital stay led to coronary reintervention, the film prior to the reintervention was taken as the follow-up angiogram. If a follow-up angiogram was performed with an interval of <3 months and no definite restenosis had occurred, the patient was asked to undergo another coronary angiogram at 6 months.

Figure 9 describes the flow chart of the in total 1442 randomized patients. Of the 1353 patients with a successful PTCA, 1234 patients had a follow up angiogram after 6 months or earlier when indicated for symptoms.

The angioplasty procedure and follow-up angiography protocol have been

*Table 10.* Summary of restenosis studies demonstrating conflicting results about the site of dilatation as risk factor for restenosis.

| | Ref | Year | Patients | Angio fup (%) | Definition of restenosis | Restenosis (%) | Coronary artery | Statistical test |
|---|---|---|---|---|---|---|---|---|
| Holmes | 43 | 1984 | 665 | 84% | NHLBI I → IV | 33.6% | no difference | multivariate |
| Kaltenbach[1)] | 44 | 1985 | 356 | 94% | DS fup < 20% of PS pre | 12% | no difference | univariate |
| | | | | | loss ⩾ 50% of gain | 16% | | |
| | | | | | ↑ DS ⩾ 30% | 17% | | |
| Mata[2)] | 7 | 1985 | 63 | 95% | ↑ DS > 30% or DS > 70% | 23% | LAD or LC > right | Multivariate |
| DiSciascio[2)] | 45 | 1986 | 191 | 21%* | loss ⩾50% of gain | 58% 1-VD, 42% 2-VD | no difference | univariate |
| Leimgruber | 8 | 1986 | 1758 | 57% | >50% DS | 30.2% | LAD > rigth > LC | multivariate |
| Myler[3)] | 46 | 1987 | 286 | 57% | >50% DS | 41% | no difference | multivariate |
| Val | 47 | 1987 | 181 | 98% | ↑ ⩾ 30% DS | 28% | no difference | multivariate |
| Vandormael[3)] | 48 | 1987 | 209 | 62% | >50% DS | 82% (Symp) 30% (No Symp) | LAD > right or LC Prox > Dist | multivariate |
| Black[4)] | 49 | 1988 | 384 | 39% | >50% DS | 31% | no difference | multivariate |
| de Feyter[5)] | 50 | 1988 | 179 | 88% | >50% DS | 32% | LAD > right or LC | multivariate |
| Fleck[1)] | 51 | 1988 | 110 | 86% | MLCA > 1 $mm^2$ (QCA) | 58% | no difference | multivariate |
| Quigley[4)] | 52 | 1989 | 114 | 88% | >50% DS | 32% | no difference | multivariate |
| Renkin | 53 | 1990 | 278 | 47%** | >50% DS | – | no difference | multivariate |
| Rupprecht[1)] | 54 | 1990 | 676 | 70% | >50% DS or loss > 50% of gain | 29.2% | no difference | multivariate |
| Present study | – | 1991 | 1353 | 91% | >50% DS relative loss | 31% 0.11 ± 0.21 | no difference | univariate Analysis of variance |

[1)] = exluded total occlusions; [2)] = multivessel dilatation; [3)] = multilesion dilatation; [4)] = for restenosis; [5)] = unstable angina; * = review of patients with clinical recurrence; ** = angiography + exercise thallium scintigraphy.

Angio fup = % of patients with angiographic follow-up; DS = Diameter Stenosis; Dist = Distal; Fup = follow-up; LAD = Left Anterior Descending artery; LC = Left Circumflexus; NHLBI = National Heart Lung Blood Institute; Prox = Proximal; RCA = Coronary Artery; Ref = References; Sympt = Symptoms; VD = Vessel Disease; Multivariate = multivariate analysis; Univariate = univariate analysis. Reproduced with permission [62].

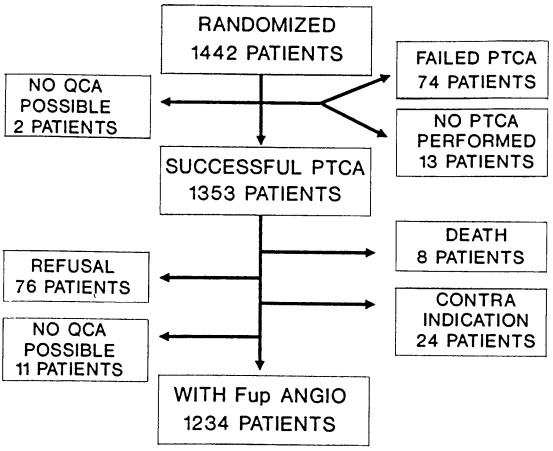


*Figure 9.* Flow chart of the 1442 randomized patients. In 74 patients the angioplasty procedure was unsuccessful, in 13 patients no PTCA was performed and in 2 patients no quantitative analysis was possible. Angiographic follow-up was obtained in 1234 patients (91%) after successful coronary angioplasty in 1353 patients. Reproduced with permission [62].

described in part I of this chapter. All cineangiograms were analyzed using the cardiovascular angiography analysis system (CAAS) which has been described and validated earlier [11, 15]. A description of a typical analysis can be found elsewhere in the book.

*Definition coronary segments*

Austen et al. [55] divided the coronary tree into 15 different segments (Fig. 10). As dilatation of the distal vessel segments did not occur frequently, it was decided to regroup these distal segments. The right coronary artery is divided into 4 segments where segment 1 corresponds with the proximal, segment 2 with the middle and segments 3 and 4 were taken together as the distal right coronary artery. The LAD is divided into 5 segments where segment 6 corresponds with the proximal LAD, segment 7 with the middle LAD and segments 8,9 and 10 were taken together as the distal LAD. The LC is divided into 5 segments where segment 11 corresponds with the proximal LC, segments 13 and 15 were taken together as the middle LC and segments 12 and 14 were taken together as the distal LC.

*Restenosis definition*

*Categorical approach*

Many criteria have been proposed by the National Heart Lung Blood Institute to assess restenosis. The most frequently used criterion by clinicians is

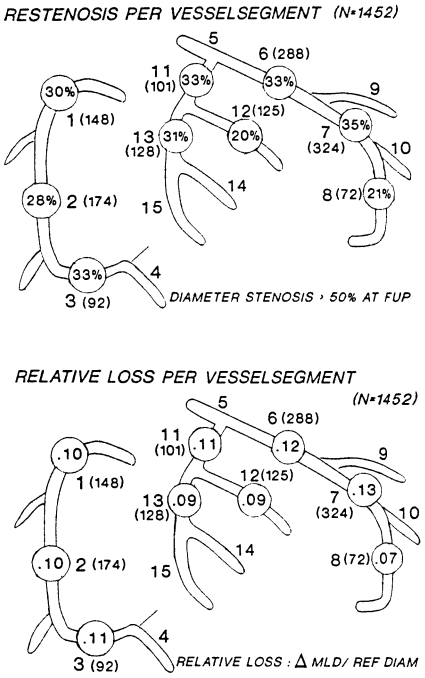


*Figure 10.* The coronary tree divided into 15 different segments with the restenosis rate (using > 50% diameter stenosis as criterion) for each segment (A) and the relative loss per coronary segment (B) shown in the circles. Between brackets are the numbers of the lesions dilated for that segment. Reproduced with permission [62].

that restenosis is present when the diameter stenosis is >50% at follow-up angiography [22]. This definition is applied to our data.

*Continuous approach*

Beside this arbitrary categorical approach for restenosis, we wanted to use absolute changes in minimal luminal diameter adjusted for vessel size which allows the comparison between vessels of different sizes and is a reflection of how the lesion behaves during and after PTCA.

Relative gain depicts the increase in minimal lumen diameter normalized for the reference diameter during PTCA:

$$\frac{\text{Minimal Lumen Diameter (post-PTCA} - \text{pre-PTCA)}}{\text{Reference Diameter pre-PTCA}}$$

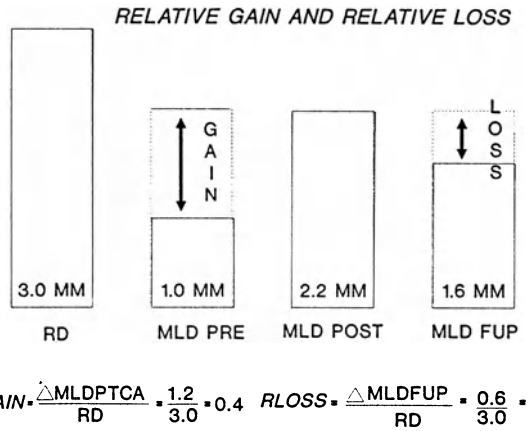


*Figure 11.* See text for explanation of relative gain and relative loss. Reproduced with permission [62].

Relative loss depicts what is lost in minimal lumen diameter normalized for the reference diameter:

$$\frac{\text{Minimal Lumen Diameter (post-PTCA – follow-up)}}{\text{Reference Diameter pre-PTCA}}$$

*Data analysis*

Data were analyzed using the BMDP statistical software package (University of California Press, Berkeley, Ca, 1990). A chi-square test was used to assess differences in categorical variables. A one-way analysis of variance was used to assess differences in continuous variables between the 3 major coronary arteries and the 9 different segments of the coronary tree. A p-value (probability value) of $<0.05$ was considered indicative of a significant difference.

*Results*

The mean time to follow-up angiography was 165 ± 42 days. In 1234 patients 1452 lesions were successfully dilated (1.2 lesion/patient). In 74 patients a totally occluded vessel segment was dilated. In 1137 patients a 1 vessel dilatation was performed, 93 patients had a 2 vessel dilatation and in 4 patients all 3 vessels were dilated. The majority of the stenoses were located in the LAD, total of 684 lesions, compared to 414 lesions in the right coronary artery and 354 lesions in the LC. Table 11 summarizes the results of the quantitative measurements of the 1452 lesions. The largest vessel was the right coronary artery with an average reference diameter of 2.86 ± 0.55 (mm). The LAD and LC had similar sizes: the average reference diameter was 2.54 ± 0.53 (mm) for the LAD and 2.55 ± 0.50 (mm) for the LC

($p < 0.001$). In addition, the average increase in minimal luminal diameter was $0.82 \pm 0.37$ (mm) in the right coronary artery, $0.71 \pm 0.36$ (mm) in the LAD and $0.72 \pm 0.35$ (mm) in the LC. If these values are "normalized for the reference diameter" (relative gain), then no significant difference are observed between either the 3 major coronary arteries (right coronary artery vs LAD vs LC; $p = 0.44$) or between the different segments of the coronary tree ($p = 0.77$). During follow-up, the average loss in minimal luminal diameter was $0.26 \pm 0.55$ (mm) in the right coronary artery, $0.30 \pm 0.48$ (mm) in the LAD and $0.25 \pm 0.48$ (mm) in the LC. If these values are normalized for the reference diameter (relative loss) no significant differences are observed between the 3 major coronary arteries (right coronary artery vs LAD vs LC; $p = 0.13$) or between the different segments of the coronary tree ($p = 0.19$). In Table 12 the restenosis rate, the relative gain and relative loss for the 3 major coronary arteries and the diverse vessel segments using either the categorical or continuous approach are summarized. No significant difference in either approach was observed .

*Discussion*

Several groups have raised the question whether the dilated vessel constitutes a risk factor for the development of restenosis. They have reported conflicting results (Table 10). The question is becoming even more relevant as new interventional techniques (such as stenting, atherectomy, laser photoablation, rotablation) have "claimed" to be more effective than conventional balloon angioplasty in certain lesion types (long lesions, total occlusions), locations or vessels (Right coronary artery, LAD, LC, bypass graft) [56], although these new techniques have not yet succeeded in reducing the restenosis rates [57, 58]. Several explanations have been put forward to explain the increased risk for restenosis in the (proximal) LAD. Mata et al. believed that a high rate of "continuous success" requires an optimal selection of the balloon/artery ratio and optimal balloon pressure application. They suggested that anatomic or procedural factors were responsible for restenosis [7]. Leimgruber et al. gave three possible explanations [8]. First, as the proximal LAD is most often the largest artery (in the view of the authors), the 3.0 mm diameter balloons most frequently used in that time, could have been undersized for the LAD and oversized for the right coronary artery and LC. This resulted in higher post-PTCA diameter stenosis which seems to be associated with a higher risk for restenosis. Secondly, a dilatation of the proximal LAD often involves the origin of the vessel and vessel branch points and this factor also seem to be associated with an increased risk of restenosis. Thirdly the proximal LAD is well recognized to develop "localized stenosis". Whether the same underlying mechanisms may predispose to recurrence of postangioplasty lesions is unknown but well conceivable. As balloon/artery mismatch was not identified as predictor for restenosis in a group of patients with multilesion coronary angioplasty, Vandormael et al.

*Table 11.* Baseline quantitative angiographic data per vessel segment dilated.

| Coronary artery | # | Pre-PTCA (mm) | RDPost-PTCA (mm) | RDFup RD (mm) | Pre-PTCA (mm) | MLDPost-PTCA (mm) | MLDFup MLD (mm) |
|---|---|---|---|---|---|---|---|
| Total | 1452 | 2.63 ± 0.54 | 2.70 ± 0.52 | 2.70 ± 0.56 | 1.02 ± 0.38 | 1.77 ± 0.36 | 1.50 ± 0.57 |
| Right | 414 | 2.86 ± 0.55 | 2.93 ± 0.52 | 2.97 ± 0.58 | 1.08 ± 0.41 | 1.91 ± 0.371.6 | 5 ± 0.65 |
| Proximal | 148 | 2.99 ± 0.55 | 3.05 ± 0.51 | 3.07 ± 0.55 | 1.11 ± 0.45 | 1.96 ± 0.39 | 1.69 ± 0.63 |
| Middle | 174 | 2.82 ± 0.50 | 2.90 ± 0.50 | 2.94 ± 0.59 | 1.08 ± 0.41 | 1.91 ± 0.34 | 1.66 ± 0.65 |
| Distal | 92 | 2.71 ± 0.59 | 2.81 ± 0.56 | 2.85 ± 0.57 | 1.02 ± 0.35 | 1.83 ± 0.40 | 1.57 ± 0.66 |
| LAD | 684 | 2.54 ± 0.53 | 2.59 ± 0.49 | 2.58 ± 0.53 | 1.01 ± 0.36 | 1.72 ± 0.35 | 1.42 ± 0.53 |
| Proximal | 288 | 2.73 ± 0.52 | 2.78 ± 0.48 | 2.76 ± 0.53 | 1.08 ± 0.35 | 1.83 ± 0.35 | 1.53 ± 0.55 |
| Middle | 324 | 2.48 ± 0.47 | 2.52 ± 0.43 | 2.52 ± 0.47 | 0.97 ± 0.36 | 1.68 ± 0.32 | 1.35 ± 0.51 |
| Distal | 72 | 2.08 ± 0.44 | 2.14 ± 0.44 | 2.13 ± 0.42 | 0.87 ± 0.35 | 1.43 ± 0.29 | 1.29 ± 0.37 |
| LC | 354 | 2.55 ± 0.50 | 2.62 ± 0.46 | 2.61 ± 0.48 | 1.01 ± 0.36 | 1.73 ± 0.34 | 1.48 ± 0.51 |
| Proximal | 101 | 2.73 ± 0.47 | 2.75 ± 0.43 | 2.74 ± 0.44 | 1.06 ± 0.42 | 1.82 ± 0.32 | 1.52 ± 0.50 |
| Middle | 125 | 2.55 ± 0.50 | 2.64 ± 0.45 | 2.61 ± 0.50 | 1.00 ± 0.34 | 1.75 ± 0.32 | 1.52 ± 0.53 |
| Distal | 128 | 2.41 ± 0.49 | 2.50 ± 0.46 | 2.52 ± 0.48 | 0.98 ± 0.34 | 1.63 ± 0.34 | 1.41 ± 0.49 |

LAD = Left Anterior Descending; LC = Left Circumflex; RD = Reference Diameter; MLD = Minimal Luminal Diameter; plus – minus values are means ± sd.

*Table 12.* Restenosis rate per segment using the categorical definition of > 50% DS at fup and the continuous approach with the relative gain and relative loss.

| | | DS (%) at follow-up > 50% | | | |
|---|---|---|---|---|---|
| | # | Yes | No | Relative gain | Relative loss |
| Total | 1452 | 444 (31%) | 1008 (69%) | 0.29 ± 0.16 | 0.11 ± 0.21 |
| Right | 414 | 123 (30%) | 289 (70%) | 0.30 ± 0.15 | 0.10 ± 0.22 |
| Proximal | 148 | 45 (30%) | 103 (70%) | 0.29 ± 0.15 | 0.10 ± 0.21 |
| Middle | 174 | 48 (28%) | 126 (72%) | 0.30 ± 0.15 | 0.10 ± 0.22 |
| Distal | 92 | 30 (33%) | 62 (67%) | 0.31 ± 0.15 | 0.11 ± 0.26 |
| LAD | 684 | 224 (33%) | 457 (67%) | 0.29 ± 0.17 | 0.12 ± 0.20 |
| Proximal | 288 | 95 (33%) | 193 (67%) | 0.29 ± 0.17 | 0.12 ± 0.19 |
| Middle | 324 | 114 (35%) | 210 (65%) | 0.29 ± 0.17 | 0.13 ± 0.21 |
| Distal | 72 | 15 (21%) | 57 (79%) | 0.27 ± 0.19 | 0.07 ± 0.15 |
| LC | 354 | 97 (28%) | 255 (72%) | 0.29 ± 0.16 | 0.11 ± 0.21 |
| Proximal | 101 | 33 (33%) | 68 (67%) | 0.29 ± 0.16 | 0.11 ± 0.18 |
| Middle | 125 | 25 (20%) | 100 (80%) | 0.30 ± 0.15 | 0.09 ± 0.21 |
| Distal | 128 | 40 (31%) | 88 (69%) | 0.28 ± 0.17 | 0.09 ± 0.21 |
| P-value (Right vs LAD vs LC) | | 0.22 | | 0.44 | 0.13 |
| | (9 segments) | 0.06 | | 0.77 | 0.19 |

LAD = Left Anterior Descending; LC = Left Circumflex; RD = Reference Diameter; plus - minus values are means ± sd; DS = Diameter Stenosis.

suggested that the different anatomic and structural features of the proximal segment of the LAD compared with the proximal segment of the right coronary artery or LC, might be responsible for the observation that dilatation of the proximal LAD is an independent risk factor for restenosis [48]. According to Califf [20], one of the methodologic caveats for a higher restenosis rate in the proximal LAD is that an ischemic response to exercise testing is more likely to be seen with proximal LAD lesions, thereby increasing the chance of preferential detection unless angiographic follow-up is complete. Secondly, a larger diameter of this vessel may increase the risk that a satisfactory initial result was not achieved in earlier series, especially before the recent development of larger balloons to approach large vessels. In the present study, no significant difference in the restenosis rate was found between the 3 major coronary arteries ($p = 0.22$) or between the 9 coronary artery segments ($p = 0.06$) selected for the purpose of the analysis. Our results contradict earlier observations of Leimgruber and Califf that the proximal LAD is the largest vessel. In the present study, almost every segment of the right coronary artery has a larger diameter than the proximal LAD. A explanation for this discrepancy might be differences in patient populations: availability of different balloon sizes with even diameters less than 2.0 mm – as compared to the early days of PTCA when only balloon

sizes of 3.7 mm were available for dilatation – may have affected the PTCA of the proximal LAD. Another argument put forward in the early years of a mismatch between balloon catheters and the proximal LAD no longer holds as in the present study all patients underwent PTCA between December 1987 and December 1989 so that in all cases matched balloons were available. The difference in restenosis rates reported by these authors is probably more related to the biased and incomplete angiographic follow-up of these studies. In contrast, the present study has an 91% angiographic follow-up rate so the biased selection of symptomatic versus asymptomatic patients is virtually ruled out.

*Definition of restenosis*

The definition of choice for restenosis has been subject of much debate [28]. Of the different restenosis criteria proposed, the 50% diameter stenosis at follow-up angiography is the most frequently used to assess restenosis, as physiologic measurements show that the threshold for chest pain is near a reduction of 50% of the lumen of a normal vessel [19]. This definition was applied to our data. However, earlier studies have shown that the reference diameter can be involved in the dilatation process so that the% diameter stenosis could underestimate the change in the severity of a stenosis after PTCA [59]. Furthermore, the 50% diameter stenosis criterion at follow-up tells us nothing about the way the lesion has behaved since the PTCA procedure. We have earlier shown that a change of $\geq$0.72 mm in minimal luminal diameter is an appropriate method to assess intimal hyperplasia seen after coronary PTCA [3, 11, 15]. However, this $\geq$0.72 mm criterion was historically assessed in vessels with an average reference diameter of 3.7 mm [11, 15]. Therefore, it should be applied to vessels of comparable reference diameter; it is unlikely to have a loss of $\geq$0.72 mm in coronary segments with a reference diameter of 2 mm and a minimal luminal diameter of 1.4 mm. In other words, criteria based on the absolute change in minimal luminal diameter are limited because they make no attempt to relate the extent of the restenosis process to the size of the vessel. To circumvent this limitation it was proposed to use the change in minimal luminal diameter, from post-PTCA to follow-up, normalized for the reference diameter (relative loss). This sliding scale criterion, that adjusts for vessel size, allows the regional assessment of the extent of the restenosis phenomenon in the entire coronary tree. No difference in relative loss between the 3 major coronary arteries ($p = 0.13$) or the coronary segments could be observed ($p = 0.19$). Restenosis should thus be viewed as a ubiquitous phenomenon which is inducible to the same extent in every segment of the coronary tree. It must be emphasized that the relative gain (change in minimal luminal diameter from pre PTCA to post-PTCA, normalized for the reference diameter) – and thus the stimulus for restenosis [60] – was similar in every segment of the coronary tree. As the subdivision of the AHA-coronary segments is somewhat arbitrary by

*Table 13.* Relative gain and relative loss per reference diameter group.

| Ref diameter (mm) | # | Absolute gain (mm) | Relative gain | Absolute loss (mm) | Relative loss | DS (%) at fup > 50% Yes | DS (%) at fup > 50% No | Bar |
|---|---|---|---|---|---|---|---|---|
| >4.0 mm | 18 | 0.72 ± 0.55 | 0.17 ± 0.13 | 0.13 ± 0.46 | 0.03 ± 0.10 | 6 (33%) | 12 (67%) | 0.77 |
| 3.5 to 4.0 mm | 81 | 0.87 ± 0.47 | 0.24 ± 0.13 | 0.10 ± 0.50 | 0.03 ± 0.13 | 23 (28%) | 58 (71%) | 0.89 |
| 3.0 to 3.5 mm | 222 | 0.83 ± 0.42 | 0.26 ± 0.13 | 0.33 ± 0.54 | 0.10 ± 0.17 | 71 (32%) | 151 (68%) | 0.97 |
| 2.5 to 3.0 mm | 507 | 0.76 ± 0.40 | 0.28 ± 0.15 | 0.28 ± 0.52 | 0.10 ± 0.19 | 153 (30%) | 354 (70%) | 1.07 |
| 2.0 to 2.5 mm | 454 | 0.72 ± 0.40 | 0.32 ± 0.17 | 0.28 ± 0.51 | 0.12 ± 0.23 | 148 (33%) | 306 (67%) | 1.20 |
| <2.0 mm | 170 | 0.61 ± 0.34 | 0.34 ± 0.20 | 0.27 ± 0.46 | 0.15 ± 0.26 | 44 (%) | 126 (74%) | 1.39 |
| Analysis of variance | | <0.001 | <0.001 | <0.02 | <0.001 | | NS | |

Plus-minus values are means ± sd; ns = not significant; bar = balloon-artery ratio (size of the balloon according manufacturer divided by the reference diameter pre-PTCA); ds = diameter stenosis.

lumping together vessels of different diameter, we reanalyzed the data by stratifying the lesions according their reference diameter.

Table 13 summarizes the results. It appear that the larger the reference diameter pre-PTCA is, the less the relative loss is at follow-up. Vice versa, the highest value of relative loss is observed in the smaller vessels. This might be explained by oversizing of the balloon in these vessels. However, if the >50% diameter stenosis restenosis criterion is applied, then similar restenosis rates are found.

*Potential limitation of the study*

Our study population consisted mainly of patients with 1 site dilatation: 1044 patients had a single site dilatation and 190 patients underwent dilatation of $\geq 2$ sites. The high incidence of 1 site dilatation reflects the fact that the study population included in these 2 trials consisted predominantly of patients with 1 vessel disease so that our findings might not be extrapolated to a population with multivessel disease. Nevertheless, in the subset of 93 patients with multivessel dilatation the overall restenosis rate per lesion was also 31%. However the relative gain and loss observed in the 1 and 2 vessel dilatation population each differed statistically; a relative gain of $0.30 \pm 0.16$ was seen for 1 vessel dilatation versus $0.27 \pm 0.16$ for 2 vessel dilatation ($p < 0.04$) and there was a relative loss of $0.12 \pm 0.21$ in the 1 vessel dilatation population compared to $0.08 \pm 0.20$ in the 2 vessel dilatation population ($p < 0.02$). Thus, in the 2 vessel dilatation population a reduced gain is associated with a reduced loss consistent with the concept that PTCA operators are less aggressive in their dilating strategy.

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*PART SEVEN: Evaluation of new devices and comparison with balloon angioplasty using QCA*

# 28. Evaluation of the clinical use of directional coronary atherectomy using quantitative coronary angiography

VICTOR A.W.M. UMANS, DAVID P. FOLEY, ANNIE ROBERT, PASCAL QUAEDVLIEG, ELINE MONTAUBAN VAN SWIJNDREGT, WILLIAM WIJNS and PATRICK W. SERRUYS

## Introduction

Directional coronary atherectomy is now accepted as a feasible alternative to conventional balloon angioplasty for the treatment of coronary artery disease [1–8]. Because restenosis remains the "Achilles' heel" of all intracoronary interventional techniques, its frequency will ultimately determine the "utility" of atherectomy. Directional atherectomy may have some theoretical advantages over balloon angioplasty in reducing the amount of intimal hyperplasia after the intervention. In theory, plaque removal may create a larger post-interventional lumen with smooth surfaces and limited elastic recoil. Whether directional atherectomy indeed has a more favorable longterm result has not been proven. Therefore, we studied the longterm results following directional atherectomy and compared them with those of balloon angioplasty, as assessed by quantitative angiography.

While examining the long-term results of intracoronary interventions and atherectomy in particular, two aspects should be considered: (1) the clinical approach in which the determinant of the long-term angiographic *outcome* (minimal luminal diameter at follow-up) is characterized and (2) the biological approach which describes the determinants of the dynamic *process* (late luminal loss) which is initiated by the injury inflicted to the vessel wall during intervention.

From a *clinical point of view*, Kuntz et al. [9] have examined predictors of a large minimal luminal diameter at follow-up and concluded that a large post-procedural lumen was the principal determinant for the best outcome at 6 months (i.e. a large lumen at follow-up) and they have advocated the motto that "bigger is better" [9]. However, this analysis was based on the relationship of the minimal luminal diameter after the intervention and at



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follow-up without taking the vessel size and proportional gain into account. The influence of these two parameter should be considered for two reasons. Firstly, coronary ectasia after atherectomy [10] as well as a large luminal gain during balloon angioplasty have been associated with an increase in clinical complications [11] and restenosis [12]. Secondly, preliminary data from stent [13] and atherectomy experience [14] suggest that the restenosis rate in larger vessels is lower than in smaller vessels.

Others [15–17] have focussed their attention on the renarrowing process and have reported the relationship between relative luminal gain and relative luminal loss (i.e. gain and loss normalized for the vessel size) as correlates of the biological response of the vessel wall after an intervention. This *biological approach* has unveiled the general biological law relating healing process to vessel wall injury and has been encapsulated in the following motto "the more you gain the more you lose": the more you traumatize the vessel wall, the more intense the healing process will be [15–17].

Initially, these two viewpoints appear contradictory but on deeper examination it may be possible to reconcile the assessment of *outcome* and *process* and find that each view, in its way, may be correct, although not considering the entire picture. The purpose of this study was to try to reconcile the clinical and biological views. Therefore, we sought to examine the principle determinants of the long-term angiographic *outcome* as well as those of the dynamic *process* of renarrowing which occurs during follow-up in a consecutive series of patients treated by atherectomy.

Furthermore, the initial consecutive 87 successfully treated de novo atherectomy lesions (83 patients) were matched (for clinical and quantitative angiographic variables) with 87 coronary artery lesions which were selected from a consecutive series of successfully dilated primary angioplasty lesions. Three recently conceived angiographic endpoints (minimal luminal diameter, relative gain versus relative loss and net gain index) at follow-up were assessed to compare the long-term results of directional coronary atherectomy and balloon angioplasty.

## Methods

### *Patients*

One hundred thirty-one patients underwent 138 successful consecutive directional coronary atherectomy procedures between September 1989 and September 1991 at the Thoraxcenter (n = 97) and at University of Louvain hospital (n = 41). All patients completed a six month clinical follow-up. Only 6 patients did not undergo a long term angiographic follow-up (5%) and were excluded from the study.

*Atherectomy procedure*

The procedure was performed as described previously [5, 6, 8]. Briefly, the atherectomy device was directed over a guide-wire and positioned across the stenosis. The support balloon was then inflated up to 7.5 psi, the cutter was retracted and balloon inflation pressure was increased to maximally 45 psi. The driving motor was activated and the rotating cutter was slowly advanced to cut and collect the protruding atherosclerotic lesion in the collecting chamber located at the tip of the catheter. After every pass the balloon was deflated and the device either removed or repositioned. On average 5.9 ± 2.8 (2 to 14) cuts in selected directions were performed across a stenosis.

While an optimum angiographic result is sought for each lesion treated, the procedure was considered angiographically successful when the residual diameter stenosis was less than 50% after tissue retrieval. Following atherectomy, the arterial and venous sheaths were usually left in place for 6 hours. Patients were monitored for 24 hr and electrocardiograms and cardiac enzyme levels were obtained twice a day. A calcium antagonist was given every 2 hr for 24 hr after the procedure and the patients were kept on aspirin medication for six months.

*Follow-up evaluation*

After a successful atherectomy procedure (i.e. <50% post-procedural diameter stenosis on visual inspection), the patients were seen at the outpatient clinic for clinical evaluation. Prior to the six months follow-up coronary angiogram, an exercise test was performed. Angiography was performed earlier if symptoms occurred within 6 months.

*Quantitative coronary angiography*

Quantitative analysis of the coronary segments was performed with the computer based Coronary Angiography Analysis System (CAAS), previously described in detail [8, 16–21].

*Matching process*

The coronary artery tree was subdivided into 15 segments according to the American Heart Association guidelines and the lesions were individually matched according to stenosis location, reference diameter, minimal luminal diameter as well as the clinical parameters gender, anginal status, diabetes and hypercholesterolemia. Unstable angina was defined as chest pain at rest while hospitalized and treated with intravenous nitroglycerin and/or heparin. Hypercholesterolemia was defined as elevated levels of serum cholesterol >6.5 mmol/l requiring treatment with lipid lowering drugs. The principles of matching by quantitative angiography are threefold: (I) the angiographic

dimensions of matched lesions are assumed to be "identical", (II) the observed difference between the two "identical" lesions must be within the range of the CAAS analysis reproducibility of 0.1 mm (= 1 SD) and (III) the reference diameter of the lesions to be matched are selected within a range of ±0.3 mm (= 3 SD; confidence limits 99%) [18–20]. To compare the result of atherectomy and balloon angioplasty, 87 coronary artery lesions from a consecutive series of 2500 successfully dilated balloon angioplasty lesions (residual stenosis <50% on visual inspection) were selected by an independent analyst according to the above mentioned selection criteria of matching. These lesions were matched with the prospectively collected consecutive series of 87 successfully atherectomized native coronary artery lesions. Late comparative analysis between atherectomy and angioplasty was performed in 79 lesions since in the atherectomy group 8 lesions were lost to late angiographic follow-up. Consequently, the 8 twin matched angioplasty lesions were also not eligible for comparative follow-up analysis.

*Restenosis*

Two different approaches (categorical versus continuous) were used to define the restenosis rate. Using the categorical approach, the criterion chosen for restenosis was an increase of the diameter stenosis from <50% after the intervention to ≥50% at follow-up. This criterion was selected since clinical practice continues to assess lesion severity by percentage stenosis with a 50% cut-off. Using a continuous approach, minimal luminal diameter at follow-up (MLD fup), gain during atherectomy and loss during follow-up, relative gain and relative loss, which relate gain and loss to the vessel size, were determined in order to assess the long-term result of directional coronary atherectomy.
*Gain*: MLD post – MLD pre
*Loss*: MLD post – MLD fup
*Relative gain*: (MLD post – MLD pre) / vessel size
*Relative loss*: (MLD post – MLD fup) / vessel size
*Net gain index*: (MLD fup – MLD pre) / vessel size

*Potential risk factors studied*

The *absolute loss in minimal luminal diameter during follow-up* and the *minimal luminal diameter at follow-up* were assessed by separate multivariate analyses, for factors reported to be predictive of luminal narrowing after an intracoronary intervention. Variables potentially predictive for restenosis were divided into three general categories.

*Patient related variables* included age, gender, diabetes, hypertension, hypercholesterolemia (defined as elevated levels of serum cholesterol >6.5 mmol/l requiring treatment with lipid lowering drugs [22] and unstable angina (defined as pain at rest requiring treatment with intravenous nitrates and

intravenous heparin). *Lesion related factors* are characteristics unique to each lesion. The following factors were assessed: vessel size, pre-atherectomy minimal luminal diameter, post-atherectomy minimal luminal diameter, diameter stenosis before and after atherectomy, absolute gain in minimal luminal diameter by atherectomy, relative gain in minimal luminal diameter by atherectomy, atherectomized vessel (left anterior descending coronary artery, left circumflex artery or right coronary artery), de novo versus restenotic lesion. *Procedure related factors* assessed included: the center where the atherectomy was performed, number of atherectomy cuts, device size, device/artery ratio (defined as device size divided by the interpolated reference diameter) and the presence of media and/or adventitia in the excised specimens.

*Statistics*

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

## Results

*Patient characteristics and procedural results* (*Table* 1)

The present study population consists of 125 consecutive patients who underwent 132 coronary atherectomy procedures for symptomatic de novo (n = 117) and restenotic (n = 15) native coronary artery disease. The mean age was 58 ± 10 years and the majority of the patients were males with single vessel disease. The target stenosis (n = 132) in these 125 patients was located in the left anterior descending artery in 89 cases, in the left circumflex in 14 cases, in the right coronary artery in 29 cases. The clinical and immediate

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

| | |
|---|---|
| Age (yr) | 58 ± 10 |
| Male gender (%) | 82 |
| Angina status (%) | |
| Stable angina | 60 |
| Unstable angina | 40 |
| Multivessel disease (%) | 23 |
| Restenotic lesion (%) | 11 |
| Angiographic follow-up (%) | 93 |

angiographic success as well as the complication rates for both centers have been described in detail elsewhere [5]. All but 23 patients were treated with a 6 French atherotome, 21 were treated with a 7 French and 2 patients with a 5 French atherotome. The angiographic follow-up rate in the present study population is 95%. Of the six patients who did not undergo repeat angiography, 1 patient died 3 days after successful atherectomy [24], 1 patient had bypass surgery 7 days after the procedure for presumed tamponade while 4 asymptomatic patients refused angiography. At six months, 38 of the 125 patients (31%) had recurrence of their anginal symptoms. Fifteen patients underwent either a balloon angioplasty, or repeat atherectomy (n = 3) or stent implantation (n = 1) for symptomatic restenosis of the previously treated segment. During the follow-up period, three patients were referred for elective coronary bypass surgery.

*Quantitative angiographic analysis* (*Tables* 2, 3)

Reference diameter did not change from pre to post procedure. The minimal luminal diameter increased from 1.16 ± 0.39 mm by 1.28 ± 0.48 mm resulting in a minimal luminal diameter of 2.44 ± 0.47 mm post-procedure. At follow-up, the minimal luminal diameter at follow-up was 1.78 ± 0.64 mm (Fig. 1). Thus the late loss was 0.65 ± 0.64 mm. Likewise percent diameter stenosis decreased from 65 ± 11% pre-atherectomy to 26 ± 11% post-atherectomy and increased during follow-up to 41 ± 18% ($p < 0.001$).

A large absolute luminal gain was associated with a severe pre-procedural lesions (diameter stenosis >65% and/or minimal luminal diameter ≤1.11 mm), and when a satisfactory results was achieved by atherectomy (diameter stenosis <26% and/or minimal luminal diameter >2.42 mm). In the present population, the restenosis rate was 28% if the 50% diameter stenosis criterion was applied. Although no statistical difference was found in luminal loss or minimal luminal diameter at follow-up between patients with stable and unstable angina, a trend towards a greater minimal luminal diameter at follow-up was observed in the stable group. "Restenotic" lesions did not differ significantly from primary lesions with respect to luminal loss during

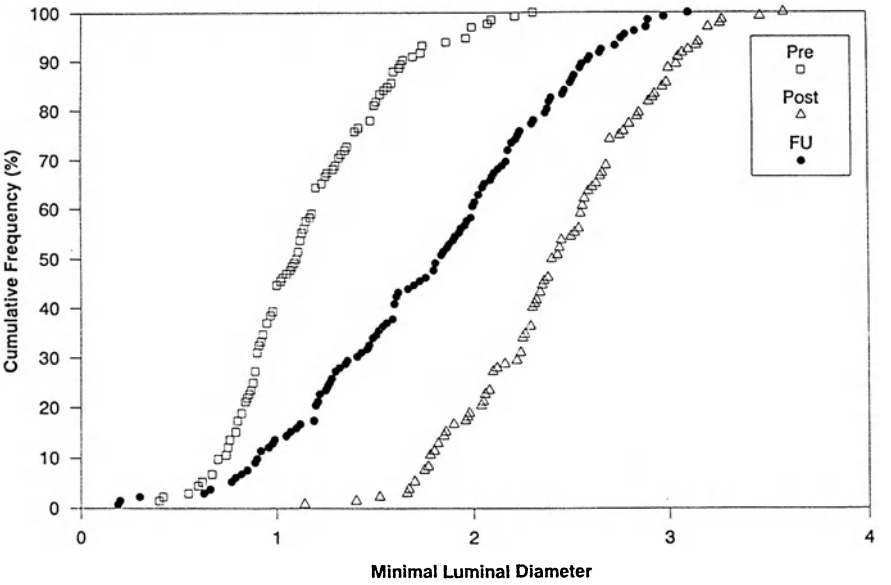


*Figure 1.* Cumulative frequency curves to illustrate the immediate and follow-up effects in minimal luminal diameter (MLD) of directional coronary atherectomy as assessed by quantitative coronary angiography. Pre = before atherectomy, post = after atherectomy, f-up = at follow-up. (With permission of the author).

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

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

F-up = follow-up; pre = before atherectomy; post = after atherectomy.

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

| | Median | N | Vessel size (mm) | MLD pre (mm) | Abs gain (mm) | Rel gain | MLD post (mm) | Abs loss (mm) | Rel loss | MLD fup (mm) | DS fup (%) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Vessel size | ≤3.25 | 67 | 2.80 ± 0.38 | 1.03 ± 0.34 | 1.30 ± 0.53 | 0.48 ± 0.21 | 2.34 ± 0.49 | 0.78 ± 0.60 | 0.25 ± 0.20 | 1.56 ± 0.58 | 43 ± 19 |
| | >3.25 | 65 | 3.79 ± 0.42 $ | 1.28 ± 0.40 $ | 1.26 ± 0.43 $ | 0.33 ± 0.12 # | 2.54 ± 0.43 # | 0.53 ± 0.66 @ | 0.15 ± 0.18 $ | 2.01 ± 0.63 | 39 ± 16 |
| MLD pre | ≤1.11 | 68 | 3.03 ± 0.61 | 0.86 ± 0.16 | 1.45 ± 0.48 | 0.49 ± 0.20 | 2.31 ± 0.47 | 0.70 ± 0.66 | 0.23 ± 0.21 | 1.62 ± 0.66 | 45 ± 19 |
| | >1.11 | 64 | 3.56 ± 0.55 $ | 1.48 ± 0.30 $ | 1.10 ± 0.41 $ | 0.31 ± 0.12 $ | 2.57 ± 0.43 $ | 0.61 ± 0.61 | 0.17 ± 0.17 | 1.96 ± 0.57 @ | 36 ± 16 @ |
| MLD post | ≤2.42 | 66 | 3.11 ± 0.57 | 1.04 ± 0.32 | 1.02 ± 0.38 | 0.34 ± 0.15 | 2.06 ± 0.28 | 0.44 ± 0.55 | 0.15 ± 0.19 | 1.62 ± 0.62 | 45 ± 18 |
| | >2.42 | 66 | 3.47 ± 0.66 @ | 1.27 ± 0.43 $ | 1.54 ± 0.43 $ | 0.47 ± 0.20 $ | 2.82 ± 0.27 $ | 0.88 ± 0.65 $ | 0.25 ± 0.19 @ | 1.94 ± 0.63 @ | 37 ± 17 @ |
| DS pre | >65 | 62 | 3.39 ± 0.58 | 0.91 ± 0.26 | 1.47 ± 0.46 | 0.44 ± 0.17 | 2.38 ± 0.45 | 0.66 ± 0.69 | 0.20 ± 0.20 | 1.72 ± 0.68 | 45 ± 18 |
| | ≤65 | 70 | 3.20 ± 0.68 | 1.38 ± 0.36 $ | 1.11 ± 0.44 $ | 0.33 ± 0.14 # | 2.49 ± 0.49 | 0.65 ± 0.60 | 0.20 ± 0.19 | 1.84 ± 0.60 | 37 ± 17 @ |
| DS post | >26 | 65 | 3.43 ± 0.59 | 1.10 ± 0.43 | 1.11 ± 0.48 | 0.32 ± 0.14 | 2.20 ± 0.42 | 0.50 ± 0.63 | 0.14 ± 0.19 | 1.71 ± 0.68 | 46 ± 17 |
| | ≤26 | 67 | 3.15 ± 0.66 # | 1.22 ± 0.43 | 1.45 ± 0.43 $ | 0.48 ± 0.20 $ | 2.67 ± 0.40 $ | 0.81 ± 0.61 @ | 0.25 ± 0.19 @ | 1.86 ± 0.60 $ | 36 ± 17 $ |
| Abs gain | ≤1.29 | 67 | 3.35 ± 0.59 | 1.30 ± 0.40 | 0.90 ± 0.27 | 0.27 ± 0.10 | 2.20 ± 0.45 | 0.47 ± 0.59 | 0.15 ± 0.19 | 1.73 ± 0.69 | 43 ± 19 |
| | >1.29 | 65 | 3.23 ± 0.68 | 1.00 ± 0.32 | 1.67 ± 0.30 # | 0.54 ± 0.16 $ | 2.68 ± 0.35 # | 0.84 ± 0.63 $ | 0.25 ± 0.19 @ | 1.84 ± 0.54 | 38 ± 16 |
| Rel gain | ≤0.38 | 66 | 3.53 ± 0.56 | 1.37 ± 0.41 | 0.93 ± 0.31 | 0.26 ± 0.07 | 2.30 ± 0.52 | 0.50 ± 0.61 | 0.15 ± 0.18 | 1.80 ± 0.70 | 42 ± 19 |
| | <0.38 | 66 | 3.05 ± 0.63 $ | 0.94 ± 0.24 $ | 1.63 ± 0.34 $ | 0.55 ± 0.15 $ | 2.58 ± 0.36 $ | 0.81 ± 0.63 @ | 0.25 ± 0.19 @ | 1.77 ± 0.58 | 40 ± 16 |
| Lesion | Restenosis | 15 | 3.07 ± 0.68 | 1.17 ± 0.40 | 1.28 ± 0.31 | 0.43 ± 0.21 | 2.45 ± 0.45 | 0.79 ± 0.64 | 0.20 ± 0.20 | 1.65 ± 0.54 | 41 ± 15 |
| | Primary | 117 | 3.32 ± 0.63 | 1.16 ± 0.40 | 1.28 ± 0.48 | 0.40 ± 0.18 | 2.44 ± 0.47 | 0.64 ± 0.64 | 0.20 ± 0.20 | 1.80 ± 0.65 | 41 ± 18 |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Vessel | LAD | 89 | 3.19 ± 0.64 | 1.12 ± 0.37 | 1.29 ± 0.49 | 0.42 ± 0.20 | 2.41 ± 0.46 | 0.75 ± 0.66 | 0.23 ± 0.20 | 1.67 ± 0.63 | 42 ± 18 |
| | Not LAD | 43 | 3.48 ± 0.60 # | 1.23 ± 0.44 | 1.26 ± 0.46 | 0.38 ± 0.16 | 2.49 ± 0.50 | 0.47 ± 0.55 # | 0.14 ± 0.17 # | 2.02 ± 0.61 @ | 38 ± 16 |
| Dev size (Fr) | ≤6 | 111 | 3.22 ± 0.63 | 1.14 ± 0.38 | 1.24 ± 0.48 | 0.40 ± 0.19 | 2.38 ± 0.45 | 0.67 ± 0.63 | 0.21 ± 0.20 | 1.71 ± 0.63 | 42 ± 18 |
| | >6 | 21 | 3.67 ± 0.52 | 1.26 ± 0.44 | 1.47 ± 0.46 # | 0.42 ± 0.17 | 2.75 ± 0.44 @ | 0.56 ± 0.67 | 0.15 ± 0.19 | 2.19 ± 0.56 @ | 37 ± 17 |
| Dev/art | >1.09 | 69 | 2.82 ± 0.40 | 1.03 ± 0.35 | 1.30 ± 0.52 | 0.33 ± 0.12 | 2.34 ± 0.48 | 0.74 ± 0.61 | 0.24 ± 0.20 | 1.60 ± 0.58 | 43 ± 19 |
| | ≤1.09 | 63 | 3.80 ± 0.42 $ | 1.29 ± 0.39 $ | 1.26 ± 0.44 | 0.47 ± 0.21 $ | 2.55 ± 0.43 # | 0.56 ± 0.66 | 0.16 ± 0.18 # | 1.99 ± 0.65 $ | 39 ± 16 |
| Cuts | >5 | 64 | 3.36 ± 0.67 | 1.12 ± 0.36 | 1.29 ± 0.45 | 0.40 ± 0.19 | 2.41 ± 0.47 | 0.63 ± 0.68 | 0.19 ± 0.21 | 1.79 ± 0.67 | 43 ± 17 |
| | ≤5 | 68 | 3.22 ± 0.61 | 1.19 ± 0.42 | 1.28 ± 0.51 | 0.40 ± 0.19 | 2.46 ± 0.47 | 0.68 ± 0.60 | 0.21 ± 0.18 | 1.78 ± 0.61 | 39 ± 18 |
| Histology | Media/adv | 22 | 3.08 ± 0.65 | 1.23 ± 0.48 | 1.19 ± 0.42 | 0.41 ± 0.20 | 2.43 ± 0.42 | 0.71 ± 0.60 | 0.22 ± 0.20 | 1.73 ± 0.73 | 43 ± 21 |
| | intima | 110 | 3.33 ± 0.63 | 1.14 ± 0.38 | 1.30 ± 0.49 | 0.40 ± 0.18 | 2.44 ± 0.48 | 0.65 ± 0.65 | 0.20 ± 0.20 | 1.79 ± 0.62 | 41 ± 17 |
| Age | >58.9 | 66 | 3.27 ± 0.58 | 1.07 ± 0.39 | 1.38 ± 0.45 | 0.43 ± 0.16 | 2.46 ± 0.49 | 0.67 ± 0.55 | 0.21 ± 0.17 | 1.79 ± 0.63 | 41 ± 18 |
| | ≤58.9 | 66 | 3.31 ± 0.70 | 1.24 ± 0.38 # | 1.18 ± 0.48 # | 0.38 ± 0.20 | 2.42 ± 0.44 | 0.64 ± 0.72 | 0.20 ± 0.22 | 1.77 ± 0.66 | 41 ± 17 |
| Gender | Female | 24 | 3.27 ± 0.74 | 1.14 ± 0.39 | 1.31 ± 0.53 | 0.43 ± 0.22 | 2.44 ± 0.49 | 0.65 ± 0.71 | 0.19 ± 0.23 | 1.80 ± 0.68 | 38 ± 20 |
| | Male | 108 | 3.29 ± 0.62 | 1.16 ± 0.40 | 1.28 ± 0.47 | 0.40 ± 0.18 | 2.44 ± 0.49 | 0.66 ± 0.62 | 0.20 ± 0.19 | 1.78 ± 0.64 | 42 ± 17 |
| Angina | Stable | 80 | 3.23 ± 0.63 | 1.14 ± 0.41 | 1.33 ± 0.46 | 0.43 ± 0.18 | 2.46 ± 0.46 | 0.65 ± 0.60 | 0.20 ± 0.18 | 1.82 ± 0.63 | 39 ± 18 |
| | Unstable | 52 | 3.39 ± 0.63 | 1.19 ± 0.39 | 1.21 ± 0.51 | 0.37 ± 0.19 | 2.40 ± 0.46 | 0.67 ± 0.70 | 0.20 ± 0.22 | 1.73 ± 0.66 | 44 ± 18 |
| Center | Rotterdam | 91 | 3.18 ± 0.57 | 1.19 ± 0.39 | 1.24 ± 0.47 | 0.41 ± 0.20 | 2.42 ± 0.52 | 0.71 ± 0.60 | 0.22 ± 0.18 | 1.71 ± 0.55 | 41 ± 17 |
| | Brussels | 41 | 3.52 ± 0.64 # | 1.09 ± 0.40 | 1.37 ± 0.50 | 0.39 ± 0.15 | 2.47 ± 0.45 | 0.53 ± 0.70 | 0.17 ± 0.22 | 1.94 ± 0.79 | 41 ± 17 |

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

*Table 4.* Quantitative comparison of the immediate and long-term results of atherectomy with balloon angioplasty in 79 stenoses.

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

Pre = before intervention, post = after intervention.

follow-up nor with respect to retrieval of subintimal tissue. The presence of subintimal tissue in the excised specimens (media (n = 19) and/or adventitia (n = 3)) was found to be related to the number of atherectomy cuts (5.69 ± 2.96 versus 7.50 ± 2.80; p = 0.04) but not to the other procedural or angiographical variables.

*Comparison between atherectomy and balloon angioplasty* (*Table* 4)

The use of this matching technique resulted in the selection of patients treated by two different interventional techniques with similar clinical and preprocedural stenosis parameters. The reference diameter did not change significantly following either atherectomy or balloon angioplasty (3.26 ± 0.62 mm to 3.29 ± 0.41 mm in the atherectomy group versus 3.23 ± 0.60 mm to 3.23 ± 0.58 mm in the angioplasty group). Atherectomy resulted in a greater increase in minimal luminal diameter than balloon angioplasty with consequently greater "initial gain" (1.27 ± 0.48 mm versus 0.79 ± 0.34 mm; $p < 0.001$) and post-procedural minimal luminal diameter (2.44 ± 0.42 mm versus 2.00 ± 0.36 mm; $p < 0.001$) and concomitantly lower percent diameter stenosis (25 ± 11% versus 37 ± 10%; $p < 0.001$).

Angiographic follow-up studies were performed in 90% of eligible patients in each group. The minimal luminal diameter at follow-up for the atherectomy and angioplasty groups was not significantly different (1.76 ± 0.62 mm versus 1.77 ± 0.59 mm; p = 0.93) nor was the net gain index (0.18 ± 0.19

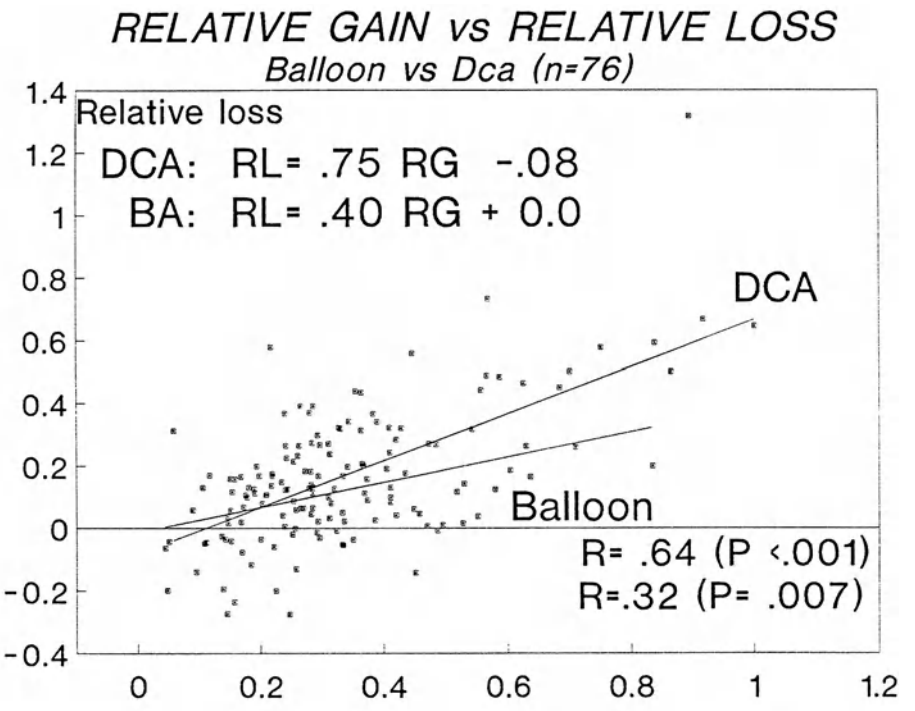


*Figure 2.* Scatter histogram of values obtained for relative gain after atherectomy (DCA) or balloon angioplasty (PTCA) and relative loss during follow-up. A linear relationship emerges for both techniques however a higher coefficient of correlation (r = 0.65 versus 0.26; $p < 0.001$ versus p = 0.007 respectively) and a steeper slope (0.77 versus 0.35; p = 0.07) is found in the atherectomy group.

versus 0.17 ± 0.17; p = 0.70). The relative gain was greater in the atherectomy group compared with the balloon angioplasty group (Fig. 2). A linear relationship exists between the relative gain and relative loss for each treatment group although the coefficient of correlation was superior in the atherectomy group (r = 0.64 versus r = 0.32). Thus, the amount of loss during follow-up is more clearly related to the gain achieved at intervention with respect to atherectomy. Furthermore, the slope of the regression line is steeper in the atherectomy group (0.75) when compared to the balloon angioplasty group (0.46), although this was not statistical significant (p = 0.07) due to a large scatter in the angioplasty group. However, the relationship between relative gain and relative loss suggests that the vessel wall injury as well as the reactive hyperplasia is more intense for the same amount of gain.

*Multivariate analysis of late outcome and renarrowing process*

*A. Clinical approach: correlates of a large minimal luminal diameter at follow-up* (*Table* 3)

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

Multivariate stepwise regression analysis was performed for all clinical, angiographic and procedural parameters significantly associated with the occurrence of a large minimal luminal diameter at follow-up. Of these variables, 1) vessel size, 2) minimal luminal diameter after atherectomy and 3) a lesion located other than in the left anterior descending coronary artery were retained in the model. The multivariate model for the prediction of large minimal luminal diameter at follow-up can be described by the following equation: MLD at follow-up = 0.21 + 0.25 × vessel size + 0.37 MLD post − 0.25 × LAD (where LAD = 1 and non-LAD = 0) (Fig. 3). Of these predictors, vessel size and stenosis location are not controllable by the operator other than by patient selection. Thus, the post-procedural minimal luminal diameter is the only predictor that may be regulated and the clinician may achieve the best final result (large lumen at follow-up) by aiming for a satisfactory procedural result (large post-atherectomy lumen). Such a satisfactory post-atherectomy results was associated with a large luminal gain achieved at atherectomy and by selecting large vessels with a non-severe lesions.

*B. Biological approach: correlates of a large absolute loss during follow-up* (*Table* 3)

Relative gain >0.38, absolute gain >1.29 mm, post-atherectomy minimal luminal diameter >2.42 mm, post-procedural diameter stenosis ≤26%, lesion located in the left anterior descending artery and device/artery ratio >1.09 were univariate predictors of a large absolute luminal loss during follow-up. The stepwise multiple regression analysis showed that relative gain in lumen achieved at atherectomy and pre-procedural minimal luminal diameter were the independent predictors for a large luminal loss during follow-up. The multivariate model for the prediction of late luminal loss can be described by the following equation: absolute loss = −0.59 + 2 × relative gain +0.399 × MLD pre (Fig. 4A). Of these predictors, only the relative gain during intervention can be modified by the operator. Namely, a large relative gain was associated with a large post-procedural minimal luminal diameter, with a severe lesion (small pre-procedural minimal luminal diameter) in a small vessel (small reference diameter). Pre-procedural minimal luminal diameter was to some extent related to vessel size. Therefore, the amount

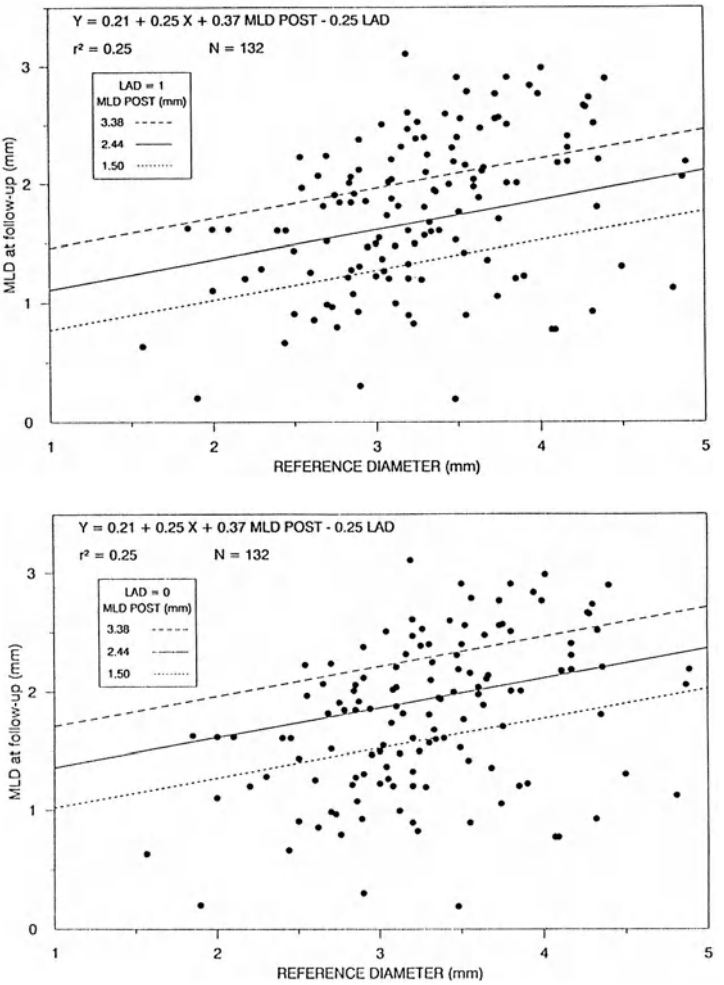


*Figure 3.* a. Plot of the minimal luminal diameter at follow-up versus the best regressor (i.e. reference diameter). The lines are projections of the 3–variates linear regression when treating a lesion located in the LAD when minimal luminal diameter after atherectomy (MLD post) equals 1.50 mm (mean − 2 SD), 2.44 mm (mean) and 3.38 mm (mean + 2 SD) respectively.

The equation with which to describe the model is provided (y = minimal luminal diameter at follow-up; × = reference diameter) MLD = minimal luminal diameter; LAD = left anterior descending artery (0 = yes, 1 = no).

b. Plot of the minimal luminal diameter at follow-up versus the best regressor (i.e. reference diameter). The lines are projections of the 3–variates linear regression when treating a lesion located in a vessel other than the LAD when minimal luminal diameter after atherectomy (MLD post) equals 1.50 mm (mean − 2 SD), 2.44 mm (mean) and 3.38 mm (mean + 2 SD) respectively.

The equation with which to describe the model is provided (y = minimal luminal diameter at follow-up; × = reference diameter) MLD = minimal luminal diameter; LAD = left anterior descending artery (0 = yes, 1 = no).

of absolute luminal loss during follow-up may be influenced by certain procedural factors (i.e. relative gain and MLD post).

Given the fact that nowadays various interventions like stenting, balloon angioplasty and atherectomy are applied in vessels of different sizes with different pre-interventional stenosis characteristics, we performed a stepwise multiple regression analysis in which the normalized luminal loss (relative loss) was the dependent variable. In this analysis relative gain was also found to be the strongest independent predictor of normalized luminal loss during follow-up (Fig. 4B).

*C. The reconciliation of the clinical and biological approach (Fig. 5)*
As appreciated in Figs 3 and 4 a linear relationship exists between absolute gain and absolute loss and between relative gain and relative loss. Although some lesions show further luminal improvement during follow-up (negative absolute/relative values), the observed linear relationships imply that a greater luminal gain achieved at atherectomy is associated with a greater luminal loss during follow-up. On the other hand a satisfactory atherectomy result (large post-atherectomy minimal luminal diameter) is predictive for a better luminal diameter at follow-up. Although these results seem contradictory, a greater gain is not fully offset by a greater loss, indicating that a beneficial longterm angiographic *outcome* (a large minimal luminal diameter at follow-up) will be achieved despite an augmented biological renarrowing *process* (a greater luminal loss).

## Discussion

Late angiographic renarrowing as assessed by coronary angiography remains the major limitation of any coronary intervention. Neither pharmacological [22, 25–27] nor alternative interventional techniques [19, 28–31] have been shown to abate the restenosis rate. The application of quantitative angiography and a regression analysis model in which various variables are combined may provide a useful tool for detecting patients at high risk for restenosis and may have important implications in selecting the appropriate intracoronary interventional technique when treating symptomatic coronary artery disease. Despite such efforts, an accurate prediction of luminal renarrowing after balloon angioplasty has so far not been achieved. Because acute gain and late loss in luminal dimensions after directional atherectomy are in general two-fold larger than after PTCA [7, 9, 17], it was hypothesized that the determinants of relative luminal gain and relative luminal loss might be more accurately identified. Thus, the present study was designed to examine whether the luminal loss and the residual lumen at follow-up can indeed be predicted more accurately by certain clinical, procedural or angiographic variables. To obtain objective, unbiased results, all patients who underwent an atherectomy procedure were scheduled for late follow-up angiography at

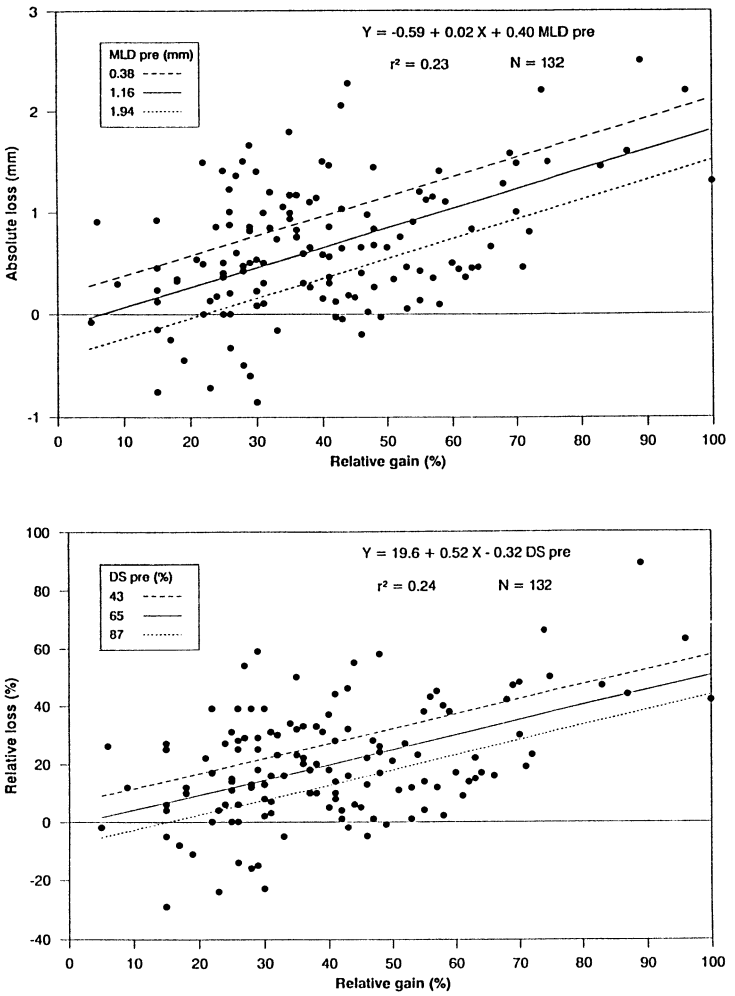


*Figure 4.* a. Scatter histogram of values obtained for relative gain achieved at directional atherectomy and absolute loss during follow-up in 132 procedures. The three lines are projections of the two-variate linear regression when minimal luminal diameter before atherectomy (MLD pre) equals 0.38 mm (mean − 2 SD), 1.16 mm (mean) and 1.94 mm (mean + 2 SD) respectively.

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

six months and a well validated quantitative angiography analysis system (CAAS) was used to objectively assess the immediate and long term angiographic outcome. Our high angiographic follow-up rate of 95% further enhances the validity of our study's conclusions.

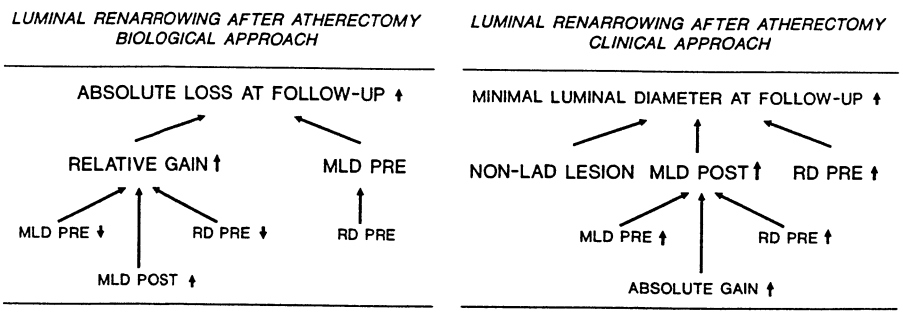


*Figure 5.* A graphical display of the multivariate analyses of the biological and clinical approach of restenosis after directional atherectomy. Absolute loss was independently predicted by (1) a large relative gain achieved at the procedure and (2) a small pre-procedural minimal luminal diameter (MLD pre). A large relative gain was associated with a small pre-pocedural minimal luminal diameter and a small vessel (RD pre) and a large post-procedural minimal luminal diameter (MLD post).

A large minimal luminal diameter at follow-up was determined by a lesion located in another coronary artery than the left anterior descending (LAD), a large post-procedural lumen (MLD post) and a large vessel (RD pre). A large post-procedural lumen was associated with a large pre-procedural lumen, a large luminal gain and a large vessel (RD pre).

↑ indicates large, ↓ indicates small.

## *Pathophysiologic approach*

It has been suggested by Liu et al. [32] that the two major factors that determine the absolute amount of intimal hyperplasia are (1) the regional flow characteristics and (2) the depth of the injury. On one hand, it is conceivable that the flow characteristics may be beneficially influenced in case of atherectomy since the improved hemodynamic behavior of the stenosis may diminish the level of shear wall stress thereby reducing the subsequent intimal thickening [33]. On the other hand, we have to take into account the important observation made by Schwartz et al. [34–36] that a larger injury score was related to a greater neointimal response during follow-up. This extensive proliferative response in his domestic swine stent model was strongly associated with the rupture of the internal elastic lamina induced by oversized overpressurized balloon inflations with or without coil implantation. In order to test this hypothesis in a clinical setting, we have substituted the concept of "injury score" and "neo-intimal hyperplasia" with the angiographically derived parameters of relative gain and relative loss [15–17]. From a biological point of view and considering the major importance of the vessel size in the short and longterm result of intracoronary interventions, we felt justified to *normalize* the gain and loss for vessel size so that the biological relationship between wall injury and the healing response could be more appropriately analyzed. It is crucial to elucidate whether the atherec-

tomy procedure can to some extent escape the implacable consequences of the fundamental biological laws governing the healing response to wall injury. The scientific value of the relationship between relative gain and relative loss lies in the fact that this relationship constitutes a unifying approach which may characterize the intrinsic efficacy of a device independently from the vessel size in which it is operational. Indeed, we found a better correlation between relative gain and relative loss following atherectomy when compared with balloon angioplasty and more importantly, the slope of the regression line was steeper in the atherectomy group than in the angioplasty group which implies that in spite of achieving the same degree of relative luminal gain, the loss is proportionally greater after atherectomy than after angioplasty presumably because the atherectomy procedure induces a vessel wall injury of another nature (excision versus dilatation) so that the reactive response is more pronounced following atherectomy than after angioplasty [17].

*Clinical approach*

Off all directly acquired measurements by quantitative angiography, the absolute value of the minimal luminal diameter has been shown to be the greatest single determinant of the hemodynamic consequences of a stenosis, since this parameter affects blood flow by the fourth power term [37]. Moreover, the minimal luminal diameter at follow-up may have some functional component; we found that a minimal luminal diameter at follow-up of 1.45 mm correlates with the recurrence of angina [38]. Thus, from a clinical point of view, the largest minimal luminal diameter at follow-up is the goal for which to strive while performing intracoronary interventions.

However, a few considerations should be kept in mind while analyzing atherectomy results. Firstly, one should acknowledge that a large post-procedural luminal diameter in absolute values is the net but confounding result of either a large gain in minimal luminal diameter during the procedure (starting with a severe lesion in a small vessel) or the result of a modest gain at atherectomy in a big vessel dealing with a moderately severe lesion. It appears that a large vessel size, a non-severe pre-procedural lesion, a large post-procedural diameter and presumably but not neccessarily a bigger absolute gain at atherectomy are associated with a large minimal luminal diameter at follow-up. Conversely, a large acute gain obtained in a small vessel treating a severe lesions would possibly result in a similar post-procedural minimal luminal diameter value but would be much more traumatizing and would, in our view, infallibly be associated with a poor longterm outcome, i.e. a small minimal luminal diameter at follow-up. We surmise that this general type of response to the atherectomy procedure may be unveiled in the recently completed CAVEAT trial, comparing balloon angioplasty and atherectomy.

*The "restenosis" paradox*

The apparent paradox of greater luminal renarrowing associated with more luminal improvement has now been demonstrated in several clinical studies [16, 39, 40]. The demonstration of a linear relationship between (relative) luminal gain at intervention and (relative) luminal loss during follow-up in this and previous reports [15, 17] together with similar clinical [4, 6–9, 11, 12, 14, 18–20] as well as experimental reports [34–36] collectively support the previous observations that the intensity of neointimal proliferation after an intervention is dependant on the depth of the vessel wall injury.

The observations made by Kuntz et al. [9] that achieving greater luminal gain with newer devices may reduce angiographic restenosis is not completely in parallel with the above mentioned findings. While our group are focusing in clinical studies mainly on the degree of renarrowing as a measure of the extent of the *biological process* i.e. the development of intimal hyperplasia, others focus on the *angiographic outcome* i.e. final minimal luminal diameter [9]. This is the difference, as has been expressed by Schwartz et al. [35] between the "doughnut and the doughnut hole". There is little doubt that a larger lumen at follow-up may be clinically "better" for the patient and this parameter is of great importance in assessing the long-term *outcome* of therapy. However, in large clinical trials directed at the prevention of renarrowing, the effect of therapy must be measured by its restricting effect on the thickness of the "doughnut", which we believe is best encapsulated angiographically by the relative luminal loss during follow-up. As described in the present report, we believe that application of both approaches (clinical outcome and biological process) to the same population yield similar findings and the apparently diverse conclusions arise not from differences in therapeutic results but from differences in focus and approach. Some preliminary studies have emphazised the influence of vessel size [13, 14] or vessel selection [41] on luminal renarrowing. In the present study, vessel size was an independent predictor of clinical *outcome*: a large minimal luminal diameter is seen in larger vessels. Also, the best procedural result (high post-atherectomy minimal luminal diameter) was achieved in large vessels. Thus the clinician may achieve the best final *outcome* (large lumen at follow-up) by aiming for an optimal procedural result (large post-procedural lumen) particularly in large vessels. On the contrary, a large (relative) luminal loss is observed in small vessels in which a large relative gain is seen. This indicates that the biological *process* (luminal loss during follow-up) is augmented when a severe lesion in a small vessel is treated by atherectomy. Therefore, it becomes apparent that atherectomy should not performed in small vessels because these vessels are subjected to greater vessel wall trauma (high relative gain) with a subsequent exaggerated healing process (high relative loss). Compared to previously published data on luminal gain and loss after atherectomy, the acute luminal gain in this patient cohort *seems* low [9, 14]. However, these differences are secondary to the applied method of analysis.

Specifically, it has been observed that measurements obtained by visual assessment tend to overestimate the severity of tight stenoses and underestimate the degree of milder ones [42–44]. In validation studies using well-known true phantom diameters, quantitative analysis has been shown to overestimate the small phantom diameters (pre-procedural minimal luminal diameter) and underestimate the large phantom diameters (post-procedural minimal luminal diameter) [45]. Therefore, visual or caliper measurements will yield higher values for luminal gain achieved at intervention when compared with quantitatively assessed measurements. Furthermore, a discrepancy between reference diameters will arise when comparing reports in which the average of the diameter of the vessel proximal and distal to the stenosis are used as the reference [9]. In order to avoid the bias introduced by the arbitrary selection of the user defined reference in the proximal and/or distal segment of the stenosis, we have implemented many years ago an *interpolated* technique, which is not user defined, to determine the reference diameter at the actual stenosis site [8, 16–21]. In the present study, no *clinical and procedural parameters* were found to be independent predictors for restenosis. In two recent multicenter restenosis trials [21, 27] diabetes was the only patient related variable found to be independently related to the amount of renarrowing at follow-up. In our study, less than 10 patients with diabetes or hypercholesterolemia underwent atherectomy. Therefore, the predictive value of this variable cannot be evaluated in this study. Using univariate analysis, the device/artery ratio was found to be correlated with luminal loss however, this was not retained in the multivariate analysis. This observation underscores the neccessity to strive for an optimal selection of the atherotome. In fact it is our clinical practice to perform on-line quantitative coronary artery measurements before, during and after the procedure. With the clinical implementation of quantitative angiography, proper device selection (device/artery ratio 1.0–1.1) can be performed and the final result can be guided by these on-line measurements.

Although patients with stable angina had a larger minimal luminal diameter at follow-up when compared with unstable patients, it did not reach the level of statistical significance and was not retained in the multivariate models. Similarly, patients who underwent balloon angioplasty for unstable angina had no higher risk for restenosis although duration of angina $<2.3$ months was an independent predictor for restenosis [39]. Also, the presence of angiographically visible thrombus after angioplasty has been retained in a multivariate analysis model as a predictor for restenosis [40]. Whether unstable angina itself, recent onset angina or rheological factors predispose to a higher degree of intimal hyperplasia has not been clearly established yet. Analysis of the CAVEAT trial data may yield further information since the subgroup of unstable angina patients is well classified and divided into three categories: recent onset angina, post-infarction angina and angina at rest.

Whether subintimal tissue retrieval leads to an increased incidence in

restenosis remains an unresolved issue with conflicting reports in the literature [46, 47]. In this observational study, medial or adventitial tissue retrieval was not an independent variable related to more extensive luminal narrowing although the frequency of retrieval of media and adventitia was only 20% compared with greater than 50% in other studies [2, 47].

### *Matching: comparing the comparable*

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

### *Clinical implications*

In analyzing the long-term results of new interventional techniques, such as directional atherectomy, the biological *process* (luminal loss during follow-up) – characterized by the vessel wall healing response – should be dissociated from the clinical *outcome* (minimal luminal diameter at follow-up) which provides no information regarding this process but conveys some index of the clinical *outcome* in the longterm.

It is clear that whereas improved clinical outcome is associated with larger vessel size and post-procedural luminal diameter, greater relative gain at intervention is strongly predictive of more extensive luminal renarrowing. This study shows that atherectomy should not be performed in small vessels, apparently because the augmented biological process is due to the greater relative gain achieved in these vessels. In matched populations, atherectomy induces a greater initial gain in minimal luminal diameter than balloon angioplasty however, the vascular wall injury induced by the device is of another nature (debulking versus dilating) which led to more relative loss over the follow-up period in the atherectomy group.

*Limitations*

Several limitations of this study are to be acknowledged. First, it is an uncontrolled, observational study limited to a subset of patients with a successful coronary atherectomy. Second, although angiography may detect luminal changes after intervention, it may not be the most reliable method to analyze the (biological) process taking place in the vessel wall itself. Because intravascular ultrasound provides an in vivo assessment of morphological changes in the vessel wall, this technique may provide more precise information, although reliable quantitative measures cannot yet be routinely obtained.

Three, it could be claimed that an acute gain of 1.28 mm represents a cautious approach to atherectomy leading to a modest angiographic result. However, the post-procedural luminal diameter in this series is comparable with other groups [48, 49] although smaller than in the series of Kuntz et al. [7]. This observation does not influence the conclusions of the present study because the linear relationship between (relative) gain and (relative) loss implies that a larger luminal gain is met by a larger loss, which is more evident in smaller vessels inwhich larger relative gains are tend to be obtained. Four, in performing multiple statistical comparisons, there is risk that some of them may reach significance by chance alone. Five, evidence obtained by animal studies suggest a direct relationship between vessel wall injury and reactive intimal hyperplasia. Although the concept of angiographic correlates for these parameters, relative gain and relative loss respectively, supports this hypothesis, further study is needed to refine this concept. Although the occurrence of elastic recoil was not studied presently, previous reports demonstrated a minimal, if any, elastic recoil after coronary atherectomy [6, 50]. Finally, although univariate and multivariate analysis identified some risk factors for restenosis, the predictive value of any of these variables may be poor and its use in selecting patients suitable for directional coronary atherectomy may be limited. The findings of this study, therefore, should be confirmed by larger, randomized trials.

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# 29. Rotational atherectomy

EUGÈNE P. McFADDEN, CHRISTOPHE BAUTERS, PHILIPPE QUANDALLE, MICHEL E. BERTRAND and JEAN-MARC LABLANCHE

## Introduction

Percutaneous transluminal coronary balloon angioplasty is now widely used as a treatment for obstructive atherosclerotic coronary disease. Soon after the initial description of the technique, it became apparent that lesions treated by coronary angioplasty often recurred [1, 2]. In our institution, where follow-up angiography at 6 months is recommended to all patients with an initially successful procedure, angiographic restenosis after balloon angioplasty, defined as a recurrent stenosis of more than 50% at the dilated site measured by quantitative coronary angiography, occurs in 42.6% of patients [3]. The other major limitation of balloon angioplasty is related to the inability to obtain a satisfactory primary result at certain types of lesion. While proximally located, concentric, non-calcified stenoses are ideal candidates for balloon dilatation which usually produces an initially satisfactory angiographic result, the immediate results after balloon dilatation of other types of lesion, such as those that are heavily calcified, long, or located distally, are often less satisfactory.

In response to these limitations, several alternative techniques of recanalisation have been developed. One such technique, coronary atherectomy, has been developed to produce an improvement in lumen diameter by direct mechanical removal of atherosclerotic material from the vessel wall. Several techniques for this purpose have been described including directional atherectomy [4)] transluminal extraction atherectomy [5], and high speed rotational coronary atherectomy [6, 7]. In this chapter we discuss the role of quantitative coronary angiography in the assessment of the results obtained using high speed rotational atherectomy with Rotablator.

## Design of the Rotablator

The Rotablator™ (Heart Technology, Inc, Bellevue, Washington, USA) consists of an abrasive tip (Fig. 1) welded to a long flexible drive shaft



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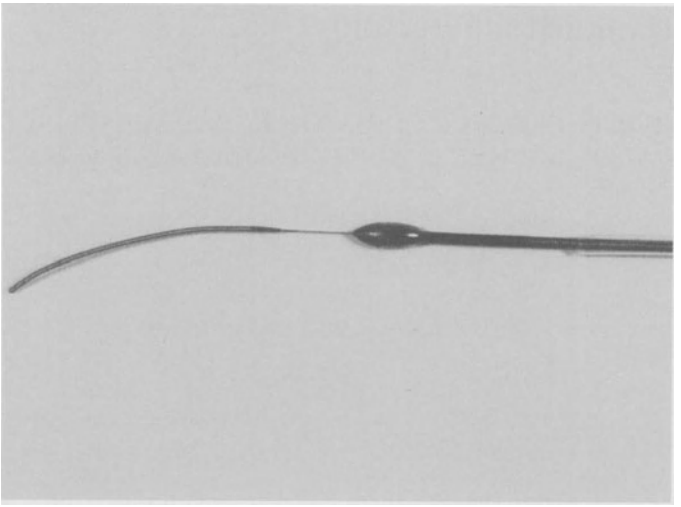

*Figure 1.* The abrasive tip of the Rotablator.

tracking along a central flexible guide wire. The abrasive tip is an elliptically shaped burr, available in various sizes (1.0, 1.25, 1.5, 1.75, 2.0, 2.15, 2.25, and 2.5 mm in diameter) whose distal portion is coated with diamond chips 30 to 50 microns in diameter. Rotational energy is transmitted by a disposable compressed air motor which drives the flexible helical shaft at speeds up to 190,000 revolutions per minute.

The number of revolutions per minute is measured by a fibreoptic light probe and displayed on a control panel. The speed of rotation is controlled by the air pressure, which is in turn controlled by the operator using a foot pedal. During rotation a small volume of sterile saline solution irrigates the catheter sheath to lubricate and cool the rotating parts. The burr and the drive shaft move freely over a central coaxial guide wire (0.009 inches in diameter), with a flexible radioopaque platinum distal part (20 mm long), which does not rotate with the burr during abrasion. The wire and the abrasive tip can be advanced independently, which allows the wire to be placed in a safe distal location before the burr is advanced into the diseased artery.

## Technique of rotational atherectomy

All patients are pretreated with aspirin and a calcium antagonist. A sheath is inserted into the femoral artery under local anaesthesia and a standard 9F (for a 2 mm burr) guiding catheter advanced to the ostium of the coronary artery. Following the intracoronary injection of isosorbide dinitrate (0.5 to 1 mg) a baseline angiogram is performed in three projections, and heparin (10,000 IU) is given intravenously.

Rotary ablation begins with the placement of the small guide wire across the lesion to a safe distal vessel location. The burr and the drive shaft are then manually advanced over the guide wire to the site of the lesion, and rotation is begun. When an adequate speed of rotation (175,000 revolutions per minute) has been achieved the abrasive tip is advanced gently over the guide wire. If resistance is encountered the tip is moved backwards and forwards to maintain a high speed of rotation. Several slow passes are usually required to achieve maximum plaque removal. Typical results of the procedure are shown in Fig. 2.

**Rotary ablation experience: The international registry**

The results obtained in 14 centres (4 in Europe and 10 in the United States) have been entered into an International Registry. As of January 1993, data was available for rotational atherectomy procedures on 2488 lesions in 2018 patients. The mean age of the patients, 72% of whom were men, was 62.6 years. Forty six percent of the patients had stable angina; 41% had unstable angina and 13% were asymptomatic. Eighteen percent of patients had previously undergone coronary artery bypass surgery, 41% had prior myocardial infarction, and 29% had previously undergone PTCA. Most (64.8%) had multiple vessel disease. Rotational atherectomy was most commonly performed on the left anterior descending coronary artery (48% of lesions), less frequently on the right (29%) or circumflex (19%) coronary arteries. A protected left mainstem lesion was treated in 3% of patients. Most of the lesions had complex characteristics. Sixty five percent were eccentric, 26% were located at bifurcations, 54% were longer than 10 mm, and 46% had at least moderate calcification. Primary success was defined as a reduction in stenosis severity by at least 20% with a residual stenosis of less than 50% in the absence of major complications (acute myocardial infarction, coronary artery bypass surgery, or in-hospital death). The primary success rate achieved with use of rotational atherectomy alone was 30%. When the residual stenosis was more than 50%, the procedure was completed by adjunctive balloon angioplasty or less frequently with another technique, yielding a final procedural success rate of 95%. Interestingly, the primary success rate was independent of lesion length. Myocardial infarction occurred in 6.4% of patients, q-wave in 5.4% and non q-wave in 1%. Emergency coronary artery bypass surgery was undertaken in 2.2% of patients. Death occurred in 0.9% of patients. The complication rate was related to the characteristics of the lesions treated. The complication rate for Type A lesions was 1.3%, for Type B lesions 3.9%, and for Type C lesions 6.2%.

The location of the treated lesions did not have a significant effect on primary success rates. The success rates at lesions that were heavily calcified, and at long lesions were similar to the results obtained at other types of lesion. The overall restenosis rate in the 825 patients who underwent angio-

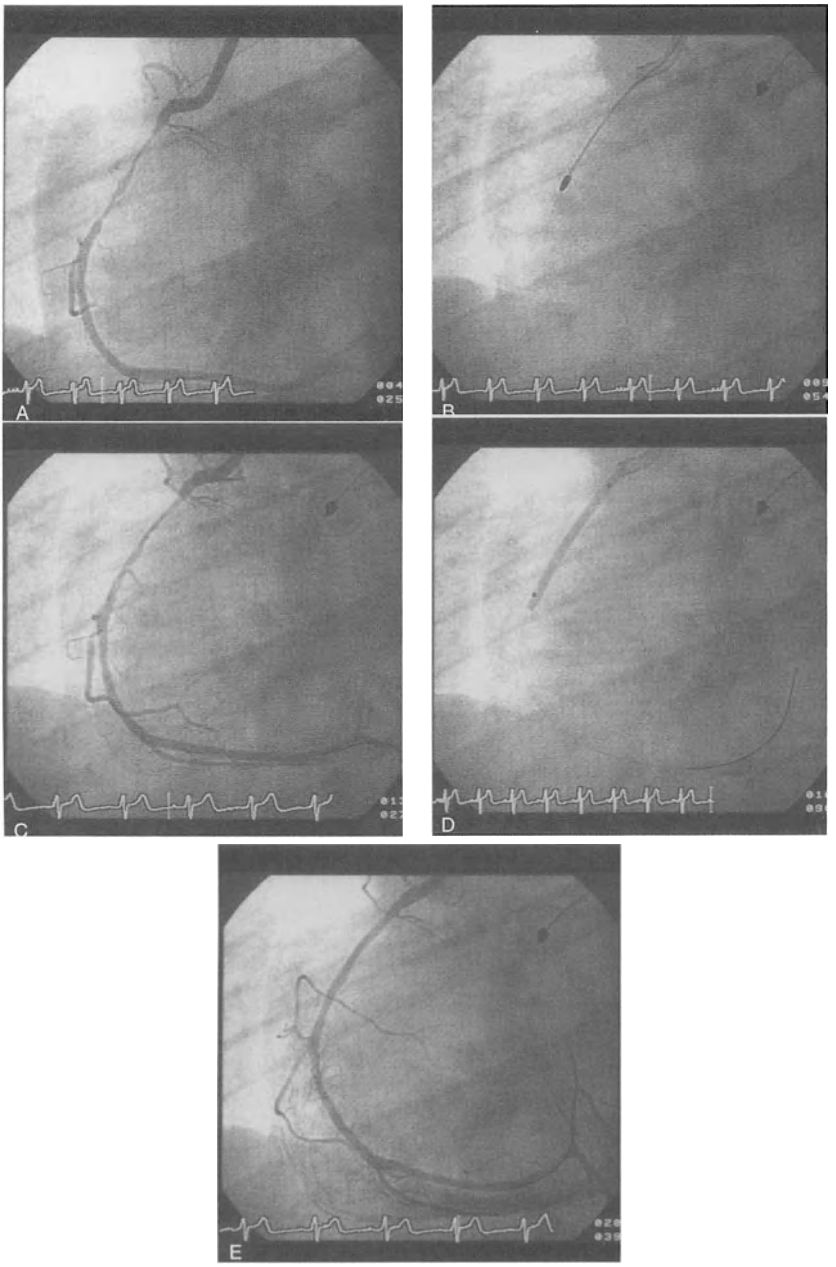


*Figure 2.* Before rotational atherectomy (Panel A) there is a long calcified lesion of the right coronary artery. The lesion was treated initially (Panel B) by rotational atherectomy. After rotary ablation alone (Panel C) there is a residual significant ( > 50%) stenosis. An adjunctive balloon angioplasty with a long balloon (Panel D) results in a satisfactory final result (Panel E).

graphic follow-up was 48%. In the patients who were treated by rotational atherectomy alone the restenosis rate was 42% compared to 54% in patients who had undergone adjunctive balloon angioplasty.

**Insights into restenosis: Contribution of quantitative coronary angiography**

For an individual patient, the aim of an angioplasty procedure is to improve symptoms and/or to improve objective evidence of myocardial ischaemia without major complications. For a variety of reasons some of which are incompletely understood, symptomatic status after angioplasty or changes in the threshold for ischaemia as assessed by exercise testing, are not directly correlated with the longterm angiographic results of the procedure, assessed by quantitative coronary angiography. The recurrence of symptoms, or the persistence of positive results on exercise testing may occur in the documented absence of angiographic restenosis.

The use of quantitative coronary angiography has provided invaluable insights into the mechanisms of coronary balloon angioplasty. The immediate objective of balloon angioplasty is to dilate a stenotic segment that is considered to be responsible for producing symptoms and/or objective signs of myocardial ischaemia. The minimal lumen diameter, immediately after the procedure should be large enough to abolish any impairment of coronary flow reserve related to epicardial narrowing at the site of the dilated lesion. The ultimate aim of the procedure is to maintain this improvement in the longterm. The elegant serial quantitative angiographic studies from the laboratory of Professor Serruys have demonstrated that if restenosis occurs, it will occur predominantly during the first 3 months after the procedure [8]. Thus, the angiographic results of the procedure at 6 months are the "gold-standard", that must be used if valid comparisons between the results of coronary balloon angioplasty and newer techniques such as rotational atherectomy are to be performed.

The use of quantitative measurements have also emphasised the inaccuracy of visual estimation of the immediate results of coronary angioplasty. There is usually a residual narrowing after angioplasty. The extent of this residual stenosis is generally underestimated by the physician who performs the procedure.

We recently compared visual estimates of residual stenosis after successful balloon angioplasty with quantitative angiographic measurements [9]. The visual estimates were prospectively recorded by the operator immediately after the angioplasty procedures which were performed on patients enrolled in a multicentre European trial on the prevention of restenosis with ticlodipine. The quantitative angiographic measurements were performed at our institution which was the core angiographic laboratory for the trial. The visually estimated mean residual stenosis after angioplasty (18.8 ± 12.3%) was significantly less than the equivalent value (37.4 ± 14%) obtained with

use of quantitative coronary arteriography. The mean residual stenosis in our laboratory after routine balloon angioplasty assessed by quantitative coronary angiography is similar.

The residual stenosis after angioplasty reflects elastic recoil that occurs immediately after balloon deflation. This extent of this "immediate elastic recoil" can be quantified by measuring the difference between the diameter of the inflated balloon during angioplasty and the minimal lumen diameter immediately after the procedure. It was hoped that the different mechanism of action of atherectomy devices that physically remove atheromatous material might yield a somewhat better immediate angiographic result. Ideally, the minimal lumen diameter immediately after a rotational atherectomy procedure should be equal to the diameter of the burr used.

**Immediate results of rotational atherectomy: Quantitative assessment**

We investigated the relationship between the diameter of the burr employed and the minimal lumen diameter immediately after the procedure in consecutive patients who were undergoing rotational atherectomy [10]. The measurements were performed on angiograms obtained under the same conditions immediately before and just after the procedure. Because vasospasm was frequently observed during our initial experience with rotational atherectomy the measurements were made on angiograms obtained after the intracoronary injection of isosorbide dinitrate. The coronary arteriograms were analysed with use of the CAESAR sysyem (Computerised Assisted Evaluation of Stenosis And Restenosis). The validation of this system together with the accuracy and reproducibility of measurements obtained under routine clinical conditions have been previously described in detail [11].

The minimal lumen diameter after rotational atherectomy as a function of the size of the burr used is presented in Fig. 3. It is obvious that the absolute minimal diameter of the residual lumen is significantly less than the diameter of the burr employed. The mean minimal lumen diameter after the procedure was 70% of the diameter of the burr used. The mean percentage residual stenosis after rotational atherectomy cannot be directly compared with that achieved by balloon angioplasty because the maximal burr size that can be used in the coronary circulation is only 2.5 mm. However the above results show that the phenomenon of immediate elastic recoil is similar to that documented after traditional balloon angioplasty. A possible explanation for this is suggested by observations in animal models, where it has been shown that the Rotablator preferentially removes calcified or atheromatous material while the "normal" more elastic portion of the arterial wall tends to be deflected away from the burr during rotation [12]. Intravascular ultrasound techniques have shown that most atheromatous lesions do not completely

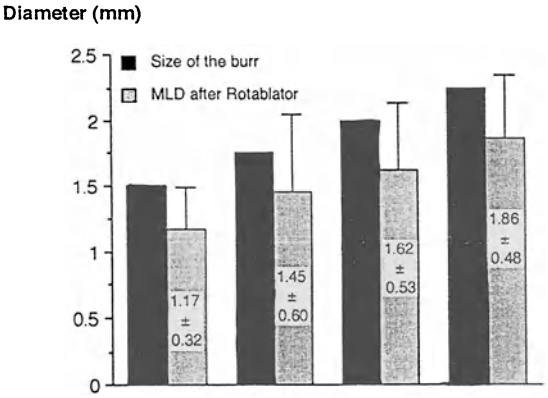


*Figure 3.* The relationship between the size of the burr employed and the minimal lumen diameter at the dilated site immediately after the procedure. The mean minimal lumen diameter after rotational atherectomy was 70% that of the burr used.

encircle the lumen of the coronary artery, although this is not always appreciated on arteriographic images.

Furthermore, it cannot be concluded that the acute gain in luminal diameter seen after rotational atherectomy is solely due to its unique mechanism of action, namely the ability to remove atheroma by grinding it into millions of tiny particles. It seems likely that a "Dottering effect" produced by the burr itself may also contribute. This mechanism has been shown to contribute to the acute gain in lumen diameter produced by directional atherectomy where the volume of tissue removed is on average insufficient to account for the improvement in luminal diameter that is observed [13].

The observation that the luminal diameter immediately after rotational atherectomy is less than the size of the burr employed is consistent with the findings of most other investigators. A recent article has however suggested that the converse is true. In a series of patients studied with intravascular ultrasound immediately after rotational atherectomy, the cross-sectional area of the lumen was significantly greater than that of the largest burr employed. However, in this study there was no consistent relationship between the intravascular ultrasound measurements of lumen diameter and the equivalent values obtained by angiography [14].

## Burr to reference diameter ratio: Implications for procedural and clinical outcome

We also examined whether the ratio between the diameter of the burr and that of the adjacent reference diameter was related to the occurrence of complications during rotational atherectomy. In 110 consecutive patients, the rate of immediate angiographic complications (occlusion, spasm, dissection)

when the burr to reference diameter ratio was <0.8 was 22% compared to 41% when the ratio was >0.8. For clinical complications, a similar pattern was observed. When the burr to reference diameter ratio was <0.8 the rate of clinical complications was 7.4% compared to 10.7% when the ratio was >0.8.

Based on these two observations, namely that the mean minimal lumen diameter to burr ratio is 0.7 after rotational atherectomy and that the incidence of complications is significantly higher when the burr to reference diameter ratio is >0.8, the mean ratio of minimal lumen diameter to burr size after uncomplicated atherectomy would be 0.56. This corresponds to a residual 44% stenosis after uncomplicated rotational atherectomy.

In the absence of any documented benefit of rotational atherectomy on the occurrence of restenosis, the major advantage of this technique lies in it's ability to tackle lesions with characteristics unsuited to balloon angioplasty. Our results suggest that a burr-balloon strategy may be the safest approach. This consists of the initial use of a deliberately undersized burr to "debulk" the lesion with adjunctive balloon angioplasty, if required, to achieve an angiographically satisfactory result.

### Quantitative angiography 24 hours after rotational atherectomy

It has been suggested that a "delayed" elastic recoil phenomenon may account for some cases of early "restenosis" after conventional balloon angioplasty. However, a study in which angiography was performed in patients 24 hr after balloon angioplasty suggested that clinically significant changes in minimal lumen diameter do not occur over this period [15]. We have recently had the opportunity to study this phenomenon in patients who were enrolled in a multicentre European trial designed to examine the effect of fraxiparine, a low molecular weight heparin, on the occurrence of restenosis after balloon angioplasty. In this study angiography is performed by protocol 24 hr after initially successful procedures. In the first 123 patients who underwent 24 hour angiography, there was no significant change in mean proximal or distal reference diameters or in mean minimal lumen diameter at 24 hr. However, the subgroup of patients who had eccentric stenoses (defined as a stenosis where the lumen appeared to lie in the outer quarter of the adjacent normal lumen in at least one projection) did have a significant decrease in minimal lumen diameter at 24 hr [16].

We studied early changes in minimal lumen diameter after rotational atherectomy alone in a group of 19 patients [17]. The patients were restudied the morning after the procedure. The angiograms were obtained after the intracoronary injection of isosorbide dinitrate. There was no significant difference between the mean minimal lumen diameter immediately after the procedure and that at 24 hr. Cumulative percent diameter stenosis curves for the patients we studied are presented in Fig. 4. These results suggest that "de-

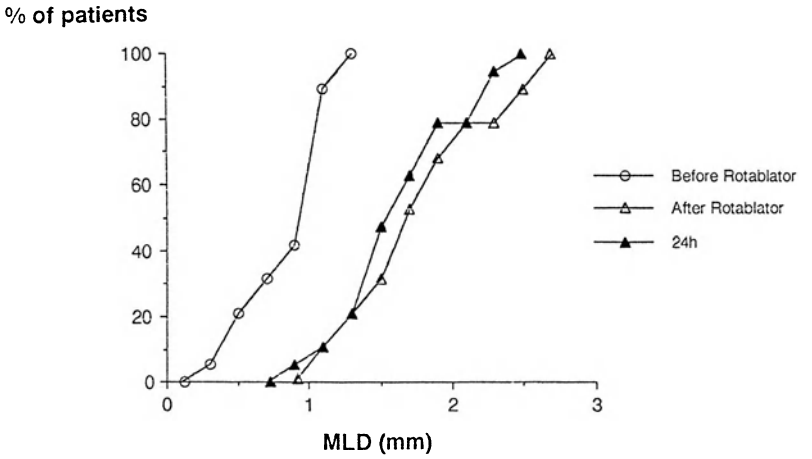


*Figure 4.* Cumulative percent diameter stenosis curves for patients who underwent rotational atherectomy alone before, immediately after, and at 24 hr after the procedure. There was no significant change in mean percent diameter stenosis in the first 24 hr.

layed" elastic recoil does not occur to a significant degree after rotational atherectomy. These results are somewhat different from those obtained by Reisman et al. who performed a similar study. The found that the mean minimal lumen diameter at 24 hr was significantly greater than immediately after the procedure [18]. It is not clear whether in this study, intracoronary nitrates were systematically administered before angiography. In our experience, much greater amounts of intracoronary nitrates are required during rotational atherectomy than during conventional balloon angioplasty to counteract the diffuse predominantly distal spasm that frequently occurs during the procedure. It is possible therefore that the improvement in luminal diameter reported by Reisman et al. at 24 hr which was greater (21%) in the group treated by rotational atherectomy alone than in the group that had adjunctive balloon angioplasty (14%) may be related to changes in vasomotor tone at the dilated site.

## Angiographic restenosis after rotational atherectomy

No randomised controlled trial has directly compared the restenosis rate after rotational atherectomy alone with the restenosis rate after conventional balloon angioplasty. One inherent difficulty in the design of such a study would be the necessity to include only lesions in arteries which could be treated by both devices as the largest burr size that can be introduced into the coronary circulation is 2.75 mm.

We compared the angiographic rate of restenosis in patients who under-

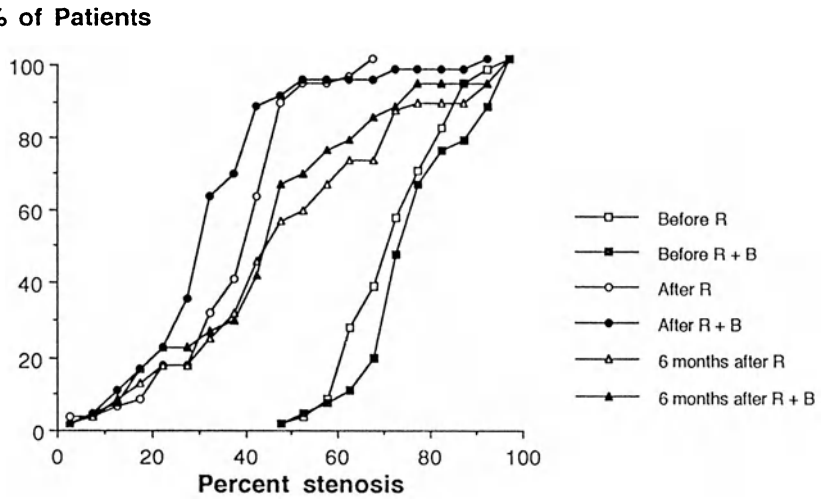


*Figure 5.* Cumulative percent diameter stenosis curves for patients treated with rotational atherectomy alone (R) or with adjunctive balloon angioplasty (R + B). The mean percent stenosis severity is similar in the two groups before dilatation. The mean percent residual stenosis after rotational atherectomy alone is greater than that after rotational atherectomy with adjunctive balloon angioplasty. However, at follow-up the two curves are almost superimposed demonstrating that the group with adjunctive balloon angioplasty had a greater relative loss between dilatation and follow-up angiography.

went rotational atherectomy alone with that in patients treated during the same time period who underwent rotational atherectomy completed by adjunctive balloon angioplasty. The patient population consists of patients who underwent rotational atherectomy during our early experience in Lille and who underwent angiographic follow-up. We identified 82 such patients; 45 (55%) of them were treated by rotational atherectomy alone, while the remaining 37 (45%) had an adjunctive balloon angioplasty because the residual stenosis after rotational atherectomy alone was >50%. Follow-up angiography was undertaken at a mean of 4.6, range 3 to 6, months after the procedure. The mean stenosis severity before the procedure was 73.7 ± 11.3% in the group treated by rotational atherectomy alone and 77.4 ± 11.4% in the group treated by rotational atherectomy with adjunctive balloon angioplasty. After the procedure the mean residual stenosis was 42.0 ± 19.2% in the group treated by rotational atherectomy alone and 36.0 ± 17% in the group treated by rotational atherectomy with adjunctive balloon angioplasty. At follow-up angiography, 44.2% of patients treated with rotational atherectomy alone had developed restenosis compared with 41.2% of those who had adjunctive balloon angioplasty. Curves showing the cumulative distribution of percent stenosis severity in the group treated by rotational atherectony alone and the group treated with adjunctive balloon angioplasty are presented in Fig. 5. The mean percent severity of the lesions

before dilatation was similar in both groups just before the procedure. The relative gain in percent lumen diameter that was achieved with rotablation alone was significantly less than that achieved with adjunctive balloon angioplasty. However, at follow-up angiography the distribution curves for the two groups are again superimposed. Thus the relative loss in diameter between dilatation and follow-up appears to be related more to the acute gain achieved by the procedure than to the method by which this was achieved.

In summary, the plethora of new devices that have been introduced to overcome the shortcomings of traditional balloon angioplasty do not appear to have any significant impact on the problem of restenosis. The injury produced by the process of dilatation, regardless of how the injury is inflicted, provides the stimulus that leads to restenosis. The degree of injury appears to be much more important than the specific technique employed. By contrast, new techniques may in specific situations, often with adjunctive balloon angioplasty, produce an adequate primary result where experience with balloon angioplasty alone has been disappointing. Rotational atherectomy, with its unique mechanism of action, appears to fulfil this role for some such lesions. Our experience suggests that in general rotational atherectomy should be used as a tool to predilate the lesion thus enabling an angiographically satisfactory result to be obtained by subsequent balloon angioplasty.

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# 30. Critical appraisal of quantitative coronary angiography and endoluminal stent implantation

PETER P. DE JAEGERE, BRADLEY H. STRAUSS, MARIE-ANGÈLE MOREL, PIM J. DE FEYTER and PATRICK W. SERRUYS

## Introduction

Quantitative Coronary Angiography (QCA) [1–12], has become the gold standard in the assessment of the immediate and long-term results of various coronary interventions, both pharmacological and mechanical. In particular, the incidence of restenosis or late luminal renarrowing after coronary intervention have become an important field of investigation [5]. With the advent of novel therapeutic interventional techniques such as intracoronary stenting, several new and unforeseen problems have emerged. In some circumstances, the principles of QCA had to be adapted to more complicated and complex situations related either to the device itself or to the effect of the intervention on the angiographic appearance of the treated artery. This chapter will focus on specific aspects of QCA and stent implantation.

## QCA and intracoronary stenting

Four types of intracoronary stents are currently used in the Thoraxcenter (Table 1). Three of these stents, the Wallstent, Palmaz-Schatz stent and the Gianturco-Roubin stent are composed of radioluscent stainless steel, whereas the Wiktor stent is radiopaque. The radiopacity of the Wiktor stent is explained by its chemical composition (tantalum) and its greater wire cross sectional area in comparison with the other stents. Tantalum has a higher atomic number than the elements contained in the stainless steel stents. Consequently, the larger electronic cloud surrounding the nucleus absorbs more X-ray energy. This in combination with the greater wire cross-sectional area result in a higher radiopacity (Fig. 1).

### *QCA and stainless steel stents*

Although it has been postulated that the ideal stent should be, among other factors, radiopaque, poor angiographic visibility does not have to hamper



*P.W. Serruys, D.P. Foley and P.J. de Feyter (eds.), Quantitative Coronary Angiography in Clinical Practice*, 573–590.

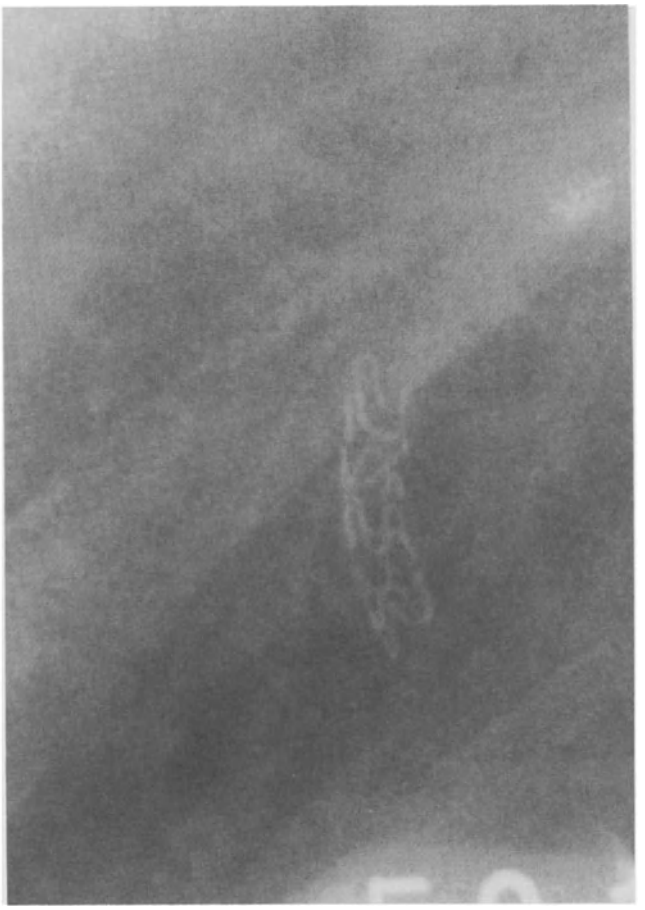

*Figure 1.* The Wiktor stent is entirely composed of tantalum which explains its radiopaque features on fluoroscopy.

*Table 1.* Intracoronary stents used in the Thoraxcenter.

| Stent | Date | Indication |
|---|---|---|
| Wallstent | Sept. '86 | venous bypass grafts |
| Wiktor stent | Jan. '90 | restenosis/bail-out |
| Palmaz-Schatz | Sept. '90 | Benestent Study/bail-out |
| Gianturco-Roubin | Nov. '92 | bail-out |

exact stent positioning. However, for the analyst, the lack of radiopacity means that the stent boundaries may be uncertain which may render the analysis of the immediate changes in stenosis geometry at the stented segment difficult that the precise location of late restenosis (within the stent or imme-

diately adjacent) may be in doubt. Nevertheless, in most instances one may discern the position of the stent by carefully reviewing the angiogram without contrast injection. Furthermore, in all our follow-up reports of stenting, we have included restenosis within and immediately adjacent to the stented segment to ensure restenosis is not underreported due to this problem [13, 14].

A second problem with angiographic analysis of stented vessels is due to the superior results immediately post stenting versus PTCA alone. One could focus on the changes in stenosis geometry at the stented segment itself or one could be interested in the overall changes in stenosis geometry of the treated coronary artery. This implies that, in the first situation, the analyst has to interfere with the automated edge detection program in order to let coincide the boundaries of the segment to be analyzed with the boundaries of the stent itself. This, we call a "stent analysis". In the second situation, there is no need for interaction with the choice of computer detected contours. The anatomical landmarks such as vessel branches are used to define the boundaries of the segment to be analyzed and is called "vessel analysis". The use of one or the other significantly influences the results of quantitative coronary angiography. For instance, in case of complete correction or even overdilation of the obstruction segment, a negative value for diameter stenosis may be found when using the "vessel analysis" method. This is explained by the fact that the minimal luminal diameter (defined within the boundaries) is actually larger than the reference diameter which is determined according to the diameter of the proximal and distal segments (Fig.2 ). In other circumstances, one may also find that the minimal luminal diameter is located outside the stent. This results in a so-called "unmasking of a lesion" (Fig. 3). In reporting our angiographic studies, we chose the pre and post PTCA frames to be analyzed by vessel, and the post stent and follow-up films according to the stent. This ensures that we obtain information related to the stent and its immediate adjacent segment rather than describing a more severe stenosis somewhere else in the coronary vessel.

The minimal luminal diameter is now widely accepted as ultimate angiographic end point of studies analyzing the immediate and long-term effects of therapeutic interventions [15, 16]. However, we have learned that the assessment of this parameter does not reflect all changes in stenosis geometry of the stented coronary artery segment. While there is still some gap between the minimal luminal diameter and the reference diameter, the mean diameter of the stented segment closely approaches the reference diameter of the treated vessel (Fig. 4 A & B).

### *QCA and radiopaque stents*

It goes without saying that the radiopacity of the Wiktor stent facilitates exact stent positioning. Furthermore, dislodgement of the stent from the balloon during implantation may easily be recognized, promoting its safety.

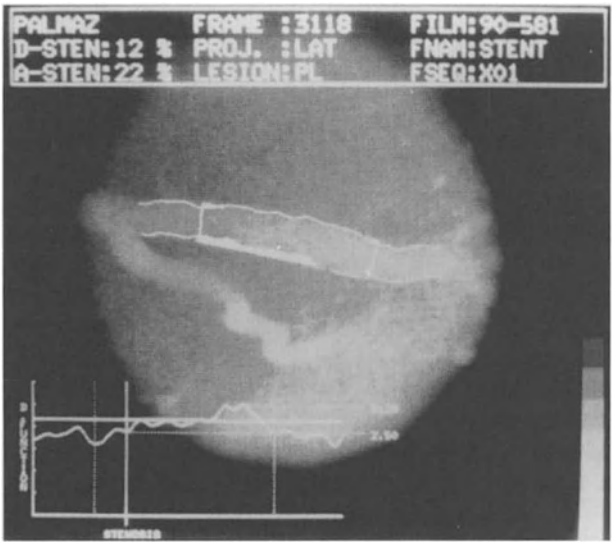


*Figure 2.* Overdilatation of the coronary segment after stent implantation results in a minimal luminal diameter which is greater than the reference diameter and as a result in a negative percent diameter stenosis.

It may be argued that the radiopacity of the stent wires interferes with contour detection. However, it is our experience that in case of adequate filling of the coronary artery with a contrast medium at a concentration of 100%, this is not the case. It is, as if automated edge detection ignores the information coming from the radiopaque stent wires. This is true for both the analysis immediately after stent implantation as for the assessment of neointimal hyperplasia within the stent at follow-up (Figs 5 and 6). This is in accordance with phantom studies from our laboratory which disclosed that automated edge detection, in contrast to videodensitometry, could adequately define the luminal boundaries of a Wiktor stent-containing plexiglass phantom (Fig. 7) [17]. However, in some cases in which neointimal hyperplasia is not clearly defined on the angiogram and appears as haziness within the stent, automated edge detection cannot accurately define the luminal boundaries. Mannual correction of the contours by the analyst would induce to much bias. It is the only situation in which videodensitometry may offer a solution despite the inevitable densitometric information coming from the stent itself. Accurate stenosis values are obtained by selecting the reference segment ("user-defined" reference diameter) within a non-narrowed segment within the stent itself (Fig. 8). In all the follow-up angiograms of the Wiktor stent, videodensitometry had to be used in 8% of the cases.

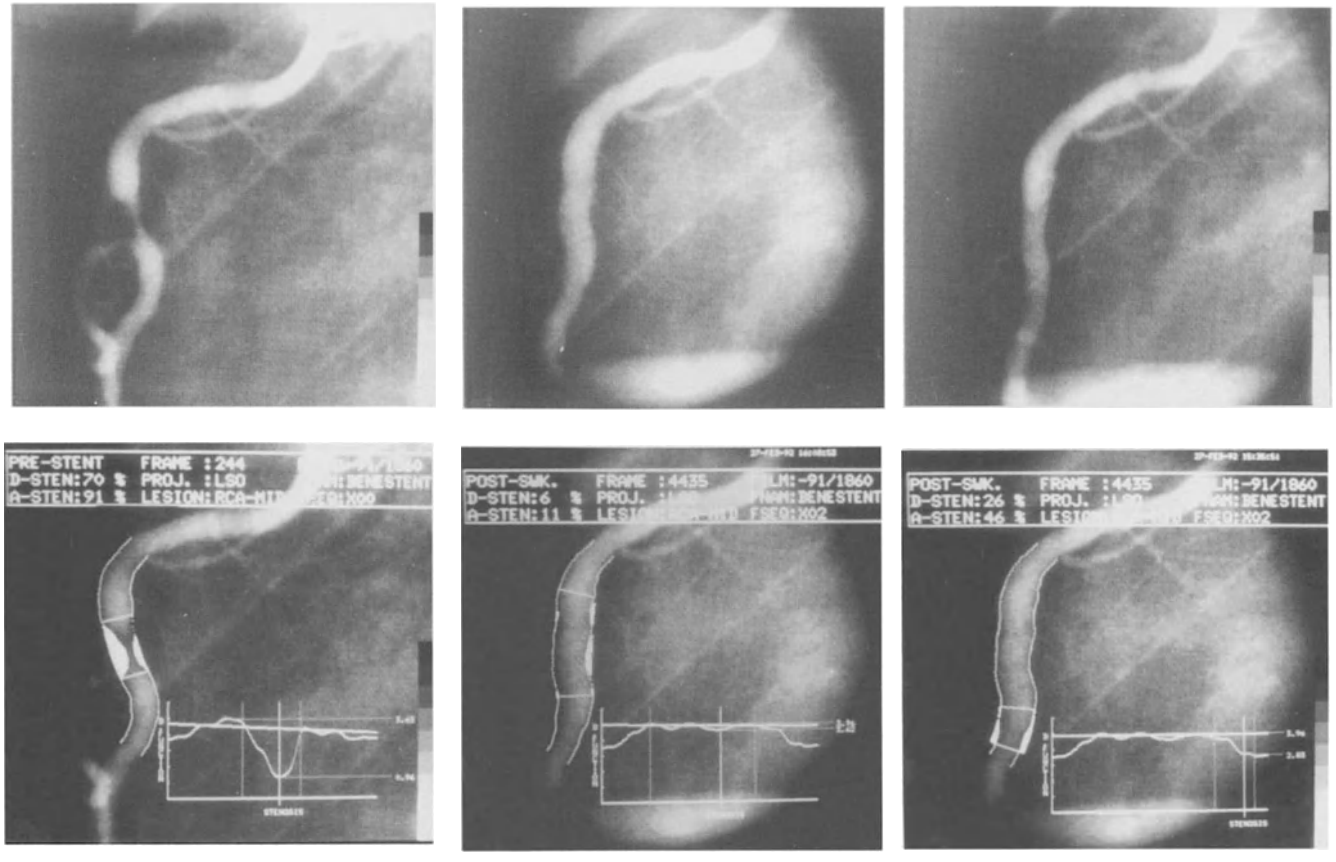


*Figure 3.* User-defined extent of the stented segment coinciding with the extent of the stent itself results is a "stent analysis". It forces the computer to analyze the changes in stenosis geometry within the stented segment. This contrasts with a "vessel analysis" in which no attempt has been made to coincide the extent of the analyzed segment with the extent of the stent. Due to the almost perfect improvement of the stenosis geometry after stent implantation, a non-significant lesion distal to the stented segment is now identified as a residual stenosis outside the stent.

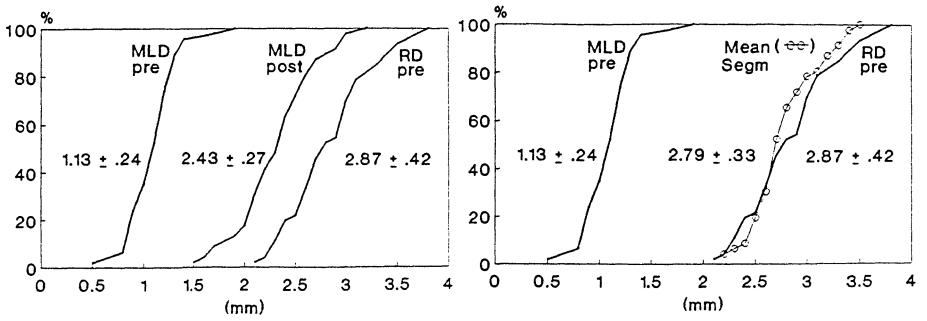


*Figure 4.* Cumulative distribution curves of the minimal luminal diameter and its changes after stent implantation (panel A) and the mean diameter post stenting in relation to the reference diameter of the target vessel (panel B). On the X-axis are shown the values of the angiographic variables and on the Y-axis the relative number of the population under investigation. It is evident that, in contrast to the mean diameter of the stented segment, there is still a gap between the minimal luminal diameter and the reference diameter.

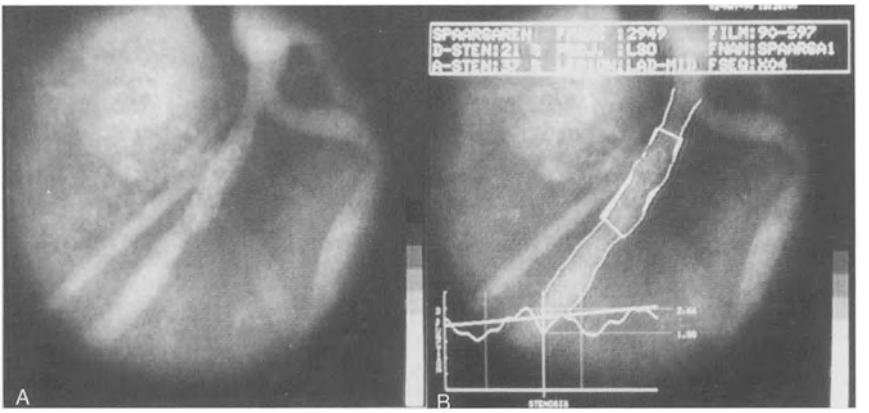


*Figure 5.* Example of a computer-assisted Coronary Angiography Analysis using automated edge detection immediately after Wiktor stent implantation. There was no interference of the radiopaque stent wires with the contour detection.

## *Specific data on videodensitomerty*

In contrast to the situation after PTCA, there is an excellent agreement between the minimal luminal cross-sectional area determined by edge detection and videodensitometry after stent implantation [18, 19]. In 19 patients who underwent balloon angioplasty followed by stent implantation, a significant improvement in the correlation and variability in the measurement of the minimal luminal cross-sectional area between edge detection and videodensitometry was observerd after stenting (Table 2) [19]. This improve-

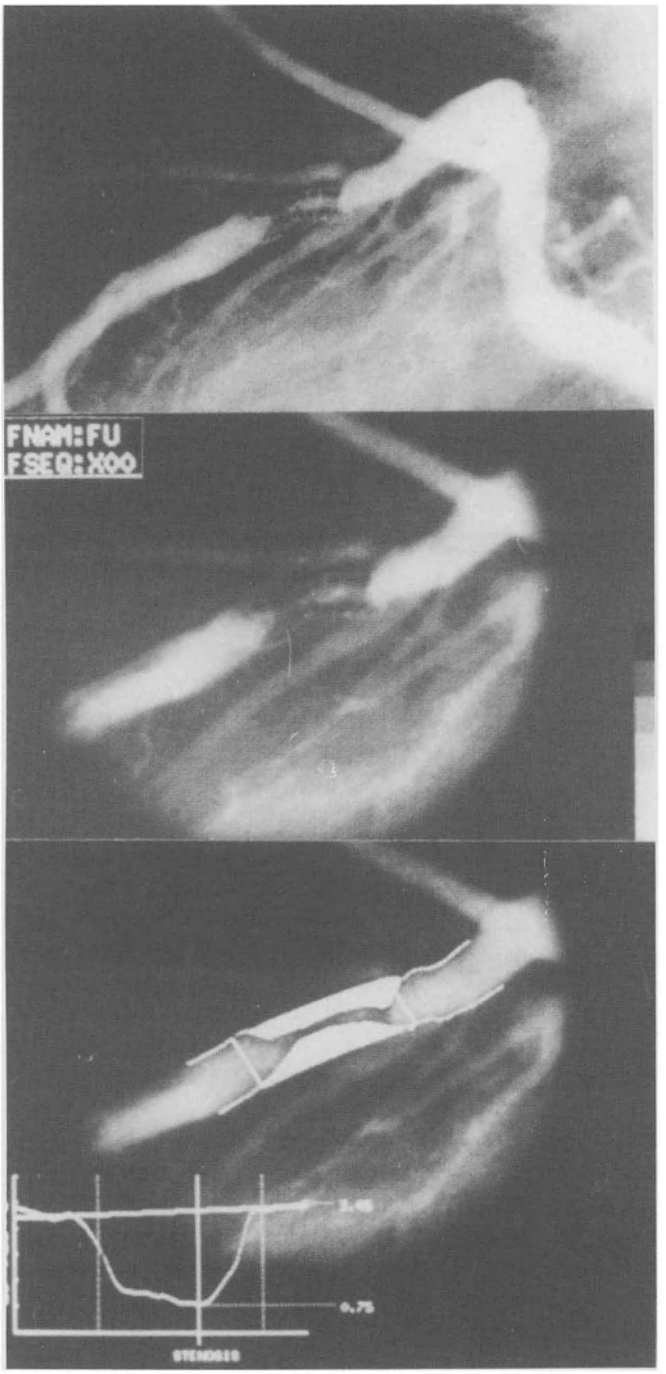


*Figure 6.* A significant luminal renarrowing within the Wiktor stent is appreciated on the angiogram. Despite the radiopacity of the stent, automated contour detection resulted in an adequate detection of the luminal contours without user interaction.

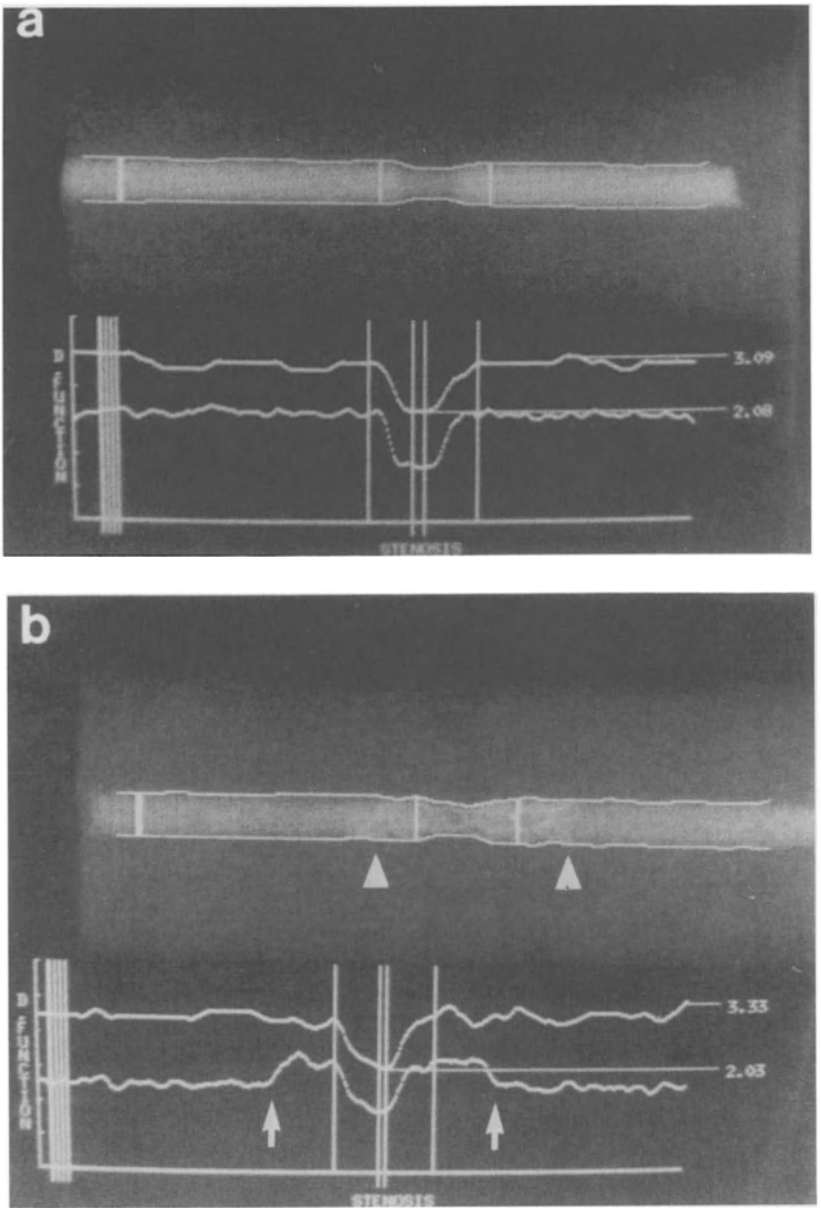


*Figure 7.* Control (a) and Wiktor stent-containing (b) plexiglass phantoms (3 × 2 mm) filled with 100% and 50% iopamidol contrast medium, respectively. Graphs show the diameter function (upper curve) and the densitometric area function (lower curve). Outside vertical lines on the graph and rightward two vertical lines on the phantom are the lesion boundaries. The inner two vertical lines represent the minimal points on the diameter and densitometric graphs, respectively. The multiple vertical lines in the left part of the graph and the lefward vertical line in the phantom represent the user-defined reference segment. The numbers in the graph represent the maximum and minimum diameters. The boundaries of the Wiktor stent are visible in the phantom (arrowheads) and as a step-up in the densitometry graph (arrow). Reproduced with permission from Strauss et al, Catheterization and Cardiovascular Diagnosis 1991; 24: 259–264.

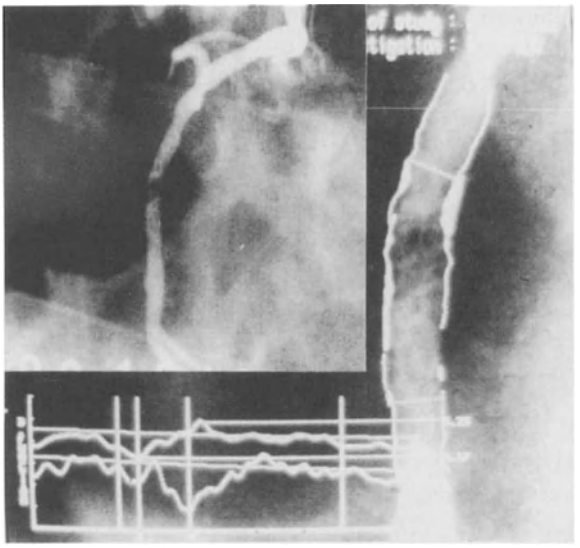

*Figure 8.* In case of haziness as expression of restenosis within the Wiktor stent, edge detection cannot define the arterial boundaries. In such circumstances, videodensitometry is used. To obtain accurate values of the minimal luminal cross-sectional area, the user selects the reference in a non-stenosed segment in the Wiktor stent itself.

*Table 2.* Correlation between edge detection and densitometry in the assessment of minimal cross-sectional area before and after PTCA and stent implantation

| | pre-PTCA | post-PTCA | post-stent |
|---|---|---|---|
| Correlation Coefficient | 0.73 | 0.59 | 0.83 |
| 95% CI | (0.41; 0.89) | (0.15; 0.83) | (0.61; 0.93) |
| Mean difference between edge detection and densitometry | $0.31 \pm 0.51\ mm^2$ | $-0.38 \pm 1.22\ mm^2$ | $0.35 \pm 0.79\ mm^2$ |

CI: Confidence Interval.

ment is likely due to smoothing of the vessel contours by the stent and remodeling of the stented segment into a more circular configuration. Therefore, we believe that both methods are appropriate to assess the immediate results after implantation of stainless steel stents. In a separate in vitro study in which stainless steel and radiopaque stents were placed in known stenoses within plexiglass phantoms, The Wallstent and Palmaz-Schatz stent had minor and likely clinically insignificant contributions to the densitometric determination of the minimal luminal cross-sectional area [17]. Conversely, the radiopacity of the Wiktor stent increased the minimal luminal cross-sectional area in these same narrowings by 10–56% depending on the concentration of contrast medium and specific stenosis [17].

**Does stent implantation prevent recoil?**

Although the precise mechanisms by which balloon angioplasty lead to luminal enlargement are still incompletely understood, there is now substantial evidence that in addition to plastic changes (e.g. plaque fracture, plaque compression, dissection), elastic changes (arterial wall stretching) occur which contribute to the dilatation process [20–23]. As a response to these elastic changes, elastic recoil after balloon angioplasty has been reported to be responsible for 32% to 47% loss of the theoretically achievable result which in turn may affect the long-term angiographic outcome [24–28]. To improve the immediate and long-term results of balloon angioplasty, intracoronary stent implantation has been advocated. At present, the stent is the only catheter technology which scaffolds the vessel and therefore may prevent recoil. Several investigators have used quantitative coronary angiography to evaluate recoil following stent implantation. In comparison with historical data on balloon angioplasty, only a limited amount of recoil was observed (Table 3) [24–28, 29–32]. The difference in recoil after Wiktor stent implantation is most likely related to the difference in definitions used [30, 31]. In the study of Popma et al., recoil was defined as the difference between the mean final balloon diameter and the minimal luminal diameter post stent implantation, while in the study of de Jaegere et al., recoil was defined as the difference in the mean final balloon diameter and the mean diameter of the stented segment. In the latter study, this definition was chosen because the behaviour of the vessel wall of the entire stented segment was evaluated. Furthermore, studies using either quantitative coronary angiography or a combination of a balloon catheter which houses a ultrasound transducer demonstrated that balloon expansion is not uniform [23, 28]. This has recently been observed in balloons on which a stent was mounted resulting in asymmetric stent expansion [33]. This suggets that one part of the dilated or stented segment may yield more easily to the mechanical force of the balloon than the other. Therefore, one segment may experience more stretch than the other and consequently more recoil [23, 28, 33]. It is noteworthy that, if the definitions proposed by other investigators to define recoil was used, it would amount to $0.65 \pm 0.30$ mm or 21% which is strikingly similar to the degree of recoil after Wiktor stent implantation reported by Popma et al. [30].

In accordance with data on balloon angioplasty, stent oversizing was found to be the strongest independent predictor of acute recoil after both Palmaz-Schatz and Wiktor stent implantation in most studies [24, 25, 27, 29, 31]. This was not found by Haude et al. [32]. This discrepancy may be related to differences in matching the stent size to the vessel size or to the fact that the amount of recoil observated by the Haude et al. was simply too small to detect such a relationship. He reported a mean elastic recoil of $0.10 \pm 0.07$ mm (3.5%) in diameter and of $0.38 \pm 0.36$ mm$^2$ in cross-sectional area (5.1%) after stenting [32].

*Table 3.* Recoil following intracoronary stenting

| Stent | Ref. | Definition recoil | Recoil |
|---|---|---|---|
| Palmaz Schatz | | | |
| Leon et al. | 29 | Final balloon diameter – MLD post stent | 15 ± 13% |
| Popma et al. | 30 | Mean final balloon diameter – MLD post stent | 17 ± 7% |
| Haude et al. | 32 | Maximal balloon diameter – MLD post stent | 3.5% |
| | | Maximal balloon area – MLCA post stent | 5.1% |
| Wiktor stent | | | |
| Popma et al. | 30 | Mean final balloon diameter – MLD post stent | 22 ± 9 |
| de Jaegere et al. | 31 | Mean final balloon diameter – mean diameter stented segment | 8.2% |
| | | Mean final balloon diameter – MLD post stent | 21% |
| Gianturco-Roubin | | | |
| Popma et al. | 30 | Mean final balloon diameter – MLD post stent | 20 ± 10% |

MLD: minimal luminal diameter, MLCA: minimal luminal cross-sectional area

In one study, the relation between acute recoil after Wiktor stent implantation and late luminal renarrowing was assessed [31]. No such a relation was found. Furthermore, in the same study, advantage was taken of the unique radiopaque properties of the Wiktor stent to determine compression or "late recoil" of the stent itself (difference between the mean diameter of the stent itself immediately after implantation and at follow-up without opacifacation of the vessel). No late compression of the Wiktor stent was observed. On the contrary, the difference between the mean diameter of the stent itself immediately after implantation and at follow-up was $-0.15 \pm 0.33$ mm, suggesting an increase in diameter of 5.0% or a negative "late recoil". The absence of late recoil in addition to the evidence that acute recoil does not contribute to late luminal renarrowing or restenosis indicate that late loss in minimal luminal diameter is due to tissue ingrowth into the lumen of the stented segment. This is in accordance with pathologic observations disclosing that the predominant cause of restenosis following balloon angioplasty or stent implantation is extensive neointimal thickening due to smooth muscle cell proliferation at the dilated or stented site [34–40].

## QCA to evaluate hemodynamic changes following intracornary stenting

To assess the physiological significance of the obstruction and its changes after stenting, several authors have used the coronary angiogram and quantitative coronary angiography to calculate the theoretic pressure drop, according to the formulae described in the literature: $Pgrad = Q.(Rp + Rt)$ where Pgrad is the theoretic transtenotic pressure decrease (mmHg) over the

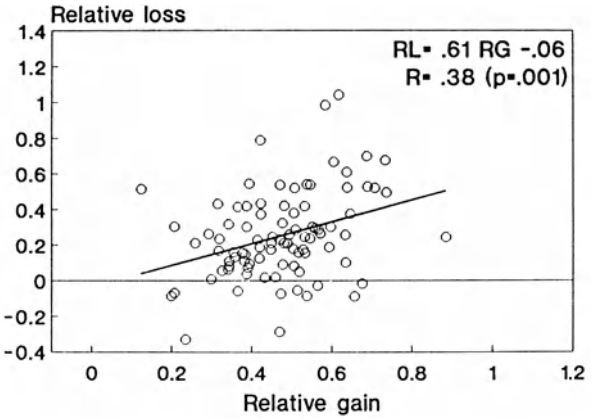


*Figure 9.* Graphic display of the relation between the relative gain (RG = increase in minimal luminal diameter immediately after stent implantation normalized to the vessel wall) and relative loss (RL = decrease in minimal luminal diameter at follow-up normalized to the vessel wall). A positive linear relation was found with a correlation coefficient of 0.38 ($p < 0.001$) with a slope of 0.61 and an intercept on the Y-axis of − 0.06.

stenosis, Q the mean coronary blood flow (ml/s), Rp the Poiseuille resistance and Rt the turbulent resistance [41–44].

These resistances have been defined as follows:

$$Rp = C1.\ (\text{length obstruction})/(\text{minimal cross-sectional area})^2$$

where $C1 = 8.\pi.(\text{blood viscosity})$ with blood viscosity = 0.03 g/cm.s.

$$Rt = C2.\ (1/\text{minimal cross-sectional area} - 1/\text{normal distal area})^2$$

where C2 = (blood density)/0.266 with blood density = 1.0 g/cm$^3$.
The theoretic transtenotic pressure drop has been calculated for theoretic coronary blood flow of 0.5, 1 and 3 ml/s. The Poiseuille and turbulent contributions to the flow resistance has been determined from stenotic geometry assessed by quantitative coronary angiography.

All authors found that the morphologic improvement after stent implantation was associated with a decrease in both the calculated turbulent and Poiseuille resistance, as well as the virtual disappearance of the theoretical transtenotic pressure drop for a theoretical flow of 0.5, 1 and 3 ml/s. The hemodynamic data after Wallstent and Wiktor stent implantation are shown in Table 4.

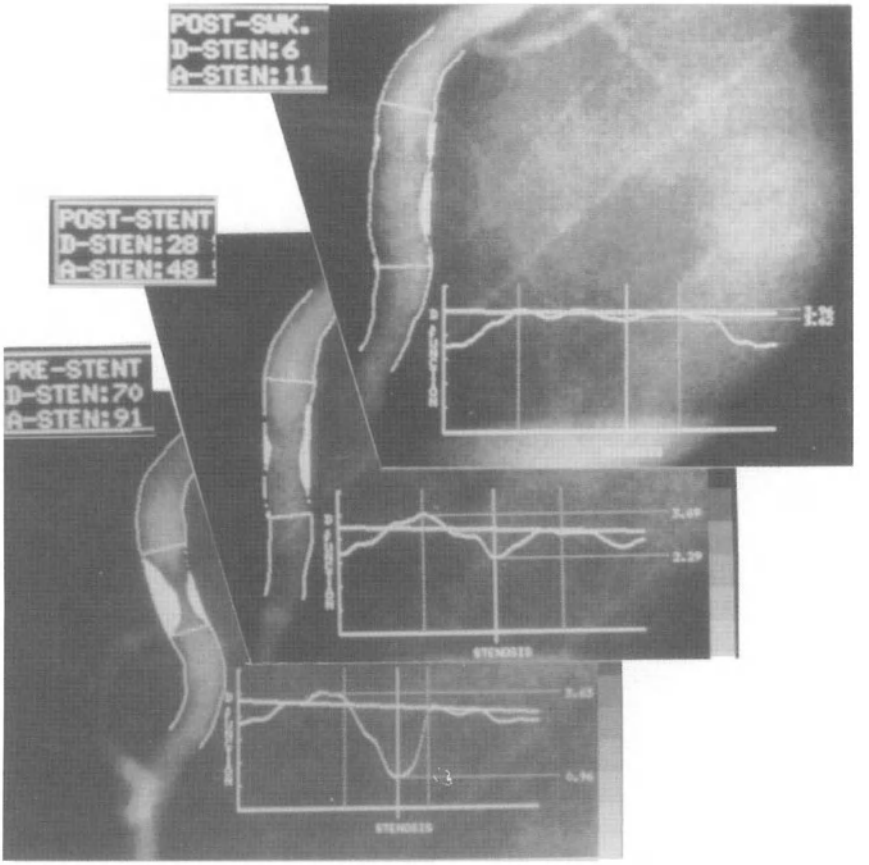


*Figure 10.* On-line quantitative coronary angiography disclosed a residual stenosis immediately after stent implantation. This information was used to further optimize the dilatation process by performing an additional balloon dilatation within the stent.

*Table 4a.* Immediate hemodynamic changes following wallstent implantation

| | pre-PTCA | post-PTCA | post-STENT | $P_1$ | $P_2$ |
|---|---|---|---|---|---|
| Rpois | 22.55 ± 61.76 | 2.34 ± 7.76 | 1.92 ± 6.58 | 0.02 | NS |
| Rturb | 7.98 ± 23.72 | 0.39 ± 0.54 | 0.04 ± 0.10 | 0.05 | 0.0002 |
| Pgrad (0.5 mL/sec) | 30.53 ± 78.73 | 2.67 ± 7.08 | 1.95 ± 7.47 | 0.02 | 0.03 |
| Pgrad (1 mL/sec) | 56.98 ± 109.73 | 5.97 ± 14.71 | 4.05 ± 15.10 | 0.002 | 0.007 |
| Pgrad (3 mL/sec) | 82.51 ± 148.00 | 9.88 ± 22.95 | 6.14 ± 22.88 | 0.002 | 0.002 |

*Table 4b.* Immediate hemodynamic changes following wiktor implantation

| | pre-PTCA | post-PTCA | post-STENT | $P_1$ | $P_2$ |
|---|---|---|---|---|---|
| Rpois | 8.71 ± 7.98 | 1.06 ± 0.77 | 0.47 ± 0.20 | 0.00001 | 0.00001 |
| Rturb | 4.47 ± 4.97 | 0.26 ± 0.36 | 0.02 ± 0.02 | 0.00001 | 0.00001 |
| Pgrad (0.5 mL/sec) | 13.19 ± 12.54 | 1.33 ± 1.05 | 5.77 ± 35.77 | 0.00001 | NS |
| Pgrad (1 mL/sec) | 34.90 ± 34.46 | 3.19 ± 2.32 | 1.01 ± 0.44 | 0.00001 | 0.00001 |
| Pgrad (3 mL/sec) | 66.44 ± 66.60 | 5.59 ± 5.10 | 1.53 ± 0.74 | 0.00001 | 0.00001 |

Rpois=Poiseuille resistance; Rturb=turbulent resistance; Pgrad=pressure drop.
Comparison between the Wallstent and Wiktor stent study group revealed no statistical difference between any angiographic parameter.
All parameters are expressed in mean ± SD.

## Why should we use QCA during stent implantation?

Restenosis should be considered as the reparative vessel wall response or perhaps as the natural healing process following injury [45, 46]. When excessive, this may lead to new symptoms and eventually to repeat intervention [47]. One of the objectives of stent implantation is to reduce the incidence of restenosis in the hope that it will favorably affect the long-term clinical outcome. Stent implantation causes substantial injury to the coronary vessel wall and therefore will invariably be associated with restenosis. Schwartz et al. demonstrated that the extent of late neointimal hyperplasia was directly related to the degree of vessel wall injury following oversized coil stent implantation in porcine coronary arteries [48]. In accordance with these data, we found that the extent of late luminal renarrowing, increases with the amount of luminal gain after stent implantation in human coronary arteries [49]. Resolution of clinical or angiographic restenosis may require the creation of the largest possible luminal diameter and the control of neointimal hyperplasia. On-line quantitative coronary angiography can beneficially be used during stent implantation to minimize vessel wall injury and to guide the operator to obtain the most optimal angiographic result. Minimizing vessel wall injury is achieved by selecting the appropriate stent size by first measuring the reference diameter of the target vessel. Once the appropriate stent size have been selected and implanted, on-line quantitative coronary angiography can be used to evaluate the immediate changes in stenosis geometry. This may be of importance to the long-term angiographic results. As outlined above, studies using quantitative coronary angiography have shown a positive linear correlation between the relative gain and relative loss (Fig. 9). However, one should realize that the greater gains are not fully offset by the increased loss in minimal luminal diameter which is reflected by the slope of the curve (<1). This once again confirms that the superior improvement in stenosis geometry after stent implantation compensates to some degree for late loss. In addition, data from other investigators who used the categorical approach to define restenosis found that a suboptimal

angiographic result after stent implantation was associated with an increased risk for restenosis according to the 50% diameter stenosis criterion [50, 51]. On-line quantitative coronary angiography is essential to assess the residual stenosis post stent implantation. If necessary, an additional balloon angioplasty within the stent can be performed to optimize the immediate results (Fig. 10). Based on the data of Strauss et al. we perform such an additional dilatation when the residual percent diameter stenosis exceeds 20% [50]. The size and inflation pressure is determined on the basis of the on-line quantitative coronary angiography.

## Conclusions

Quantitative coronary angiography has been developed to assess objectively the efficacy of modern therapeutic procedures in the catheterization laboratory. The advent of new and innovative therapeutic interventions have raised unforeseen problems. In most instances, they have effectively been addressed and even solved thanks to the knowledge and understanding of the technical limitations of this analysis method. This system does not only provide accurate assessment of the immediate and long-term changes in stenosis geometry following coronary intervention, but can also be used as a tool to understand the mechanisms of luminal enlargement and the pathophysiology of restenosis.

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# 31. Excimer laser angioplasty

SIPKE STRIKWERDA, ELINE MONTAUBAN VAN SWIJNDREGT and PATRICK W. SERRUYS

## Introduction

After the invention of laser (acronym for light amplification by stimulated emission of radiation) in 1960 [1], it was not until the 1980's that laser radiation received considerable attention as a possible new modality in the treatment of obstructive atherosclerotic disease. Continuous wave (CW) laser light from argon ion, $CO_2$ and Nd:YAG laser sources was shown to cause vaporization of atherosclerotic plaque [2–5] and to recanalize partially as well as totally obstructed arteries [3–7]. In contrast to balloon angioplasty, in which a stenotic lesion is merely remodelled, laser radiation can bring about ablation (that is, removal) of atherosclerotic plaque. Laser ablation of plaque tissue has been proposed to potentially lead to better short- and long-term results by

1) removal of atherosclerotic tissue mass ('debulking')
2) decreasing medial arterial wall injury, and
3) leaving behind a smoother, less thrombogenic surface.

### *The laser catheter*

The first catheters for the percutaneous transluminal delivery of laser light consisted of a standard guide catheter incorporating a bare optical fiber [6–8]. This approach was frequently complicated by arterial perforation, either mechanical or thermal from activation of the laser [7–10]. Aneurysm formation [9, 11] and extensive thermal damage to adjacent vascular structures [12] have also been reported after using excessive doses of CW laser energy. The problems associated with these early studies were primarily related to the simplicity of the fiber optic catheter system and to inadequate understanding of laser light dosimetry. To improve control of intra-arterial delivery of laser energy, and to create a larger diameter arterial lumen than would be possible using a single bare optical fiber, a variety of fiber optic catheters was constructed for contact ablation of tissue employing sapphire, metal or silica ball tips [13–17]. These modifications reduced the incidence of acute



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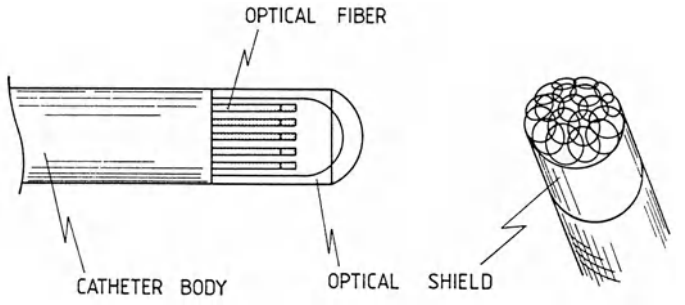


*Figure 1.* Schematic diagram of the output end of a multifiber shielded laser catheter; only five fibers are shown (left panel). The light spots produced by individual fibers overlap providing coverage of the entire front surface of the catheter tip (right panel). Adapted from Cothren et al. [25, 26].

complications considerably. The laser-heated metal ('hot-tip') probe attached to an optical fiber was found to be a safe and useful recanalization device in peripheral arteries [18]. The first clinical trials of coronary artery recanalization in man using the hot-tip catheter, however, were fraught with difficulties. The smaller, more tortuous coronary arteries limits trackability of the device and thermally induced thrombosis, spasm and vessel wall damage were observed [19–21]. The potential applicability of the hot-tip probe in human coronary arteries therefore remains doubtful.

An alternative approach to the design of fiber optic catheters emerged from the concept of enclosing the output tip of an optical fiber in a transparent quartz shield [22]. Unlike most other ablation schemes, like the 'hot-tip' probe, tissue removal with this type of catheter is primarily brought about by *direct* laser-tissue interaction. In addition, the relevant laser beam parameters governing the tissue ablation process can be accurately controlled with this device. Dosimetry studies using this catheter for ablation of atheromatous plaque in vitro demonstrated that high power exposures of short duration in the msec range from a CW argon ion laser result in predictable tissue removal with a minimum of carbonization and coagulation damage [23, 24]. Ablation studies using an optical shield catheter incorporating multiple optical fibers [25] (Fig. 1) yielded promising results [26]. The fibers produce a pattern of overlapping light spots completely covering the hemispherical output surface of the shield. This enables the removal of large diameter sections of atheromatous tissue producing a lumen wide enough for the catheter to pass through.

*Pulsed radiation and the excimer laser*

Pulsed laser systems emit short, high peak-power pulses in the nsec range and have been shown to further reduce adjacent thermal injury during ablation of

cardiovascular tissues [27, 28]. If the pulse duration is sufficiently brief and if the interval between pulses is relatively long, then the heat generated by each pulse may be sufficiently dissipated before delivery of the subsequent pulse. However, effects of short-pulsed laser radiation on tissue may also rely on non-linear processes. The deposition of light is so rapid and intense that formation of a 'plasma' can occur, a gaseous state of free electrons and ions. Upon formation, the plasma rapidly expands outward, thereby generating a shock wave that can cause mechanical disrupture of tissue [29]. The tissue surrounding a zone of optical breakdown suffers no appreciable heating.

Ablation by pulsed ultra-violet (UV) radiation has been proposed to represent still another category of laser-tissue interaction which would be predominantly photochemical in nature. The photon energy at UV wavelengths is sufficiently high to break intramolecular bonds. Long chain molecules at the irradiated surface are directly broken into smaller volatile fragments which then ablate away, a process termed 'ablative photodecomposition' [30, 31]. Pulsed UV radiation from an excimer laser has been shown to precisely remove arterial tissue in air with minimal thermal damage to remaining vessel wall [27, 30–32]. The exact mechanism by which excimer laser radiation interacts with tissue, i.e., the (relative) involvement of photochemical and photothermal processes and, perhaps, plasma formation is still under investigation. The strong absorption and minimal scattering of UV radiation in tissue [33], and the short-pulsed nature of excimer laser light may account for the highly localized effect and the relative absence of peripheral thermal damage when biological tissue is irradiated in air by an excimer laser.

When excimer laser irradiation of tissue takes place via an optical fiber under saline, however, effects are strikingly different. Recently, van Leeuwen et al. [34] demonstrated that the interaction between a XeCl excimer laser pulse at 308 nm and aortic tissue in light contact with an optical fiber caused the formation of a hemispheric vapor bubble on top of the tissue surface. But when the fiber was forced (0.1 N) on tissue, visible bubble formation was replaced by tissue elevation as soon as the fiber tip had penetrated the tissue after 5–10 pulses. Histologic examination of the thoracic aortic wall of pigs three days after XeCl laser irradiation via a ball tip optical fiber under force (0.5 N) showed dissections extending from the crater wall that ran parallel to the intimal surface. Adjacent to the crater, a zone of necrotic tissue was observed. The authors conclude that formation and forceful expansion of a vapor bubble within the tissue cause tissue elevation and dissections, and that necrosis is probably due to heat accumulation by multiple laser pulses [34]. The effects of pulsed XeCl excimer laser light delivered through a clinically used multifiber laser catheter in forced perpendicular contact with aortic tissue submerged in saline was investigated by Gijsbers et al. [35]. Considerable lateral mechanical damage was observed on histological

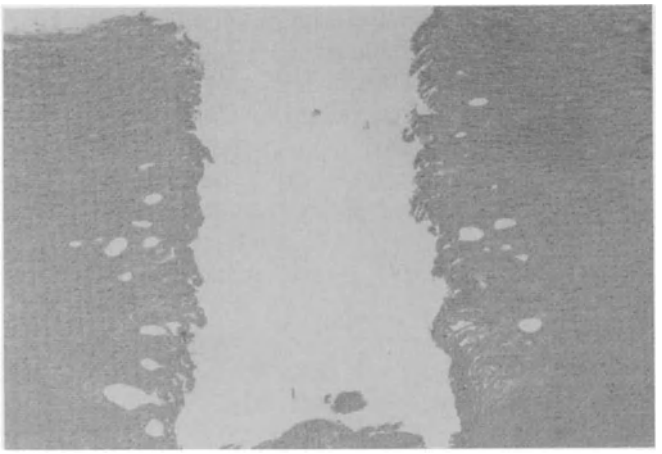

*Figure 2.* Photomicrograph of a crater in aortic tissue made by XeCl excimer laser radiation (60 mJ/mm$^2$ at 20 Hz) delivered through an AIS 1.6 mm diameter laser catheter (12 × 200 um optical fibers) immersed in saline solution. Note the vacuoles adjacent to the crater wall which are attributed to lateral expansion of gaseous debris produced in the ablation process. Original magnification 40x. (Courtesy of G.H.M. Gijsbers, Laser Center, Academic Medical Center, Amsterdam) [35].

examination (Fig. 2), which was attributed to expansion of gaseous ablation products trapped under the tip of the laser catheter.

Since the introduction of excimer laser angioplasty in the clinical setting, profound modifications were brought into catheter construction. The first laser catheter for coronary application contained twelve 200 um tipped optical fibers and came in only one diameter of 1.6 mm [36]. At present, catheters are available in multiple sizes ranging from 1.3 to 2.4 mm containing hundreds of 50 um fibers. The incorporation of a greater number of optical fibers of smaller diameter has increased catheter flexibility and also reduced the area at the tip of the catheter not available for laser ablation (the socalled 'dead space'; Fig. 3) . A reduction in dead space should reduce the mechanical dilating or 'Dottering' effect of the laser catheter, increase the efficiency of ablation and decrease the incidence of intimal dissection. The laser catheters generally available, however, do not show overlapping light spots at the tip (as in Fig. 1 ) and still have a dead space of around 80% of the total tip area. The newer catheters should have a significantly reduced dead space. Recently, preliminary results were reported [37] of 308 nm excimer laser-tissue interaction studies using a modified version of a multifiber catheter delivering a homogeneous 'donut'-shaped light beam with an outer diameter of 1.6 mm. Segments of fresh porcine aorta were immersed in a saline bath or blood field at room temperature and irradiated perpendicularly in forced contact with the laser catheter. In comparison to the standard 1.6 mm diameter catheter containing 200 fibers of 50 um diameter, the modified laser

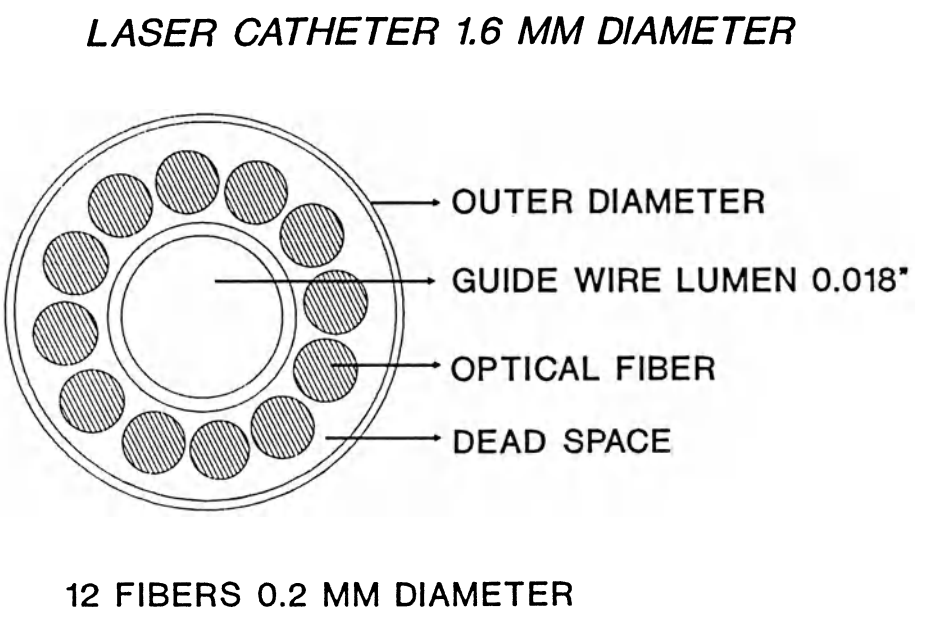


*Figure 3.* Schematic front view of the distal tip of a 1.6 mm diameter laser catheter containing 12 optical fibers of 200 um diameter grouped around a central guide wire lumen. The dead space is the area of the catheter tip surface not covered by laser light.

catheter produced single smooth craters with sharp crater wall edges and no damage to surrounding endothelium (Fig. 4).

## Excimer laser coronary angioplasty in man

### *Multicenter results*

The pulsed XeCl excimer laser with a wavelength of 308 nm in combination with catheters containing multiple optical fibers has emerged as the system of choice for many investigators to treat coronary stenoses or occlusions that can be crossed with a guide wire. Removal of atherosclerotic plaque by excimer laser ablation may potentially increase immediate success rates, reduce acute complication rates and improve long-term results in the percutaneous treatment of complex coronary lesions. Since the first patient with

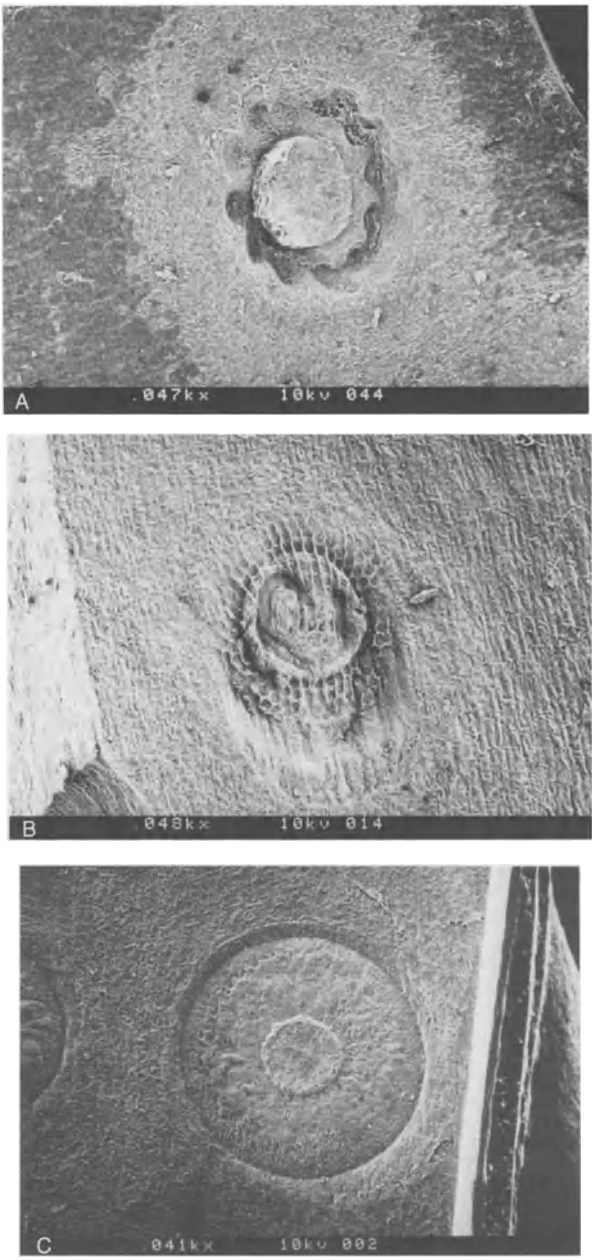


*Figure 4.* Scanning electronmicrographs of porcine aortic tissue after XeCl excimer laser irradiation (40 pulses of 200 nsec at 20 Hz; fluence 30 mJ/mm$^2$) through laser catheters with an outer diameter of 1.6 mm, (A) containing 12 optical fibers of 200 um, (B) containing 200 optical fibers of 50 um, and (C) modified with a dispersing lens tip producing a homogeneous light beam. Note the regular tissue ablation with the modified tip catheter. (Courtesy of J. Hamburger, Laser Center, Academic Medical Center, Amsterdam) [37].

coronary artery disease was treated with excimer laser coronary angioplasty (ELCA) in July 1988 [38], experience with this technique has grown rapidly. Early and late results of ELCA using a pulsed XeCl excimer laser at 308 nm in combination with multiple-fiber over-the-wire laser catheters of various diameters developed by Advanced Interventional Systems (AIS) [36, 39, 40], Spectranetics [41, 42] and Technolas [43] have been reported. Recently, multicenter results were presented involving more than 2100 patients and 2500 lesions treated with ELCA using these respective laser systems [44–46].

Immediate results obtained in the first patients treated with a XeCl excimer laser have been reported earlier. Litvack et al. achieved 84% laser success [>20% reduction of diameter stenosis after ELCA alone] and 93% procedural success [<50% residual stenosis after ELCA with or without adjunctive balloon dilatation (PTCA)] in the first 55 patients undergoing ELCA with the AIS system in a prospective, nonrandomized, multicenter trial [36]. Sanborn et al. reported a 75% laser success and a 100% procedural success rate in the first 50 patients treated with the Spectranetics laser [41]. Karsch et al. [43] reported a 70% laser success and an 88% procedural success rate in the first 60 patients treated with the Technolas system. Laser success was somewhat lower in the latter patient series, possibly as a result of catheter technology and/or sub-threshold fluences for laser ablation of atherosclerotic tissue used in this protocol. Cook et al. [39] reported the experience with ELCA in the first 100 patients treated at the Cedars-Sinai Medical Center in Los Angeles with the AIS system between July 1988 and March 1990, when new laser catheters of 1.3, 1.6, and 2.0 mm diameter became available. Coronary angiograms were analyzed using a modification of the method described by Brown et al. [47], a computer-assisted visual analysis in which luminal contours are hand-traced. Immediate laser success was thus obtained in 84% and procedural success in 94% of patients. The American College of Cardiology/American Heart Association (ACC/AHA) Task Force classification of coronary lesion morphology [48] was used as a basis to compare the results of ELCA with the anticipated initial success rates of conventional PTCA. In type A, B, and C lesions, immediate laser successes were 83%, 88%, and 85%, respectively, versus 92%, 81%, and 61% for balloon PTCA as reported by Ellis and coworkers [49]. In addition, results were independent of lesion length, a separate ACC/AHA Task Force classification characteristic. For stenoses and total occlusions shorter than 10 mm, of 10–20 mm, and longer than 20 mm, laser success rates were 88%, 82%, and 80%, respectively, which differed not significantly. Complication rates with ELCA in type B and C lesions (2% and 0%, respectively) also compared favorably with PTCA (6% and 21%, respectively) [49]. It can be concluded from this study [39] that ELCA may be a useful therapy with potential advantage over standard balloon PTCA in lesions with certain type B and C characteristics.

After it was recognized that ELCA did not appear to have an advantage

over PTCA in uncomplicated and discrete coronary lesions (e.g., ACC/AHA Task Force type A morphology) with respect to immediate outcome, there is a trend toward treating coronary lesions with ELCA that are not ideal for conventional PTCA, particularly ostial lesions, tubular and diffuse disease, saphenous vein grafts, and chronic total occlusions. On the basis of this development, one may anticipate a downward shift in immediate success rates as would be expected for PTCA. Data from the AIS [44] and Spectranetics [45] registries, however, show that lesion length and complexity do not seem to influence results. The procedural success rate in the ELCA registry of AIS containing 1570 patients was as high as 89% [44], and clinical success in a registry of Spectranetics laser procedures (487 patients) was obtained in 85% [45], irrespective of lesion length or ACC/AHA Task Force classification, respectively. Also, the frequency of major complications (CABG, myocardial infarction, death) did not differ significantly between lesions with simple or complex angiographic morphology [44, 45]. With respect to long-term outcome, the six month angiographic restenosis rate after ELCA does not appear to be lower than after balloon PTCA alone, averaging between 40 and 45% [40, 42, 43, 50].

*Thoraxcenter experience*

*Patients*

From December 1990 until March 1992, 69 patients with 78 lesions were deemed eligible for ELCA on the basis of previous experience with ELCA by us and other groups. However, 46 patients with 53 lesions were scheduled for ELCA since 23 patients with 25 lesions were allocated to balloon angioplasty in the setting of a randomized trial of ELCA versus conventional PTCA which started September 1991 (AMRO-trial; see below). All patients to undergo ELCA had symptomatic coronary artery disease and/or objective evidence of myocardial ischemia. The male/female ratio was 35/11 and the mean age was 55 years with a range of 39 to 77 years. Most patients (34 out of 46; 74%) were in New York Heart Association functional class III or IV for angina pectoris (Fig. 5, left panel). Twenty-nine lesions were located in the distribution of the left anterior descending (LAD) coronary artery, 15 in the right coronary artery (RCA), and 9 lesions were located in the left circumflex (LCX) coronary artery. Forty-four of the 53 lesions (83%) were classified as type B or C according to the joint American College of Cardiology/American Heart Association (ACC/AHA) Task Force criteria [48] (Fig. 5, right panel). Eighteen lesions were (sub)total occlusions and 12 were restenosis lesions after a previous intervention. With growing experience, more patients with type B and C lesions were included in the series.

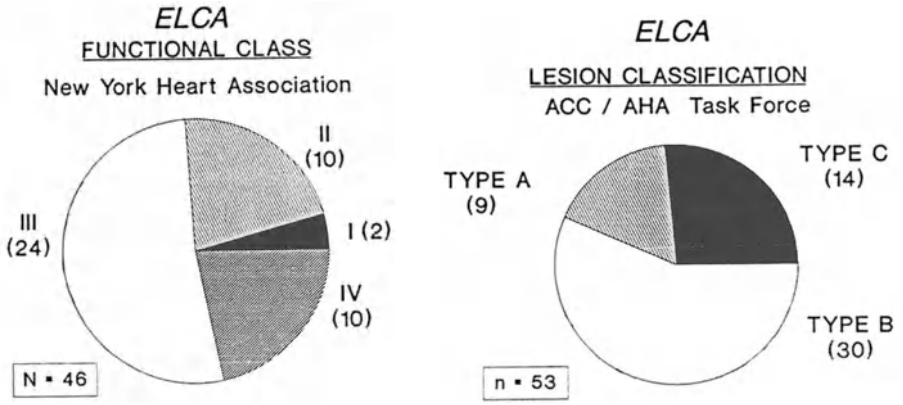


*Figure 5.* Distribution of severity of angina pectoris according to the New York Heart Association functional classification in 46 patients (left panel), and distribution of coronary lesion complexity according to the American College of Cardiology/American Heart Association (ACC/AHA) Task Force criteria of 53 lesions (right panel) selected for excimer laser coronary angioplasty (ELCA).

## *Methods*

The laser system used consisted of a XeCl excimer laser (Advanced Interventional Systems, Inc., Irvine, CA) emitting light pulses at 308 nm in the ultraviolet portion of the electromagnetic spectrum with a pulse duration of about 200 ns and a repetition rate of 20 Hz. Multifiber over-the-wire laser catheters of 1.3, 1.6, and 2.0 mm diameter were coupled to the laser and fluence at the catheter tip was set at levels of 45 to 60 mJ/mm$^2$.

All patients were pre-treated with a calcium-channel entry blocker and aspirin was either continued orally or given intravenously at the beginning of the procedure. After insertion of arterial and venous introducer sheaths into the femoral vessels, a heparin bolus was administered of 10.000 IU. Additional doses of 5.000 IU heparin were given in order to achieve an activated clotting time (ACT) of at least 400 sec. for the duration of the procedure. Standard coronary angioplasty guide catheters (Schneider, Inc., Minneapolis, MN) of 9F for the 1.3 mm laser catheter, and 9F-superflow for 1.6 and 2.0 mm laser catheters were used. Intracoronary nitroglycerin was given to reduce vasomotor tone and contrast arteriography was performed in at least two projections, orthogonal if possible. After passage of a 0.018 inch guide wire across the stenosis into the distal part of the vessel under fluoroscopic control, fluence at the laser catheter tip was calibrated and the catheter advanced over the guide wire until its tip was just proximal to the lesion. The laser was then activated for 2–3 sec. and the fiber-optic catheter slowly advanced over the guide wire without forceful pushing. During laser activation, the guide wire was kept under slight tension or slowly retracted.

Each 2–3 sec. pulse train was followed by a 3–5 sec. pause with repositioning of the guide wire into the most distal part of the vessel. In all but two cases in which the lesion was passed twice, only one pass with a laser catheter was performed through the lesion, after which a control angiogram was made. If the residual stenosis was more than 50%, the lesion was passed with a larger diameter laser catheter or adjunctive balloon PTCA was performed. When the result was considered satisfactory, i.e., a diameter stenosis of less than 50% on visual inspection, final control angiography was performed in multiple projections after intracoronary administration of nitroglycerin. After ELCA, the patients were monitored for 24 hr and 12–lead electrocardiograms and cardiac enzyme levels were obtained twice a day. Six hours after the procedure, the sheaths were pulled out. After recanalization of a (sub)total occlusion, however, the patient was maintained on a heparin drip until the morning after ELCA; then heparin was discontinued and the sheaths removed. After the start of the AMRO-trial, all patients were given heparin overnight as part of the treatment protocol. The specific post-ELCA drug regimen consisted of aspirin for 6 months after the procedure.

Laser success was prospectively defined as a more than 20% reduction in diameter stenosis after ELCA alone as assessed by visual analysis of the angiogram. Procedural success was considered a less than 50% residual stenosis on visual assessment at the end of the procedure, whether achieved by ELCA alone or after adjunctive balloon PTCA. Clinical success was defined as procedural success without death, non-fatal myocardial infarction, coronary artery bypass grafting (CABG) or repeat PTCA during the same hospitalization period as the laser procedure. Myocardial infarction was thought to be present, when serum creatine kinase rose over twice the normal upper limit of our laboratory, along with a typical elevation of the MB fraction.

*Procedural and clinical results*

Results of attempted ELCA of 53 lesions in 46 patients are summarized in Fig. 6 (intention-to-treat analysis). Fifty lesions underwent actual treatment with the laser system; in 1 patient, an intimal dissection occurred during guide wire manipulation after which ELCA was cancelled and in 2 other patients it was not possible to cross the lesion with a guide wire. Immediate laser success was achieved in 44 out of 50 lesions having ELCA. Forty-two lesions underwent adjunctive balloon angioplasty (84%). Procedural success was achieved in 46 lesions. Two patients had a 'sustained' coronary occlusion after ELCA despite multiple balloon dilatations, stent implantation and intracoronary thrombolysis. After an autoperfusion balloon catheter was positioned and coronary flow was adequately restored, these patients were referred for emergency CABG. Another patient developed a distal coronary occlusion after dissection of the treated segment containing two consecutive lesions, and suffered a small myocardial infarction. After completion of

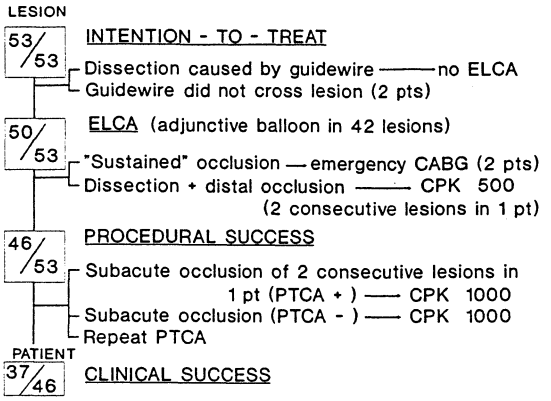


*Figure 6.* Flow chart showing procedural and clinical complications in 46 patients (pts) with 53 lesions selected for excimer laser coronary angioplasty (ELCA). For definitions of success, see text. CABG: coronary artery bypass grafting. CPK: serum creatine kinase, elevated due to myocardial infarction. PTCA: percutaneous transluminal coronary balloon angioplasty.

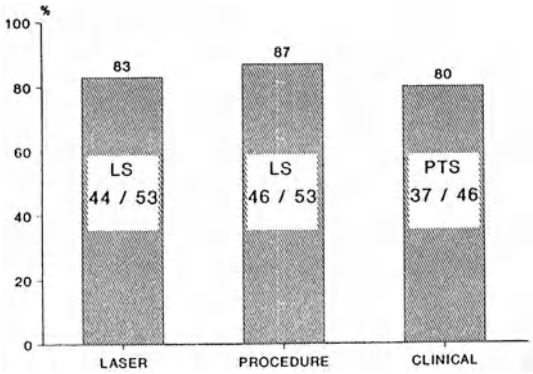


*Figure 7.* Success rates in 46 patients (pts) with 53 lesions (ls) (intention-to-treat analysis) selected to undergo excimer laser coronary angioplasty (ELCA) based on visual assessment of the angiogram using categorical cut-off criteria. For definitions of success, see text.

the procedure (ELCA with or without adjunctive balloon angioplasty) and removal of the guide catheter, 3 patients developed symptoms and signs of myocardial ischemia within 24 hrs of the initial procedure, necessitating coronary angiography and repeat intervention. In 2 patients, a total occlusion was found causing a myocardial infarction in both, despite successful balloon PTCA in one patient. Another patient underwent successful repeat PTCA because of early recurrence of the previously treated stenosis causing angina pectoris. Overall, clinical success was achieved in 37 out of 46 patients (80%). In Fig. 7 success rates are depicted graphically. Figure 8 shows a totally

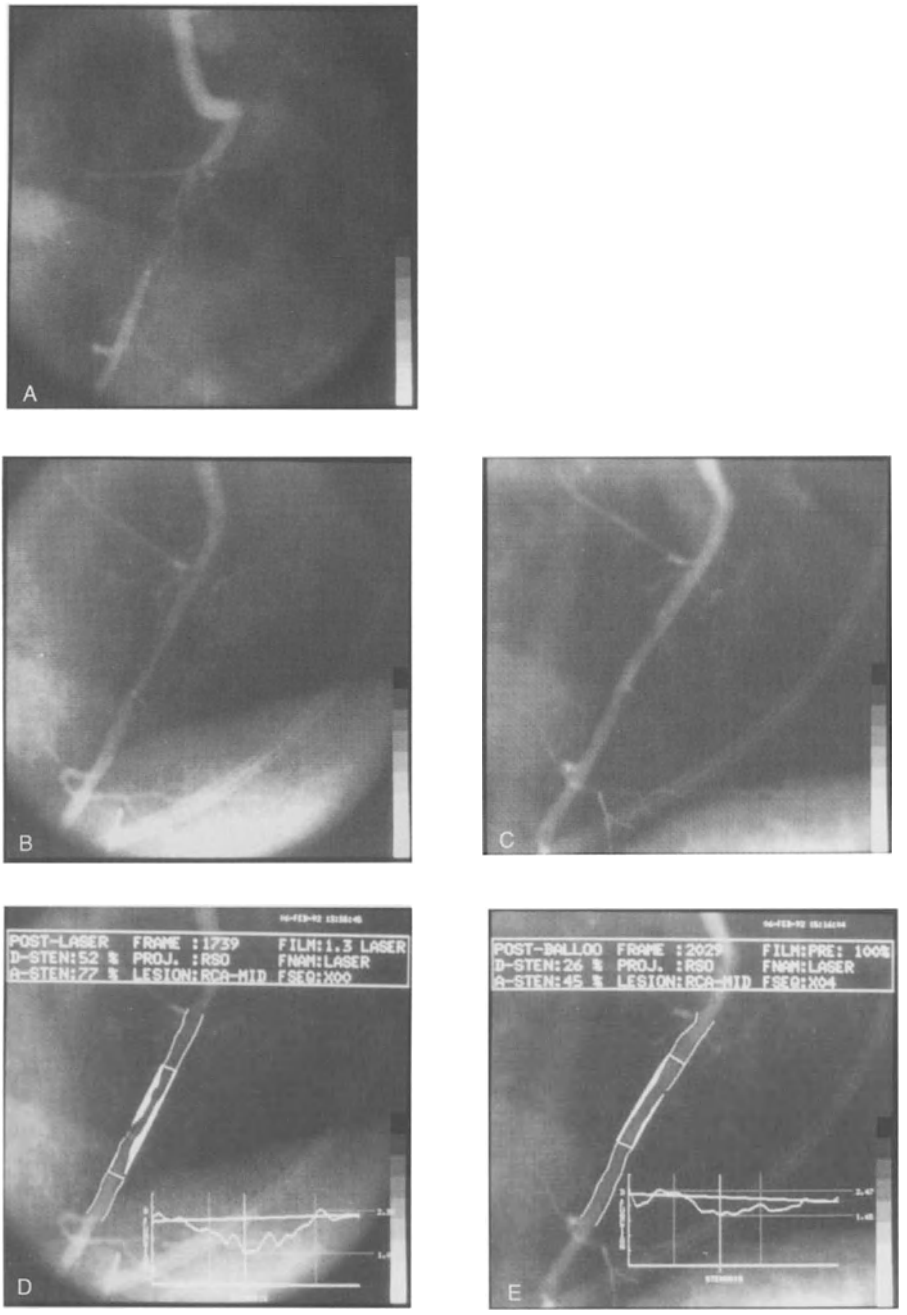


*Figure 8.* Angiograms of a proximally occluded right coronary artery before intervention (A), after excimer laser angioplasty with a 1.3 mm diameter catheter (B), and after adjunctive dilatation with a 2.5 mm diameter balloon catheter (C). Results of quantitative angiographic analysis after laser angioplasty (D) and adjunctive balloon angioplasty (E) are shown.

*Table 1.* Procedural complications associated with attempted excimer laser coronary angioplasty (ELCA) of 53 lesions in 46 patients (pts).

| | |
|---|---|
| Intimal dissection: | 31 lesions / 26 pts |
| Thrombus formation: | 9 lesions / 8 pts |
| Transient occlusion: | 3 lesions / 3 pts |
| 'Sustained' occlusion: | 2 lesions / 2 pts |
| Spasm: | 2 lesions / 2 pts |
| Embolization: | 2 lesions / 1 pt |

*Table 2.* Clinical complications in ranking order associated with attempted excimer laser coronary angioplasty (ELCA) of 53 lesions in 46 patients (pts).

| | |
|---|---|
| Death: | 0 pts (0%) |
| Non-fatal MI: | 3 pts (7%) |
| Emergency CABG: | 2 pts (4%) |
| Repeat PTCA: | 1 pt (2%) |

MI = myocardial infarction; CABG = coronary artery bypass grafting; PTCA = balloon coronary angioplasty.

occluded right coronary artery, successfully recanalized by ELCA and followed by adjunctive PTCA.

Procedural complications, i.e., occurring before removal of the guide catheter, are summarized in Table 1. Intimal dissection was primarily associated with adjunctive PTCA after ELCA and was limited to types A and B according to the classification of Dorros et al. [51]. A transient occlusion after ELCA of 3 lesions in 3 patients could be resolved by subsequent balloon PTCA. No coronary perforations, i.e., extravasation of contrast medium, were noted. Clinical complications occurring during the hospitalization period are listed in Table 2, and are mutually exclusive, that is, only the most severe event in the ranking order: death, non-fatal myocardial infarction, emergency CABG and repeat PTCA is counted in an individual patient.

## Quantitative coronary analysis after excimer laser angioplasty

### *Quantitative angiographic results*

Quantitative coronary angiography (QCA) was performed on the lesions selected for treatment with ELCA in the Thoraxcenter, as described above. Coronary angiograms before ELCA (n = 53), after ELCA (n = 50) and, if applicable, after adjunctive balloon PTCA (n = 42) were analyzed quantitatively with the computer-assisted Cardiovascular Angiography Analysis System (CAAS), which has previously been described in detail [52]. The CAAS computer algorithm automatically detects the contours of the vessel lumen filled with radiographic contrast medium, and a minimal luminal diameter

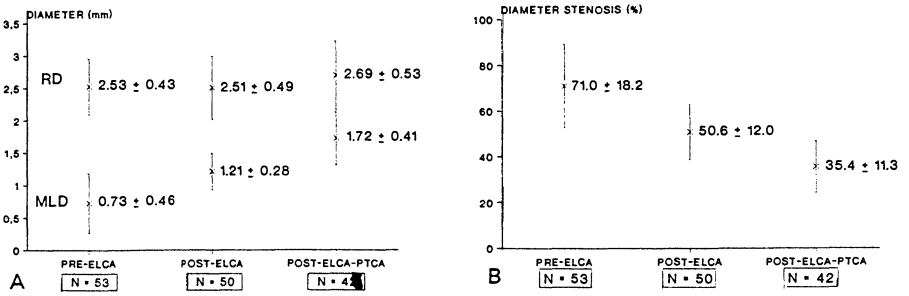


*Figure 9.* Changes in reference diameter (RD) and minimal luminal diameter (MLD) (A), and percent diameter stenosis (B) before (n = 53) and after (n = 50) excimer laser coronary angioplasty (ELCA), and after adjunctive balloon angioplasty (PTCA) (n = 42). Eight lesions had stand-alone ELCA.

and an interpolated reference diameter are determined in absolute millimeters using the guide catheter as a scaling device. A percent diameter stenosis can then be calculated.

Results of QCA are presented as mean value ±1 standard deviation (SD). Comparison between groups (pre-ELCA, post-ELCA and post-PTCA) was performed using paired and unpaired two-tailed Student's t-tests. A p-value of $<0.05$ was considered to indicate a significant difference. The immediate efficacy of ELCA with adjunctive balloon angioplasty as assessed by QCA is shown in Fig. 9. Preprocedural minimal luminal diameter was $0.73 \pm 0.46$ mm. ELCA significantly improved minimal lumen diameter to $1.21 \pm 0.28$ mm ($p < 0.0001$), and with PTCA, it further increased to $1.72 \pm 0.41$ mm ($p < 0.0001$). Reference diameter did not change significantly. Thus, percent diameter stenosis was reduced from $71 \pm 18\%$ to $51 \pm 12\%$ ($p < 0.0001$) after ELCA, and further to $35 \pm 11\%$ ($p < 0.0001$) following adjunctive PTCA.

When the criteria for visual assessment of the intervention – as described in the previous section – are applied on individual QCA measurements of pre-ELCA, post-ELCA and post-PTCA angiograms, laser-, procedural and clinical successes in the present population were 43%, 81%, and 76%, respectively. Thus, there is considerable discrepancy between visual and quantitatively determined success rates particularly after ELCA alone using arbitrary, categorical cut-off criteria. This may be due to the frequently observed hazy appearance of the vessel and unclear luminal borders after ELCA precluding an accurate visual assessment of the result (see Fig. 8). It underscores the importance of automated quantitative coronary angiographic analysis in the evaluation of ELCA procedures. Consequently, new criteria based on absolute measurements of coronary luminal dimensions should be designed or developed to assess results of ELCA in an objective manner.

*Quantitative angiographic comparison with balloon angioplasty based on matched lesions*

Limited comparative data exist on the relative efficacy of excimer laser and balloon angioplasty in the treatment of coronary artery stenoses [39]. Awaiting the results of randomized trials (see below) [53, 54], we compared the acute and long-term effects of excimer laser-assisted balloon angioplasty (EL-BA) with those of balloon angioplasty (BA) alone using quantitative angiographic analysis. For this purpose, the initial consecutive 35 successfully treated EL-BA-lesions were matched with 35 coronary artery lesions selected from a consecutive series of lesions successfully treated by BA. The coronary artery tree was subdivided into 15 segments according to the American Heart Association guidelines and the lesions were individually matched according to reference diameter and minimal luminal diameter. The principles of matching by quantitative angiography are as follows: 1) the angiographic dimensions of matched lesions are assumed to be 'identical', and 2) the observed difference in reference diameter and minimal luminal diameter between the two 'identical' lesions must be within the range of twice the variability of the quantitative analysis system of 0.10 mm ( = 1 SD) [52]. Thus, lesion pairs were selected in which the difference between these angiographic variables did not exceed 0.2 mm (twice the variability; 95% confidence limits). Matching was performed by an independent analyst according to the above mentioned criteria. All patients in the EL-BA and BA groups had 6–months follow-up angiography for quantitative coronary analysis of the previously treated lesion(s). At the time of selection, the analyst was unaware of the 6–months angiographic outcome and was thus blinded.

Matching was considered adequate since the reference diameter and minimal luminal diameter at baseline were equal in both groups; 2.67 ± 0.38 mm and 0.72 ± 0.50 mm for the EL-BA-group, and 2.66 ± 0.40 mm and 0.71 ± 0.49 mm for the BA-group, respectively (Table 3). Clinical baseline characteristics (sex, age, diabetes, hyperlipidemia) of the two patient groups were similar. In Table 3 the immediate and long-term results of EL-BA and BA as assessed by quantitative analysis are summarized. Maximum balloon diameter was 2.59 ± 0.35 mm and 2.58 ± 0.37 mm and balloon/reference diameter ratio was 1.00 ± 0.16 and 1.02 ± 0.19 in the EL-BA and BA-groups, respectively. Changes in minimal luminal diameter are presented in Fig. 10. Both interventions resulted in a significant increase in minimal luminal diameter (i.e., the 'acute gain') of 1.03 ± 0.59 mm and 1.10 ± 0.59 mm, respectively, relative to baseline. At follow-up, the decrease in minimal luminal diameter relative to post-intervention (i.e., the 'late loss') was somewhat higher in the EL-BA-group (0.57 ± 0.62 mm), but not significantly different from that in the BA-group (0.42 ± 0.68 mm).

In conclusion, no significant difference in immediate and long-term efficacy of EL-BA and BA could be detected with quantitative coronary analysis in this limited population of successfully treated lesions. A prospective,

*Table 3.* Quantitative comparison of the immediate and long-term results of EL-BA with BA in 35 stenoses.

| Coronary | EL-BA | BA | t-test |
|---|---|---|---|
| Reference diameter (mm) | | | |
| pre | 2.67 ± 0.38 | 2.66 ± 0.40 | NS |
| post | 2.79 ± 0.48 | 2.69 ± 0.40 | NS |
| follow-up | 2.67 ± 0.56 | 2.60 ± 0.51 | NS |
| Minimal luminal diameter (mm) | | | |
| pre | 0.72 ± 0.50 | 0.71 ± 0.49 | NS |
| post | 1.75 ± 0.40 | 1.81 ± 0.34 | NS |
| follow-up | 1.18 ± 0.60 | 1.39 ± 0.61 | NS |
| Diameter stenosis (%) | | | |
| pre | 73.0 ± 18.8 | 73.2 ± 18.6 | NS |
| post | 37.0 ± 10.9 | 31.9 ± 9.9 | NS |
| follow-up | 55.8 ± 20.8 | 45.9 ± 20.9 | NS |

EL-BA = excimer laser-assisted balloon angioplasty; BA = balloon angioplasty alone; pre = before intervention; post = after intervention; NS denotes a non-significant difference.

randomized trial of excimer laser versus balloon angioplasty in which patient and lesion characteristics are balanced has been undertaken to assess the relative benefits of these techniques in the treatment of a specific and well-defined coronary lesion pathology. In this setting, automated quantitative coronary angiography is used to objectively determine whether 'debulking' of an atherosclerotic lesion by excimer laser radiation result in superior immediate and late outcomes as compared to balloon angioplasty alone.

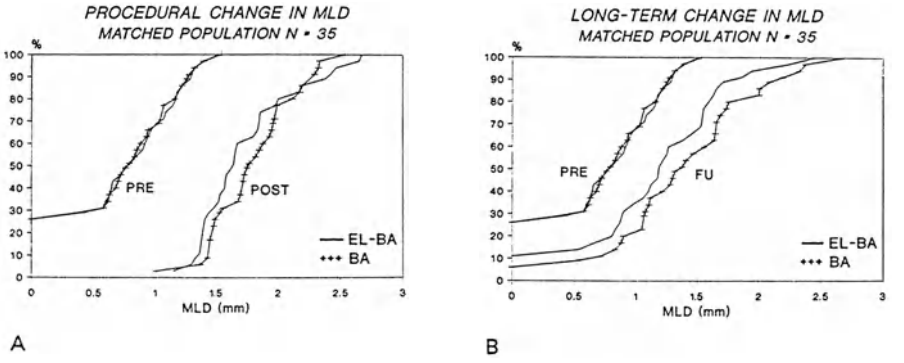


*Figure 10.* Cumulative frequency curves showing changes in minimal luminal diameter (MLD) to illustrate the immediate (A) and long-term effects (B) of excimer laser-assisted balloon angioplasty (EL-BA) and balloon angioplasty alone (BA).

PRE = before intervention; POST = after intervention; FU = at follow-up.

**Randomized trial comparing excimer laser and balloon coronary angioplasty**

In September 1991, the Academic Medical Center (Amsterdam) and the Thoraxcenter (Rotterdam) have initiated a cooperative randomized study of the efficacy of ELCA versus balloon PTCA in the treatment of long ($\geq$10 mm) coronary stenoses or occlusions (AMRO-trial) [53, 54].

*Patient selection*

The target population includes patients with stable angina pectoris and objective signs of myocardial ischemia scheduled to undergo a percutaneous intervention for a coronary stenosis (>50% diameter reduction) or occlusion of 10 mm or longer as visually assessed on the diagnostic angiogram. Clinical exclusion criteria are unstable angina, evolving or recent (within past 2 weeks) myocardial infarction, and contraindication for emergency CABG. A life expectancy of less than 1 year and factors making clinical or angiographic follow-up unlikely also form exclusion criteria. Angiographic exclusion criteria are intended angioplasty of a venous coronary bypass graft, unprotected left main disease, extreme tortuosity of the vessel segment to be treated, highly eccentric lesions, bifurcation lesions, intended angioplasty of a lesion with angiographical evidence of thrombus, and total occlusion with a very low chance of crossing by guide wire. A total of 300 patients will be enrolled in 2 years.

*Randomization and treatment*

After written informed consent is obtained, patients undergo a base-line exercise test including $^{99\,m}$Tc methoxyisobutyl isonitrile (MIBI) single photon emission computed tomography (SPECT), and are then randomly assigned to one of two treatment groups (PTCA or ELCA). All patients are pretreated with a calcium-channel entry blocker, and receive the intervention within two days of randomization. Aspirin is given before and for six months after the procedure, heparin is given at the beginning and during the procedure to keep the ACT above 400 sec., and intracoronary nitroglycerin is given during the procedure at the operators' discretion. All patients are maintained on an overnight heparin drip until the morning after the procedure. Until hospital discharge, nifedipine 20 mg tid is given. PTCA is performed using standard technique and modern balloon catheter equipment. The technical details of ELCA are described above and will be in accordance with the latest insights using the newest available laser catheters.

*Follow-up*

After discharge, patients are seen after one and six months. If symptoms recur after successful angioplasty, medical therapy is first optimized. Six

months after randomization or when symptoms dictate, exercise testing with $^{99m}$Tc MIBI SPECT and repeat quantitative coronary angiography is performed. During follow-up exercise testing and myocardial perfusion studies, all medication for angina pectoris will be withdrawn if clinical status permits.

*End points*

Primary clinical end points of the study are the occurrence of any of the following: cardiac death, myocardial infarction, CABG, stent implantation and repeat PTCA after the initial procedure. The primary scintigraphic end point is the extent of myocardial perfusion as assessed by $^{99m}$Tc MIBI SPECT at follow-up. The primary angiographic end point is the minimal luminal diameter at the treated coronary site at six months relative to base-line as determined by quantitative analysis using an automated contour detection technique (CAAS), described above. Secondary end points include patients' functional class for angina pectoris, other quantitative angiographic parameters (percent diameter stenosis, reference diameter, plaque area) at six months relative to base-line and evidence of restenosis in the two treatment groups according to the various criteria. Finally, a cost-benefit analysis will be performed.

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# 32. Evolving quantitative angiographic approaches to the comparative assessment of luminal renarrowing and longterm outcome after different transluminal coronary interventions

DAVID P. FOLEY, WALTER R. HERMANS, VICTOR A. UMANS, BENNO J. RENSING, PETER P. DE JAEGERE, JAVIER ESCANED, PIM J. DE FEYTER and PATRICK W. SERRUYS

## Introduction

Since its inception as a specialist discipline, interventional cardiology, has been, and still is to the present time, preoccupied with the achievement of a greater understanding, and ultimately, control, of the biological healing process after percutaneous transluminal coronary angioplasty [1, 2], the apparent enigma of "restenosis" [3]. Introduction and application of a wide variety of alternative and adjunctive treatment modalities (endoluminal coronary stent implantation [4], directional, extractional or rotational [5–7] atherectomy, laser balloon angioplasty [8] and laser angioplasty [9, 10]), as well as a wide variety of pharmacological agents have, thusfar, failed to suppress this ubiquitous process [11–17].

Innovators and exponents of new treatment modalities may allow their enthusiasm to compromise their objectivity and thus many interventionalists, armed with the latest device, acquire the expertise to use it largely through self-training techniques. As physicians and human beings we tend to assess the therapeutic impact of various modalities by clinical observations in the short term and allow our judgement to be influenced more by anecdotal experience, than by the results of carefully controlled prospective clinical studies. It is vital that the value of all new treatment modalities must be submitted to objective and critical assessment through such objective non-biased studies, using the best available methodological analytical techniques [18–20].

The advent of computer assisted quantitative coronary angiography [21–23], has demonstrated the fallibility of traditional visual and user-dependant techniques for assessment of the coronary cineangiogram [24], on which most of, if not all, the early reports on restenosis following angioplasty are based. Tenets founded on the results of early clinical studies must, therefore, be re-examined in the light of new revascularization and imaging technology, and we must be prepared to consider potential changes in basic philosophical and methodological approaches to both the treatment of coronary disease



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*Table 1.* A number of angiographic definitions of restenosis which have been used in various clinical studies. NHLBI 1, 2, 3, and 4 are criteria for angiographic restenosis, as laid out by the National Heart, Lung, and Blood Institute of the United States.

1. A diameter stenosis ≥50% at follow up [33].
2. An immediate post-PTCA diameter stenosis <50% that increases to ≥50% at follow up [34, 37].
3. As for 2 above, but a diameter stenosis ≥70% at follow up (NHLBI 2) [35].
4. Loss during follow up of at least 50% of the initial gain at PTCA (NHLBI 4) [36].
5. A return to within 10% of the pre-PTCA diameter stenosis (NHLBI 3) [37].
6. Loss ≥20% diameter stenosis from post PTCA to follow up [38].
7. Loss ≥30% diameter stenosis from post PTCA to follow up (NHLBI 1) [34].
8. A diameter stenosis ≥70% at follow up [39].
9. Area stenosis ≥85% at follow up [40].
10. Loss ≥1 $mm^2$ in stenosis area from post PTCA to follow up [41].
11. Loss ≥0.72 mm in minimal luminal diameter from post-PTCA to follow-up [42].
12. Loss ≥0.5 mm in minimal luminal diameter from post-PTCA to follow-up [43].
13. Diameter stenosis >50% at follow up with >10% deterioration in diameter stenosis since PTCA of a previously successfully dilated lesion (defined as diameter stenosis <50% with a gain of >10% at PTCA) [44].

and evaluation of outcome following treatment, as a consequence of fresh insights provided.

In the following paragraphs we outline the main discrepancies in the "restenosis literature", and discuss the basis for quantitative angiographic techniques and their clinical impact. We introduce and describe new methodological approaches, using quantitative coronary angiography, for the assessment of immediate and, particularly, long term, outcome following balloon angioplasty and the newer devices for percutaneous coronary revascularization. Through these new approaches, we explore the experimentally demonstrated and hypothetically inferred clinical relationship between vessel wall injury at intervention and subsequent "restenosis" [25–32], and, hopefully, provide a plausible angiographic strategy for clinical study of this phenomenon.

### *Ambiguous categorical restenosis definition criteria*

At this time, there appears to be no agreement on how to "define" "restenosis", and there have been at least 13 different 'definitions', based on coronary angiographic findings, applied by various clinical investigators attempting to address the problem of restenosis through clinical studies in recent years (Table 1), [22–33]). As a consequence of "definition" inaccuracy, in addition to variable angiographic follow up rates (57–100%), as well as the continued use of visual assessment of the coronary angiogram by most investigators, the reported "incidence of restenosis" varies widely from 12–60% [20] and most of these studies are not usefully comparable. Applying three different and widely used definitions to a series of 398 lesions serially measured during

six month follow-up, our group [42] demonstrated that: (a) the greatest single determinant of the "restenosis rate" is the choice of "definition" and (b) even if the eventual "incidence of restenosis" is similar, different "definitions" identify different patient populations, making risk factor determination (and indeed meaningful study of the natural history of the restenosis process) impossible [18]. These diversities are almost certainly responsible for much of the confusion surrounding the concept of restenosis following PTCA.

Although some of the definitions commonly used (eg diameter stenosis at follow up $\geqslant 50\%$) are based on historical physiological concepts [45], the measurement used is percent diameter stenosis, which is inherently flawed by the method of computation. Percent diameter stenosis is traditionally calculated by assuming a "normal" diameter value for a segment of coronary vessel immediately proximal or distal to area of interest as a reference point. This assumption has been shown to be erroneous, particularly in the context of multivessel disease when there is virtually always diffuse intimal and/or subintimal thickening [46, 47] as well as variable age-related or compensatory ectasia [48], and following interventions when the "reference diameter" becomes involved in the restenosis process [49–51]. In recent years, quantitative angiographic studies have, in fact, clearly and definitively revealed that absolute luminal measurements such as minimal luminal diameter (MLD) or minimal cross sectional area of coronary narrowings, provide more reliable and meaningful information than percentage diameter stenosis, with regard to haemodynamic significance of an obstructive coronary lesion [52–56].

*The interpolated reference diameter*

To circumvent the potential for inaccuracy with respect to percent diameter stenosis measurements calculated using an arbitrarily selected "reference segment" by the observer, the computer based Cardiovascular Angiographic Analysis System (CAAS) (described further below) generates the "interpolated reference diameter" [23, 55, 56] (Fig. 1). The contour detection algorithm "reconstructs" how the arterial borders of the segment of interest should appear in the disease-free state, by the technique of "interpolation". According to this process, the actual "lesion" itself (obstructed region/segment) is excluded, using the curvature analysis, which detects the proximal and distal ends of the lesion (this process may be less accurate in diffusely diseased vessels than where there is a discrete stenosis). Then, in a continuous fashion, on the basis of the detected contours of the proximal and distal segments and allowing for anatomical vessel tapering, using a second degree polynomial function, the arterial contours over that segment are "interpolated". The measurement taken as the reference diameter then, is the "interpolated reference diameter" (from the so called "diameter function curve") at the site of the minimal luminal diameter (Fig. 1). The theoretical basis of and actual mathematical steps involved in this process have been described

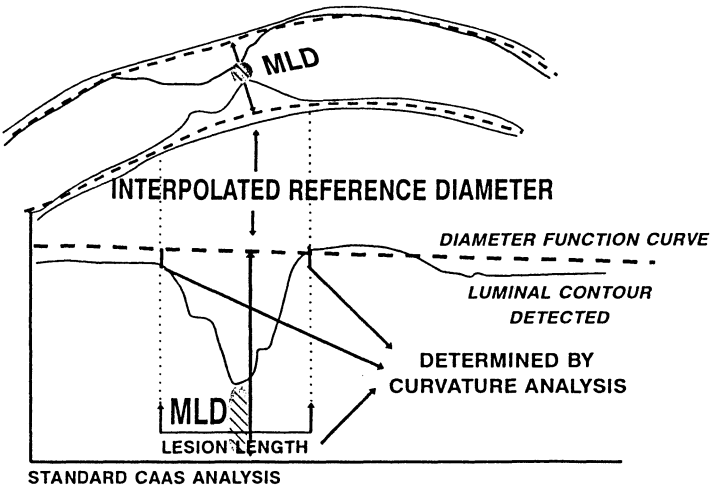


*Figure 1.* Graphic representation of the CAAS measurement of interpolated reference diameter. The actual luminal contour is detected by the edge detection technique. The proximal and distal extremities of the obstructive lesion are determined from the curvature analysis of the detected contour and the thus identified lesion is then excluded from the determination of the interpolated reference diameter. A second degree polynomial function is applied to diametric measurements made from each scanline (every 0.1 mm) of the segment proximal and distal to the lesion, anatomical vessel tapering is taken into consideration and the vessel contours in the area of the lesion are "reconstructed" and interpolated into the diameter function curve (shown as the dashed line in the analysis and corresponding upper and lower vessel contours). The actual "interpolated reference diameter" used then is the diametric measurement, from the diameter function curve, at the point of the minimal luminal diameter, as shown. MLD = minimal luminal diameter.

in detail in technical publications in the past and are discussed in other areas of this book.

Figure 2 illustrates the potential pitfalls of the arbitrary selection of proximal and/or distal coronary segments as a reference point and how a more objective measurement of percent diameter stenosis can be derived using the interpolated reference diameter. Nevertheless, even with use of interpolated reference diameter, inaccuracy introduced by the presence of diffuse arterial disease (and post intervention) is not surmounted, and the use of minimal luminal diameter appears more reliable for the purpose of important clinical research, as elaborated upon in later sections.

### *Coronary luminal measurement by quantitative coronary angiography – the CAAS approach*

At this time the coronary cineangiogram is still the only universally available imaging modality for examination of coronary anatomy, and quantitative angiographic techniques, as described below, have emerged as the gold

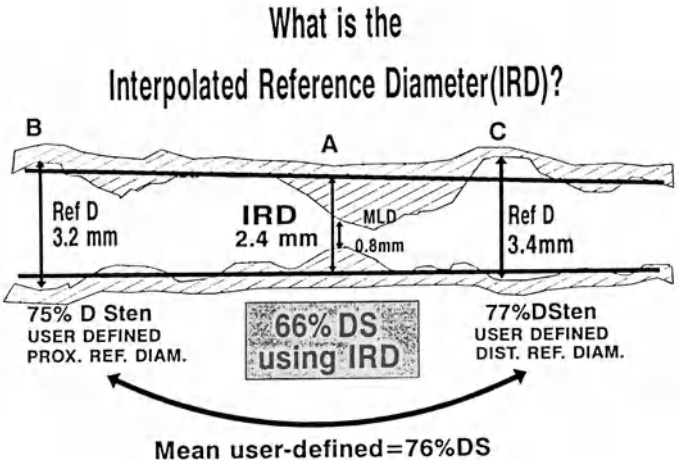


*Figure 2.* Graphic to demonstrate variability in percent diameter stenosis measurements of the same lesion due to arbitrary selection of the reference diameter by the "user", and the more objective derivation of percent diameter stenosis by the user-independent method of the interpolated reference diameter. For a stenosis where the minimal luminal dfiameter is measured at 0.8 mm, if a user defined proximal or distal reference segment or mean of both is selected then the resultant measure of percent diameter stenosis for the obstructing lesion is 75%, 77% or 76% respectively. If the computer determined interpolated reference diameter (shown as the upper and lower thick dark lines) is used a diameter stenosis measurement of 66% is obtained. Prox. ref. diam. = proximal reference diameter, dist = distal, MLD = minimal luminal diameter,%DS = percent diameter stenosis.

standard for the accurate and objective analysis and description of the basic cineangiogram, particularly in the context of large, multicentre "restenosis prevention" clinical studies and trials of percutaneous coronary revascularization devices.

Quantitative coronary angiography (QCA) has been used at our institution for a decade [12–14, 21–23, 42, 49, 53–94] and is becoming increasing available with the development of on-line quantitative angiographic computer software for digital cineangiographic imaging (DCI) equipment in the catheterization laboratory. The CAAS system has been rigorously and extensively validated and the methodology is described in detail elsewhere [21–23, 67, 68, 75–77].

Of all the measurements acquired by quantitative angiography, the absolute value of the minimal luminal diameter (MLD) has been shown to be the greatest single determinant of the haemodynamic consequences of a stenosis, since this parameter affects blood flow by a fourth power term [53, 95–97]. It is therefore the most unambiguous, objective and reproducible parameter to use for primary measurement of coronary luminal calibre and changes therein resulting from interventions (ie. the angiographic gain after

intervention and subsequent loss during follow up, and, as described later, the proportional angiographic gain and loss (so called "Relative Gain" and "Relative Loss"), which normalize the gain and loss for the actual vessel size). Important multicentre trials examining the impact of various treatment strategies on restenosis have, in recent years, been availing of central, standardized, blinded, computer assisted, quantitative angiographic analysis in angiographic core laboratories [78, 79, 89, 90, 98, 99, 107], and have begun to employ the minimal luminal diameter (MLD) as the most objective and useful measurement [100].

In the past, our group used the long term minimal luminal diameter measurement variability of the CAAS system as a means of identifying lesions undergoing "significant" or detectable luminal change during follow up after balloon angioplasty [68]. The standard deviation of the mean difference between MLD measurements of the same lesions at different points in time where no intervention was carried out was measured under a "worst case" scenario and found to be 0.36 mm. Two standard deviations, would identify, with 95% confidence, lesions undergoing a real, detectable or "significant" change. Using the long term lesion measurement variability it was felt might present an objective approach to dividing patients followed up after PTCA into "restenosis" and "non restenosis".

That study may now be considered as somewhat obsolete since, as highlighted by Ellis and Muller [3], and as we ourselves had already recognized, a large number of limitations to this "definition of restenosis" are now evident. Firstly, the developmental study used vessels with an average reference diameter of 3.7 mm [68] whereas in two recent large multicentre restenosis prevention studies the mean reference diameter of treated vessels was 2.6 mm [89, 90]. Furthermore the initial study used a "worst case scenario" whereas extensive standardization measures (use of intracoronary nitrates to control vasomotor tone, performance of angiography in exactly matched multiple projections, careful identification and selection of an end-diastolic cine-frame for QCA analysis etc.) are now carried out in modern multicentre studies [89, 90], and furthermore *post-PTCA* measurement variability cannot be inferred from the original study as no intervention was carried out.

We have now completed a pilot study as described in a separate chapter of this book [60] which provides clear angiographic data in this regard, whereby among 110 lesions (mean vessel size of 2.67 mm), studied post balloon angioplasty and at 24 hr (under optimally standardized conditions ie. matched angiographic projections, intracoronary nitrate prior to angiography, full therapeutic anticoagulation), there was no difference in MLD (.007 mm, $p = 0.79$) and the standard deviation of the mean difference was 0.2 mm. By extrapolation from these data, it can be concluded that the post PTCA lesion measurement variability of the CAAS system is 0.2 mm, thus a change of 0.4 mm in MLD can be considered, with 95% confidence, to represent a real change and thus as a *potential* criterion for detection of significant luminal loss or renarrowing. In the light of the well recognized

difficulties of angiographic interpretation of the post balloon angioplasty result, we believe this measurement variability to be eminently acceptable.

It must be noted that the criterion we propose for detecting "significant change" in MLD over a period of time is the measurement variability of the analytical system being used. The figure of 0.4 mm represents the variability of the CAAS system and may not be relevant to other systems. Ultimately, as alluded to already, and as discussed further below, the application of dichotomous criteria to the description of long term outcome following intervention is fraught with imprecision, conflict, controversy and dissension.

*New insight to the restenosis process facilitated by QCA*

*Restenosis is a time-related ubiquitous phenomenon which is normally distributed in the treated population*

The first major contribution of quantitative angiography to the understanding of the restenosis process after balloon angioplasty was the virtually simultaneous demonstration by our group [42] and Nobuyoshi et al. [43] that lumen renarrowing develops to some degree in virtually all treated lesions to a greater or lesser degree and progresses to about 4 months after angioplasty with minimal further deterioration up to a period of one year. This finding stimulated our strong recommendation that in clinical trials, all patients should be followed up by coronary angiography and the long term outcome should be described in terms of the "change" in lumen during follow up instead of applying rather arbitrary and meaningless categorical definitions of "restenosis" [42].

Subsequently, Beatt et al. demonstrated, in a number of clinical studies focusing on various aspects of the restenosis problem, that quantitatively measured changes in minimal luminal diameter and in reference diameter, during the months after PTCA, are, in fact, normally distributed [49, 101–103]. This view of a continuous unimodal distribution for luminal change after balloon angioplasty, although strongly challenged at that time, became the nidus of our philosophy regarding methodological approach to addressing the problem of restenosis [61, 62, 74, 80–94]. The Beth Israel group subsequently strongly corroborated these early reports, demonstrating similar distribution patterns of luminal change following intervention in patients undergoing directional atherectomy or stent implantation [104, 105].

At a later date, however, the Emory group examined, by clinical estimation of percent diameter stenosis, a large cohort of patients undergoing balloon angioplasty and follow up angiography. They found a bimodal distribution and concluded that there was either a physiological bimodal distribution or a systematic measurement error around the 50% diameter stenosis mark when clinically evaluating cineangiograms [106]. This finding, if confirmed, would therefore justify a categorical approach to the assessment of angiographic outcome in clinical trials thereby challenging the emerging

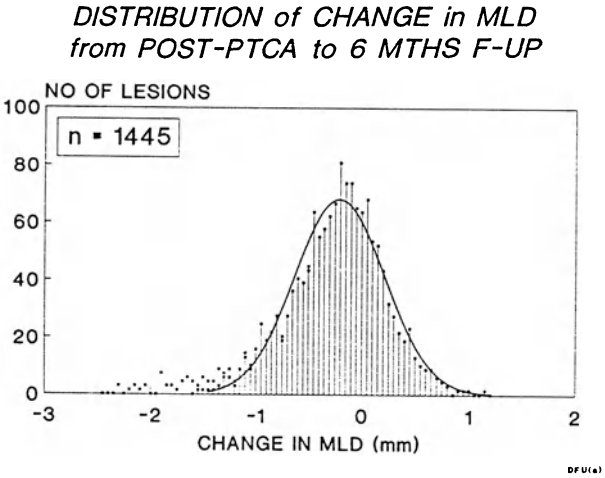


*Figure 3.* Histogram of change in minimal luminal diameter during 6 month follow up of 1445 primary lesions treated by coronary balloon angioplasty during two large restenosis prevention trials. The theoretical gaussian curve, given the mean and standard deviation, is superimposed, clearly illustrating that luminal renarrowing is a normally distributed phenomenon. (Reproduced with permission from [74].

assumptions of a continuous distribution arising from the separate findings of our group and the Beth Israel group. This prompted our group to reinvestigate this phenomenon in a much larger patient population than had been studied in the original studies [49, 101–103], and under more standardized and consistent quantitative angiographic conditions. In this study of 1234 patients, it was demonstrated unequivocally that luminal renarrowing after PTCA, whether assessed using minimal luminal diameter or percent diameter stenosis at follow up or the change in these measurements during follow up, clearly follows a Gaussian or normal distribution (Fig. 3; [74]), in agreement with our own earlier findings [49, 62], and the reports by Kuntz et al. in patients treated by other devices [105]. These corroboratory findings appear to identify a basic flaw in the clinical impression of a bimodal phenomenon. It is our contention, on this basis, that a dichotomous view of restenosis is inappropriate and that categorically generated restenosis rates should no longer be the *main* focus of important scientific studies or discourse in this vital area.

There may be sound clinical reasons for selecting particular angiographic definitions of restenosis, but in the context of scientific studies or restenosis prevention trials, the use of a blanket categorical cut-off point (eg. $> 50\%$ diameter stenosis) conveys no measure of the extent of luminal renarrowing and therefore cannot provide a comprehensive assessment of the effect of a particular therapeutic approach for the control of the biological *process of restenosis*. Furthermore, since the threshold level for absolute (or relative)

luminal renarrowing which is physiologically or clinically significant is unknown, it is much more realistic and meaningful (as well as requiring much fewer patients [19]) to study the overall effects of an intervention in terms of the mean change in minimal luminal diameter for the entire group [89, 90].

Detailed examination of comprehensive quantitative angiographic data prospectively collected during two European trials for the prevention of restenosis after coronary balloon angioplasty has provided further important and valuable insights to the restenosis process. Whether considered according to a categorical cut-off point or as a continuous process of luminal loss, restenosis was found to be evenly distributed throughout the coronary tree [80]. Furthermore, in multivariate analysis of clinical procedural and angiographic factors in a number of separate studies, the strongest predictor of restenosis (considered categorically or as luminal loss during follow up) was consistently found to be the relative luminal gain at angioplasty [61, 62, 91, 94]. In addition, it has become clear that following balloon dilatation the restenosis process involves the entire segment dilated including apparently "normal" vessel adjacent to the target lesion [51]. This finding confirmed an earlier report from our group, which showed progressive decrease in the "reference diameter" during follow up [49], and re-iterates the weakness of percent diameter stenosis measurements, as already described.

### *Comparative assessment of new devices using MLD as the central measurement*

New dilemmas have arisen as a result of the explosion of new interventional coronary treatments with respect to comparison of results, particularly long term outcome. Broad comparisons between the various devices is difficult and may be considered to be invalid, since it is generally recommended that atherectomy devices and endoluminal stents should not be used in coronary vessels less than 3 mm in diameter, whereas PTCA can be carried out in arteries less than 2 mm in size and rotational atherectomy and excimer laser therapy are best suited to smaller vessels.

Due to the need for comparison of immediate and long term effects between devices we have devised two approaches, based on quantitative angiography, for comparing the incomparable.

(*i*) *Matching – a temporary but convenient surrogate for randomization*
The first method enables us to actually "compare the comparable", by "matching" the lesions in each treatment group, for severity, location and vessel size, thereby defining a population in which any of the treatment modalities to be compared, may reasonably be employed. There are three basic principles, **(i)** the angiographic dimensions of the matched lesions are assumed to be identical, **(ii)** the observed difference between the two "identical" lesions must be within range of reproducibility of the computer analysis

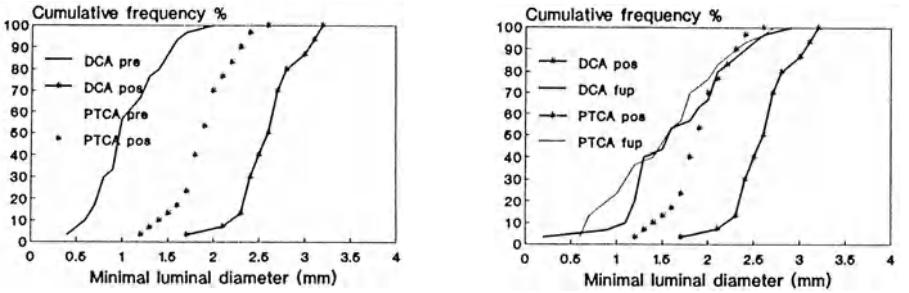


*Figure 4.* Cumulative frequency(distribution) curves to illustrate the differential immediate (pre – post) and follow-up (post – follow-up) effects of PTCA versus directional coronary atherectomy (DCA) on "matched" coronary lesions, with regard to absolute minimal luminal diameter(MLD) measured by quantitative coronary angiography, (see text for explanation).(Reproduced, with permission, from [14]).

system being used (for the CAAS system this is±0.1 mm ie. 1 SD of the difference between repeated measurements of the same angiogram); and **(iii)** the reference diameter of the vessels to be matched are selected within a range of±3 SD (0.3 mm) giving confidence limits of 99% [14, 84].

Comparing the immediate angiographic results of PTCA, directional coronary atherectomy (DCA) and intracoronary stenting, using this technique, illustrates the usefulness of the approach and shows that both DCA and stenting yield a more favourable early result than PTCA [83]. Application of the matching principles to a direct comparison of immediate and long term angiographic outcome following PTCA and DCA or stent implantation using cumulative distribution curves (Figs 4, 5), [83, 93] is similarly rewarding in its clarity and simplicity. Since the lesions are matched for reference diameter, approximate overall improvement in luminal diameter (gain) at intervention and loss in minimal luminal diameter during follow up can be easily gleaned from the figure, and directly compared. It is appreciated that although DCA is associated with a significantly greater initial gain (improvement) in MLD, the loss (restenosis) following DCA is also significantly greater than following PTCA, so that the ultimate outcome (minimal luminal diameter **at** follow-up) is similar for both treatment modalities. Using this technique to compare immediate and long term angiographic results following PTCA and self expanding stainless steel stent implantation in 93 matched lesions, has revealed that although associated with a greater loss in luminal diameter during follow-up, stenting yields a significantly larger vessel lumen (reflected by a larger MLD) than PTCA, **at** follow-up [84].

The matching process, by its principles, may be justifiably used at this time, as a "surrogate" for randomised studies [84], facilitating otherwise invalid comparisons between interventions in relatively small patient groups. It is noteworthy that observations emerging from matching of patients under-

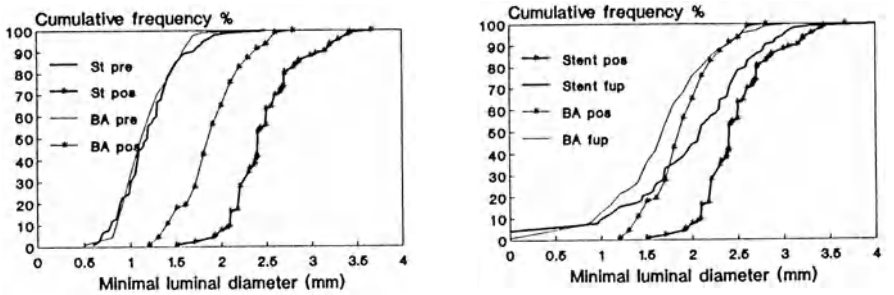


*Figure 5.* Graphic representation of the immediate (pre-post) and long term (post-fup) angiographic outcome of a matched study in 93 patients having balloon angioplasty or self-expanding stainless steel stent implantation. The superior initial gain by stenting is somewhat counterbalanced by a greater luminal loss during follow up. Nevertheless luminal diameter at follow up remains significantly greater than for balloon angioplasty. (Reproduced with permission from [84]).

going DCA and PTCA [86] have been confirmed by preliminary results of the CAVEAT trial [107], thus demonstrating a real and undeniable clinical use for this matching approach. In this context of comparable patient groups, in terms of baseline clinical and angiographic characteristics, the long term angiographic outcome can justifiably and objectively be assessed and compared using the minimal luminal diameter at follow up. For reasons given previously, percent diameter stenosis at follow up cannot be relied upon. The practical clinical value of minimal luminal diameter at follow up has been demonstrated in a recent European multicentre restenosis prevention study, reported by our group [92]. It was demonstrated that minimal luminal diameter less than or equal to 1.45 mm predicted recurrence of angina in 70% of cases and a positive exercise test in 60% (Fig. 6).

Furthermore, superior angiographic results, in terms of MLD at follow up, of DCA and stenting over "historical" PTCA results, as has been reported by Kuntz et al. [105, 110, 111] are put in a slightly different perspective by results obtained from matching. It is clear that the mean vessel size in patients treated by DCA and stent implantation are considerably greater (3.09 mm and 3.35 mm respectively,[ 105]) than in PTCA studies (2.6 mm) [89, 90]. Therefore, direct comparison of absolute angiographic results obtained by these "devices" with those obtained by balloon angioplasty becomes somewhat irrelevant, without either matching the groups to be compared or normalizing for the individual vessel size, as described in the next section.

The limitations of the basic matching approach to the comparison of interventional therapies are, of course, that other potentially influential clinical and angiographic parameters are not taken into account in the matching process, and, therefore, the effect of anginal status, medication, diabetes, lesion length, eccentricity, calcification, etc., on the comparative outcome of the treatment modalities, is ignored. However the matching study of stent

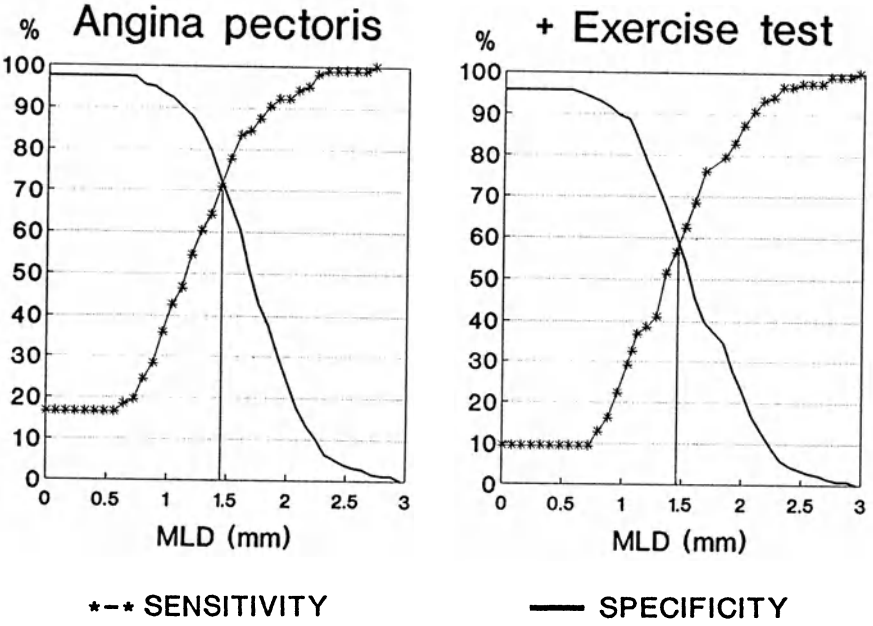


*Figure 6.* Derived from Rensing et al. [92](with permission). Cumulative frequency of recurrence of angina (left graph) and positive exercise test (bicycle ergometry, right graph) according to minimal luminal diameter at follow up, measured by CAAS, displayed as "sensitivity" of MLD for prediction of symptomatic recurrence or positive exercise test. The "specificity" curve in each graph depicts the cumulative frequency of freedom from angina and of a negative exercise test, according to the measured minimal luminal diameter at follow up. The intersection of the "sensitivity" and "specificity" curves in each graph identify the point of greatest diagnostic accuracy for the prediction of symptomatic recurrence and positive exercise test from measured minimal luminal diameter at follow up angiography. It is notable that this corresponds to 1.45 mm in each graph, implying that a minimal luminal diameter greater than this value is likely to be associated with freedom from angina in 70% of patients and a negative exercise test in 60%.

implantation and balloon angioplasty, [84] in fact, addressed this issue of potential disparity between patient groups with regard to these other variables, and found no significant differences in their distribution between the groups being compared. Furthermore, the matching comparison of balloon angioplasty with directional atherectomy [86] also took account of age, gender, diabetes and anginal status and found that this additional consideration did not affect the ultimate findings, as already described [87], thus perhaps vindicating the application of the simple basic angiographic matching principles employed.

*(ii) Relative gain and relative loss in minimal luminal diameter*

The second proposed method of comparison of therapeutic devices arose originally from the need to create some type of "sliding-scale" criteria to

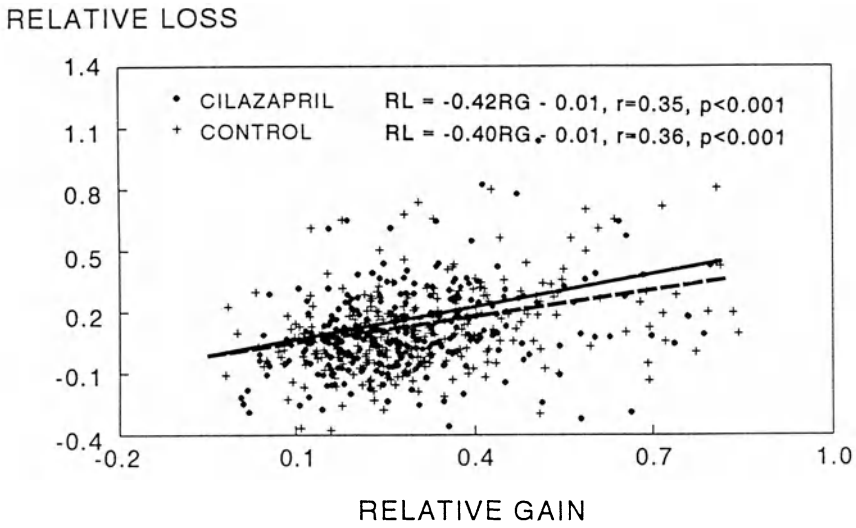


*Figure 7.* Scatter-histogram of all the values obtained for relative gain following PTCA and relative loss during follow-up in a large European multicentre restenosis prevention trial [90] for both placebo and treatment groups. A linear relationship emerges which is identical for both groups, although the coefficient of correlation is low at 0.4. (The full line represents the control group and the dashed line the treatment group)(See text for explanation).

circumvent the previously described limitations of the categorical "loss ≥0.72 mm" criterion for assessing the outcome of balloon angioplasty in vessels of different sizes. The concepts of "relative gain" and "relative loss" in minimal luminal diameter were therefore introduced to adjust luminal changes for individual vessel size, by normalizing the **absolute** change in MLD after intervention and during follow-up, for the reference diameter of the coronary segment in question [61, 62, 80], in a continuous approach. The net difference between relative gain and relative loss is termed the "net gain index" and is a measure of the ultimate net benefit of intervention.

These simple calculations may be presented as follows:

**Relative gain** = MLD post intervention – MLD pre intervention / vessel size
**Relative loss** = MLD post intervention – MLD at follow-up / vessel size
**Net gain index** MLD at follow up – MLD pre intervention / vessel size

The vessel size is represented by the interpolated reference diameter of the lesion pre intervention since this is the closest possible objective angiographic approximation of the "normal" disease-free vessel size (Figs 1, 2). Following intervention and at follow up, the interpolated reference diameter is subject to greater potential for measurement variability as a direct consequence of the intervention itself and of the restenosis process, respectively [49–51].

Kuntz et al. previously presented a relationship between absolute gain at

intervention and late loss during follow up in their patients treated by directional atherectomy and stent implantation [104]. However due to the wide variability in reference vessel size among lesions treatable by current interventional devices, we believe the application of relative gain and relative loss to be more appropriate and informative, for comparative purposes. Using data accumulated prospectively during each of 2 restenosis prevention trials [89, 90], we plotted the relative gain and relative loss values for all treated lesions (Fig. 7), and found a direct linear relationship between relative gain and relative loss (even though the co-efficient of correlation was low, at 0.4). Kuntz et al. have described a similar relationship between acute gain and late loss in their patients undergoing DCA or stent implantation [104] and also more recently a number of other investigators [108, 109] have produced concurring reports. This relationship between luminal increase at intervention and subsequent renarrowing is in agreement with widely reported experimental and pathological observations that neo-intimal hyperplasia is a direct function of the extent of vessel wall injury [25–32]. The actual regression relationship between relative luminal gain and relative luminal loss is not dissimilar (although somewhat weaker) from the relationship demonstrated by Schwartz et al. between depth of vessel wall injury and thickness of the subsequent neointimal hyperplasia in an experimental porcine model [29].

*The influence of vessel size on the restenosis process*

Exploration of the relationship of the vessel size itself to the process of luminal renarrowing reveals that the relative loss (proportional loss of lumen during follow up) decreases significantly as vessel size increases in increments of 0.5 mm as shown in Fig. 8. However, when it is similarly found that relative gain shows a parallel pattern it becomes evident that it is the relationship between relative gain and relative loss, as already described, which is of central importance to addressing the injury/hyperplasia phenomenon, from an angiographic viewpoint. To further investigate this finding we examined the relative gain/relative loss relationship within the lesion groups, as previously defined by increments of vessel size (Fig. 9) and found that this relationship did not vary with vessel size. Thus it could be concluded that vessel size itself does not influence the restenosis process, which appears to be determined mainly by the degree of luminal increase achieved at intervention (which in turn must be considered to reflect an index of the extent of wall injury imparted), regardless of the vessel size.

We could speculate that the reason for the greater relative gain observed in small vessels is due to the clinical requirement for a "good" angiographic result in the catheterization room. This demands considerable luminal gain in small vessels given the usual angiographic magnification limitations. In addition perhaps balloon (or device) oversizing is more likely or frequent in small vessels. With the greater relative gain, more extensive wall injury is

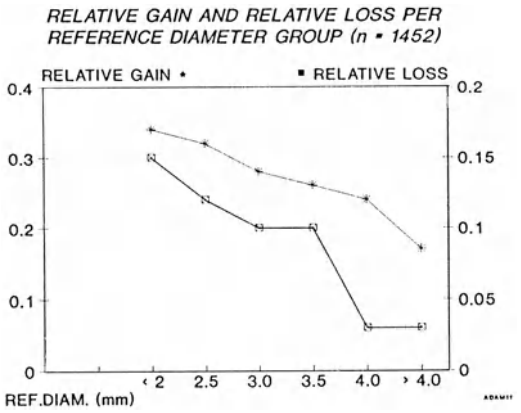


*Figure 8.* Relative gain and relative loss (on the Y axes) plotted against reference diameter in increments of 0.5 mm on the X axis. A parallel trend of decrease in both variables is observed with increasing reference diameter. (See text for explanation).

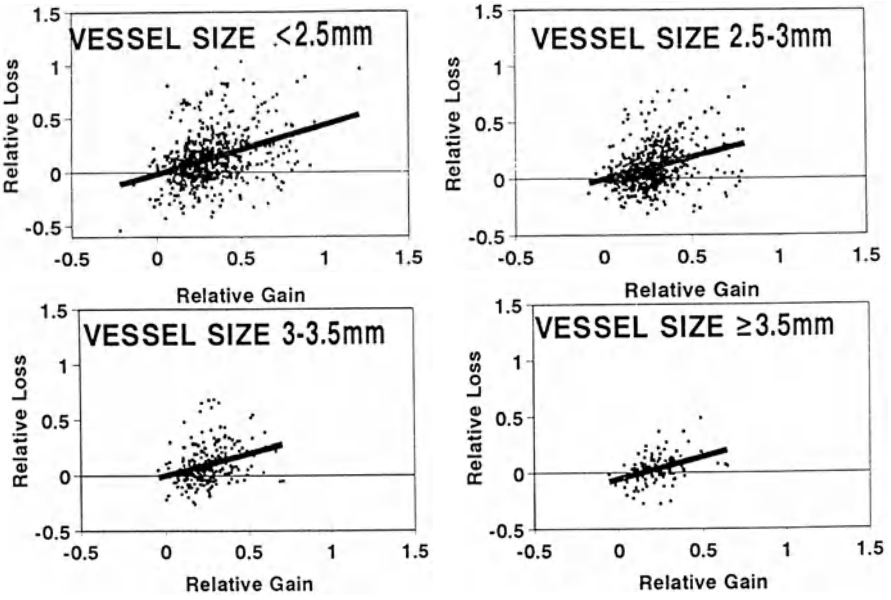


*Figure 9.* Linear regression of relative loss on relative gain according to the increments of vessel size as shown in Fig. 8. The relationship between the variables is similar for each group. It is also possible to glean from the receding scatter plots with increasing vessel size that the degree of relative gain is less in larger vessels as shown in Fig. 8, and the much greater frequency of balloon angioplasty procedures in smaller vessels.

imparted, provoking a more intense healing response, with formation of thicker neointimal layer, which is reflected by greater angiographic relative loss in lumen during follow up. This may be a simplistic but practical speculation on what is undoubtedly a complex and multifactorial phenomenon.

We have also examined the relationship between relative luminal gain at intervention and relative loss during follow up for other percutaneous coronary revascularization devices and preliminary results also demonstrate a direct linear relationship (Fig. 10) [81]. In the light of available evidence from previous clinical studies from our own institution [12–14, 17, 73, 85] and others [15, 16, 50, 105] as well as experimental reports [29, 30], and the commonly held belief that "restenosis" is a tissue response to vessel wall injury, the demonstration of such a relationship between relative luminal gain and loss is not all that surprising. The Mayo Clinic report [29] (of a proportional neointimal response to graded vessel wall injury) observing that the extent of coronary artery injury was more closely related to the actual thickness of the neointimal layer than to percent luminal area stenosis highlights the importance, in clinical angiographic restenosis studies, of attempting to measure the volume of the "doughnut" as well as the "doughnut hole". Collectively, all these studies sustain the contention that categorical restenosis definitions are inherently limited in their ability to describe the ubiquitous process of luminal renarrowing following interventions.

### *Clinical implications and applications of "Relative Gain" and "Relative Loss"*

This direct relationship between restenosis, as represented by "relative loss" in luminal diameter during follow up, and luminal improvement or "relative gain" at intervention, has important ramifications, not only for clinical trials but also perhaps for clinical decision making in individual patients. With the impending widespread availability of quantitative coronary angiographic facilities for the catheterization room precise measurements will be readily accessible "on-line", allowing a step by step objective and accurate assessment of progress during intervention, rather that the current practice of "eyeballing" the video screen, with its inherent limitations. This should facilitate appropriate selection of balloon and device sizes to avoid excessive vessel wall injury caused by oversizing.

As confirmed by the considerable scatter of data points in the regression analyses shown in Figs 7 and 9, the phenomenon of wall injury and healing response is clearly multifactorial and it would be fallacious to attempt to give individual guidelines as to the ideal relative gain for which to aim. Since the relative gain/relative loss relationship reveals that the expected relative loss would be approximately 0.42 of the relative gain, it is clear that increasing acute luminal improvements will ultimately yield a greater net angiographic benefit (despite provoking concomitantly greater relative luminal loss). Therefore, in the final analysis, achievement of the greatest luminal improve-

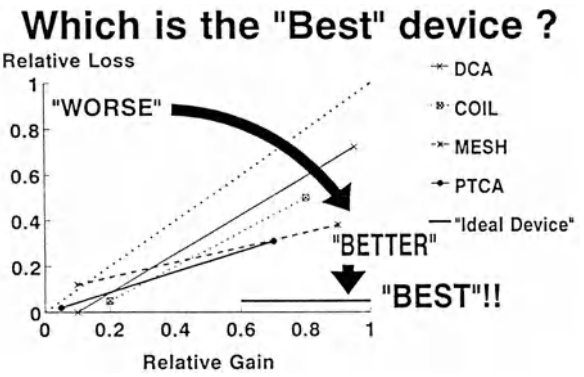


*Figure 10.* Linear regression relationship of relative gain/relative loss of patients who underwent therapy by 4 different interventional devices are shown, with the line of identity. The data points are omitted for the sake of clarity. An imaginary regression line for the "ideal" interventional device is included. It is clear that a device whose regression line crosses the identity line can be considered to provide a "worse" angiographic outcome than one with a gentler line slope. The ideal device has a horizontal regression line slope so that with increasing relative gain there is no increase in relative loss. According to this, the self-expanding stainless steel mesh stent appears to have the most favourable profile of the devices compared (marginally "better" than balloon angioplasty). DCA = directional atherectomy(n = 123 lesions), COIL = balloon-expandable tantalum coil stent(n = 101 lesions), MESH = self-expanding stainless steel mesh stent (n = 110 lesions), PTCA = percutaneous transluminal coronary (balloon) angioplasty (n = 1435 lesions).

ment possible, by the least traumatic means, and avoiding precipitation of acute complications, must still be the ultimate goal of percutaneous intervention.

Application of the relationship demonstrated between relative gain and relative loss in MLD to randomized trials will be the ultimate test of this approach, which we believe may present a simple, integrated and potentially unifying method for comparison of the therapeutic effectiveness of all interventional devices (Fig. 10). The "ideal device" would achieve appropriate levels of luminal improvement (depending on the degree of narrowing and the vessel size) yet be attended by minimal subsequent luminal loss, which would be relatively constant, regardless of the luminal gain. Such a device may take the form of a stent, since of the 4 devices compared in the figure representing actual clinical experience [82], the mesh stent appears to have the most promising profile. It is clear, however, that the considerable problems of stent thrombosis and haemorrhagic complications of the consequently necessary anti-coagulant therapy, as well as the ubiquitous hyperplastic tissue response, must be surmounted before this device may be considered "ideal". Extensive biological and experimental research is being carried out in this area with major new innovations in stent design and manufacture, including

bio-degradable, temporary and specially coated prostheses, which may ultimately provide important clinical benefit.

## Summary and conclusion

Restenosis after percutaneous coronary revascularization can be appreciated by quantitative coronary angiography as a process of luminal renarrowing which is ubiquitously and normally distributed among the treated population.

A proportional relationship can be identified between luminal renarrowing and luminal gain at intervention for a number of interventional devices which confirms that "restenosis" is unavoidable consequence of any therapy which inflicts injury on the arterial wall. We have no erudite solutions to this Achilles' heel of interventional therapy, and it is clear that the search for a "magic bullet" is now more compelling than ever.

We believe that the continuing search for this magic bullet would be facilitated by the adoption of a universally applied objective angiographic approach to the measurement of luminal changes after intervention and during follow up. In that regard we propose relative gain and relative loss in luminal diameter as the best correlates of wall injury and fibroproliferative response, for the study of the restenosis process, and we recommend minimal luminal diameter at follow up as the simplest, most objective and clinically useful angiographic end-point, for use in randomised clinical trials.

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*PART EIGHT: QCA applied to the national history of atherosclerosis*

# 33. Progression or regression of coronary atherosclerosis: Assessment with quantitative coronary angiography

PIM J. DE FEYTER, JEROEN VOS, CARLO DI MARIO, PATRICK W. SERRUYS and JOS R.T.C. ROELANDT

## Introduction

Recently published serial angiographic studies to assess retardation of progression or regression of coronary artery disease have only focussed on changes of pre-existing lesions or on the development of new lesions [1–9]. The observed changes have been expressed in terms of changes of percent diameter stenosis or absolute measurement of the minimal luminal diameter (mm) of a stenosis. However, progression and possibly regression, of coronary atherosclerosis is a complex process that is not limited to focal areas of the coronary artery tree but that frequently involves the entire arterial wall [10, 11].

Therefore, to assess the effect of an intervention on coronary atherosclerosis, both focal and diffuse changes of progression and regression should be measured. Quantitative coronary angiography has emerged as an useful technique to accurately quantify lesion characteristics and to assess both focal and diffuse changes of atherosclerosis [12].

## Limitations of serial angiography to assess progression or regression of coronary atherosclerosis

Coronary angiography is a two-dimensional shadowgram of an opacified vessel and therefore coronary atherosclerosis can only be detected if arterial wall disease encroaches upon the contour of the arterial lumen and consequently the underlying pathologic process can be identified only by inference. However, atherosclerotic changes of the arterial wall do not always produce changes on the contour of the lumen that can be detected accurately by angiography. Many studies [10, 13–24] have shown that coronary angio-



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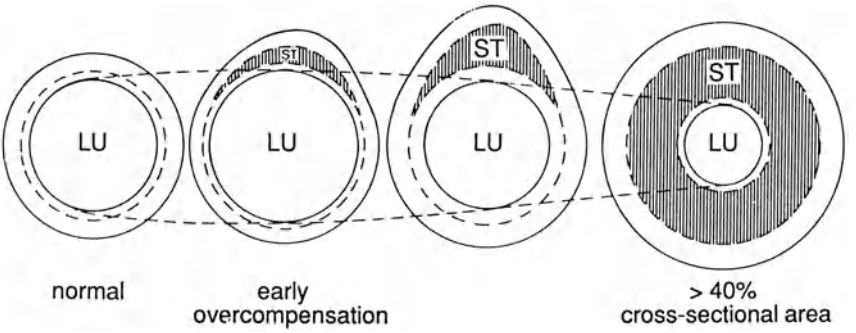



*Figure 1.* Diagrammatic representation of the sequence of luminal changes during the development of an early lesion to a severe atherosclerotic plaque. LU = lumen vessel, ST = stenosis, □ = internal elastic lamina. (adopted from Glagov et al.; N Engl J Med 1987; 316: 1371–1375 and Stiel et al.; Circulation 1989; 80: 1603–1609).

graphy frequently underestimates the severity of coronary artery lesions or even misses significant narrowings. The major reason appears to be the diffuseness of the atherosclerotic process. Diffuse atherosclerotic disease may narrow the entire lumen of a segment of a vessel smoothly so that angiography is unable to detect its existence. Furthermore, underestimation and overestimation of coronary arterial stenosis at clinical arteriography also has been explained by the use of inadequate radiological views to visualize elliptical or D-shaped lumens [10, 17, 19].

Another factor that complicates angiographical evaluation of coronary atherosclerosis is the occurrence of coronary artery remodelling. Compensatory enlargement of human atherosclerotic coronary arteries may occur during the early stages of plaque formation [25–28]. This compensatory enlargement results in preservation of a nearly normal lumen cross-sectional area, and in the very early stages of disease even to overcompensation of the artery, so that an atherosclerotic plaque would have less hemodynamic effect (Fig. 1). This implicates that angiography may severely underestimate or may be unable to detect early stages of coronary atherosclerosis or may misinterpret overcompensation as regression.

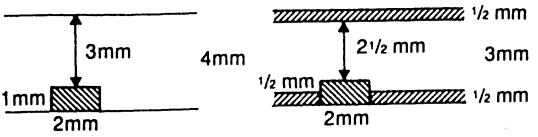
Finally, another form of lumen compensation is the process of medial thinning, that occurs beneath an severe atheromatous plaque [29].

Furthermore, processes other than atherosclerotic changes such as arterial spasm, intimal dissection, thrombosis or embolism, which may cause abnormalities on the angiogram, cannot always be distinguished angiographically from atherosclerosis.

**Limitations of assessing progression or regression from the changes in severity of local narrowing**

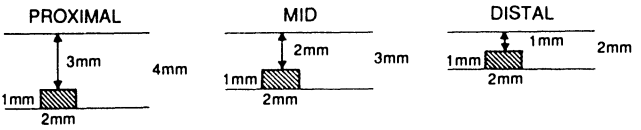
There are several reasons why measurement of the severity of lesions to assess progression or regression is associated with several limitations, irrespective of whether the severity is expressed as percent diameter stenosis or as minimal luminal diameter (mm).

1. Measurement of lesions only does not take into account that progress or regress may proceed as a diffuse process, so that progression or regression will be unnoticed angiographically.
2. Diffuseness of progression or regression may have unexpected effects on the measurement of the severity of a narrowing, because it may involve only the "normal" diameter that is used as reference to determine the severity of stenosis. This may result in a calculated less severe lesion (Fig. 2), suggesting regression, whereas actually progression has occurred, and therefore this should be regarded as pseudoregression.
3. An equal "volume" of progression of a new local atheroma in different vessel sizes would result in substantial differences in the calculated percent diameter stenosis severity (Fig. 3).
4. An equal "volume" of progression or conversely regression of coronary artery disease, will, depending on the three-dimensional orientation within the vessel, have profound differences in calculated percent diameter stenosis severity (Fig. 4).
5. Percent diameter stenosis does not accurately reflect the functional significance of a coronary lesion because it fails to account for other geometric-anatomic lesion characteristics such as lesion length, absolute diameters of diseased and normal segments, entrance and exit angles all causing a different hemodynamic behaviour for different magnitudes of coronary blood flow [30–37]. For instance a 50% narrowing in a vessel with a diameter of 4 mm has a totally different haemodynamic impact than a 50% narrowing of a vessel with a 2 mm diameter (Fig. 5).
6. The relative percent diameter stenosis is determined by comparing the diameter at the site of maximal reduction with the diameter in adjacent areas that appear either normal or only minimally diseased. Thus these measurements are highly dependent on the diameter of the reference area. In cases with focal obstructive disease and an adjacent angiographic non-diseased area, the determination of a reference area is simple and straightforward. However, the nearby "normal" portion of the vessel lumen, may be dilated by the aging process [38–40] or by poststenotic turbulence [41, 42] or it may be narrowed by diffuse atherosclerotic narrowings [43–45] so that these segments show combinations of stenotic and ectatic areas and determination of a "normal" reference diameter poses important problems. Selection of different reference areas may result in significant differences in calculated percent diameter stenosis (Fig. 6). Absolute measurements (mm),




| | | |
|---|---|---|
| **Mean width segm. (mm)** | **3.75** | **2.9** |
| **Min. lum. diam. (mm)** | **3.0** | **2.5** |
| **DS %** | **25** | **17** |

*Figure 2.* Progression of diffuse coronary atherosclerosis in a segment with pre-existing stenosis. Relative measurement (DS% = % diameter stenosis) suggests regression of severity of lesion, whereas, in reality absolute measurements mean width and minimal luminal diameter (mm) show progression of disease.



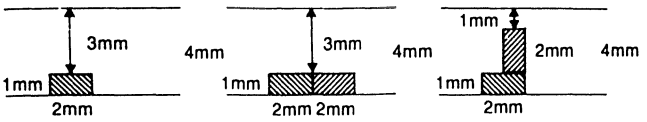

| | | | | |
|---|---|---|---|---|
| MEAN WIDTH | MM | 3.75 | 2.75 | 1.75 |
| MIN. LUM. DIAM. | MM | 3.0 | 2.0 | 1.0 |
| DIAM. STENOSIS | % | 25 | 33 | 50 |

*Figure 3.* Impact of equal volume of atheroma on absolute and relative measurements in different vessel sizes.

not depending on the selection of a reference segment, are therefore considered to be more accurate.

## How to measure changes of focal and diffuse coronary atherosclerosis

Conceptually, changes of focal and diffuse coronary atherosclerosis assessed with serial angiography can only be measured as a difference of the "volume" of the opacified lumen of the coronary artery tree, thereby assuming that progression or regression of arterial wall disease is reflected in changes of the contour of the opacified lumen. This implies that one should measure changes of the luminal "volume" of the opacified coronary artery tree. However, due to the complex coronary anatomy, the varying course of the arteries in a three-dimensional plane, and the cyclic changing caliber of the coronary arteries, complicated by the beating heart, it is impossible to measure the "volume" of the coronary tree in man with current angiographic techniques.




| | | | | |
|---|---|---|---|---|
| MEAN WIDTH | MM | 3.75 | 3.5 | 3.5 |
| MIN. LUM. DIAM. | MM | 3.0 | 3.0 | 1.0 |
| DIAM. STENOSIS | % | 25 | 25 | 75 |

*Figure 4.* Diagrammatic representation of progression of the same "volume" of atherosclerosis with a different distribution within the vessel lumen to demonstrate the significant differences in stenosis measurements.

Therefore, a simplified two-dimensional approach must be employed (Fig. 7). It appears that by using this approach the derived mean width (mm) can be considered as a measure that is able to assess in a two-dimensional plane changes, both focal and/or diffuse, independent of shape and orientation in that plane.

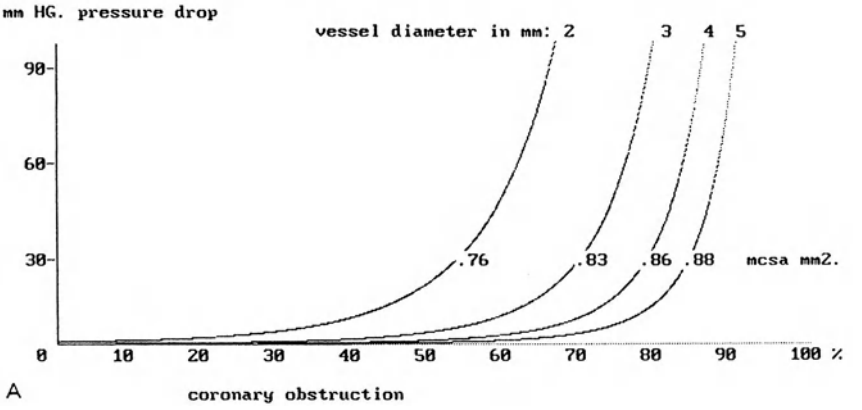
Focal atherosclerosis should be measured as an absolute measurement of the minimal luminal diameter (mm) or as a relative measurement percent diameter stenosis (attempt to select same reference area).

In Table 1 we propose a set of measurements derived from quantitative coronary angiography. The mean width of segment (mm) is the most important measurement, because it is able to assess progression or regression of diffuse atherosclerotic disease. It is also able to measure changes of focal atherosclerotic disease and it is the single measurement able to assess the combination of diffuse and focal atherosclerosis.

The absolute measurement, (minimal luminal diameter in mm) of lesions is extremely valuable to assess changes of focal atherosclerosis. Although relative measurements are subject to many drawbacks it may be useful to present these to meet the traditional clinical practice of grading stenoses as percent stenosis.

It is common clinical practise to present the efficacy of an intervention on a per patient-oriented basis.

A total global score can be derived by averaging that mean width of all analysable segments of a coronary tree per patient or by averaging the minimal luminal diameter of all lesions per patient. From the clinical point of view it is important also to be informed about the response of an individual lesion or coronary segment. A trial should address the following questions. Which patient will respond favourably to an intervention and to what extent? Which lesion or segment will respond favourably, will worsen, or is immutable?



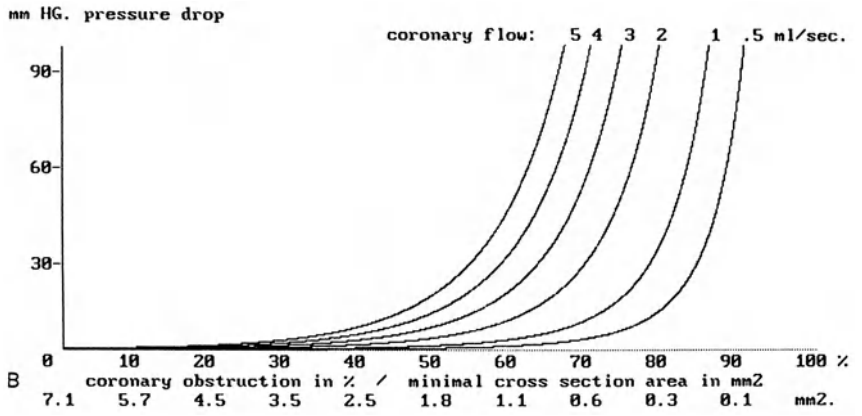




*Figure 5A,B.* An example of a computer-derived functional estimate, using quantitative angiography to measure dimensions of percent narrowing, absolute diameter and lesion length. These were combined into a fluid dynamic equation to provide a single integrated measure of haemodynamic severity i.e. pressure gradient over the lesion. The following equation was used:

$$\Delta P = fQ + sQ^2 \text{ (Kikeeide et al. JACC 1986; 7: 103–13).}$$

MCSA $mm^2$: minimal cross-sectional area. Where

$$f = \frac{8\pi\mu L}{A_s^2} \quad \text{and} \quad s = \frac{\rho}{2} \times \left[\frac{1}{A_s} - \frac{1}{A_n}\right]^2$$

When $\Delta P$ is pressure loss across the stenosis, $\mu$ is absolute blood viscosity, L is stenosis length, $A_n$ is the cross-sectional area of the normal artery, $A_s$ is the cross-sectional area of the stenotic segment, Q is volume flow and $\rho$ is blood density. From the available morphologic data of the obstruction, the Poiseuille and turbulent resistances at different flows ranging from 0.5 ml – to 5 ml (simulating conditions at rest or maximal exercise) and thus the resulting transstenotic pressure gradients can be computed. (A) Relation between pressure drop, varying degrees of severity of stenosis and varying vessel size (2, 3, 4 and 5 mm in diameter) with fixed coronary flow. (B) Relation between pressure drop, varying coronary flow (0, 5, 1, 2, 3, 4, 5 ml/sec), and varying degrees of severity of stenosis in fixed vessel diameter.

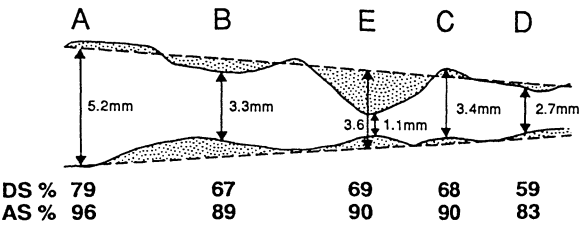



*Figure 6.* Influence of determination of reference area in a tapering vessel with diffuse atherosclerosis on relative percent diameter and area stenosis (assuming circular cross sections).

## New techniques to assess progression or regression

### *Pressure drop across a stenosis*

The physiological significance of a coronary stenosis is difficult to appreciate with routine coronary angiography. In the presence of a moderate to severe coronary stenosis, a significant pressure drop across the lesion develops. This results in decrease of coronary blood flow and diminished coronary blood flow reserve [30, 31, 33–37, 46]. The pressure loss across the stenosis is mainly related to the geometry of the stenosis, including percentage narrowing, absolute area (diameter), length and shape. The absolute area and the length mainly contribute to viscous friction losses and the percent narrowing and the shape to separation losses. Gould et al. [46] from animal experiments derived a simplified equation:

$$\Delta P = FV + SV^2$$

Where V = velocity, $\Delta P$ = pressure gradient across the stenosis, F = coefficient of viscous friction loss:

$$F = \frac{8\pi\mu L}{A_1}\frac{A_0}{A_1}$$

and S is the coefficient of separation loss

$$S = \frac{\rho K}{2}\left(\frac{A_0}{A_1} - 1\right)^2$$

From the equation it appears that at high flow, separation loss will contribute greater to the total pressure drop than viscous loss, inasmuch as the separation losses are generated by the second power of the velocity.

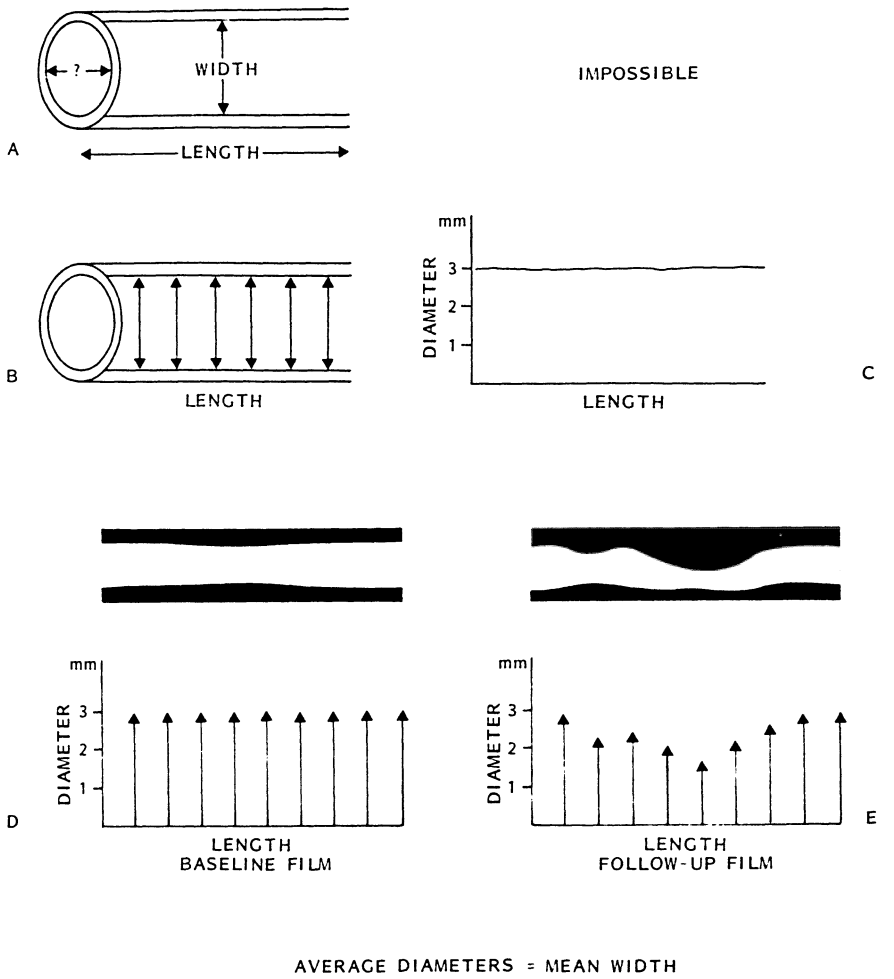



*Figure 7.* A) Measurement of width and length of a segment in a two-dimensional plane. The diameter of the segment perpendicular to that plane is unknown. B) Determination of diameter at different sample points. The average of all diameters is the mean width. C) Determination of mean width in baseline film. D) Reflection of progression of disease on mean width (decrease) in follow-up film. It is of note that all changes (diffuse and focal) contribute to the change in mean width. The minimal luminal diameter is taken at the sampling point with the smallest diameter.

## *Coronary blood flow reserve*

The physiological significance of a coronary stenosis can be assessed by its effect on the coronary blood flow reserve capacity, based on the fact that

*Table 1.* Significance of measurements used to assess progression or regression of coronary atherosclerosis

| | Diffuse atherosclerosis | Focal atherosclerosis | Combination of diffuse and focal atherosclerosis |
|---|---|---|---|
| | Coronary segment score | | |
| 1. Mean width per vessel segment (mm) | ++ | + | ++ |
| | Coronary lesion score | | |
| 1. Absolute measurements: Minimal luminal diameter (mm) | ± | ++ | + |
| 2. Relative stenosis measurements: Diameter stenosis % | − | + | ± |

physiological significant obstructive lesions should decrease the vasodilator reserve [30, 31, 33–37, 46–50].

Coronary blood flow reserve is the ratio between maximum coronary blood flow to resting coronary blood flow. Coronary flow reserve begins to decrease at 40% to 50% diameter stenosis for a vasodilatory stimulus, increasing flow normally to four to five times baseline [46–50].

However, a major problem in assessing the effect of a coronary stenosis on coronary blood flow is that myocardial perfusion is the integrated response of the entire coronary vascular system consisting of several components including stenosis geometry, characteristics of epicardial vessel, endothelial function, distal vascular bed, myocardium, collateral circulation, aortic pressure, coronary vascular tone and the effectiveness of the coronary vasodilator stimulus.

Several new techniques are now available to assess the physiological significance of a stenosis in terms of pressure drop or coronary reserve.

### "*Estimated*" *pressure drop across a lesion*

Quantitative coronary angiography provides an accurate delineation of the geometry of the stenosis including absolute diameter of normal area and minimal luminal area, lesion length, entrance and exit angle. From these measurements and assuming different coronary blood flow magnitudes (1 ml, 2, or 5 ml per second simulating conditions at rest, at moderate or at maximal exercise) the pressure drop across the lesion, the Poiseuille and turbulent resistances can be computed [34, 37, 46] (Fig. 8a, b, c).

Serial measurements will enable us to estimate the haemodynamic impact

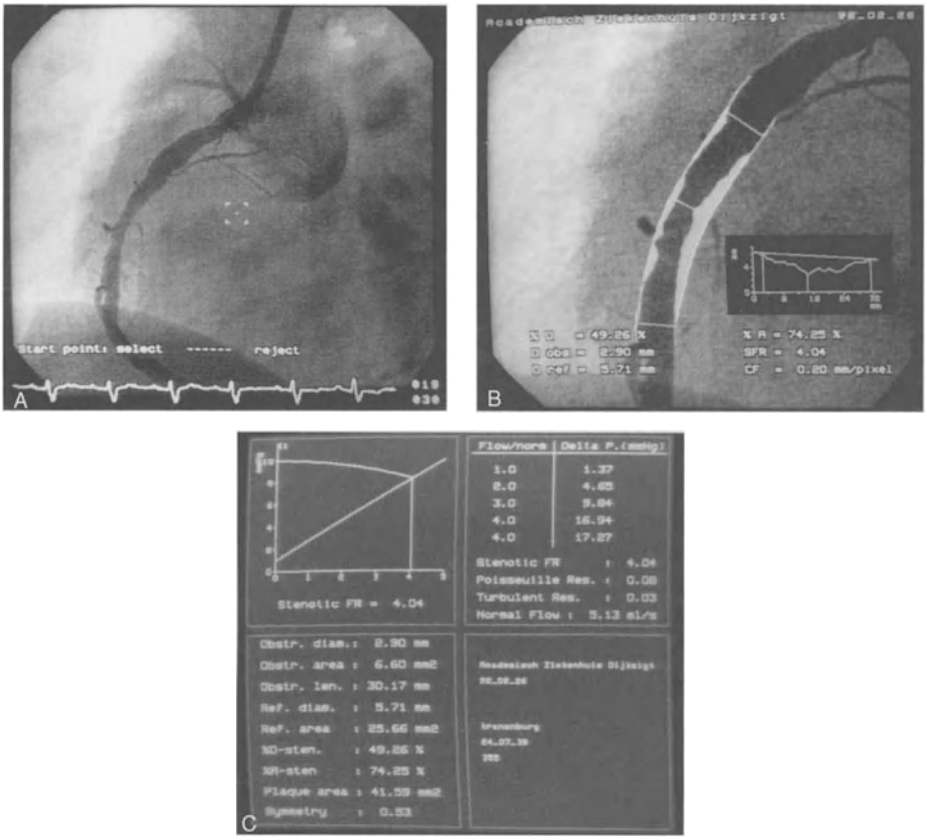



*Figure 8.* A) Right coronary artery, B) quantitative coronary angiography, C) calculated coronary stenotic flow reserve.

of progression or regression of a single lesion, assuming the above described conditions.

Obviously, the significance of the "estimated" pressure drop has its limitation and should not be taken as the ultimate physiological significance for a patient, inasmuch as they single out one component of the total coronary vascular bed and do not account for the effects of pulsatile flow, curved vessels, non-compliant lesions, more than one lesion per vessel, diffusely diseased vessel, collateral circulation or perfusion of areas of non-viable myocardium.

*Real pressure drop across a lesion*

With the use of a pressure guide wire, after crossing the lesion, one can reliably measure the pressure drop across the stenosis [51]. The pressure

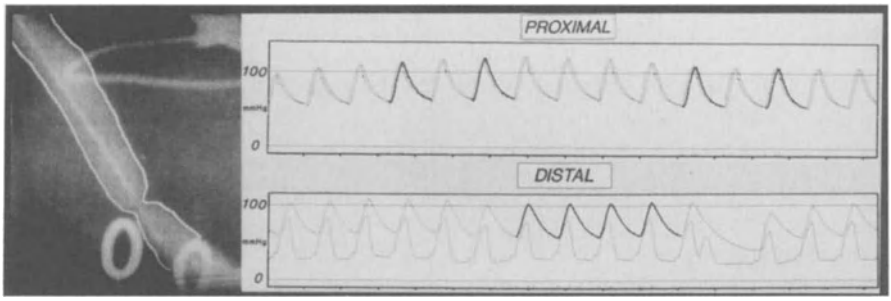



*Figure 9.* Measurement of pressure drop across coronary lesion with pressure guide wire.

guide wire is a device that consists of a 0.018″ guide wire with a 3 cm soft tip and a pressure sensor of only 0,46 mm in diameter mounted at the tip. The sensor is developed using fiber optics and measures the static pressure. The small size of the wire across the stenosis garantees only minimal overestimation of the pressure drop. Progression or regression of a stenosis following intervention should be reflected in a change of the pressure drop (Fig. 9). The driving blood pressure, coronary blood flow, and vasomotion have an impact on the magnitude of the pressure drop across a lesion and should be similar during serial measurements. However, it is unlikely that even under basal resting conditions this assumption is correct. Therefore, one should standardize the conditions: same vasodilation (intracoronary nitrates), and maximal coronary blood flow by inducing maximal peripheral myocardial vasodilation (i.c. papaverine, or i.v. adenosin).

*Digital angiographic technique to assess coronary blood flow reserve*

The functional significance of a coronary lesion can be assessed during cardiac catheterization by calculating the coronary flow reserve from both myocardial contrast appearance time and density in the resting and hyperemic state determined from digitized coronary cine-angiograms [47].

This parametric imaging technique can be performed rapidly during coronary angiography, but it requires special attention to atrial pacing, ecg triggered power injection, patient motion and same fixed inspiration level. The short, medium and longterm variability of this method is acceptable for clinical use [50].

This, or similar, technique(s) may prove useful to examine the effects of an intervention on progression or regression of coronary atherosclerosis.

*Coronary blood flow velocity to assess coronary blood flow reserve*

Currently it is possible to measure intracoronary blood flow velocity without disturbing the flow pattern, with the use of a doppler guide wire (diameter:

0.46 mm; cardiometrics) [52]. The coronary reserve can be determined by the ratio between the maximal velocity to resting flow velocity (Fig. 10). The effects of progression or regression should be reflected in the change of the coronary reserve.

*Stenosis flow reserve assessed by quantitative coronary arteriography*

From elegantly performed animal studies Gould and Kerkeeide [46] have shown that the geometry of a stenosis accurately predicts the pressure-drop flow relation across the stenosis. These data suggested that the physiological significance of a stenosis should be expressed as its potential to limit flow and they developed the concept of stenosis flow reserve as a single measure of severity derived from the geometry obtained by quantitative coronary angiography [37]. They created a standardized test to derive stenosis flow reserve in terms of the capacity of a stenosis to carry blood flow.

To derive this stenosis flow reserve the following assumptions are made: aortic pressure is 100 mmHg, the maximally vasodilated pressure-flow relation for the distal bed goes from 0 relative flow at 10 mmHg to 5 times resting flow at 100 mmHg, the flow velocity is 15 cm/sec and the flow rate is the product of flow velocity times the normal cross-sectional area of the arterial segment. An illustrative example is shown in Fig. 8.

It should be appreciated that the stenosis flow reserve considers only one component, the stenosis, and its pressure-drop flow relation in an otherwise assumed normal epicardial artery under standardized conditions and it excludes the other components of the entire coronary vascular system that also determine coronary flow reserve.

## Intracoronary ultrasound imaging

Contrast angiography, even with the use of digitizing techniques, does not provide sufficient information about vessel wall and plaque characteristics and is therefore limited to guide interventions on regression of coronary atherosclerosis [12].

Intravascular imaging should provide information on the lumen of the vessel, the vessel wall (thickness and composition) the plaque (identification of plaque composition) and plaque disruption [53–57].

Intravascular ultrasound techniques are useful to detect early stages of atherosclerosis, and diffuse disease, both conditions where angiography fails to provide adequate or no information (Fig. 11).

However, one should bear in mind that intimal thickening is not necessarily atherosclerosis or a precursor of atherosclerosis. But ultrasound should be able to distinguish between a fibrous plaque or lipid containing plaques, and thus provide clues for the potential efficacy of cholesterol lowering drugs

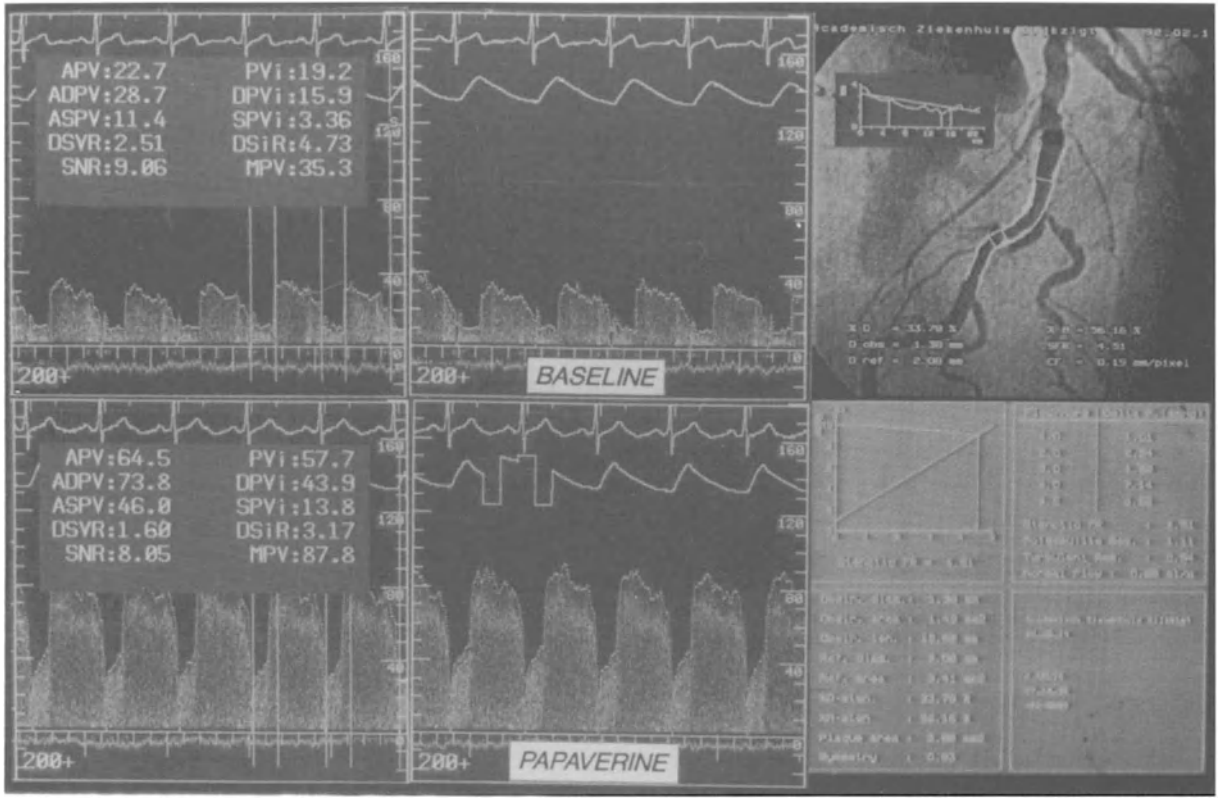



*Figure 10.* Measurement of coronary blood flow velocity in coronary artery at rest (baseline) and after maximal vasodilation with 12 mg papaverine injected intracoronary to assess the coronary blood flow reserve. Right panel shows the quantitative measurements of the lesion.

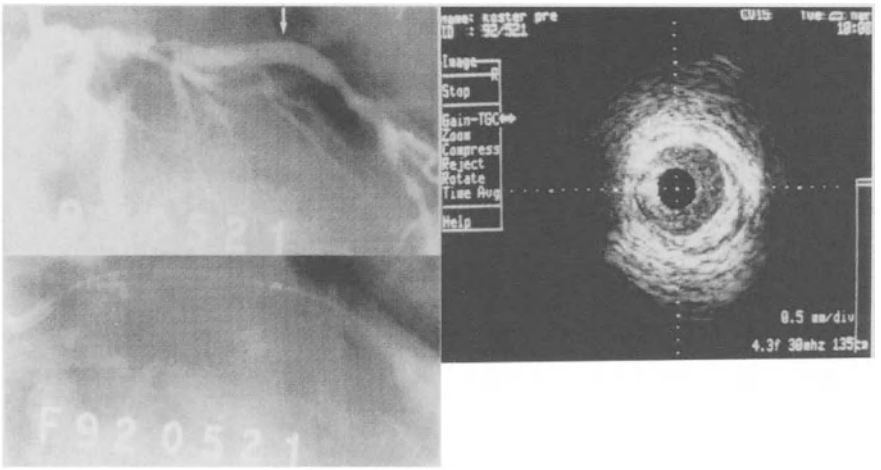



*Figure 11.* Left upper panel: Coronary angiogram of left anterior descending artery with severe proximal lesion and angiographically normal mid segment. Left lower panel: intravascular ultrasound device inserted into mid segment of left anterior descending artery, at the same level of white arrow. Right panel: ultrasound image obtained at site of arrow. There is an intimal plaque extending from 2 to 6 o'clock.

and it should be able to monitor interventions, or to assess progression or regression of coronary atherosclerosis.

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# 34. Coronary atherosclerosis intervention trials using serial quantitative angiography

JEROEN VOS and PIM J. DE FEYTER

## Introduction

Epidemiologic studies have provided extensive evidence that certain characteristics are associated with a high probability on coronary heart disease [1–5]. Hypercholesterolemia, smoking, overweight, stress, physical inactivity, hypertension and diabetes mellitus are identified as risk factors.

In animal models atherosclerotic lesions regressed after a change in diet or the administration of lipid-lowering drugs [6–8], psychosocial stress impaired the coronary vessel response [9] and Calcium antagonists prevented the development of atherosclerosis [10]. In these experiments, however, lesions characterized by large amounts of intracellular lipids, in contrast to the extra-cellular lipid accumulations in humans, were induced in a short time (3–24 months) by diets that resulted in excessively high plasma cholesterol levels ($\geq$20 mmol/L) [8]. It remains to be seen whether these results also can be obtained in humans. Currently the only method that can asses the effect of an intervention on coronary atherosclerosis in humans is serial angiography [11]. In this chapter the controlled clinical trials using serial coronary angiography, both visual and quantitative, are reviewed. Three different treatment modalities were addressed: lipid-modifying treatment with drugs or surgery, lifestyle changes and treatment with Calcium antagonists.

## Methods

### *Selection*

Studies were included when they met the following criteria. First, the coronary artery anatomy was the object at study. Second, serial coronary angiography was performed. Third, the study was controlled. In order to find trials that could fit the criteria a computer assisted literature search was performed and references of papers were checked.



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The following trials were selected. Trials with a lipid-modifying treatment: NHLBI type II [12], CLAS [13], POSCH [14], FATS [15], SCOR [16] and STARS [17]. Trials with lifestyle changes: Lifestyle Heart Study [18, 19], STARS [17] where only the usual care – and the low-fat diet group were compared, and the study of Schuler et al. [20, 21]. Trials with Calcium channel blockers: INTACT [22] and Waters et al. [23].

One study was rejected since the lipid-lowering treatment was ineffective [24], 2 studies were not included since the control group was not properly selected. One trial [25] compared initial responders with non-responders to lipid-lowering, another study [26] compared the lipid-modified group with a group of patients from another trial. Two studies were excluded because they did not give sufficient information [27, 28].

### *Statistics*

For each trial relative risks with 95% confidence intervals for progression and regression of atherosclerosis were calculated [29]. The relative risk is greater than 1 in case the number of patients with progression or regression of coronary atherosclerosis is increased in the index group. Since the definitions of change in coronary status differed between the trials and no common angiographic endpoint could be defined, the definitions of progression and regression applied in each individual study were used. For FATS and STARS in the analysis of the lipid-modifying studies the 2 active treatment groups were combined. For the analysis of the lifestyle changes studies a comparison was made between the usual care- and the diet group from STARS. To obtain an overall measure of effect, the combined relative risks for progression and regression of coronary atherosclerosis were calculated. The studies were pooled according to therapies applied e.g. lipid-modifying therapy, lifestyle changes and treatment with Calcium antagonists. For each category an adjusted Mantel-Haenszel relative risk with 95% confidence interval was calculated [30].

## Description of the trials

### *Lipid-modifying treatment*

Brensike et al.[12, 31] treated patients with Type II hyperlipoproteinemia, LDL in the upper 10th of the distribution of the general population, and proven coronary atherosclerosis with diet (n = 72) or with diet and cholestyramine (n = 71) in a randomized double-blind manner. Coronary angiography was performed at baseline and after 5 years. Angiograms were assessed visually by a panel of experts. A decrease of 16% in total cholesterol, 21% in LDL, and an increment of 6% in HDL, were accomplished.

In the Cholesterol Lowering Atherosclerosis Study (CLAS) [13, 32] non-

smoking, male patients with previous coronary bypass surgery, and with plasma cholesterol levels between 4.8 and 9.1 mmol/L received either diet alone (n = 94) or diet, colestipol and nicotinic acid (n = 94). Before randomization all eligible patients received the lipid-modifying drugs and only those patients who had a reduction in total cholesterol of ≥15% entered the trial. The study was randomized and double-blind for treatment, plasma lipid values and angiograms. Coronary angiograms were repeated after 2 years of treatment and were judged by a panel of experts. Each patient was classified according a global score of change taking into account both native coronaries and bypass grafts [33]. Total cholesterol went down with 26%, LDL with 43%, and HDL went up with 37%.

Buchwald et al. [14, 34, 35] performed a large survival trial in patients after a first myocardial infarction, with total cholesterol levels of ≥5.7 mmol/L, or ≥5.2 mmol/L in combination with a LDL level of ≥3.6 mmol/L while on diet. Patients were randomly allocated to diet and partial ileal bypass surgery [36] (n = 421) or diet only (n = 417). The analyses were performed on the basis of the intention to treat principle. The mean duration of follow-up was 8,7 years. The main endpoint of the trial was total mortality. Apart from the clinical endpoints sequential coronary angiography was performed at baseline and after 3, 5, 7, and 10 years. Angiograms were assessed as in the CLAS trial [33]. Total cholesterol and LDL decreased 32% and 35% respectively, and HDL increased 6%. Total mortality was reduced with 22% (95% confidence interval – 17%, 47%), cardiovascular death combined with non-fatal acute myocardial infarction with 35% (95% confidence interval 9%, 53%).

Brown et al. [15, 37] reported a randomized study in men with apolipoprotein B levels ≥125 mg/Dl, proven coronary atherosclerosis and a positive family history of vascular disease. Patients were treated with diet and placebo (n = 27) or colestipol (n = 20), lovastatin and colestipol (n = 38), and nicotinic-acid and colestipol (n = 36). Patients were followed for 2.5 years. The coronary angiograms were analyzed both visually and quantitatively [38]. Total cholesterol was reduced with 30% and 19%, LDL with 38% and 25%, and HDL increased with 20% and 35% for the colestipol/lovastatin and nicotinic-acid/colestipol group respectively relative to the conventionally treated group.

In the SCOR trial [16] both males and females with heterozygous familial hypercholesterolemia, proven coronary atherosclerosis, tendon xanthomas, LDL cholesterol ≥5.2 mmol/L triglycerides ≥ 3.1 mmol/L, or without tendon xanthomas but a first-degree relative with xanthomas and LDL ≥6.5 mmol/L, were provided with conservative treatment (n = 49) or a combination of LDL lowering drugs (n = 48) in a randomized, unblinded fashion. Drugs used were colestipol, resin, nicotinic-acid and lovastatin. Quantitative coronary analysis was performed at baseline and after 2 years [38]. Total cholesterol, LDL, and HDL was changed by −23%, −37% and 25%.

The St Thomas' Atherosclerosis Regression Study [17] tested a lipid-lower-

ing diet alone and a diet in combination with cholestyramine to neither diet or medication. In the lipid-lowering diet total fat intake was reduced to 27% of dietary energy. Saturated fatty acid constituted 8 to 10% of dietary energy. Male patients with total cholesterol between 6.0 and 10.0 mmol/L, without previous revascularization procedure, were enroled in a short trial to test tolerability and responsiveness to cholestyramine. Quantitative coronary angiography was performed at baseline and after 3 years [39]. Ninety patients were recruited. Total cholesterol went down with 12% and 23%, LDL with 13% and 33% in the diet and diet-cholestyramine group respectively. HDL remained at the same level in all treatment groups.

*Lifestyle changes*

The Lifestyle Heart Study [18] investigated whether comprehensive lifestyle changes could influence coronary atherosclerosis. Patients with proven coronary atherosclerosis were randomly assigned to a control group (n = 20) and to an experimental group (n = 28) that was exposed to a low-fat vegetarian diet, stress management techniques, individually prescribed exercise, and twice-weekly (4 hr) group meetings for social support to adhere to the treatment programme. Dietary energy consisted for 10% of fat intake of which less than 50% was unsaturated fat. No lipid-modifying drugs were allowed. Angiograms were assessed quantitatively [40] at baseline and after 1 year. Differences between the groups in total cholesterol, LDL and HDL were −19%, −31% and 0%. An additional analysis [19] of the coronary angiograms also showed a beneficial effect of the lifestyle changes on stenosis geometry, which resulted in an increase in the theoretical stenosis flow reserve [41].

For the STARS [17] we compared in this analysis the usual care group (n = 24) with the diet group (n = 26). Blood lipids did not change in the usual care group. Total cholesterol and LDL was reduced by 14% and 16% in the diet group. HDL remained constant.

Schuler et al. [21] treated patients with stable angina and proven coronary atherosclerosis with usual care (n = 57) or with a low-fat diet and intensive physical exercise (n = 56). No lipid-lowering drugs were used. Angiograms were assessed quantitatively after 1 year. Total cholesterol and LDL were reduced by 10% and 8% respectively. HDL was increased by 3%. Lipids did not change in the usual care group.

*Treatment with calcium antagonists*

Lichtlen et al. [22] reported the International Nifedipine Trial on Antiatherosclerotic Therapy in which the antiatherosclerotic effect of nifedipine were determined. Patients with proven mild coronary atherosclerosis and at least one risk factor were randomized to placebo (n = 211) or nifedipine 80 mg/day

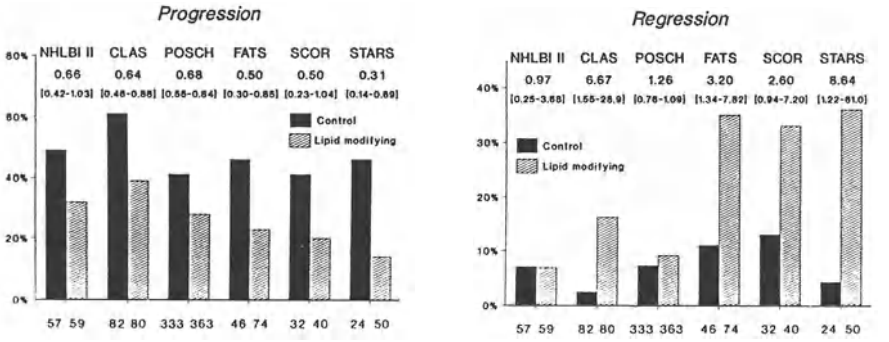


*Figure 1.* Percentages of patients with progression, relative risks and 95% confidence intervals in brackets for the lipid-modifying trials on the left, the same variables for regression on the right. The number of patients in each group is placed at the bottom.

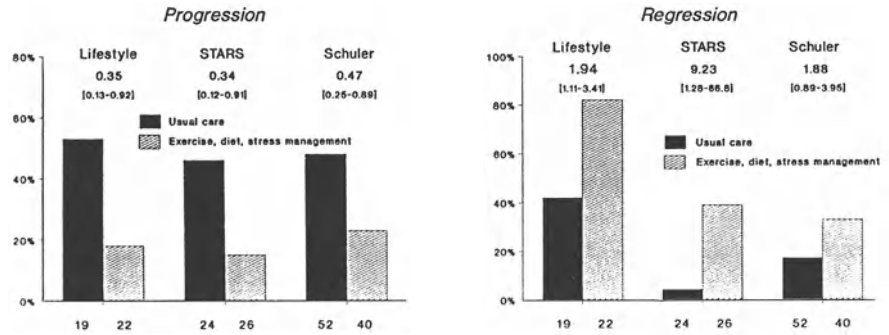


*Figure 2.* Identical as Fig. 1 but for the trials with lifestyle changes.

(n = 214). Quantitative coronary angiography was performed at baseline and after 3 years [42].

Waters et al. [23, 43] studied the effect of nicardipine on coronary atherosclerosis. Patients with a 80% probability of coronary atherosclerosis progression according to the extent of coronary atherosclerosis related to age [44], were randomly allocated in a double-blind fashion to placebo (n = 191) or nicardipine 120 mg/day (n = 192). Angiograms were repeated after 2 years and analyzed quantitatively [42].

## Results

The angiographic results of the trials are shown in Figs 1 to 4.

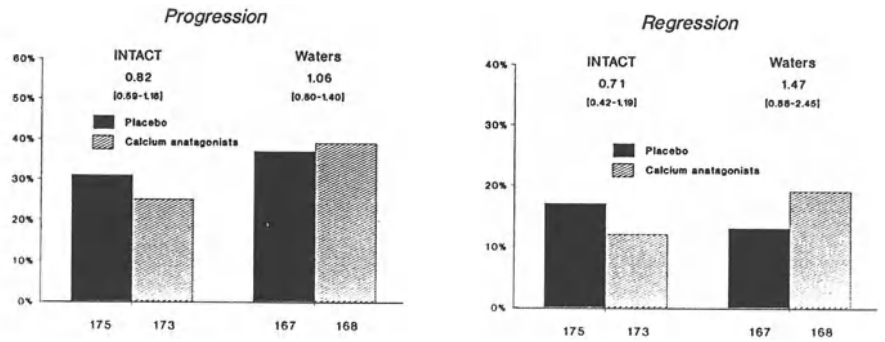


*Figure 3.* Identical as Fig. 1 but for the trials with Calcium antagonists.

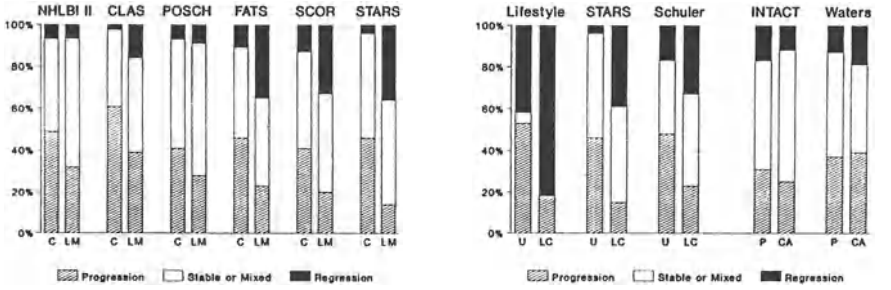


*Figure 4.* Changes in coronary anatomy in the trials with a lipid-modifying treatment on the left, and the trials with lifestyle changes and Calcium antagonists on the right. P: placebo LM: lipid modifying treatment, U: usual care, LC: lifestyle changes, CA: Calcium antagonists.

## *Pooled results*

For the trials with lipid-modifying treatment the overall relative risk (ORR) for progression of coronary atherosclerosis was 0.62 (95% confidence interval: 0.54–0.72). The ORR for regression was 2.13 (95% confidence interval: 1.53–2.98) (Fig. 5). The overall results for the trials with lifestyle changes were an ORR for progression of 0.40 (95% confidence interval: 0.26–0.63) and an ORR for regression 2.35 (95% confidence interval 1.54–3.58). For the studies using a Calcium antagonist the ORR for progression was 0.95 (95% confidence interval: 0.77–1.18) and for regression 1.02 (95% confidence interval: 0.72–1.46).

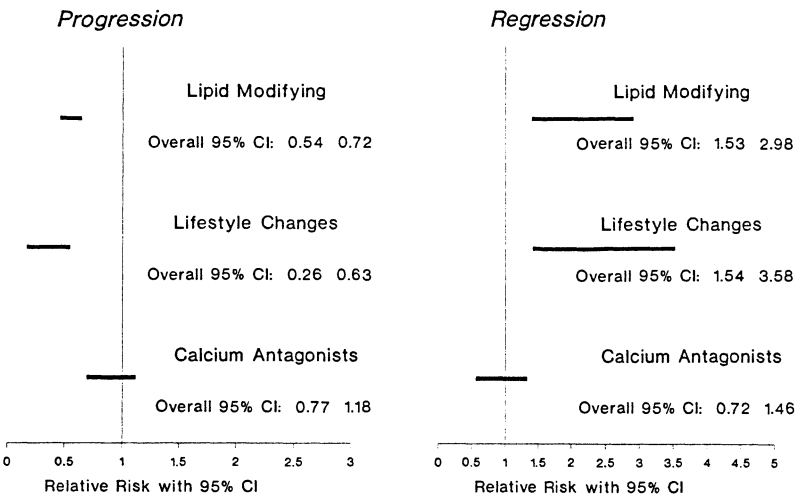


*Figure 5.* Overall relative risks for progression of coronary atherosclerosis on the right and regression on the left for each treatment modality. The horizontal bars indicate the 95% confidence interval. For progression the portion left to the line of unity indicates a beneficial effect (reduction in progression); for regression the portion right to the line of unity indicates a beneficial effect (increase in regression).

## Discussion

### *Angiographic methods*

The methods used for the assessment of the coronary anatomy in the selected trials were diverse. In the earlier trials angiograms were assessed visually. Recent trials all used quantitative techniques. Most assessments were based on the relative percent diameter stenosis of coronary lesions. The criteria for clinically significant lesion- and patient change used were various (Table 1). A criterion for lesion change that was applied by several trials was a change of $\geqslant$10% in percent relative diameter stenosis. The most recent trial, the STARS study, used mean- and minimal vessel diameter, absolute measures, as primary angiographic endpoints. The diversity of angiographic methods applied illustrates that yet no consensus exists how to assess changes in coronary artery dimensions.

### *Effect of lipid-modifying therapy*

The common object in these trials was to induce regression of coronary atherosclerosis by a beneficial change in the lipid profile. Different therapies to achieve such a shift were applied: from diet and one lipid-modifying drug, to multitherapy to partial ileal bypass surgery. All these treatment regimes

*Table 1.* Definitions of progression and regression of coronary atherosclerosis applied.

| | | |
|---|---|---|
| *Trials with lipid-modifying therapies* | | |
| NHLBI Type II Trial | definite progression: | ≥1 lesion with definite progression and no lesion with regression |
| | probable progression: | ≥1 lesion with probable progression and no lesion with regression or definite progression |
| | probable regression: | ≥1 lesion with probable regression and no lesion with definite regression or any progression |
| | definite regression: | ≥1 lesion with definite regression and no progression |
| | mixed response: | regression and progression: lesion pro- and regression in the same patient, whether definite or probable |
| | no change: | no lesion observed as changed by at least 2 panels |
| CLAS | CLAS consensus global change score: 0 = no change, 1 = definitely discernable, 2 = moderate, 3 = extreme, −: regression, +: progression | |
| POSCH | CLAS consensus global change score: 0 = no change, 1 = definitely discernable, 2 = moderate, 3 = extreme, −: regression, +: progression | |
| FATS | progression: 10% increase in percentage stenosis, regression vice versa | |
| SCOR | 10% increase in percentage stenosis, regression vice versa; change in% area stenosis | |
| STARS | progression: loss of ≥0.17 mm in mean absolute width, regression gain ≥0.17 mm | |
| *Trials with lifestyle changes* | | |
| Lifestyle Heart Trial | change in% stenosis as a continuous measure, positive: progression, negative: regression | |
| STARS | progression: loss of ≥0.17 mm in mean absolute width, regression gain ≥0.17 mm | |
| Schuler et al. | change in minimal luminal diameter | |
| *Trials with Calcium antagonists* | | |
| INTACT | progression: a decrease of >0.4 mm in minimal lumen diameter, an increase in% stenosis of >20%, regression: vice versa | |
| Waters et al. | progression: a decrease of >0.4 mm in minimal lumen diameter, an increase in% stenosis of >10%, regression: vice versa | |

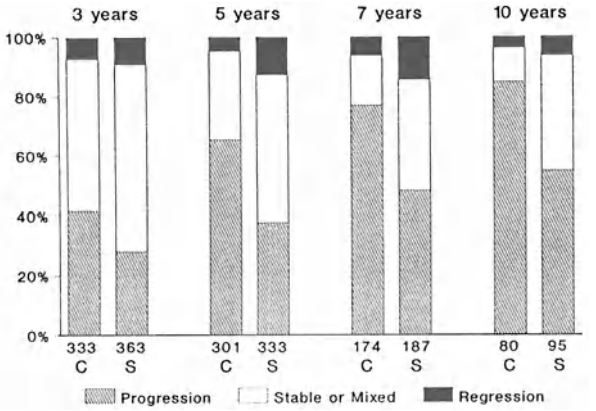


*Figure 6.* Changes over time in the POSCH trial. C: control group, S: partial ileal bypass surgery. Coronary angiography was performed at 3, 5, 7, and 10 years after randomization. Numbers indicate the numbers of patients at each time interval for each treatment group.

resulted in substantial reductions in total cholesterol and LDL, and in large elevations of HDL. Pooling of the selected trials presents evidence that extensive beneficial changes in the lipid-profile results in retardation, arrest of progression, or regression of coronary artery disease (Fig. 5). In the 1240 patients (666: lipid-modified group, 574: control group) a substantial reduction in the number of patients who showed progression of coronary atherosclerosis was seen: 184 (28%) in the lipid-modified group versus 261 (46%) in the control group. Furthermore, a less substantial increase in the number of patients who showed regression of coronary atherosclerosis: 107 (16%) in the lipid-modified group versus 40 (7%) in the control group was found.

POSCH is the only trial that presents data on the long-term effects of lipid-lowering. Figure 6 shows that the angiographic benefit is present after 3 years and remains constant while the absolute incidence of progression increases over the years with a progression rate of more than 85% in the control group and 55% in the operated group after 10 years. The effect on regression increased up to 7 years with 6.3% in the control group and 14.4 in the surgery group.

### *Effect of lifestyle changes*

These trials show that diet changes, resulting in amelioration of the lipid profile, daily physical exercise and stress management can result in a large reduction of the percentage of patients that show progression of coronary atherosclerosis and a large increase in the incidence of regression. However, the total number of patients in these trials is small (183) so that proof of the

effectiveness of these interventions is in fact scarce and should be looked at with caution. However, the results of lifestyle changes trials are promising.

*Effect of calcium channel blockade*

The two studies had in all aspects identical designs. The pooled results therefore represent a valid and, since the number of patients is substantial, also a precise estimate of the effect of dihydropyridine calcium antagonists on coronary atherosclerosis. No effect of Calcium channel blockade on progression or on regression of coronary atherosclerosis was seen. Only a small benificial effect on angiographically new- or minimal lesions occurred. Thus, although animal studies have shown antiatherosclerotic properties of several Calcium antagonists [10], still no irrefutable benefit of Calcium antagonists on human coronary atherosclerosis is found.

## Conclusion

The superiority of quantitative over visual methods of angiographic analysis in relation to clinical trials is clearly established and many trials have made use of these techniques.

The 2 trials using Calcium antagonists, that were well designed, that used an extensively validated quantitative analysis system, and that enrolled a sufficient number of patients, did not show a clear beneficial effect of these agent on coronary anatomy. However, a favourable effect on the development of angiographically new lesions might exist.

The 3 trials applying lifestyle changes showed remarkable beneficial effects on the progression of coronary atherosclerosis. However, the number of patients was small and the duration of the studies short so that generalization of these results might be preliminary.

The body of evidence that lipid-lowering therapy has beneficial effects on the coronary anatomy in patients with elevated blood lipids, at high risk for progression of coronary atherosclerosis, has become large. In the 1240 patients included in this quantitative review the relative risk for progression of coronary atherosclerosis was 0.62 and for regression 2.13. Thus, progression was reduced with 38% and the incidence of regression, although in absolute terms not as frequent as progression, was doubled. However, the induced angiographic changes in the individual patient are relatively small and exert only minimal effects on the functional significance of lesions. Most striking is the fact that the disease process could be stabilized in a majority of the patients. Apart from the POSCH trial, the interventions were maintained only 1 to 3 years. We don't know whether these effects are cumulative and functional more impressive if extended for a much longer time period.

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# 35. Short- and long-term quantitative angiographic follow-up after cardiac transplantation

MARC M.J.M. VAN DER LINDEN, AGGIE H.M.M. BALK and PIM J. DE FEYTER

## Introduction

Survival after cardiac transplantation has improved over the last years with a 1-year survival rate of greater than 80% in most transplant centers [1]. At present, one of the most limiting factors for medium and long-term survival is the process of graft vasculopathy, an accelerated and diffuse form of coronary atherosclerosis [2]. It accounts for approximately 60% of all retransplantation procedures [3].

The exact cause of this disease is thought to be immunologic, however direct proof is lacking. A major problem comparing the incidences at individual centers are the different definitions and methods to assess this diffuse vasculopathy. Therefore quantitative coronary angiography is thought to be a more sensitive and objective method for assessment, which offers potential for better understanding the pathophysiology and for investigating the influence of different treatment strategies on this process.

In the beginning of this century the first experimental work on cardiac transplantation was performed by Carrel and Guthrie. They transplanted the heart of one dog into the neck of another dog: the first heterotopic transplantation. The first successful clinical cardiac transplantation was performed by Barnard in 1967. Following this promising experience a large number of transplants were performed throughout the world. However, the immediate results after transplantation did not meet the expectations, because of acute allograft rejection and infection and consequently only a few centers continued with the development of this technique. During the 1970's indications and contraindications for cardiac transplantation were defined. Treatment of rejection was greatly enhanced by the use of rabbit antithymocyte-globulin. The detection and surveillance of rejection were facilitated by the introduction of transvenous right ventricular biopsy and the development of a grading system for the histologic findings [4–6].

One year survival increased from 22% in 1968 to 65% in 1978 [7]. The greatest step forward however, has been made in the early 1980's by the introduction of cyclosporin A for immunosuppression [8].



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As a result of the use of cyclosporine, cardiac transplantation has been developed to a generally accepted treatment for end-stage heart disease. According to the ninth report of the Registry of the International Society for Heart and Lung Transplantation, up to december 1991 over 19,000 heart transplantations have been performed and the one-year survival rate has increased to approximately 80% [1].

## Accelerated coronary artery disease

With the improvement of short term survival, it became clear that the process of accelerated coronary artery disease is one of the important factors limiting the long term survival of cardiac transplant recipients [2]. Due to the lack of innervation of the cardiac allograft, angina pectoris is usually absent, and electrocardiographic signs of myocardial infarction, congestive heart failure or sudden death may be the first signs of graft coronary arteriosclerosis [9].

The histologic findings of graft coronary arteries after human transplantation were first described by Bieber et al. [10] and confirmed by others [11–14]. The earliest change consists of concentric fibrosis and smooth muscle cell proliferation with collagen accumulation creating diffuse intimal thickening. This is seen as early as one week after transplantation. Subsequently, these lesions may progress to diffuse obliterative lesions creating longitudinal narrowing and distal pruning. The lesions are generally present in the large epicardial vessels as well as in the small intramyocardial branches. Therefore, because of the diffuse nature of the process, standard revascularization techniques such as bypass grafting and percutaneous transluminal coronary angioplasty are of limited value.

To detect the onset and progression of coronary disease in an early phase, coronary angiography is performed annually in most transplant centers. Gao et al. [15] first described the specific angiographic morphology of the lesions found after transplantation by dividing them into 3 categories: type A, discrete or short tubular stenosis in the proximal, middle or distal segments of major coronary arteries or their branches; type B, diffuse concentric luminal narrowing in the middle to distal segment branches; and type C, diffusely narrowed irregular distal branches that are squared of and end abruptly, the latter two groups both unique to the post-transplant patients (Fig. 1). Despite this clear categorization, the reported incidences of visually detectable coronary artery disease vary considerably, ranging from 2 to 34% at 1 year, and ranging from 50 to 73% at 6 years after transplantation [15–23]. Thus, visual interpretation of coronary angiography has limitations for both clinical and research purposes: The results of different transplant centers are not comparable, and the influence of different treatment strategies cannot be assessed.

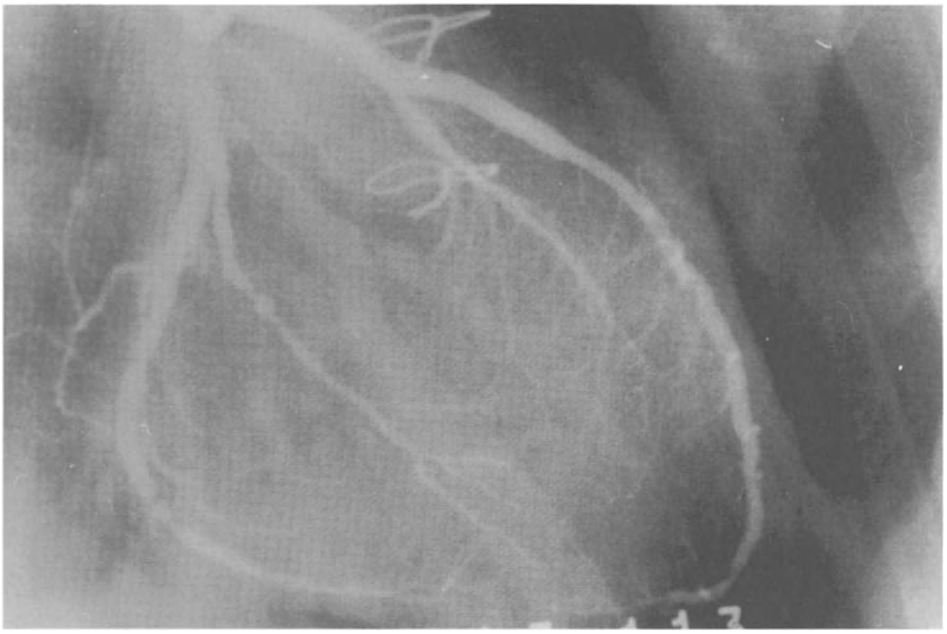

*Figure 1.* Example of a coronary angiogram in right anterior oblique view of a 60 year old male cardiac transplant recipient, 5 year after transplantation, showing the typical diffuse wall-irregularities and local stenoses.

## Quantitative coronary angiography

Quantitative coronary angiography has the advantage of being more accurate and reproducible for the assessment of coronary artery disease. De Feyter et al. [24] discussed the value of quantitative coronary angiography in clinical trials concerning progression or regression of coronary artery disease. A specific tool to assess the progression of *diffuse* coronary artery disease is the mean segment width measured in millimeters. It is also the single measurement to detect both *diffuse* and *focal* atherosclerosis. Therefore mean segment width should be the appropriate measurement to be used in cardiac transplant recipients. The description of progression and regression of allograft coronary artery disease should include 2 parameters: Firstly, a description based on the coronary status of an individual patient: *the patient global score*, which is defined as the average of the mean width of all analyzable segments of the coronary tree (including those with lesions) per patient. The patient global score change is defined as the average change in the mean width of the segments (Table 1). Secondly, a description based on all the segments measured in a study: *the segment global score*, which is defined as the mean of the coronary segment widths of all these measured

*Table 1.* Example of the calculation of patient global score and patient global score change in a cardiac transplant recipient.

| Segment number* | Baseline (mm)† | Follow-Up (mm)‡ | Change (mm) |
|---|---|---|---|
| 1 | 3.75 | 3.64 | −0.11 |
| 2 | 3.65 | 3.28 | −0.37 |
| 3 | 3.29 | 3.23 | −0.06 |
| 4 | 4.00 | 3.47 | −0.53 |
| 5 | 4.44 | 3.99 | −0.45 |
| 6 | 3.19 | 3.23 | 0.04 |
| 7 | 2.40 | 2.28 | −0.12 |
| 8 | 2.70 | 2.57 | −0.13 |
| 11 | 2.24 | 2.13 | −0.11 |
| 13 | 3.30 ± 0.74 | 3.09 ± 0.63 | −0.20 ± 0.20 |
| Patient global score | | | |

* Segment number according to the American Heart Association Classification [25].
† Mean segment width at baseline coronary angiography.
‡ Mean segment width at follow-up coronary angiography.

segments. Segment global score change is defined as the average change of all segments (Table 1).

O'Neill et al. [23] was the first to report a significant reduction of coronary luminal diameter, using quantitative coronary angiography in cardiac transplant recipients. Mean coronary diameter of the left main coronary artery decreased from 5.4±0.9 mm at 1 year to 4.7±0.8 mm at 3 years after transplantation in 20 patients having serial coronary angiography. The coronary luminal diameters of the proximal and mid left epicardial artery segments also showed a significant decrease. However, distal epicardial segments did not change significantly. Quantitative analysis was performed by two observers. In this study vessel borders were manually traced in end diastolic frames and measured using digital calipers. The patient global score was not presented. Furthermore no relation was found between these changes and potential risk factors for development of accelerated coronary artery disease.

Stanford University reported the use of quantitative coronary angiography by automated computerized edge detection in a study describing the changes in coronary luminal diameter in the first year after transplantation [26]. In a group of 25 patients mean coronary diameter decreased from 2.44±0.26 mm at an average of 5.1 weeks after transplantation to 2.21±0.34 mm at 1 year follow-up ($p < 0.001$). Although absolute changes were less in smaller arteries, there was no significant difference between large ($> 2.9$ mm), medium (2.0–2.9 mm) and small ($< 2.0$ mm) vessels with regard to percentage change ($-9.4$, $-10.9$ and $-6.4\%$, respectively). In this study also no relation with potential risk factors for transplant coronary artery disease could be found. Mills et al. [27] recently reported coronary artery segment measurements in 18 patients from 1 to 3 years after cardiac transplantation, using cine-videodensitometry. All angiograms were visually interpreted as

"normal" by an experienced investigator, using side-by-side projectors. No loss of distal branches was seen. Using quantitative analysis, all segments, except the proximal left anterior descending segment, showed a significant decrease from the first to the third postoperative year (range −0.19 to −0.48 mm). They concluded that graft arteriopathy is ubiquitous in heart transplant recipients, however no new insights on the pathogenesis of graft arteriopathy were given.

## The thoraxcenter experience

Visual analysis of the coronary angiograms of all patients who underwent a cardiac transplantation between June 1984 and May 1990 at the Thoraxcenter, made as part of their annual follow-up protocol, revealed a prevalence of abnormalities of the epicardial vessels in this patient group increasing from 34% at one year to 79% after 5 years. A very low threshold for assessment of visual coronary artery disease was used by two observers experienced in the reading of post transplant coronary angiograms. However, the prevalence of anatomical significant lesions (>50% stenosis in the epicardial branches or abrupt ending/proximal occlusion of tertiary branches) was only 1% at one year and 11% after 5 years [20].

In order to provide a more accurate and objective evaluation of the development of coronary artery disease, a study was initiated at the Thoraxcenter to describe the changes in coronary luminal diameter of the epicardial branches using serial quantitative coronary angiography. Furthermore, these changes were correlated with potential risk factors, as described in the literature.

## Patients

All cardiac transplant recipients who underwent a coronary angiography, as part of their annual follow-up protocol, between September 1989 and September 1990 were included in this study. Five subgroups could be identified: The first group consisted of 30 patients undergoing early angiography within one month after transplantation. The second, third, fourth and fifth groups consisted of 28, 21, 23 and 9 patients having angiography 1, 2, 3, and 4 years after cardiac transplantation respectively (Tables 2 and 3). In the subsequent year all patients underwent follow-up coronary angiography, thus achieving serial one year follow-up coronary angiography.

Six patients were excluded from this study: 1 patient died before follow-up angiography, in 2 patients follow-up angiography was not performed because of severe kidney failure, and in 3 patients follow-up angiography was postponed because of either infective disease or rejection.

Early prophylactic immunosuppressive therapy consisted of either poly-

*Table 2.* Clinical data.

| | Group 0–1 yr | Group 1–2 yr | Group 2–3 yr | Group 3–4 yr | Group 4–5 yr |
|---|---|---|---|---|---|
| Number of patients | 30 | 28 | 21 | 23 | 9 |
| Number of segments | 249 | 227 | 173 | 186 | 75 |
| Immunosuppressive regimen* | | | | | |
| – Cyclosporine and prednisone (pts) | 25 | 25 | 17 | 20 | 8 |
| – Triple therapy (pts) | 5 | 3 | 4 | 3 | 1 |
| Recipient age (yr)† | 45 ± 12 | 45 ± 11 | 47 ± 7 | 44 ± 10 | 36 ± 13 |
| Donor age (yr) | 26 ± 8 | 25 ± 8 | 23 ± 7 | 24 ± 8 | 21 ± 8 |
| Gender (F/M) | 2/28 | 4/24 | 2/19 | 2/21 | 1/8 |
| Gender mismatch (pts) | 9 | 9 | 7 | 10 | 5 |
| HLA-mismatch (NRS) | | | | | |
| A | 1.4 ± 0.6 | 1.3 ± 0.7 | 1.3 ± 0.6 | 1.3 ± 0.6 | 1.2 ± 0.7 |
| B | 1.6 ± 0.5 | 1.6 ± 0.6 | 1.5 ± 0.5 | 1.5 ± 0.7 | 1.7 ± 0.5 |
| DR | 1.5 ± 0.7 | 1.4Z ± 0.7 | 1.5 ± 0.6 | 1.2 ± 0.5 | 1.3 ± 0.9 |
| Rejection episodes between angiography median (range) | 1 (0–5) | 0 (0–1) | 0 (0–1) | 0 (0–1) | 0 (0–1) |
| Cholesterol (mmol/l)‡ | 7.4 ± 1.7 | 7.0 ± 1.6 | 7.9 ± 1.5 | 7.3 ± 1.5 | 7.6 ± 1.2 |
| Triglyceride (mmol/l)‡ | 2.3 ± 0.8 | 2.2 ± 0.8 | 2.4 ± 0.9 | 2.4 ± 1.3 | 2.5 ± 1.0 |
| HDL-cholesterol (mmol/l)‡ | 1.5 ± 0.5 | 1.3 ± 0.4 | 1.5 ± 0.5 | 1.3 ± 0.4 | 1.5 ± 0.3 |
| Donor heart ischemia (min) | 154 ± 31 | 169 ± 38 | 151 ± 38 | 159 ± 45 | 190 ± 44 |
| Smoking (Yes/No)* | 7/23 | 6/22 | 1/20 | 5/18 | 2/6 |
| Diabetes (pts)* | 2 | 1 | 1 | 1 | 2 |
| CMV infection (pts)* | 12 | 3 | 3 | 3 | 1 |
| CMV disease (pts)* | 7 | 0 | 0 | 0 | 0 |
| Use of nifedipine (pts)§ | 20 | 18 | 14 | 16 | 5 |

F = female; M = male; CMV = cytomegalo virus; HDL = High Density Lipoprotein; * = during the follow-up period; † = at the time of the transplantation; ‡ = mean during the follow-up period; § = at follow-up catheterization.

*Table 3.* Patient global score.

| | Number of patients | Patient global score (mm) | | Patient global score change | | |
|---|---|---|---|---|---|---|
| | | Baseline | Follow-up | mm | % | |
| Group 0–1 yr | 30 | 3.39 ± 0.34 | 3.35 ± 0.34 | −0.05 | −1.5 | NS |
| Group 1–2 yr | 28 | 3.18 ± 0.37 | 3.19 ± 0.39 | 0.01 | 0.3 | NS |
| Group 2–3 yr | 21 | 3.34 ± 0.40 | 3.26 ± 0.38 | −0.08 | −2.3 | NS |
| Group 3–4 yr | 23 | 3.17 ± 0.27 | 3.16 ± 0.41 | −0.01 | −0.3 | NS |
| Group 4–5 yr | 9 | 3.23 ± 0.51 | 3.23 ± 0.46 | 0.00 | 0.0 | NS |

clonal anti-T cell antibodies (Horse anti-thymocyte globulin, anti-thymocyte IgG2, Lymphoglobulin, Institute Merieux) or monoclonal anti-T cell therapy (OKT3, Ortho Pharmaceutical, Raritan, N.J.) [28]. Maintenance immunosuppression consisted of low dose steroids and cyclosporine. Azathioprine was added to this regimen in 16 patients because of recurrent rejection, detected and monitored by endomyocardial biopsies. The histologic findings of these biopsies were graded according to Billinghams criteria [5] until December 1990, and by the guidelines of the International Society for Heart and Lung Transplantation [6] from January 1991. In cases of moderate rejection with definite myocyte necrosis (Billingham grade 2) or grade 3A according to latter criteria, additional treatment was instituted, consisting of pulsed high dose steroids and poly- or monoclonal anti-T cell therapy.

In Cytomegalo virus (CMV) seronegative recipients, anti-CMV hyperimmunoglobulin (Cytotect, Pharma GmbH, Dreiech, Germany) was administered during the first 10 weeks after transplantation [29]. CMV infection was defined as any rise in serum IgM, isolation of CMV from urine throat or blood, or evidence of CMV immediate early antigen. CMV disease was defined as infection accompanied with fever >38°C for at least 2 days, and either leukocytopenia ($<2.5 \times 10^9$/l) and thrombocytopenia ($<100 \times 10^9$/l), or symptoms of organ involvement [29].

In patients, who never received a blood transfusion before transplantation, a transfusion was administered pre-operatively [30]. All patients were treated with antiplatelet agents, consisting of either dipyridamole 75 mg tid or aspirin 80 mg daily. Hypertension was preferably treated with nifedipine.

## Quantitative coronary angiography

All patients underwent left heart catheterization and selective coronary angiography by the femoral approach. Right heart catheterization with pressure measurements was performed and five endocardial biopsies were obtained, using the percutaneous transjugular approach.

To reduce the influence of dynamic vessel tone, isosorbide-dinitrate (5 mg)

was given sublingually before contrast injection. At baseline coronary angiography, standard projections were used and replicated at follow-up.

Off-line quantitative analysis was performed using the computer-assisted Cardiovascular Angiography Analysis System (CAAS), which has been described in detail previously [31, 32].

Nine epicardial coronary segments, identified by anatomic landmarks [25], were selected and analyzed in two orthogonal views avoiding foreshortening. Of the right coronary artery the proximal, mid and distal segment were analyzed; of the left coronary artery the main branch and segments 6, 7, 8, 11 and 13 were chosen for analysis.

The results were expressed in a patient global score and a segment score as described before.

## Statistical analysis

All data are presented as the mean ± SD. Statistical analysis was performed using the Wilcoxon Matched-pairs Signed-ranks test. Unpaired *t* tests, one-way analysis of variance and logistic regression were used to compare differences in potential risk factors for accelerated coronary artery disease. Statistical significance was defined as a p value of 0.05 or less.

## Results

### *Clinical data*

The clinical data of the cardiac transplant recipients in the different subgroups are described in Table 2. The number of rejections and Cytomegalo-virus infections was, as expected, higher in the first year after transplantation in comparison with the other periods. There was no significant difference between groups for mean recipient- and donor age, gender mismatch, HLA-A + B or -DR mismatch, total serum cholesterol, triglyceride, high-density lipoprotein cholesterol levels, and the other described risk factors for graft atherosclerosis. The only risk factor we could identify was the presence of coronary artery disease prior to transplantation. In the first subgroup of patients, a significantly larger patient global score change was found in patients with this disease (N = 14), than in patients with other indications for transplantation ($-0.13 \pm 0.17$ mm versus $0.03 \pm 0.20$ mm, $p < 0.05$). The changes in minimal luminal diameter were $-0.15 \pm 0.16$ mm and $0.04 \pm 0.23$ mm ($p = 0.01$), respectively.

*Table 4.* Segment global score.

| | Number of segments | Segment global score (mm) | | Segment global score change | |
|---|---|---|---|---|---|
| | | Baseline | Follow-up | mm | |
| Group 0–1 yr | 249 | 3.40 ± 0.82 | 3.36 ± 0.83 | −0.05 | p = 0.007 |
| Group 1–2 yr | 227 | 3.17 ± 0.85 | 3.17 ± 0.82 | 0.00 | NS |
| Group 2–3 yr | 173 | 3.35 ± 0.87 | 3.28 ± 0.81 | −0.07 | p = 0.005 |
| Group 3–4 yr | 186 | 3.18 ± 0.78 | 3.19 ± 0.83 | 0.00 | NS |
| Group 4–5 yr | 75 | 3.23 ± 0.90 | 3.24 ± 0.86 | 0.00 | NS |

*Quantitative angiograhy*

In the 5 different subgroups of patients 249, 227, 173, 186 and 75 segments were analyzed respectively. Only one patient in the last subgroup showed a significant narrowing (>50%) of the left anterior descending artery.

*Patient global score*
The results are outlined in Table 3. The largest decrease in patient global score occurred in the first and third postoperative year. These changes didn't prove to be significant.

*Segment Global Score*
In Table 4 the results of segment global score calculations are described. It can be appreciated that, according to these calculations, the largest changes also occurred in the first and third year after transplantation. This decrease was 0.05 and 0.07 mm respectively, and proved to be statistically significant.

## Discussion

In view of the described studies, the changes in this group of patients were small, both for patient global score and segment global score, ranging from −0.08 to 0.01 mm in the different yearly postoperative periods.

The exact cause of accelerated coronary artery disease is not yet elucidated. However, it is widely believed that immune mediated phenomena play an important role in the pathogenesis of this disease, because of it's diffuse nature, involving the entire lenght of the coronary artery tree with sparing of the native vessels, and it's development in patients of all ages. The "response to injury mechanism", due to damage to the endothelium during graft rejection, is widely believed to be the most basic etiologic factor, although both in this study as in others this hypothesis could not be confirmed [19, 20, 26, 33, 34]. A number of potential additional risk factors such as the presence of Cytomegalo virus infection [35–37], the presence of B-cell

antibodies [38] or anti-HLA antibodies [39], the immunosuppressive regimen [40], plasma triglycerides [41], diabetes mellitus [42], donor age [37, 39, 42] could also not be confirmed by other studies. Please note that most of these studies are based on visual, and thus subjective, interpretation of coronary angiography. Our study shows that quantitative coronary angiography offers potential for a better and more objective description of the changes in the coronary artery tree and for investigating the factors that influence the development of the disease.

One of the first studies comparing the effect of different treatment strategies using an objective edge detection system was described recently in a report of Stanford [43]. In a placebo controlled study in 106 patients, the beneficial effect of the calcium-antagonist diltiazem to inhibit early post-transplant coronary luminal narrowing was described. In the 57 patients, who received placebo, segment global score decreased significantly from $2.41 \pm 0.27$ mm at baseline (median, 19 days after transplantation) to $2.22 \pm 0.26$ mm at 2 year follow-up. In the same period, segment global score of the patients who received the calcium-antagonist, changed from $2.32 \pm 0.22$ mm to $2.36 \pm 0.22$ mm, a not statistically significant change. In our study most transplant recipients also received a calcium-antagonist (nifedipine), but no relation was found between the use of nifedipine and the development of post transplant coronary artery disease.

An increase in coronary artery dimension was first reported by Von Scheidt et al. [44] in 5 out of a group of 68 patients after transplantation (7.3%). No causal relation with clinical data could be determined. However, this process was assessed by visual interpretation of coronary angiography and has not been confirmed by quantitative methods.

## Conclusion

The coronary luminal diameter, expressed in a patient global score and a segmental score, decreased in the first and third year after cardiac transplantation. However, we observed only minimal changes in comparison with other post transplant studies [23, 26, 27]. Furthermore, these changes seemed to be clinically insignificant. Pre-transplant coronary artery disease of the recipient was identified as a risk factor for the development of transplant coronary atherosclerosis in the first postoperative year. No relation was found with other described potential risk factors.

To overcome the differences in definition of accelerated coronary artery disease, serial quantitative coronary angiography, if used in larger studies, can be an objective method to assess the incidence of this disease. Therefore, it offers potential for better understanding the pathophysiology of accelerated coronary artery disease, and for investigating the influence of different treatment protocols on this process.

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# 36. Does coronary lumen morphology influence vessel cross-sectional area estimation? An in vitro comparison of intravascular ultrasound and quantitative coronary angiography

JAVIER ESCANED, PIERRE DORIOT, CARLO DI MARIO, DAVID P. FOLEY, JÜRGEN HAASE, JOSE BAPTISTA, NICOLAS MENEVEAU, AD DEN BOER, JURGEN LIGTHART, JOS R.T.C. ROELANDT and PATRICK W. SERRUYS

## Introduction

Over the last 10 years quantitative coronary angiography has clearly emerged as the gold standard coronary imaging modality. However, despite the objectivity and reproducibility of coronary luminal measurements provided by quantitative angiographic analysis systems, a number of important limitations have been identified through their application to interventional procedures [1]. In particular, complex coronary lesions (for example, thrombus containing or ulcerated lesions) or the modifications in luminal geometry caused by percutaneous interventions, may yield inaccurate and unreliable luminal measurements [1–6]. These pitfalls of quantitative coronary angiography have been highlighted in recent years through the emergent clinical application of intracoronary ultrasound and angioscopy. Intravascular ultrasound imaging itself continues to undergo rapid evolution and has been advanced by its proponents as having a superior capacity for demonstrating luminal morphology, especially after coronary interventions [7–9].

In fact, there is already considerable evidence displaying potential sources of error [10, 11] and major disagreement between coronary luminal measurements obtained with quantitative angiography and intravascular ultrasound, mainly in the aftermath of balloon angioplasty [12–14]. So far the interpretation of these highlighted discrepancies has been limited by the necessity for speculation due to lack of hard information on actual lumen dimensions and lack of knowledge regarding the influence of lumen morphology on the respective measurement processes involved in these imaging modalities [10, 11].

This study was undertaken to objectively investigate the variability of



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luminal measurements obtained with intravascular ultrasound imaging and quantitative angiography in two types of coronary artery phantoms. The first were obtained from post-mortem atheromatous human coronary arteries using a negative cast technique, and showed a luminal morphology with variable degrees of irregularity and eccentricity. The second type of phantom were made by precision drilling holes of various diameters in epoxy blocks. This yielded a smooth circular morphology. In both types of phantom, true luminal areas and eccentricity were measured and documented. Both intravascular ultrasound and quantitative angiography were used to acquire appropriate images of both sets of phantoms. Using intravascular ultrasound data, the intraobserver variability, accuracy and precision of area measurements obtained in coronary phantoms with irregular lumen was calculated and compared to that found in phantoms with circular morphology. Furthermore, results obtained with ultrasound imaging were compared with those obtained with quantitative angiography.

## Methods

### *Epoxy phantoms*

Coronary phantoms were obtained from 3 coronary arteries, which had been obtained during separate post-mortem studies, showing diffuse and extensive atherosclerotic disease. The technique of negative casting was developed by Doriot et al. [15] and has been previously used by in validation studies of quantitative angiography [15]. First, the vessels were flushed with saline and then injected in situ with silicon paste to obtain positive luminal casts. Once the filling mass had hardened the main arteries were dissected and coronary tissue removed using a concentrated KOH solution. The positive casts corresponding to three obviously atheromatous segments were selected. From these, negative casts were obtained by suspending each silicon segment was suspended in a Teflon mold an casted with epoxy resin. On each epoxy block, regular slices (at intervals of 3–8 mm) were obtained by sawing with a rotating disk of 0.3 m thickness. In total, 22 sections were performed. After careful removal of the silicon paste, the surface of each block was smoothed with emery cloth and photographed under a microscope. A precision scale was also photographed at the same magnification and used for calibration. The areas of the 22 luminal were measured using a computer-assisted system allowing for 12–fold optical magnification of the film images. All measurements were made by two observers, with an interobserver variability less than 0.5% for each lumen. The mean differences between the areas of two corresponding luminal was 0.28 $mm^2$. The area at each particular section was obtained the average of the two values. The eccentricity of the lumen at each particular section was defined as the ratio between the largest and the smallest observed diameters. Mean eccentricity was 1.17 (range 1–1.65),

corresponding to the most circular and most eccentric lumen obtained respectively. Once those measurements were obtained each block was reconstructed by careful gluing of the slices with a molecular glue. In order to locate each section site later during angiography two metal balls were attached at the level of each section in opposite corners to act as radiopaque markers. Finally, an inlet and an outlet to fill the phantom with water or contrast medium was provided.

In addition to the coronary casts, eight circular phantoms were built using 7 cm long plexiglass blocks in which circular luminal with fixed diameters of 2 to 5 mm were precision-drilled.

*Image acquisition: intravascular ultrasound*

Phantoms were filled with water at room temperature and free of air bubbles. A 20 MHz intravascular ultrasound probe (Cardiovascular Imaging Systems, Inc., Sunnyvale, California) was prepared, introduced through one of the inlets in the phantoms and positioned under visual control at the site of interest, the latter operation being facilitated by the transparency of the phantom and the presence the metal ball markers. Measurements were performed on-line independently by two observers with expertise in intravascular ultrasound imaging in two separate sessions. Hard copies of all measurements and videotape recordings were done for further documentation. Each observer was free to adjust gain, magnification and other settings to obtain optimal visualization of the luminal borders in the same way as during clinical practice.

*Image acquisition: angiography*

Cineangiograms of the phantoms were obtained with a Phillips DCI system. A focus-to-object distance of 90 cm and a object-to-image intensifier distance of 13 cm were used to simulate the conditions found during standard coronary angiography. The x-ray beam was perpendicular to the long axis of the phantom. Prior to image acquisition, phantoms were filled with contrast medium (Iopamidol-370). Additional plexiglass blocks (12.5 cm thick anteriorly and 5 cm thick posteriorly to each phantom) were used to render kV (75 kV) and X-ray scatter levels similar to those existing in routine clinical angiography. Each section was filmed in the isocenter of the X ray beam. The same procedure was repeated in a orthogonal (90°) angulation. The obtained cineangiograms were processed routinely and analyzed quantitatively.

The films were analyzed in an edge detection quantitative angiography system (CAAS 2, Pie Data, Maastricht, The Netherlands) [16], which represents a new generation of a previously validated system [17]. Methodological aspects of the CAAS measurement approach have been discussed in detail in other sections of this book. The analysed areas were studied while in

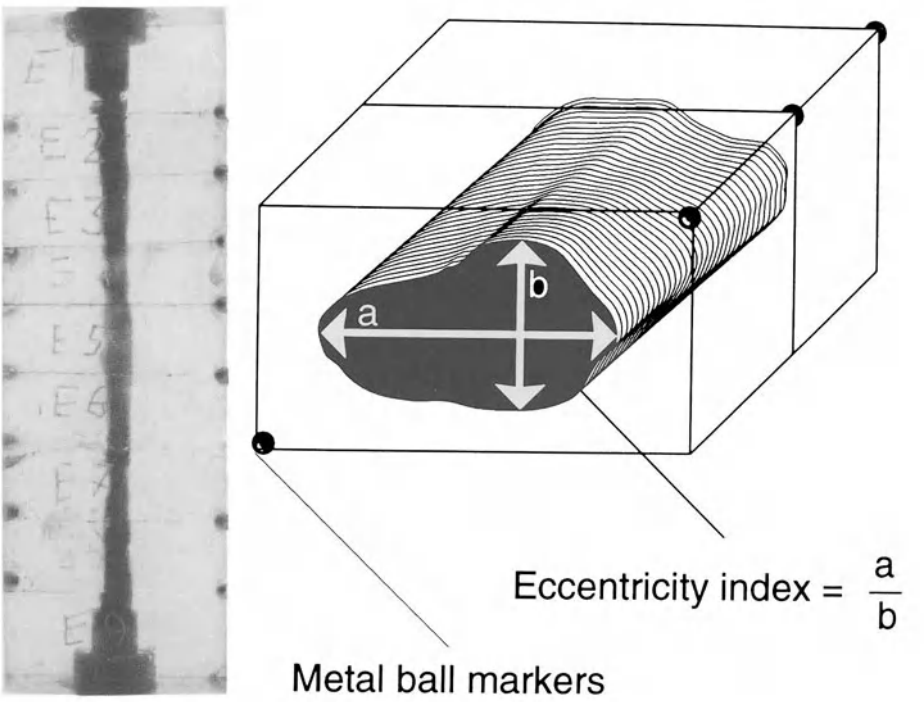


*Figure 1.* Coronary phantoms were obtained from human coronary arteries with diffuse atherosclerotic luminal narrowing. The blocks obtained by negative casting were first sawn in slices. Luminal area and diameters were measured. An eccentricty index was calculated from the latter by dividing the largest by the smallest luminal diameter. During the reconstruction of the phantoms the sections were identified by radiopaque metal ball markers.

the angiographic isocenter. Angiographic identification of each section was facilitated by metal balls acting as radiopaque markers (Fig. 1). The diameter of the vessel at the level of the analysed section was measured at the level of the radiopaque markers. These measurements were converted to absolute values by using an empty coronary guiding catheter of known dimensions that was filmed in parallel with the phantom. Using the obtained luminal diameter of the section, luminal area was calculated assuming a circular morphology.

*Statistical analysis*

The correlation between intravascular measurements and phantom luminal dimensions was analyzed using the product-moment coefficient and the between-method differences [18]. Once multiple measurements were obtained, the precision of intravascular ultrasound was judged using the mean differ-

ence between intravascular measurements and phantom luminal areas; likewise, its accuracy was judged using the dispersion (standard deviation) of such differences. Mean values of paired data were compared using paired 2–tailed Student's t tests. A p value $<0.05$ was considered statistically significant.

## Results

### *Coronary phantoms*

The mean luminal area measured at the level of the sections performed in the coronary casts was $8.79 \pm 1.62$ mm$^2$ (range 6.40–13.01 mm$^2$), while in the circular phantoms was $10.59 \pm 6.62$ mm$^2$ (range 3.14–19.63 mm$^2$). In the coronary phantoms the eccentricity of the luminal was $1.17 \pm 0.16$ (range 1–1.65).

*Interobserver variability of ICUS measurements*
Figure 2 shows the correlation between luminal measurements obtained using intracoronary ultrasound by two independent observers. In the coronary phantoms the correlation coefficient and mean difference ± SD between measurements obtained by both observers were 0.77 and $0.80 \pm 0.98$ mm$^2$ respectively, while in the circular phantoms the obtained values were 0.99 and $-0.81 \pm 1.38$ mm$^2$ respectively ($p = 0.003$). It is interesting that in the coronary phantoms the discrepancy (absolute difference) between measurements obtained by the two observers was directly related to the degree of eccentricity of the sections ($r = 0.40$, $p = 0.06$).

*Accuracy and precision of ICUS area measurements*
The agreement between intracoronary ultrasound measurements and actual luminal dimensions of the phantoms was performed using the average of measurements obtained by the two observers. Correlation coefficient and mean differences ± SD between ultrasound measurements and phantom areas were 0.90 and $0.63 \pm 0.71$ mm$^2$ in the coronary phantoms, and 0.99 and $-0.08 \pm 0.39$ mm$^2$ in circular phantoms respectively ($p = 0.012$) (Fig. 3). There was no significant relation between the error of the measurements and the degree of eccentricity of the sections.

*Accuracy and precision of quantitative angiography*
The mean area calculated from averaged orthogonal views was $8.20 \pm 1.30$ mm$^2$ and $9.73 \pm 5.32$ mm$^2$ for the coronary and circular phantoms respectively. Luminal areas derived from quantitative angiographic data correlated well with the true luminal areas of coronary ($r = 0.91$, mean difference $0.59 \pm 0.67$ mm$^2$) and circular phantoms ($r = 0.99$, mean difference $0.86 \pm 1.38$ mm$^2$) (Fig. 4). There was no statistically significant difference

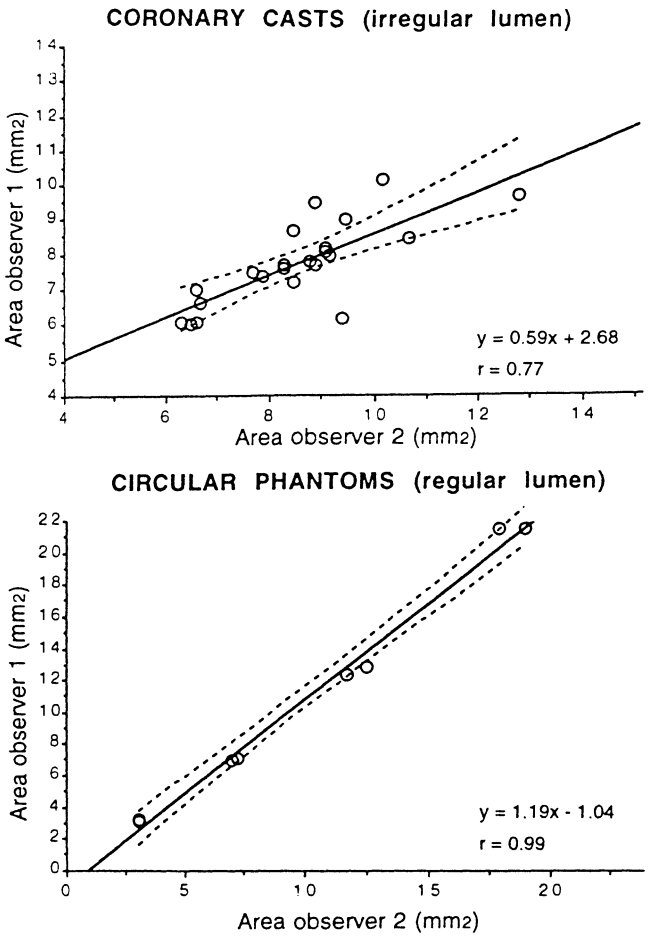


*Figure 2.* Correlation between luminal area measurements obtained with intravascular ultrasound imaging obtained by two independent observers in coronary and circular phantoms.

between these measurements. Likewise, no relation was found between the degree of eccentricity and the discrepancy between true luminal areas and those calculated from single plane or biplane angiography.

*Correlation between quantitative and ICUS measurements*

The correlation coefficient between luminal areas calculated from a single angiographic view and ICUS measurements were 0.72 and 0.84 in the frontal and lateral projections respectively. The discrepancy between intravascular ultrasound and quantitative angiographic measurements kept a mild correlation with the eccentricity of the lumen ($r = 0.40$, $p = 0.06$).

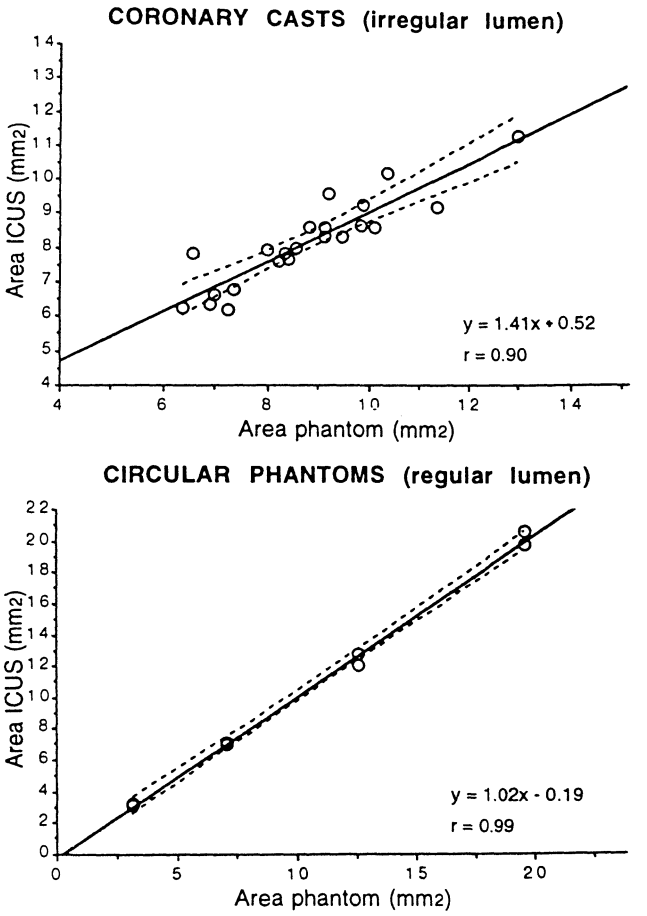


*Figure 3.* Correlation between phantom dimensions and luminal area measurements obtained with intravascular ultrasound imaging (average of both observers) in coronary and circular phantoms.

## Discussion

Although the circular or moderately elliptical lumen has been shown to be the dominant pattern of non-complicated coronary segments [19], major changes in luminal geometry can be observed in complicated coronary plaques [20, 21] and after percutaneous interventions [22, 23]. The accuracy of quantitative angiographic measurements has been shown to decrease immediately after balloon angioplasty [2–5]. Preferential use of videodensitometry, which theoretically is independent of luminal morphology and angulation used, has so far failed to provide a practical solution to this problem [4–6,

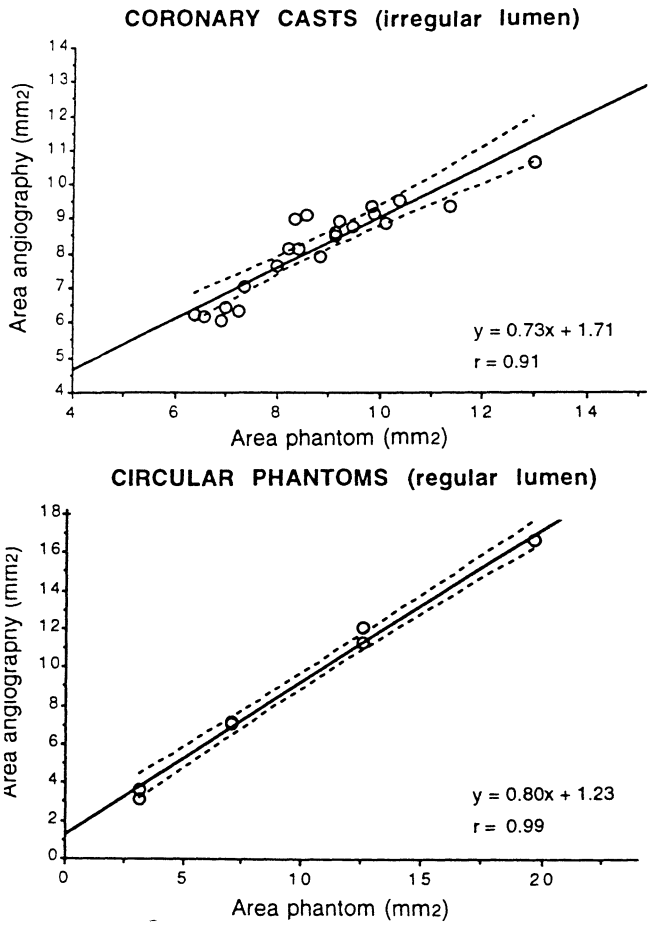


*Figure 4.* Correlation between phantom dimensions and luminal area measurements obtained with quantitative angiography (two orthogonal views averaged) in coronary and circular phantoms.

24]. Intravascular ultrasound to estimate luminal area by planimetry has been advanced as an attractive alternative for the solution of this problem [8, 9]. Experimental studies have demonstrated a good correlation between IVUS and histological measurements [25–27], although little emphasis has been placed on the influence of luminal morphology on measurement accuracy and precision. Application of intravascular ultrasound in the clinical field has provided less convincing results the results. A good correlation between quantitative coronary angiography and intravascular ultrasound measurements has been documented in normal vessels and even in atherosclerotic vessels with circular luminal contour [13]. By contrast, moderate [28] or no

correlation [14, 28] has been found in similar studies performed after balloon angioplasty.

Since no known standard was used in clinical studies comparing intravascular ultrasound and quantitative angiography, it is not possible to infer whether measurements with IVUS represent a better estimate than those obtained with quantitative angiography. Furthermore, no information is available in the literature on the influence that lumen morphology has on the interobserver variability of ultrasonic area measurements, a fact that is of considerable importance since so far all available systems rely in user-defined contours of the lumen. The purpose of this study was to address these issues by comparing intravascular ultrasound and quantitative angiography in the measurement of phantoms with known dimensions and of both circular and irregular morphology.

The first conclusion is that luminal morphology clearly affects the reliability of luminal area measurements obtained with intravascular ultrasound imaging.This may be partly due to increased interobserver variability in phantoms with an irregular cross-section. As with coronary angiography, subjective identification of luminal borders may be the root of this problem. A more circular morphology facilitates accurate tracing of the luminal borders, perhaps because the observer is guided by a perception of a circular luminal shape (Fig. 5). As the circular pattern is lost, an increasing degree of uncertainty is introduced in the observation. In addition, loss of perpendicularity of the ultrasonic beam to the vessel wall may contribute to a poorer definition of the image, contributing to further errors in tracing during planimetry [10, 11]. Non-coaxial orientation of the ultrasound catheter has also been shown to cause errors of up to 20% of the area measurements in circular wells [29, 30]. These factors may explain the correlation found in this study between the degree of eccentricity and the interobserver variability, and may contribute to a greater average error in the calculated dimensions.

In contrast with intravascular ultrasound, the precision of quantitative angiography was not significantly influenced by the type of phantom used, although a better correlation was present in those with a circular lumen. as has been reported by Moriuchi et al. [31], we found a trend towards overestimation of luminal area in irregular phantoms (intercept $+1.71$ mm$^2$ versus $+1.20$ mm$^2$ in irregular and circular phantoms respectively) to that reported by Moriuchi [31] in acrylamide casts. It is also noteworthy that averaged ultrasonic measurements compared favorably with quantitative angiography in both types of lumen (intercept $+0.71$ versus $-0.19$ in irregular and circular phantoms respectively).

Intravascular ultrasound was not significantly superior to edge detection in assessing luminal area. However, an average of two orthogonal views was used since significant variability would be expected in irregular lumina measured from a single angiographic projection [3, 5], as illustrated in the current study by the proportional relationship between lumen eccentricity and the discrepancy between corresponding orthogonal angiographic views.

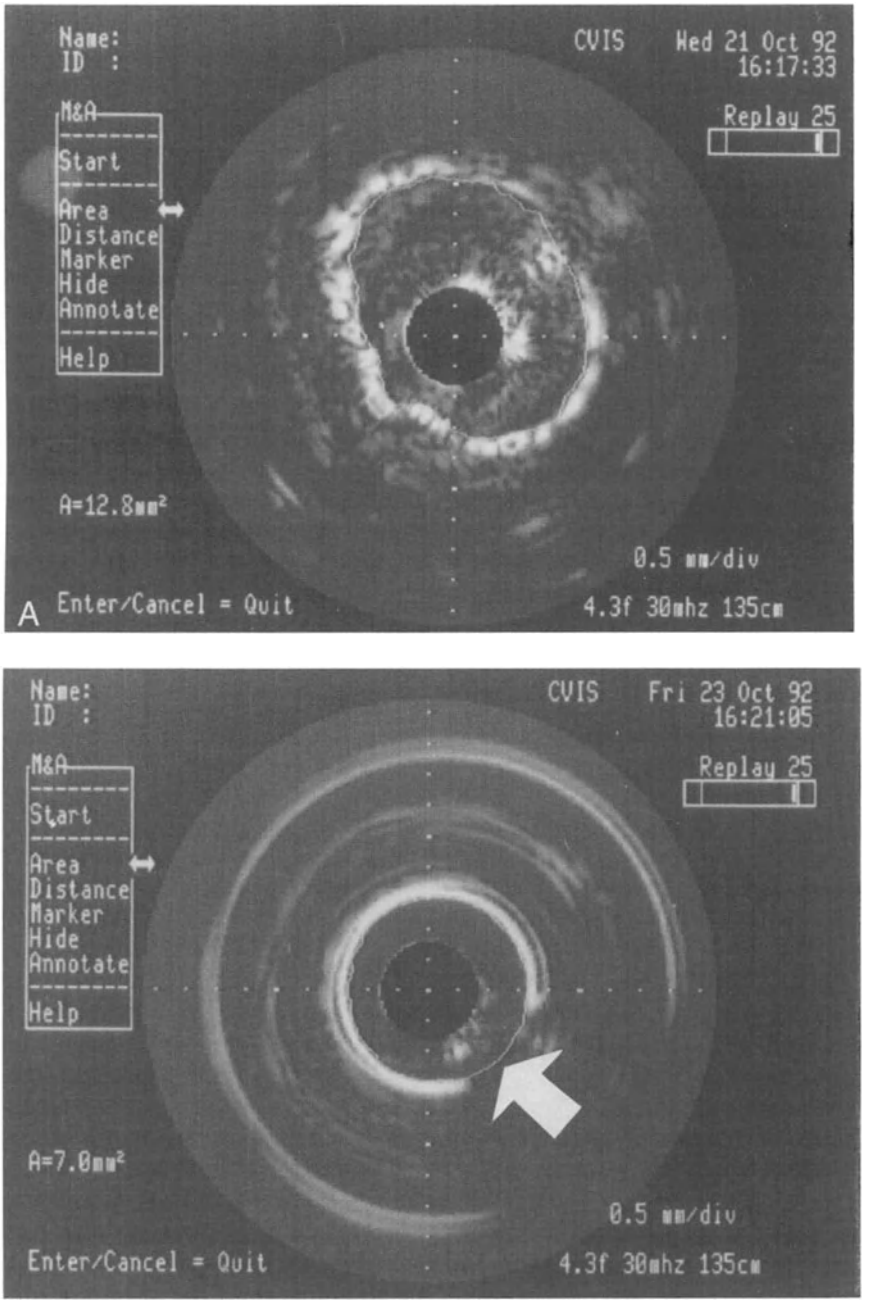


*Figure 5.* Intravascular ultrasound imaging of a coronary cast (A) and a n engineered circular phantom (B). Identification of the lumen by one of the observers can be seen in both images. In circular lumina the perception of a circular morphology may have contributed to a more accurate tracing of the luminal borders in areas where artifactual imaging of the vessel wall occurred (arrows), contributing to a better corelation with the actual dimensions of the phantom (see text for more details).

True orthogonality of the angiographic views was chosen since the obtained averaged value is known to be more reliable than that obtained from non-orthogonal views [32]. Unfortunately, in clinical practice the presence of branch overlap, bifurcations and other anatomical features render routine application of this approach extremely difficult and often impossible.

In accordance with the results obtained in a clinical study by Nissen at al [13], the discrepancy between measurements obtained with intravascular ultrasound and quantitative angiography was proportional to lesion eccentricity. In that study, due to the inability to measure actual lumen eccentricity, a "circular shape factor" was calculated from the ultrasonic images as an index of the degree of deviation of the lumen area from a perfect circle. Using this index, vessels were then divided into those with concentric or eccentric lumina, the former showing a better correlation between angiography and intravascular ultrasound ($r = 0.93$) than the latter ($r = 0.77$). In the present study lumen eccentricity was used as a continuous variable to assess its influence on different aspects of dimensional quantification with angiography and intravascular ultrasound. It is possible to speculate therefore, on the basis of the findings of these two separate studies, that discrepancies between quantitative angiography and intravascular ultrasound may arise from a combination of the impact of lumen eccentricity on the inter-observer variability of intravascular ultrasound and on the precision of edge detection in calculating luminal area.

### *Study limitations*

It is self-evident that plexiglass phantoms are different from real coronary arteries. However, they have optimal echogenicity and more stable luminal dimensions that histological preparations. Since there was no backscatter due to circulating blood, the quality of the images obtained would be expected differ from those obtained in clinical practice. For the sake of simplicity the experiments were performed at room temperature and water was used to fill the phantoms. Although this practice may have interfered in the measurements performed with intravascular ultrasound [11], it would be expected that such interference would be systematic in irregular and circular phantoms (in which an excellent correlation was found between actual and measured dimensions). Although we believe that the echo transducer was positioned at identical points in repeated measurements (using both the ball landmarks and the transparency of the phantoms), errors derived from minor discrepancies in transducer location during the second observation cannot be ruled out. The degree of luminal irregularity and eccentricity of the coronary phantoms may not be representative of to that found after percutaneous interventions. This must be kept in mind when our results are compared with others performed in clinical settings.

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# 37. Intravascular ultrasound: An evolving rival for quantitative coronary angiography

CARLO DI MARIO, JOS R.T.C. ROELANDT, PETER P. DE JAEGERE, PIM J. DE FEYTER and PATRICK W. SERRUYS

## Introduction

Quantitative angiography has been used to validate the accuracy of the measurement obtained with the early intravascular ultrasound catheters [1–3]. In more recent reports [4–12] it was suggested that intravascular ultrasound can be superior to quantitative angiography in the assessment of complex lesions (eccentric stenosis, asymmetric lesions, vascular dissections). In this article, advantages and limitations of the two techniques in the assessment of vascular dimensions are discussed based on the results reported in the literature and of our experience in 72 patients with coronary artery disease.

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

The results of 11 clinical studies in which quantitative angiography and intravascular ultrasound were compared are summarized in Table 1. Differences in equipment and methods of analysis limit the comparison and interpretation of data. Linear regression analysis is most commonly used as a statistical test in these studies. However, a regression coefficient close to 1 is not sufficient to conclude that the two techniques provide similar quantitative measurements [13]. The mean difference of the paired measurements and indexes of dispersion along the line of identity are more meaningful parameters but are not always reported. With the exception of Tobis [6] the results indicate that there is a good correlation between intravascular ultrasound and angiographic measurements in normal or moderatey diseased segments (Fig. 1). In general larger cross-sectional areas were measured with intravascular ultrasound than with angiography [6, 8, 9, 11, 12]. A major limitation for a precise comparison is that the measurement of the same arterial cross-section is difficult. This is especially true when a major change of vascular cross-sectional area occurs along a very short segment. An angiogram of sufficient quality to be quantitatively analyzed can not be obtained



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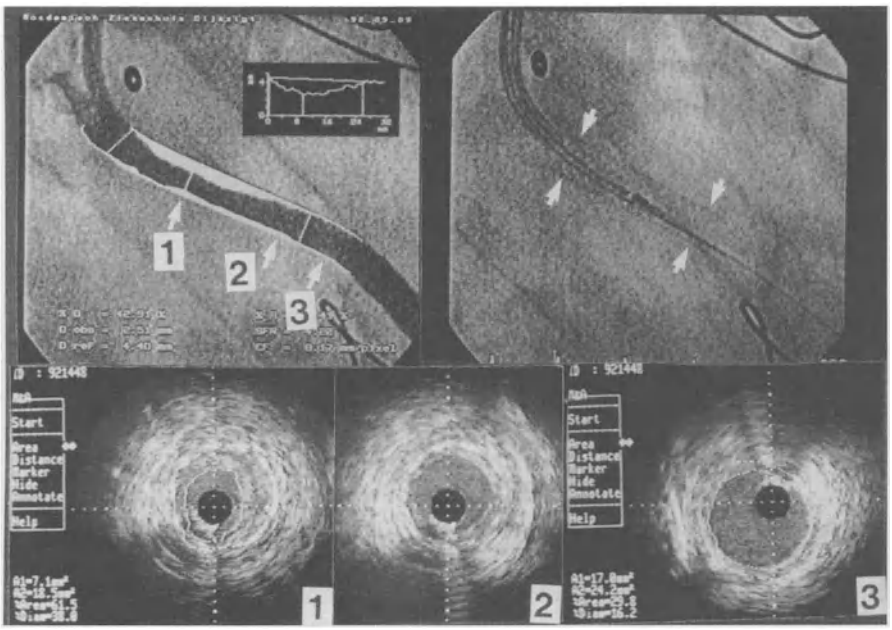


*Figure 1.* Digital angiogram of a Palmaz-Schatz stent 4 months after implantation in a saphenous vein graft used as aorto-coronary bypass conduit. In the fluoroscopic image the poorly radioopaque stent, indicated with arrows, is examined with a 4.3 rotating mirror ultrasound catheter. The minimal lumen of the moderate (re-)stenosis observed within the stent (position 1) corresponds with ultrasound to a homogeneous area of poorly echogenic intimal thickening. Note that intravascular ultrasound in this case overestimates the minimal luminal cross-sectional area (4.94 $mm^2$ with angiography vs 7.10 $mm^2$ with ultrasound). A diffuse area of intimal thickening within the stent is detected also in position 2, a relatively normal segment angiographically. Calibration: 0.5 mm.

during the echographic measurements since the catheter positioned in the stenotic segment partially occludes blood flow and hampers the run-off of contrast medium. In eccentric lesions or lesions treated with balloon angioplasty a poor correlation and a large scatter of the paired measurements was found. After angioplasty, Tobis measured with intravascular ultrasound cross-sectional areas which were up to 50% larger than the corresponding angiographic cross-sectional areas calculated assuming a circular model [6].

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

The use of different reference measurements for the calculation of relative vascular dimensions with quantitative angiography and intravascular ultrasound explains the large discordance of the results obtained with the two

*Table 1.* Quantitative angiography vs intravascular ultrasound: clinical comparative studies.

| Authors | Patients | Examined Arteries | "r" | SEE | Mean Diff. | % Diff |
|---|---|---|---|---|---|---|
| Davidson et al. [2] | 21 pts undergoing cardiac cath. | femoroiliac arteries | 0.97 | 1.83 | | |
| Sheikh et al. [3] | 15 pts undergoing cardiac cath. | femoral arteries | 0.95 | 0.91 | | |
| The et al. [4] | 8 pts undergoing cardiac cath. | femoroiliac arteries | 0.96 | 0.47 | | |
| Bartorelli et al. [5] | 8 pts undergoing cardiac cath. | normal common femoral arteries | 0.96 | | 0.3 mm | 4% |
| Tobis et al. [6] | 27 CAD pts undergoing PTCA | normal sites | 0.26 | | 2.1 $mm^2$ | 30% |
| | | stenosis post-PTCA | 0.18 | | 1.7 $mm^2$ | 51% |
| Nissen et al. [7] | 8 normal subjects | normal coronaries | 0.92 | 0.21 | −0.05 mm | 1% |
| | 43 CAD pts | coron. art. (all les.) | 0.86 | 0.43 | −0.05 mm | 2% |
| | | eccentric lesions | 0.77 | 0.77 | 0.06 mm | 2% |
| Werner et al. [8] | 14 CAD pts | normal sites | 0.86 | | | |
| | | stenosis post-PTCA | 0.48 | | | |
| StGoar et al. [9] | 20 cardiac transplant recip. | normal coronaries (angiographially) | 0.86 | 0.07 | 0.04 mm | 12% |
| Jain et al. [10] | 6 CAD patients | SVBG | 0.96 | | | |
| Hodgson et al. [11] | 34 CAD patients undergoing PTCA | reference segment | 0.77 | | | |
| | | stenosis post-PTCA | 0.63 | | | |
| Haase et al. [12] | 20 CAD patients | stenosis post-PTCA | 0.53 | | 2.3 $mm^2$ | |

CAD: coronary artery disease; PTCA: percutaneous transluminal coronary angioplasty; SVBG: saphenous vein bypass grafts.

techniques (Fig. 2). Reference diameter and cross-sectional area are measured in an angiographically normal segment of the vessel with quantitative angiography. In muscular arteries intravascular ultrasound allows a direct measurement of the area inside the internal elastic lamina, the so called original lumen area which equals to the sum of lumen and plaque area. This area is used as a reference in intravascular ultrasound. Intimal thickening is often present in angiographically normal reference segments (Fig. 3). Furthermore, a compensatory enlargement of the vessel can be present at the stenotic site [14]. These reasons explain why the lumen cross-sectional area used as angiographic reference is smaller than the ultrasonic reference area [15] so that less severe percent diameter and cross-sectional area stenosis will be calculated with quantitative angiography than with intravascular ultrasound. In the diagram of Fig. 2A, in the presence of a 1/2 mm thick intimal lesion in the reference segment, a major difference is observed in percent diameter and cross-sectional area stenosis between quantitative angiography and intravascular ultrasound. The practical occurrence of this phenomenon is

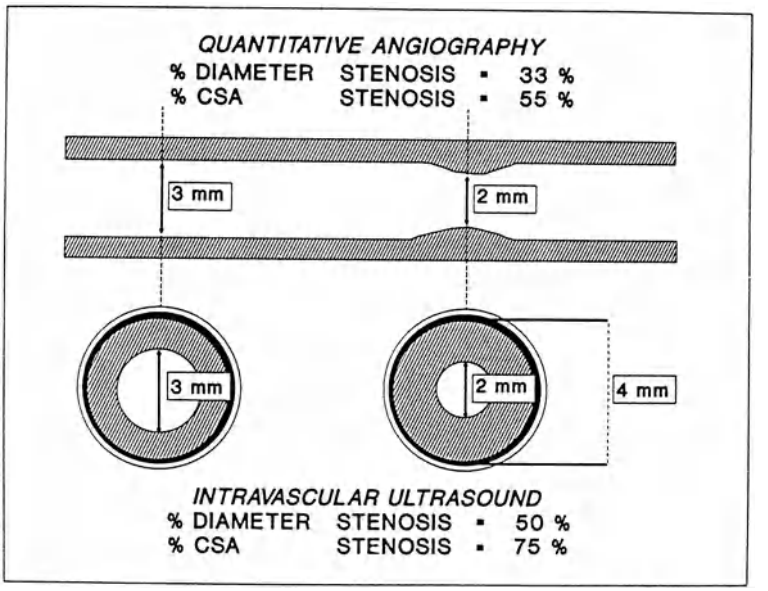


*Figure 2.* A) Calculation of percent diameter and cross-sectional area stenosis based on intravascular ultrasound and quantitative angiographic measurements. The reference lumen diameter is measured with quantitative angiography in the normal segments of the vessel while intravascular ultrasound directly measures the thickness of the atherosclerotic plaque at the stenosis site. In the presence of compensatory enlargment of the stenotic site or, as in this example, of a diffuse concentric intimal thickening involving also the angiographic reference segment, the intravascular ultrasound reference diameter, traced within the black band representing the muscular media, is larger than the angiographic reference diameter. As a result the angiographically moderate percent stenosis is considered more severe, "significant" according to the normally used criteria ($\geq$50% diameter stenosis and $\geq$75% cross-sectional area stenosis) with intravascular ultrasound.

illustrated in the example of Fig. 1B, showing the presence of a large concentric plaque in the angiographic reference segment.

Percent diameter and cross-sectional area stenosis are physiologically important parameters and are major determinants of the pressure drop across a stenosis [16]. However, the results obtained from animal models of acute external constriction of normal vessels [17] can not be simply applied to the percent lumen reduction measured with quantitative angiography. Harrison showed that the stenosis-related impairment of post-occlusion reactive hyperemia can not be predicted based on the coronary angiographic assessment of percent diameter and cross-sectional area stenosis [18]. Awareness of these drawbacks has already contributed to focus the interest in the measurement of absolute rather than relative lumen stenosis in quantitative angiography [19]. Intravascular ultrasound can directly measure plaque area and avoid the use of a reference measurement in a potentially diseased segment of the vessel. However, this reference area does not necessarily reflect the

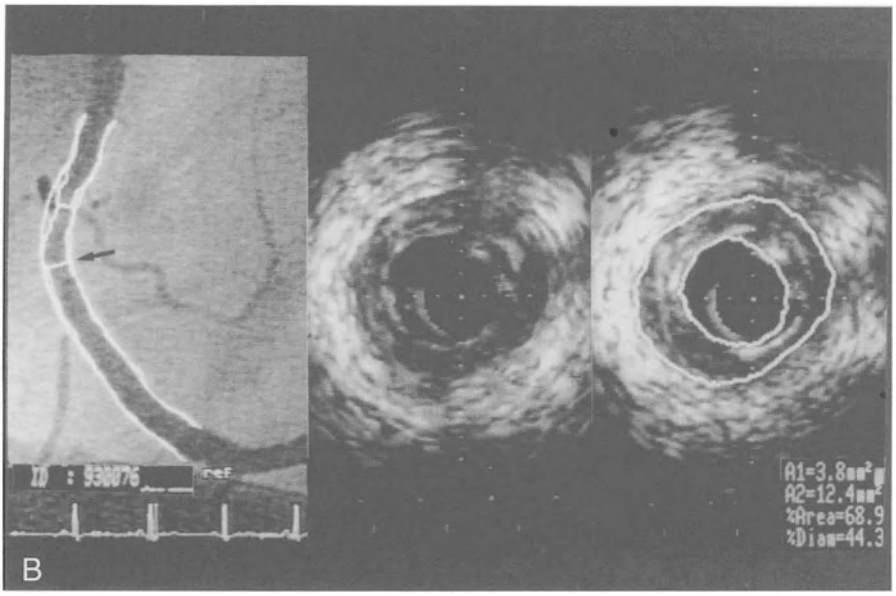


*Figure 2.* B) Digital angiogram of a right coronary artery with the reference diameter positioned at the site examined with intracoronary ultrasound. Note that in this angiographically normal reference segment intracoronary ultrasound shows the presence of a concentric plaque inducing a 44% diameter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

physiologically ideal vascular dimension because of the already mentioned compensatory enlargement. In particular the presence of a crescentic plaque with an outward remodelling of the vessel is likely not to influence the dimension of the vascular lumen. The presence of a reduction of the "ideal" dimension of lumen cross-sectional area is more difficult to be judged in the presence of a diffuse circular ring of intimal thickening (Fig. 3) [20]. Therefore the assessment of the physiologic significance of a vascular stenosis requires different approaches such as the measurement of trans-stenotic velocity increase or of the pressure drop at maximal hyperemia across the stenosis or the calculation of coronary flow reserve based on angiographic or Doppler measurements.

## Advantages of intravascular ultrasound

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

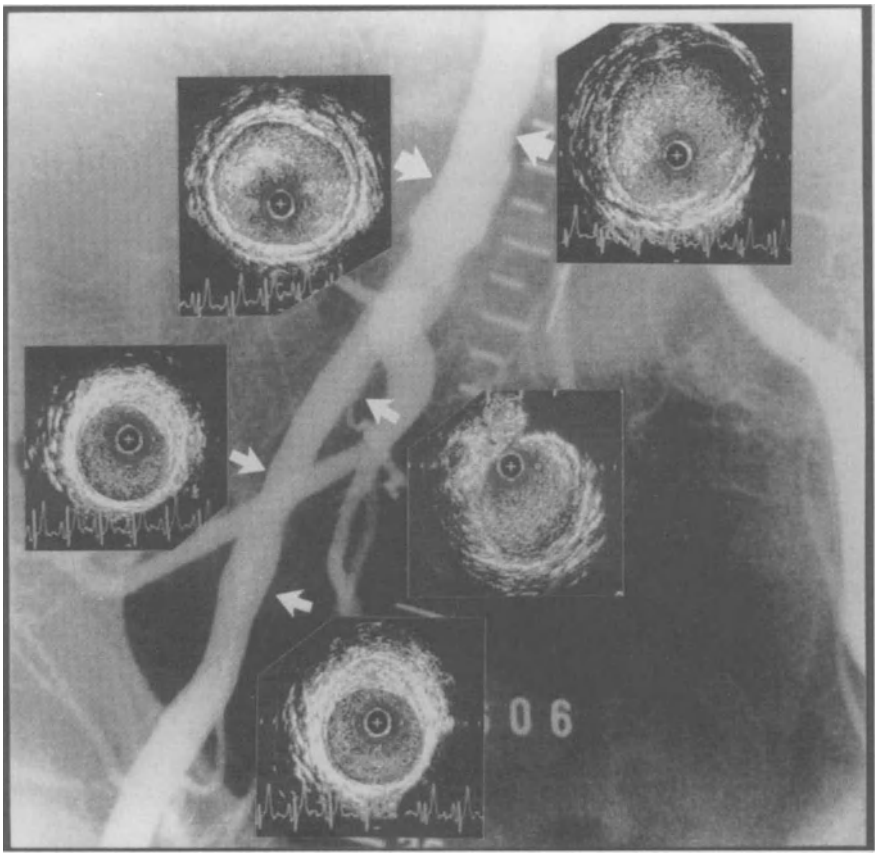


*Figure 3.* Digital angiogram of a right iliac artery showing multiple edge irregulaties and a mild stenosis. The arrowheads indicate the position of the ultrasound transducer during the acquisition of the displayed arterial cross-sectional images. Note the relatively concentric bright ring of intimal thickening in the two upper images, corresponding to an apparently normal circular lumen at angiography. In the following cross-section an eccentric, fibrocalcific plaque is shown in a segment of moderate lumen diameter stenosis with quantitative angiography. Note that the two lowest ultrasonic cross-sections, corresponding to a normal angiographic segment at angiography and showing a semilunar bright eccentric atherosclerotic plaque not protruding inside the regular circular lumen at ultrasound. Calibration: 1 mm.

*No calibration is required*

For angiography the measurement of a radiopaque structure of known dimension is required for calibration. When the tip of the catheter is used as a scaling device, possible sources of error are off-plane position of the catheter and of the examined vessel, tapering of the catheter at the distal end and discordance between true catheter diameter and the diameter reported by

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

| Advantages of intravascular ultrasound | Limitations of intravascular ultrasound |
|---|---|
| 1) No calibration required | 1) Introduction of the catheter is necessary |
| 2) Instantaneous and continuous measurements available | 2) Potential errors due to catheter malalignment |
| 3) No contrast medium required | 3) Artifacts from non-uniform rotation[1], near-field artifacts[2], low sampling rate[2] |
| 4) Independent of lumen eccentricity or complex lumen geometry (dissection) | 4) Automatic edge-detection difficult |
| 5) Simultaneous morphometric analysis of wall components | 5) Reproducibility of the measurements not yet tested |

[1] Single element mechanically rotating systems; [2] multielement synthetic aperture array systems.

the manufacturer [21]. Furthermore, calibration must be repeated for every angiographic view. A potentially more precise but even more cumbersome approach is the geometric correction for beam divergence, based on the measurement of the distances between x-ray source, imaged object and image amplifier (isocenter technique) [22].

The measurement of a distance with ultrasound is based on the wavelength of the ultrasound beam and the velocity of sound in the medium. When the instrument is calibrated for the ultrasound speed in blood (1,560 m/s) a negligible overestimation occurs when saline is injected to replace the more echogenic blood and delineate the intimal contour.

### *Instantaneous measurements are available*

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

### *No contrast medium required: A continuous monitoring is possible*

Angiography requires the injection of contrast material to delineate the vascular lumen. As a consequence, angiography can not be used for a continuous monitoring of vascular dimension. Other disadvantages of the use of contrast medium are the modification of the intraluminal pressure during the forceful injection of contrast and the vasoactive properties of these agents.

Intravascular ultrasound allows a continuous real-time measurement of vascular dimensions, a great potential advantage for monitoring interventions and assessment of the effects of vasoactive agents on vascular dimensions and dynamics [23].

*Morphometric analysis of the vessel wall*

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

The possibility to provide information on plaque morphology and dimension at the same time makes intravascular ultrasound an ideal technique for the assessment of the mechanism of the different coronary interventions and the modalities of progression/regression of the atherosclerotic plaque. Wall stretching and wall dissection have been reported as the main operative mechanism of balloon angioplasty in both coronary [30] and peripheral arteries [31]. A significant plaque compression (absolute reduction of plaque area) has been more recently reported [32]. Standard methods used in quantitative angiography for the assessment of regression of atherosclerosis are the measurement of mean luminal area and severity of edge irregularities [33] (roughness profile). A long-term follow-up of large cohorts of patients is necessary to show a statistically significant trend towards regression or delayed progression of plaques in peripheral [34, 35] and coronary [36, 37] atherosclerotic disease.

Intravascular ultrasound has the potential of detecting atherosclerotic wall

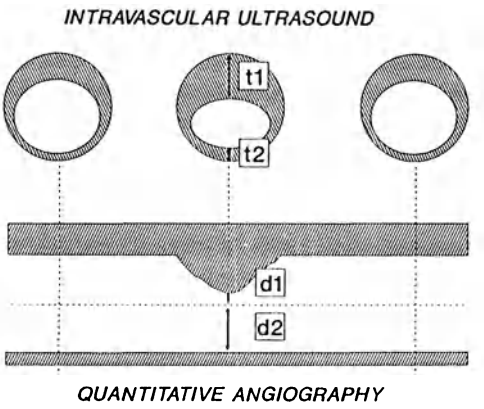


*Figure 4.* A) Eccentricity index calculated with quantitative angiography and intravascular ultrasound. Intravascular ultrasound allows the direct assessment of the wall thickness (t) so that the eccentricity index is based on the ratio between plaque thickness and thickness of the opposite wall. Quantitative angiography estimates the eccentricity of a plaque from the distance (d) between the center of the lumen and the luminal contours at the site of the stenosis. In this example, however, the presence of a different thickness of the wall also in the angiographically normal segment induces an underestimation of the plaque eccentricity.

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

*Plaque eccentricity*

In most cases, with the use of multiple projections, an angiogram perpendicular to the maximal thickness of the plaque can be obtained. In less than 50% of the cases, however, appropriate orthogonal projections, amenable to quantitative analysis, can be obtained to measure lumen area from its long- and short-axis when an elliptical area is present [44]. Furthermore, angiography determines the eccentricity of a stenosis comparing the proximal and distal segments of the vessel, assumed as "normal" reference segments so that a misinterpretation is possible if the eccentric plaque involves also the reference segments (Fig. 4).

Intravascular ultrasound detects the eccentricity of the lesion from a direct

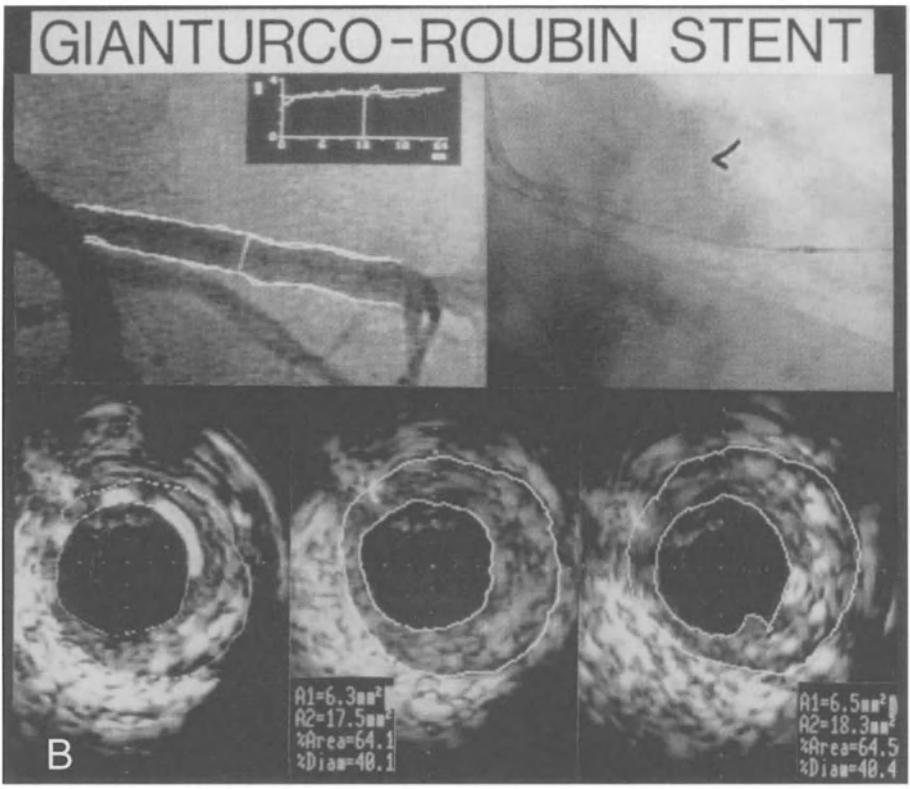


*Figure 4.* B) Digital angiogram showing a regular lumen after implantation of a Gianturco Roubin stent in a proximal left anterior descending coronary artery. The stent is barely visible in the fluoroscopic image obtained during the ultrasound examination but the circumferentially arranged metallic wires of the stent show a high echogenicity with ultrasound. Note that an eccentric residual plaque is shown despite the regular circular lumen (echographic images on the right), with a small protrusion of the plaque tissue through the wires of the stent. Calibration: 0.5 mm.

measurement of the maximal and minimal thickness of the plaque. The eccentricity index calculated with intravascular ultrasound is independent from the characteristics of the contiguous segments [45]. The advantage of the direct visualization of eccentric plaques is obvious in the guidance of a selective removal of plaque, avoiding a potentially dangerous treatment in areas of thin, normal wall [46].

*Complex lumen geometry (wall dissection)*

Pathology studies have shown that splitting of the vessel wall is extremely frequent after balloon angioplasty and is one of the major mechanisms of

effective lumen enlargement [47, 48]. Only large dissections are angiographically evident after balloon angioplasty. Several reports [6, 30–32, 49–51] have confirmed that intravascular ultrasound is more sensitive than angiography in the detection of plaque rupture. The absence of echographically evident plaque rupture has been recently reported to increase the risk of restenosis [52]. The quantitative measurement of residual stenosis early after balloon angioplasty is a poor indicator of the functional result of the procedure as assessed by coronary flow reserve [53] and persistence of scintigraphic and electrocardiographic signs of reversible myocardial ischemia. Several reasons may explain this finding but in some cases the comparison between echographic and quantitative angiographic measurements suggests that an overestimation of the lumen really available for blood passage may occur when a geometric technique (edge-detection) is used (Fig. 5). Densitometric measurements have been suggested in order to overcome the limitations of edge-detection in lesions of complex geometry (including stenosis post-angioplasty and eccentric lesions) [54]. Densitometry, however, requires a homogeneous filling of the lumen with contrast and a perfect orthogonality of the x-ray beam to the vessel lumen, is highly dependent on the radiographic setting and modalities of film processing and cannot directly provide absolute measurements [55].

## Limitations of intravascular ultrasound (Table 2)

### *Necessity of catheter insertion*

Intravascular ultrasound requires the insertion of the echo-catheter along the entire vascular segments to be studied. Instrumentation of a coronary vessel is the current practice for all the interventional techniques. However, especially in the examination of the coronary arteries, the insertion of the echo-catheter increases the complexity and duration of the procedure and carries out a potential risk of complications. Recent improvements in catheter flexibility and miniaturization allow the examination of the proximal and middle coronary arteries in most patients. A possible limitation, however, concerns the examination of severe coronary stenosis before interventions, one of the most interesting potential applications of intravascular ultrasound. A quantitative angiographic study of large cohorts of candidates to balloon angioplasty [56] has shown that the measured minimal luminal diameter before balloon dilatation ($1.02 \pm 0.37$ mm) is similar to the diameter of the recently introduced second generation of catheters (from 3.5 to 4.3 French, equal to 1.15–1.4 mm), Fig. 6.

The intravascular ultrasound examination after successful therapeutic interventions is facilitated by the increased lumen diameter. However, recrossing large, unstable dissection flaps carries a potential risk of acute occlusion. Furthermore, a correct assessment of the real morphology of a complex

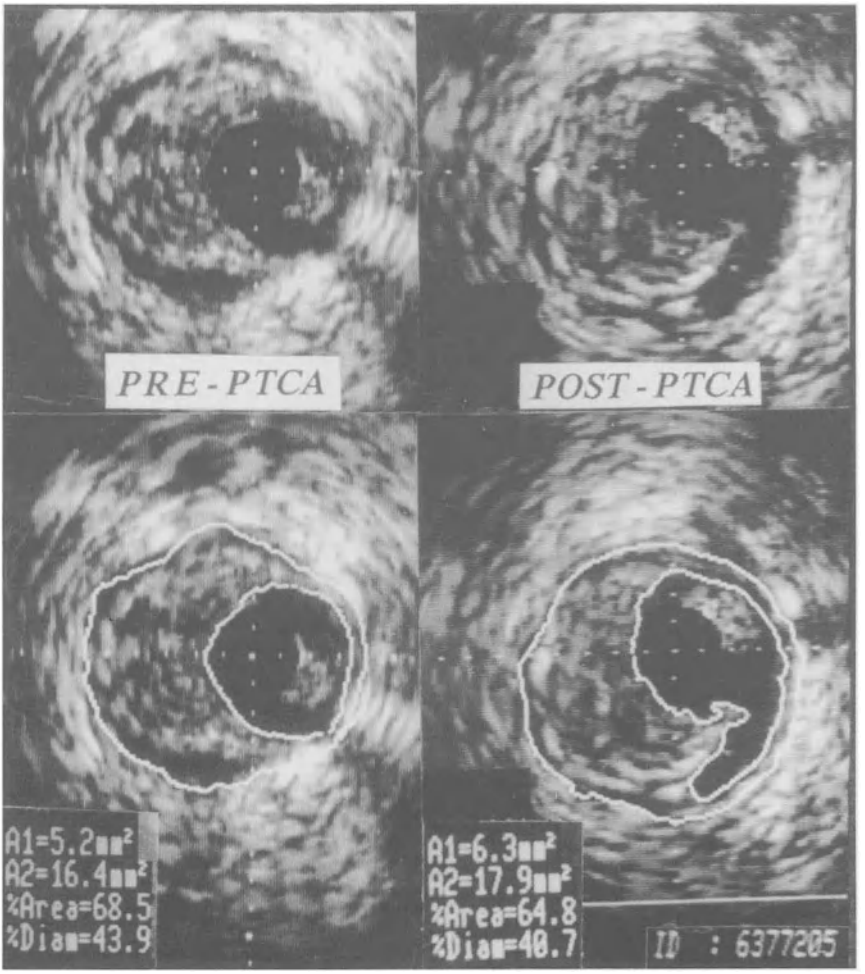


*Figure 5.* Intravascular ultrasound cross-sections of a severe stenosis in a left circumflex artery before and after balloon dilatation. Note that the eccentric plaque has been dissected at the site of its insertion on the normal wall. The complex lumen after angioplasty can not be correctly measured in any angiographic projection. Note that in this case the increase in lumen area seems to be largely dependent from the induction of a wall dissection and the stretching of the arterial wall, while no significant changes were observed in the plaque dimensions. Calibration: 0.5 mm.

spiral dissection and the consequent impairment to blood passage is difficult because it would require a three-dimensional reconstruction of the ultrasonic cross-sections [57–61] and because the communication between true and false lumen is modified by the physical presence of the catheter. Proximal injection of saline or agitated contrast can help to delineate the lumen and

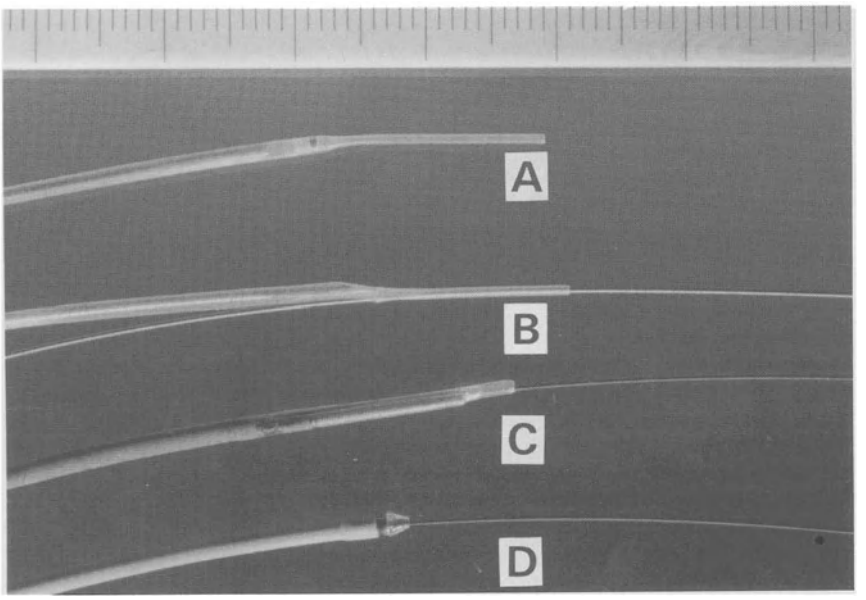


*Figure 6.* The distal end of four intravascular ultrasound coronary catheters is shown. A) Single element rotating mirror (arrow) catheter characterized by a completely independent external sheath and inner catheter; this system has the potential for an extreme miniaturization (3.5 French catheters are in clinical use) but has the limitation that the insertion of the guidewire requires the removal of the ultrasound catheter; B) rotating element 4.1 French 30 MHz ultrasound catheter, characterized by a very small Monorail lumen at the distal end (DuMed, Rotterdam, The Netherlands); C) Single element rotating mirror intravascular ultrasound catheter (Cvis, Sunnyvale, CA, USA) allowing the continuous use of a guidewire using a Monorail technique (diameter: 4.3 French); D) Multielement dynamic array catheter (a 5 French catheter is shown but 3.5 French catheter and combined balloon/ultrasound catheters are available, Endosonics, Costa Mesa, CA, USA); 64 elements are aligned circumferentially around the tip so that a central lumen is available for catheter insertion and the shaft can be very flexible because no driving cable is required; the small dimension of the elements, however, is responsible for a lower image quality in comparison with the mechanical scanners.

detect the presence of stagnant blood flow but an effective injection through the proximal guiding catheter is not always possible with the relatively large ultrasound catheters in place.

An example of another possible limitation of intravascular ultrasound in the presence of wall dissection is shown in Fig. 7 in which drop-outs occur in segments of dissected wall which are explored with an unfavourable angle of incidence of the ultrasound beam [62]. Furthermore, the underlying structures cannot be imaged. In our experience, these complex artifacts are more frequent in peripheral than in coronary arteries, because in these latter small vessels the physical presence of the ultrasound catheter modifies the orientation of the dissected flap.

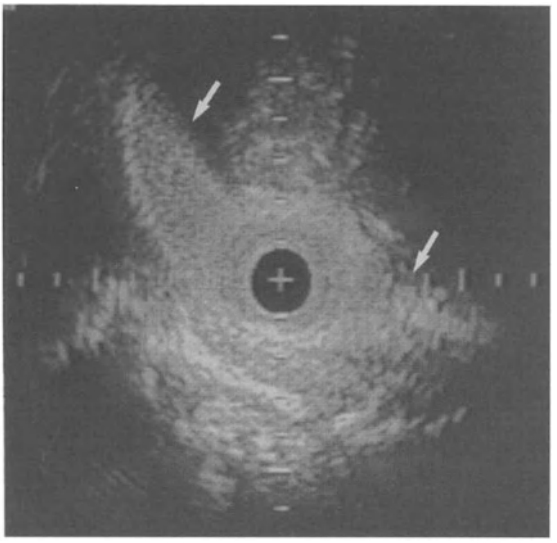

*Figure 7.* In vivo intravascular ultrasound image of a human femoral artery after balloon dilatation. The echogenic blood clearly delineates the vascular lumen. An almost complete drop-out, however, occurs in the segments in which the vessel wall and the underlying perivascular structures (arrows) are oriented at a narrow angle with the direction of the ultrasound beam. This sudden disappearence of the vessel wall can be clearly distinguished from drop-outs due to attenuation from blood, which would lead to a more progressive reduction in echo-intensity and would mainly affect the wall opposite to the position of the catheter. Courtesy of Dr. Pieterman/Dr. Gussenhoven, Radiology Department, Dijkzigt Academic Hospital, Rotterdam. Calibration = 1 mm.

The combination of intravascular ultrasound imaging and balloon angioplasty or alternative debulking techniques in the same catheter can make the evaluation with intravascular ultrasound before and after interventions easier and more practical and can allow continuous monitoring and guidance during the procedure. At present, however, only prototypes of catheters for directional atherectomy mounting ultrasound crystals are in the phase of preliminary clinical evaluation and in the already available echo-balloon catheters the transducer is mounted proximal to the balloon [63, 64]. This configuration maintains a low profile of the balloon and avoids the artifacts induced by the balloon membrane but precludes the possibility of a continuous assessment before, during and immediately after balloon dilatation.

### *Catheter malalignment*

A central position of the catheter in the vessel lumen is not frequent in intravascular ultrasound. With a simple eccentricity of the catheter position, the echographic cross-section is still perpendicular to the long-axis of the

vessel so that no change in the measured area is expected. When the catheter is not only eccentric but also non-parallel to the long-axis of the vessel the vascular lumen is distorted, with an angle-dependent overestimation of the vascular lumen. In a bending artery, however, despite the centering effect of an over-the-wire system, the ultrasound catheter can frequently assume a non-parallel orientation with the long-axis of the vessel. Fortunately, in coronary arteries the small size of these vessels relative to the catheter diameter limits the practical relevance of this problem [9].

*Non-uniform rotation, near field artifact, inadequate sampling rate*

With mechanically rotating catheters, a 1:1 rotation of the ultrasound element (or mirror) can be impossible if the catheter is inserted in very tortuous vessels, resulting in a variable distortion of the ultrasound image.

In the multielement systems these artifacts are not present. A limitation of these systems, however, is that the near-field artifact is partially obscuring the structures close to the catheter.

Artifacts can also result from the systo-diastolic changes of vascular dimensions or of the position of the catheter inside the vessel throughout the cardiac cycle if a sufficiently high sampling rate is not obtained.

*Application of automatic measurements*

Sophisticated techniques of edge-detection or videodensitometry have been developed for quantitative angiography [65]. The difference in brightness between the radiographic contrast filling the vascular lumen and the background facilitates the application of the proposed algorithms for computer-assisted automatic contour detection.

In intravascular ultrasound, on the contrary, the relatively similar echoreflectivity of blood in comparison with the underlying vessel wall is of potential obstacle to fully automatic measurements of lumen area. The frequently necessary manual corrections may increase the subjectivity of the results [66]. In our Center a fully automatic technique, based on the measurement of the vessel wall displacement from a semiautomatic defined template image, is successfully used to measure the systo-diastolic changes of vascular dimensions [67].

*Reproducibility of the measurements*

Changes in vascular tone, variability of repeated measurements, modifications of radiographic projections and setting, cardiac and respiratory movements influence short- and long-term reproducibility of the angiographic measurements, making the assessment of the development of real changes in vascular dimensions more difficult. Intravascular ultrasound is not limited by some of these factors. A crucial element for reproducibility of repeated

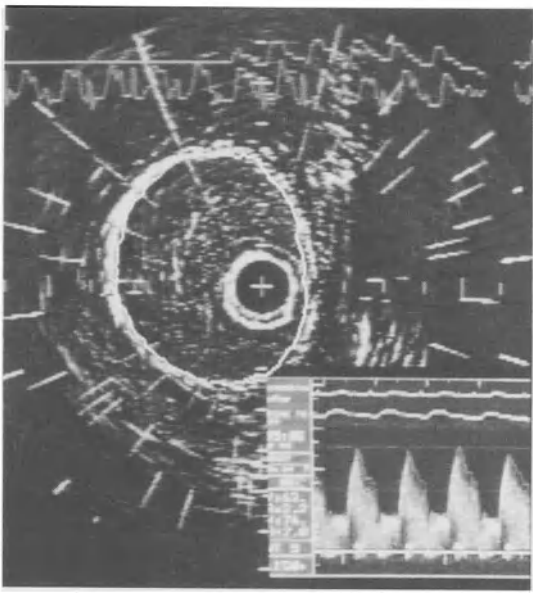

*Figure 8.* Intravascular ultrasound cross-section of a proximal normal left circumflex artery 6 months after cardiac transplantation. The simultaneous recording in the same position of flow velocity with a Doppler guidewire (Cardiometrics, CA, USA) allows the calculation of the instantaneous absolute flow. Calibrations: intravascular ultrasound = 1 mm; Doppler = 120 cm/s.

measurements, however, is a position of the catheter exactly at the same site in the vessel, a trivial requirement which is practically very difficult to satisfy.

*No assessment of blood flow*

Various angiographic techniques have been described which use the contrast medium as a marker of flow and calculate relative changes of blood flow based on contrast appearance time and/or on changes in the density of the myocardium [68–70]. This principle is not applicable with the current intravascular ultrasound imaging catheters. An alternative ultrasound-based technique is the measurement of the Doppler shift induced by the motion of the red blood cells to directly calculate blood flow velocity. Prototypes of combined imaging-Doppler catheters have been described [71, 72] and Doppler guidewires which can integrate the ultrasound imaging catheters are in current clinical use [73–75] (Fig. 8).

## Conclusions

Intravascular ultrasound can accurately assess luminal dimensions and has potential advantages on quantitative arteriography in the presence of eccentric lesions and lumens of complex geometry. The application of this technique, however, increases duration, risk, complexity and cost of a conventional diagnostic or interventional procedure based on a purely angiographic quantitative assessment. In clinical practice, therefore, it seems unlikely that quantitative arteriography can be replaced by intravascular ultrasound as a routine technique of measurement of luminal dimensions.

Intravascular ultrasound has a potential role as a research tool for the assessment of vessel dynamics and effects of pharmacologic interventions. The information concerning characteristics and composition of the atherosclerotic plaque is not available with angiography and makes intravascular ultrasound potentially more suitable than angiography for the follow-up of interventions aimed at the regression of atherosclerotic lesions. Improvements in catheter technology can make quantitative intravascular ultrasound a valuable tool for the correct planning and guidance of interventional procedures.

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