EXPERIMENTAL VALIDATION AND CLINICAL COMPARISON OF QUANTITATIVE CORONARY ANALYSIS SYSTEMS

EXPERIMENTEELE VERIFICATIE EN KLINISCHE VERGELIJKING VAN KWANTITATIEVE CORONAIR ANALYSE SYSTEMEN

PROEFSCHRIFT

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Cover:

Stenosis phantom with a luminal diameter of 0.7 mm for percutaneous insertion in swine coronary arteries mounted at the tip of a 4F Fogarty catheter (left upper figure: long axis view; right upper figure: short axis view; the entrance of the artificial stenosis channel is marked by an arrow).
Digital angiography following insertion of the phantom in the left anterior descendent artery (left bottom figure) with subsequent on-line geometric measurements at the position of the artificial coronary stenosis using the Automated Coronary Analysis Package of the Philips DCI system (right bottom figure).

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To
Renate, Jeannine, and Wolfgang

Contents

Chapter 1

Introduction

Introduction

Since the introduction of percutaneous coronary balloon angioplasty by Andreas Grüntzig in 1977 (1), the ineptitude of quantification of coronary stenoses by the visual assessment of contrast angiograms has been increasingly recognised (2). Subsequently, computer-based quantitative coronary angiography (QCA) has become established in both clinical practice as well as scientific research over the last decade: automated edge detection provides objective measurements of geometric dimensions of coronary lesions in multiple planes (3); videodensitometry can assess luminal dimensions from a single angiographic view (4); and digital acquisition of coronary flow reserve can evaluate the functional significance of coronary artery lesions (5).

While QCA was heralded as a reference tool for the evaluation of new interventional techniques and restenosis (6), the rapid growth of commercially available QCA systems and the eruption of core angiographic laboratories coupled with the more recent introduction of intracoronary ultrasound (7) have once again raised the concern of quantitative validity. During the establishment of QCA, validation studies were performed in an ad-hoc manner and were primarily based on the in vitro assessment of accuracy and precision of individual software packages. The artificial nature and underestimation of errors by the exclusive use of in vitro models was subsequently realised and the desirability of the incorporation of in vivo models to more closely mimic clinical conditions was recognised (8).

The kernel topic of this thesis is the validation of QCA systems by a new experimental approach involving the percutaneous insertion of coronary stenosis phantoms in swine coronary arteries. The reliability of digital as well as cinefilm-based QCA systems has been compared on the basis of this experimental approach using different calibration techniques as well as on the basis of more traditional in vitro experiments and the practical value of various quantitative geometric parameters is discussed. In a comparative analysis with geometric coronary measurements, currently available software packages for videodensitometric analysis have been validated using experimental and clinical data and the potential role of videodensitometry for intracoronary volume estimation has been evaluated. Furthermore, on-line and off-line techniques for estimation of coronary flow reserve have been compared. Finally, the assessment of coronary artery luminal dimensions by intracoronary ultrasound has been compared with corresponding measurements obtained by quantitative angiography and basic methodological differences between both techniques are reviewed.

In chapter 2 of this thesis, the experimental approach of percutaneous transluminal insertion of coronary stenosis phantoms in an anesthetized swine model is described and the validation of digital geometric coronary measurements by the ACA package of the Philips DCI system as well as cinefilm-based measurements using the initial version of the Cardiovascular Angiography Analysis System (CAAS I) is presented. To assess the influence of various calibration techniques on the outcome of geometric coronary measurements, calibration at

the isocenter is compared with catheter calibration. A comparative validation of geometric and videodensitometric coronary measurements by CAAS I using the same experimental approach is presented in chapter 3. The practical value of various geometric parameters for quantitation of coronary artery dimensions is compared in chapter 4 using digital and cinefilm analysis of pre and post PTCA lesions.

In chapter 5, a comparative validation of one software package for geometric coronary analysis applied to a digital as well as a cinefilm-based quantitative coronary angiography analysis system has been performed and the possible reasons for differences in accuracy, precision and reliability are discussed. This comparison is based on in vitro and in vivo experiments, as well as on clinical angiograms from pre- and post-PTCA lesions acquired digitally and on cinefilm.

In chapter 6, geometric and videodensitometric coronary measurements by the new version of the Cardiovascular Angiography Analysis System (CAAS II) are validated using identical stenosis phantoms for in vitro testing as well as for percutaneous insertion in an anesthetized swine model. Based on the results of this validation, the practical value of geometric and videodensitometric measurements is compared. The reliability of a single view assessment of coronary lesion cross sectional area at the mid segment of the right coronary artery using geometric and videodensitometric measurements is evaluated in chapter 7.

In chapter 8, off-line assessment of coronary flow reserve using time-density analysis of digitally subtracted myocardial contrast images is compared to on-line analysis of coronary flow reserve and the potential advantage of the off-line approach for evaluation of multicenter studies is discussed.

In chapter 9, luminal cross sectional area measurements at the site of coronary artery lesions obtained by intravascular ultrasound are compared with corresponding measurements using quantitative angiography. Deviations in the outcome of cross-sectional area estimations using both techniques are related to methodological differences. The impact of luminal morphology on the estimation of vessel cross sectional areas using intracoronary ultrasound and quantitative coronary angiography is evaluated in chapter 10.

A new experimental approach towards intracoronary volume assessment using videodensitometry is presented in chapter 11. The volume of post mortem human coronary casts measured by fluid-filling was used as a reference for this validation study carried out with the recent version of the Cardiovascular Angiography Analysis System (CAAS II).

In chapter 12, the comparative validation of ten quantitative coronary angiography systems from Europe, Canada and the United States of America is presented using cinefilms from stenosis phantoms in an in vitro model as well as inserted in swine coronary arteries. In this multicenter study, a uniform standard of validation based on the calculation of accuracy, precision, linear regression analysis and reproducibility is provided.

The goal of this thesis is twofold. After ten years of development of computerized systems for quantitative coronary angiography, we are facing a huge number of commercially available software packages providing quantitative parameters for the assessment of coronary artery dimensions. Future scientific work on progression or regression of coronary artery

disease as well as the comparative evaluation of the efficiency of new interventional devices has to rely on quantitative analysis systems which should be validated in a standardized and uniform manner imitating clinical conditions as closely as possible. Thereby, standardization of validation procedures becomes an important prerequisite for the reliability of future multicenter investigations using quantitative angiography. The prospective role of quantitative angiography will have to be redefined since intracoronary ultrasound has opened a new area of intracoronary imaging. New insights in the methodological differences between the two approachs towards quantification of intracoronary dimensions may help to take advantage of the complementary features of both technologies.

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Chapter 2

In Vivo Validation of On-line and Off-line Geometric Coronary Measurements Using Insertion of Stenosis Phantoms in Porcine Coronary Arteries

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In-Vivo Validation of On-Line and Off-Line Geometric Coronary Measurements Using Insertion of Stenosis Phantoms in Porcine Coronary Arteries

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Geometric coronary artery measurements with the Phillips Digital Cardiac Imaging System (DCI) and the Cardiovascular Angiography Analysis System (CAAS) were validated using percutaneous insertion of radiolucent stenosis phantoms in swine coronary arteries. Angiographic visualization of the stenosis lumens (ϕ 0.5, 0.7, 1.0, 1.4, 1.9 mm) was simultaneously recorded on DCI and cinefilm. The acquisition systems were calibrated by either the diameter of the guiding catheter (catheter CAL) or the isocenter method (isocenter CAL). Minimal luminal diameters (MLD) obtained with CAAS and DCI on 20 corresponding cineframes were compared with the true phantom diameters (PD). The accuracy of MLD measurements with the CAAS using isocenter CAL was −0.07mm, the precision 0.21 mm ($r=0.91$; $y=0.30+0.79x$; SEE = 0.19), with catheter CAL the accuracy was 0.09 mm, the precision 0.23 mm ($r=0.89$; $y=0.19+0.74x$; SEE = 0.19). The accuracy of MLD measurements using the DCI with isocenter CAL was 0.08 mm, the precision 0.15 min ($r=0.96$; $y=0.08+0.86x$; SEE = 0.14), with catheter CAL the accuracy was 0.18 mm, the precision 0.21 mm ($r=0.92$; $y=0.09+0.76x$; SEE = 0.17). DCI underestimated PD with isocenter CAL ($p < 0.05$) and with catheter CAL ($p < 0.001$). MLD can be measured with high accuracy, both applying on-line digital as well as off-line cineangiographic analysis. The results of digital measurements demonstrate high reliability of the new digital software package. © 1992 Wiley-Liss, Inc.

Key words: Quantitative coronary arteriography, anesthetized pigs, coronary artery disease

INTRODUCTION

The geometric quantification of coronary stenoses plays a deciding role in the evaluation of coronary artery disease. Although the functional significance of an obstructive lesion cannot always be settled from the arteriogram alone [1], quantitative coronary arteriography still remains the most important approach for the assessment of short- and long-term outcome of interventional therapies, as well as for the investigation of progression or regression of coronary heart disease [2].

Measurement of absolute coronary luminal dimensions has been well documented to be more reliable and reproducible than percent diameter stenosis estimations, which rely on the assumption of "normality" of a reference contour [3–5]. There is still some uncertainty, however, about the accuracy and precision of computer systems that perform these measurements either from conventional cinefilms or from digitally acquired coronary arteriograms [6–13].

The aim of this study was to compare the new Automated Coronary Analysis analytical software package (ACA) operating on-line on the Philips Digital Cardiac Imaging System (DCI) with the well-established Cardiovascular Angiography Analysis System (CAAS), which is applied to off-line analyses of cinefilms. Geometric coronary luminal measurements obtained by each system were validated in vivo by performing controlled coronary

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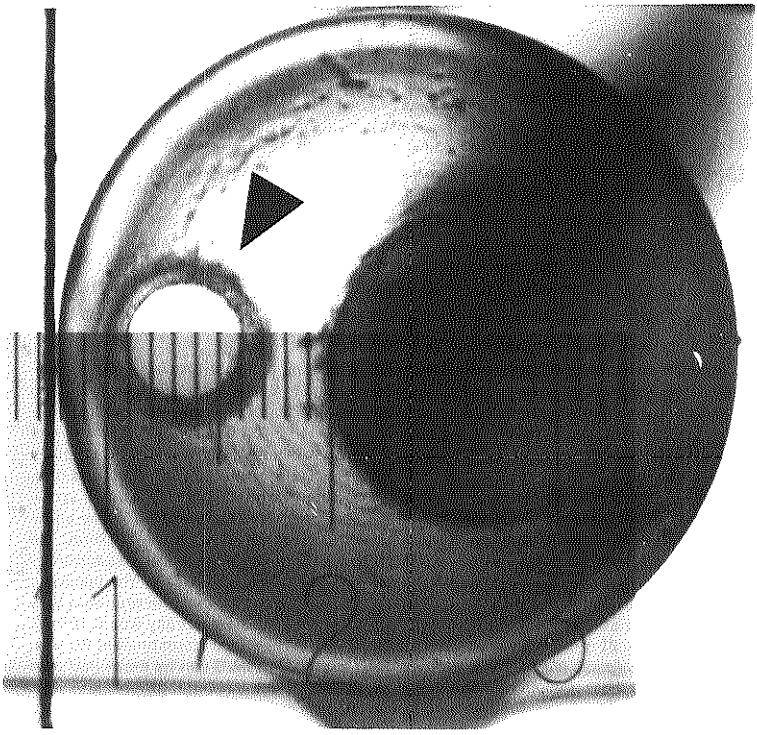

Fig. 1. View at the opening (arrow) of the stenosis channel of a 0.5 mm plexiglass phantom (outer diameter 3.0 mm).

angiography in a domestic swine model with simulated coronary artery stenoses produced by serial percutaneous insertion of graded stenosis "phantoms." In order to investigate the influence of standard calibration techniques on the accuracy and precision of geometric coronary measurements, analyses with calibration carried out at the radiographic isocenter were compared with those using the angiographic catheter for calibration purposes.

METHODS

Stenosis Phantoms

The stenosis phantoms were produced at the Workshop of the Erasmus University Rotterdam and consisted of radiolucent plexiglass (acrylate) or polymide cylinders with precision-drilled eccentric circular lumens (tolerance 0.01 mm) or 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. 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 intracoronary insertion of the phantoms as well as for their positioning in the radiographic isocenter (Fig. 2).

Animal Preparation

We used 4 Yorkshire pigs of average weight, 45–50 kg, which were kept fasting for 8 hr and sedated using intramuscular ketamine (20 mg/kg) and intravenous metomidate (5 mg/kg). The animals were intubated and connected to a Servo-ventilator (Elema, Schönander, Sweden) for volume-assisted 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

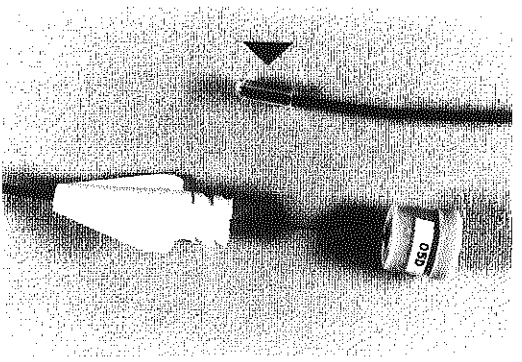

Fig. 2. Phantom catheter with removable metal wire. At the tip of the catheter the 0.5 mm phantom is mounted (arrow).

(>150 mmHg). Anesthesia 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 (disposible microtip catheter, type 811/160, Crodis-Sentron, Roden, The 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

Two different calibration methods were applied to both coronary analysis systems. (1) 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). (2) Conventional catheter calibration: The nontapering part of the tip of each 8F polyurethane guiding catheter (El Gamal, Type 4, Schneider, Minneapolis, MN) 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 each system.

Using these two approaches to calibration, two series of measurements were obtained for both the digital and cinefilm angiographic acquisition system.

Coronary Angiography and Placement of Stenosis Phantoms

After engaging the guiding catheter in the left main coronary artery, isosorbide-dinitrate (1 mg) was administered intracoronarily to control the coronary vasomotor tone prior to the insertion of the phantoms, then a first angiogram was carried out, for orientation purposes. Coronary angiography was performed by ECG-triggered injection of 10 ml iopamidol 370 (Schering, Berlin, Germany; 370 mg iodine/ml) at 37°C with an injection rate of 10 ml/second (rise time = 0) using a pressure injector (Mark V, Medrad, Pittsburgh, PA). 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 X-ray 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 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 (kVp, 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 that 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 [14].

The corresponding 35-mm cineframes (CFE Type 2711, Kodak, Paris, France) were used for off-line anal-

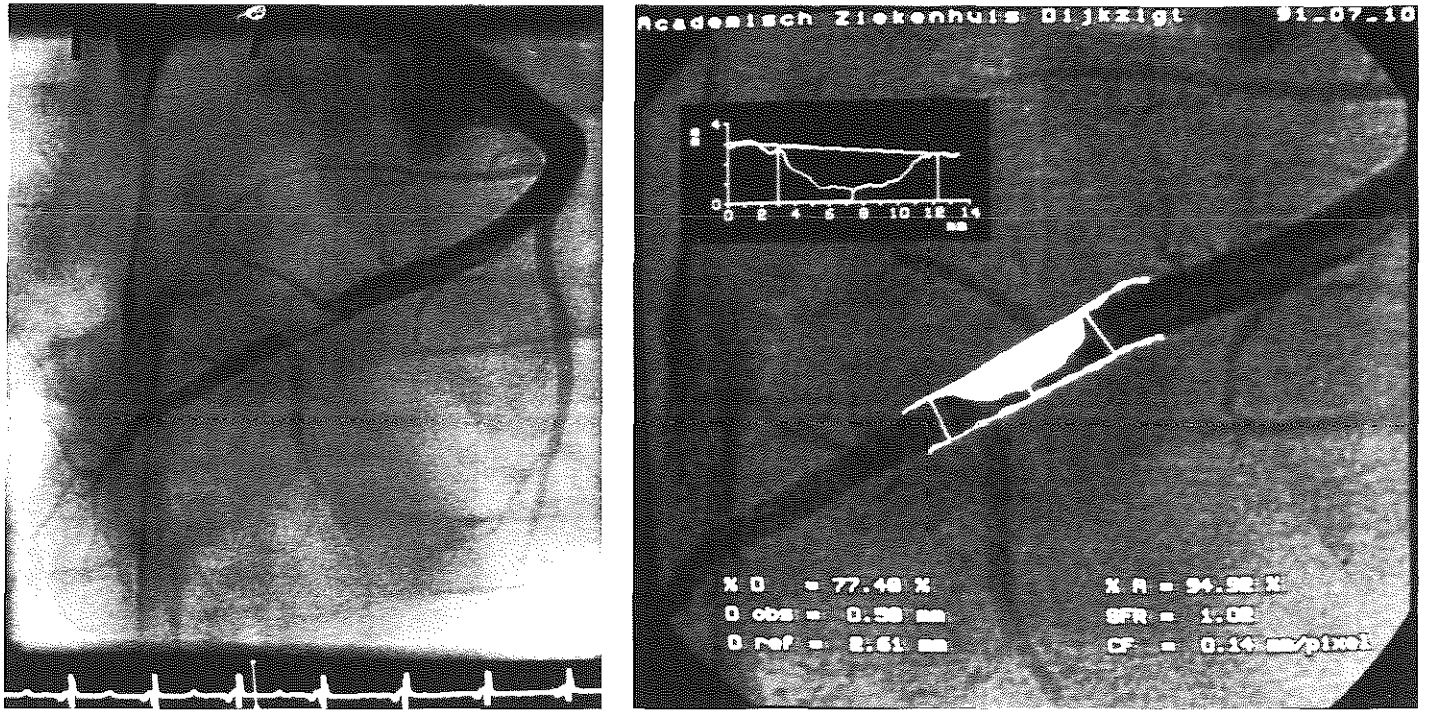

Fig. 3. Angiographic visualization of the artificial coronary obstruction produced by a 0.7 mm stenosis phantom in the left anterior descending artery with subsequent digital measurement of MLD.

ysis with the CAAS system [15]. This procedure allows the digital selection of a 6.9 × 6.9 mm region-of-interest (ROI) out of the 18 × 24 mm cineframe for digitization into a 512 × 512 pixel matrix using a CCD camera (8 bits = 256 density levels). Effectively, this means that the entire cineframe of size 18 × 24 mm can be digitized at a resolution of 1,329 × 1,772 pixels. A correction for pincushion distortion was applied in the CAAS system.

Measurement of Minimal Luminal Diameter

Twenty corresponding end diastolic frames were suitable for measurement of the minimal luminal diameter of the stenosis phantoms both digitally and from cinefilm. A sufficiently long segment of the artery including the stenosis phantom 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. On the DCI 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 both the DCI system and CAAS 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 [14, 15].

With CAAS, 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, a ROI centered around the defined arterial segment is digitally magnified by a factor of two with bilinear interpolation. Furthermore, the edge detection algorithm is modified to correct for the limited resolution of the entire X-ray imaging chain [14]. This allows a more accurate determination of vessel sizes less than 1.2 mm diameter.

We took occasional advantage of the opportunity to correct the automatically traced centerline on the DCI during the analysis of the smallest stenosis phantom (0.5 mm). Manual corrections to the automatically detected contours were found, in general, to be unnecessary, either with DCI, or CAAS, with the site of minimal luminal diameter in the stenosis phantom being defined satisfactorily by the automatic measurement systems. When a degree of obstruction due to cellular material or partial thrombosis was obvious within the phantom channel the site of MLD-assessment was then user-defined. An example of digital and cinefilm measurements of minimal luminal diameter in a stenosis phantom of 1.9 mm is shown in Figure 4.

Statistical Analysis

Using both calibration methods (calibration at the isocenter, catheter calibration), the individual data for minimal luminal diameter obtained by CAAS and DCI were compared with the true phantom diameters by a t-test for paired values. The mean of the signed differences between individual minimal luminal diameter and phantom diameter values was considered an index of accuracy and the standard deviation of the differences an index of precision. The minimal luminal diameter values acquired with both systems (CAAS, DCI) and both calibration methods were plotted against the phantom diameter values and a linear regression analysis was applied. Minimal luminal diameter values obtained by CAAS and DCI with both calibration methods were similarly compared using a linear regression analysis. To assess the agreement between the image acquisition systems the individual differences between the minimal luminal diameter measured by CAAS and the minimal luminal diameter measured by DCI were plotted against the individual mean values according to the statistical approach proposed by Bland and Altmann [16]. The precision of the minimal luminal diameter measurements obtained by the two different calibration methods were compared, for both CAAS and DCI, using Pitman's test [17].

RESULTS

The individual minimal luminal diameter measurements obtained by a CAAS and DCI using the calibration at the isocenter are listed in Table IA. The mean phantom diameter was 1.12 mm; the mean minimal luminal diameter measured by CAAS was 1.19 mm and by DCI 1.04 mm.

The measurements of minimal luminal diameter (MLD) obtained with each system using catheter calibration are listed in Table IB. The mean minimal luminal diameter was 1.05 mm for the CAAS and 0.96 mm for the DCI system.

Cinefilm Assessment of Minimal Luminal Diameter with Calibration at the Isocenter

The accuracy of minimal luminal diameter measurements using the CAAS system with calibration at the isocenter was −0.07 mm, the precision 0.21 mm. The

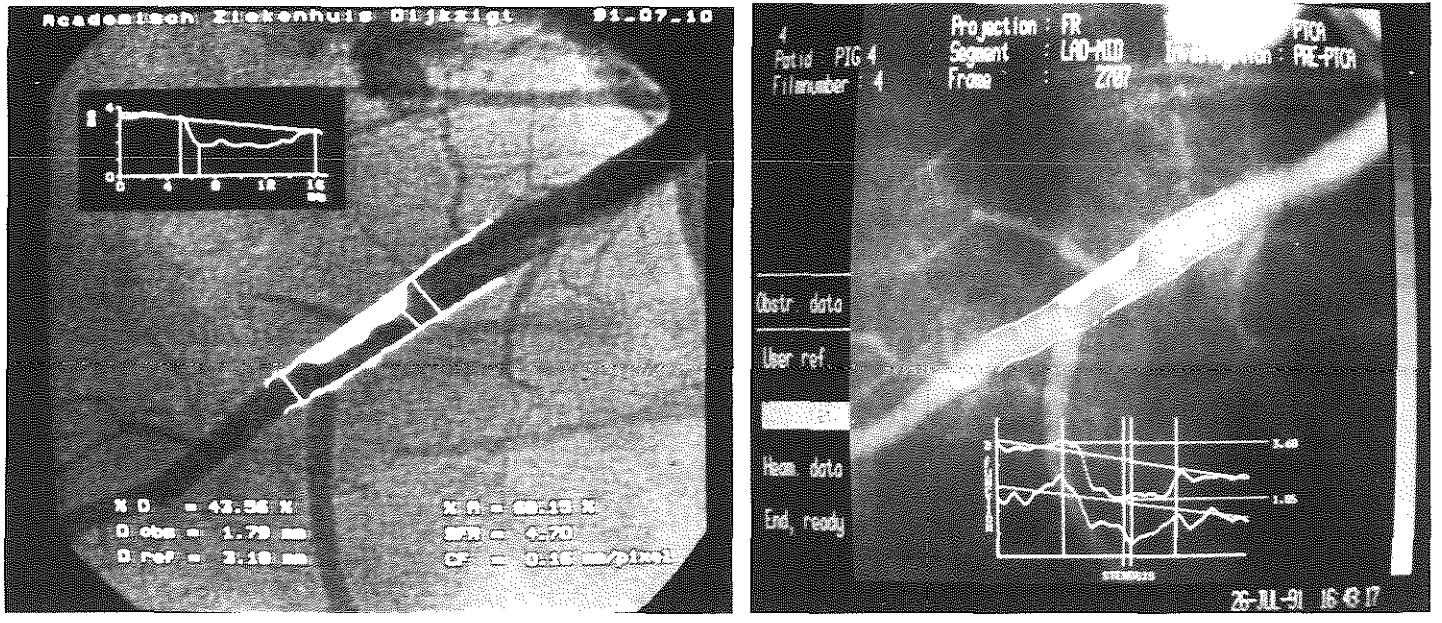

Fig. 4. Angiographic image of a 1.9 mm stenosis phantom with digital (left) and cinefilm (right) assessment of MLD on corresponding enddiastolic frames.

TABLE I. True Phantom Diameters (PD) Listed with Minimal Luminal Diameters (MLD) Obtained by the Cardiovascular Angiography Analysis System (CAAS)—CAAS MLD—and the MLDs Assessed by the Digital Cardiac Imaging System (DCI)—DCI MLD—Including Differences Between True Diameters and Measurement Values

NB	PD (mm)	CAAS MLD (mm)	Difference PD—CAAS MLD (mm)	DCI MLD (mm)	Difference PC—DCI MLD (mm)
A. The phantom diameter (PD) measured with the CAAS- and DCI-system					calibration at the isocenter
1	1.4	1.14	0.26	1.21	0.19
2	0.7	0.70	0.00	0.76	−0.06
3	0.5	0.94	−0.44	0.67	−0.17
4	1.9	2.03	−0.13	1.96	−0.06
5	1.9	1.82	0.08	1.70	0.20
6	1.4	1.36	0.04	1.33	0.07
7	1.4	1.31	0.09	1.36	0.04
8	1.0	1.05	−0.05	1.01	−0.01
9	1.0	0.92	0.08	0.83	0.17
10	0.7	0.81	−0.11	0.66	0.04
11	0.7	0.79	−0.09	0.58	0.12
12	0.5	0.65	−0.15	0.45	0.05
13	0.5	0.69	−0.19	0.50	0.00
14	1.9	1.85	0.05	1.79	0.11
15	1.4	1.66	−0.26	1.44	−0.04
16	1.0	0.88	0.12	0.74	0.26
17	0.7	0.75	−0.05	0.69	0.01
18	0.5	1.20	−0.70	0.50	0.00
19	1.9	1.90	−0.00	1.35	0.55
20	1.4	1.42	−0.02	1.29	0.11
		n.s.			
			$p<0.05$		
Mean	1.12	1.19	−0.07	1.04	0.08
Sd			0.21		0.15
B. The phantom diameter (PD) measured with the CAAS- and DCI-system					catheter calibration
1	1.4	1.18	0.22	1.00	0.4
2	0.7	0.57	0.13	0.72	−0.02
3	0.5	0.67	−0.17	0.93	−0.43
4	1.9	1.95	−0.05	1.60	0.3
5	1.9	1.86	0.04	1.88	0.02
6	1.4	1.16	0.24	1.27	0.13
7	1.4	1.17	0.23	1.20	0.2
8	1.0	0.93	0.07	0.85	0.15
9	1.0	0.79	0.21	0.78	0.22
10	0.7	0.70	0.00	0.55	0.15
11	0.7	0.79	−0.09	0.58	0.12
12	0.5	0.45	0.05	0.44	0.06
13	0.5	0.57	−0.07	0.47	0.03
14	1.9	1.51	0.39	1.41	0.49
15	1.4	1.42	−0.02	1.32	0.08
16	1.0	0.79	0.21	0.58	0.42
17	0.7	0.63	0.07	0.64	0.06
18	0.5	1.16	−0.66	0.42	0.08
19	1.9	1.45	0.45	1.40	0.5
20	1.4	1.33	0.07	1.23	0.17
		n.s.			
			$p<0.001$		
Mean	1.12	1.05	0.09	0.96	0.18
Sd			0.23		0.21

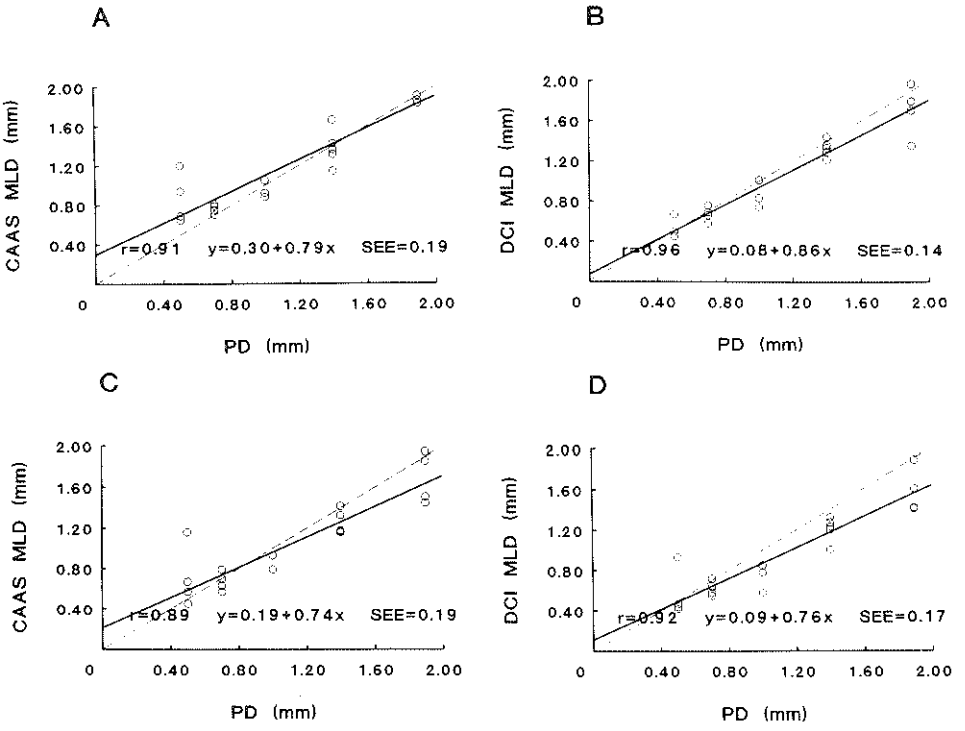

Fig. 5. Cinefilm (A) and digital (B) assessment of MLD with calibration at the isocenter in comparison to cinefilm (C) and digital (D) assessment of MLD using catheter calibration with linear regression analyses and lines of identity.

results of a linear regression analysis are depicted in Figure 5A (correlation coefficient: $r = 0.91$, $y = 0.30 + 0.79x$, standard error of estimate: $SEE = 0.19$). Plotted against the true phantom diameters, the minimal luminal diameter values obtained by CAAS lay close to the line of identity except for the smallest phantom diameter, where a nonsignificant trend towards overestimation was observed.

Digital Assessment of Minimal Luminal Diameter with Calibration at the Isocenter

The digital measurements of minimal luminal diameter obtained with calibration at the isocenter yielded an accuracy of 0.08 mm and a precision of 0.15 mm. The values of minimal luminal diameter and phantom diameter correlated well as illustrated by Figure 5B ($r = 0.96$; $y = 0.08 + 0.86x$, $SEE = 0.14$). However, a paired t-test revealed significant underestimation of the true phantom lumen diameter using the digital assessment of minimal luminal diameter ($p < 0.05$), which was more pronounced for the larger stenosis diameters.

Cinefilm Assessment of Minimal Luminal Diameter with Catheter Calibration

Using catheter calibration the measurements of minimal luminal diameter by CAAS gave an accuracy of 0.09 mm and a precision of 0.23 mm. Again, there was good correlation between the values of minimal luminal diameter and phantom diameter ($r = 0.89$; $y = 0.19 + 0.74x$, $SEE = 0.19$), although as with calibration at the isocenter a non-significant trend towards overestimation was observed for smaller phantom sizes (Fig. 5C). The measurement precision using this approach to calibration was similar to calibration at the isocenter.

Digital Assessment of Minimal Luminal Diameter with Catheter Calibration

The digital measurements of minimal luminal diameter using the DCI system with the calibration performed

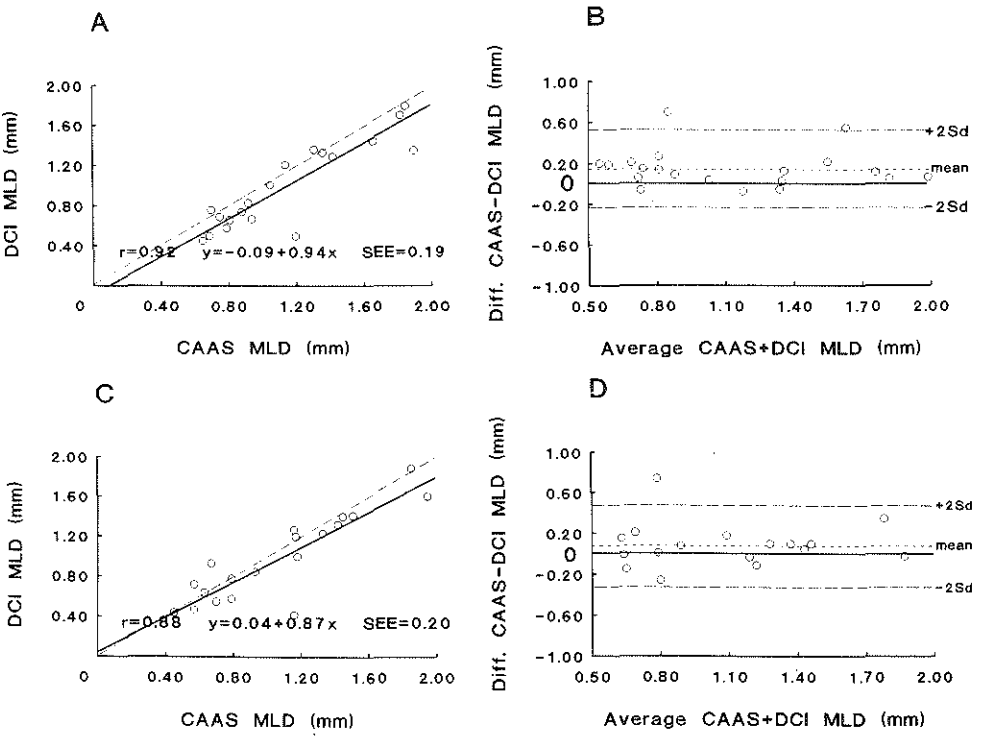

Fig. 6. Comparison between digital and cinefilm measurements of minimal luminal diameter (MLD) using calibration at the isocenter (A, B) and catheter calibration (C, D). Left: plots of digital (DCI) against cinefilm (CAAS) measurements with the linear regression analyses and lines of identity. Right: plots of differences between the MLD measurements acquired by the two systems vs. means of the measurements, with the mean difference and 2-fold standard deviation displayed.

on the catheter yielded an accuracy of 0.18 mm and a precision of 0.21 mm. Although there was good correlation ($r = 0.92$, $y = 0.09 + 0.76x$, $SEE = 0.17$) between minimal luminal diameter measurements and phantom diameter values (Fig. 5D), the t-test for paired values again showed a significant underestimation of true stenosis phantom diameters ($p < 0.001$) as was the case with calibration at the isocenter. The differences in precision between both calibration methods were not significant (Pitman's test).

Comparison Between Digital and Cinefilm Measurements

A direct comparison between DCI and CAAS measurements is shown in Figure 6. As demonstrated, there was good correlation between both measurements using calibration at the isocenter ($r = 0.92$, $y = -0.09 + 0.94x$, $SEE = 0.19$) and catheter calibration ($r = 0.88$, $y = 0.04 + 0.87x$, $SEE = 0.20$), depicted in A and C, respectively, of Figure 6. The plot of differences between CAAS-MLD and DCI-MLD values versus the mean values from both shows satisfactory agreement between digital and cinefilm measurements over the whole range of phantom sizes. This holds for calibration at the isocenter (Fig. 6B) as well as for catheter calibration (Fig. 6D).

DISCUSSION

Quantitative coronary arteriography, originally designed as an off-line cinefilm analysis technique on the Cardiovascular Angiography Analysis System (CAAS), has recently been adapted for on-line use with the Digital Cardiac Imaging System (DCI). The latter approach is

expected to make an important contribution to interventional cardiology, because it enables the operator to assess the size of interventional devices as well as to objectively define the result of interventions during the catheterization procedure [6]. The variable shape of human coronary artery stenoses [18] has prompted the use of noncircular stenosis phantoms for the validation of quantitative coronary angiographic analysis systems [9]. This approach seems to be particularly relevant for the measurement of minimal cross sectional area by densitometry [19]. Cylindric phantoms, however, fulfill the requirements for the application of two-dimensional geometric measurements and therefore are eminently satisfactory as surrogate of coronary obstructions.

In the present study two calibration methods have been investigated. Calibration at the isocenter [20] is normally used for in vitro phantom trials, so our results may be directly compared with these. Catheter calibration, in contrast, represents the calibration method conventionally used in clinical studies [21].

The use of angiographic catheters for the calibration of quantitative coronary analysis systems may influence the outcome of minimal luminal diameter measurements. Varying catheter composition may result in varying X-ray attenuation [22] and therefore in differences in the automated detection of the contour points. In our study only one type of catheter was used for calibration and therefore the influence of different materials on calibration was excluded. A further geometric error is introduced if the planes of calibration and measurement are not identical [20]. This error can be circumvented by out of plane correction as proposed by Wollschläger [23], or by calibration at the isocenter of the X-ray system.

The results of our study show that, in general, the values of both digital and cinefilm measurement with catheter calibration are smaller than with 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. This could explain the smaller values of measurements when catheter calibration was applied.

Validation in vitro of minimal luminal diameter assessments has already been performed with CAAS and the DCI system. Reiber et al. found an overall accuracy of -0.03 mm and a precision of 0.09 mm for the measurement of minimal luminal diameter from plexiglass phantoms using CAAS [15]. The variability of measurements from clinical cineangiograms was 0.10 mm, whereas the medium-term variability in an angiographic follow-up was 0.22 mm [7]. In vitro phantom studies assessing the DCI system yielded an accuracy of -0.02 mm and a precision of 0.09 mm [24]. From digital coronary arteriograms, a medium-term measurement variability of 0.17 mm has been reported [25].

The results of this study also show high accuracy and precision of geometric measurements obtained by CAAS with an accuracy of -0.07 mm and a precision of 0.21 mm using calibration at the isocenter. The corresponding values for catheter calibration differed only slightly (accuracy = 0.09 mm; precision = 0.23 mm). A tendency toward overestimation of small diameters was observed and represents a phenomenon that has already been described for other automated coronary measurement systems, in which no correction was applied for the limited resolution of the entire X-ray chain [10].

In comparison to the cinefilm determination of MLD, the digital analysis underestimated the true stenosis phantom diameter. This underestimation was shown to be significant for the calibration at the isocenter (0.08 mm; $p < 0.05$) as well as for the catheter calibration (0.18 mm; $p < 0.001$).

From Figure 5, it is also apparent that, particularly for the smaller stenosis dimensions, the digital measurements using the Automated Coronary Analysis Package (ACA) are very close to the true phantom dimensions, whereas CAAS clearly overestimates these dimensions. This is probably due to the ACA-package correcting for the limited resolution of the entire X-ray imaging chain. If such a correction procedure is not carried out, as on the CAAS, overestimations occur which are particularly apparent for the sizes below about 1.0 mm.

The data from this study clearly show the great advantage of the newer approach, which represents a novel contribution to the field of quantitative coronary angiography where obstruction dimensions in the range of 0.5–1.5 mm are important. The reason why the larger lumen dimensions of phantoms are underestimated with the digital system may be an overcorrection for the limited resolution of the X-ray imaging chain. In addition, the ACA-package does not correct for pincushion distortion, which is especially relevant to catheter calibration technique, where the catheter image may inadvertantly be slightly magnified due to the distortion at the periphery of the image field. Since the catheter is used as a calibration device, it is clear that structures imaged at locations where there is less distortion (such as at the phantom positions) will be measured as being smaller than they really are.

The linear regression analysis of digital measurements where calibration at the isocenter had been performed yielded the highest correlation with true stenosis phantom diameters as well as the smallest standard error of the estimate, implying that the ACA package provides highly reliable geometric measurements.

Comparing digital and cinefilm assessments in terms of the different calibration methods, it should be pointed

out that the mean difference of the cinefilm measurements changes from −0.07 (calibration at the isocenter) to +0.09 (catheter calibration), whereas the mean difference of the digital measurements changes from 0.08 (calibration at the isocenter) to 0.18 (catheter calibration). Taking these differences into account, a minor influence of catheter calibration on the accuracy of digital measurements can be assumed. In contrast, the actual digital and cinefilm measurements demonstrate that conventional catheter calibration introduces additional variability, which is most pronounced for the digital measurements, although the difference in variabilities between the calibration methods was not shown to be significant (Pitman's test). It appears that a more radiopaque structure (the drill bit) gives rise to less variation in calibration factors, and thus in stenosis measurements.

The somewhat lower accuracy and precision values of our in-vivo results in comparison to the findings of in vitro phantom studies can be explained by the influence of radiographic inhomogeneity of surrounding tissue (beam scattering) as well as by motion blurr. This latter disturbing factor was reduced to a minimum, as we selected end diastolic frames and interrupted ventilation during contrast injection. It is possible that microthrombi may have formed within the phantoms making an additional contribution to the measurement variability.

In principle, the use of minimal luminal diameter as the parameter of choice for comparison with true phantom stenosis diameter can be criticized. The size of the stenosis channel theoretically could be underestimated if the automatic edge detection algorithm is influenced by the presence of cellular debris collected in the phantom lumen during insertion or by the development of microthrombosis. These occurrences may also explain the frequency of underestimation of the true phantom lumen by all techniques. In our study, the minimal luminal diameter has been selected for the comparative assessment of the cinefilm and digital system because it represents a nonarbitrary measurement obtained by fully automated analysis of the entire coronary segment.

With respect to the calibration technique as used in clinical practice, it must be taken into account that online assessment of coronary dimensions is not compatible with the measurement of catheter tips using a micrometer prior to the angiographic procedure unless such a measurement could be carried out under sterile conditions. On-line calibration using the catheter sizes indicated by the manufacturer would interfere with the accuracy of digital coronary measurements because of the well known variability of true catheter diameters from that indicated on the package. This is more pronounced with nylon than woven dacron catheters [26].

In conclusion, the automated measurement of obstruction diameters in coronary vessels can be performed with a high degree of accuracy both on-line from digitally acquired images and off-line from cineangiograms. Superior results are obtained when systems are calibrated using a well defined structure at the radiographic isocenter. Conventional catheter calibration results in a slightly lower level of precision. The new software technology for the digital assessment of geometric coronary dimensions provides highly reliable measurements.

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Chapter 3

Edge Detection Versus Densitometry in the Quantitative Assessment of Stenosis Phantoms: An in Vivo Comparison in Porcine Coronary Arteries

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Edge detection versus densitometry in the quantitative assessment of stenosis phantoms: An in vivo comparison in porcine coronary arteries

The aim of this study was the in vivo validation and comparison of the geometric and densitometric technique of a computer-assisted automatic quantitative angiographic system (CAAS system). In six Landrace Yorkshire pigs (45 to 55 kg), precision-drilled phantoms with a circular lumen of 0.5, 0.7, 1.0, 1.4, and 1.9 mm were percutaneously introduced into the left anterior descending or left circumflex coronary artery. Twenty-eight coronary angiograms obtained with the phantom in a wedged intracoronary position could be quantitatively analyzed. Minimal lumen diameter, minimal cross-sectional area, percent diameter stenosis, and cross-sectional area stenosis were automatically measured with both the geometric and densitometric technique and were compared with the known phantom dimensions. When minimal lumen diameter was measured using the geometric approach, a nonsignificant underestimation of the phantom size was observed, with a mean difference of -0.06 ± 0.14 mm. The larger mean difference observed with videodensitometry (-0.11 ± 0.20 mm) was the result of the failure of the technique to differentiate the low lumen videodensities of two phantoms of smaller size (0.5 and 0.7 mm) from a dense background. Percent cross-sectional area stenosis measured with the two techniques showed a good correlation with the corresponding phantom measurements (mean difference between percent cross-sectional area stenosis calculated from the quantitative angiographic measurements and the corresponding phantom dimensions was equal to $2 \pm 6\%$ for both techniques, correlation coefficient = 0.93 with both techniques, SEE = 5% with the geometric technique and 6% with the densitometric approach). In an in vivo experimental setting mimicking diagnostic coronary angiography, single-plane quantitative angiography showed a high accuracy and precision in the measurement of stenosis hole phantoms with both the geometric and the densitometric approach. The failure of densitometry in the measurement of some of the most severe stenoses explains the better results obtained with the geometric technique. (Am Heart J 1992;124:1181.)

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Computer-based automatic edge detection angiographic analysis systems have reduced the variability resulting from visual and caliper-determined vessel sizing.[1] 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 it is not governed by the shape of the lesion. In vitro studies have demonstrated a high accuracy of videodensitometry in the measurement of hole phantoms[2-6] and its superiority to edge detection in the measurement of eccentric stenoses.[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 un-

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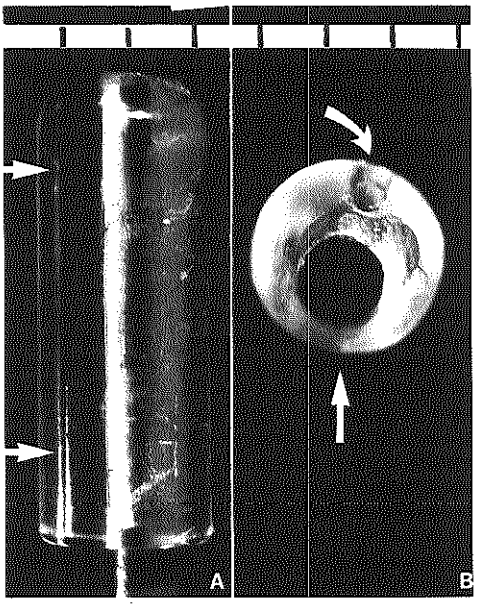

Fig. 1. A, Magnified tip of one of the catheters used for mounting the stenosis phantom and a millimeter ruler for orientation. Note the transparent radiolucent cylinder connected to the tip of the catheter, with a channel of 0.7 mm diameter indicated by *arrowheads*. **B,** Catheter tip photographed perpendicular to the long-axis of the phantom lumen. Note the almost perfect circularity of the precision-drilled lumen (diameter 1.4 mm, *arrow*). The catheter lumen used for guide wire insertion is indicated with *a curved arrow*.

derstand the limitations of these two quantitative angiographic techniques, the comparison must be performed with lumens of known sizes.

The 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 to 1.9 mm) were inserted into the coronary arteries of six closed-chest pigs, and a standard selective cineangiogram was performed.

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 (Plexiglas, Rohm and Haas Co., Philadelphia, Pa.) and polyamide with a diameter of 3.0 and 3.5 mm and a length of 8.4 mm. This material was chosen because of its extremely high radiolucency and its suitability for precision drilling. An optical calibration with a fortyfold magnification showed a mean difference of 3 ± 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 4F radiolucent catheters containing a movable radiopaque guide wire for catheter insertion (Fig. 1).

Animal preparation. Studies were performed in accordance with the position of the American Heart Association on research animal use and under regulations of Erasmus University Rotterdam. After sedation with intramuscular ketamine and intravenous metomidate, six 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 12F 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 was used for administration of drugs or fluids when necessary. To prevent clot formation, all animals were treated with an intravenous bolus of acetylsalicylic acid (500 mg) and heparin (10,000 I.U.) and a continuous intravenous infusion of 10,000 I.U./hr of heparin.

Image acquisition. After intracoronary administration of 1 mg of isosorbide dinitrate and performance of 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 8F El-Gamal guiding catheter (Schneider AG, Zürich, Switzerland) was engaged in 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/sec (Mark V pressure injector, Medrad Inc., Pittsburgh, Pa.). 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 (Soft-Touch, Schneider AG.) was chosen and the tip was measured at the end of the procedure with a micrometer.

A single-plane Philips Poly Diagnost C2 machine was used, equipped with an MCR x-ray tube and powered by an Optimus CP generator (Philips Medical Systems International BV, Best, The Netherlands). The 0.8 mm focal spot and the 5-inch (12.5 cm) field of view of the image intensifier were used for all angiograms. The pulse width was maintained unchanged at 5 msec. The kVp and mA range were 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/sec using an Arritechno 90 cine camera (Arnold & Richter, Munich, Germany) with an 85 mm lens. A Kodak CFE cine film (Eastman Kodak, Rochester, N.Y.) was used and was developed with a Refinal (M) developer (Agfa-Gevaert, Leverkusen, Germany) for 4 minutes at 28° C. The film gradient was measured in all cases to ensure that the optical densities of interest were on the linear portion of the sensitometric curve. 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. An end-diastolic cine frame was selected for off-line analysis with the CAAS System (Pie Medical, Maastricht, The Netherlands). A 6.9 × 6.9 mm region of interest was selected from the 18 × 24 mm image area on the 35 mm cine frame and was digitized into a 512 × 512 pixel matrix with 256 grey levels. The image calibration factor was calculated using the catheter as a scaling device in each projection.

Contour analysis. The diameter of the coronary arteries and of 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 scan line perpendicular to the vessel centerline.[16] Manual corrections of the automatically determined contours were allowed by the system but were never performed for these measurements. In four measurements the automatically determined distal or proximal ends of the stenotic segments were modified to avoid the measurement of the minimal luminal diameter at the site of a discrete intraluminal filling defect (thrombus) or of a localized spasm distal to the phantom lumen. 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 a normal coronary segment distal to the stenosis as a reference diameter for the calculation of percent diameter and cross-sectional area stenosis and as a calibration of the densitometric measurement (Fig. 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 vessel.

Videodensitometry. The brightness profile of each scan line 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 (Fig. 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.

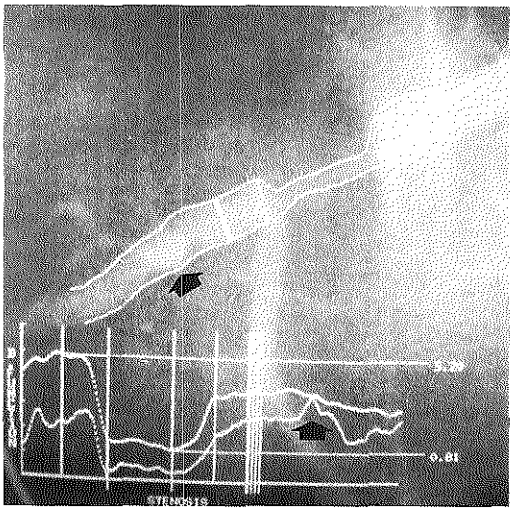

Fig. 2. Magnified image of the middle segment of the left anterior descending artery in the left anterior oblique view (60 degrees angulation). The automatically detected vessel contours are displayed in the segment analyzed and the *graph below* shows the segment length, from proximal to distal, on the x-axis and the lumen diameter on the y-axis. The lumen of the stenosis phantom (diameter: 1.00 mm) was underestimated with the edge detection technique (minimal lumen diameter: 0.81 mm), as shown in the intermediate curve of the graph. The densitometric profile, shown by the *lower curve*, strictly followed the diameters detected with the geometric technique, with the exception of a localized increase at the site of a side branch (*arrows* in the graph and in the angiographic image) and of the proximal segment of the vessel in which the videodensity was reduced because of the presence of the phantom-mounting radiolucent catheter. Because of this, for all measurements a user-defined reference diameter was selected immediately distal to the stenosis (multiple line in the graph and superimposed on the coronary angiogram).

Statistical analysis. The minimal lumen diameter, min-

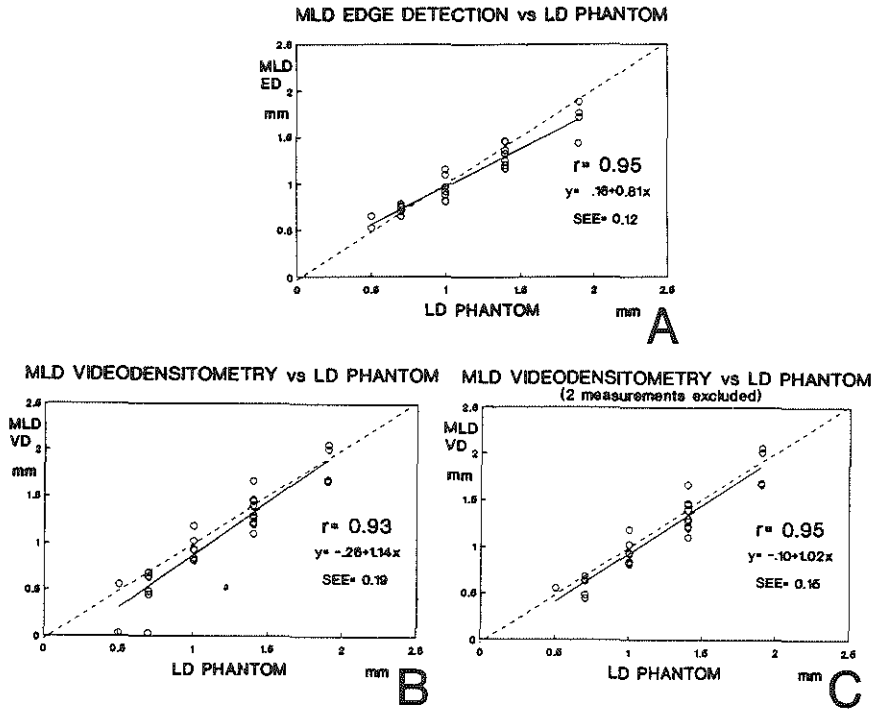

Fig. 3. Linear regression analysis of the phantom lumen diameter *(LD)* versus the minimal lumen diameter *(MLD)* measured with edge detection *(ED)* **(A)** and videodensitometry *(VD)* **(B)**. *Dashed lines* and *continuous lines* correspond to the line of identity and the line of regression, respectively. **C** shows the videodensitometric results when the two failed measurements (aligned on the x axis in **B**) are excluded.

imal 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 were 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[18] (modified). The standard deviations of the differences with the geometric and densitometric technique were compared using the Pitman's test. A p value < 0.05 was considered statistically significant.

RESULTS

Forty-two coronary cineangiograms were obtained after intracoronary insertion of the stenosis phantoms. Three cineangiograms (7%) 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), or inadequate arterial filling (4). This last finding was observed in three 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 below.

Minimal lumen diameter. In Fig. 3 the minimal lumen diameters measured with the geometric and densitometric techniques are compared with the phantom diameters using a linear regression analysis. The lower correlation coefficient and higher SEE of videodensitometry (Fig. 3, *B*) were largely the result of 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 geomet-

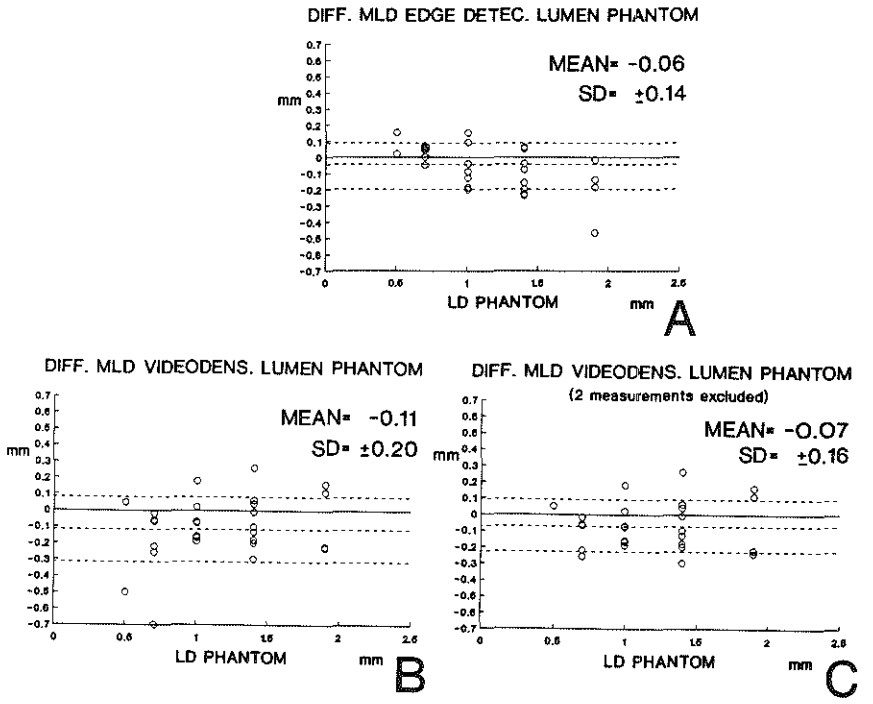

Fig. 4. Differences between minimal lumen diameter *(MLD)* measured with edge detection **(A)** and with videodensitometry **(B)** and phantom lumen diameter *(LD)* are plotted against the lumen diameter of the phantoms (on the x axis, 0.5, 0.7, 1.0, 1.4, and 1.9 mm). *Dashed lines* indicate the mean difference and the standard deviation of the signed differences, respectively. In **C** the two failed measurements with videodensitometry, shown in the *lower left corner* in **B**, are excluded.

ric technique. When these measurements were excluded from the analysis (Fig. 3, *C*), videodensitometry showed a regression coefficient and SEE similar to the geometric approach, with the regression line almost aligned with the line of identity ($y = 1.02 \times -0.10$). Both edge detection and videodensitometry underestimated the phantom diameter (mean difference = -0.06 ± 0.14 mm and -0.11 ± 0.20 mm, respectively; p = ns) (Fig. 4). However, when the results were compared without the two previously described failures of the densitometric approach, the mean difference of the densitometric technique (-0.07 ± 0.15 mm) was comparable with the previously reported mean difference obtained using the geometric approach.

Minimal cross-sectional area. The absolute cross-sectional areas (in mm^2) of the stenosis phantoms were correlated with the quantitative angiographic measurements of minimal cross-sectional area (Fig. 5). The discrepancies between corresponding geometric and densitometric measurements occurred 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 versus 0.24 mm^2 with the geometric technique). The mean difference of the angiographically measured minimal cross-sectional areas and the phantom lumen cross-sectional area was -0.15 ± 0.30 and -0.12 ± 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

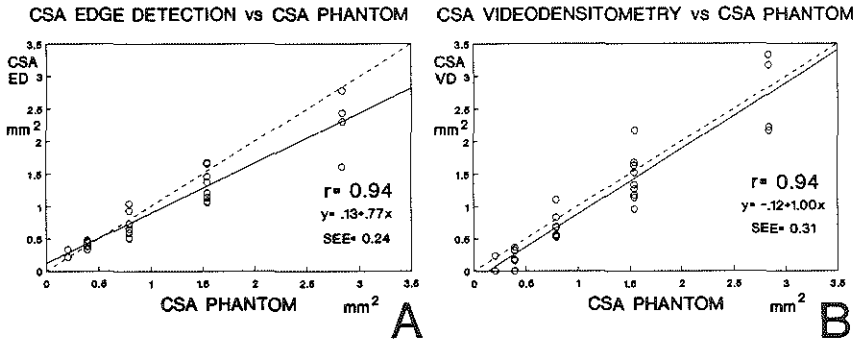

Fig. 5. Linear regression analysis of the phantom cross-sectional area *(CSA)* measured with edge detection *(ED)* **(A)**, and videodensitometry *(VD)* **(B)**. *Dashed lines* and *continuous lines* correspond to the line of identity and the line of regression, respectively.

phantom-derived percent cross-sectional area stenosis, with a mean difference between angiographic and phantom-derived percent cross-sectional area stenosis of 2 ± 6% for both techniques.

DISCUSSION

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 the density of a thin-walled, contrast-filled angiographic catheter.[2] Phantoms with a large lumen diameter were less accurately measured with videodensitometry, most likely the result of the nonlinearity between iodine content and the optical density of the radiographic image induced by the spectral hardening of the polyenergetic x-ray beam. On the contrary, videodensitometry has not shown the overestimation observed with edge detection in the measurement of stenoses sizes < 1 mm.

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, and inhomogeneous filling of the vessel during injection are conditions that can not be assessed in in vitro studies. Some of the most important sources of the nonlinearity of densitometry such as scatter/veiling glare and beam hardening are also 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 in this technique of quantitative analysis. Single-plane videodensitometric analysis was found to be an accurate and convenient method for quantifying the relative stenosis of 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[10,11] 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. Other reports,[13] however, showed comparable quantitative angiographic measurements with both techniques. Doubts concerning the possibility of reliably assessing vascular dimensions from one projection, and in general of 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, can be considered a critical condition for the application of any quantitative angiographic technique and videodensitometry can also provide unreliable measurements

because of inadequate mixing caused by blood turbulence or intraluminal dissections.[20, 21] Not surprisingly, the large discrepancies of the edge detection and videodensitometric measurements immediately after angioplasty are largely reduced after stent implantation, probably because of remodeling of the stented segment into a more circular configuration and the sealing of wall dissections.[22] 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 known dimension is measured.

Previous in vivo phantom studies: Comparison with present results. Simons et al.[23] measured with a videodensitometric technique a large series of coronary stenoses induced by the inflation of silicone elastomer 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 preshaped intracoronary phantoms can reduce the variability induced by the inaccuracies of the measurement of the true stenotic lumen. This approach, however, is outweighted 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 et al.[24] and by Mancini et al.[25] (14 measurements in 10 dogs and 25 measurements in 16 dogs, respectively). Wiesel et al.[24] observed a mean difference between calculated cross-sectional area and known phantom lumen cross-sectional area of 0.65 mm^2 with videodensitometry and one 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 stenotic lumens and by the lower number of pixels per millimeter 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.[25] into the coronary arteries of open-chest dogs. When the analysis was performed on the cine film, 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 were 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 four cases the visualization of these severe stenosis phantoms was so poor as to preclude any quantitative measurement. 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 data base of our laboratory, where quantitative angiographic measurements from more than 4600 patients included in large multicenter trials[26, 27] have been collected, show that in more than 10% of the cineangiograms before coronary angioplasty densitometry failed to measure the lumen diameter because of the combined effect of low density of a severe stenosis, a dense background, or the presence of parallel vessels interfering with the background subtraction. Edge detection, on the contrary, could be used in almost all cases.

With the exception of some of the measurements of the most severe lesions, the accuracy and precision of the videodensitometric results were comparable with the accuracy and precision of the geometric results. In this study, however, only cineangiograms with an optimal orientation of the incident x-ray beam to the evaluated segment, cineangiograms without overlapping vessels, and cineangiograms with an adequate homogeneous lumen filling were analyzed. It is noteworthy that more than one fourth of the 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. This finding might suggest a more limited applicability of videodensitometry in comparison with edge detection in the analysis of large series of cineangiograms from clinical investigations.

Limitations of the study. The use of phantoms of regular circular lumina 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.[28, 29] Beam hardening, another well-known limitation of this technique, is a function of iodine density that 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, 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, can probably explain 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. Therefore the calculation of absolute videodensitometric measurements of the stenosis was based on the geometric measurement of the luminal cross-sectional area of the reference segment. In this study, because of the presence of the catheter mounting the stenosis phantom in the proximal coronary arterial segment, a user-defined reference segment distal to the stenosis was selected. The videodensitometric measurement of minimal cross-sectional area was dependent, as an integration of densitometric and edge detection measurements, on the accuracy of the geometric measurement of the reference segment. Inaccuracies in the geometric measurement can be caused by an erroneous calculation of the magnification factor using the catheter as a scaling device. Catheters not filled with contrast, with a highly radiopaque wall, and without tapering of the measured segments were used to minimize some of the possible sources of error.[30-33] 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[34] 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 caused by the geomagnetic field,[35] 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 to 1.9 mm) inserted in porcine coronary arteries and filmed with care taken to avoid foreshortening, vessel overlapping, and incomplete filling of the stenotic segment. The 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.

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Chapter 4

Digital Geometric Measurements in Comparison to Cinefilm Analysis of Coronary Artery Dimensions

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Digital Geometric Measurements in Comparison to Cinefilm Analysis of Coronary Artery Dimensions

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Six months follow-up post-PTCA angiograms from 31 patients were acquired digitally and on cinefilm and used for a comparison of geometric coronary measurements at the site of the previous dilatation. On 70 images of 34 coronary segments quantitative analysis was performed both on-line, using the Automated Coronary Analysis package of the Philips Digital Cardiac Imaging System (DCI, pixel matrix 512 × 512) and off-line, using the Cardiovascular Angiography Analysis System (CAAS). With the CAAS a cine-video conversion is performed and a 6.9 × 6.9 mm region of interest from the 18 × 24 mm cineframe is digitized into a 512 × 512 pixel matrix. In both systems the vascular contours are assessed by means of operator-independent edge detection algorithms. The angiographic catheter was used for calibration.

Best agreement between DCI and CAAS was found for obstruction diameter and minimal luminal diameter, respectively ($r=0.82$; $y=0.12+0.97x$; $SEE=0.29$). The reconstructed reference diameter related to a computed reference contour yields lower correlation ($r=0.76$; $y=0.27+0.91x$; $SEE=0.37$). Worst results were obtained from the relative measure of percent diameter stenosis as well as from the derived parameter of plaque area.

The on-line digital approach of geometric coronary assessments provides good agreement with cinefilm analysis when direct measurements of coronary dimensions are applied.

Key words: quantitative coronary angiography, coronary artery disease, percutaneous transluminal coronary angioplasty

INTRODUCTION

Quantitative coronary analysis aims at geometric as well as functional evaluations of coronary artery stenoses [1,2]. Geometric measurements allow the immediate assessment of coronary diameters in two dimensions using operator-independent edge detection algorithms [3], whereas coronary flow studies based on time-density analysis before and after application of vasodilators give precise information about the coronary flow reserve [4]. Although both approaches are complementary they still differ in practical applicability and time consumption. These differences favour the geometric measurements of coronary dimensions with respect to the use in interventional cardiology when rapid assessment of coronary artery dimensions can be performed on-line using digital systems [5] and with regard to the evaluation of large randomized trials when the analysis can be carried out off-line in core laboratories [6,7].

Geometric measurements of digital as well as cinefilm analysis systems have previously been validated in experimental studies [8–14] demonstrating high accuracy and precision for both techniques. The goal of the present investigation is a clinical comparison between on-line acquired measurements with the new Automated Coronary Analysis package (ACA) of the Philips Digital Cardiac Imaging system (DCI) and off-line assessments using the well established Cardiovascular Angiography Analysis System (CAAS). Parameters of comparison are

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the absolute measurement value of minimal luminal diameter (MLD) provided by the CAAS with the so-called obstruction diameter (OD) obtained with the DCI. In addition, the reference diameter (RD) derived from a computed reference contour, the relative value of percent diameter stenosis (DS), as well as the calculation of plaque area with both methods were studied.

MATERIALS AND METHODS

Coronary Angiography, Image Acquisition, and Processing

In a group of 31 patients who underwent successful percutaneous transluminal coronary angioplasty (PTCA) at the Thoraxcenter, a follow-up coronary angiography was performed after 6 months. Seven French (F) diagnostic polyurethane catheters (Type Judkins, Cordis, Miami) were used, isosorbide-dinitrate (1–2 mg) was injected intracoronary 1 minute prior to contrast application for controlling vasomotor tone [15], and coronary angiography was then performed by manual injection of iopamidol (Schering, Berlin; 370 mg iodine/ml) at 37°C.

During coronary angiography simultaneous digital and cineangiographic acquisition was performed in two projections using the 5″-field mode of the image intensifier.

The digital angiograms were acquired on the Philips DCI system which employs a matrix size of 512 × 512 pixels (average horizontal pixel size: 200 μm, density resolution: 8 bits = 256 gray levels) and the images were stored on a 474 MB Winchester disk. The views were selected to minimize foreshortening of the involved coronary segments and to separate them from adjacent intervening structures as much as possible. From each digital angiogram that fulfilled the requirements of image quality for automated quantitation (no superimposition of surrounding structures, no foreshortening of the vessel at the site of the lesion) a homogeneously filled end-diastolic coronary image was selected. Thereby, 70 frames of 34 coronary segments were available for on-line quantitative analysis during the catheterization procedure using the ACA package of the DCI system [5]. Lesions of the left anterior descending artery were involved in 29 of the 70 frames (41%), lesions of the circumflex artery in 18 (26%), and lesions of the right coronary artery in 23 frames (33%). The corresponding 35 mm cineframes (CFE Type 2711, Kodak, Paris) were visually selected and used for off-line analysis with the CAAS system [7]. With the CAAS the entire 18 × 24 mm cineframe is digitized at a resolution of 1,329 × 1,772 pixels with 256 density levels (=8 bits) using a CCD (Carge Coupled Device) video camera. Next, a region of interest of size 512 × 512 pixels encompassing the catheter or coronary segment of interest is selected by the user for further analysis.

A correction for pincushion distortion has historically been applied at the early stage in the CAAS and the correction was usually available for a grid-film in the a-p (anterior-posterior) projection [7]. With the DCI until now no attempt has been made to correct for pincushion distortion, since it has been recently realized that pincushion distortion is influenced by geomagnetism [16] and would have to be corrected for each position of the image intensifier and therefore for each possible angiographic view. Until now, no satisfactory practical solution to this theoretical approach has been proposed and implemented in a commercially available system.

Calibration of the Quantitative Coronary Analysis Systems

Both coronary analysis systems were calibrated using the measurement of the catheter tip by automated edge detection technique resulting in the corresponding calibration factors (mm/pixel). In case of the DCI system the catheter size indicated by the manufacturer was introduced for on-line calibration. In case of the CAAS the non-tapering part of the tip of each catheter was measured with a precision-micromanometer (No. 293–501, Mitutoyo, Tokyo) before the CAAS analysis.

Automated Contour Detection

On the 70 corresponding end-diastolic images available for quantitative analysis, the automated contour detection was obtained digitally and from cinefilm (Fig. 1). Anatomical landmarks were used 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. On the DCI 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 [17].

On both the DCI system and the CAAS, 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 [5,7].

With CAAS, the edge detection algorithm is carried out in two iterations. First, the scanlines are defined perpendicular to the initially defined centerline and with the second iteration, the model is a recomputed centerline, determined automatically as the midline of the contour positions detected in the first iteration; in the second iteration the scanlines are defined perpendicular to this new centerline.

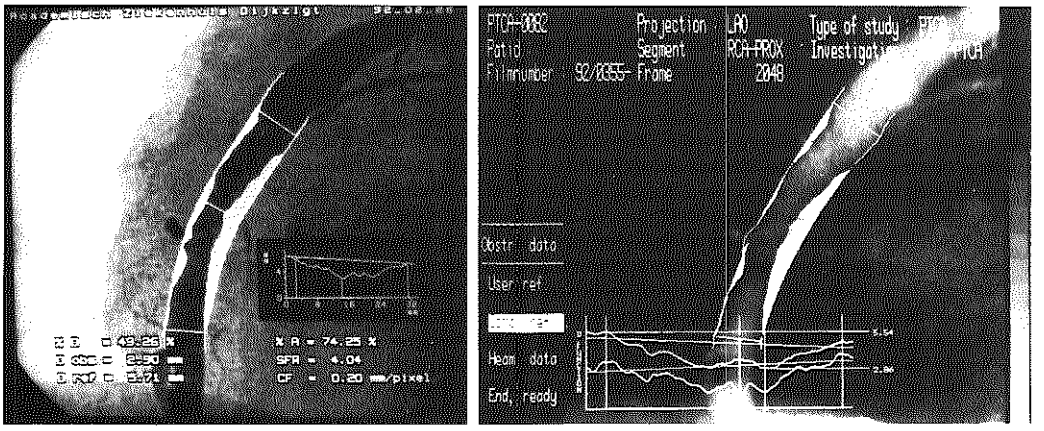

Fig. 1. Follow-up angiogram 6 months after successful PTCA of a proximal stenosis in the right coronary artery with digital geometric analysis at the site of the lesion during the control angiogram (left) and cinefilm analysis on the corresponding image (right).

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 pathline 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. In the second iteration, a ROI (region of interest) centered around the defined arterial segment is digitally magnified by a factor of 2 with bilinear interpolation. Furthermore, the edge detection algorithm is modified to correct for the limited resolution of the entire X-ray imaging chain [5]. This allows a more accurate determination of vessel sizes less than 1.2 mm diameter.

Assessment of Obstruction Diameter and Minimal Luminal Diameter

Once the contours of the obstructed coronary segment are defined in one plane, the diameter of the coronary obstruction is derived from the diameter function on the digital as well as on the cinefilm based system.

On the CAAS, the classical parameter of "minimal luminal diameter" is taken as the shortest distance between the two vessel contours [7]. On the commercially available software package proposed by Philips (ACA-package), the so-called "obstruction diameter" does not necessarily represent the absolute minimum of the diameter function curve but refers to the diameter measured at the site of maximum percent diameter stenosis [5]. Here, the absolute measure of minimal luminal diameter is not made available for the operator and currently it is not possible to correlate the potentially significant different values of obstruction diameter and minimal luminal diameter. In Figure 2 the difference in definition between OD and MLD is illustrated using the schematic diameter function curve of a coronary artery obstruction.

Calculation of Reference Diameter, Percent Diameter Stenosis, and Plaque Area

On the CAAS and the DCI system, an estimation of the "normal" or pre-disease luminal wall contour of the coronary artery is defined by the computation of an interpolated reference contour based on the vessel diameter proximal and distal to the obstructed segment. On the CAAS, this reference contour is obtained on the basis of a second degree polynomial computed through the diameter values of the proximal and distal portions of the arterial segment followed by a translocation to the 80th percentile level [18]. On the DCI, the reference contour is defined by the so-called iterative linear regression technique [19]. Tapering of the vessel to account for a decrease in arterial caliber associated with branches is taken care of in these two approaches. The RD is now taken as the value of the reference diameter function at the location of the MLD. Percent DS is calculated from RD and MLD as follows: DS = (1 − MLD/RD) × 100%.

The integral of the distances between the luminal and the reference contours over the obstructive region of the coronary artery is defined as "plaque area" in the digital as well as in the cinefilm system.

Statistical Analysis

The individual data from obstruction diameter and minimal luminal diameter, as well as the data from ref-

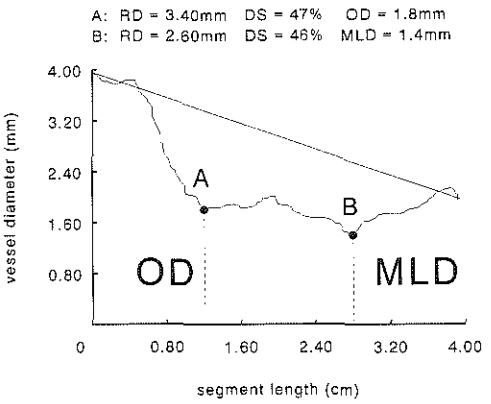

Fig. 2. Schematic display of the diameter function curve of a coronary artery obstruction. At position B the minimal luminal diameter of the obstruction is measured. Due to the tapering of the vessel, B is not necessarily identical with the site of maximum percent diameter stenosis represented by position A where the obstruction diameter is defined (OD, obstruction diameter; MLD, minimal luminal diameter; RD, reference diameter; DS, percent diameter stenosis).

erence diameter, percent diameter stenosis, and plaque area obtained by DCI and CAAS were compared to each other with a t-test for paired values. Mean values of the signed differences from the parameters obtained with both acquisition systems including the respective standard deviations were calculated. The individual data acquired with the DCI system were plotted against those obtained by CAAS and a linear regression analysis was applied for each parameter. To assess the agreement between both measurement systems the individual differences between DCI and CAAS values were plotted against the individual mean values from both according to the statistical approach proposed by Bland and Altman [20].

RESULTS

Obstruction Diameter and Minimal Luminal Diameter

Plotted against the MLD measurements obtained by CAAS, the individual values for OD from 70 measurements assessed with the DCI system lay close to the line of identity, as depicted in Figure 3A. The mean difference and standard deviation from DCI and CAAS were 0.07 ± 0.29 mm. We found a relatively good correlation between both series of measurements ($r = 0.82$; $y = 0.12 + 0.97x$; $SEE = 0.29$); however, obstruction diameters acquired on DCI were significantly larger than minimal luminal diameters assessed by the CAAS ($p < .05$). The plot of differences versus mean values from both systems shows the agreement of the two measurement parameters over the whole range of diameters (Fig. 3B).

Reference diameter

Figure 3C shows that the individual values for reference diameter obtained by the DCI system also lay close to the line of identity when plotted against those obtained by the CAAS. Although the mean difference between reference diameter measurements obtained from DCI and CAAS was 0.02 ± 0.37 mm, the correlation between both series of measurements was inferior in comparison to the correlation of obstruction diameter and minimal luminal diameter assessments ($r = 0.76$; $y = 0.27 + 0.91x$; $SEE = 0.37$). The differences from DCI and CAAS are plotted versus the mean values from both in Figure 3D.

Percent Diameter Stenosis

As depicted on Figure 3E, the individual values for percent diameter stenosis obtained by the DCI system tend to be lower than the values for percent diameter stenosis as calculated with the CAAS although this difference was statistically not significant. The mean difference from DCI and CAAS was $-2.18 \pm 10.92\%$. The correlation between both measurements has shown to be inferior in comparison to those observed for obstruction diameter and minimal luminal diameter or reference diameter, respectively ($r = 0.68$; $y = 6.47 + 0.78x$; $SEE = 10.65$). In Figure 3F the differences from DCI and CAAS are plotted versus the mean values from both.

Plaque Area

The theoretical parameter of "plaque area" calculated with DCI gave a relatively low correlation with the corresponding values obtained by CAAS ($r = 0.69$; $y = 1.08 + 0.62x$; $SEE = 3.09$). The mean value of signed differences between both series was -1.41 ± 3.55 mm^2. As shown by the paired t-test, the plaque areas as determined by the DCI system were significantly smaller than those calculated with the CAAS ($p < .01$).

DISCUSSION

Quantitative coronary angiography, originally designed as an off-line cinefilm analysis technique on the CAAS [7], has been extended to an on-line digital instrument on the DCI system [5]. This approach is expected to become an important element of interventional cardiology, because it enables the operator to assess the size of the vessel prior to the intervention as well as the matched size of the device to be used. Finally, the result of interventions can be defined objectively during the catheterization procedure [21,22].

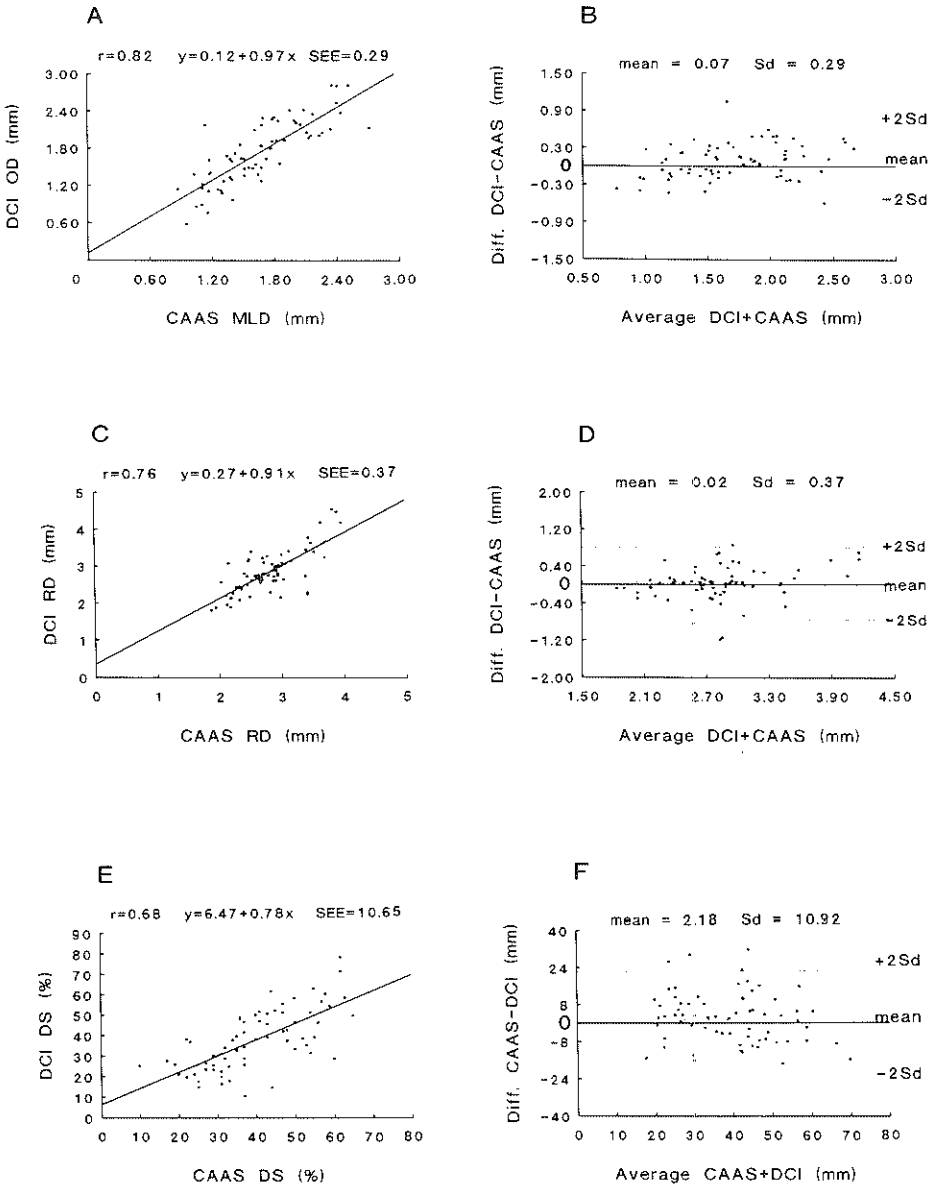

Fig. 3. On the left-hand graphs, the individual values of (A) obstruction diameter (OD), (C) reference diameter (RD), and (E) percent diameter stenosis (DS) assessed with the DCI system are plotted against the corresponding values obtained by the CAAS (On CAAS the corresponding measure to obstruction diameter is "minimal luminal diameter", MLD). The plots include the lines of identity and the results of the linear regression analyses. On the right-hand graphs, the corresponding differences from DCI and CAAS values are plotted against the mean values from both for (B) OD/MLD, (D) RD, and (F) DS, according to the statistical approach proposed by Bland and Altman [20]. The plots include the lines of the mean of signed differences (dotted) and the lines of the 2-fold standard deviation (dashed).

The geometric quantitation of coronary artery dimensions as available in both systems offers a couple of parameters for the definition of severity and morphology of coronary artery obstructions. Only one of these parameters, the minimal luminal diameter as provided by the CAAS, is obtained by absolute measurement. The corresponding obstruction diameter as available on the ACA-package of the DCI system is measured at the site of maximum percent diameter stenosis. Parameters such as reference diameter, percent diameter stenosis, and plaque are based on extrapolated calculations using the computer-defined contour of the non-obstructed vessel as a reference. The extrapolation of a reference contour, however, is obtained by different algorithms on both systems which seems to result in less agreement between these derived parameters [18,19]. On the other hand, the assessment of minimal luminal diameters in different projections has already shown to be a more reliable measure for changes in coronary artery dimensions than the calculation of relative values [23–27]. This means with regard to the present investigation that a comparison between geometric measurements obtained by DCI and CAAS can only be based on the analysis of obstruction diameter and minimal luminal diameter assessments, respectively.

The measurement of obstruction diameter with the ACA-package of the DCI system has previously been validated, demonstrating an accuracy of -0.02 mm with a precision of ± 0.09 mm in vitro [28] and an accuracy of 0.08 mm with a precision of ± 0.15 mm in vivo [14]. From digital coronary arteriograms a medium-term variability of 0.17 mm has been reported [29].

For the assessment of minimal luminal diameter with the CAAS system from plexiglass phantoms, Reiber et al. described an overall accuracy of -0.03 mm and a precision of ± 0.09 mm [7]. The reproducibility of measurements from clinical cineangiograms was 0.10 mm, whereas the medium-term variability in an angiographic follow-up was 0.22 mm [7]. Using the percutaneous insertion of stenosis phantoms in swine coronary arteries we found an accuracy of -0.07mm and a precision of ± 0.21 mm [14].

As depicted on Figure 3A,B, our clinical comparison between both systems demonstrated good agreement of obstruction diameters and minimal luminal diameters using digital and cinefilm analysis, respectively. As explained earlier in this paper, the algorithms defining obstruction diameter and minimal luminal diameter are not identical, which means that in contrast to the absolute measurement of minimal luminal diameter the value of obstruction diameter may be influenced by the computed reference contour (Fig. 2). The relatively good agreement between both parameters, however, shows that the slight discrepancy in definition seems to be of minor practical importance.

Another possible reason which theoretically could impair the correlation between obstruction diameter and minimal luminal diameter measurements on both systems could be the fact that correction for pincushion distortion is implemented in the CAAS only. However, as already explained, correction for pincushion distortion has been implemented in the CAAS for a-p projection only and the impact of geomagnetism on pincushion distortion has not yet been taken into account [16]. For coronary angiography in multiple views, as performed in this study, it can be assumed that correction for pincushion distortion on an a-p film-grid is insufficient. Therefore, the lack of correction for pincushion distortion on the DCI system should not have significant impact on the correlation between obstruction diameters and minimal luminal diameters.

Compared with other parameters of the present study, obstruction diameters and minimal luminal diameters showed the highest correlation coefficient and the lowest standard error of estimate ($r = 0.82$; $y = 0.12 + 0.97x$; $SEE = 0.29$).

In contrast to the experimental in vivo study [14], the comparison of obstruction diameters and minimal luminal diameters demonstrated higher values for the DCI measurement ($p < .05$). This finding is compatible with the difference in definition between obstruction diameter and minimal luminal diameter (Fig. 2). Looking at our in vivo validation study, it should be pointed out that the range of diameters included very small values as present with high grade coronary stenoses. Luminal diameters below 0.6 mm, overestimated by CAAS in the experimental setting, were not present in this clinical series due to the fact that patients with successful PTCA only were included. In comparison to the analysis of obstruction diameters and minimal luminal diameters assessed with both systems, parameters mainly based on the assessment of an interpolated reference contour showed a lower degree of correlation and also less agreement. In principle, the use of different algorithms for the definition of a reference contour on both systems could explain this finding [18,19]. In a recent study, however, we found a similar disagreement between digital and cinefilm-based computation of reference diameters although exactly the same algorithm was used for reference contour definition [30]. Another possible reason for the differences in reference contour related parameters could be the fact that the definition of the segment length is a primary and non-automated procedure, carried out by the user and influencing the computation of the reference contours [5]. Moreover, manual corrections of the "normal" vessel contour were performed and might have caused additional shift of reference coordinates, thus affecting the related parameters. As a consequence of these influences on the calculation of relative geometric mea-

sures, the comparison of reference diameters as assessed with DCI and CAAS (Fig. 3C) showed a relatively poor correlation ($r = 0.76$; $y = 0.27 + 0.91x$; SEE = 0.37).

In principle, the use of an interpolated reference contour may be criticized, because the computation of an interpolated reference contour derived from the so-called "normal" diameter present in the proximal and distal segment remains a simplistic and unrealistic assumption, since we are dealing with the shadowgraph of the contrast-filled lumen of a coronary artery without knowledge of the disease process in the vessel wall and without knowledge of the real position of the interface between adventitia and media. However, in trying to determine the reference of a "normal" vessel contour it should be realized that the interpolated diameter obtained by various different algorithms despite all the above-mentioned pitfalls is still far more superior to an arbitrary chosen reference diameter since the lack of reproducibility in selection by the operator has been extensively demonstrated in the past [31].

It is not surprising that the relative parameter of percent diameter stenosis related to the previously computed reference diameter demonstrates an inferior correlation as shown by Figure 3E. For this parameter, DCI assessments of severe stenoses lay clearly below those obtained by the CAAS. However, due to the high standard error of estimate this difference was statistically not significant. The linear regression analyses, depicted in Figure 3, illustrate that the random error observed with the assessments of OD or MLD and RD is cumulating in the relative parameter of percent DS.

The derived parameter "plaque area" plays a minor role in clinical practice [3]. The low correlation of plaque areas as assessed on DCI and CAAS may be illustrated by Figure 1 and can be explained as follows. First of all, the computation of plaque area depends on the so-called "length of obstruction" which is determined by different algorithms on both systems [5,7]. The algorithm used on the CAAS tends to give higher values for the length of obstruction than the algorithm used on the DCI system. Moreover, as already explained earlier, the computed reference contours are defined using two different algorithms as well [18,19]. A third factor that could cause discrepancies in the definition of plaque areas with both systems might be the different approach of centerline determination, because the dimension of plaque areas is affected by the spatial relation between computer-defined pathline and reference contours.

An inherent limitation of the present clinical comparison between geometric measurements using the DCI system and the CAAS is the different approach of calibration. The CAAS always implies preceeding measurement of the catheter tip. In contrast to experimental validation studies, however, where the catheter tip can be measured with a precision-micrometer before the angiographic procedure [14], this is not possible for the calibration of an on-line analysis system when used in clinical practice, unless such a measurement could be carried out under sterile conditions. Therefore, the catheter size as indicated by the manufacturer was introduced for the digital measurements. It is clear that the well-known variations of catheter dimensions remained uncorrected in the digital part of our comparison. These variations are more pronounced with nylon and less with woven dacron catheters [32].

In conclusion, a high level of agreement was found for the assessment of obstruction diameter obtained with the digital and minimal luminal diameter assessed with the cinefilm analysis system, although the definition of both parameters is not identical. An ideal quantitative coronary analysis system should provide the operator with the unprocessed minimal luminal diameter since this value is non-ambiguous and determined by direct measurement. Relative parameters for the assessment of coronary dimensions based on the calculation of reference contours are less satisfactory for a comparative quantitative analysis.

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Chapter 5

Can the Same Edge Detection Algorithm be Applied to On-line and Off-line Analysis Systems?

Validation of a New Cinefilm-based Geometric Coronary Measurement Software

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ABSTRACT

In the Coronary Measurement System (CMS) the edge detection algorithm which was primarily designed for the Philips Digital Cardiac Imaging System (DCI) is applied to cinefilms. Comparative validation of CMS and DCI was performed in-vitro and in-vivo using intracoronary insertion of stenosis phantoms in anesthetized pigs. The "obstruction diameter" (OD) was measured at the artificial stenoses visualized by angiography using calibration at the isocenter (ISO) and catheter calibration (CATH) and compared with the true phantom diameters. A clinical comparison of OD, reference diameter (RD) and percent diameter stenosis (DS) was performed on 70 corresponding images from post-PTCA angiograms.

Results: In-vitro: OD (CMS) yielded an accuracy of 0.18±0.14mm with 100% (correlation coefficient: r=0.97,y=0.06+0.75x, standard error of estimate: SEE=0.09), and 0.19±0.15mm with 50% contrast (r=0.94,y=0.02+0.81x). OD (DCI) gave an accuracy of 0.11±0.06mm with 100% (r=0.99,y=-0.03+0.91x,SEE=0.05) and 0.24±0.13mm with 50% (r=0.94,y=0.29+6.69x,SEE=0.12). In-vivo: OD (CMS) yielded an accuracy of 0.18±0.23mm with ISO (r=0.89,y=0.02+0.83x,SEE=0.22) and 0.26±0.24mm with CATH (r=0.89,y=0.06+0.72x,SEE=0.19). OD (DCI) gave an accuracy of 0.08±0.15mm with ISO (r=0.96,y=0.08+0.86x,SEE=0.14) and 0.18±0.21mm with CATH (r=0.92,y=0.09+0.76x,SEE=0.17). The clinical comparison showed reasonable agreement for OD only (r=0.81,y=0.26+0.81x,SEE=0.29).

Conclusion: Transformation of an edge detection algorithm from a digital to a cinefilm-based system can lead to impairment of measurement reliability.

INTRODUCTION

Cinefilm-based automated geometric measurements still represent the most common approach for the application of quantitative coronary analysis (1,2). Advantages of this technology are the accurate calibration technique based on direct measurement of the catheter tip (3,4) as well as the opportunity of retrospective analysis in core laboratories where large multicenter trials can objectively be evaluated by independant investigators (5). Continuous improvement of digital imaging techniques, however, prompted the development of "filmless" catheterization laboratories with commercially available analytical software packages allowing on-line application of quantitative coronary measurements on digital images during the catheterization procedure (6). The co-existence of cinefilm-based as well as digital approaches for quantitative geometric coronary analyses raises the question whether specific edge detection algorithms developed for the assessment of coronary dimensions can be applied to both imaging systems without alteration of measurement reliability.

In the new cinefilm-based Cardiovascular Measurenent System (CMS; Medis, Nuenen, The Netherlands) an edge detection algorithm which was primarily developed for the Digital Cardiac Imaging system (DCI; Philips, Best, The Netherlands) is adapted for application on conventional cinefilm (7).

Goal of the present investigation is the validation of this new quantitative coronary analysis software both in vitro using a phantom model as well as in vivo using percutaneous intracoronary insertion of stenosis phantoms in anesthetized pigs. To define the influence of different calibration techniques on accuracy and variability of in vivo geometric coronary measurements by the new system, analyses with calibration at the radiographic isocenter were compared with those using the angiographic catheter as a reference. Finally, we compared both CMS and DCI systems during the analysis of coronary arteriographic images from patients with coronary artery disease.

METHODS

A) EXPERIMENTAL VALIDATION USING STENOSIS PHANTOMS

Stenosis phantoms

For the in vitro as well as the in vivo validation we used radiolucent cylindrical plexiglass or polyimide stenosis phantoms with precision-drilled eccentric circular lumens (tolerance 0.003 mm) 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. 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 radiopaque metal wire which was used for intracoronary insertion of the phantoms as well as their positioning in the radiographic isocenter during the in vivo experiments.

In vitro experiments

The stenosis phantoms were serially inserted in the center of cylindrical plexiglass models with an concentric channel of 3.0mm and 3.5mm in diameter. The plexiglass channel including the artificial stenosis was then filled with contrast medium (iopamidol 370, Schering, Berlin, Germany; 370mg iodine/ml) at a concentration of either 100% or 50%. Digital as well as cinefilm 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 the plexiglass blocks results in a more appropriate kV-level (75kV) and in a scatter medium which more closely approximates the radiologic scatter in the humen thorax during angiography. On each phantom filled with contrast medium the measurement of the obstruction diameter was carried out by the DCI system. The studies were then repeated with the second concentration of the contrast medium. Subsequently, the cinefilms were processed routinely and analyzed off-line on the CMS.

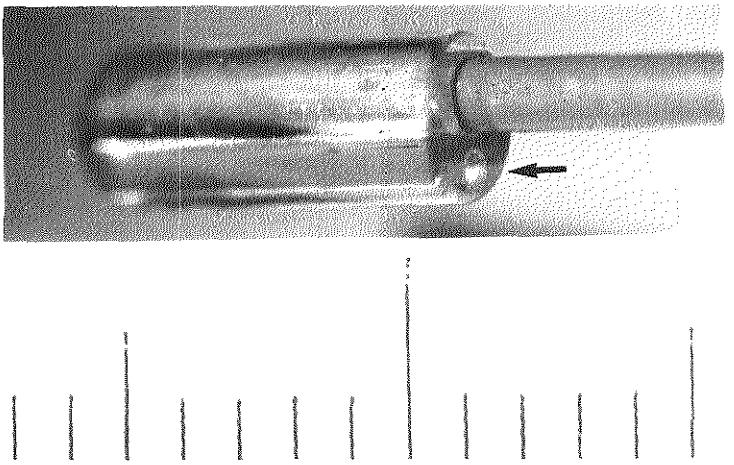


Figure 1

Plexiglass stenosis phantom with an eccentric lumen of 0.5 mm (outer diameter 3.0 mm, legth 8.4 mm), mounted at the tip of a 4 F Fogarty catheter for percutaneous insertion in a swine coronary artery. The entrance of the stenosis channel is marked by an arrow.

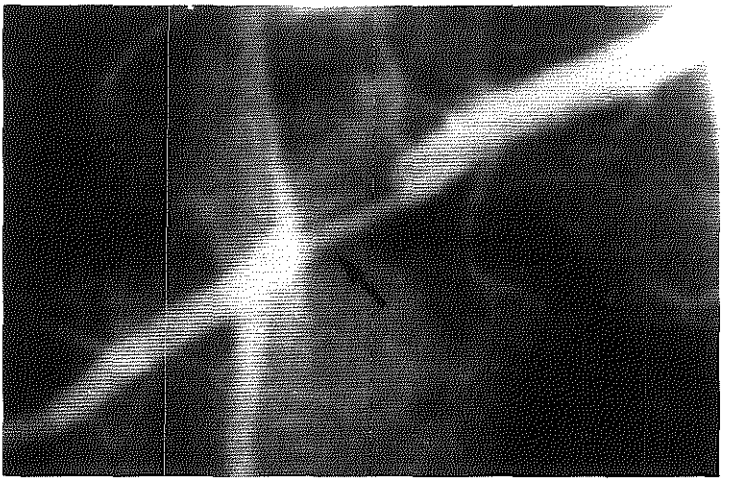


Figure 2

Angiographic visualization of a 1.4 mm stenosis phantom (arrows) in intracoronary wedge position of the left anterior descending artery.

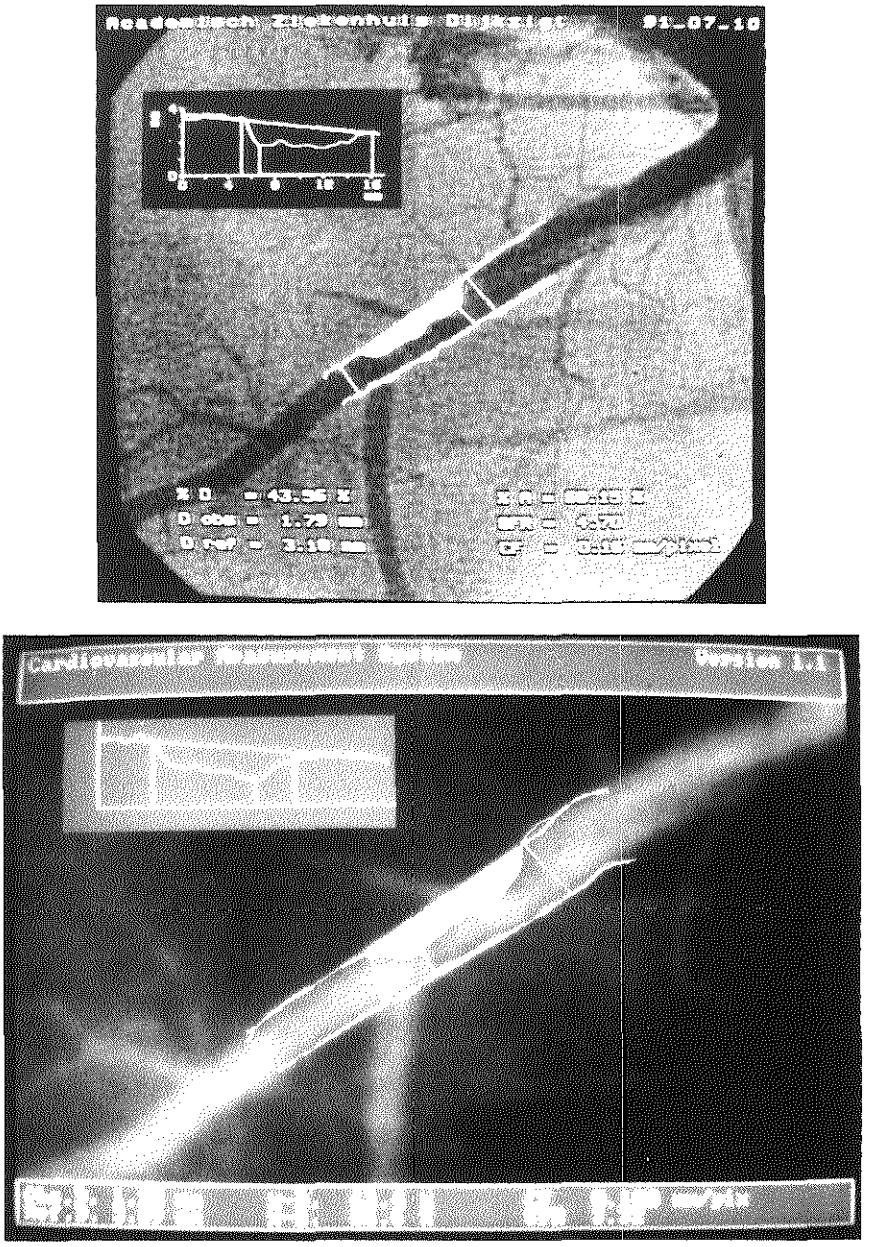


Figure 3

Angiographic image of a 1.9mm stenosis phantom with digital (A) and cinefilm (B) assessment of obstruction diameter on corresponding enddiastolic frames.

In vivo experiments

The experimental approach employing the catheter mounted stenosis phantoms in normal coronary arteries of anesthetized pigs has already been described elsewhere (3). Again two different calibration methods were applied to both coronary analysis systems: calibration at the isocenter and conventional catheter calibration. Using these two approaches to calibration, two series of measurements were obtained for both the digital and cinefilm angiographic acquisition system.

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 and to avoid overlap with other vessels or structures.(Fig. 2) The 5"-field mode of the image intensifier (focal spot 0.8mm) was selected and the radiographic system settings were kept constant (kVp, 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 x 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 and quantitative analysis of the stenosis phantom was performed on-line with the Automated Coronary Analysis (ACA) analytical software package (6).
The corresponding 35-mm cineframes (CFE Type 2711, Kodak, Paris, France) were used for off-line analysis with the CMS (7). This procedure includes the recording with a CCD-camera (pixel matrix: 760 horizontal x 576 vertical) using a CAP-35E cine-video converter (Medis, Nuenen, The Netherlands) and transfer to the analogue-digital-converter of the CMS system (pixel matrix: 512 x 512).

Edge detection analysis

10 in vitro and 19 corresponding in vivo frames were suitable for measurement of the obstruction diameter at the site of the inserted stenosis phantoms both digitally and from cinefilm.
A sufficiently long segment of the contrast filled lumen including the stenosis phantom 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 DCI system as well as on the CMS 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 both the DCI system and CMS the basic automated edge detection technique is identical; it is based on the weighted sum of the first and second derivative

functions applied to the brightness profiles along scanlines perpendicular to a model using minimal cost criteria. The algorithm primarily developed for the digital system has been tuned for the use on cinefilms with the CMS (6,7).
The edge detection is 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 512x512 matrix resolution. Here, the contours detected in the first iteration function as scan models. In the second iteration, a ROI (region of interest) centered around the defined arterial segment is digitally magnified by a factor of two with bilinear interpolation. On CMS as well as on DCI the obstruction diameter is determined as the distance between the two vessel contours at the site of maximal percent diameter stenosis.
During the analysis of the smallest stenosis phantom (0.5mm), the automatically traced centerline was occasionally corrected on the DCI as well as on the CMS. Manual corrections to the automatically detected contours were found to be unnecessary, either with DCI, or CMS, with the site of obstruction diameter in the stenosis phantom being defined satisfactorily by the automatic measurement systems. When a degree of obstruction due to cellular material or partial thrombosis was obvious within the phantom channel the site of obstruction diameter assessment was then user-defined. An example of digital and cinefilm measurements of obstruction diameter in a stenosis phantom of 1.9 mm is shown in Figure 3.

Assessment of reproducibility

To assess the variability of repeated obstruction diameter measurements carried out with the CMS, one representative cineangiographic frame of each size of the stenosis phantoms (0.5, 0.7, 1.0, 1.4, 1.9 mm) was analyzed fifteen times by the same operator using the fully automated software without any user-interaction on contours of the artificial lesion and on the site of obstruction diameter assessment.

B) CLINICAL COMPARISON OF CMS- AND DCI-MEASUREMENTS

Post-PTCA angiograms from 31 patients were acquired digitally and on cinefilm and used for a comparison of geometric coronary measurements at the site of the previous dilatation. Parameters of comparison were the absolute measurement value of obstruction diameter

(OD), the reference diameter (RD) derived from a computed reference contour and the relative value of percent diameter stenosis (DS).

Coronary angiography, image acquisition and processing

In a group of 31 patients who underwent successful percutaneous transluminal coronary angioplasty (PTCA), a follow up coronary angiography was performed after six months. Seven French (F) diagnostic polyurethane catheters (Type Judkins, Cordis, Miami, Florida, USA) were used, isosorbide-dinitrate (1-2mg) was injected intracoronarily one minute before contrast injection to control vasomotor tone and coronary angiography was performed by manual injection of iopamidol 370 at 37°C.

During coronary angiography simultaneous digital and cineangiographic acquisition was performed in two projections using the 5"-field mode of the image intensifier.
The digital angiograms were acquired on the Philips DCI system. The views were selected to minimize foreshortening of the involved coronary segments and to separate them from adjacent structures as much as possible. From each digital angiogram that fulfilled the requirements of image quality for automated quantitation (no superimposition of surrounding structures, no foreshortening of the vessel at the site of the lesion) a homogeneously filled enddiastolic coronary image was selected. Thereby, 70 frames of 34 coronary segments were available for on-line quantitative analysis during the catheterization procedure using the ACA package of the DCI system (6). Lesions of the left anterior descending artery were involved in 29 of the 70 frames (41%), lesions of the left circumflex artery in 18 (26%) and lesions of the right coronary artery in 23 frames (33%). The corresponding 35-mm cineframes (CFE Type 2711, Kodak, Paris, France) were visually selected and used for off-line analysis with the CMS system (7).

Calibration of the quantitative coronary analysis systems

Both coronary analysis systems were calibrated using the measurement of the catheter tip by automated edge detection technique resulting in the corresponding calibration factors (mm/pixel). In case of the DCI system the catheter size indicated by the manufacturer was introduced for on-line calibration. In case of the CMS the non-tapering part of the tip of each catheter was measured with a precision-micromanometer (No. 293-501, Mitutoyo, Tokyo, Japan) before the CMS analysis.

Assessment of obstruction diameter

On the 70 corresponding enddiastolic images available for quantitative analysis, the obstruction diameter (OD) was assessed digitally and from cinefilm (Fig 3). Anatomical landmarks (side-branches) were used to define the same segment length to be analyzed on corresponding digital and cinefilm images. The algorithm for the determination of obstruction diameter used on DCI and CMS is described earlier in this paper.

Calculation of reference diameter and percent diameter stenosis

On both the CMS and the DCI system an estimation of the normal or pre-disease arterial size and luminal wall location is obtained on the basis of a second degree polynomial computed through the diameter values of the proximal and distal portions of the arterial segment followed by the so-called iterative linear regression technique (6,11). Tapering of the vessel to account for a decrease in arterial caliber associated with branches is taken care of in these two approaches. The reference diameter (RD) is now taken as the value of the reference diameter function at the location of the minimal luminal diameter (MLD). Percent diameter stenosis (DS) is calculated from reference diameter (RD) and minimal luminal diameter (MLD) as follows: $DS = (1 - MLD/RD) \times 100\%$.

C. STATISTICAL ANALYSIS

To validate the CMS system the individual values of obstruction diameter obtained by CMS and DCI using both calibration techniques were compared with the true phantom diameters by a paired t-test. The mean of the signed differences between phantom diameter values and individual obstruction diameters was considered an index of accuracy and the standard deviation of the differences an index of variability. Corresponding variability values were compared using Pitman's test (12). To assess the agreement between the image acquisition systems the individual differences between the obstruction diameter measured by CMS and the obstruction diameter measured by DCI were plotted against the individual mean values according to the statistical approach proposed by Bland and Altman (13). The standard deviation of the mean value from of fifteen obstruction diameter measurements on the same angiographic phantom was considered a measure of reproducibility. This value was calculated separately for all five stenosis phantoms. The mean reproducibility was defined

as the mean value from those five reproducibility values. For the clinical comparison of geometric measurements using both systems the individual data for obstruction diameter, reference diameter and percent diameter stenosis obtained by DCI and CMS were compared to each other with a paired t-test. Mean values of the signed differences from the parameters obtained with both acquisition systems including the respective standard deviations were calculated. The individual data acquired with the CMS system were plotted against those obtained by DCI and a linear regression analysis was applied for each parameter.

RESULTS

Assessment of obstruction diameter in vitro

With the CMS, an accuracy of 0.18mm and a variability of ±0.14mm was obtained using 100% contrast medium (Fig. 4A). The linear regression analysis demonstrated high correlation between obstruction diameter and phantom diameter values ($r=0.97$, $y=0.06+0.75x$, SEE=0.09). However, the true phantom diameters were significantly underestimated by the measurement of obstruction diameter ($p<0.01$). The corresponding analyses with 50% contrast gave an accuracy of 0.19mm and a variability of ±0.15mm ($r=0.94$, $y=0.02+0.81x$,SEE=0.14), but also underestimated the true phantom diameters ($p<0.01$).

The corresponding digital measurements on 100% contrast medium gave an accuracy of 0.11mm and a variability of ±0.06mm with an excellent correlation ($r=0.99$, $y=-0.03+0.91x$, SEE=0.05), as depicted in Figure 4 B. The difference in variability for digital and cinefilm-based measurements was significant ($p<0.05$). Using 50% contrast medium, the accuracy of the digital system was 0.24mm, the variability ±0.13mm ($r=0.94$,$y=0.29+0.69x$,SEE=0.12).

Assessment of obstruction diameter in vivo

Using calibration at the isocenter (Fig 5A) an accuracy of 0.18mm and a variability of ±0.23mm was obtained with the CMS. Obstruction diameters and true phantom diameters correlated well ($r=0.89$, $y=0.02+0.83x$, SEE=0.22), although most of the obstruction diameter values lay below the line of idendity except for the smallest phantom diameter. The underestimation of the true phantom diameter by the CMS measurement was statistically significant ($p<0.01$).
When the calibration was performed on the angiographic catheter, the obstruction diameter measurements by CMS gave an accuracy of 0.26mm and a variability of ±0.24mm. As shown on Figure 5 B, there was good correlation between obstruction diameter measurements and phantom diameter values ($r=0.89$, $y=0.06+0.72x$, SEE=0.19), however, the degree of underestimation was more pronounced ($p<0.001$).

The digital measurements of obstruction diameter obtained with calibration at the isocenter yielded an accuracy of 0.08mm and a variability of ±0.15mm. Obstruction diameter and phantom diameter values correlated well ($r=0.96$, $y=0.08+0.86x$, SEE=0.14). Similar to CMS, an underestimation of the true phantom lumen diameter using the digital approach ($p<0.05$) was observed. Again this underestimation was more pronounced for the large stenosis phantoms (Fig. 5 C). The variability of digital measurements, however, was

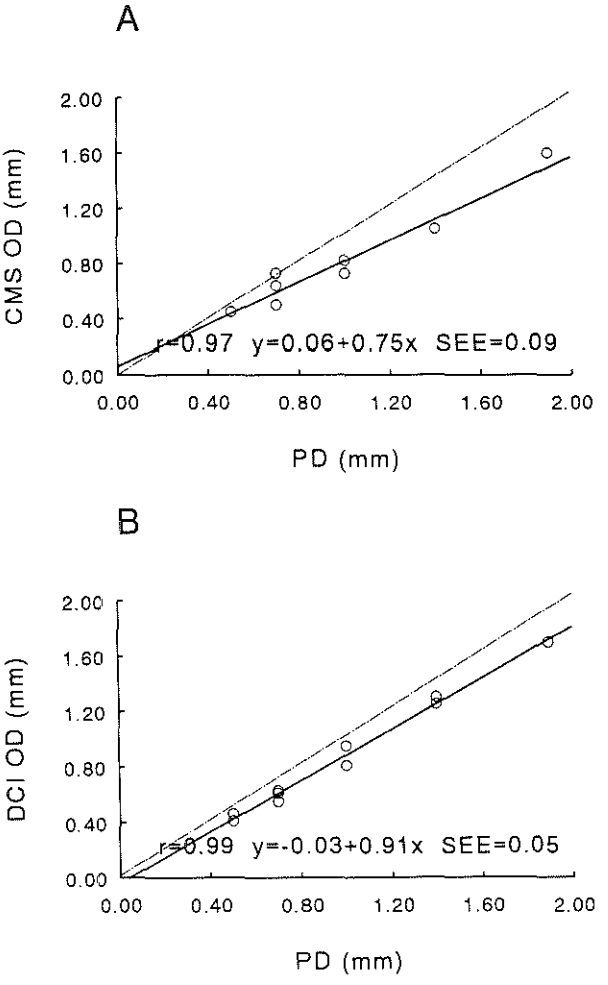


Figure 4

Results of validation with in vitro experiments using 100% of contrast medium:
In graph A, the obstruction diameters (OD) obtained by the Cardiovascular Measurement System (CMS) are plotted against the true phantom diameters (PD); in graph B, the OD values acquired with the Digital Cardiac Imaging System (DCI) are plotted against the phantom diameters. The graphs include the lines of identity and the results of the linear regression analyses.

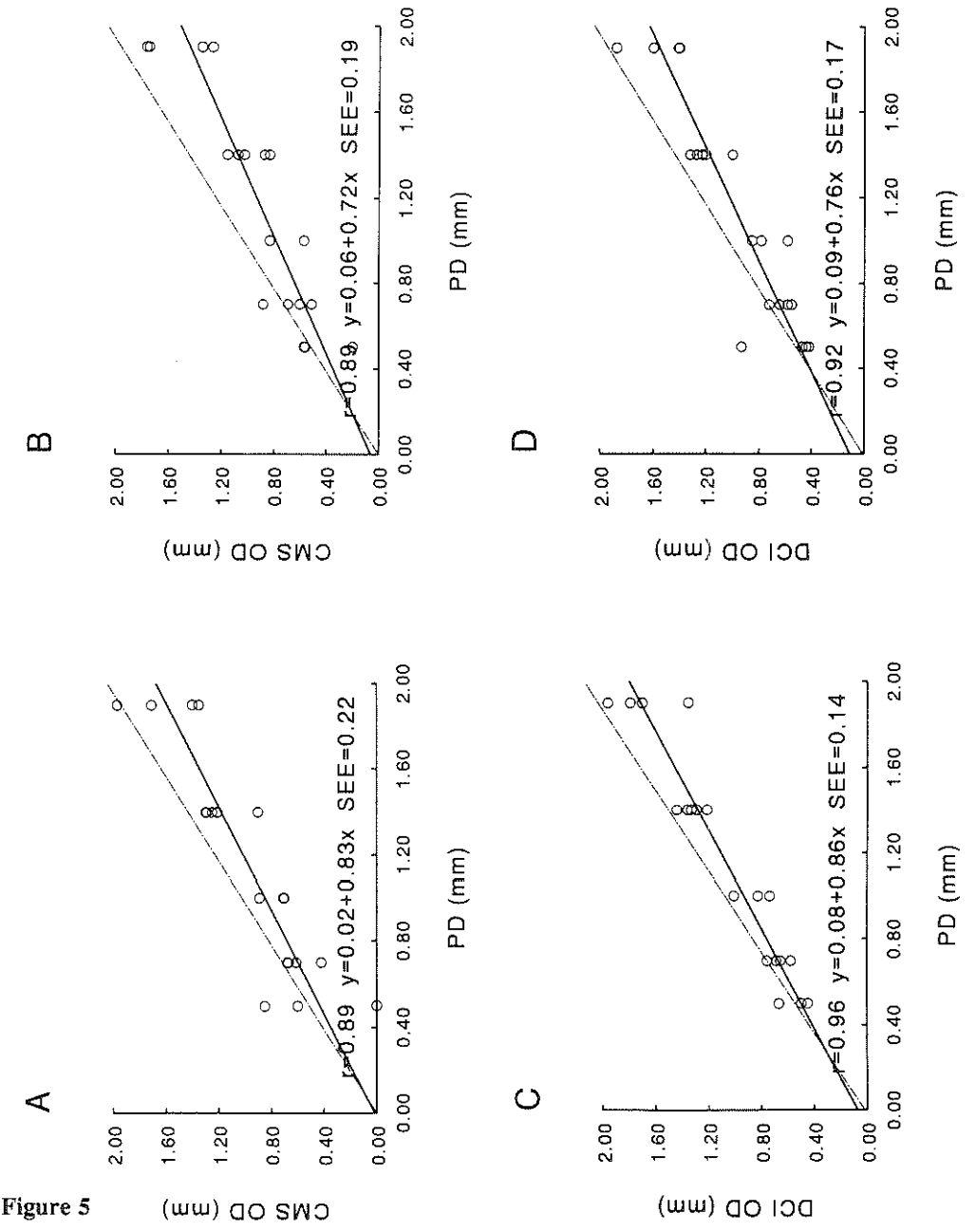


Figure 5

Results of validation with animal experiments: The obstruction diameter values (OD) assessed with the Cardiovascular Measurement System (CMS) using calibration at the isocenter (A) and catheter calibration (B) are plotted against the true phantom diameters (PD); the corresponding measurement points from the Digital Cardiac Imaging System (DCI) are plotted in graph C and D. The graphs include the lines of identity as well as the results of the linear regression analyses.

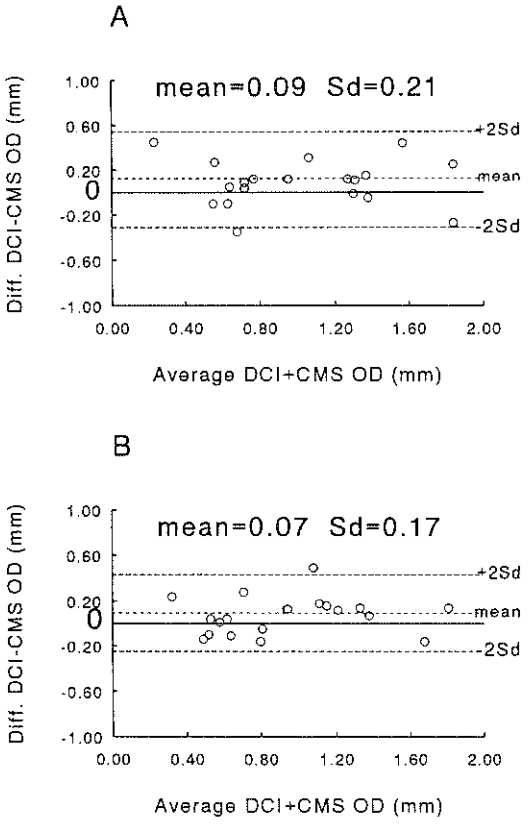


Figure 6

Comparison of digital and cinefilm-based measurements: Plot of differences between digital (DCI) and cinefilm measurements (CMS) versus mean values from both using calibration at the isocenter (A) and catheter calibration (B) with the mean difference and 2-fold standard deviation displayed.

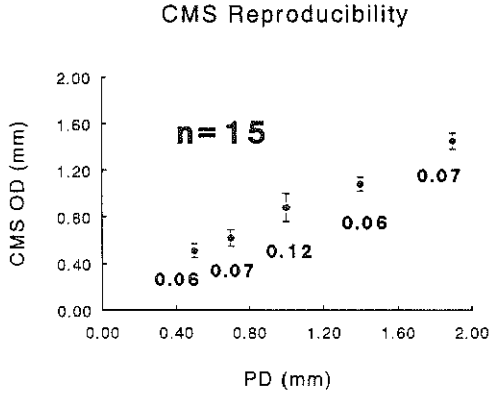


Figure 7

Reproducibility of the Cardiovascular Measurement System: Mean values from 15 measurements of obstruction diameter obtained with the Cardiovascular Measurement System 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.

significantly less ($p<0.05$) compared to CMS measurements. The corresponding measurements with catheter calibration (Fig. 5 D) yielded an accuracy of 0.18mm and a variability of ±0.21mm. Although there was good correlation between obstruction diameter measurements and phantom diameter values ($r=0.92$, $y=0.09+0.76x$, $SEE=0.17$) a similar degree of underestimation ($p<0.001$) was demonstrated.

Comparison between cinefilm and digital measurements in vivo

A direct comparison between CMS and DCI measurements is shown in Figure 6. The plot of differences from CMS-OD and DCI-OD values versus the mean values from both shows the agreement between digital and cinefilm measurements over the whole range of phantom sizes. This holds for calibration at the isocenter (Fig. 6 A) as well as for catheter calibration (Fig. 6 B).

Reproducibility of CMS measurements

The results of fifteen repeated analyses of obstruction diameter of each stenosis phantom are depicted in Figure 7. The variability of measurements was ±0.06mm for the 0.5mm and 1.4mm phantom, ±0.07mm for the 0.7mm and 1.9mm phantom and ±0.12mm for the 1.0mm phantom. Thus, the mean reproducibility for all phantom sizes was ±0.08mm.

Clinical comparison

The comparative assessments of obstruction diameter (OD), reference diameter (RD) and percent diameter stenosis (DS) obtained with the Coronary Measurement System (CMS) and the Digital Cardiac Imaging System (DCI) are shown in Figure 8. Plotted against the digital measurements the majority of data points for obstruction diameter from 70 measurements obtained by the Coronary Measurement System lay below the line of idendity (Fig. 8 A). The mean difference and standard deviation from DCI and CMS were 0.07mm and 0.31mm, respectively. The correlation between both series of measurements was reasonable ($r=0.81$, $y=0.26+0.81x$, $SEE=0.29$) and there was no statistically significant difference.
The individual values for reference diameter obtained by the CMS show a higher degree

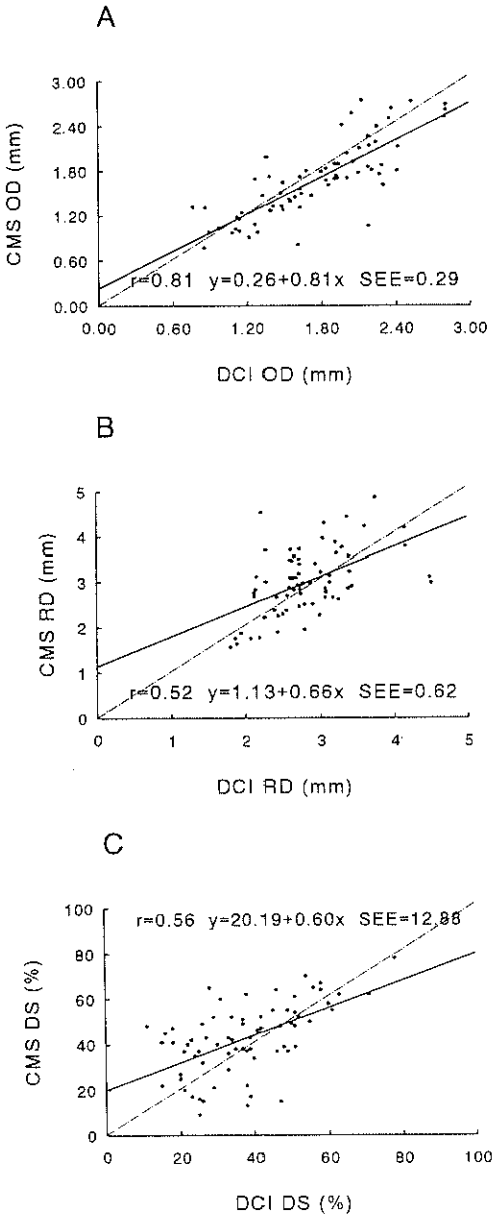


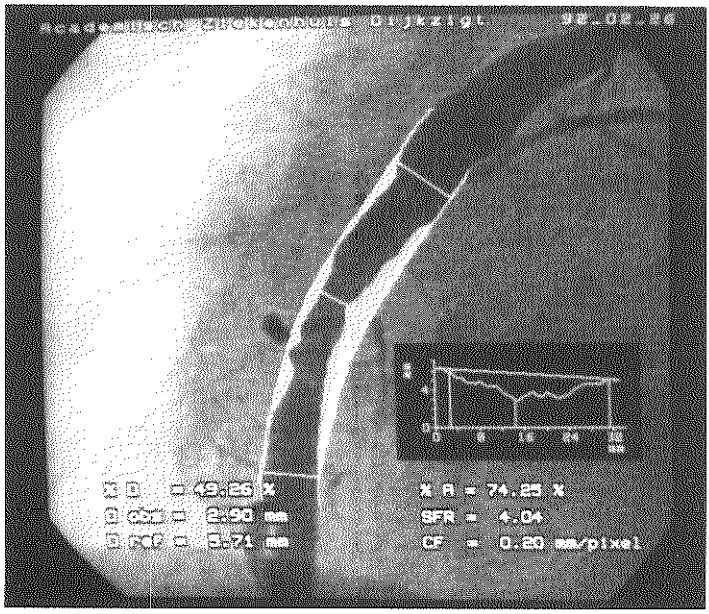
Figure 8

Clinical comparison of digital and cinefilm-based measurements: The digitally aquired values of obstruction diameter (A), reference diameter (B) and percent diameter stenosis (C) are plotted against the corresponding values obtained by the cinefilm-based system. The plots include the lines of idendity and the results of the linear regression analyses.

of scatter along the line of identity when plotted against those obtained by the digital system (Fig. 8 B). The mean difference between the DCI system and the CMS was -0.18mm ±0.65mm. There was a statistically significant overestimation of the reference diameter by the CMS system ($p<0.05$). The correlation between both series of measurements was poor for this parameter ($r=0.52$, $y=1.13+0.66x$, $SEE=0.62$).

A similar low correlation is found for the relative parameter of percent diameter stenosis (DS), as depicted in Figure 8 C. The mean difference between the values obtained by the DCI system and the CMS was -5.14 ± 14.04%. The overestimation of percent diameter stenosis by the cinefilm-based analysis system was statistically significant ($p<0.01$). An example of fully automated geometric measurements on both systems following succesful PTCA of a stenosis in the proximal right coronary artery is shown in Figure 9. This example demonstrates that the application of the same edge detection algorithm on corresponding frames from two different imaging systems can lead to different results.

A



B

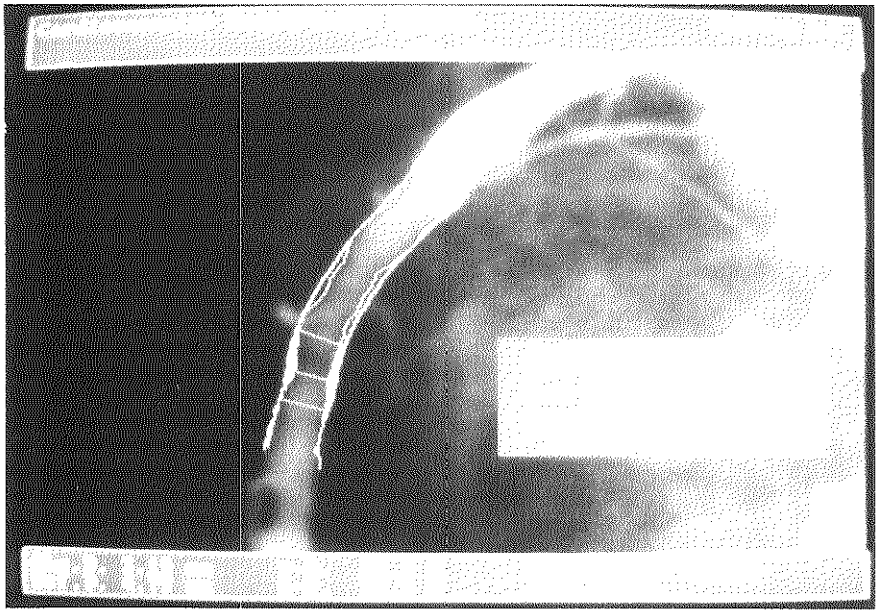


Figure 9

Geometric coronary measurements 6 months after successful PTCA of a stenosis in the proximal right human coronary artery obtained with the digital (A) and the cinefilm-based (B) quantitative measurement system on corresponding enddiastolic images.

DISCUSSION

The development of "filmless" catheterization laboratories is creating a transitional stage during which cinefilm-based systems will co-exist with completely digitized facilities. Quantitative geometric measurements, however, will be carried out in both types of catheterization laboratories, thus being applied on different imaging systems. The present validation compares the same quantitative coronary analysis software but applied to different types of imaging systems with respect to accuracy, variability and reproducibility both in vitro and in vivo. The software of the new Cardiovascular Measurement System (CMS) is based on an edge detection algorithm that has been developed for the Automated Coronary Analysis package of the Philips Digital Cardiac Imaging system (DCI) and was tuned later on for the application on cinefilms (6,7). Geometric measurements by the Automated Coronary Analysis package of the DCI system have been validated in a recent study at the Thoraxcenter using intracoronary insertion of angiographic stenosis phantoms in an anesthetized swine model (3). The same experimental approach was used in the present investigation to compare the new cinefilm-based CMS with the DCI system.

In vitro measurements of stenosis phantoms

The measurement of obstruction diameter using 100% of contrast medium revealed a change of accuracy values from 0.11 to 0.18mm 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 ($p<0.01$) which 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 Figure 4 B and A, respectively. We also observed an increase of variability from ±0.06mm to ±0.14mm ($p<0.05$). Using 50% of contrast medium, accuracy and variability were similar with both systems, probably due to a higher degree of scatter with both measurement systems. Nevertheless, the underestimation of phantom diameters using assessments on the cinefilm-based system was again significant ($p<0.01$).

In vivo measurements of stenosis phantoms

The results of these in vitro studies are confirmed by the outcome of our animal experiments in which we serially implanted the same stenosis phantoms into porcine coronary arteries. Calibrated at the radiographic isocenter (corresponding to the in vitro trial) we found a change in accuracy values for obstruction diameter from 0.08mm to

0.18mm when the algorithm was applied on cinefilm images and an increase of variability from ±0.15mm to ±0.23mm ($p<0.05$). The underestimation of true phantom diameter values which has already been 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 on the angiographic catheter, we found a change of accuracy values from 0.18mm (digital measurements) to 0.26mm (cinefilm-based measurements), while the variability increased from ±0.21mm to ±0.24mm. It appears from Figure 5 that these differences are explained by a higher degree of scatter as well as a more pronounced underestimation of large phantom diameters.

Stenosis phantom geometry

The variable shape of human coronary artery stenoses (14) has prompted the use of non-circular stenosis phantoms for the validation of quantitative coronary angiographic analysis systems (15). This approach seems to be particularly relevant for the measurement of minimal cross sectional area by densitometry (16). Cylindric phantoms which have been used for our experiments, however, fulfill the requirements for the application of two-dimensional geometric measurements and therefore are eminently satisfactory as surrogate of coronary obstructions.

Calibration at the isocenter versus catheter calibration

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 is used for in vitro settings, and catheter calibration which represents the calibration technique conventionally used in clinical studies (17).
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 (18) 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 (19). This error can be circumvented by out of plane correction as proposed by Wollschläger (20), 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 thowse 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 both systems are not correcting. Both factors could explain the smaller values of measurement when catheter calibration was applied.

Gray scale representation and matrix mismatch

The loss of accuracy as well as the increase of variability occuring 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 gray scale representation on digital and cinefilm images. If the tuning 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 x 576 V) and the AD-converter (512 x 512) might have additional impact on the outcome of corresponding geometric measurements.

Although the adaption of an edge detection algorithm to various imaging systems may impair the accuracy of geometric measurements, direct comparison of DCI and CMS assessments of phantom "obstruction diameters" gave an acceptable aggreement over the range of phantom sizes (Fig. 6). This comparison, however, does not take into account that both systems underestimate true stenosis diameters.

In spite of the above mentioned disadvantages, the adaption of the edge detection algorithm from digital to cinefilm-based assessments did not affect the high reproducibility of automated geometric coronary measurements. The reproducibility for obstruction diameter measurements with the CMS system ranged from ±0.06mm to ±0.12mm which corresponds to the reproducibility of the digital system (21,22).

Haemorheologic factors influencing measurements on stenosis phantoms

In principle, the use of obstruction diameter as the parameter of choice for the 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 all techniques (3,23). In our experimental study, the obstruction diameter has been selected for the comparative assessment of the cinefilm and digital system because it represents a non-arbitrary measurement obtained by fully automated analysis of the entire coronary segment and because it is available on both systems.

Clinical comparison

Our clinical study demonstrates that the absolute measure of obstruction diameter shows the highest correlation when digital and cinefilm-based analyses are compared (Fig 8A). The extremely low correlation of reference diameters (Fig 8B), based on a computed reference contour, could theoretically be explained by the same reasons which may be the cause for a loss of measurement accuracy and an increase of measurement variability. Relatively large diameters (reference diameter) should be affected more than relatively small diameters (obstruction diameter) by differences in gray scale representation on digital and cinefilm images as well as by a mismatch in pixel matrix between cinevideo-converter and CMS system. Figure 8 illustrates that the slope of the regression line is decreasing progressively from 8A to 8C where assessments of percent diameter stenosis are plotted. This phenomenon is not surprising because the random error of obstruction diameter and reference diameter measurements is cumulating in the assessment of percent diameter stenosis.

Conclusion

In conclusion, 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 independant from calibration techniques. A significant increase of measurement variability was observed when the acquisition systems were calibrated at the radiographic isocenter. We would recommend a proper matching of pixel matrix at the level of cine-video conversion whenever a system is adapted for quantitative analysis on cinefilms. Tuning of an algorithm for the application on another imaging system should be guided by the result of simultaneous in vitro and in vivo validation studies in order to guarantee high reliability of automated coronary measurements.

Acknowledgements:

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Chapter 6

Experimental Validation of Geometric and Densitometric Coronary Measurements on the New Generation Cardiovascular Angiography Analysis System (CAAS II)

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ABSTRACT

Computer-assisted contour detection and videodensitometric cross sectional area assessment of coronary artery obstructions on the CAAS II system were validated in vitro and in vivo by angiographic cinefilm recording and automated measurement of stenosis phantoms (luminal diameter 0.5, 0.7, 1.0, 1.4, 1.9mm) which were first inserted in a plexiglass model and then serially implanted in swine coronary arteries. "Obstruction diameter" (OD) and "obstruction area" (OA) values obtained from 10 in vitro and 19 in vivo images at the site of the artificial stenoses were compared with the true phantom dimensions.

The in vitro assessment of OD yielded an accuracy of 0.00±0.11mm (correlation coefficient: r=0.98, y=0.18+0.82x, standard error of estimate: SEE=0.08), whereas the in vivo measurement of OD gave an accuracy of -0.01±0.18mm (r=0.94, y=0.22+0.82x, SEE=0.15). The assessment of OA gave an accuracy of -0.08±0.21mm² in vitro (r=0.97, y=0.08+0.99x, SEE=0.22) and -0.22±0.32mm² in vivo (r=0.95, y=0.21+1.01x, SEE=0.33). The mean reproducibility was ±0.09mm for geometric measurements and ±0.21mm² for videodensitometric assessments, respectively.

Thus, due to inherent limitations of the imaging chain, the reliability of geometric coronary measurements is still far superior to videodensitometric assessments of vessel cross sectional areas.

INTRODUCTION

Since automated edge detection techniques diminish the variability from visual assessments of coronary artery dimensions or hand-held calipers (1), the use of quantitative coronary angiography has gained ground in the field of invasive cardiology allowing on-line measurement of vessel diameters using digital systems (2) and off-line application of geometric as well as videodensitometric algorithms on cinefilms (3,4). While previous validation studies already demonstrated that geometric measurements of coronary arteries potentially represent a reliable approach (5-12), the value of videodensitometric assessments remains controversial (13-21). Moreover, the comparative validation of current quantitative coronary analysis systems has shown that new software development for quantitative coronary measurement requires separate validation studies to maintain quality control (22). The present investigation was performed to define accuracy, reliability and reproducibility of geometric as well as videodensitometric assessments of the new version of the Cardiovascular Angiography Analysis System (CAAS II). Stenosis phantoms of known diameter mimicking the narrowings of human coronary arteries were used as a reference both in an in vitro plexiglass model as well as after serial insertion in the coronary arteries of anesthetized pigs. Geometric validation was assessed by measuring the absolute value of "obstruction diameter" within the artificial stenoses which has already been shown to be more reliable than relative measures of coronary artery dimensions based on the definition of a reference contour (23-26). To assess the influence of different calibration techniques on the outcome of geometric measurements in vivo, calibration at the isocenter was compared with catheter calibration as conventionally used in clinical practice. Finally, the densitometric measurement of the "obstruction area" computed with digital subtraction of background density, was used for a comparison with the true phantom cross sectional areas. The reliability of video-densitometric measurements was studied with and without application of an algorithm which corrects for the contribution of side branches to background density.

METHODS

Stenosis phantoms

The stenosis phantoms used in the in vitro as well as in vivo model 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. 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). Optical calibration of the stenosis channels using 40-fold magnification gave a tolerance of 0.003mm. 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 intracoronary insertion of the phantoms as well as for their positioning in the radiographic isocenter.

In vitro experiments

The stenosis phantoms were serially inserted in the center of cylindrical acrylate models (diameter 25mm, length 120mm) with an concentric channel of 3.0mm in diameter. The plexiglass channel including the artificial stenosis was then filled with contrast medium (iopamidol 370, Bracco, Milano, Italy; 370mg iodine/ml) at a concentration of 100%. Digital as well as cinefilm acquisition was performed with an additional thickness of plexiglass blocks (12.5cm anterior and 5cm posterior to the models) to approximate the density of water. The addition of plexiglass blocks results in a more appropriate kV-level (75kV) and in a scatter medium which more closely approximates the X-ray scatter in the human thorax during fluoroscopy. Each phantom filled with contrast medium was recorded on cinefilm which was processed routinely and analyzed off-line on the Cardiovascular Angiography Analysis System II (Pie Medical, Maastricht, The Netherlands).

In vivo experiments

The experimental approach employing the catheter mounted stenosis phantoms in normal coronary arteries of anesthetized pigs has already been described in a recent study from our group (12). Two different calibration methods were applied to geometric measurements. Calibration at the isocenter was carried out by radiographic acquisition of a drill-bit

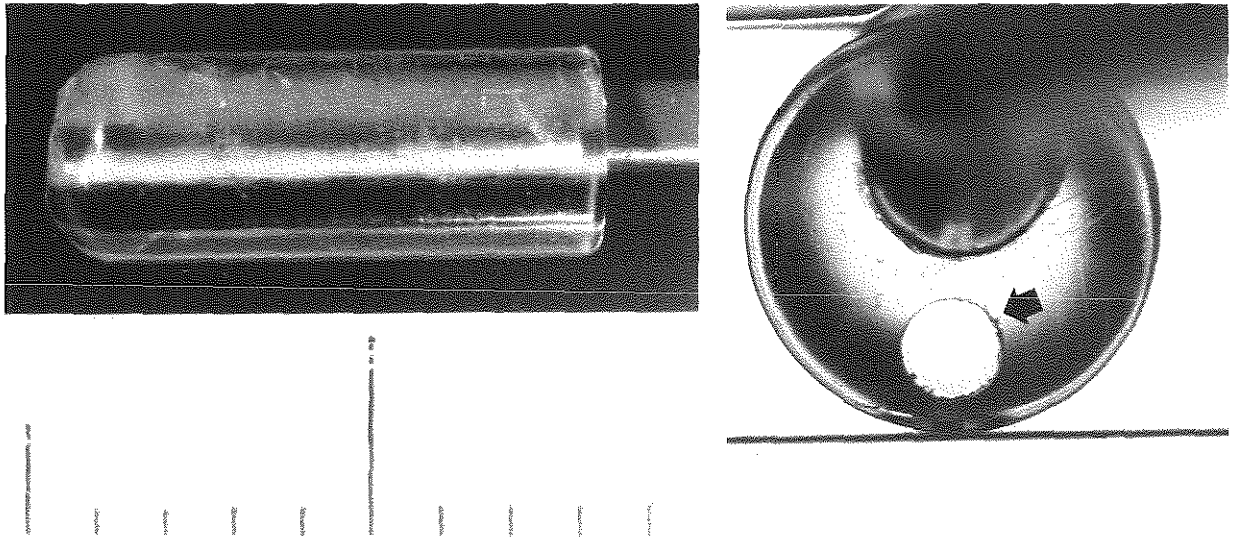

Figure 1
Catheter mounted cylindrical plexiglass stenosis phantom (length 8.4mm, diameter 3.0mm) in two projections. On the short axis view (right hand side) the entrance of the 0.7mm stenosis channel is indicated by an arrow.

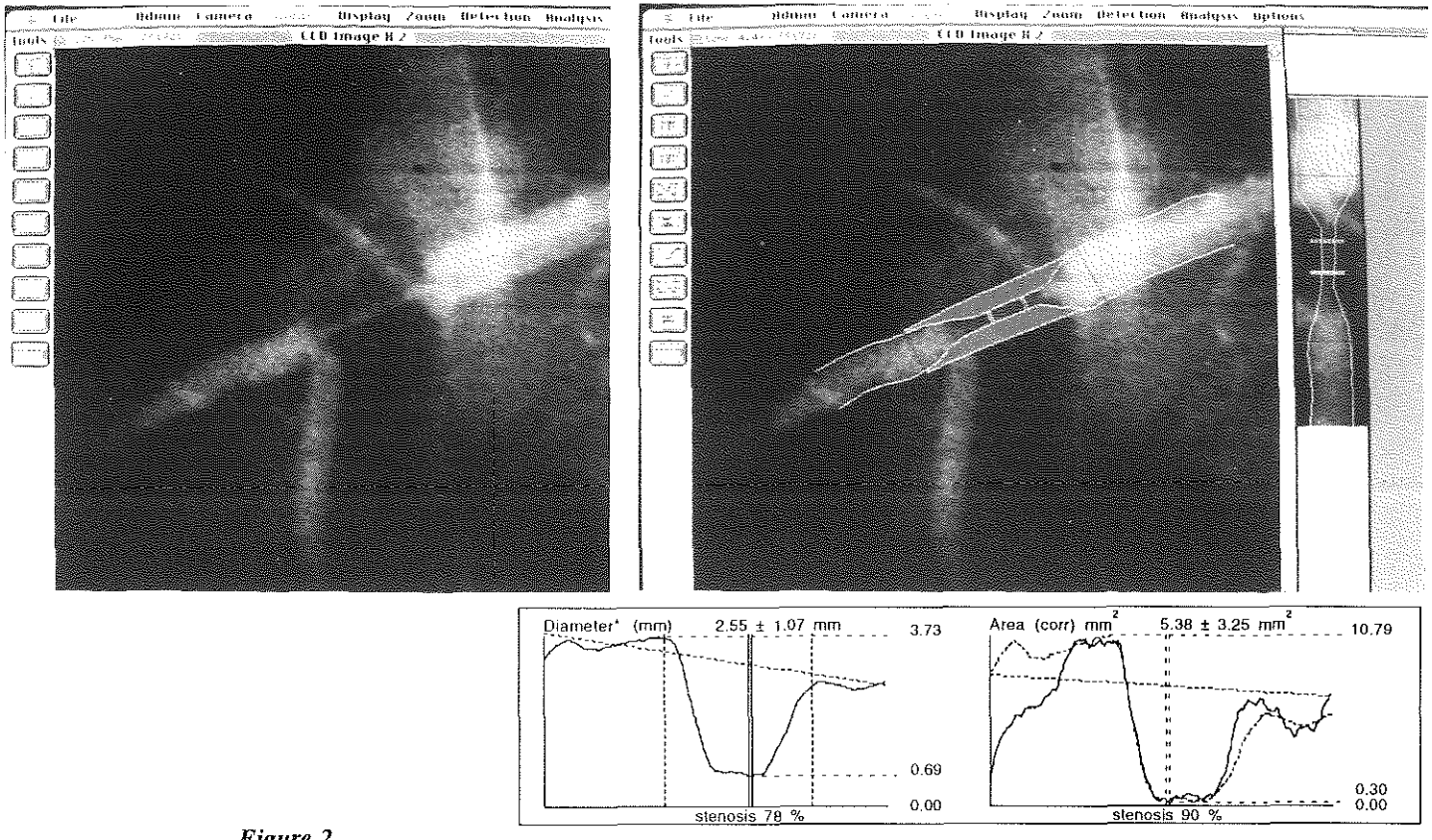

Figure 2

Angiographic visualization of a 0.7mm stenosis phantom in coronary wedge position (left hand side) with consecutive geometric and videodensitometric analysis (right hand side). Vessel diameter function and cross sectional area function with background correction are displayed in the bottom graphs. The dotted curve in the right graph displays calculated cross sectional area values as derived from the geometric vessel diameter function.

(diameter 3mm) within the isocenter of the x-ray system before angiography. Catheter calibration was performed by acquisition of the unfilled tip of the contrast catheter as conventionally recommended for clinical routine (27). The diameter of the non-tapering part of this catheter was assessed with a precision micrometer (No. 293-501, Mitutoyo, Tokyo, Japan; accuracy 0.001mm), resulting in the respective calibration factor (mm/pixel). Using these two methods of calibration, two series of results were obtained allowing an estimation of the potential geometric error introduced by non-isocentric calibration.

Image acquisition and processing

The 5"-field mode of the image intensifier (focal spot 0.8mm) was selected and the radiographic system settings were kept constant (kV, mA, x-ray pulse width) in each projection. All phantoms were imaged isocentrically in two projections and acquired on 35-mm cinefilm (CFE Type 2711, Kodak, Paris, France) using a frame rate of 25 images/s. Particular care was taken to minimize foreshortening of the segment of interest and to avoid overlap with other vessels or structures. The cinefilms were routinely processed and used for off-line analysis on the CAAS II system (28). From each angiogram that fulfilled the requirements of quantitative analysis (no superimposition of surrounding structures, no major vessel branching at the site of the phantom position), a homogeneously filled end-diastolic coronary image was selected and geometric as well as densitometric analysis was carried out after cine-video conversion in the CAAS II system (Figure 2). This procedure allows the digital selection of a 6.9 x 6.9mm region-of-interest (ROI) out of the 18 x 24 mm cineframe for digitization into a 512 x 512 pixel matrix using a CCD camera (8 bits = 256 density levels). Effectively, this means that the entire cineframe (18 x 24 mm) can be digitized at a resolution of 1329 x 1772 pixels. A correction for pincushion distortion was not yet available in the evaluated experimental version of the CAAS II software package.

Edge detection analysis

Ten in vitro and 19 in vivo frames were suitable for quantitative analysis of the artificial stenoses. A sufficiently long segment of the contrast filled lumen including the stenosis phantom was selected on all images.
On the CAAS system, the edge detection algorithm is based on the first and second derivative functions applied to the brightness profiles along scanlines perpendicular to a model using minimal cost criteria (3, 28). The contour definition is carried out in two iterations. First, the user defines a number of centerline points within the arterial segment which are interconnected by straight lines, serving as the first model. Subsequently, the program recomputes the centerline, determined automatically as the midline of the contour positions which were detected in the first iteration. Smoothing of the contours and derived

diameter function is like in the previous CAAS (3). In the new version of the CAAS system (CAAS II), the edge detection algorithm is modified to correct for the limited resolution of the entire X-ray imaging chain. This modification is based on a look-up table derived from edge detection of simulated density profiles. These profiles are convolved with a Gaussian shaped point spread function (PSF) to reflect the limited resolution of X-ray imaging (32). It was shown that smaller diameter values are overestimated by the influence of the PSF. The used preliminary version of the correction algorithm converts an observed diameter value into a true diameter value assuming a PSF size of 0.4mm.
Manual corrections to the automatically detected contours were found to be unnecessary, with the position of the obstruction diameter in the stenosis phantom being defined satisfactorily by the automatic measurement system. The obstruction diameter is determined as the value measured at the "geometric center" of the obstruction, which is defined as the middle between the two closest diameter values that exceed the minimal luminal diameter of the stenosis by 5% (Fig 3). When a degree of obstruction due to cellular material or partial thrombosis was obvious within the phantom channel, the position of obstruction diameter assessment was then user-defined. This happened in three out of 20 angiographic images obtained during the in vivo experiments.

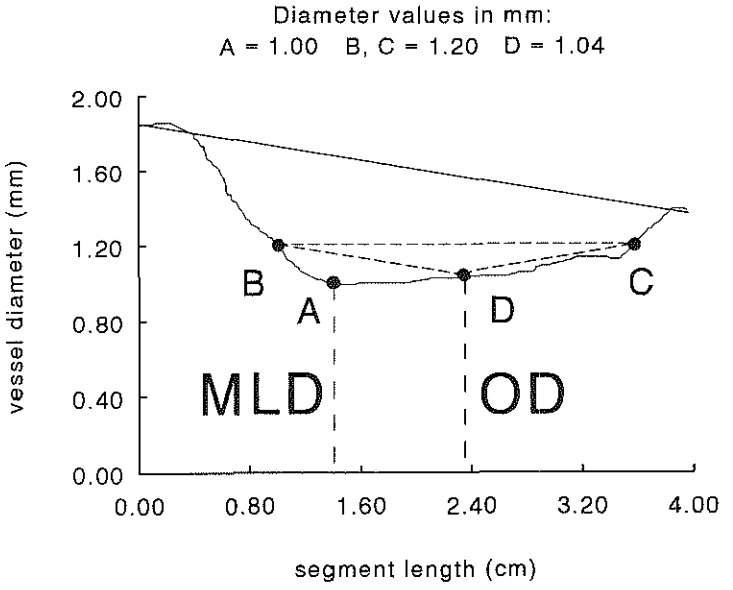

Figure 3
Definition of "obstruction diameter" on Caas II:
Schematic display of the diameter function curve of a coronary artery stenosis with illustration of the so-called "geometric center" of the obstruction, defined as the middle (D) between the two closest diameter values which exceed the minimal luminal diameter (A) of the stenosis by 5% (B,C). At position D, the "obstruction diameter" is calculated (OD = obstruction diameter; MLD = minimal luminal diameter).

Videodensitometric analysis

In the videodensitometric analysis modality, the brightness profile of each scanline perpendicular to the centerline of the lumen is transformed into an absorbtion profile according to the Lambert-Beer law by means of a simple logarithmic transfer function. The background contribution is estimated by computing the linear regression line through the mean of the brightness in two positions located 2 and 3 pixels outside the left and right detected contours (30). Subtraction of this background portion from the absorption profile yields the net cross sectional absorption profile. By repeating this procedure for all scanlines the cross sectional area function is obtained. The new version of the CAAS provides the operator with two cross sectional area functions, one with a correction of the background densities for vessel branching, and one without such correction (28).

In the clinical setting, an absolute reference for densitometric area values is calculated using the diameter measurements obtained from edge detection technique assuming a circular vessel geometry in a user defined reference segment outside the stenosis. In our experiments, the circular cross sections of the phantoms served as a reference where the minimal cross sectional areas were directly calculated using the automated computer program. In the event of artifactual obstruction within the phantom channel, calibration for the densitometric brightness profile was carried out manually within an unaffected portion of the stenosis phantom. Finally, the values of obstruction diameters were calculated from the cross sectional areas assuming a circular model.

Assessment of reproducibility

To assess the variability of repeated obstruction diameter and minimal cross sectional area measurements carried out with the CAAS II system, one representative cineangiographic frame of each size of the stenosis phantoms (0.5, 0.7, 1.0, 1.4, 1.9mm) was analyzed fifteen times by the same operator using the fully automated software without any user interaction on contours of the artifical lesion and on the position of obstruction diameter assessment.

Statistical analysis

The individual data for obstruction diameter and minimal cross sectional area were compared with the true phantom diameters as well as the derived cross sectional areas using paired t-test and linear regression analysis. A similar comparison was performed for the obstruction diameter values derived from the densitometric cross sectional areas with the respective phantom diameter data. The mean of the signed differences between measured

values or mathematically derived values with the respective reference data was considered an index of accuracy and the standard deviation of the differences an index of precision. The standard deviation of the mean value from thirty geometric and fifteen videodensitometric measurements on the same angiographic phantom was considered a measure of reproducibility. These values were calculated separately for all five stenosis phantoms. The mean reproducibility was defined as the mean value from those five reproducibility values.

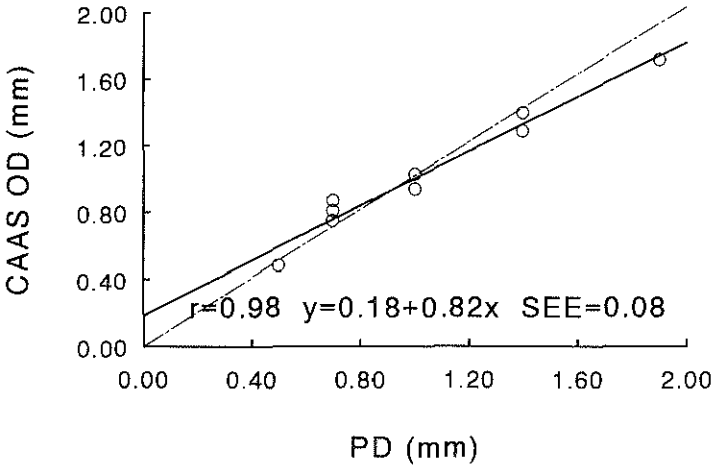

Figure 4
Plot of obstruction diameter (OD) measurements versus true phantom diameters (PD) using stenosis phantoms (diameter 0.5, 0.7, 1.0, 1.4, 1.9mm) inserted in a plexiglass model to mimick the radiographic scatter of the human thorax. The graph includes the line of identity as well as the result of the linear regression analysis.

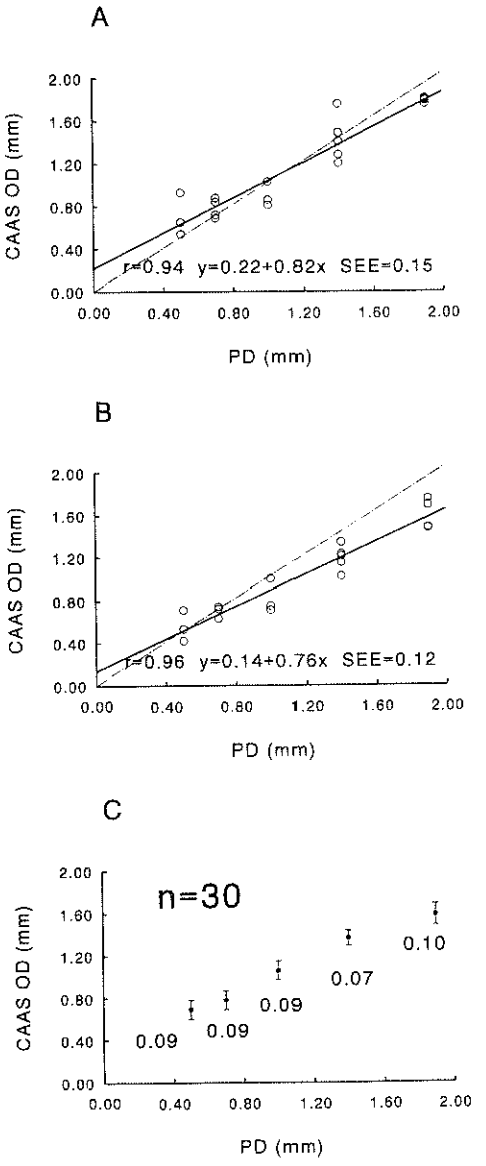

Figure 5
Obstruction diameter (OD) measurements are displayed versus true phantom diameters (PD) using percutaneous insertion of the stenosis phantoms in porcine coronary arteries with calibration at the isocenter (A) and catheter calibration (B). The reproducibility of obstruction diameter assessments is reflected by the standard deviation of 30 repeated obstruction diameter measurements on one representative stenosis phantom of each size (C).

RESULTS

A. VALIDATION OF GEOMETRIC MEASUREMENTS

In vitro measurements of phantom diameters

Measurements of the obstruction diameters in vitro yielded an accuracy of 0.00mm and a precision of ±0.11mm. As demonstrated on Figure 4, there was a high correlation between obstruction diameter and phantom diameter values (r=0.98, y=0.18+0.82x, SEE=0.08), with a slight tendency to underestimate large phantom diameters (p=N.S.).

In vivo measurements of obstruction diameters

With calibration at the isocenter, the in vivo assessments of obstruction diameters at the site of the stenosis phantoms gave an accuracy of -0.01mm and a precision of ±0.18mm. Figure 5 A shows that obstruction diameter values and phantom diameters correlate well (r=0.94, y=0.22+0.82x, SEE= 0.15), although there is some tendency to overestimate small and underestimate large stenosis phantom diameters. The differences between measured values and reference values were statistically not significant.
Using the angiographic catheter for calibration we obtained an accuracy of 0.14mm and a precision of ±0.17mm. The measurement points of the smallest phantom diameter lay very close to the line of identity (Figure 5 B), 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).

Reproducibility of geometric measurements

The results of thirty repeated analyses of obstruction diameter on each stenosis phantom using one angiographic image per phantom size are depicted in Figure 5 C. The variability of measurements was ±0.07mm for the 1.4mm phantom, ±0.09mm for the 0.5mm, 0.7mm and 1.0mm phantoms, and ±0.10mm for the 1.9mm stenosis phantom. Thus, the mean reproducibility of geometric measurements for all phantom sizes was ±0.09mm.

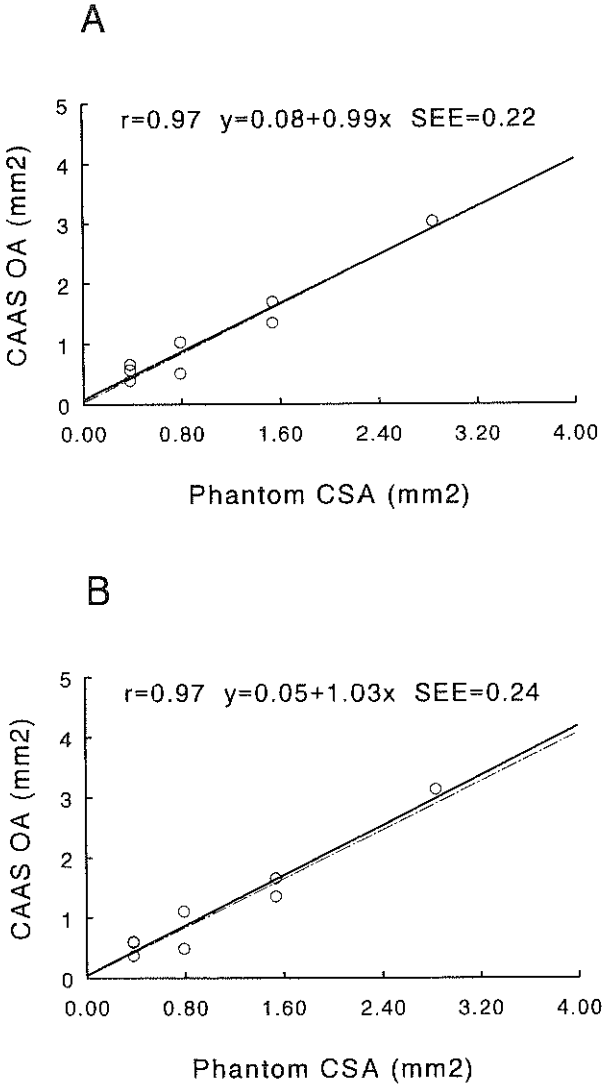

Figure 6
Videodensitometric assessment of phantom cross sectional areas using the plexiglass model. In graph A individual obstruction area (OA) measurements are plotted against the true phantom cross sectional areas (CSA) using a correction on the background subtraction. In graph B the corresponding values obtained without background correction are displayed. The contour of the 0.5mm phantom could not be detected automatically due to overlap with the radiographic shadow of the 4F insertion catheter.

B. VALIDATION OF VIDEODENSITOMETRIC MEASUREMENTS

In vitro measurements of minimal cross sectional areas

In Figure 6, the measurements of obstruction areas (OA) in vitro are plotted against the true phantom cross sectional areas (CSA) with correction of the background for vessel branching (Fig 6 A) and without such correction (Fig 6 B). Using the correction of the digitally subtracted background density, these measurements yielded an accuracy of -0.08mm² and a precision of ±0.21mm². As illustrated by Figure 6 A, the videodensitometric assessment of phantom obstruction areas correlated very well with the true cross sectional area values (r=0.97, y=0.08+0.99x, SEE=0.22). Without correction of background (Fig 6 B), the videodensitometric measurements yielded an accuracy of -0.09mm² and a precision of ±0.23mm² and showed a similar high correlation of measured values and reference values (r=0.97, y=0.05+1.03x, SEE=0.24).

The accuracy and precision values as well as the linear regression analyses of obstruction diameters as derived from measured phantom minimal cross sectional areas with and without background correction compared with the respective results from the direct measurement of obstruction diameters are listed in Table 1 A.

In vivo measurements of minimal cross sectional areas

The results of in vivo assessments of minimal luminal cross sectional areas at the position of the stenosis phantoms are plotted against the respective reference values in Figure 7 A and B.
Using background correction, the measurements of minimal cross sectional area yielded an accuracy of -0.22mm² and a precision of ±0.32mm². Figure 7 A illustrates that the correlation and standard error of estimate are clearly improved by correction of background density (r=0.95, y=0.21+1.01, SEE=0.33). However, true cross sectional area values are significantly overestimated ($p<0.01$).
Without background correction, the measurements of minimal cross sectional area gave an accuracy of -0.21mm² and a precision of ±0.61mm². The measurement points of small obstruction areas lay close to the line of identity (Figure 7 B), however the assessment of large cross sectional areas yielded a large scatter of measurement values producing a high standard error of estimate (r=0.82, y=0.37+0.87x, SEE=0.61).
The accuracy and precision values as well as the linear regression analyses of obstruction diameters as derived from measured phantom minimal cross sectional areas, with and without background correction compared with the respective results from the direct measurement of the obstruction diameter, are listed in Table 1 B.

Reproducibility of videodensitometric measurements

The results of fifteen repeated measurements of each phantom minimal cross sectional area with and without background correction are plotted in Figure 7 C and D, respectively. Without correction of background density, the variability of measurements was ±0.09mm² for the 0.5mm and 1.0mm phantom, ±0.14mm² for the 0.7mm phantom, ±0.26mm² for the 1.4mm and ±0.27mm² for the 1.9mm stenosis phantom (Fig 7 D). Using background correction, the variability of measurements was ±0.09mm² for the 0.7mm, ±0.13mm² for the 0.5mm and 1.0mm phantom, ±0.26mm² for the 1.4mm and ±0.43mm² for the 1.9mm phantom (Fig 7 C). Thus, the mean reproducibility of densitometric measurements was ±0.17mm² without and ±0.21mm² with background correction.

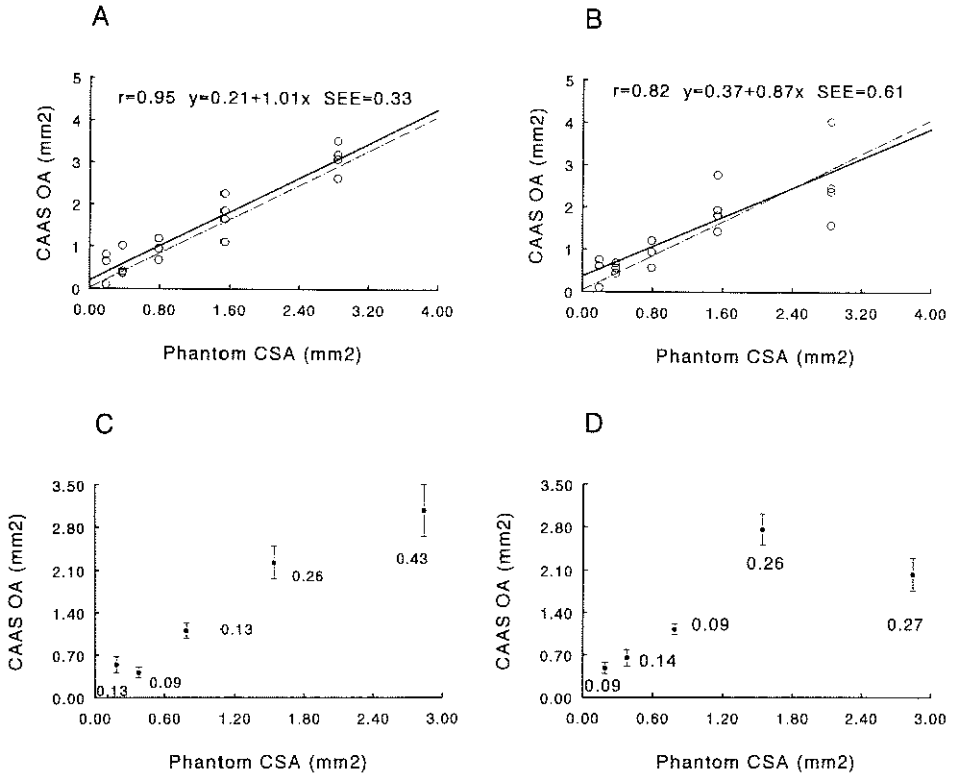

Figure 7

In vivo validation of videodensitometric cross sectional area assessments using percutaneously inserted stenosis phantoms in swine coronary arteries with (A) and without (B) a correction of the digitally subtracted background density. The reproducibility of 15 repeated measurements on one representative stenosis phantom of each size reflected by the respective standard deviation values shows a high degree of scatter for the assessment of cross sectional areas larger than 1.0sqmm for both, measurements with (C) and without (D) background correction.

DISCUSSION

Although several studies have confirmed that videodensitometric assessment of brightness profiles along the cross section of a contrast filled vessel can be used to estimate the cross sectional area of eccentric coronary lesions from a single plane (13,14), the reliability of these measurements remains controversial, particularly when compared with biplane assessment of coronary artery diameters (13-21). However, it has been found that small vessel cross sectional areas are assessed with considerable accuracy, whereas the assessment of large vessel cross sectional areas produces highly scattered values, a phenomenon which is most likely due to the non-linear relation between iodine content and the optical density of the radiographic image induced by the spectral hardening of the polyenergetic X-ray beam (31).

Geometric coronary measurements, on the other hand, provide highly accurate and reliable assessments of coronary artery dimensions, although the geometric unsharpness depending on the size of the focal spot is a limiting factor for the accurate assessment of small vessel diameters (32), which is crucial for the evaluation of high grade coronary artery stenoses. Looking at the different ranges at which video-densitometric and geometric coronary measurements have the highest potential of reliability, a combined use of both approaches theoretically could be considered.

The present validation of the new version of the Cardiovascular Angiography Analysis System compares accuracy, precision and reproducibility of geometric and videodensitometric coronary measurements in order to elucidate the practical value of both techniques.
The variable shape of human coronary artery narrowings (33) has prompted the use of non-circular luminal cross sections in stenosis phantoms as reference for experimental validation of quantitative coronary analysis systems. Under these conditions, the potential of densitometric measurement techniques can be evaluated adequately (34). For the comparative validation of geometric and videodensitometric assessments, however, the use of circular shaped stenosis phantoms has two advantages. First, the calibration of densitometric measurements which is normally based on the assumption of a circular vessel cross section proximal to a coronary stenosis, can be carried out correctly at the site of the circular shaped stenosis phantom. And second, the calculation of diameter values derived from the densitometric areas can be compared directly with the respective values obtained by the edge detection technique.

Theoretically, the validation of geometric coronary measurements may be affected by the length of an artificial stenosis, when a smoothing algorithm is applied. The short and abrupt change in vessel diameter without tapering transition cannot necessarily be tracked by an edge detection algorithm incorporating integrated smoothing, so it may result in an overestimation of the obstruction diameter (3). Thus, if accuracy, precision and reliability of a specific edge detection algorithm should be validated as done in the present

investigation, a sufficient length of the stenosis phantom is obligatory to exclude the possible influence of smoothing on the outcome of diameter measurements.

In our study, we used the so-called "obstruction diameter" as a parameter for the validation of geometric coronary measurements. In the new version of the CAAS this parameter is defined as the value at the "geometric center of the obstruction" (Fig 3), which represents the middle between the two closest diameter values which exceed the absolute minimum by 5% (28). This averaging offers the potential to circumvent possible underestimation of the phantom diameter caused by the use of an absolute minimum in the presence of micro-thrombosis within the phantom channel or quantum noise of the imaging system (12). In contrast to the obstruction diameter obtained by the Automated Coronary Analysis package of the Digital Cardiac Imaging system (35) this parameter still represents an absolute measure and therefore is suitable for the purpose of validation. The "obstruction area" as defined in the videodensitometric program of the CAAS II was used as the parameter of validation for densitometric assessments. It equals the "minimal cross sectional area" of coronary obstructions which closely reflects the hemodynamic significance of the stenotic lesion (36). The in vitro geometric measurements of our present validation study yielded superior results of accuracy (0.001mm) and similar results of precision (±0.11mm), when compared to initial reports from the first version of the CAAS (3), although a slight tendency to underestimate large phantom diameters was still present (r=0.98; y=0.18+0.82x; SEE=0.08) as illustrated by Figure 4. The superiority of the new software version, however, is more evident from the in vivo results of our investigation using edge detection measurements on the percutaneously inserted stenosis phantoms in swine coronary arteries (Fig 5).
When calibrated at the radiographic isocenter the new software version yielded an accuracy of -0.01mm and a precision of ±0.18mm (r=0.94, y=0.22+0.82x, SEE=0.15), whereas the identical experimental approach with the previous version of the CAAS (12) gave an accuracy value of -0.07mm and a precision of ±0.21mm (r=0.91, y=0.30+0.79x, SEE=0.19). Using catheter calibration by which geometric conditions similar to clinical routine were simulated, the new software version also demonstrated some improvement although less impressive due to a similar tendency to underestimate true phantom diameters, a phenomenon which may be explained by out of plane manification of the catheter tip (12). The high level of reproducibility throughout the range of all phantom sizes (Fig 5 C) is comparable to current digital as well as cinefilm-based quantitative coronary analysis systems (11,22,37). The improvement of measurement reliability in comparison with the previous software version is based mainly on the experimental correction of the algorithm for overestimation of small stenosis diameters (29).

The videodensitometric software of the new version of the CAAS has been improved in one way. The operator can select a menu option to correct the background density for vessel branching before subtracting it from the cross-sectional absorption profile (28).
It is not surprising that the influence of background correction is minimal with in vitro measurements. This is illustrated by the almost identical results shown in Figure 6 A and B.

B. On the other hand, background correction seems to improve the reliability of videodensitometric cross sectional area assessments obtained in our animal model (Fig 7 A,B). However, the assessment of reproducibility based on the standard deviation of 15 consecutive analyses on each phantom clearly demonstrates that even the use of the improved digital subtraction technique to correct for background density cannot overcome the limitation of current videodensitometric measurements of large vessel cross sectional areas due to the effects of beam hardening, scattering and veiling glare (Figure 7C). A more sophisticated approach towards calibration of videodensitometric assessments based on the use of reference phantoms with various cross sectional areas to correct for the non-linearity of the entire energy/brightness function possibly could help to solve this problem. At the present stage, however, the potential of highly reliable densitometric assessments is confined to the measurement of cross sectional areas below 1 mm^2 (31).

Calibration with perfectly circular cross sections such as those of the precision-drilled stenosis phantoms used in our experiments provides ideal conditions for the measurement of cross sectional areas. With respect to videodensitometric assessments in clinical practice which uses a "normally" shaped portion of the coronary artery as a reference, any morphological irregularities which deviate from the assumed circular shape will affect the reliability of cross sectional assessments at the position of the coronary lesion. Furthermore, the influence of vessel branching and foreshortening of the segment by non-orthogonal imaging are some of the additional sources of error which potentially impair the reliability of videodensitometric measurements.

In conclusion, the experimental validation of the new version of the Cardiovascular Angiography Analysis System demonstrates that the high reliability of geometric coronary measurements based on edge detection technique has been improved further. However, even in the presence of ideal reference cross sections, accuracy and precision of videodensitometric measurements remain limited by the effects of beam hardening, scattering and veiling glare.

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We gratefully acknowledge the technical assistance of Rob van Bremen, Ronald van den Perk, and Folkert Tijdens (Pie Medical, Maastricht).

	accuracy	precision	r	y	SEE
OD	0.14	0.07	0.99	-0.05+0.92x	0.07
COD	-0.05	0.14	0.95	0.11+0.95x	0.15
COD corr.	-0.05	0.14	0.95	0.13+0.92x	0.14

Figure 1 A

Four epoxy blocks with negative casts of diffuse diseased human coronary arteries were used as a reference for videodensitometric assessment of intracoronary volume.

	accuracy	precision	r	y	SEE
OD	-0.01	0.18	0.94	0.22+0.82x	0.15
COD	-0.09	0.25	0.89	0.19+0.91x	0.25
COD corr.	-0.12	0.19	0.93	0.21+0.92x	0.19

Figure 1 B

The volume of each coronary segment of the epoxy blocks was measured by fluid-filling using a precision micro dispenser (tolerance < 0.01µl).

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Chapter 7

Quantitative Angiography During Coronary Angioplasty Using a Single Angiographic View: A Comparison of Automated Edge Detection and Videodensitometric Techniques

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ABSTRACT

Little information is available on the reliability of coronary luminal measurements obtained from quantitative analysis of a single angiographic view, an approach that is central to the practical use of on-line quantitative angiography. In the present study we investigated the contribution of two different techniques of quantitative angiography, edge detection (ED) and videodensitometry (VD), to the application of this concept during coronary angioplasty.

Methods: Forty-six balloon angioplasty procedures were included in the study, all of them performed in a stenosis located in the mid right coronary segment. The latter coronary location was chosen to optimize data collection on luminal morphology and to minimise the number of factors that may adversely affect quantitative analysis with both techniques. In all cases two orthogonal angiographic projections were obtained before, after balloon dilatation and at follow-up. Correlation coefficients and differences between orthogonal measurements obtained with each technique were used to evaluate the agreement between orthogonal readings at every stage of the procedure.

Results: The obtained correlation coefficients and mean differences (MD) between orthogonal measurements were as follows: before PTCA, 0.67 (MD 0.01±0.47 mm^2) and 0.57 (MD 0.05±0.64 mm^2) for ED and VD respectively (Pitman's test for SD: $p<0.05$); after balloon dilatation, 0.32 (MD -0.56±1.53 mm^2) and 0.53 (MD -0.15±1.43 mm^2) for ED and VD respectively (Paired t-test for MD: $p<0.05$); and at follow-up 0.79 (MD -0.15±0.97 mm^2) and 0.73 (MD 0.17±1.16 mm^2) for ED and VD respectively (p=NS). The presence of coronary dissection did not influence the variability in measurements observed after balloon dilatation.

Conclusion: A considerable variability between orthogonal cross-sectional area measurements obtained with ED and VD was observed at all stages of coronary angioplasty, a finding that does not support the clinical application of area measurements with ED or VD from a single view. Similar observations were done after the exclusion of angiographically evident dissections. However, after balloon dilatation the agreement between orthogonal area measurements was significantly better with VD than ED. Our results provide new insights to the problems posed by coronary intervention to the on-line angiographic assessment of its results and to its potential solution. With any of these two quantitative techniques area measurements obtained from a single angiographic view should be interpreted with caution.

INTRODUCTION

The growing demand for the use of on-line quantitative angiography during interventional procedures is currently hampered by two major limitations. First, although averaging of measurements obtained in different angiographic views is accepted as the optimal method for quantifying coronary stenosis (1-3), this approach appears too cumbersome for its application during coronary intervention. Second, quantitative analysis of intervened segments appear to be less reliable than that performed in non-intervened ones (3-7).

It remains unclear whether any of the two main alternative techniques of quantitative analysis, namely videodensitometric and edge detection, can offer a distinct solution to these problems. The routine use of quantitative angiography would be facilitated and more widely applied during interventional procedures if accurate measurements could be obtained from the analysis of a single angiographic view. To that end videodensitometry might be the most preferable technique since, at least theoretically, measurements are independent of the angiographic projection used. Other authors have suggested that analysis of a selected single angiographic view, using edge detection, may also be accurate enough for clinical purposes (8). With regard to the loss of accuracy of quantitative angiography post-intervention, no clear agreement has been reached on the mechanisms causing increased variability of measurements in the intervened segment. Should this be due to complex changes in luminal geometry, videodensitometry might be the method of choice since luminal area measurement by this technique is independent of lumen morphology. However, up to now videodensitometric studies in the context of balloon angioplasty have yielded conflicting results (4-7,9-10).

To shed further light on these topics we investigated the degree of agreement between cross-sectional area measurements obtained in two orthogonal angiographic projections during balloon angioplasty. Our first objective was to test whether the use of a single angiographic view is sufficiently accurate for its clinical use. Furthermore, we wanted to test whether in this regard videodensitometry is superior to edge detection analysis. Finally, we investigated whether the agreement between measurements obtained in two orthogonal views changes significantly during the different stages of coronary intervention.

By limiting the study to a selected coronary segment with ideal characteristics for both videodensitometry and edge detection, the effect of luminal changes caused by balloon dilatation on both types of quantitative analysis was highlighted. Edge detection and videodensitometry analysis was performed separately. Qualitative analysis of the dilated segment was also performed to assess the impact of angiographically evident dissection on single plane analysis and on both modalities of quantitative angiography.

METHODS

Study population

The study population was formed by the 653 balloon angioplasty procedures that were included in the efficacy analysis of the Multicenter European Research trial with Cilazapril after Angioplasty to prevent Transluminal coronary Obstruction and Restenosis (MERCATOR) (11). The study showed that cilazapril 5 mg b.i.d. does not influence the development of restenosis nor patient clinical outcome during the first six months after balloon angioplasty. All the 653 patients had had a successful procedure and underwent follow-up angiography at 26 ± 3 weeks after the procedure or earlier if symptoms had recurred.

All 72 PTCA procedures performed in a mid right coronary artery stenosis were initially considered. This segment was chosen as presenting the ideal anatomical characteristic for quantitative angiographic analysis: minimal foreshortening in the right and left anterior oblique views, few side branches, and virtual absence of vessel overlap. Lack of orthogonal angiographic projections or follow-up angiography, and total coronary occlusion at any stage of the study were exclusion criteria.

Image acquisition

Image acquisition was standardised to ensure exact reproducibility of the measurements before, after PTCA and at follow-up. Same angiographic angulations were used throughout the study. Intracoronary nitrates (nitroglycerine 0.3 mg or isosorbide dinitrate 1 mg) were given prior to image acquisition to ensure full vasodilation of epicardial vessels. In order to be used as a scaling device during quantitative analysis, all catheter tips were filmed empty of contrast medium before each injection and stored after the procedure for future micrometric measurement (12).

Quantitative angiographic analysis

All 35 mm films were analysed at a core laboratory (Cardialysis, Rotterdam) using the Cardiovascular Angiography Analysis System (CAAS). The automated edge detection and videodensitometric techniques used by this system have been described in detail elsewhere (13-16), as well as its validation in vitro (13) and in vivo using precision-drilled perspex

models inserted percutaneously in an anesthetized swine model (17,18). All measurements were performed in end-diastolic frames with optimal vessel opacification. Prior to quantitative analysis all contour positions of the catheter tip and arterial segment were corrected for pincushion distortion induced by the individual intensifiers.

Edge detection

After a region of interest of 512 x 512 pixels was selected and digitised using a high-fidelity charge couple device (CCD) videocamera, luminal edges were detected using a weighted sum of the first and second derivative function of the brightness profile of each vessel scanline. A diameter function was determined by computing the shortest distance between the left and right contour positions. Conversion of these measurements to absolute values was achieved by using the catheter tip as a scaling device. From the diameter function, a computer-derived estimation of the original arterial dimension at the site of obstruction, or interpolated reference diameter, was also calculated.

Videodensitometry

Videodensitometry is based on 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 was obtained. Subtraction of patient structure noise was applied after computing the linear regression line through the background pixels located left and right of the detected luminal contours. A cross-sectional area function on the analysed segment was obtained by obtaining consecutive densitometric profiles in all scan-lines perpendicular to the vessel. From this area function an interpolated reference area was calculated in a similar way to that described in the edge detection algorithm. Conversion of the individual videodensitometric profiles to absolute values was performed after a transformation of the videodensitometric profile found at the reference diameter with the corresponding geometrical area (calculated from the reference diameter and assuming a circular cross-section at that point). The cross-sectional area at the narrowest point was identified and expressed in mm^2. No correction for veiling glare was introduced.

Assessment of dissection

Coronary dissection following balloon angioplasty was recorded by 2 independent observers using a modification of the criteria defined by the National Heart, Lung and Blood Institute (19). A dissection was classified as a small radiolucent area within the lumen of the vessel (type A), a non-persisting or persisting extravasation of contrast medium (type B or C respectively), a spiral-shaped filling defect with or without delayed antegrade flow (types E and D respectively), or a filling defect causing total coronary occlusion (type F). The presence of angiographic dissection may constitute a source of variability during quantitative analysis. Following the recommendations of the angiographic committee of the MERCATOR study, identification of the luminal borders in vessels with evident angiographic dissection was performed always using the automated edge detection mode and never manually corrected by the analyst. In this way, subjective bias was minimised.

Statistical analysis

Mean values $\pm$ standard deviation were calculated for all measurements obtained before, after PTCA and at follow-up. Pearsons product moment correlation coefficients were calculated for orthogonal measurements. The agreement between orthogonal measurements was also studied using the mean (accuracy) and standard deviation (precision) of the differences between measurements obtained in orthogonal views (20). Quantitative data was compared using one-way analysis of variance. Paired 2-tailed t-tests were used when required to compare mean values. Comparisons between standard deviations were performed using Pitman's test. A p value < 0.05 was considered statistically significant.

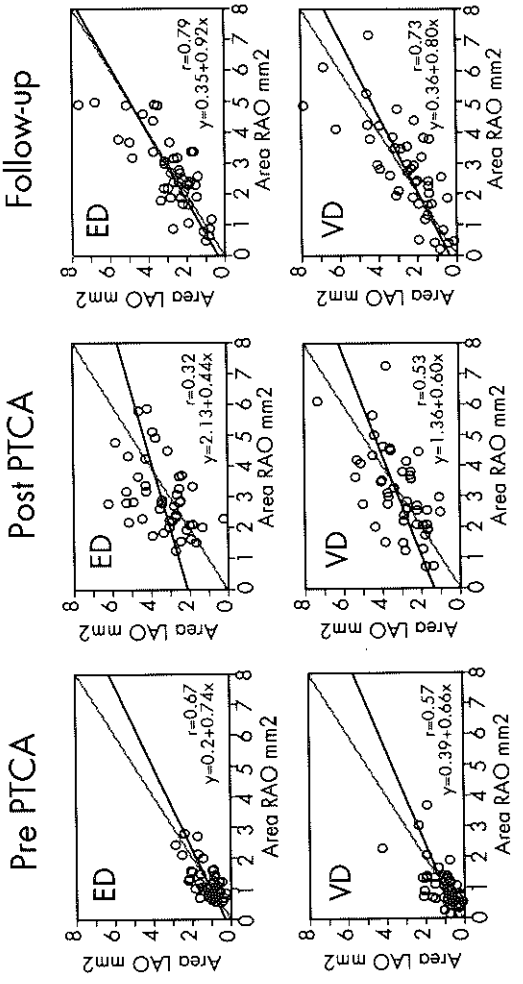

Figure 1

Correlation between minimal luminal cross-sectional area measurements obtained in two orthogonal projections. The results obtained with automated edge detection and videodensitometric analysis in each stage of the study are shown separately.
ED = edge detection; VD = videodensitometry; LAO = left anterior oblique view; RAO = right anterior oblique view.

RESULTS

Of the 72 successful PTCA procedures performed in the mid segment of the right coronary artery 8 were total occlusions at baseline or follow up and were excluded. In addition, 18 cases lacked satisfactory orthogonal angiographic assessment and were also excluded. The remaining 46 cases constitute the population of this study. Orthogonality between right and left anterior oblique views was 90.00 ± 14.43 degrees. Coronary dissection immediately after PTCA was documented in 16 cases. The dissection was classified as type A in 6 cases, B in 9 cases and E in 1 case. Negative videodensitometric measurements were obtained in 2 cases before-PTCA and in 1 case at follow-up. The cause of negative readings may be found in an excessive background subtraction when bright areas are close enough to the analysed vessel to fall within the region of interest. These cases were excluded only from the analysis at that particular stage of the study (pre-PTCA and follow-up respectively).

The mean minimal luminal cross-sectional areas ($\pm$SD) obtained by averaging videodensitometry values from orthogonal views were 1.00 ± 0.96, 3.1 ± 1.68 and 2.6 ± 1.50 mm^2 before, after PTCA and at follow up respectively. Averaged edge detection measurements were 1.11 ± 0.53, 3.17 ± 1.05 and 2.63 ± 1.31 mm^2 respectively.

Figure 1 shows the correlation between pairs of orthogonal measurements obtained by using either videodensitometry or edge detection. The degree of agreement between these values is further illustrated with the mean difference between both measurements and its standard deviation (Fig 2). 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 ± 1.43 mm^2 and -0.56 ± 1.53 mm 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 (Figure 3). No significant difference in the mean value or the standard deviation of the difference between orthogonal values was found between groups.

At follow-up, the difference between orthogonal views was 0.17 ± 1.16 mm^2 and -0.15 ± 0.97 mm for videodensitometry and edge detection respectively. There was no significant difference in the precision of these measurements.

To study the contribution of recorded vessel dissection to the loss of agreement between orthogonal views after balloon dilatation, a separate analysis of the between-projection differences in minimal luminal area was applied to vessels with and without dissection (Figure 3).

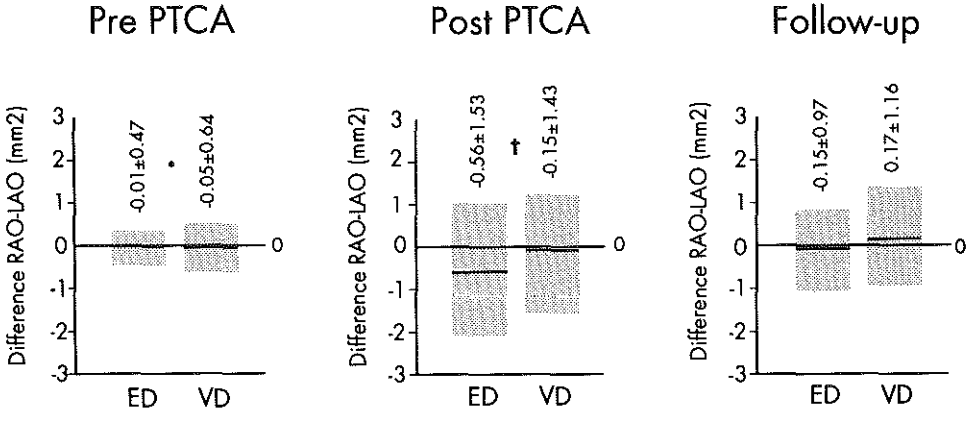

Figure 2

Mean differences between minimal luminal cross-sectional area measurements obtained in two orthogonal projections with automated edge detection and videodensitometric analysis ± 1 standard deviation (shadowed area).The results obtained during the different stages of the study are shown separately. ED = edge detection; VD = videodensitometry.

The mean difference in cases without dissection was -0.62±1.21 and -0.19±1.49 mm^2 for edge detection and videodensitometric measurements respectively. In those cases with angiographically detectable dissection the differences obtained were -0.46±2.04 and -0.06±1.35 mm^2 for edge detection and videodensitometric measurements respectively. No significant differences in accuracy or precision were found between with regard to the type of analysis applied (edge detection or videodensitometry) nor to the presence or absence of recorded coronary dissection.

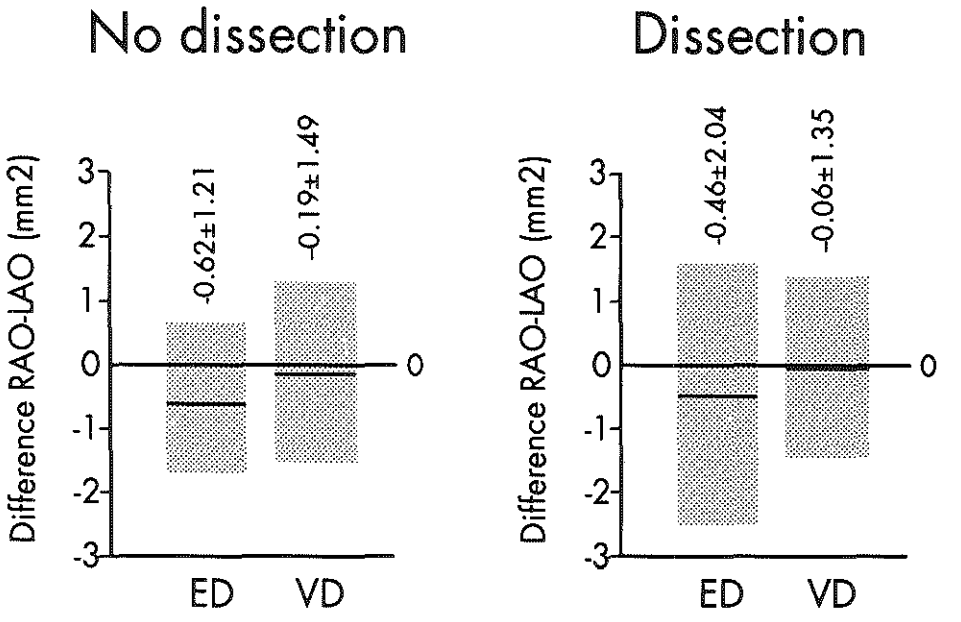

Figure 3

Mean differences between minimal luminal cross-sectional area measurements obtained in two orthogonal projections immediately after balloon dilatation. The results obtained in cases with and without angiographically detectable dissection are shown separately. The mean difference ± 1 standard deviation (shadowed area) are shown. ED = edge detection; VD = videodensitometry.

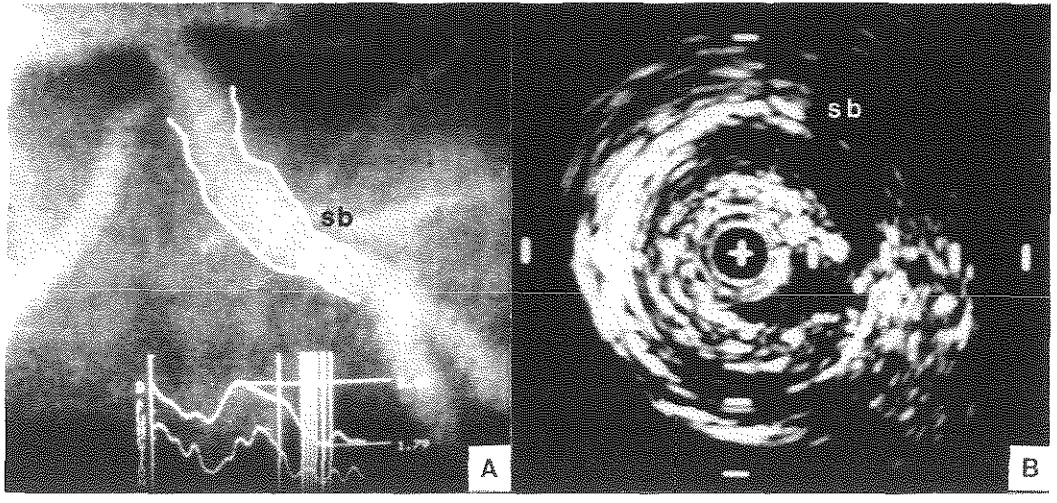

Figure 4

Quantitative analysis performed immediately after balloon dilatation of a stenosis in the circumflex coronary artery (A). Although no angiographic dissection was evident and edge detection analysis suggested a major improvement in luminal area, intravascular ultrasound revealed that the detected edges corresponded to a nearly complete plaque dehiscence from the surrounding media and that luminal gain was clearly overestimated by angiography. During ultrasound imaging a sidebranch (sb) located at the dilatation site was chosen as a landmark.

DISCUSSION

Edge detection and videodensitometric algorithms are built-in features of most new digital angiographic systems, a fact that may contribute to the widespread use of on-line quantitative coronary angiography in the near future. Although the performance of quantitative analysis from a single angiographic view is central to the practical use of these systems during routine procedures, little information is available on the variability between measurements obtained from orthogonal views. It has been argued that a significant variability would be expected when non-circular lumens are measured from different angiographic projections. Two main alternatives have been put forward to solve this problem. Lesperance et al (8) suggested that limiting the analysis to the angiographic view in which the stenoses appears most severe might fulfill the degree of accuracy required in clinical practice. A second approach, based on initial results obtained in in vitro phantoms, suggested that the use of videodensitometry would be advantageous since accurate measurements were obtained with independence of angiographic projection and lumen morphology (5,21,22). Validation studies of videodensitometry in conditions closer to those found in clinical practice have been performed, including videodensitometry in postmortem specimens (23) or in engineered angiographic phantoms implanted in animal models (18, 24). However, conflicting results have been reported when videodensitometry was used during coronary angioplasty. The correlation for individual measurements obtained in orthogonal views both before and after balloon angioplasty has been found by different authors to be high (8), moderate (5) or poor (4). The deterioration caused by balloon angioplasty in the agreement of videodensitometric measurements obtained from different angulations has also been reported in one study and found to be unacceptably large (6).

Two of the objectives of the present study were to test whether the use of a single angiographic view is sufficiently accurate for its clinical use, and whether in such regard the use of videodensitometry offers any advantages over edge detection. We found that in the post angioplasty period videodensitometry yields a significantly better agreement between orthogonal measurements than edge detection. However, further analysis of the results obtained demonstrated that the clinical relevance of this difference may be negligible. This was done by setting the limits of agreement on the standard deviation of the differences observed between orthogonal measurements, according to the method proposed by Bland and Altman (20), and led us to conclude that the overall variability between orthogonal measurements of cross-sectional area observed before and after coronary angioplasty makes single plane quantitative angiography with either edge detection or videodensitometry too unreliable to be used in routine clinical practice. Although our conclusions are based on the analysis of a single coronary segment and therefore should be extrapolated with caution to other vascular segments, the fact that the mid-right coronary segment represents the "best scenario" for quantitative analysis make us believe that even worse correlations would be expected if other segments of the coronary tree would be included.

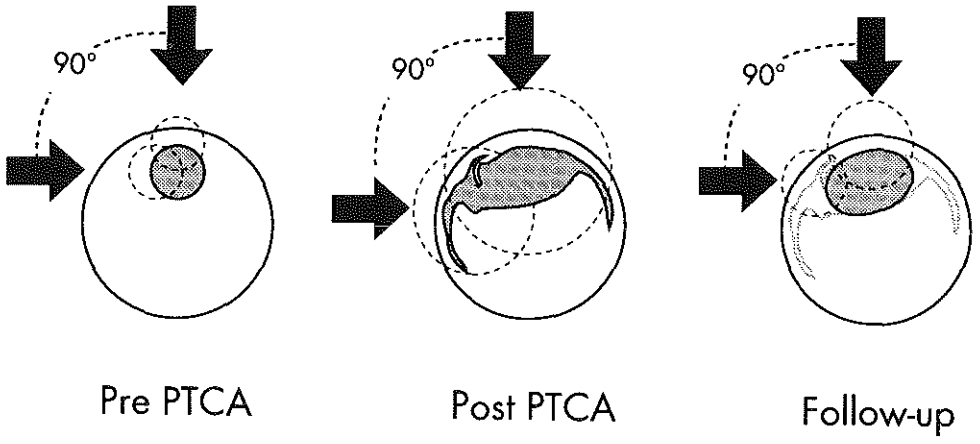

Figure 5

Proposed anatomopathological basis for the loss of agreement between orthogonal measurements during the different stages of balloon angioplasty. Following balloon dilatation the luminal cross-sectional area is overestimated by the use of geometric measurements (dotted circles) as a results of the identification of disrupted edges as true luminal borders and the non-circular luminal geometry. Healing of luminal disruptions leads to a more regular luminal morphology and to a better agreement between orthogonal measurements at follow-up (see text for details).

We investigated also whether the agreement between orthogonal measurements changes significantly during percutaneous intervention. In fact, we found that the agreement between single orthogonal cross-sectional area measurements obtained with either of the two techniques considered deteriorates significantly after balloon dilatation. Since tearing of the intima and atherosclerotic plaque, dehiscence of plaque from the tunica media, and variable degrees of medial and adventitial disruption are known to be common after balloon dilatation (25), observations similar to ours have been attributed to the effect of these histopathological changes on angiographic accuracy (3,4,6,26). However, given the characteristics of these studies such relationship could not been clearly established: experimental phantoms have a fixed luminal morphology and are free of wall disruption, and most previous clinical works have excluded or not recorded the presence of coronary dissection.

To provide further insights, we limited the collection of angiographic data to a coronary segment with ideal characteristics for quantitative analysis. In doing so, a true "in-vivo vascular phantom" was obtained in which the occurrence and type of vessel dissection was also documented. As shown in Figure 3, one of our conclusions is that the increased variability between orthogonal measurements observed after balloon angioplasty may not be ascribed solely to the presence of angiographically evident dissection. This suggest that lesser or occult changes in vessel morphology must account for the loss of accuracy of quantitative angiography at this stage. Two major types of 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 (27, 28), ultrasound (29) and pathological studies (30). When opacified during angiography, these irregularities can be wrongly identified as the 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 (25). Pathological studies have shown that slit-like or very irregular lumens are rarely seen in native vessels with non-complicated atherosclerotic plaques (31), a fact that may explain the excellent agreement between orthogonal measurements obtained with both edge detection and videodensitometry in a in vitro study using human coronary stenosis (23), as well as a better agreement between orthogonal edge detection measurements found at baseline in the present study (Figures 1 and 2). These two potential sources of error are illustrated in Figure 4, where the result of balloon dilatation in a circumflex stenosis is assessed using edge detection quantitative angiography and intravascular ultrasound.

It has been shown above that, although the overall variability in orthogonal cross-sectional area measurements was very high, videodensitometry was less influenced by balloon dilatation than edge detection. This observation may be related to its theoretical independence from lumen morphology and to its relative insensitivity to imprecise border positioning (22) and although its application may be currently hampered by technical factors (e.g. unsatisfactory background subtraction) it may constitute a valid alternative in the future to the topic discussed in this article. On the contrary, the identification of disrupted luminal edges and the assumption of an unlikely circular lumen morphology by edge detection algorithms easily leads to discrepancies with measurements obtained from a different angiographic view or with videodensitometric analysis, as illustrated in Figure 5. In this regard, a previous work (26) has shown that coronary stenting reduces the variability between videodensitometric and edge detection measurements. This is presumably a result of the scaffolding effect of the stent on intraluminal irregularities and the achievement of a

more circular luminal cross-section, as documented by intravascular ultrasound studies performed immediately after stent implantation (32). In our work the improvement in agreement between orthogonal area measurements at follow-up may be explained with the development of a more regular luminal cross-section by filling of intraluminal flaps and smoothing of luminal irregularities during the reparative vessel response that follows balloon dilatation (25)(Fig 5).

Study limitations

Since this study was limited to the mid right coronary artery segment, some of the results obtained are not necessarily applicable to other coronary locations. Errors can be introduced during the calibration of the system when catheters are used as scaling devices (24). In order to minimise some of the possible sources of error, all catheter tips were filmed unfilled, saved after the procedure and micrometered at the time of quantitative analysis (12). However, inaccuracies induced by out-of-plane position of the catheter may have occurred. Although correction for pincushion effect in the individual intensifiers was performed, other described sources of distortion cannot be ruled out (34), but their effect on measurements in the size range of coronary arteries is expected to be negligible. The effect of some of the physical variables potentially affecting videodensitometric analysis may be higher in the mid right coronary than in other coronary segments. Beam hardening and veiling glare is more intense in regions of rapid transition from dark to bright areas (35), as often happens when the mid right coronary artery is visualised in the left anterior oblique view. Although proposed by other authors (35, 36), no correction for these factors was introduced in the analysis.

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Chapter 8

On-line Versus Off-line Assessment of Coronary Flow Reserve

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ABSTRACT

Various methods can be applied to measure coronary flow reserve (CFR) as a functional parameter of the severity of coronary artery disease. Angiographic assessment of CFR was originally performed on-line, but the off-line implementation of the method to cinefilm is feasible. In 18 cardiac transplant recipients off-line assessment of CFR, based on time-density analysis of digital subtraction cineangiographic images on the Cardiovascular Angiography Analysis System (CAAS), was compared with the respective on-line technique on the Phillips Digital Cardiac Imaging System (DCI), which has been recently validated using Doppler flow velocity measurements.

Results: From 68 myocardial regions of interest (3.7 per patient) a good correlation between both methods was found for CFR values below 5.0 (correlation coefficient $r = 0.82$, $y = 0.37 + 0.88\ x$, standard error of estimate: SEE = 0.56) with a mean difference of 0.11 ± 0.56.

Conclusion: Like on-line assessment of CFR using time-density analysis of digitally subtracted myocardial contrast images, the corresponding off-line approach is a reliable technique to assess CFR, which can be used for independent and objective evaluation of CFR in multi-center trials, analyzed in a central core laboratory.

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 [2,3,4].

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 [3,4,5,6,7]. 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 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 a core laboratory, where the selection of ROI's can be carried out by an independent analyst, not 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].

The aim of the present study was 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 x 512) with the corresponding on-line software, which is implemented in the Phillips Digital Cardiac Imaging System (DCI, pixel matrix 512 x 512).

Patients

At the Thoraxcenter, 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, left ventriculography, selective coronary angiography and assessment of CFR, the latter as part of a follow-up study in this group of patients. 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

Coronary angiography was carried out by femoral approach using Judkins technique. The arterial blood pressure was continuously recorded throughout the procedure. An 8 French guiding catheter (Type Judkins, Cordis, Miami, Florida, USA) was advanced to the aortic root and selective angiography of both coronary arteries was performed. To assess coronary flow reserve, a fixed amount of non-ionic contrast medium (Iopamiro, Bracco, Italy; 370 mg iodine/ml) was injected at 37°C into the left coronary artery using an ECG-triggered infusion pump (Medrad IV, Medrad, U.S.A.). The injection rate of the contrast medium was judged to be adequate when back flow of contrast medium into the aorta occurred. In all patients 10 cc of contrast, given with an injection rate of 6 cc/second and an injection pressure of 150 pounds/inch^2, were found to be sufficient. The heart was atrially paced at a level approximately 10 beats/minute above spontaneous heart rate, ranging from 90 to 120 beats/min (mean 109 ± 10). Filming speed was set at 50 images per second. The X-ray exposure per frame was kept constant by selecting the lock-in mode on the X-ray generator. Simultaneous videocamera acquisition and cinefilm exposure was made possible by selecting the CINE-DCI mode, using a standard half transparent silver mirror.

After intracoronary administration of 2 mg isosorbide dinitrate, basal coronary angiography was performed in either 90° left anterior oblique or 30° right anterior oblique projection. Thirty seconds after pharmacologically induced maximal hyperemia, using an intracoronary bolus injection of 12.5 mg papaverine, the angiogram was repeated.
To assess left ventricular function, left ventricular angiography was performed in 60° left anterior oblique and 30° right anterior oblique projection. Left ventricular ejection fraction (EF) was calculated by the Dodge technique [13], 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 [14].

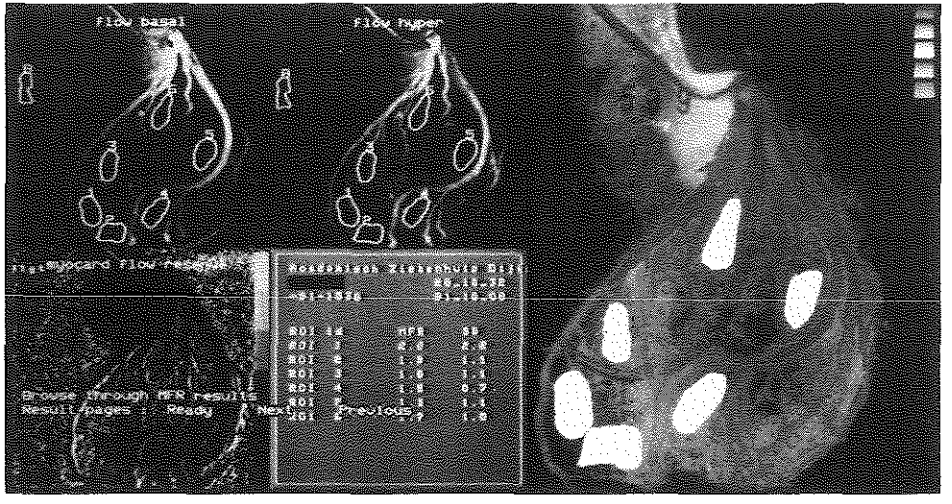

Figure 1
Illustration of the image acquisition in this study in a 58 year old male heart transplant recipient. Left: On-line assessment of CFR. Right: Off-line assessment of CFR.

Coronary flow reserve measurements off-line

Coronary flow reserve measurement with digital subtraction cineangiography from 35 mm cinefilm has been implemented in the 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 [15], 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 injection. Arrival time numbers are displayed color coded. 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)

Coronary flow reserve measurements on-line

The on-line method as implemented in the Phillips DCI system 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 contrast density is divided by the arrival time.

When parametric images are obtained under the baseline and hyperemic conditions, a fourth image, a CFR image, can be obtained by exactly superimposing 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.
To compare both on-line and off-line methods a print-out was made of the CFR image with the selected regions of interest, to allow off-line assessment of CFR in the same areas, using anatomical landmarks (Figure 1).

Statistical methods

Statistical analysis was performed using linear regression analysis and the Student's T test and Wilcoxon Matched-pairs signed-ranks test 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 .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. Mean blood pressure at the time of hyperaemia was 119 ± 15 mmHg (systolic) and 84 ± 11 mmHg (diastolic). All patients had a normal left ventricular function with normal regional wall motion. Ejection fraction could be assessed in 17 patients. Mean ejection fraction was 69 ± 7%.
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 correlation between CFR measurements using the DCI and CAAS system (r=0.88, y = -0.17 + 1.19 x, SEE = 0.81). However, the CAAS measurements (mean 2.62 ± 1.70) were significantly higher than the DCI measurements (mean 2.33 ± 1.25) (p = 0.01, Wilcoxon Matched-pairs signed-ranks test). According to the approach of Altman and Bland, as shown in Figure 3, the mean difference between both methods was 0.28 ± 0.84.

As illustrated by Figure 2, the difference between the results of on- and off-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 the 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 + 0.88 x, SEE = 0.56), as shown in Figure 4. There was no significant difference between the results of both measurements. The mean value for off-line measurements was 2.26 ± 0.97, for the DCI system 2.15 ± 0.91. The mean difference between both methods was 0.11 ± 0.56
(Figure 5).

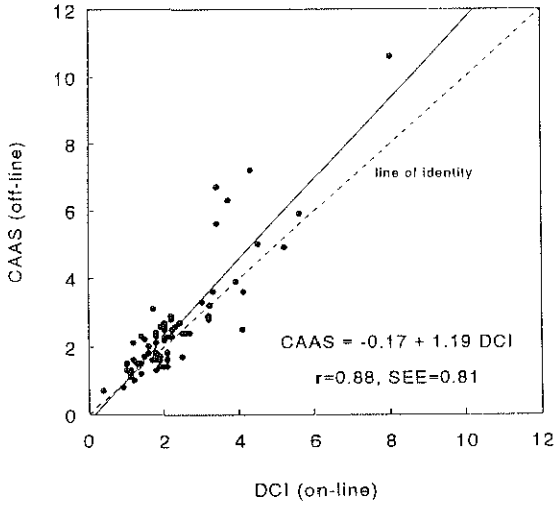

Figure 2
Results of comparison of digital and cinefilm measurements: The CFR results of the CAAS are plotted against the results obtained by the DCI system. The results of the linear regression analysis and the line of identity are included in the graph.

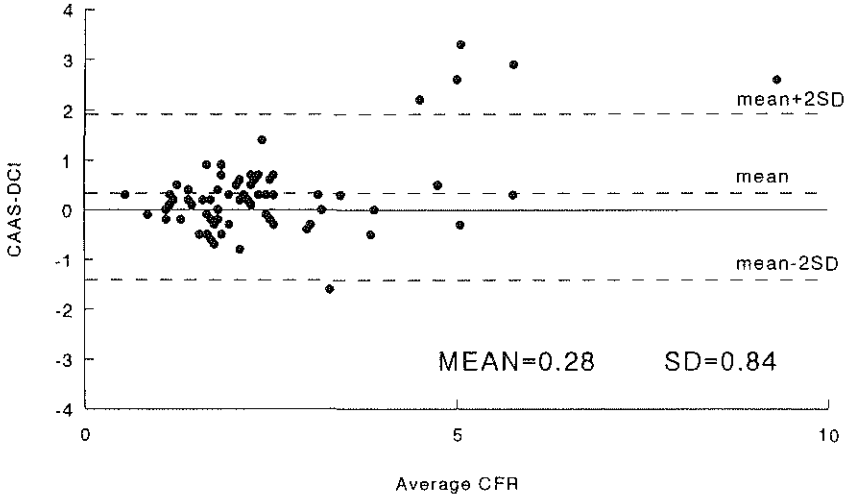

Figure 3

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.

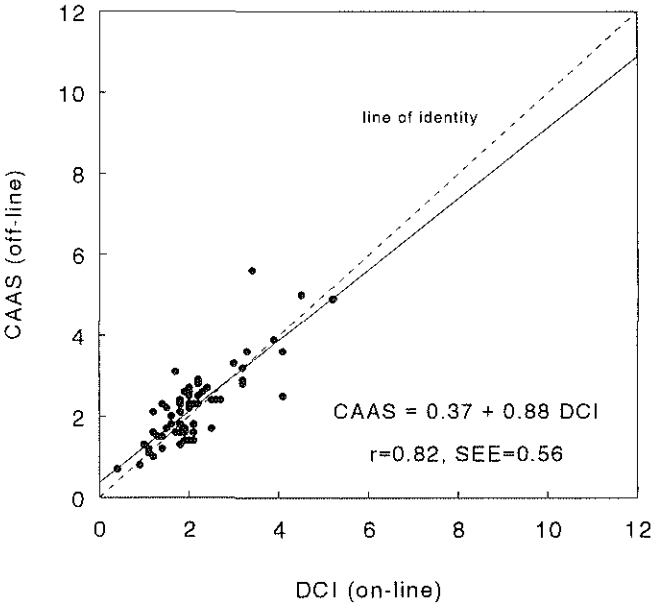

Figure 4
Results of comparison of cinefilm and digital measurements, excluding the 2 patients with high values for CFR as assessed by the off-line (CAAS) system.

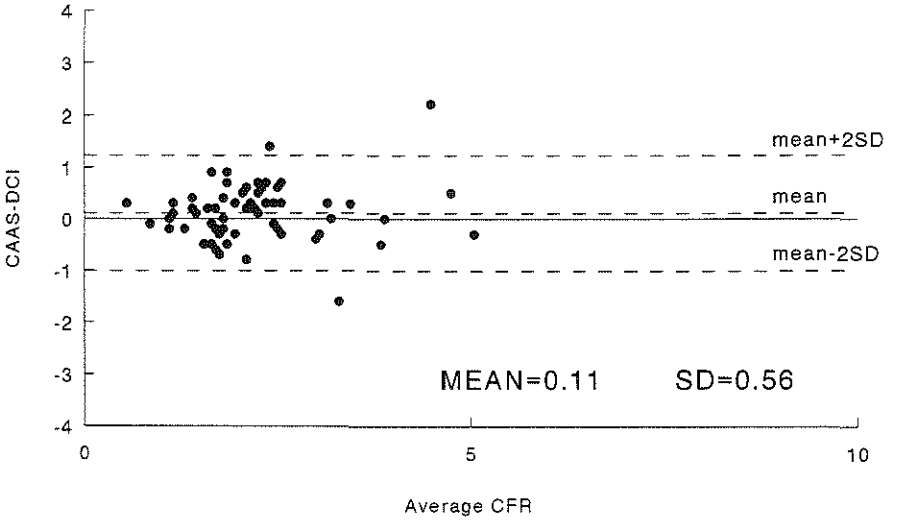

Figure 5
Comparison of digital and cinefilm measurements according to the method of Altman and Bland [16], excluding 2 patients with high values for CFR as assessed by the CAAS system.

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 nor by quantitative measurement of its geometric dimension [17,18]. Additional assessment of myocardial blood flow provides better insight in the functional significance of a coronary stenosis [2,19]. Furthermore, assessment of CFR provides information concerning the specific characteristics of myocardial perfusion in patients with cardiomyopathy and syndrome X, as well as in those with diffuse coronary artery disease, as present in cardiac transplant recipients. Finally, the influence of different treatment strategies on myocardial perfusion can be assessed by 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.
Validation studies of videodensitometric CFR measurements on myocardial regions of interest have shown excellent results [12,20]. Animal experiments using microspheres revealed a good relation between videodensitometric measurements of CFR and the application of microspheres (N=86, r=0.79, $y = 0.58 + 0.81\ x$, SEE = 0.80) [12]. In vivo validation studies using intravascular Doppler assessment of blood flow velocity are eminently relevant because of the differences in methodological approach of both techniques. In a study of 21 patients undergoing elective PTCA for angina pectoris [20], videodensitometric CFR measurements (VD) 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 limited by the severity of the stenosis ($VD = 0.88\ DOP + 0.12$, $r = 0.85$, SEE + 0.38) only, or whether additional factors were present with potential influence on the outcome of CFR measurements like left ventricular hypertrophy or coronary artery dissection ($VD = 0.96\ DOP + 0.01$, $r = 0.87$, SEE = 0.34).

However, since the analysis of the cineangiogram includes the selection of ROI's on the end-diastolic images, and the boundaries are drawn by the observer using a writing tablet, interfaced with the computer, the videodensitometric procedure can introduce some interobserver variability. 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 [21]. 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 taken 5 minutes apart and including 13 regions of interest, was -0.02 ± 0.26, the medium-term variability, based on repeated coronary cineangiograms within 1 - 3 hours, 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.

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 was performed at the Thoraxcenter. In 17 patients with single vessel coronary artery disease, and 12 patients with normal coronary artery dimensions, a good relation was found 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 [20,21] a normal CFR was defined as greater or equal to 3.4 (2 SD below the mean CFR of angiographically normal coronary arteries).

In the current 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 CFR is measured, which is not an unexpected finding in such a group of patients [22].

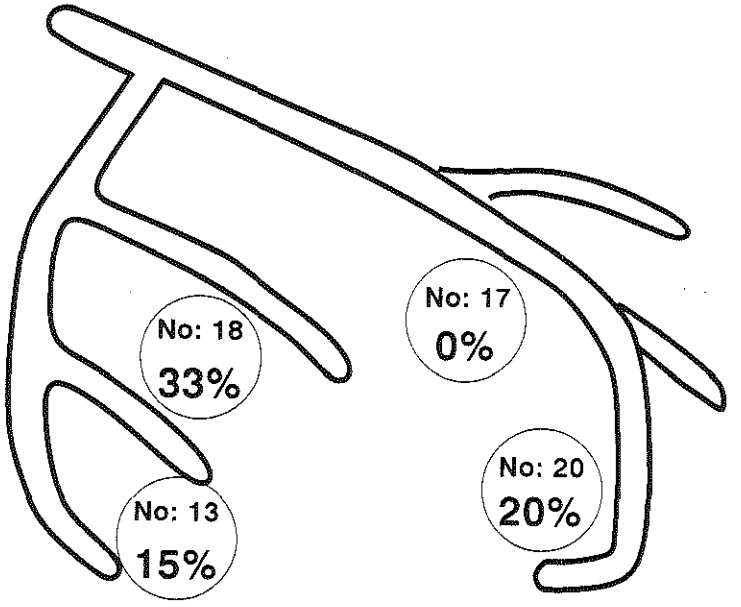

Figure 6
Distribution of the 68 ROI's over the myocardium with reference to the coronary artery tree. In bold the percentage of ROI's having a normal CFR is given.

The results of this study show that where estimated CFR was ≤ 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. A few methodological differences between both systems may account for this discrepancy. Despite the applied logarithmic substraction technique, non-linear terms may remain in the transfer function between contrast and videosignal level, as a result of the different sign for the relation between the local amount of contrast and the resulting video brightness (i.e. negative for DCI and positive for CAAS). The DCI shows non-linear amplification stages during the processing of the images. On cinefilm the relation between light exposure and its resulting optical transparency is not linear.

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, however, uses a threshold of 50% of maximal pixel intensity for the calculations of contrast arrival time 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 used in this study, may disturb blood flow less than ionic agents [15,23]. Furthermore, because longterm variability is 0.11 ± 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 [24] 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 systems it is reasonable to propose the use of the off-line technique to assess CFR in large multicenter trials where cinefilm is used.

Acknowledgements:

We gratefully thank Jurgen Ligthart for his technical assistance and Cornelis J. Slager for reviewing the manuscript. This study was supported by grant no. 88.240 of the Dutch Heart Foundation, The Hague.

	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

Table 1: Reproducibility of the digital subtraction technique (21).

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Chapter 9

Can Intracoronary Ultrasound Correctly Assess the Luminal Dimensions of Coronary Artery Lesions? A Comparison with Quantitative Angiography

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(submitted to the European Heart Journal)

ABSTRACT

In 62 patients with angina pectoris Canadian Class III and IV, the luminal dimensions of 25 pre-PTCA and 56 post-PTCA lesions which could be examined with a 4.3 F 30MHz mechanical ultrasound imaging catheter without wedging, were analyzed off-line using ultrasound cross-sectional area (U-CSA) measurement from s-VHS-video-images ($n=81$). In addition, 54 angiographically normal coronary segments were examined. At the site of the examination, the U-CSA was integrated central to the leading edge echo and the corresponding angiographic cinefilm images were analyzed with edge detection technique using the Cardiovascular Angiography Analysis System. The obstruction diameter (at the lesions) and the mean vessel diameter (at normal sites) were used to calculate the angiographic cross-sectional area (A-CSA) assuming a circular model. U-CSA values were compared with the corresponding A-CSA values using t-test and linear regression analysis.

Results: U-CSA overestimates A-CSA ($p<0.0001$). An acceptable correlation was found between U-CSA and A-CSA values at normal coronary segments (correlation coefficient: $r=0.73$). The correlation was poor at the site of pre-PTCA lesions ($r=0.62$) and deteriorated following PTCA ($r=0.47$). No correlation was found between the degree of lumen eccentricity measured with intracoronary ultrasound (ICUS) and the individual differences between U-CSA and A-CSA values.

Conclusion: Poor delineation of the leading edge echo at the site of coronary lesions impairs the correlation between U-CSA and A-CSA assessments. This is less of a problem at angiographically normal coronary segments. Basic methodological differences between both techniques may explain the overestimation of cross sectional areas by ICUS.

INTRODUCTION

Quantitative coronary angiography is currently the "reference method" for the assessment of intracoronary dimensions providing accurate and reproducible assessment of intraluminal lesion diameters (1-10). In addition to quantitative data, intracoronary ultrasound provides tomographic images of the arterial lumen and wall and allows the detection of intimal lesions even at angiographically normal portions of coronary arteries (11,12). The technique enables the clinician to differentiate between fibrous, calcific and lipid containing plaques during the catheterization procedure (13-15).

Although both methods have shown high correlations for the measurement of cross-sectional area and luminal diameter of non-obstructed coronary segments (12,16-18), the reliability of ultrasonic luminal measurements at the site of coronary lesions remains controversial (16,19). Irregularities at the surface of atherosclerotic plaques with inhomogeneous echogenicity and disruptions of the intimal layer following balloon angioplasty complicate identification of leading edge echos and hamper the correct assessment of luminal dimensions (18). Nevertheless, it might become an important issue for the interventional treatment whether intracoronary ultrasound can provide reliable measurements of stenosis dimensions, especially when its combined use with new interventional devices is considered (20-24).

To define the role of intracoronary ultrasound for quantitative assessment of coronary artery lesions, we compared minimal luminal cross-sectional areas obtained with an ultrasonic catheter at the site of coronary lesions before and after PTCA, as well as at angiographically normal segments with the corresponding values derived from the edge detection technique using the new version of the Cardiovascular Angiography Analysis System (25).

METHODS

Patient selection

In 62 patients with symptomatic coronary artery disease, 62 lesions which were selected for PTCA, were examined by intracoronary ultrasound. The pre-PTCA examination of 37 patients (60%) had to be excluded because of a complete occlusion of the coronary obstruction by wedging the ultrasonic catheter (cross sectional area = 1.61 mm^2). In 25 patients (40%), pre-PTCA ultrasonic examination was possible. In 19 of these 25 patients a post-PTCA ultrasonic examination was performed. Thus, in 6 of the 25 patients only quantitative angiography was performed post-PTCA. In the 37 patients without ultrasonic pre-PTCA examination, a post-PTCA ultrasound examination was possible. Thereby, a total of 81 coronary lesions was examined with 25 lesions being examined before PTCA, and 56 lesions beeing examined after PTCA.

From the 62 patients included in this study, 55 were male (89%), and 7 female (11%). Unstable angina Canadian Class IV was present in 43 cases (69%), while 19 patients complained of exertional angina Canadian Class III (31%). In 29 cases, the site of the target lesion was the left anterior descending artery (47%), in 20 cases the right coronary artery (32%), in 10 cases the left circumflex artery (16%), and in 3 cases an aorto-coronary bypass graft (5%). Fifty-five angiographically normal coronary segments of the 31 patients which were included, served as a control for assessment of vessel cross-sectional area by intracoronary ultrasound.

Intracoronary ultrasound examination

Before and immediatly after ballon angioplasty 1-2mg intracoronary isosorbide-dinitrate was administered and a coronary angiogram was performed by hand injection of 10 ml non-ionic contrast medium (iopamidol 370, Bracco, Milano) at 37°C using an 8 or 9F guiding catheter. The angiograms were recorded on cinefilm in two orthogonal projections whenever possible. Following each angiogram a mechanical 4.3 F intravascular ultrasound catheter (INSIGHT"3" ultrasound system, CVIS, Sunnyvale, CA) was introduced over a 0.14" high torque floppy guide wire. The target lesion was examined at a length of at least 2 cm proximal and 2 cm distal to the obstruction and the ultrasonic examination was continuously recorded on s-VHS-videotape. To improve the delineation of the leading edge echo, intracoronary injection of saline was applied when necessary. After a careful review of each videotape recording, one image at the site of the minimal luminal cross sectional area before and after PTCA was selected, the measurement system was digitally calibrated, and the respective minimal luminal cross-sectional area was measured off-line as the area within the leading edge echo of the arterial wall (Fig 1).

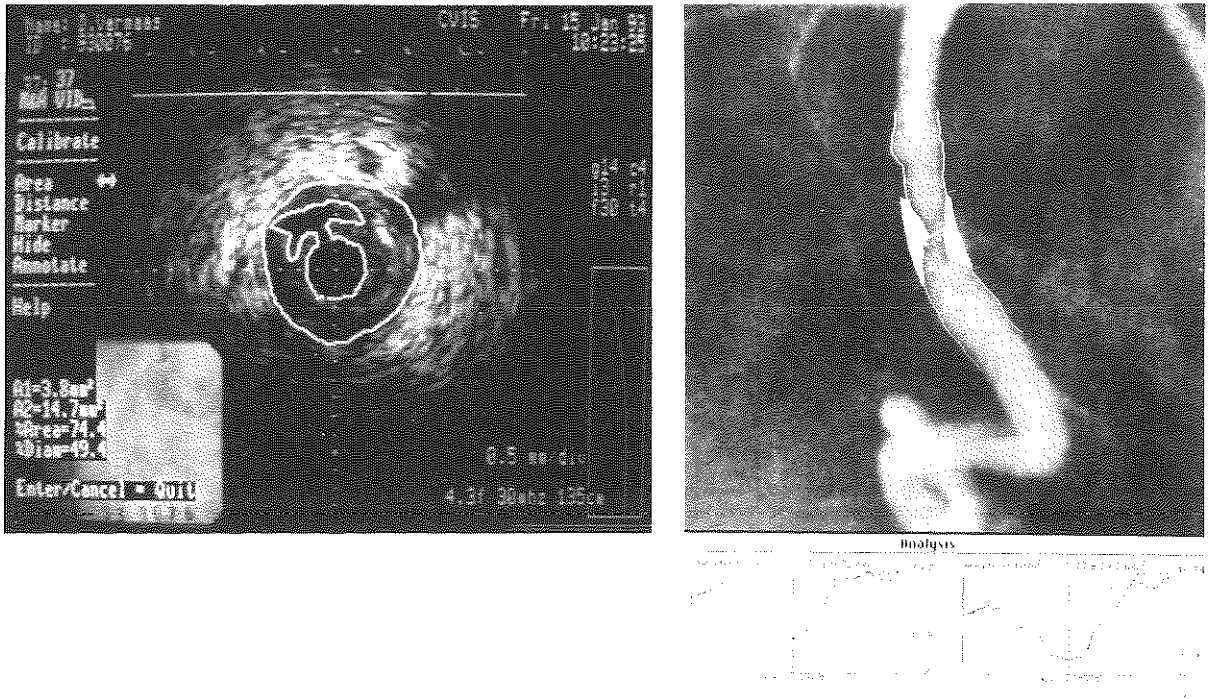

Figure 1 A
Intracoronary ultrasound image of a pre-PTCA proximal right coronary artery stenosis with planimetric assessment of minimal luminal cross-sectional area (left) and computer-assisted measurement of the obstruction diameter at the corresponding cineangiographic image (right).

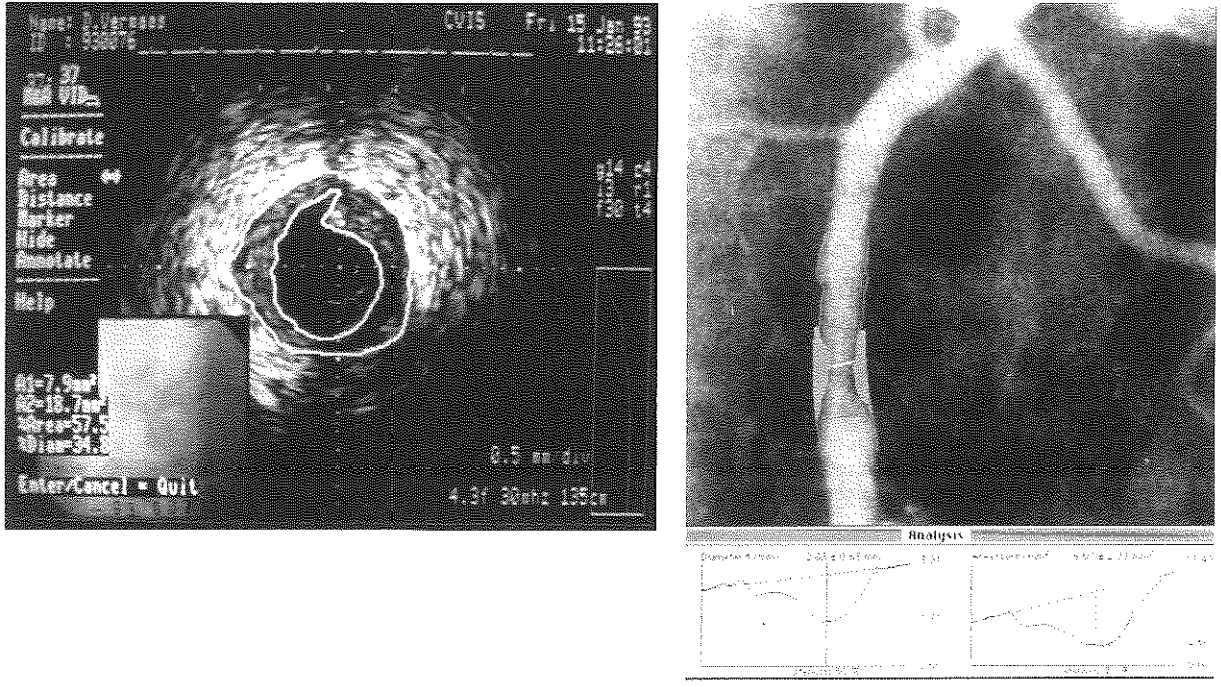

Figure 1 B
Corresponding post-PTCA images obatined by intracoronary ultrasound for minimal luminal cross-sectional area measurement (left) and obstruction diameter assessment by quantitative angiography (right).

Edge detection analysis of coronary angiograms

The cinefilms were processed routinely and from each angiogram acquired before and after balloon angioplasty an enddiastolic frame with optimal contrast filling and without forshortening of the segment of interest or superimposition of other vessels or stuctures was selected, the catheter tip was used for calibration, and quantitative analysis was performed using the new version of the Cardiovascular Angiography Analysis System (PieMedical, Maastricht, The Netherlands). In this system, an operator independent edge detection algorithm based on the first and second derivative function on the brightness profile of scanlines perpendicular to a previously defined pathline within the contrast filled vessel is used to compute the obstruction diameter at the site of the lesion (25).

Comparison of both techniques

Twenty-five matched ultrasonic and angiographic images obtained pre PTCA and 56 matched images acquired after PTCA were available for quantitative analysis (n=81). The comparison between both techniques was based on the assessment of the minimal luminal cross-sectional area with intracoronary ultrasound and the corresponding area value derived from the obstruction diameter obtained by CAAS. When biplane angiographic images (70%) were available for analysis, the mean of the two corresponding obstruction diameters was taken, while in monoplane angiographic images (30%), the single obstruction diameter value was used to calculate a mimimal luminal cross-sectional area assuming a circular model.
The cross-sectional areas of 54 angiographically normal coronary reference segments were assessed by intracoronary ultrasound and compared with the respective angiographic area values derived from the mean vessel diameter.

Calculation of eccentricity

To determine the lumen eccentricity of the coronary lesions, an eccentricity index was calculated from the ultrasound images as the largest diameter of the luminal cross sectional area divided by the shortest diameter at the site of the obstruction (16). The eccentricity values of all lesions were used for a comparison with the individual differences in minimal luminal cross sectional area and obstruction diameter assessment between both techniques.

Interobserver Variability

The planimetric assessment of lesion cross-sectional areas on identical ultrasound videoframes was performed by two independent observers. Interobserver variability was calculated in 20 cases before PTCA and in 20 cases after PTCA, as well as for the combined group of 40 cases.

Statistical Analysis

The agreement of cross-sectional area values from both techniques was analyzed by calculation of the mean $\pm$ standard deviation of signed differences, by application of the t-test, and by a linear regression analysis. Differences were considered to be statistically significant at $p < 0.05$. The individual differences between the measurement series were compared with the individual values of eccentricity from intracoronary ultrasound using a linear regression analysis. Interobserver variability was assessed by paired t-test as well as by linear regression analysis.

RESULTS

Cross-sectional areas at angiographically normal coronary segments

The comparison of 42 corresponding cross-sectional area assessments by intracoronary ultrasound and quantitative angiography at angiographically normal segments of the coronary arteries gave an acceptable correlation between both techniques ($r=0.73$, $y=3.15+0.66x$, $SEE=1.09$) with a mean difference of 1.44 ± 1.22 mm^2 (Fig 2). Intracoronary ultrasound significantly overestimated the corresponding cross-sectional area values derived from quantitative angiography ($p<0.0001$).

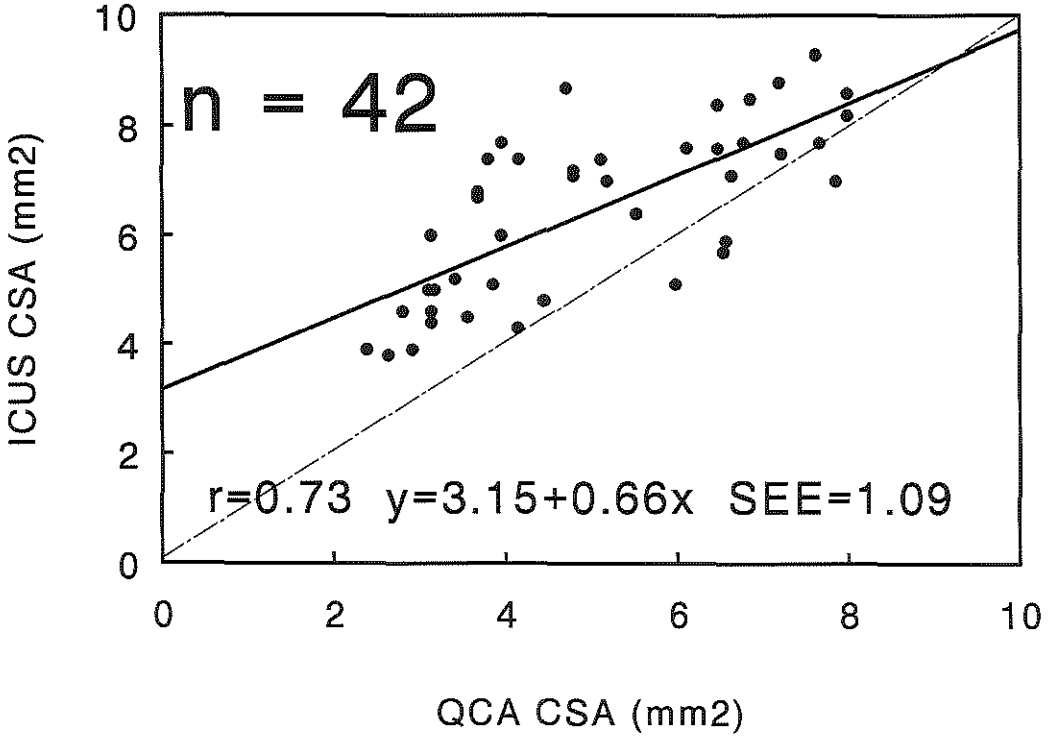

Figure 2
At angiographically normal coronary segments, cross-sectional area assessments by intracoronary ultrasound (ICUS) and cross-sectional area calculations derived from quantitative coronary angiography (QCA) show good agreement (correlation coefficient: r=0.94, y=1.15+1.13x, SEE=3.02), although the overestimation of QCA values by ICUS (mean difference = 2.19±3.15mm²) is statistically significant (p<0.01).

Cross sectional-areas at the site of coronary lesions

The comparison of 81 corresponding cross-sectional area assessments at the site of the coronary lesions before and after PTCA resulted in a mean difference of 1.44 ± 1.95 mm^2 with a significant overestimation of the area values as assessed by intracoronary ultrasound ($p < 0.0001$). The intracoronary ultrasound catheter did not wedge in a great number of lesions where quantitative coronary angiography indicated a cross-sectional area below the cross-sectional area of the ultrasonic device (1.61mm^2) (Fig 3A). At the site of coronary lesions, the correlation between cross-sectional area assessments by both techniques was poor ($r=0.60$, $y=3.14+0.52x$, $SEE=1.61$).

When cross-sectional area values pre PTCA were compared with the corresponding values derived from quantitative angiography ($n=25$), a mean difference of 1.81 ± 1.14 mm^2 was observed. The exclusion of post PTCA lesions resulted in an increase of the slope of the regression line with a limited improvement of the correlation between both techniques ($r=0.62$, $y=2.22+0.78x$, $SEE=1.14$) (Fig 3B). However, the overestimation of angiographic measurements by intracoronary ultrasound was similar ($p < 0.0001$). In segments of small cross-sectional area, intracoronary ultrasound continued to indicate a free unwedged lumen even when QCA indicated a cross-sectional area less than the intracoronary ultrasound catheter size.

Post-PTCA lesions gave the worst correlation between cross-sectional area measurements from intracoronary ultrasound and quantitative coronary angiography ($r=0.47$, $y=3.87+0.40x$, $SEE=1.72$) (Fig 3C). The mean difference between both measurement series was 1.28 ± 2.20mm^2 and intracoronary ultrasound showed a significant overestimation of angiographically assessed cross sectional areas ($p < 0.0001$). However, due to the effect of PTCA, the discrepancy between cross-sectional area of the intracoronary ultrasound catheter and the area as assessed by quantitative coronary angiography has almost completely disappeared.

Lumen eccentricity

Lumen eccentricity at the site of the lesion did not correlate with the individual differences between minimal cross-sectional area assessment by intracoronary ultrasound and edge detection technique; similar results were obtained for pre PTCA ($r=-0.25$) as well as for post PTCA lesions ($r=-0.14$). At normal coronary segments, however, a modest correlation between eccentricity and differences in area measurement between intracoronary ultrasound and quantitative angiography was observed ($r=0.73$).

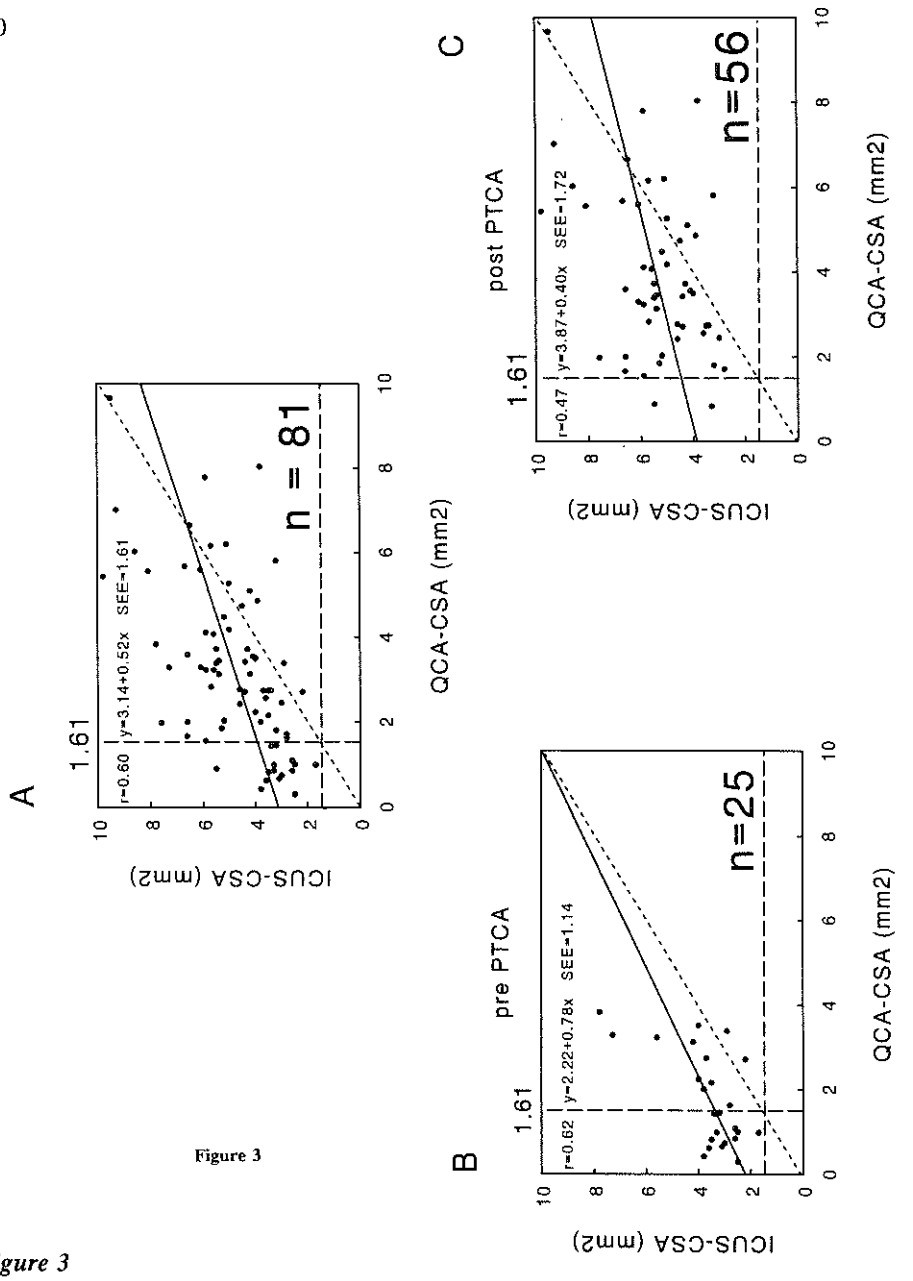

Figure 3

Figure 3

At the site of coronary lesions, the correlation between cross-sectional area assessment by intracoronary ultrasound (ICUS) and quantitative coronary angiography (QCA) is modest:

A. Minimal luminal cross-sectional areas (CSA) by ICUS versus CSA by QCA (obstruction diameters (r=0.60, y=3.14+0.52x, SEE=1.61).

B. Minimal luminal cross-sectional areas (CSA) by ICUS versus CSA by QCA at pre-PTCA lesions (r=0.62, y=2.22+0.78x, SEE=1.14).

C. Minimal luminal cross sectinal areas (CSA) by ICUS versus CSA by QCA at post-PTCA lesions (r=0.47, y=3.87+0.40x, SEE=1.72).

The dotted lines represent the lines of identity. The dashed lines delineate the cross sectional area of the ultrasonic catheter (1.61mm²).

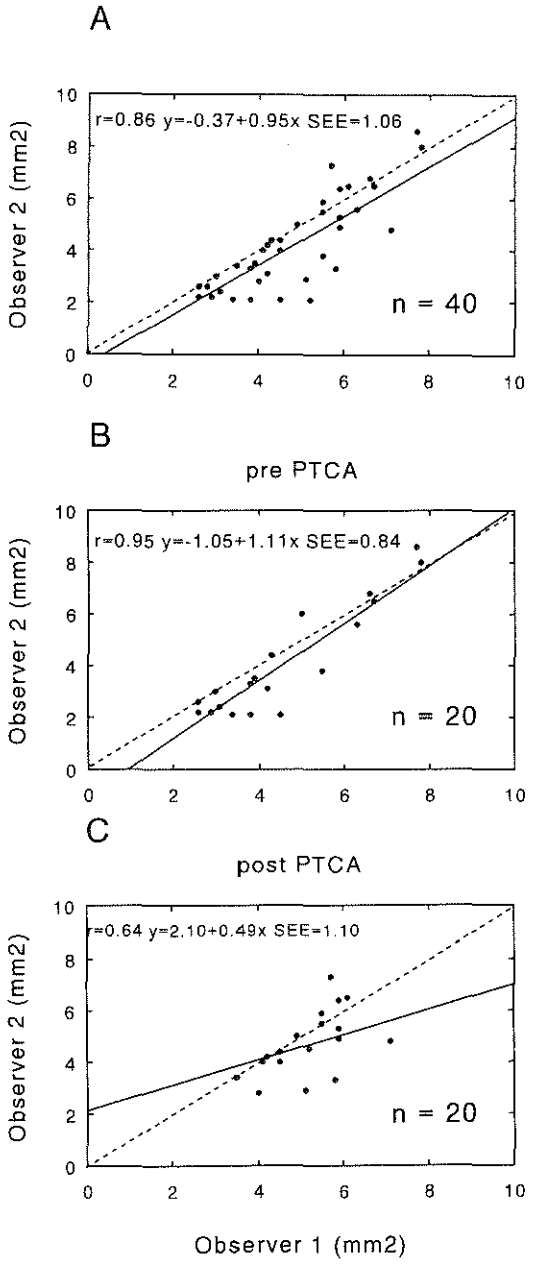

Figure 4

Figure 4

At the site of coronary lesions, assessment of minimal luminal cross-sectional areas with intracoronary ultrasound by two observers shows good agreement;

A. Correlation between the cross-sectional area assessments of all lesions by two independent observers (n=40).

B. Correlation between the cross-sectional area assessments of pre-PTCA lesions by two independent observers (n=20).

C. Correlation between the cross-sectional area assessment of post-PTCA lesions by two independent observers (n=20).

Interobserver Variability

The mean difference of the measurements of all lesion cross-sectional areas by both observers was $0.61 \pm 1.05 mm^2$ and was statistically significant ($p < 0.001$). Figure 4 A shows the correlation between the two series of measurements ($r = 0.86$, $y = -0.37 + 0.95x$, $SEE = 1.06$). The two observers yielded an excellent correlation in the subgroup of pre-PTCA lesions ($r = 0.95$, $y = -1.05 + 1.11x$, $SEE = 0.84$) (Fig 4B). In this group, the mean difference between the area assessment of both observers was $0.48 \pm 0.85 mm^2$ with a lower level of significance ($p < 0.05$). The worst correlation was obtained with post-PTCA lesions ($r = 0.64$, $y = 2.10 + 0.49x$, $SEE = 1.10$) (Fig 4C). In spite of the relatively high mean difference between both observers ($0.79 \pm 1.40 mm^2$) the degree of statistical significance was low ($p < 0.05$) due to the high scattering of measurement values.

DISCUSSION

Potential advantages of intracoronary ultrasound

Although the use of intracoronary ultrasound for quantitation of coronary artery obstructions is still investigational, the technique has potential advantages over quantitative coronary angiography. While quantitative angiographic analysis requires a complex calibration procedure using the diameter of an angiographic catheter tip as a reference, the ultrasound measurements are based on the wavelength and velocity of ultrasound in blood. Thereby, possible angiographic sources of measurement error due to image distortion or out of plane magnification of the catheter tip (25-27) as well as the potential variability of catheter dimensions (28) are circumvented. Moreover, intracoronary ultrasound provides continuous monitoring of tomographic images of the arterial lumen and wall without the necessity of contrast injections and use of X-radiation. Finally, ultrasonic tomography allows the quantitation of atherosclerotic alterations in the arterial wall at a stage in which the luminal dimensions are not yet affected (11,12).

Previous studies comparing both techniques

Several investigators have reported good correlations between vessel cross-sectional areas at angiographically normal coronary arteries obtained by intracoronary ultrasound and edge detection measurements (12,16,17). Tobis et al., however, reported a marked discordance between arterial cross-sectional areas as assessed by intracoronary ultrasound and quantitative angiography as well as a significant overestimation by intracoronary ultrasound (19). In general, less agreement between intracoronary ultrasound and quantitative angiography was observed in coronary lesions following PTCA (23), and there was some evidence for a possible relation beweeen lumen eccentricity at the site of coronary lesions and the deterioration of correlation (16,21).

Intracoronary ultrasound and quantitative angiography at normal coronary arteries

According to the recent study of J. Hodgson et al. (23), the results of the present investigation show a moderate correlation for arterial cross-sectional areas at angiographically normal coronary segments ($r=0.73$). Similar to the results of Tobis et al. (19), however, a significant overestimation of area values by ultrasound is observed ($p < 0.0001$).
Basic methodological differences between direct ultrasonic imaging of arterial cross-sections

and area estimations derived from the shadowgram of the contrast filled lumens may explain such differences. In case of an elliptical shape of the coronary cross-sectional area, its assessment by intracoronary ultrasound is clearly superior to quantitative angiography, since coronary angiography even in two projections is unlikely to visualize the coronary artery in a projection which is orthogonal to the longest elliptical axis. As a result, true arterial cross-sectional area is underestimated by angiography. Furthermore, the position of the ultrasonic catheter tip within the angiographically normal artery or successfully dilated lesion can produce elliptic image distortion if the axis of the catheter tip is not parallel to the long axis of the artery which is more likely in curved than in straight vessels. This situation would lead to an overestimation of vessel cross-sectional areas by intracoronary ultrasound (34).

Intracoronary ultrasound and quantitative angiography at coronary lesions

Very little has been published on the ultrasonic cross-sectional area estimation at the site of coronary lesions (16). In comparison to the results from angiographically normal coronary arteries (22), our findings at the site of coronary stenoses show a much worse correlation of cross-sectional area assessment by intracoronary ultrasound and quantitative angiography ($r=0.60$, $y=3.14+0.52x$, $SEE=1.61$). The irregular surface of coronary obstructions with heterogenous echogenicity may explain this observation. It is not surprising that the linear regression analysis shows some improvement when the observation is confined to pre-PTCA lesions ($r=0.62$, $y=2.22+0.78x$, $SEE=1.14$). Before balloon angioplasty, obstructive coronary lesions often show a less irregular intimal surface and plaque disruptions or dissections are not yet present in most cases. Nevertheless, pre-PTCA lesions demonstrated a relatively high mean difference between cross-sectional area assessments by intracoronary ultrasound and quantitative angiography ($1.81\pm1.14mm^2$). This discrepancy is illustrated by the fact, that even below the angiographically assessed area of 1.61 mm^2 (cross-sectional area of the ultrasonic catheter), intracoronary ultrasound continues to visualize free intracoronary lumen without complete wedging of the lesion (Fig 3 B). Theoretically, this finding could be explained by the fact that the nose cone of the ultrasonic catheter might alter the morphology of the lumen area by tacking back soft material protruding within the lumen, thus creating a larger cross-sectional area than obtained by angiography (Fig 5B). This mechanism is supported by the finding of angioscopic studies in patients with unstable angina, where the surface morphology of soft lesions is described (29). In the presence of incompressible (calcified) lesions, stretching of the adjacent vessel wall due to insertion of the ultrasonic catheter may account for overestimation of minimal luminal cross-sectional areas (Fig 5C). Another possible explanation of cross-sectional area overestimation by intracoronary ultrasound at the site of stenotic lesions might be the fact that in case of impossible passage of the catheter nose cone, the more proximal position of the mirror may suggest a wider cross-sectional lumen area than present within the tightest site of the obstruction (Fig 6). These potential sources of cross-sectional area overestimation by intracoronary ultrasound are supposed to be eliminated by successful angioplasty. Accordingly, we found a lower mean difference between intracoronary ultrasound and quantitative angiography in post-PTCA lesions ($1.28\pm2.20mm^2$). However, balloon angioplasty deteriorates the echogenic properties of the intima creating disruptions and

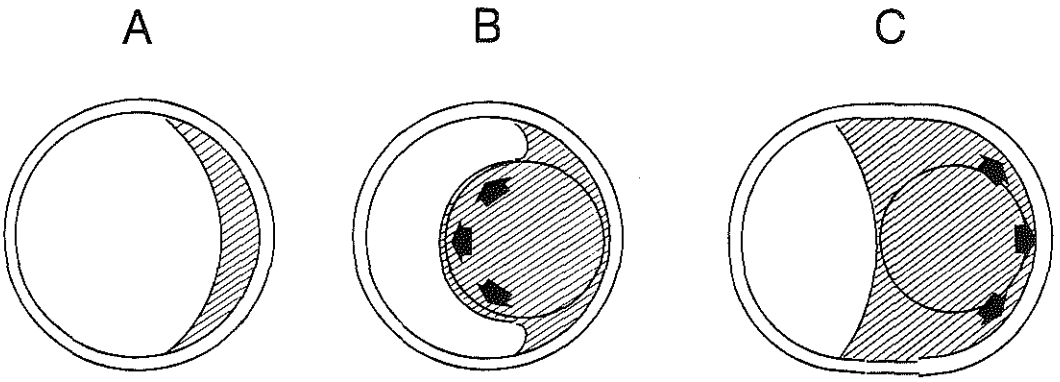

Figure 5
Potential mechanisms of lesion reshaping by the intracoronary ultrasound catheter:
A: Minimal luminal cross-sectional area below the cross-sectinal area of the ultrasonic catheter (1.61 mm²).
B: At soft coronary obstructions, the ultrasonic catheter may compress the lesion, thus creating an overestimation of minimal luminal cross-sectional area.
B: At the site of incompressible coronary lesions, overestimation of minimal luminal cross-sectional area may be produced by distension of the vessel wall.

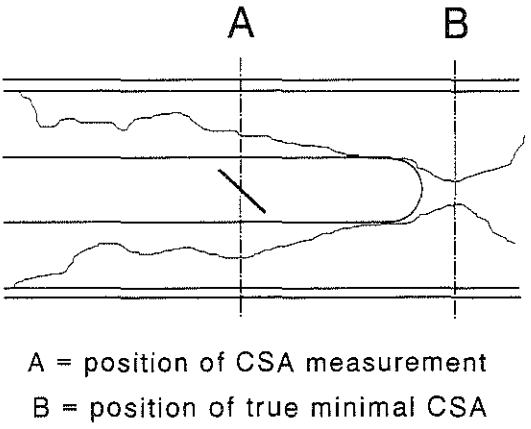

Figure 6
In case of impossible passage of the ultrasonic catheter nose cone, the more proximal position of the mirror may suggest a wider cross-sectional luminal area than present within the tightest site of the obstruction.

dissections by which the continuity of the leading edge echo is interrupted and the planimetric integration of minimal luminal cross-sectional areas is hampered and decreased. As a result, the correlation between ultrasonic and angiographic assessment of cross-sectional areas deteriorates in this group ($r=0.47$, $y=3.87+0.40x$, $SEE=1.72$).

Lumen eccentricity

Similar to the results of Nissen et al. (16), we have found a positive correlation between lumen eccentricity and the individual differences between cross-sectional area assessment by intracoronary ultrasound and quantitative angiography at angiographically normal coronary artery segments ($r=0.73$). The limitation of correct area estimations by angiographic imaging in two projections in case of elliptically shaped vessel cross-sections may explain the discrepancy between both techniques. In contrast to these results, however, we found no correlation between lumen eccentricity and individual differences in cross-sectional area assessments between both techniques at the site of coronary lesions. Irregular endothelial surface and vessel wall disruptions producing heterogenous edge echos may explain this finding.

Interobserver variability

Similar to previous studies (16,19), we found a relatively low degree of interobserver variability for the assessment of lesion cross-sectional areas by intracoronary ultrasound. It is not surprising that the best correlation between two independent observers was found in pre-PTCA lesions ($r=0.95$), where irregular endothelial surface and wall disruptions are less frequent than in post-PTCA lesions which showed a weaker interobserver correlation ($r=0.64$).

Limitations of the study

It has to be pointed out that a comparison of luminal dimensions assessed by intracoronary ultrasound and quantitative coronary angiography is limited by the differences in methodology. Since coronary angiography cannot be carried out simultaneously with the ultrasonic examination because the presence of the ultrasonic catheter within the segment of interest disturbs the angiographic image and impairs the run-off of contrast medium, off-line determination of the corresponding position of cross-sectional area assessment cannot always be avoided and implies non-exact spatial as well as temporal correspondence of the examined

site. This problem is most prominent at the site of tight coronary lesions, where the nose cone of the ultrasonic catheter wedges the obstruction while the mirror being more proximally located provides a larger cross-sectional area.

Several studies have confirmed that intracoronary ultrasound is more sensitive than angiography in the detection of plaque ruptures (11,30-33) which represents another potential reason for a relative overestimation of lesion cross-sectional area in comparison with the corresponding value derived from angiography; any plaque disruption or arterial wall dissection which is detected by intracoronary ultrasound but not filled out with contrast medium (stagnant blood or thrombus) may contribute to the observed overestimation of vessel cross-sectional areas by intracoronary ultrasound. Elliptic image distortion on the other hand, which might explain overestimations of lumen cross-sectional areas in angiographically normal coronary arteries (35), is less probable at the site of coronary obstructions, where the position of the ultrasonic catheter is normally stabilized by the vessel wall.
Although the above mentioned differences in methodology will persist, it can be expected that the limited resolution of intracoronary ultrasound technique (0.018mm), which reputedly impairs the visualization of coherent edge echos at the irregular surface of atherosclerotic lesions by drop out phenomena, will be improved and the guidewire artefact will be eliminated in the near future.

Conclusion

In conclusion, arterial cross-sectional area assessment by intracoronary ultrasound significantly overestimates the corresponding values derived from quantitative angiography. The modest correlation between both techniques at the site of coronary lesions can be explained by basic methodological differences and the limited resolution of intracoronary ultrasound imaging.

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Chapter 10

Impact of Luminal Morphology in the Estimation of Vessel Cross Sectional Area Using Intravascular Ultrasound and Quantitative Coronary Angiography: An In Vitro Study Using Casts of Human Coronary Arteries

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INTRODUCTION

Although the development of quantitative angiography during the last 10 years has contributed to maintain coronary angiography as the ultimate reference method in the diagnosis of atherosclerotic disease, new and unexpected demands for the technique continue to appear. The generalization of percutaneous coronary interventions and the concommitant widespread use of quantitative angiography have demonstrated that in a variety of clinical situations even computerized analysis of the angiograms provide inaccurate results. This is particularly the case of arterial segments that contain complex atheromatous plaques (1) or that have undergone percutaneous intervention (2-6). Catheter-based ultrasound imaging has the potential to solve many of the demands posed by interventional cardiology to coronary angiography (7), among them to serve as an alternative to quantitative angiography in the estimation of coronary luminal dimensions (8,9).

However, intracoronary ultrasound may be far from being a new gold standard for the quantification of lumen size. As more experimental information is gained on the potential sources of error of ultrasonic measurements (10,11), initial results from the clinical application of intravascular ultrasound reveal that major disagreement with quantitative angiography is common, particularly in the context of balloon dilatation (12-14). The interpretation of these discrepancies is limited by the lack of information on the morphology and actual dimensions of the segment studied with both techniques and the lack of information on the influence that lumen morphology has on the interobserver variability and precision of intravascular ultrasound planimetry.

To shed further light on this topic we investigated the variability of luminal measurements obtained with intravascular ultrasound imaging and quantitative angiography in two types of phantoms. The first were obtained from atheromatous human coronary arteries using a negative cast technique, and showed a luminal morphology with variable degrees of irregularity and eccentricity. The second were precision drilled phantoms with smooth circular morphology. In both types of phantoms luminal areas and eccentricity were documented. Using intravascular ultrasound, 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. The findings were compared with similar measurements obtained with quantitative angiography.

METHODS

Epoxy phantoms

Coronary phantoms were obtained from 3 coronary arteries showing diffuse and extensive atherosclerotic disease which were obtained during separate post-mortem studies. The technique of negative casting was developed by Doriot et al. (15) and has been previously used by in vitro 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 in a Teflon mold an casting with epoxy resin. On each epoxy blocks regular slices of few millimeters were obtained by sawing with a rotating disk of 0.3 mm 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 cross-sections 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 cross-sections was 0.28 mm^2. The area at each particular section was obtained as 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 lumens with fixed diameters of 2 to 5 mm were precision-drilled.

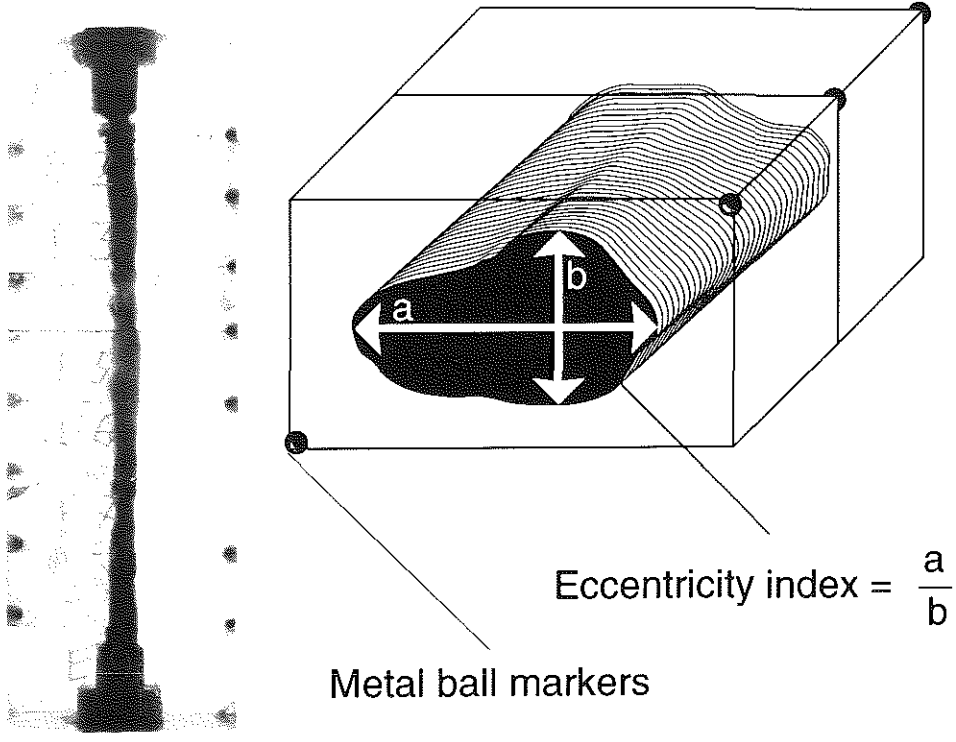

Figure 1

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.

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 of 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 simmulate 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 an orthogonal (90°) angulation. The obtained cineangiograms were processed routinely and analyzed quantitatively.

The films were analyzed in a 3rd generation edge detection quantitative angiography system (CAAS 2, Pie Data, Maastricht, The Netherlands) (16,17). The first step in the analysis consisted in the selection of an angiographic frame showing the phantom section in the angiographic isocenter. The position of the section was facilitated by metal balls acting as radiopaque markers. Using a high-fidelity charge couple device (CCD) videocamera, a region of interest of 512X512 pixels enclosing the section was digitized. Following the identification of the vessel centerline by the computer algorithm, a number of scanlines perpendicular to it were obtained. Luminal edges were detected on the basis of a weighted sum of the first and second derivative function of the brightness profile of each of these scanlines. From the identified luminal contours the vessel diameter function was determined by computing the shortest distance between the left and right edge positions. Finally, the diameter of the vessel at the level of the analysed section was measured at the level of the radiopaque markers (Figure 1). These measurements were converted to absolute values by using an empty coronary guiding catheter of known dimensions that was filmed along the phantom. Using the obtained luminal diameter of the section, luminal area was calculated using a circular model.

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 difference 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±1.62 mm^2 (range 6.40-13.01 mm^2), while in the circular phantoms was 10.59±6.62 mm^2 (range 3.14-19.63 mm^2). In the coronary phantoms the eccentricity of the lumen was 1.17±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. The degree of agreement between these values and the mean difference between both measurements and its standard deviation is given in Table 1. In the coronary phantoms the correlation coefficient and mean difference± SD between measurements obtained by both observers were 0.77 and 0.80±0.98 mm^2 respectively, while in the circular phantoms the obtained values were 0.99 and -0.81±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±0.71 mm^2 in the coronary phantoms, and 0.99 and -0.08±0.39 mm^2 in circular phantoms respectively (p=0.012) (statistically significant for absolute differences as well) (Figure 3, Table 2). 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 ± 1.30 mm2 and 9.73 ± 5.32 mm2 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 ± 0.67 mm2) and circular phantoms ($r=0.99$, mean difference 0.86 ± 1.38 mm2) (Figure 4, Table 3). There was no statistically significant difference 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 angiography 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 ($r=0.40$, $p=0.06$).

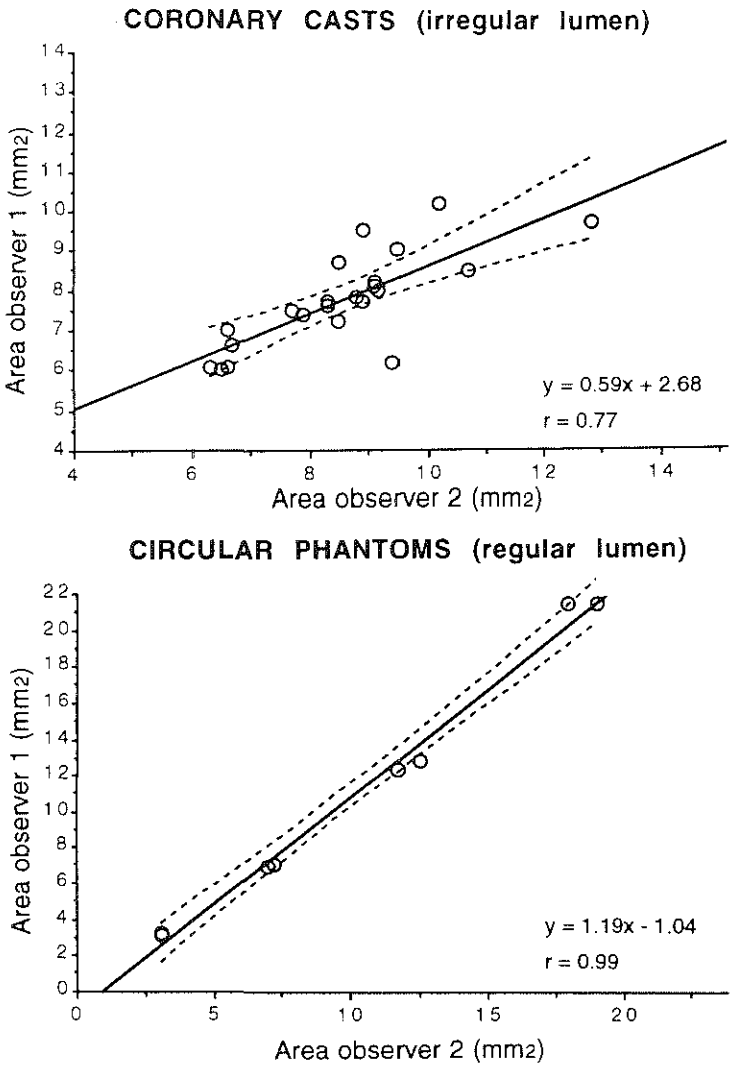

Figure 2

Correlation between luminal area measurements obtained with intravascular ultrasound imaging obtained by two independent observers in coronary and circular phantoms.

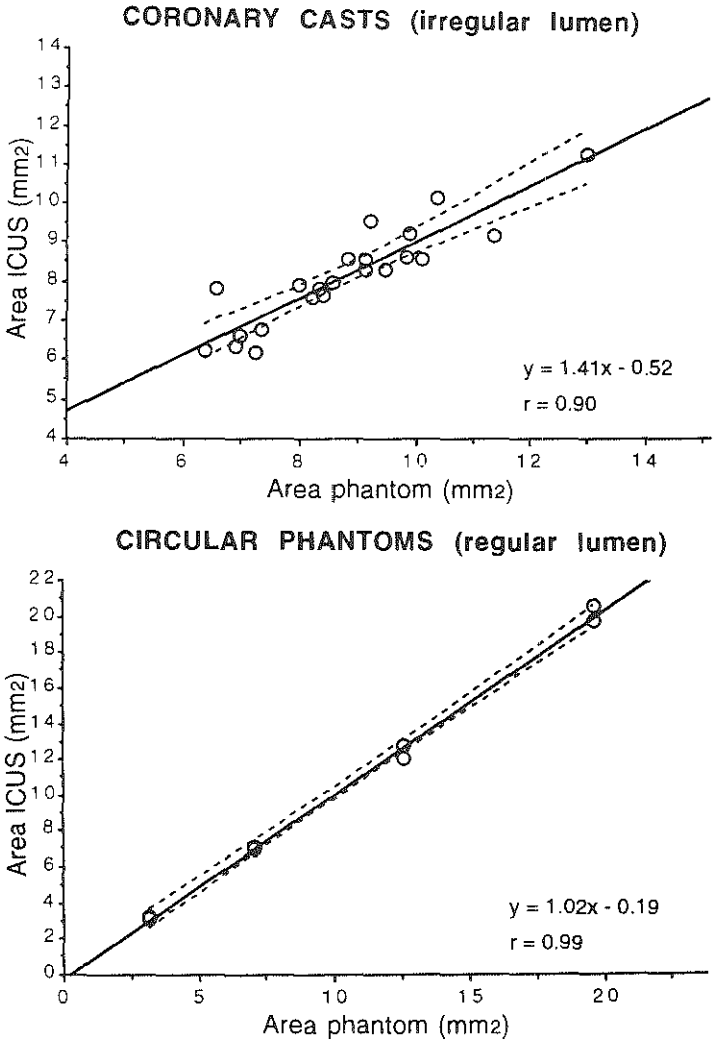

Figure 3

Correlation between phantom dimensions and luminal area measurements obtained with intravascular ultrasound imaging (average of both observers) in coronary and circular

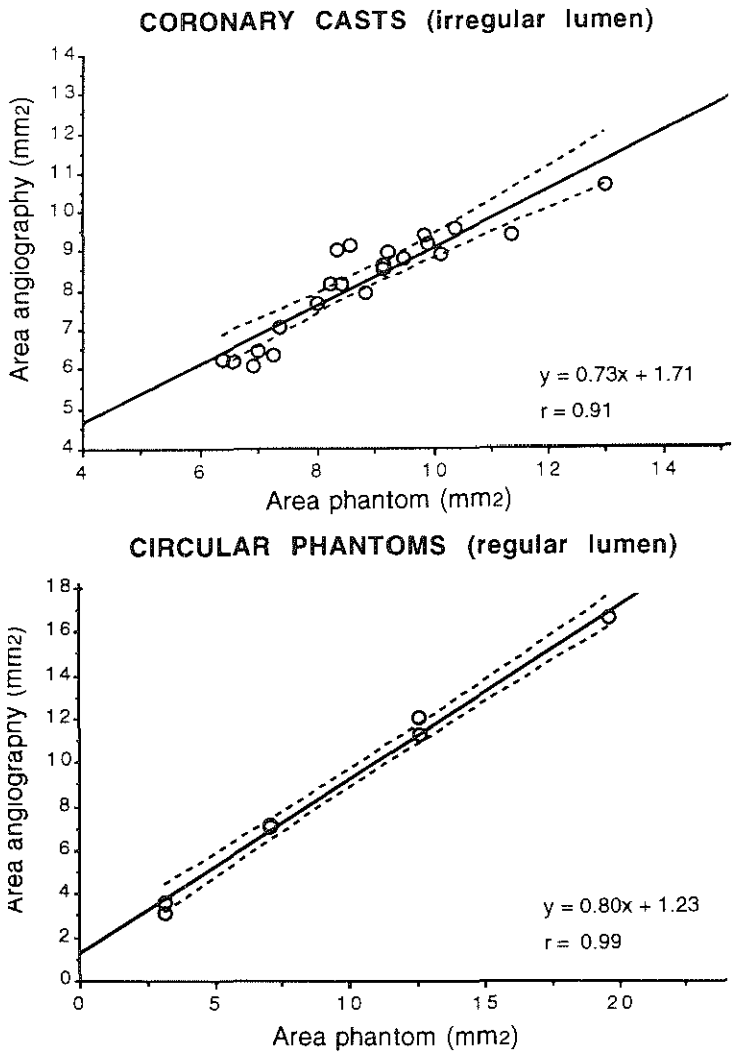

Figure 4

Correlation between phantom dimensions and luminal area measurements obtained with quantitative angiography (two orthogonal views averaged) 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). Several authors have shown that the accuracy of quantitative angiographic measurements decreases immediately after balloon angioplasty (2-5). So far, the alternative use of videodensitometry, which theoretically is independent of luminal morphology and angulation used, have failed to provide a practical solution to this problem (4-6,24). In this context, the possibility of using intravascular ultrasound to estimate luminal area by planimetry appears as an attractive alternative (8-9). Previous work in experimental conditions demonstrated a good correlation between IVUS and histological measurements (25-27), although little emphasis was put on the influence of luminal morphology in the measurements. When the application of intravascular ultrasound has been tested in the clinical field the results are more controversial. A good correlation between quantitative coronary angiography and intravascular ultrasound measurements in normal vessels and even in atherosclerotic vessels with circular luminal contour (13). On the contrary, just a moderate correlation at normal sites has been reported by other authors (28) or even no correlation (14,28) has been found in similar studies performed after balloon angioplasty.

From the results obtained in clinical studies it is not possible to infer whether measurements with IVUS represent a better estimate than those obtained with quantitative angiography, since there is no standard with which compare both techniques. 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 present study was design as a compromise between the need of testing both techniques in the laboratory in a controlled fashion and the use of reliable phantoms with a luminal morphology representative of that found in atherosclerotic vessels.

The first conclusion of this study is that luminal morphology affects the reliability of luminal area measurements obtained with intravascular ultrasound imaging. Part of this phenomenon may be due to increased interobserver variability in phantoms with an irregular cross-section. Like in the case of coronary angiography, the subjective identification of the luminal borders may cause this problem. The results suggest that a more circular morphology facilitates accurate tracing of the luminal borders, since the observer is guided by his perception of a circular luminal shape (Figure 5). As the lumen loses its circular pattern a higher degree of uncertainty is introduced. In this regard, the 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).

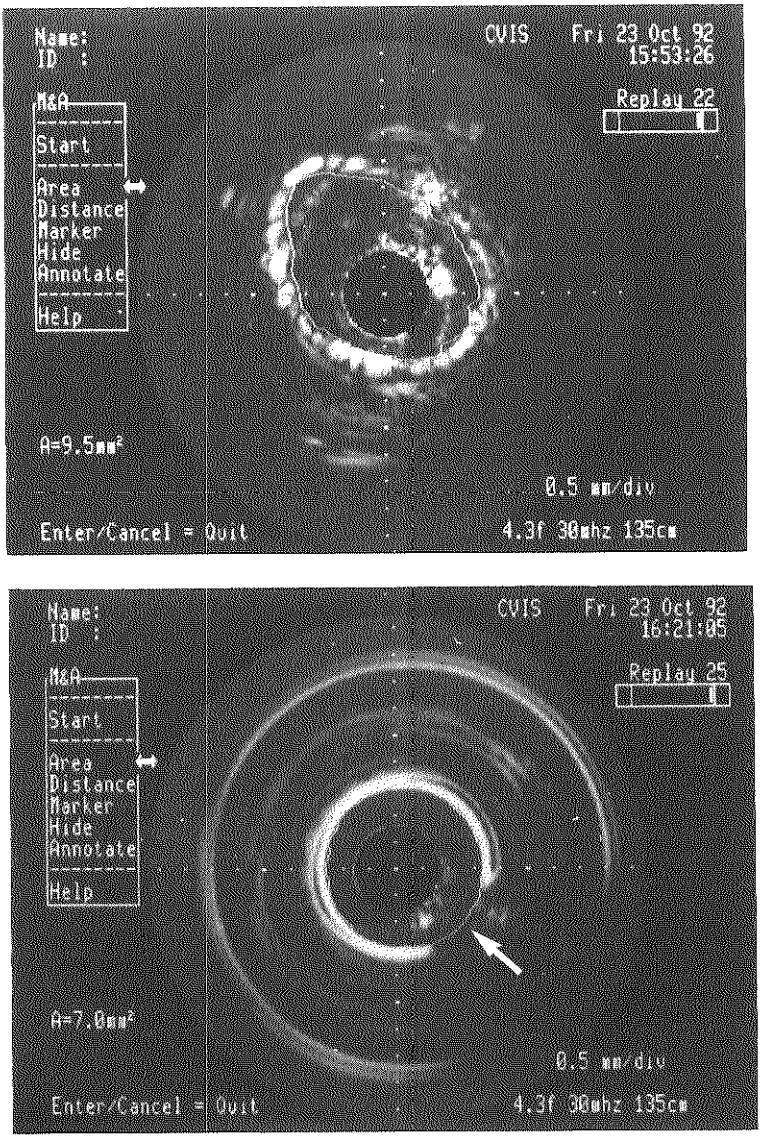

Figure 5

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 (arrow), contributing to a better correlation with the actual dimensions of the phantom (see text for more details).

Furthermore, a non-coaxial orientation of the ultrasound catheter has been shown to cause errors of up to 20% of the area measurements in circular wells (30-31). This factors may explain the disclosed correlation between the degree of eccentricity and the interobserver variability, and contribute to a higher mean error in the calculated dimensions.

At a difference with intravascular ultrasound, the precision of quantitative angiography was not significantly influenced by the type of phantom used, although a better correlation coefficient was found in those with a circular lumen. We found a similar trend to 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 (30) in acrylamide casts. In that regard, averaged ultrasonic measurements compared favorably to 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. It must be remembered, however, that an average of two orthogonal views was used. This was done since a significant variability would be expected in irregular luminal area measured from a single angiographic projection (5), as illustrated in the current study by the proportional relation between lumen eccentricity and the discrepancy between both angiographic views. True orthogonality of the angiographic views was chosen since the obtained averaged value is more accurate than that obtained from non-orthogonal views (31). The application of this principle in clinical practice, however, may be difficulted by the presence of branch overlap, bifurcations and other anatomical features.

The discrepancy in the measurements obtained with intravascular ultrasound and quantitative angiography was proportional to the eccentricity of the lesion, in agreement with a previous work by Nissen et al (13). In that study 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, due to the inability to measure the actual eccentricity of the lumen. Using this index, vessels were divided in those having either 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 work lumen eccentricity was used as a continuous variable to assess its influence on different aspects of lumen quantification with angiography and intravascular ultrasound. On the grounds of these separate studies it can be suggested that the discrepancies between quantitative angiography and intravascular ultrasound may result from a combination of the impact of eccentricity on the interobserver variability of intravascular ultrasound and on the precision of edge detection in calculating luminal area.

Study limitations

Plexiglas phantoms area clearly different from real coronary arteries, but have an optimal echogenicity and have more stable luminal dimensions than histological preparations. Since

there was no backscatter due to circulating blood, the quality of the images would be expected to be different from those obtained in clinical practice. For the sake of simplicity the experiments were performed at room temperature and using water to fill the phantoms. This may have interfered in the measurements performed with intravascular ultrasound (11), although it would be expected that it has occurred identically in irregular and circular phantoms, the latter showing an excellent correlation with the actual dimensions of the phantom. Although we believe that the echo transducer was positioned at identical point in repeated measurements (using both the ball landmarks and the transparency of the phantoms), errors derived from positioning the transducer at a different location during the second observation cannot be ruled out. The degree of luminal irregularity and eccentricity of the coronary phantoms may be inferior to that found after percutaneous interventions. This must be kept in mind when our results are compared with others performed in clinical settings.

Table 1

Correlation between ultrasonic luminal meaurements obtained by two observers in coronary (irregular) and precision-drilled (circular) phantoms.

Type of phantom	Correlation between observers		Mean area error (mm^2)	
			Signed	Absolute
Coronary casts	$y = 0.59x + 2.68$	0.77	0.80±0.98	0.91±0.87
Circular phantoms	$y = 1.19x - 1.04$	0.99	-0.81±1.38	0.93±1.35**p**
			= 0.003	**p = NS**

Table 2

Correlation between luminal area measured with intravascular ultrasound (average of both observers) and true luminal dimensions in coronary (irregular) and precision-drilled (circular) phantoms.

Type of phantom	Correlation with true luminal areas x (mm2)		Mean areaerror (mm^2)	
			Signed	Absolute
Coronary casts	y = 1.41x - 0.52	0.90	0.63±0.71	0.77±0.54
Circular phantoms	y = 1.02x - 0.19	0.99	-0.08±0.39	0.23±0.32
			p = 0.012	**p = 0.014**

Table 3

Correlation between luminal area measured with quantitative angiography (average of both orthogonal views) and true luminal dimensions in coronary (irregular) and precision-drilled (circular) phantoms.

Type of phantom	Correlation with true lominal areas		Mean area error (mm^2)	
Mean area error (mm^2)				
Coronary casts	y = 0.73x + 1.71	0.91	0.59±0.67	0.70±0.54
Circular phantoms	y = 0.80x + 1.23	0.99	0.86±1.38	1.03±1.24
			p=NS	**p=NS**

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Chapter 11

Videodensitometric Quantification of Intracoronary Volume: A Reliable New Approach to the Study of Progression and Regression of Coronary Artery Disease?

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ABSTRACT

Background: Changes in intracoronary volume reflect the hemodynamic significance of progression or regression of diffuse coronary artery disease where intracoronary catheters cannot be applied for direct measurements due to small vessel dimensions.

Methods: We have validated the videodensitometric measurement of intracoronary volume with epoxy casts of post mortem human coronary arteries. The volume of 31 coronary segments (cross-sectional areas ranging from 2 to 13mm^2) measured by fluid-filling using a precision dispenser was compared with the respective intracoronary volume assessments obtained by the videodensitometric algorithm of the new generation Cardiovascular Angiography Analysis System (CAAS II). The true and measured values of volume were compared by calculation of the mean of the signed differences $\pm$ standard deviation and by linear regression analysis.

Results: Videodensitometric measurement of intracoronary volume correlate well with fluid-filling of human coronary artery casts (correlation coefficient: $r = 0.99$, $y = 1.96 + 0.99x$, standard error of estimate: SEE = 3.96) with a significant trend towards overestimation of true volume values (mean difference = 1.73 ± 3.64 mm^3, $p < 0.05$).

Conclusion: Intracoronary volume estimations can be used to measure changes of luminal dimensions of coronary arteries and may offer a new approach to assessment of progression or regression of diffuse coronary artery disease.

INTRODUCTION

Since the introduction of computerised quantitative angiography (QCA), progression and regression of coronary artery disease have been assessed by the two dimensional measurement of luminal diameter and cross sectional area (1). Two dimensional measurements of luminal dimension at the site of focal atherosclerotic lesions can be used to assess alterations in coronary flow reserve (2,3). The progression or regression of atherosclerosis as well as the functional significance of diffuse coronary artery disease, however, cannot always be adequately evaluated by two dimensional measurements. Diffuse intimal hyperplasia for example reduces intracoronary volume without focal stenosis (4). Theoretically, the three dimensional reconstruction of coronary arteries by intracoronary ultrasound imaging should enable the quantification of changes in intracoronary volume when diffuse coronary atherosclerosis is present (5). However, the caliber and stiffness of intracoronary ultrasound catheters remain strong limitations to the investigation of coronary arteries with small diameters (6). Videodensitometry, on the other hand, has been shown to be a potentially reliable technique for the assessment of intracoronary dimensions (7).

In the present investigation, the volume of epoxy phantoms produced by a negative cast technique from human coronary arteries was used as a reference to investigate the potential of videodensitometry for the quantification of intracoronary volume.

MATERIAL AND METHODS

Epoxy phantoms

The coronary arteries of three human hearts removed post mortem were flushed thoroughly with saline and then injected in situ with a fluid silicon paste to obtain positive luminal casts (8). After hardening, the main arteries were dissected and put into a potassium hydroxide solution for removal of tissue. The positive casts of four atheromatous coronary arterial segments were selected. After removal of all ramifications, each segment was suspended in a Teflon mould and cast with epoxy resin. Four epoxy blocks with negative casts of diffusely diseased human coronary arteries were thus obtained (Fig 1).

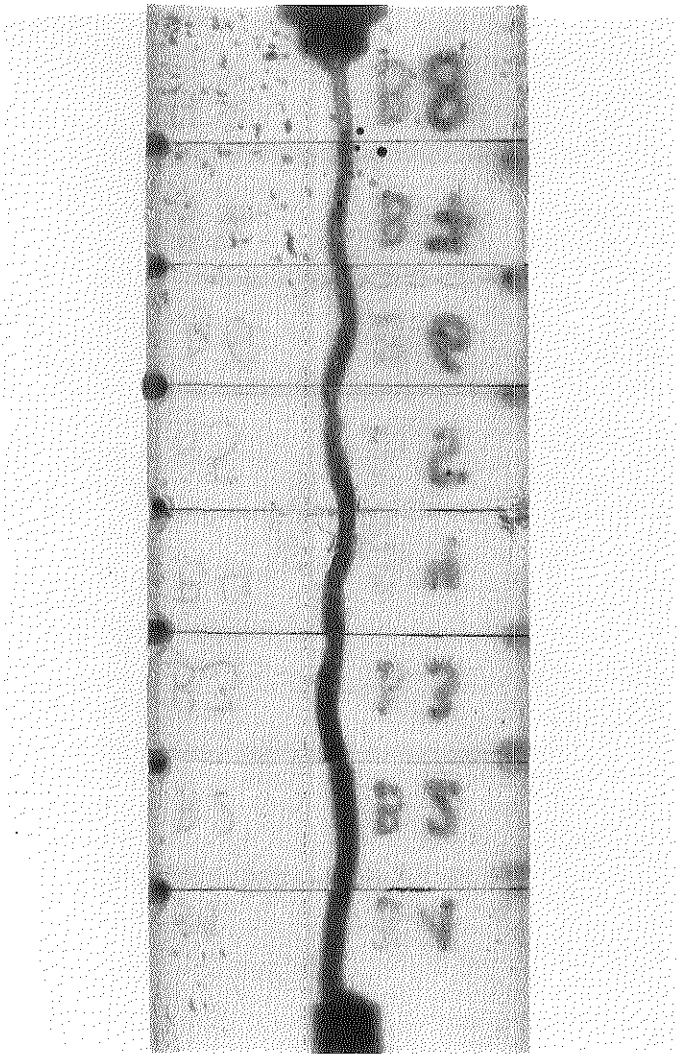

Figure 1 *A*

Four epoxy blocks with negative casts of diffuse diseased human coronary arteries were used as a reference for videodensitometric assessment of intracoronary volume.

Figure 1 B

The volume of each coronary segment of the epoxy blocks was measured by fluid-filling using a precision micro dispenser (tolerance < 0.01µl).

Assessment of cast volume

To each epoxy block a radiopaque scale with metal markers was attached producing a series of subsegments (length ranging from 5 to 9mm, cross sectional area ranging from 2 to 13 mm^2) and the cast lumen was filled with coloured water using a precision micro dispenser (Fig 2). The tolerance of the micro dispenser was less than $0.01mm^3$ (Microlab M, Hamilton Bonaduz AG, Bonaduz, Switzerland). The precise volume of each cast segment delineated by the scale was recorded. Thereby, a series of 31 volumetric segments was obtained, serving as a reference for videodensitometric analysis.

Image acquisition

The phantoms were filled with 100% contrast medium (Iopamidol 370, Bracco, Milano, Italy; 370 mg iodine/ml) and positioned in a water bath between plexiglass blocks (12.5cm anterior and 5 cm posterior) to approximate the X-ray scatter in the human thorax with an energy level of 75 kV during fluoroscopy. Subsequently, each phantom was recorded on 35mm cinefilm using a Philips DCI system with a focal spot of 0.8mm, a focus-to-object distance of 90 cm and an object-to-image intensifier distance of 13cm. The cinefilms were obtained at a frame rate of 25 images/sec using an Arritechno 90 cinecamera (Arnold & Richter, Munich, Germany) with an 85mm lens. A Kodak CFE cinefilm (Eastman Kodak, Rochester, N.Y.) was used and processed by a Refinal (M) developer (Agfa-Gevaert, Leverkusen, Germany) for 4 minutes at 28°C. The film gradient was measured in all cases to ensure that the optical densities of interest were on the linear portion of the densitometric curve.

Image processing

The cinefilm images of each coronary phantom were analyzed using geometric and videodensitometric algorithms by the new version of the Cardiovascular Angiography Analysis System (CAAS II, PieMedical, Maastricht, Netherlands). This procedure is based on the digital selection of a 6.9x6.9mm region-of-interest out of the 18x24mm cineframe for digitization into a 512x512 pixel matrix using a CCD camera with 8 bits (256 gray levels). Effectively, this means that the entire cineframe of size 18x24mm can be digitized at a resolution of 1329x1772 pixels.

Videodensitometric analysis

The videodensitometric volume measurement of 31 coronary segments (mean length 0.5 ± 0.1cm) was calibrated using a circular cross-sectional area calculation at the tubular inlet of each epoxy block by an edge detection technique (9). Calibration of diameter measurements by the edge detection technique was performed using a 3mm drill-bit as a scaling device. Thereby, the cross-sectional area derived from the diameter was used as a measure for videodensitometric cross-sectional area assessment. Subsequently, each coronary segment underwent separate videodensitometric analysis. Thereby, the brightness profile of each scanline perpendicular to the centerline of the lumen is transformed into an absorption profile according to the Lambert-Beer law by means of a simple logarithmic transfer function. The background contribution is estimated by computing the linear regression line through the mean of the brightness at two positions located 2 and 3 pixels outside the left and right detected contours (9). Subtraction of this background portion from the absorption profile yields the net cross-sectional absorption profile allowing the calculation of the cross-sectional area and the cross-sectional volume by multiplication with the distance between the scanlines. Subsequently, the segment volume is calculated by the summation of all contained cross-sectional volumes.

Statistical analysis

Videodensitometric measurements of volume were compared with the directly measured volumes by fluid-filling using a t-test as well as calculation of the mean of the signed differences and the respective standard deviations. A linear regression analysis was applied and individual differences were plotted against the mean values from both measurements using the statistical approach of Bland and Altman (10). Finally, interobserver and intraobserver variability of volume measurements by fluid filling was assessed by calculation of the mean of signed differences $\pm$ standard deviation.

RESULTS

The individual data of videodensitometric volume calculations on 31 coronary segments have been plotted against the direct measurements using fluid-filling with a precision micro dispenser in Figure 2A. Both series of measurements show excellent correlation ($r=0.99$, $y=1.96+0.99x$, $SEE=3.69$), although videodensitometric assessments of intracoronary volume significantly overestimate the corresponding measurements by fluid-filling of the coronary casts ($p<0.05$).

The mean difference between both series of measurements was $1.73 \pm 3.64 mm^3$.
According to the statistical approach proposed by Bland and Altman, the plot of individual differences against the respective mean values from both series demonstrates a homogenous distribution of signed differences along the range of volume sizes, illustrating good agreement between videodensitometric estimation of intracoronary volume and the corresponding measurements by fluid-filling (Fig 2B).

The intraobserver variability for intracoronary volume assessment of epoxy casts by fluid-filling was $0.86 \pm 1.07 mm^3$ while the interobserver variability was $1.0 \pm 1.41 mm^3$.

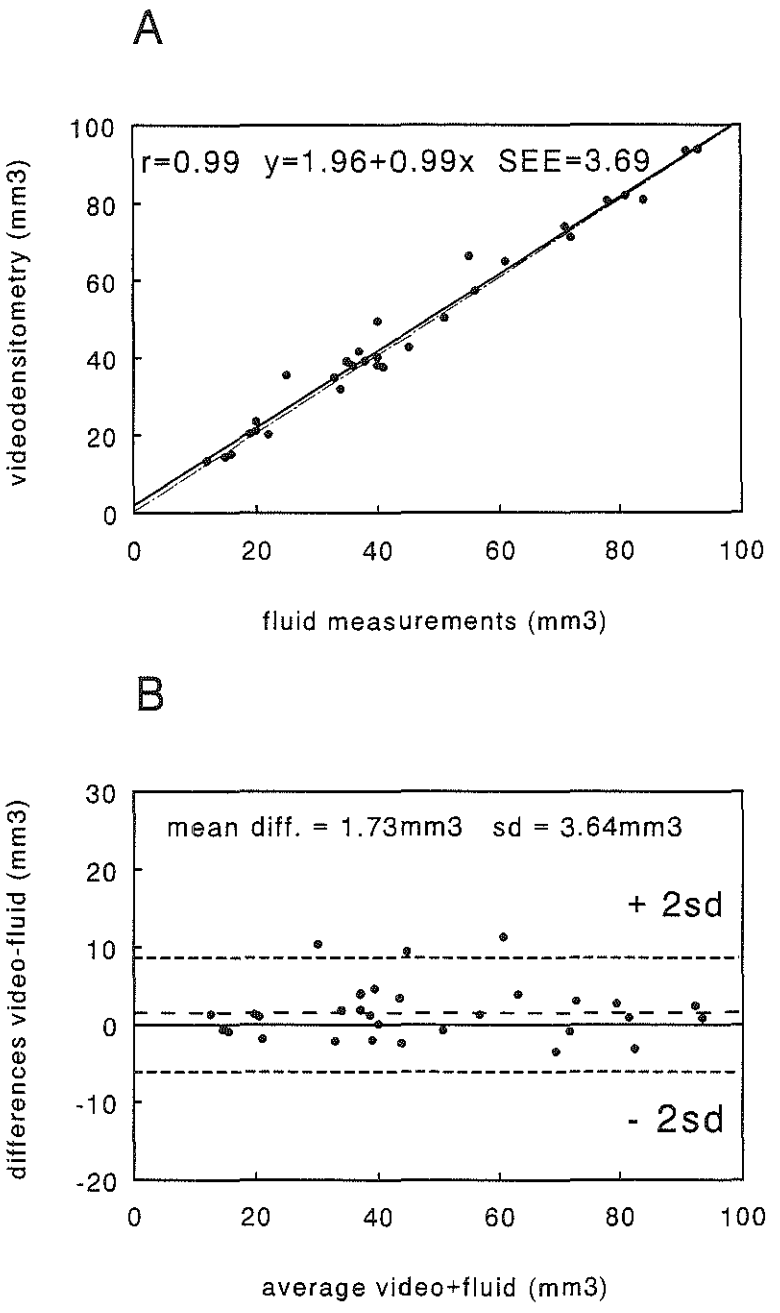

Figure 2

A. Videodensitometric assessments of the volume of each coronary segment are plotted against the values obtained by fluid measurements (range of cross-sectional areas: 2-13mm^2). **B.** The differences between volume measurements using videodensitometry and fluid-filling are plotted against the mean values from both methods.

DISCUSSION

Intracoronary ultrasound

Despite the potential value of quantification of luminal volume in the study of progression and regression of diffuse coronary artery disease, previous attempts at the measurement of arterial volume have been limited to the three dimensional reconstruction of intracoronary ultrasonic examinations (5). An inherent limitation of quantification by intracoronary ultrasound, however, is the obligatory intraluminal insertion of an ultrasonic catheter which wedges in severe coronary stenoses as well as in coronary vessels of small diameter (6). This results in stretching of the vessel wall and thus restricts the application of three dimensional intracoronary ultrasound to large vessels without severe stenoses.

Geometric measurements by quantitative coronary angiography (QCA)

QCA offers two approaches to the assessment of intracoronary volume, geometric and densitometric coronary measurements. Two dimensional geometric measurements of vessel diameters by an edge detection technique can be used to calculate luminal cross-sectional areas assuming a circular model. If the length and function of the cross sectional area for a given segment of a coronary artery is known, an estimation of intracoronary volume can be derived. In principle, the use of edge detection algorithms provides highly reliable measurements (11-13), however, the assumption of a circular model does not take into account the irregular shape of human coronary arteries in the presence of intimal hyperplasia and obstructive atherosclerosis (14). Averaging of area values from two orthogonal planes reduces the error introduced by the assumption of a circular cross-sectional area from one single view (15), but multiple view analysis would be necessary to reconstruct the true area of irregular cross-sections.

Densitometric measurements by QCA

Single view densitometric cross-sectional area measurement is superior to geometric measurement, on account of the direct transformation of the brightness profile of irregular shaped coronary cross-sections (16,17) and subsequent incorporation into volumetric calculations. Although accuracy and precision of videodensitometric measurements remain

limited by the effects of scattering, beam hardening and veiling glare (13), and reservations over the practical applicability of videodensitometry in clinical cardiology have been previously raised (15-23), it has been shown by recent validation studies that small vessel cross sectional areas can be assessed with a high degree of reliability and reproducibility (7,13). It would appear therefore, that videodensitometry offers potentially an effective method of quantification of intracoronary volume in patients with diffuse coronary artery disease.

Experimental model for validation

An experimental approach to validation of intracoronary volume measurements by videodensitometry must accommodate the irregular shape of atherosclerotic coronary arteries. Smooth regular shaped phantoms, which are appropriate for the assessment of edge detection algorithms (12), are inadequate for this purpose.
To imitate the asymmetric geometry of coronary arteries in patients with coronary atherosclerosis, we used epoxy phantoms produced by a negative cast technique from post mortem human coronary arteries (8) directly reflecting luminal irregularities and vessel tortuosity. The calibration of 31 volumetric segments by fluid filling with a precision micro dispenser (tolerance < 0.01mm^3) provided a series of reference values for comparison with volumetric measurements derived from videodensitometry. The low inter- and intraobsever variability in the assessment of intracoronary volume using fluid-filling, enhanced the suitability of this experimental approach to volumetric validation.

The results of this study show that the videodensitometric algorithm of the new version of CAAS provides highly reliable measurements of intracoronary volume in vitro for cross-sectional areas ranging from 2.00 up to 13.00 mm^2. Within this range, a low mean difference (1.73mm^2) and standard error of estimate (SEE=3.64) indicated good agreement between measured values and reference volumes (Fig 2), although the trend towards overestimation of reference values was statistically significant ($p<0.05$).

Recent in vitro studies have demonstrated, that reliable videodensitometric assessment of luminal dimensions may be limited to cross-sectional areas below 13.00 mm^2 (7). In principle, inaccurate assessment of large vessel cross sectional areas may be explained by the non-linear relation between iodine content and the optical density of the polyenergetic X-ray beam. However, our own experience using the videodensitometric algorithm of the recent version of the CAAS for cross-sectional measurements of stenosis phantoms in swine coronary arteries indicated that area dimensions even above 1.00 mm^2 may be assessed with a lower degree of reproducibility (13). A systematic error due to the isolated use of a single cross-sectional area for densitometric calibration may explain this limitation which is clearly more evident when inhomogenous background has to be processed by digital subtraction in vivo.

Calibration

The use of circular shaped cross-sectional areas for the purpose of videodensitometric calibration may hamper the transformation of the present volumetric validation to conditions present in the clinical situation. In our study using human coronary casts, videodensitometric calibration of CAAS was performed at the conically shaped inlet of the epoxy phantoms. Thereby, a higher degree of accuracy was produced than could be obtained in clinical practice where a coronary segment which appears to have an approximately homogeneously circular cross-section is recommended for calibration.
Finally, the use of angiographic catheters for the calibration of geometric measurements by edge detection technique may introduce additional errors due to out of plane magnification of the catheter tip (24), which may affect the outcome of videodensitometric volume assessments. However, at least for the volumetric assessment of coronary artery segments with small cross-sectional area, the above mentioned systematic errors should be negligible.

Conclusion

The results of this experimental approach to volumetric validation indicate that commercially available videodensitometric software packages can be used to provide a measurement of intracoronary volume in coronary arteries of small luminal cross-sectional area with a high degree of reliability. This new application of videodensitometry may offer a new and practical approach to the investigation of progression and regression of diffuse coronary artery disease.

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Chapter 12

Comparative Validation of Quantitative Coronary Angiography Systems: Results and Implications from a Multicenter Study Using a Standardized Approach

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

We have validated 10 QCA systems which are currently in use and undergoing continuous refinement in Europe and North America. Cinefilms were made of stenosis phantoms of known diameter (0.5 - 1.9mm) under four experimental conditions: in vitro (plexiglass model) with 50% contrast and 100% contrast and in vivo (porcine model) calibrated by the isocenter method or by the use of the catheter as a scaling device thus providing a total of four validation tests. The cinefilms were analysed by each automated QCA system without observer interaction. Accuracy and precision were taken as the mean and standard deviation of the signed differences between the true phantom diameters and the measured minimal luminal diameters. The correlation coefficient (r), the standard error of the estimate (SEE), the y intercept (a) and the slope (b(x)) were derived by linear regression. Reproducibility (R) was taken as the standard deviation of 15 repeated measurements of each stenosis phantom. Performance of the 10 QCA systems ranged widely : Accuracy +.05 to +.31mm : Precision ±.10 to ±.24mm : correlation (r) .97 to .89 : SEE ±.09 to ±.16mm : intercept (a) +.08 to +.31mm : slope ((b)x) .64 to .86 : Reproducibility ±.02 to ±0.16mm.

Conclusion: There is a marked variability in performance between systems when assessed over the range of 0.5 - 1.9 mm. The range of accuracy and intercept (a) values of this report suggests that absolute measurements of minimal luminal diameter from one multicenter study may not be directly comparable to those of another core laboratory or indeed directly applicable to on-line analysis in clinical practice. The range of precision values reported suggests that some QCA systems may fail to detect small differences in study populations. This study may guide the fine-tuning of algorithms incorporated within each system and facilitate the maintenance of high standards of QCA for scientific studies.

INTRODUCTION

Computerised quantitative coronary angiography (QCA) has fundamentally altered our approach to the assessment of interventional techniques and strategies aimed at the prevention of restenosis and progression of coronary artery disease (1,2). With an increasing number of QCA systems being developed, and a growing number of core laboratories for the analysis of multicenter angiographic trials, it has become essential that the performance of QCA systems, upon which much of our scientific understanding has become integrally dependent, is evaluated in an objective and uniform manner (3).

QCA systems with poor precision may fail to detect small but significant differences in study populations while QCA systems with poor accuracy may provide misleading results of absolute measurements of minimal luminal diameter (MLD). The results of studies based on unreliable QCA systems may not be directly comparable to those of more reliable systems. To render the results of angiographic studies meaningful and universally applicable, it is important that QCA systems be validated in a systematic and standardised fashion. Results of single center validation studies will vary according to the models and quality of the stenosis phantoms deployed (4). Without a standardised approach to validation it becomes difficult to assess to what degree individual angiographic studies are reliable, and how much weight should be attributed to absolute values of MLD derived from individual QCA systems and the significance of their failure to detect relative changes in MLD. Furthermore, it is only by detailed validation studies that systematic errors in QCA systems can be identified and thereby provide guidance for the refinement of algorithms incorporated in QCA software.

The present investigation was performed to determine the range of accuracy, reliability and reproducibility offered by ten QCA systems currently in use and undergoing continuous refinement in North America and Europe. Stenosis phantoms of known diameter were used as a reference both in an in vitro plexiglass model as well as after serial insertion in the coronary arteries of pigs (5-7). The QCA systems were assessed by their measurement of the absolute value of "obstruction diameter" within the artificial stenoses which has previously been shown to be more reliable than relative measures of coronary artery dimensions based on the definition of a reference contour (8-10). To assess the influence of different calibration techniques on the outcome of geometric measurements in vivo, calibration at the isocenter was compared with catheter calibration as conventionally used in off-line analysis.

METHODS

Stenosis phantoms

The stenosis phantoms used in the in vitro as well as the in vivo model 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. The outer diameters of the cylinders were 3.0 or 3.5 mm, the length was 8.4 mm. 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). Optical calibration of the stenosis channels using 40-fold magnification gave a tolerance of .3μm. Parallel to the stenosis lumen, a second lumen of 1.3 mm in diameter was drilled in the cylinders to enable their attachment to the tip of 4 F Fogarty catheters (Vermed, Neuilly en Thelle, France). The central lumens of the Fogarty catheters contained a removable metallic stilette, which aided the intracoronary insertion of the phantoms as well as their positioning in the radiographic isocenter. Details of our experimental approach to QCA validation have been previously described (5-7).

In vitro experiments

The stenosis phantoms were serially inserted in the center of cylindrical acrylate models (diameter 25mm, length 120mm) with a concentric channel of 3.0mm diameter. The plexiglass channel including the artificial stenosis was then filled with contrast medium (iopamidol 370, Bracco, Milano, Italy; 370mg iodine/ml) at concentrations of 50% and then 100%. An additional thickness of plexiglass blocks (12.5cm anterior and 5cm posterior to the models) was added to produce a more appropriate kV-level (75kV) and a scatter medium which more closely approximates the X-ray scatter in the human thorax. Each stenosis phantom filled with contrast medium was recorded on cinefilm.

In vivo experiments

The stenosis phantoms were inserted in the coronary arteries of anesthetized Yorkshire pigs (45 - 50kg). Twelve F introducer sheaths were surgically placed in both carotid arteries to allow the sequential insertion of the stenosis phantoms on 4F Fogarty catheters and the insertion of the angiographic guiding catheter. Each animal received an intravenous bolus of acetylsalicylic acid (500mg) and heparin (10.000 IU) and a continuous infusion of heparin (10,000 IU/h) was maintained throughout the procedure to prevent clot formation.

Mechanical ventilation was temporarily discontinued immediately prior to each angiographic run.

Two different calibration methods were applied to geometric measurements. Calibration at the isocenter was carried out by radiographic acquisition of a drill-bit (diameter 3mm) within the isocenter of the X-ray system before angiography. Catheter calibration was performed by acquisition of the unfilled tip of the contrast catheter as conventionally recommended for routine practice (11). The diameter of the non-tapering part of this catheter was assessed with a precision micrometer (No. 293-501, Mitutoyo, Tokyo, Japan; accuracy 0.001mm), resulting in the respective calibration factor (mm/pixel). Using these two methods of calibration, two series of results were obtained allowing an estimation of the potential geometric error introduced by non-isocentric calibration.

Image acquisition and processing

A single plane Philips Poly Diagnost C2 machine was used equipped with an MCR X-ray tube and powered by an Optimus CP generator (Philips Medical Systems International BV, Best, The Netherlands). The 5" (12.5cm) field mode of the image intensifier (focal spot 0.8mm) was selected and the radiographic system settings were kept constant (kV, mA, X-ray pulse width) in each projection. All phantoms were imaged isocentrically in two projections and acquired on 35-mm cinefilm (CFE Type 2711, Kodak, Paris, France) at a frame rate of 25 images/s, using an Arritechno 90 cine camera (Arnold & Richter, Munich, Germany) with an 85 mm lens. Particular care was taken to minimize foreshortening of the segment of interest and to avoid overlap with other vessels or structures. The cinefilms were processed by a Refinal (m) developer (Agfa-Gavaert, Leverkusen, Germany) for 4 minutes at 28^{0}C. The film gradient was measured in all cases to ensure that the optical densities of interest were on the linear portion of the densitometric curve. From each angiogram which fulfilled the requirements of quantitative analysis (no superimposition of surrounding structures, no major vessel branching at the site of the phantom), a homogeneously filled end diastolic coronary image was selected. Ten in vitro and 19 in vivo frames were suitable for quantitative analysis of the artificial stenoses. A sufficiently long segment of the contrast filled lumen including the stenosis phantom was selected on all images.

Quantitative angiographic analysis

The cinefilms of the stenosis phantoms were analysed off-line by ten QCA systems in nine participating centers. Each center had a unique combination of QCA software and hardware. Technical details from the included QCA systems are given in Table 1. One of the investigators (EMvS) visited all the centers, bringing the same set of films for analysis to each center consecutively. A technician working at each center, performed the automated

QCA analysis of all cineframes without observer interaction in the presence of the investigator.

Assessment of reproducibility

To assess the variability of repeated measurements, one representative cineangiographic frame of each size of the stenosis phantoms (0.5, 0.7, 1.0, 1.4, 1.9mm) was analyzed fifteen times consecutively by the same technician using the fully automated QCA system.

Statistical analysis

The individual geometric measurements of minimal luminal diameter were compared with the true phantom diameters by one way analysis of variance and linear regression analysis. The mean of the signed differences between measured values and the known diameter of the stenosis phantoms was considered an index of accuracy and the standard deviation of the differences an index of precision. The standard deviation of the mean value of fifteen repeated measurements on the same angiographic phantom was considered a measure of reproducibility. These values were calculated separately for all five stenosis phantoms. The mean reproducibility was defined as the mean value of the five reproducibility tests.

RESULTS

Indices of agreement

Accuracy of the 10 QCA systems ranged from .05 to .31 mm (Table 2). The mean intercept (a) [where $y = a + bx$] of the regression line was positive for all 10 QCA systems and ranged from +.08 to +.31 mm (Table 3). The correlation coefficient (r) ranged from .97 to .89 (Table 4) and the slope (b) of the regression line ranged from .86 to .65 (Table 3).

Indices of consistency

Precision of the 10 QCA systems ranged from $\pm$.10 to $\pm$.24 mm (Table 2) and the standard error of the estimate ranged from $\pm$.09 to $\pm$.16 mm (Table 4). Reproducibility ranged from .02 to .16 mm (Table 5). Furthermore, it can be seen from Tables 2 - 5, that the performance of each individual system varied from one validation test to another: Overall, most QCA systems performed better when 100% contrast was used instead of 50% contrast in the in vitro series and when calibration was performed by the isocenter method rather than by catheter calibration in the in vivo series.

DISCUSSION

This study demonstrates the wide range of performance provided by 10 QCA systems currently in use in North America and Europe. The clinical implications of such widely different results are significant. Not only is it of concern that such a large variability exists between QCA systems in current use, but more importantly measurements of some systems are so inaccurate compared to the true phantom diameters that application of the absolute results from such systems may be misleading. Most systems had a positive intercept and slope < 1 and thus many clinical studies to date may have underestimated the acute gain in minimal luminal diameter following coronary intervention. Furthermore, the precision and standard error of the estimate provided by some systems were found to have such a high absolute value (up to .24 and .16 mm respectively) that it is unlikely that such systems could

detect small but significant differences in patient populations undergoing serial angiographic studies. If the absolute value of precision for a QCA system exceeds the absolute value of a difference in minimal luminal diameter (MLD) between two treatment groups, then the difference between the study groups may go undetected or fail to reach statistical significance on account of their high standard deviations.

The tables of results provided by this study also contain a crude average of the four validation tests for each QCA system. It is, however, debatable whether the results of in vivo (where veiling glare and scatter are heterogenous) and in vitro (where veiling glare and scatter are homogenous) tests calibrated by different methods should be grouped together and thus attributed equal importance in view of their unique characteristics and implications (12-14). The results of the in vivo validation test calibrated by the catheter most closely reflect the practice of off-line analysis as occurs in multicenter angiographic trials with a core laboratory, and in most of the ten systems these results were worse than those of the other three validation tests where calibration was performed by the isocenter.

The influence of the camera and cine-video converter on the final result of QCA analysis is highlighted by this study where it was seen that although four centers had the same software package, remarkably different results were obtained on account of their unique combinations of hardware components (projector, camera / cine-video converter). It is clear from the results of this study that it would not be possible for follow-up studies to be performed by two different QCA systems, even if only one link of the analytical chain was altered eg even if the QCA software was the same but the camera or cine-video converter was changed or if the same QCA software was upgraded by a more recent version (7). This is of particular relevance to progression regression trials where a QCA system of four years of age is likely to have been superceded at the core lab by more modern versions of the software (4).

It is expected that the results of this study will be used by the producers of each QCA system to refine the algorithms incorporated within each system. Many of the systematic errors detected by this study could be corrected by recalibration of the QCA software or tuning of the weighting of the 1st to the 2nd derivative in the edge detection algorithm, while it would be expected to be more difficult to clear a system of noise which usually reflects hardware impediments.

Study limitations

The technique of QCA analysis in this study may not exactly reflect routine practice in core angiographic laboratories where the operator may intervene and enter soft and hard corrections when gross errors in edge detection occur due to the superimposition of side branches of coronary vessels. The cinefilms of the stenosis phantoms in this study, however, were acquired under optimal angiographic conditions for both the in vivo as well as the in vitro series. Furthermore, the stenosis phantoms themselves were discrete, of consistent and smooth contour and of 8.4mm length which should have further facilitated their edge detection by each system compared to the irregular shorter or more diffuse lesions found in

clinical practice. Therefore, with a competent QCA system, operator intervention should have been unnecessary in the analysis of this study. Indeed, in view of the optimal settings of the phantom series, it could be even suggested that the inaccuracy and imprecision of QCA systems highlighted by this study may underestimate the inaccuracy and imprecision of each system during routine practice.

The positive intercept values of the regression line for most systems in this study indicate that most QCA systems tend to overestimate in the lower range of luminal diameters (< 1mm). The slope (b), however, was < 1 for all systems indicating (on the probability of a linear function) that for larger reference vessels, the QCA systems tested would underestimate the true lumen diameter. This should be confirmed by the production of a standardised set of phantoms of larger diameter for future multicenter studies to comprehensively assess the performance of QCA systems over the complete range of vessel size. The intracoronary insertion of stenosis phantoms of large diameter may, however, prove to be difficult in the porcine model in view of the limited size of the coronary artery lumen.

Even when QCA systems are validated in a uniform manner by the same set of stenosis phantoms, it still remains unclear as to which statistical parameter provides the most relevant information and which parameters should be used for direct comparisons between systems. For this reason, the issue of statistical approach to comparative validation will be discussed in the following section.

Which parameters of QCA system's performance should be used for comparative validation?

Traditionally, validation of quantitative coronary angiography (QCA) systems has been based on the statistical parameters of accuracy, precision, correlation coefficient, standard error of the estimate and the equation of linear regression given by the intercept and slope. While each parameter provides a unique index of a QCA system's performance, direct comparisons between QCA systems is confounded by the interdependence of all parameters and the application of one parameter in isolation can be misleading. The contribution of each of these traditional parameters are considered below and a new statistical approach is proposed based on normalisation of all parameter values for an intercept of zero and a slope of 1, thereby permitting the comparative assessment of measurement systems by only two parameters; standard error of the estimate and correlation coefficient.

When comparing a set of measured values with known true values, the parameters accuracy and precision are defined as the mean and standard deviation of all signed differences between the measured and true values, while the parameters of intercept, slope, standard error of the estimate and correlation coefficient describe the relationship between the true and measured values and are derived by simple regression. To demonstrate the relative contribution of each parameter, a series of eight graphs are given in Figure 1, illustrating the effect of shift, slope, absolute noise, number and range of observations on each parameter.

The unpredictable (random) error of a measurement system, consists of two components:
(i) the contribution of absolute noise as demonstrated in the above examples which is independent of the range of true values
(ii) the contribution of relative noise, which is related to the true values.
Relative noise typically increases at higher true values, while absolute noise remains constant throughout the full range of true values (the difference between absolute and relative noise is illustrated in Figure 2).

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.
- standard error of the estimate is dependent on the absolute noise values.
- correlation coefficient is dependent on the noise values related to the range of true values. Extending the range will raise the correlation coefficient up towards 1. Absolute noise ceases to influence the correlation coefficient when the range becomes large (Figure 2a). In the presence of relative noise (Figure 2b), the correlation coefficient cannot reach 1 by extending the range as the ratio of noise to the true value is constant.

For these reasons, a comparison of different QCA systems based on the parameters accuracy and precision is influenced by the range of true reference values and by the combined effect of the slope and shift of the relationship between measured and true values and even an accuracy of zero is not intuitively associated with an optimal system. Assimilation of the contribution of relative noise does not alter these conclusions.

Many previous comparative studies have used the statistical approach proposed by Bland and Altman (15), however, this approach provides little additional information over linear regression analysis. Bland and Altman designed their statistical method to display the agreement between two measurement systems in the absence of a golden standard and thus their approach is of limited value to a study when the true value of the measured objects are known.

One method of addressing the problem of comparative validation would be to express accuracy and precision at any given true value of a phantom stenosis in a categorical manner. If a consensus was reached on the most relevent absolute value of diameter at which accuracy and precision of QCA systems should be compared (eg 1.5mm) then one value for accuracy and precision could be given for each QCA system. Alternatively a series of three accuracy and precision values could be given for each system for three true values of lumen dimension, eg 0.8, 1.8 and 3.0 mm roughly corresponding to likely measurements of minimal luminal diameter (MLD) pre and post coronary intervention and of reference vessel diameter. Such a categorical approach would, however, only convey a superficial indication of each QCA system's overall performance.

Based on the above limitations we propose that a more effective and useful comparison of QCA systems can be accomplished by correcting for the systematic error, i.e. by correcting for the intercept and slope of the regression equation of each system. For the relation $y = a + bx$, the corrected measurement values become $y_c = (y-a)/b$. 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 almost be equal, both expressing a measure in absolute terms of the unpredictable error which persists in the corrected system. The correlation coefficient provides a measure of the unpredictable error in relation to the range of measured values. As an example the corrected relation of $y = 0.5 x + 1.5 \pm 0.5$ (Figure 1, graph h) is shown in Figure 3 as $y_c = x$. When compared with $y = x$ (Figure 1, graph c), the absolute error of the corrected system, indicated by precision and SEE, is doubled while the correlation coefficient decreased because of the relative increase in noise in the considered range.

Applying this proposal of normalisation for a y intercept of zero and a slope of 1 to the results of our study of the in vivo series calibrated by the catheter, a simplified model for the comparison of various quantitative coronary analysis systems is presented, based on the exclusive use of the corrected correlation coefficient (rc) and corrected standard error of the estimate (SEEc) (Table 6).

By this approach, an overall comparison of the unpredictable error and its relation to the mean measurement values of QCA systems is possible. However, individual trends towards over- or underestimation of true values are not expressed. Thus comparative validation of QCA systems should be based on the combined use of the here proposed and the traditionally used parameters.

Study implications

QCA validation studies should be performed in an uniform and standardised manner in order to provide meaningful data which can be used to compare the performance of QCA systems, to guide the recalibration of QCA algorithms and to facilitate the maintainance of high standards of QCA for clinical practice and scientific studies.
The entire chain of a QCA system should be revalidated each time the version of QCA software is upgraded or a hardware component is exchanged.
Results of validation studies should be given both as the normalised (corrected) values in addition to the absolute values of the parameters.
In the reporting of angiographic studies, absolute values of luminal diameter and values of statistical significance for differences between study populations should be accompanied by the results of the appropriate validation parameters of the QCA system deployed in order to facilitate the interpretation of the study's findings.

Conclusion

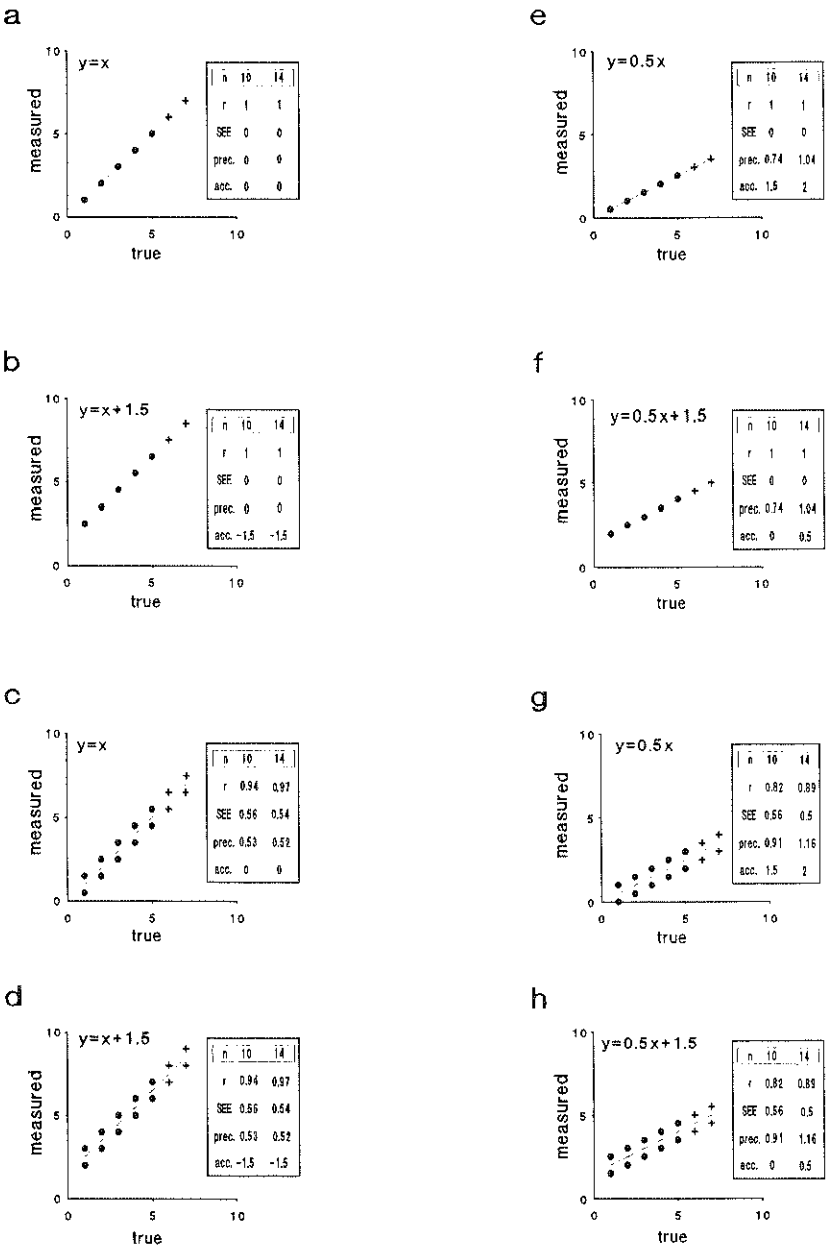
Wide differences exist between currently available QCA systems and it can be envisaged that small differences in patient populations may go undetected by some QCA systems. The

difficulties in attempting to make direct comparisons of absolute measurements of one angiographic study with those derived from a different system or with on-line analysis in clinical practice have been highlighted by this study. The results of this study will guide the refinement of the algorithms incorporated within each QCA system and facilitate the maintainence of high standards of quantitative angiography for scientific studies.

APPENDIX:

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

Beth Israel Hospital, Boston; D. Baim
Brigham and Women's Hospital, Boston; C.M. Gibson
Cardiology Center, Washington; J. Popma
Cleveland Clinic Foundation, Cleveland; E.J. Topol
George Washington University, Washington; J. Garner, A. Ross
Hopital Universitaire St. Jacques, Besançon; J.P. Bassand
Mount Sinai Hospital, Toronto; A. Adelman
St. Michaels Hospital, Toronto; P.W. Armstrong, A. Langer, B.H. Strauss
Thomas Jefferson Hospital, Philadelphia; D. Fischman, S. Goldberg
Thoraxcenter, Rotterdam; C. Di Mario, J. Haase, D. Keane, E.M. van Swijndregt, P.W. Serruys, C.J. Slager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n 10 14
r 1 1
SEE 0 0
prec. 0 0
acc. 0 0
e
y=0.5x
n 10 14
r 1 1
SEE 0 0
prec. 0.74 1.04
acc. 1.5 2
b
y=x+1.5
n 10 14
r 1 1
SEE 0 0
prec. 0 0
acc. -1.5 -1.5
f
y=0.5x+1.5
n 10 14
r 1 1
SEE 0 0
prec. 0.74 1.04
acc. 0 0.5
c
y=x
n 10 14
r 0.94 0.97
SEE 0.56 0.54
prec. 0.53 0.52
acc. 0 0
g
y=0.5x
n 10 14
r 0.82 0.89
SEE 0.56 0.5
prec. 0.91 1.16
acc. 1.5 2
d
y=x+1.5
n 10 14
r 0.94 0.97
SEE 0.56 0.54
prec. 0.53 0.52
acc. -1.5 -1.5
h
y=0.5x+1.5
n 10 14
r 0.82 0.89
SEE 0.56 0.5
prec. 0.91 1.16
acc. 0 0.5
measured
true
0
5
10

Figure 1

Figure 1

Each of the eight graphs has a range of 5 and 7 true values and for each true value two corresponding measured values are displayed, thus providing a total of 10 and 14 observations respectively :

Graphs 1a - 1d :
a) For y = x, all parameters describe the system to be perfect.
b) Adding a shift, y = x + 1.5, only influences accuracy.
c) Adding noise to y = x, does not influence accuracy. The minor difference between SEE and precision (SD) reflects a different correction for the number of observations. For an infinite set of observations both parameters will equal 0.5. Correlation coefficient is slightly improved by extending the range.
d) Adding shift and noise gives a combination of the above.

Graphs 1e - 1h :
e) A systematic measurement error characterized by y = 0.5 x, yields a score for both precision and accuracy different from zero, which is also dependent on the range of data. SEE continues to be zero.
f) Now adding a shift, y = 0.5 x + 1.5, again influences accuracy. As shown accuracy may even become zero, suggesting a perfect system!
g) Adding noise to the set y = 0.5 x, again increases the numerical 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, (graph 1c), SEE has the same value but the correlation coefficient decreases because the addition of noise has a greater contribution when the slope = 0.5.
h) Adding shift and noise gives a combination of the above.

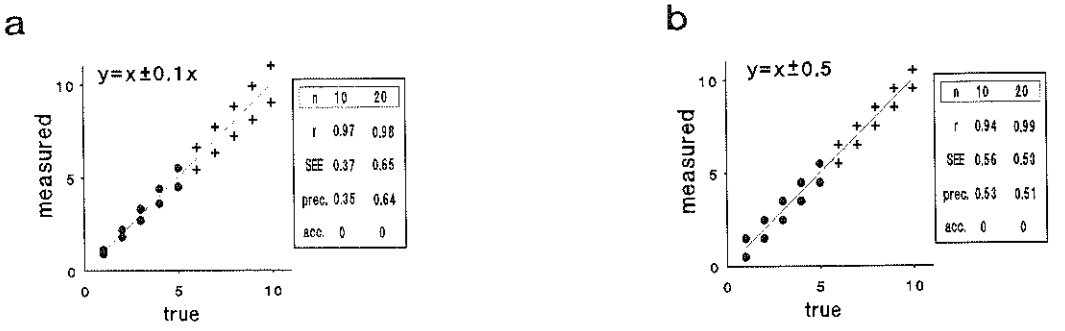

Figure 2

Figure 2 illustrates the difference between absolute and relative noise in a QCA system. Extending the range will raise the correlation coefficient up towards 1 (Figure 2a). Absolute noise ceases to influence the correlation coefficient when the range becomes large. In the presence of relative noise (Figure 2b), the correlation coefficient cannot reach 1 by extending the range as the ratio of noise to the true value is constant.

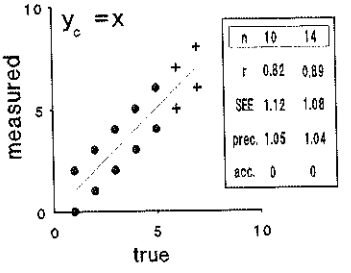

Figure 3

The corrected relation of $y = 0.5\,x + 1.5 \pm 0.5$ (Figure 1, graph h) is shown in Figure 3 as $y_c = x$. When compared with $y = x$ (Figure 1, graph c), the absolute error of the corrected system, indicated by precision and SEE, is doubled while the correlation coefficient decreased because of the relative increase in noise in the considered range.

Site	Cine Projector	Optical Magnification of cinefilm images	Camera (video converter)	Video Camera Pixel Matrix	QCA System	Manufacturer of QCA	Correction for Pincushion Distortion	Digital Magnification to image for analysis	Final Pixel Matrix of QCA	Algorithm principle
1	VANGUARD XR35	Yes	Vidicon Tube	ANALOGUE	Artrek Version 1.6; 1992	ImageComm U.S.A.	NO	Yes	512 480	1st & 2nd derivative
2	TAGARNO 35AX	Yes	Vanguard TV-6	ANALOGUE 525 line	Artrek Version 1.6; 1992	ImageComm U.S.A.	NO	Yes	512 480	1st & 2nd derivative
3	TAGARNO 35AX	Yes	Newicon		Artrek Version 1.36; 1991	ImageComm U.S.A.	NO	Yes	512 480	1st & 2nd derivative
4	CAP 35B	Yes			Artrek Version 1.6; 1991	ImageComm U.S.A.	NO	Yes	512 480	1st & 2nd derivative
5	ARRIPRO 35	Yes	CCD chip	756 581	AWOS	Siemens Germany	NO	Yes	512 512	Optimal Convolution
6	TAGARNO 35CX	Yes	CCD array	1770 1330	CAAS I	Pie Medical the Netherlands	YES	No	512 512	1st & 2nd derivative
7	TAGARNO 35CX	Yes	CCD array	1770 1330	CAAS II	Pie Medical the Netherlands	YES	Yes	1770 1330	1st & 2nd derivative
8	CAP 35E	Yes	CCD chip	512 480	CMS	Medis the Netherlands	NO	Yes	512 512	1st & 2nd derivative
9	Sony SME 3500	Yes	CCD chip	512 480	home grown	in house	YES	Yes	512 512	1st & 2nd derivative
10	TAGARNO 35CX	No	CCD chip	1320 1035	home grown	in house	NO	No	1320 1035	Density profile of tracker boxes

CCD = Charged Coupled Device
CAP = Cine Angiography Projector
CAAS = Coronary Angiography Analysis System
CMS = Cardiovascular Measurement System
AWOS = Artery Work Station

Table 1

MULTICENTRE QCA VALIDATION STUDY - ACCURACY (A) & PRECISION (P)

	in vivo catheter		in vivo isocenter		in vitro 50%		in vitro 100%		average	
	A	P	A	P	A	P	A	P	A	P
1	.09	.23	-.07	.21	.12	.10	.01	.18	.07	.18
2	-.14	.17	.01	.18	.01	.16	-.14	.07	.08	.15
3	-.20	.24	-.14	.31	-.16	.17	-.17	.14	.17	.22
4	-.35	.23	-.11	.15	-.28	.06	-.13	.14	.31	.15
5	-.19	.13	-.09	.16	-.25	.13	-.15	.13	.17	.14
6	-.13	.26	-.01	.22	-.12	.14	-.07	.24	.08	.22
7	-.30	.25	-.07	.22	-.29	.13	-.23	.13	.22	.18
8	-.28	.26	-.25	.20	-.41	.18	-.13	.17	.27	.20
9	-.33	.26	-.26	.22	-.29	.20	-.09	.28	.24	.24
10	-.24	.30	-.15	.24	-.31	.17	-.21	.19	.23	.23

Accuracy (A) and Precision (P) are the mean and standard deviation of the differences (mm) between the measurement of luminal diameter derived by QCA and the true diameter of the phantom stenoses.

in vivo catheter : in vivo series of measurements calibrated by the catheter
in vivo isocenter : in vivo series of measurements calibrated by the isocenter
in vitro 50% : in vitro series of measurements with 50% contrast
in vitro 100% : in vitro series of measurements with 100% contrast
average : crude (unweighted) average of the absolute (signed) results

Table 2

MULTICENTRE QCA VALIDATION STUDY - REGRESSION EQUATION (y = a + b x)

	in vivo catheter	in vivo isocenter	in vitro 50%	in vitro 100%	average
1	Y=.19+.74X	Y=.30+.79X	Y=.03+.87X	Y=.30+.69X	Y=.20+.77X
2	Y=.14+.76X	Y=.22+.82X	Y=.25+.77X	Y=-.05+.92X	Y=.17+.82X
3	Y=.15+.69X	Y=.32+.59X	Y=.10+.76X	Y=.10+.76X	Y=.17+.70X
4	Y=.04+.66X	Y=.11+.81X	Y=-.19+.92X	Y=.10+.77X	Y=.11+.79X
5	Y=.00+.83X	Y=.08+.85X	Y=-.19+.95X	Y=.05+.81X	Y=.08+.86X
6	Y=.34+.58X	Y=.37+.66X	Y=.11+.80X	Y=.40+.52X	Y=.31+.64X
7	Y=.12+.63X	Y=.23+.73X	Y=-.20+.92X	Y=-.08+.85X	Y=.16+.78X
8	Y=.05+.71X	Y=.03+.75X	Y=-.17+.78X	Y=.18+.68X	Y=.11+.73X
9	Y=.17+.57X	Y=-.03+.80X	Y=-.05+.78X	Y=.44+.46X	Y=.17+.65X
10	Y=.20+.60X	Y=.22+.67X	Y=-.11+.81X	Y=.18+.60X	Y=.18+.67X

The regression equation (y = a + b x) is derived by linear regression where the true values of the phantom stenoses are independent and the measured values are dependent. The equation is composed of an intercept (a) and a slope (b).

in vivo catheter : in vivo series of measurements calibrated by the catheter
in vivo isocenter : in vivo series of measurements calibrated by the isocenter
in vitro 50% : in vitro series of measurements with 50% contrast
in vitro 100% : in vitro series of measurements with 100% contrast
average : crude (unweighted) average of the absolute (signed) results

Table 3

MULTICENTRE QCA VALIDATION STUDY - CORRELATION & STANDARD ERROR OF ESTIMATE

	in vivo catheter		in vivo isocenter		in vitro 50%		in vitro 100%		average	
	r	SEE	r	SEE	r	SEE	r	SEE	r	SEE
1	.89	.19	.91	.19	.97	.09	.94	.12	.93	.15
2	.96	.12	.94	.15	.94	.13	.99	.07	.96	.12
3	.89	.19	.81	.23	.93	.14	.96	.10	.90	.16
4	.91	.16	.97	.12	.99	.05	.97	.10	.96	.11
5	.98	.09	.95	.15	.95	.14	.97	.10	.96	.12
6	.91	.14	.94	.13	.96	.11	.94	.09	.94	.12
7	.90	.16	.91	.17	.95	.14	.96	.12	.93	.15
8	.87	.22	.92	.16	.91	.17	.97	.09	.92	.16
9	.91	.14	.91	.20	.89.	19	.86	.13	.89	.16
10	.83	.22	.90	.18	.92	.16	.98	0.6	.91	.16

The correlation coefficient (r) and the standard error of the estimate (SEE) are derived by linear regression where the true values of the phantom stenoses are independent and the measured values are dependent.

in vivo catheter : in vivo series of measurements calibrated by the catheter
in vivo isocenter : in vivo series of measurements calibrated by the isocenter
in vitro 50% : in vitro series of measurements with 50% contrast
in vitro 100% : in vitro series of measurements with 100% contrast
average : crude (unweighted) average of the absolute (signed) results

Table 4

MULTICENTRE QCA VALIDATION STUDY - REPRODUCIBILITY

	phantom size					average
	0.5 mm	0.7 mm	1.0 mm	1.4 mm	1.9 mm	
1	±.03	±.02	±.02	±.03	±.02	±.02 mm
2	±.06	±.07	±.12	±.06	±.07	±.08 mm
3	±.06	±.12	±.21	±.06	±.09	±.11 mm
4	±.10	±.06	±.08	±.06	±.08	±.08 mm
5	±.03	±.05	±.04	±.06	±.06	±.05 mm
6	±.10	±.08	±.08	±.12	±.05	±.09 mm
7	±.13	±.28	±.11	±.07	±.18	±.15 mm
8	±.15	±.23	±.27	±.04	±.09	±.16 mm
9	u/a	u/a	u/a	±.06	u/a	±.06 mm
10	±.16	±.17	±.20	±.07	±.16	±.15 mm

All reproducibility values are based on 15 repeated measurements of phantoms stenosis by each system.

u/a = unavailable

Table 5

MULTICENTER QCA VALIDATION STUDY - COMPARATIVE STATISTICS : CORRELATION (r) AND CORRECTED STANDARD ERROR OF THE ESTIMATE (SEEc):

	in vivo catheter		in vivo isocenter		in vitro 50%		in vitro 100%		average	
	r	SEEc	r	SEEc	r	SEEc	r	SEEc	r	SEEc
1	.90	.27	.91	.24	.97	.11	.94	.17	.93	.20
2	.96	.16	.94	.19	.94	.17	.99	.08	.96	.15
3	.89	.27	.81	.39	.93	.19	.96	.13	.90	.25
4	.91	.24	.97	.14	.99	.06	.97	.12	.96	.14
5	.98	.11	.95	.17	.95	.15	.97	.12	.96	.14
6	.91	.23	.93	.20	.96	.14	.94	.18	.94	.19
7	.90	.25	.91	.24	.95	.15	.96	.14	.93	.20
8	.86	.31	.93	.21	.91	.21	.97	.13	.92	.22
9	.91	.24	.91	.24	.89	.24	.86	.29	.89	.25
10	.83	.36	.90	.26	.92	.20	.98	.11	.91	.23

The correlation coefficient (r) and the corrected standard error of the estimate (SEEc) are derived by linear regression where the true values of the phantom stenoses are independent and the measured values are dependent. See text for description of the methodology of correction to derive the SEEc.

in vivo catheter : in vivo series of measurements calibrated by the catheter
in vivo isocenter : in vivo series of measurements calibrated by the isocenter
in vitro 50% : in vitro series of measurements with 50% contrast
in vitro 100% : in vitro series of measurements with 100% contrast
average : crude (unweighted) average of the absolute (signed) results

Table 6

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Conclusion

Currently, QCA systems using edge detection technique represent an important approach to assess the dimensions of coronary artery lesions with a potentially high degree of reliability both on-line and off-line.

Ideal conditions for the quantitative assessment of coronary artery dimensions are provided by isocentric calibration, whereas the use of the angiographic catheter as a scaling device produces a systematic error due to out of plane magnification of the catheter tip resulting in underestimation of vessel diameters.

It has been shown, that absolute parameters for the geometric assessment of vessel dimensions are a more reliable measure for comparative quantitative analysis than relative parameters such as percent diameter estimations, which can be explained by the variability of reference diameters when obtained from automatically defined reference contours and by uncertainties in the spatial definition of reference sites when arbitrarily defined by the coronary segment proximal or distal to the obstruction.

Whenever edge detection algorithms are applied to different imaging harware systems, considerable differences in accuracy, precision and reliability of measurements may occur, as all elements of the imaging chain can potentially affect the outcome of quantitative assessment. This finding has two implications; first, any alteration of image quality such as post-processing of digital images (edge enhancement) may directly influence the result of quantitative measurements, and second, it can be concluded that such alterations of image quality require additional adjustments of edge detection algorithms to maintain the reliability of geometric measurements. Adjustments of edge detection algorithms, however, imply the performance of validation studies in a standardized and uniform manner. This requirement is supported by the disconcerting variations detected in the multicenter validation of quantitative coronary angiography systems in Europe, Canada and the United States.

In spite of its theoretical superiority compared with geometric assessments, the practical application of videodensitometry in vivo still fails to demonstrate clear advantages in the quantitative assessment of coronary artery obstructions. This observation may be due to insufficient calibration techniques as available in current videodensitometric software packages. At small vessel cross-sectional areas, however, videodensitometric measurements can be carried out with high accuracy and reproducibility and even complex quantitative measurements like intracoronary volume assessment are feasable with a considerable degree of reliability.

Although coronary flow studies based on time-density analysis of myocardial images before and after application of vasodilators provide functional assessment of coronary artery obstructions, the application of this technique which requires a trained team of investigators,

is currently limited to specialized institutions. Off-line analysis of such coronary flow studies represents a new approach which allows centralized evaluation of multicenter trials at independent core laboratories.

While quantitative angiography continues to be the "reference method" for the assessment of intracoronary dimensions, intravascular ultrasound provides tomographic images of the arterial cross section allowing the morphological assessment of the vessel wall. Direct comparison of luminal cross-sectional area assessments at the site of coronary lesions using intravascular ultrasound and quantitative angiography shows many discrepancies due to the higher sensitivity of ultrasound towards vessel wall dissections, due to the dilating effect of the ultrasonic catheter, and last but not least due to spatial deviations of measurement positions using both techniques.
Diameter and stiffness of currently used ultrasonic catheters remain strong limitations for the investigation of tight coronary lesions or diffuse coronary artery disease. In large epicardial vessels, however, quantitative coronary angiography and intracoronary ultrasound can be used as complementary techniques to assess the geometry and morphology of coronary artery lesions as well as the result of interventional procedures.

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On April 1991, I availed of the unique opportunity to take up a research fellowship in interventional cardiology at the Thoraxcenter.

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