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Technologic Considerations and Practical Limitations in the Use of Quantitative Angiography During Percutaneous Coronary Recanalization

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ALTHOUGH the development of selective coronary arteriography[1] rapidly led to its acceptance by cardiologists as the "gold standard" in the diagnosis of atherosclerotic coronary artery disease (CAD), many authors have reported on the pitfalls associated with visual interpretation of the coronary angiogram.[2-9] The variability associated with visual quantification of stenosis has been shown to be related not only with the degree of compromise of the arterial lumen,[7] but also with the lack of uniformity in identifying the narrowest point of the lesion,[8] with the quality of the angiograms,[5] and with multiple anatomical factors, including lesion length, vessel irregularity, and branch overlap.[2] Selection of the angiographic view showing the stenosis at its most severe is equally affected by variability.[6] Although the variability associated with visual interpretation of coronary arteriograms can be reduced by a consensus panel,[9] it is self evident that such an approach is cumbersome, time-consuming, and cannot be applied during on-line analysis in cardiovascular interventions.

The advent of computerized image analysis and quantitative coronary angiography (QCA) has made possible the objective study of angiographic images over the past 15 years. During the same time period, the generalization in the use of percutaneous revascularization techniques using balloon angioplasty and other techniques such as coronary atherectomy and stenting has expanded the use of QCA in both the clinical and research fields. As a result of application of these interventional techniques, the data obtained have to be used to provide the operators with reliable information not only about the severity of the stenosis but also about aspects relevant to procedural decisions. Matching the size of the interventional device to the artery is required during recanalization to minimize vessel damage that may precipitate acute vessel occlusion and late restenosis.[10,11] Objective information on the changes in luminal dimensions obtained by the technique during the procedure may be required to decide whether discontinuation of the procedure or further recanalization is needed.[12,13] For the researcher, quantitative angiography has become the main tool to assess not only the primary efficacy of a particular technique but also the luminal renarrowing in the long term.[14]

The purpose of this article is to understand the advantages and limitations of QCA in the field of interventional cardiology. The Cardiovascular Angiography Analysis System (CAAS),

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developed at our institution and previously described in detail elsewhere,[15-18] will be used as an example, because it incorporates the two modalities of analysis that are more widely used, namely detection of luminal contours (so-called edge detection) and densitometry. These two types of analysis are discussed separately. A detailed comparison highlighting the similarities and differences between the CAAS and other QCA systems can be found in several reviews in the literature.[19,20]

CONTOUR-DETECTION QUANTITATIVE ANGIOGRAPHY

The first approach used in quantitative angiography consists of the analysis of the distances found between the leading edges of the luminal silhouette. From an historical point of view, this constitutes the first attempt to quantify vessel dimensions using calipers, either manual,[21,22] sometimes with optical magnification,[23] or digital.[24] Luminal diameters are widely used in quantitative angiography given the ease of measurement and probably because the fact that, at least at first glance, the information obtained with automated edge detection conveys information comparable with that used during visual interpretation of the angiogram or hand-held calipers (although this aspect has been questioned by the work of Fleming et al,[25] who found a better correlation between visual estimation of stenosis severity and luminal area derived from QCA analysis).

Despite its apparent simplicity, contour detection requires a sophisticated methodology for its adequate application. Because the borders of the luminal silhouette in the cineangiogram consist of a gradient of densities, identification of the true luminal borders is still uncertain and is a major cause of variability in the measurements. The problem posed to automated systems of edge detection is to establish at which level the transition between background and luminal densities of the opacified vessel occurs (Fig 1). In most automated systems, a two-dimensional analysis of the density observed in individual scanlines perpendicular to the vessel centerline solves this problem. Critical changes in brightness are detected by using the first and second derivatives of the density. The automated search is performed in consecutive scanlines that are repeated at close intervals over

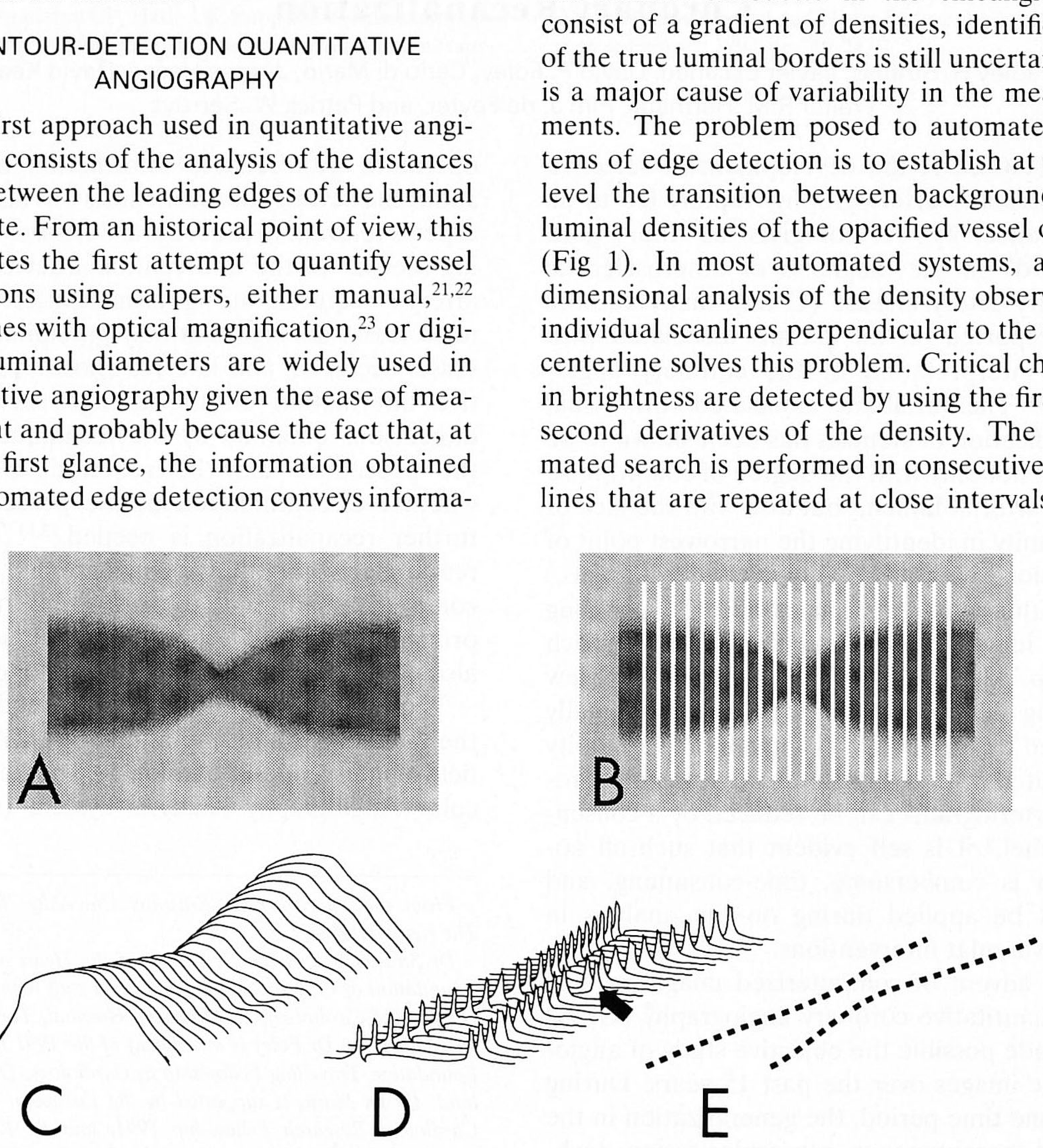


Fig 1. Steps followed during automated detection of luminal borders from the cineangiogram are shown. (A) The borders consist of a gradient of densities, posing the problem of establishing at which level the transition between background and luminal densities of the opacified vessel occurs. (B) A two-dimensional analysis of the density observed in individual scanlines perpendicular to the vessel centerline is performed. (C) The density observed in these consecutive scanlines is obtained. (D) Critical changes in brightness, corresponding to the transition between background and opacified lumen, are detected by using a combination of the first and second derivatives of the density. (E) The identification of luminal edges is based not only on individual scanlines but also on the overall information obtained from neighboring scan lines, which decreases the contribution of spurious variations in density that are observed a single scanline (arrow in D).

the studied segment. The information contained in an individual scanline may be influenced by local sources of error in edge detection, such as originating branches or overlying structures; therefore, the automated identification of luminal edges is based not only on individual scanlines but also on other neighboring scanlines. This identification is performed using so-called minimal cost algorithms, which facilitate edge detection over the length of the arterial segment being analyzed. By restricting the relevance of the information of each individual scanline, minimal cost analysis assumes that no drastic change in the contour of the vessel will occur in a very short segment. Thus, when complex angiographic morphologies with overhanging edges or abrupt changes are analyzed, errors derived from pitfalls in edge detection can occur. Finally, for a more precise detection of the luminal edges, an iterative method, which involves recalculation of the centerline and a new detection of the luminal contour, is applied. Each of these steps is fully automatic, and the only requirement for the user is the selection of the segment to be analyzed and the identification of a few arbitrary centerpoints within that segment.

Once the luminal diameters have been obtained, the distance between the edges at the level of each individual scanline can be easily calculated in pixel units. Calibration of the system with a structure of known dimensions, such as the filmed catheter, makes possible the transformation from pixels to absolute units. When the diameter values are plotted against the length of the analyzed segment, a so-called diameter function is obtained (Fig 2). Application of specific algorithms to the diameter function makes possible the calculation of a number of angiographic parameters. For example, in the CAAS system, the application of a curvature-detection algorithm to the diameter function identifies the location where a critical decrease in luminal dimensions (that is, one that is attributable to the stenosis and not to spurious variations in luminal diameter) occurs. The same principle is applied to identify both limits of the stenosis. Minimal luminal diameter (MLD) is easily identified in the diameter function as the point with the lowest diameter value.

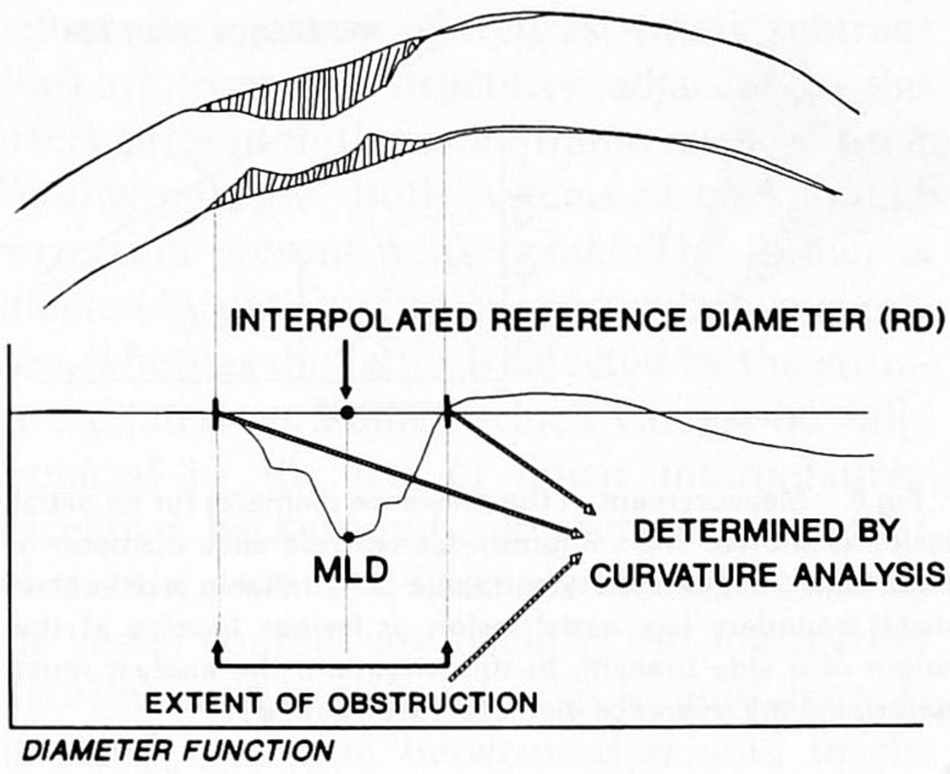


Fig 2. Schematic representation of a diameter function curve shows MLD, interpolated reference diameter, and the extent (or length) of the obstruction as determined by the curvature analysis.

For the calculation of relative measurements (percent diameter stenosis), MLD is compared with a reference segment. Although the latter can be defined by the user, it is obvious that visual identification of a reference segment would be associated with a similar variability as the point of minimal diameter, particularly in cases where the proximal part of the arterial segment shows a combination of stenotic and ectatic areas or in cases where a "normal" portion is just not clearly available. In an attempt to provide a solution to this problem, the CAAS system incorporates an interpolated reference diameter that is derived solely from the information conveyed by diameter function. In the CAAS system, the algorithm used for interpolation of the reference dimensions involves the calculation of a first degree polynomial, computed through the diameter values of the proximal and distal portions of the arterial segment, followed by a translation to the 80th percentile level (Fig 2). Interpolated reference diameter techniques are also useful when repeated measurements of the same segment are required, such as during follow-up studies after intervention. However, it is not possible to apply this technique when no reliable proximal or distal segment is present, such as in ostial lesions or in segments with incomplete opacification of the distal segment (Fig 3). In those cases, the selection of a reference segment by the user is justified (Fig 4).

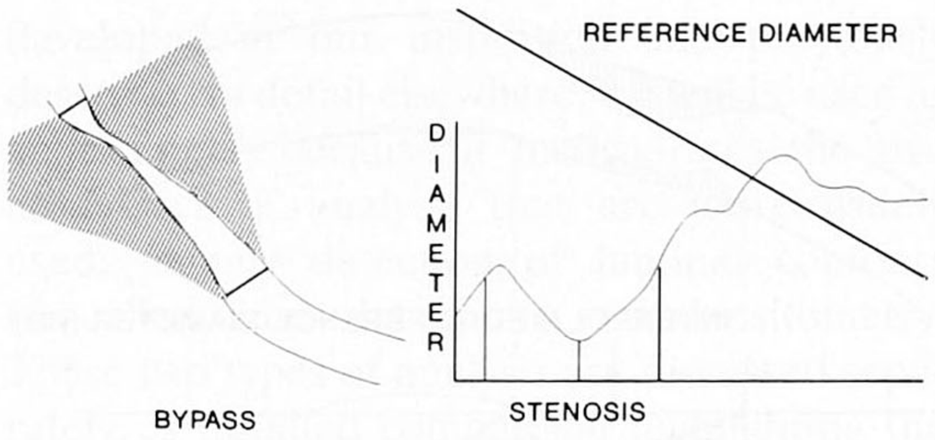


Fig 3. Measurement of the reference diameter for an ostial lesion is shown. The computer-defined reference diameter is inaccurate in situations where there is no reliable proximal or distal boundary (eg, ostial lesion or lesions located at the origin of a side branch). In this situation, the analyst must determine the reference diameter (user-defined).

In the CAAS system, the combined use of the interpolated reference dimensions over the analyzed segment and the detected luminal edges yields an estimate of the protrusive area of the atheromatous plaque (Fig 5). Similarly, a symmetry index is calculated as the ratio of the angiographic plaque observed at both luminal edges.

The curvature value is an attempt to convey a measure of the degree of curvature or bending of the coronary segment being analyzed (Fig 6). The angiographic projection in which the vessel appears to be the least foreshortened (ie, where the measured absolute distance between the proximal and distal boundaries of the segment is greatest) is chosen for the curvature analysis. The inflow and outflow angles are derived from the slope of the diameter function at the descending and ascending limb of the diameter-

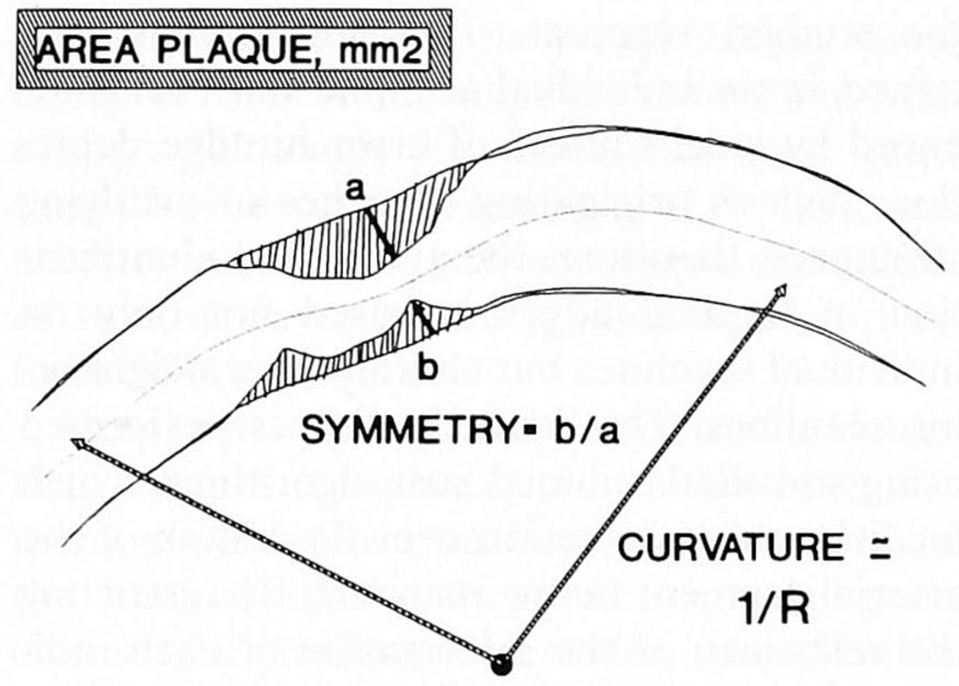


Fig 5. Determination of the area plaque, symmetry, and curvature values is shown (see text for details).

function curve at the defined site of the obstruction (Fig 6). The information derived from these parameters may be relevant in characterizing the hemorrheologic behavior of the stenosis and has been helpful in studying the characteristics of coronary artery lesions at risk of thrombotic occlusion[26] and in assessing the modifications in stenosis morphology after coronary stenting.[27]

DENSITOMETRY

The basic principle on which densitometry is based is the existing relationship between the attenuating power of the lumen filled with contrast medium, which is a function of luminal area, and the x-ray image intensity.[28] From this information, a densitometric profile that is proportional to the cross-sectional area of the

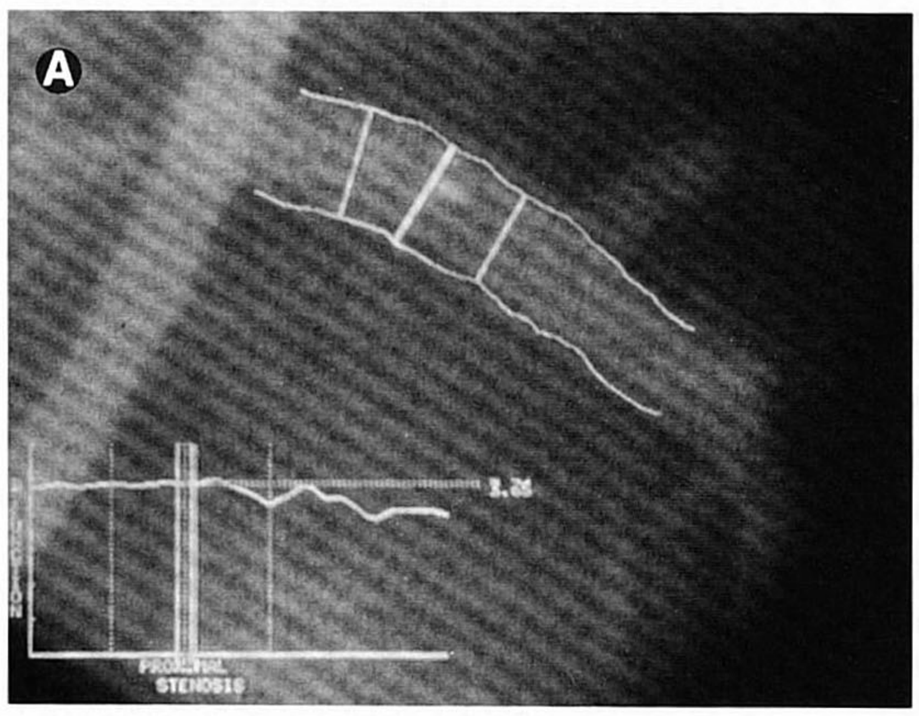


Fig 4. The user-defined reference diameter is also useful when the exact diameter is required at a specific location in the coronary artery. (A) In the validation studies of intravascular echo catheters, the tip of the echo-catheter is visible, and the diameter of the segment (3.26 mm) has been determined by the CAAS analysis. (B) It is also clear from the schematic diagram that different diameters are measured by the two methods, when the intravascular echo catheter is placed in a bend in the coronary artery.

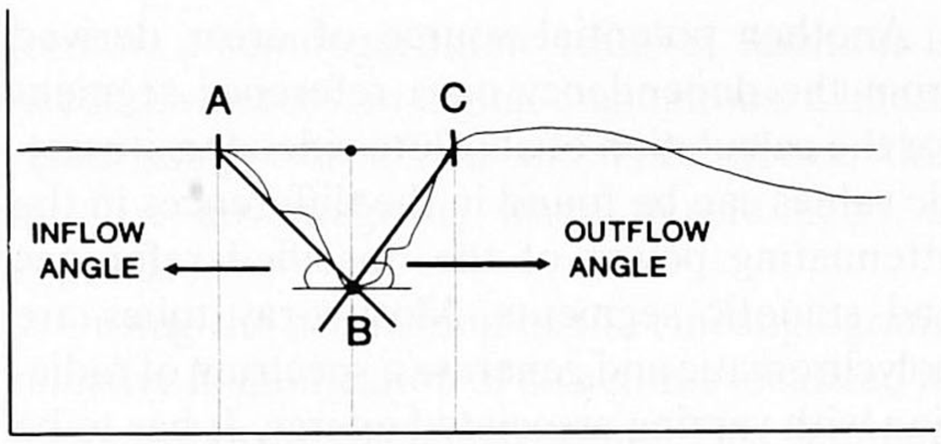


Fig 6. Determination of inflow and outflow angles from the diameter function is shown (see text for details). Inflow angle is the average slope of the DF between B and A; outflow angle is the average slope of the DF between B and C.

lumen is obtained, irrespective of its morphology. Thus, whereas edge detection analysis yields luminal diameters, densitometry provides an estimate of luminal area. A potential advantage associated with the use of area measurements is that it may yield more relevant physiologic information than luminal diameter measurements.[29-33] Furthermore, luminal area is calculated without making assumptions on lumen morphology and, theoretically, with independence from the angiographic angulation used.[28] On the other hand, the basic assumption of a correspondence between density and luminal area can be lost at every step of the collection, transfer, and analysis of data. Let us review some of these limitations.

To obtain a reliable correlation between luminal dimensions and videodensity, complete replacement of blood by contrast medium during each injection should be ideally obtained by the operator. Failure to do so may induce streaming of contrast that may affect the detection of the true luminal borders. Similarly, a decrease in concentration of iodine within the artery may cause errors during the calculation of luminal area from the densitometric profile. Perpendicularity of the x-ray beam to the analyzed segment is also important.

A major problem in videodensitometric analysis is derived from the presence of overlapping densities, corresponding to other anatomical structures, that can interfere with the calculation of luminal area. To correct for such patient structure noise, subtraction of the background has to be applied to obtain a net cross-sectional videodensitometric profile. Information obtained either from an identical image obtained before the injection of contrast (mask subtraction) or from the structures adjacent to the artery present in the same frame must be used for this purpose. Both systems of background correction present weak points. The former is affected by patient motion, particularly respiration, whereas the latter is affected by the structure-related variability, which cannot be fully replaced by the use of linear interpolation. Excessive background subtraction can occur when other vascular structures located close to the vessel contour are used by the subtraction algorithm or when the vessel is located in areas of rapid transition between dark and bright areas. In those cases, the subtraction can be so intense that the calculated cross-sectional area may even assume a negative value (Fig 7).

Not all brightness observed at the end of the cineangiogram-video chain can be attributed to the attenuation of the x-ray beam by the opacified vessel and anatomical structures. Both x-ray scatter and light reverberation within the optical systems, such as the image intensifier and video cameras (veiling glare), contribute up to 80% of the total light intensity.[34] When no correction is applied, these measured intensities are introduced in the calculation of luminal

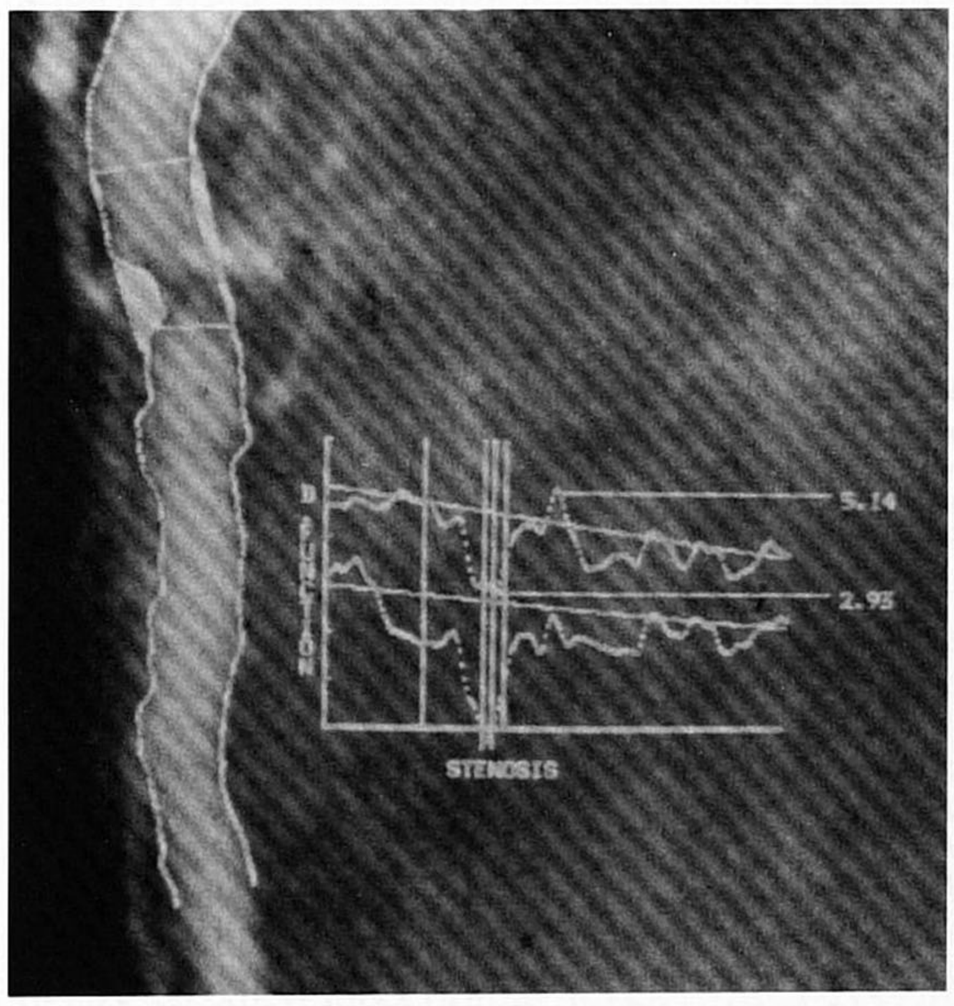


Fig 7. Densitometry measurements are affected and inaccurate in the presence of overlapping side branches. In this example, the upper curve (the diameter function) shows an MLD of 2.93 mm. However, because of interference from side branches from the background subtraction, the densitometric-determined MLCA (lower curve) is a negative value.

area and may constitute an important source of error.[34,35] The contribution of scatter and veiling glare varies with the location across the thorax, reaching maximum values when the coronary arteries are projected in areas with a rapid transition between the cardiac silhouette and the lung field, and makes correct positioning of angiographic wedge filters mandatory during image acquisition to minimize this source of error.

In the CAAS system, a luminal area function is constructed in an analogous fashion to that described for the edge detection modality and can be used in the calculation of interpolated reference area. However, a critical difference in the calculation of absolute values with both techniques is that densitometry relies on the calibration of the system using a reference videodensitometric profile, which is obtained in a segment of known dimensions. In the CAAS system, this reference profile is usually obtained in a computer-defined disease-free segment, which serves as a reference area and in which luminal area is calculated simultaneously from the luminal diameter assuming that the lumen has a circular morphology (Fig 8). When this is not the case, such as in diffusely diseased vessels, errors in area calculation can occur.

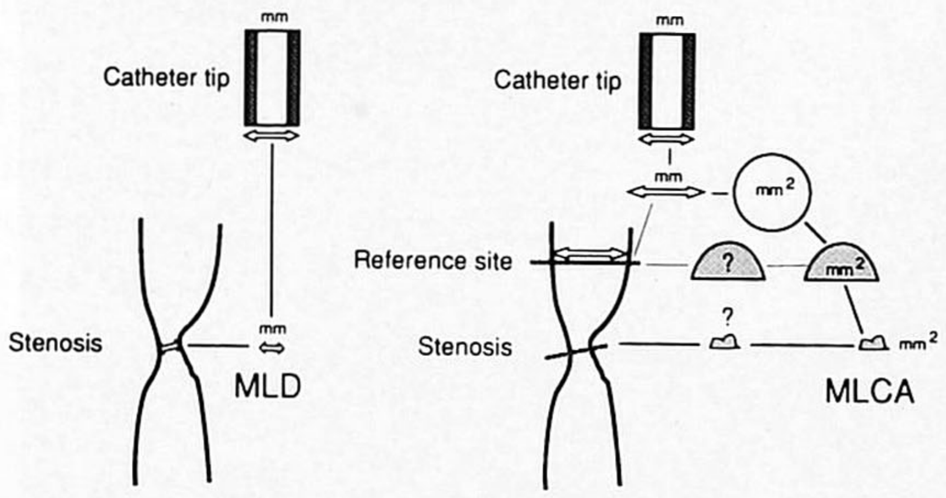


Fig 8. Calculation of absolute vessel dimensions by edge detection and videodensitometric analysis. In edge detection, the calculation of MLD is obtained by direct comparison with the diameter of the filmed catheter, which is used to calibrate the system. Videodensitometry yields a densitometric profile that has to be compared with a segment of known luminal area. This is achieved by automatic selection of a reference site where it is assumed that no occlusive atheromatous disease is present and that the lumen is circular. From the reference diameter (calculated from direct comparison with the coronary catheter as described above), geometric circular cross-sectional area at the reference site is calculated and compared with the densitometric profile at the same site. In this way, density units are transformed into area units (mm^2). By direct comparison of the densitometric area, thus calculated at the reference site, and of the smallest densitometric profile in the stenotic segment, MLCA is derived.

Another potential source of error derived from the dependency on a reference segment for the calculation of absolute videodensitometric values can be found in the differences in the attenuating power of the opacified reference and stenotic segments. Most x-ray tubes are polychromatic and generate a spectrum of radiation with varying associated energy. It has to be remembered that the Lambert Beer law, which is used in most QCA videodensitometric systems,[20] requires a monochromatic source of x-rays. When the less energetic fraction of the radiation produced by the x-ray tube is selectively attenuated by a opaque structure, a substantial modification of brightness at the level of the image intensifier occurs because of the penetration of a "harder" x-ray beam (beam-hardening effect). Furthermore, because the column of contrast medium at this reference site has a higher attenuating power than that existing at the stenotic site, the characteristics of the densitometric profile can be modified by this so-called beam-hardening effect. Differences in the beam-hardening caused by the different attenuating power of the contrast column existing at the reference and stenotic segments can, when not corrected, affect all subsequent calculations of stenosis severity (Fig 8).

IMAGE ACQUISITION AND ANALYSIS IN CONTOUR DETECTION AND DENSITOMETRY

Edge detection and densitometry share common limitations and requirements that must be kept in mind during their applications. In the following paragraphs several of these aspects are discussed. At the present time, images for QCA are obtained from cineangiograms or digital systems. The main advantages of using cine films stems from the fact that they have a higher spatial resolution than digital images. Furthermore, by using adequate zooming with optical systems, a section of the image encompassed in the cine frame can be selected and digitized for further analysis. When digital systems are used, the spatial resolution of the images is currently hampered by the size of the matrix being used (512 × 512 pixels). The use of cineangiograms or digitally acquired images also has implications for the type of transfer function used during image analysis. In the

former, a semilogarithmic transfer function is needed, whereas, in digital angiograms, a linear relationship exists.[20] As discussed above, this may be advantageous when densitometry is applied.

During the acquisition of the cineangiogram, selective magnification of structures localized in the periphery of the image occurs. This phenomenon is termed "pincushion distortion," and can be minimized by the operator through proper manipulation of the table and gantry to ensure a location of the stenosis as close to the angiographic isocenter as possible. Pincushion distortion has been markedly decreased in new generation image intensifiers. In addition to the above-mentioned precautions, correction for the images obtained can be performed during off-line analysis. For this purpose, a centimeter grid must be filmed in each mode of the image intensifier and later used by the CAAS system to calculate a correction factor for each intersection position of the grid wires so that the pincushion distortion can be corrected.[36]

An additional important practical point for the physician in all serial studies is the requirement for coronary vasodilation using agents of comparable efficacy for every study. In a recent study of 202 patients,[14] the mean diameter of a normal segment of a nondilated vessel pre-percutaneous transluminal coronary angioplasty (pre-PTCA), post-PTCA, and at follow-up was analyzed (Table 1). Of these patients, 34 who received intracoronary nitrates pre-PTCA but not before the post-PTCA angiography showed a decrease of 0.11 mm in the reference diameter versus the small increase of 0.02 mm in the group that did receive postprocedural nitrate. Vasomotion should be controlled in QCA studies by means of a vasodilator drug that produces fast and complete vasodilation without significant effects on the peripheral circulation. At our institution, 0.1 to 0.3 mg of nitroglycerine or 1 to 3 mg of isosorbide dinitrate are used before angioplasty, after the last balloon inflation, and at follow-up angiography. Furthermore, the use of nonionic contrast medium is probably recommended because of its less intense effect on coronary vasomotion.[14] Warming of contrast medium to body temperature is also recommended to minimize potential vasomotor effects.

Table 1. Influence of Vasomotor Tone on QCA Measurements of Nondiseased Segments

Mean Diameter (mm)	Without Nitro Post-PTCA (n = 34)		With Nitro Post-PTCA (n = 168)
Pre-PTCA	3.12 ± 0.63		2.74 ± 0.63
Post-PTCA	3.01 ± 0.64		2.75 ± 0.59
F-Up	3.18 ± 0.55		2.82 ± 0.63
Δ Post-pre	−0.11 ± 0.27	↔	+0.02 ± 0.21*
Δ F-up–pre	+0.06 ± 0.22	↔	+0.07 ± 0.22†

Thirty-four patients did not receive intracoronary nitroglycerin post-PTCA. In the nondiseased segments adjacent to the dilated site, in these patients the mean diameter decreased by 0.11 mm after angioplasty compared with the pre-PTCA values (where nitroglycerine had been administered). This change was not seen in the group who received nitroglycerine post-PTCA. Such change in reference diameter will affect the determination of percentage diameter stenosis.

Abbreviations: Nitro, nitroglycerin; F-up, follow-up.

*$P < 0.001$.

†P value is not significant.

The ability to obtain reliable measurements from a single angiographic view would simplify enormously the use of on-line quantitative angiography. Although routinely applied in many laboratories, little information is available on the variability related with this approach. When edge detection is used, Lesperance et al[37] have suggested that restricting the analysis to the angiographic view in which the stenoses appears most severe fulfills the degree of accuracy required in clinical practice. However, the conclusions of this study were limited by the lack of a true standard for the assessment of precision and accuracy. Densitometry is an appealing alternative to edge detection, because the obtained measurements should not be influenced by the angulation used, a principle supported by experimental in vitro studies.[38-41] However, major controversy remains as to the application of this principle in the clinical field. The correlation for individual measurements obtained in orthogonal views both before and after balloon angioplasty has been found by different authors to be high,[42] moderate,[43] or poor.[44] It has also been found to be influenced by the stage of the intervention, deteriorating after balloon angioplasty to an unacceptable level.[45] In a recent study,[46] we have found that the variability of measurements obtained from two orthogonal views in a selected coronary segment was too high to recommend its application routinely. Although this was observed for both edge detec-

tion and videodensitometric data at all stages of balloon angioplasty, after balloon dilatation, densitometry showed significantly less variability between orthogonal measurements than did edge detection.

TECHNICAL ASPECTS OF QCA IN SPECIFIC RECANALIZATION TECHNIQUES

As stated in the introduction, the development of a variety of percutaneous recanalization techniques has introduced unexpected requirements for the analysis of vascular segments with conventional QCA systems. The different mechanisms of action associated with each technique have major implications for the performance and interpretation of QCA analysis. In the following paragraphs, we discuss some of these aspects in the case of conventional balloon angioplasty, stent implantation, directional atherectomy, rotational plaque ablation, and excimer laser angioplasty.

Balloon Angioplasty

Balloon angioplasty constitutes the most widely used percutaneous recanalization technique in the coronary arteries. The mechanism of action of angioplasty has been described in detail and involves tearing of the intima and atherosclerotic plaque, dehiscence of plaque from the tunic media, and variable degrees of medial and adventitia disruption.[47,48] From the point of view of this article, we can group the changes into three different categories: (1) the development of large disruption that can be visually identified in the coronary angiogram as dissection (Fig 9);[49] (2) the presence of intraluminal flaps and irregularities not actually identified angiographically but documented in angioscopic,[50-52] ultrasound,[53-55] and pathologic studies;[56] and (3) the change to noncircular lumen geometry secondary to balloon dilatation.[47] Several authors have suggested that these histopathologic changes are responsible for the decrease in angiographic accuracy observed after balloon dilatation.[57-61] When opacified during angiography, these irregularities may be wrongly identified as true luminal borders by edge detection algorithms, leading to a false estimation of luminal diameter.

Dissections are a frequent occurrence after PTCA, and the resulting haziness, irregular borders, or extravasation of contrast medium makes edge detection difficult (Fig 9). Few methodologic recommendations are available as to the QCA analysis of those cases. During the design of the MERCATOR trial, the Angiographic Steering Committee of the study decided that, during edge detection analysis, the automated mode of the computer "decides" whether the extraluminal defect is included or excluded from the analysis.[49] This is based on the assumption that if there is no clear separation between the lumen and the extravasation (because of the existence of large communicating channel), the application of minimum cost criteria during edge detection (see above) would incorporate the extravasation as part of the true lumen. On the contrary, the exclusion of the extravasation would be, presumably, caused by the presence of a steep difference in brightness

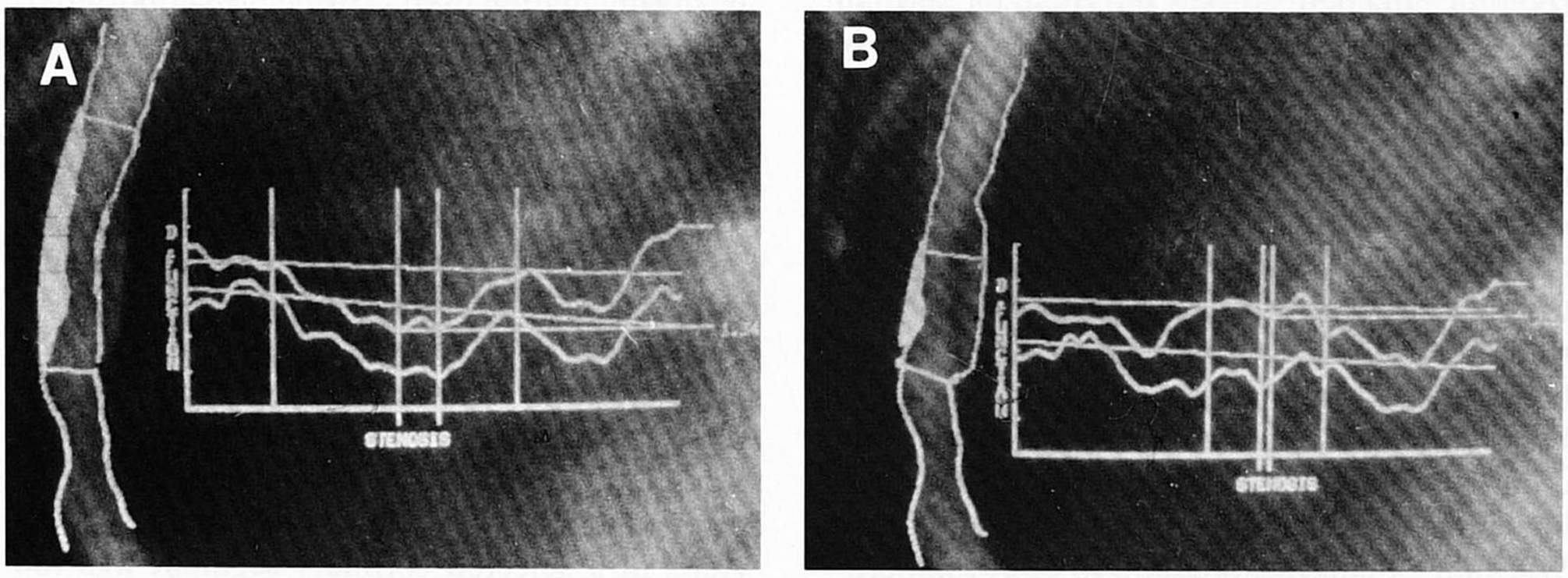


Fig 9. Edge detection of a lesion after PTCA has induced a large dissection. (A) Excluding dissection, the MLD is 1.34 mm. (B) Including the dissection, the MLD is 2.53 mm.

between the extravasation and the true lumen. The validity of these assumptions has yet to be shown and constitutes an empirical approach aimed to reduce subjective bias during angiographic analysis.

The reliability of videodensitometric measurements taken under circumstances similar to those found after balloon angioplasty has not been clearly established in an experimental setting. Such experimental settings have been based on the use of engineered phantoms either in vitro[38-41] or after percutaneous insertion in animal models.[62,63] This may explain the differences found with results obtained in clinical practice, where conflicting results suggesting a high variability in the obtained measurements have been reported (Fig 10).[57-60,64-69]

In a previous study,[46] we found, using edge detection before and after balloon angioplasty, that the agreement between single orthogonal measurements deteriorates significantly after balloon dilatation. However, this deterioration was not related to the presence of angiographically evident dissection. As mentioned above, we could also note that the variability between orthogonal measurements obtained with densitometry was less influenced by balloon dilatation than was that for edge detection. This observation may be related to the discussed theoretical independence from lumen morphology and to its relative insensitivity to imprecise border positioning[70] of videodensitometric measurements. Thus, although the application of densitometry may be currently hampered by the technical limitations discussed above, further progress in solving these problems may lead to a satisfactory application of the technique.

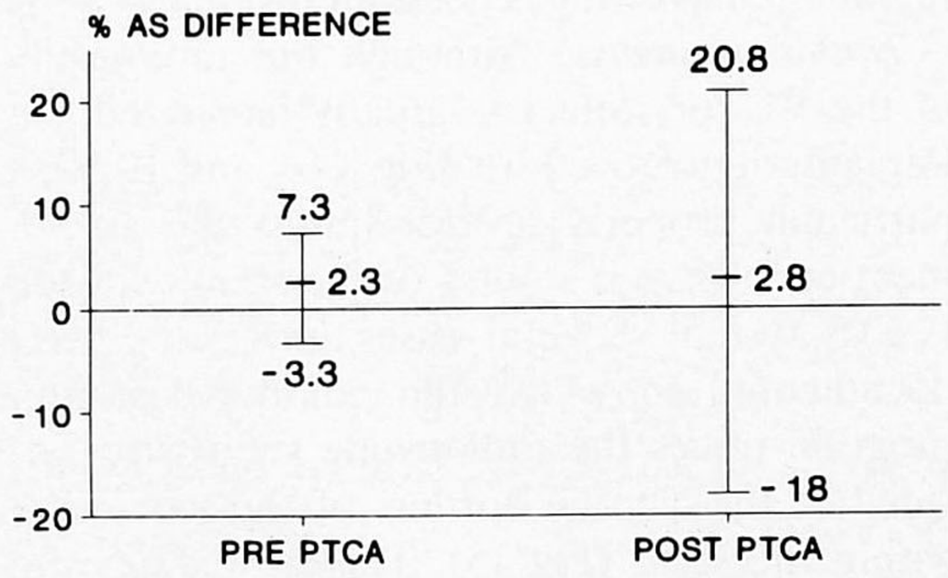
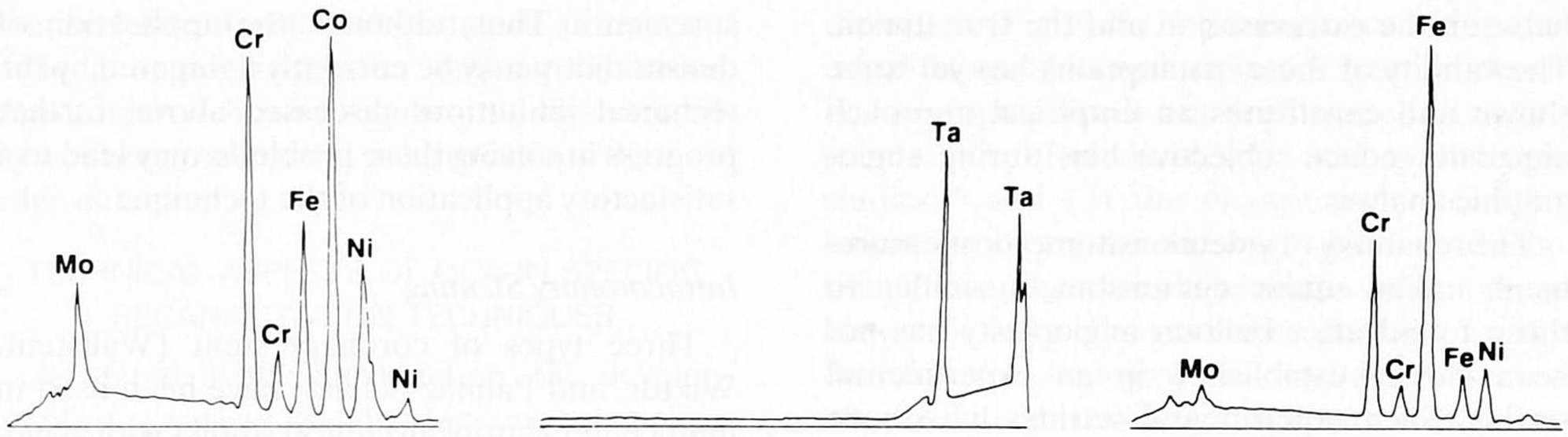


Fig 10. Agreement between densitometric percentage of area stenosis and the circular (edge detection) percentage of area stenosis pre- and post-PTCA is shown. The mean difference (and standard deviation) for percentage of area stenosis between the two methods was 2.3% ± 4.0% pre-PTCA and 2.8% ± 18% post-PTCA. Important discrepancies (ie, large standard deviation) between the two methods after PTCA are likely related to the noncircular, asymmetric configuration of the lesion after angioplasty.

Intracoronary Stenting

Three types of coronary stent (Wallstent, Wiktor, and Palmaz-Schatz) have been used in multicenter European clinical studies with angiographic follow-up and subsequent detailed QCA analysis at the Thoraxcenter Core Laboratory,[27,71-74] and a fourth (Gianturco-Roubin) is currently being evaluated in the "bail-out" setting. In all cases, the radiopacity of the stent has implications both for implantation and for the subsequent angiographic analysis, because its presence in the artery can interfere with edge detection algorithms.[61] The Wallstent and the Palmaz-Schatz stent are composed primarily of relatively radiolucent stainless steel, whereas clear, radiopaque tantalum is the principle constituent of the Wiktor stent (Figs 11A, B, and C).

A second problem with angiographic analysis of stented vessels is caused by the superior angiographic result immediately after stenting. Because routine mild oversizing of the stent has been recommended,[75] the stenosis may not only be completely corrected but also may be overdilated in comparison with the reference diameter before stenting. This may cause particular problems with the algorithms that measure lesion length and the calculation of the interpolated reference diameter. To bypass this problem, we arbitrarily define the length of the lesion after stenting as the actual length of the stent (which requires manual selection of the stent boundaries). Thus, the stented segment is defined for future follow-up analyses. An alternative to this type of analysis "per stent" is to perform a fully automated analysis "per vessel" by choosing landmarks located proximally and distally to the stented site (eg, branching points). In reporting our angiographic studies, we chose the pre- and post-PTCA frames to be analyzed "per vessel," and the post-stent and follow-up films to be analyzed "per stent." This ensures that we can obtain measurement data relating to the stent itself and its immediately adjacent segment, rather than obtaining measurement of



Wallstent (Medinvent) Wiktor stent (Medtronic) Palmaz-Schatz stent (J & J)

Fig 11. The metal composition according to x-ray energy dispersion spectrometry used in three currently investigated coronary stents. Ta, tantalum; Mo, molybdenum; Cr, chromium; Co, cobalt; Fe, iron; Ni, nickel. (Reprinted with permission.[76])

a more severe stenosis at a separate site in the coronary vessel.

Stenting has also highlighted a limitation of the CAAS system in determining a reference diameter in an overdilated segment. Theoretically, this should result in a negative value for diameter stenosis, because the MLD (which, as we already mentioned, was defined within the boundaries of the stent) was actually larger than the reference diameter (which is determined according to the diameter of the proximal and distal segments; see Figs 12A and B). However, for reasons that are unclear, a negative diameter stenosis has rarely occurred, and the reference diameter has virtually always remained larger than the MLD, in contrast to the post-stent measurements reported by other groups. This may be explained in many cases by detection of an MLD within the stent because of the protrusion of intima between the struts or at the articulation point. Thus, whereas the average diameter within the stent may appear greater than that of the adjacent segments outside the stent, detection of a single diameter measurement less than the reference diameter will provide a percentage of diameter stenosis greater than 0%. A further confounding factor in the determination of the reference diameter after stenting is that the marked vasospasm, occasionally seen immediately proximal and distal to the stent, may persist despite nitrate administration. This factor must be taken into account during "per vessel" analysis.

Stainless steel stents. The main problem with these stents is their poor radiographic visibility (Figs 13A and B). In particular, the Palmaz-Schatz stent, which is the most difficult stent to visualize, can be dislodged from the balloon catheter and embolize distally without radiographic evidence. Additionally, it can be quite difficult to ensure ideal placement of the stent across a lesion. For the analyst, it may be difficult or impossible to satisfactorily identify the stent boundaries, and the precise location of a recurrent lesion at follow-up angiography (within the stent or immediately adjacent) may be in some doubt. Careful review of the contrast-free cineframes may be needed to detect the position of the Wallstent. In our follow-up reports of stenting, we have always included lesions within and immediately adjacent to the stented segment to ensure that the degree of luminal renarrowing is not underestimated.[73]

Tantalum stents. Although the radiopacity of the Wiktor stent has greatly facilitated the implantation procedure (Fig 14A and B), this particular property severely limits the assessment of follow-up studies of the stent with the CAAS system. Several cases have now been documented in which the contour-detection program traces the radiopaque stent wires instead of the arterial borders of the narrowing within the stent (Fig 15). This invalidates the computer-derived data and requires manual correction of the contours by the analyst, which is also difficult in a segment containing radiopaque wires.

Densitometry in stented vessels. In contrast to the situation after PTCA, there is excellent agreement between minimal luminal cross-

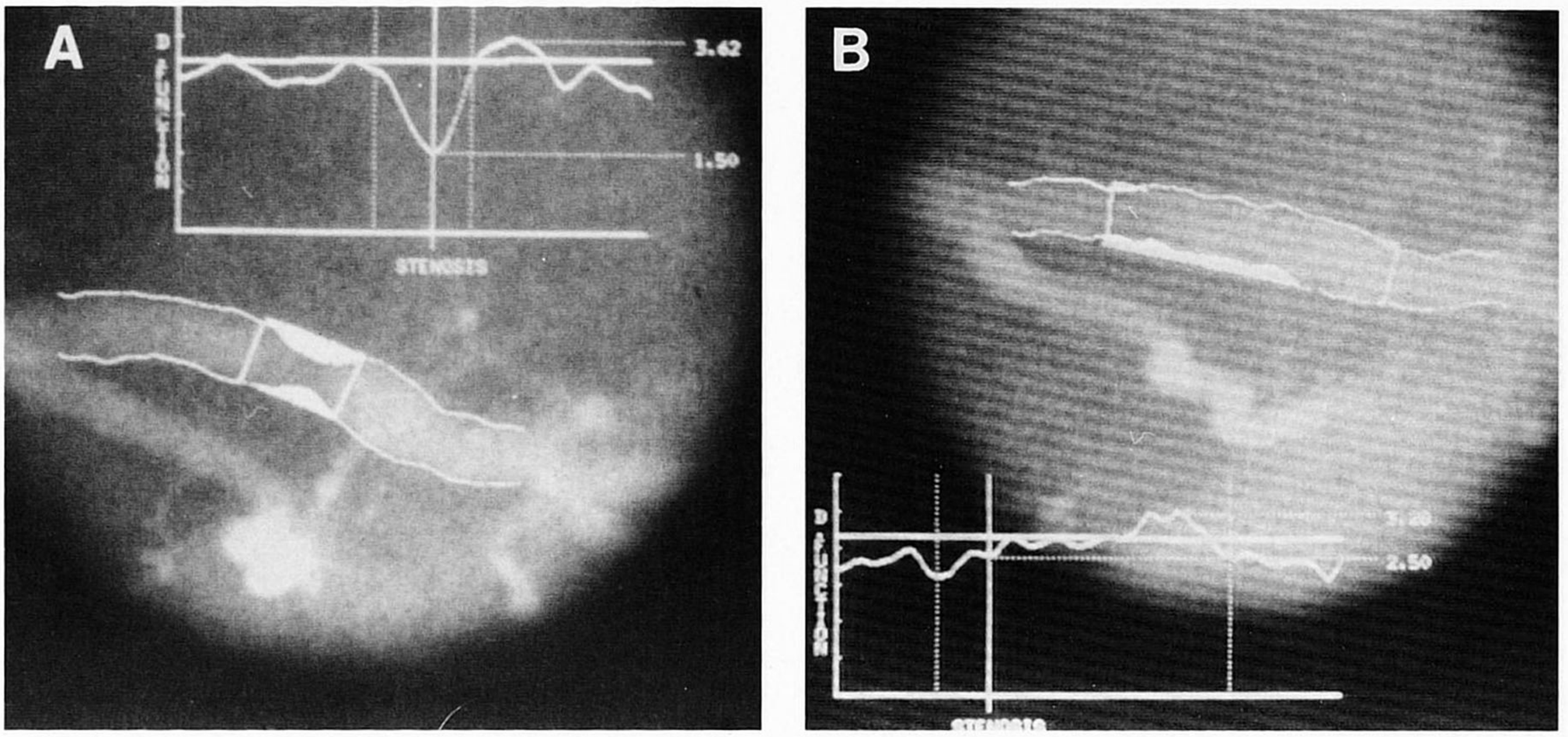


Fig 12. Coronary segment overdilated by a Palmaz-Schatz stent, (A) pre-stent (B) post-stent is shown. Although MLD in the stented segment should be greater than its reference diameter (which is determined for the stented segment by the algorithm, for the most part, from the smaller proximal and distal segments), the measurement given by the interpolated technique yields a reference diameter that is actually larger than the MLD, for reasons which are not entirely clear. Thus, the diameter stenosis within the stented segment after implantation of an oversized stent is positive (12%) rather than negative.

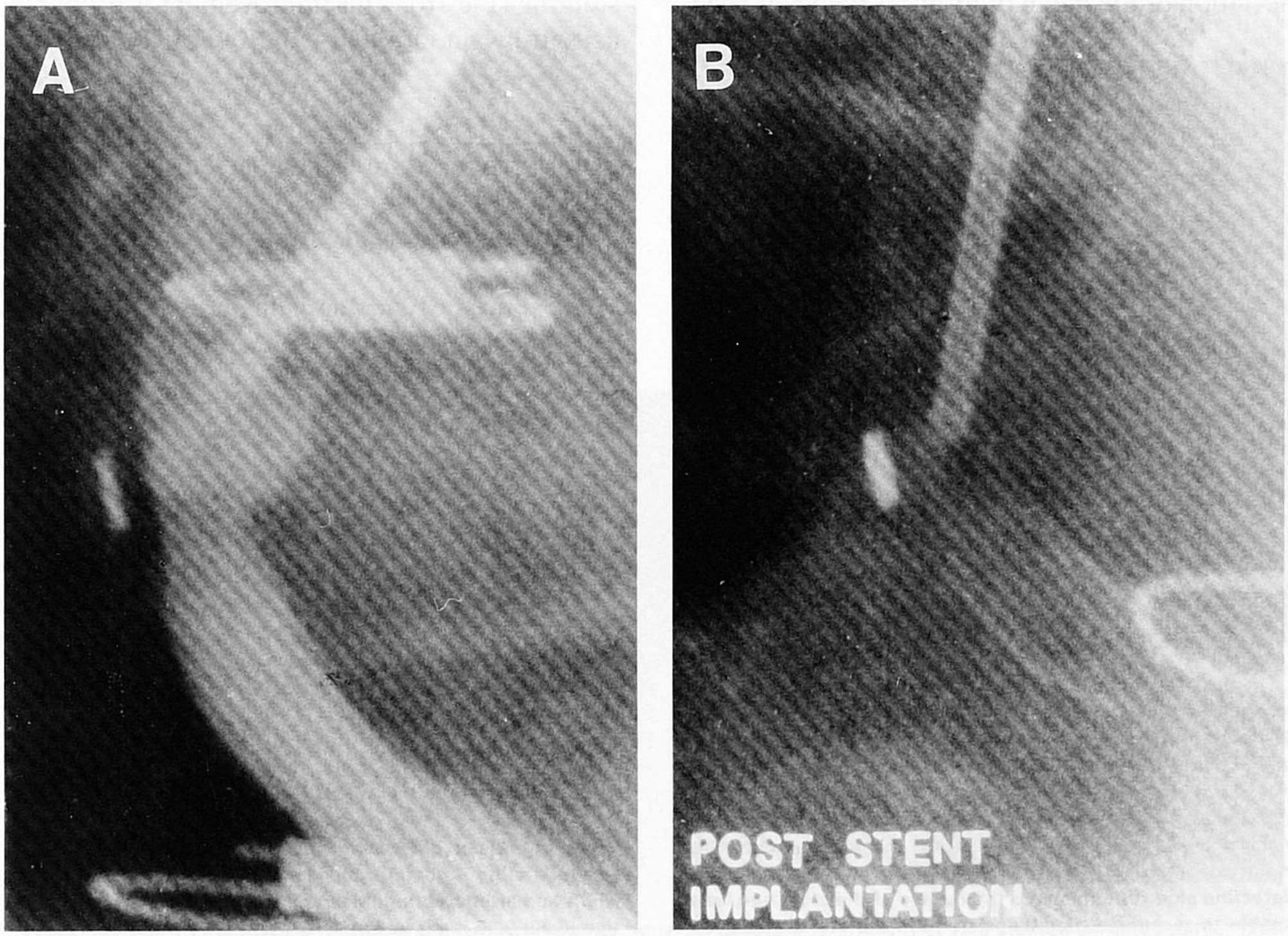


Fig 13. The Wallstent (poor radiopacity), after implantation in a saphenous vein bypass graft, is shown, on the left (A), in vessel opacified by contrast and, on the right (B), in vessel without contrast.

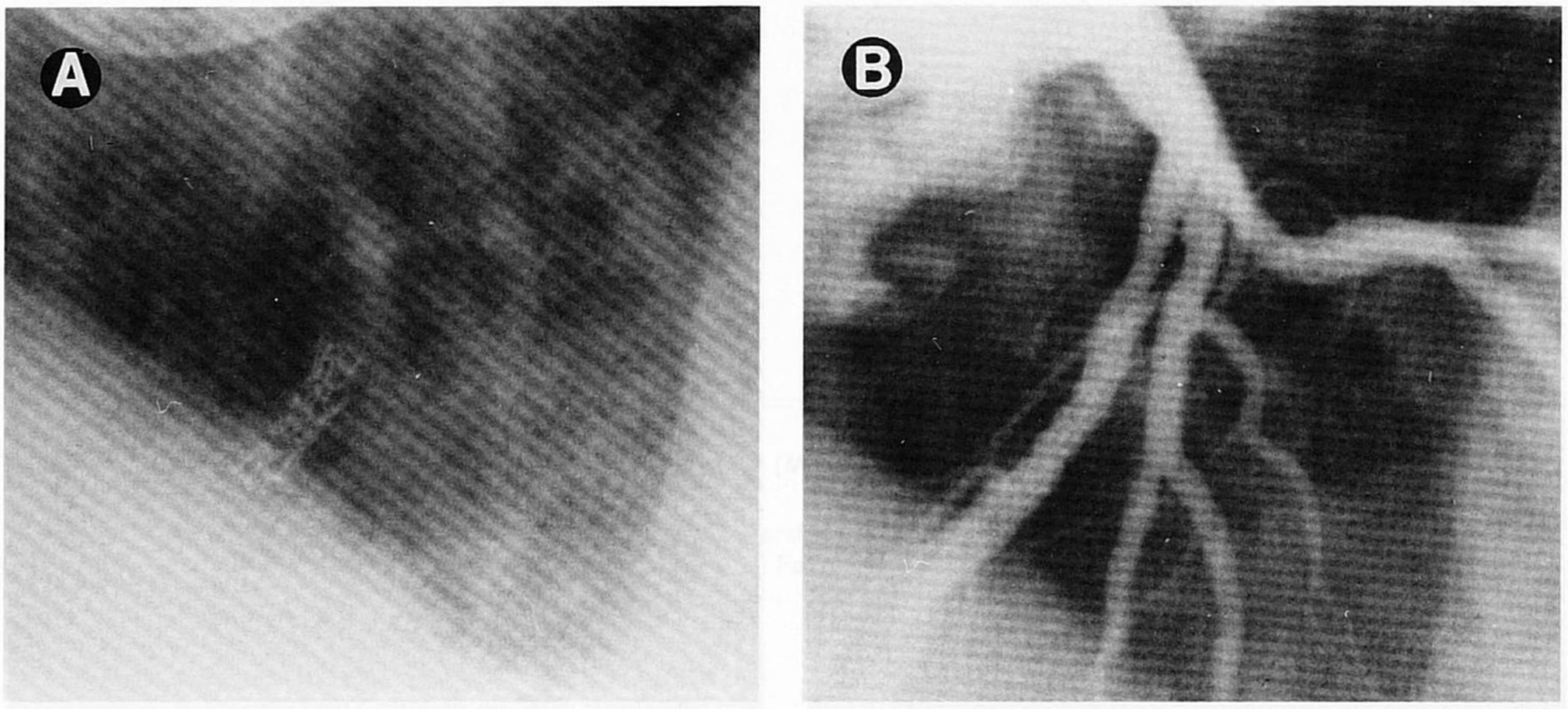


Fig 14. Wiktor stent after implantation in left anterior descending artery is shown (A) in vessel without contrast. (B) In vessel filled with contrast, the stent remains clearly visible.

sectional areas (MLCAs) determined by edge detection and by densitometry after stent implantation with the Wallstent.[61] The standard deviation of the mean differences between edge detection and densitometric determination of MLCA were 0.51 mm^2 pre-PTCA, 1.22 mm^2 after angioplasty, and 0.79 mm^2 after coronary stenting (Fig 16). This improvement is probably caused by smoothing of the vessel contours by

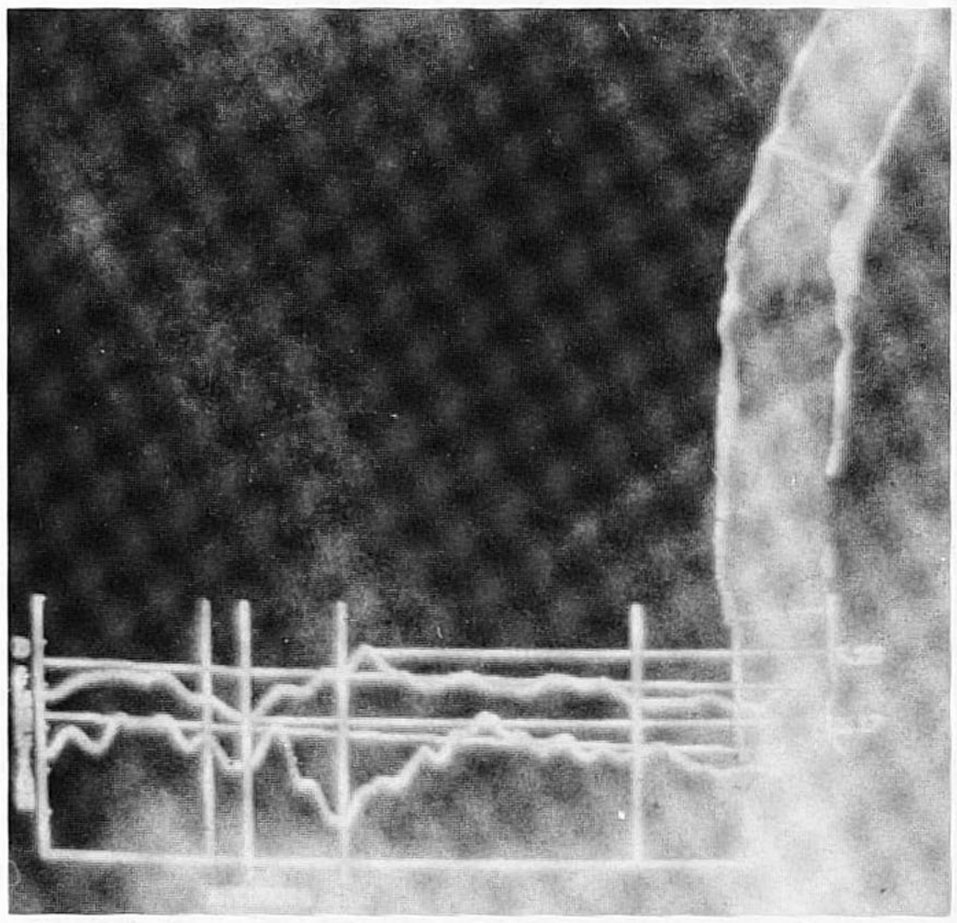


Fig 15. Restenosis within a coronary Wiktor stent not recognized by edge detection is shown. Graph shows the diameter function (upper curve) and the densitometric area function (lower curve). Outside vertical lines on the graph and two horizontal lines in the angiographic image are the corresponding boundaries of the analyzed segment. The inner two vertical lines on the graph represent the minimal points on the diameter and densitometric graphs respectively. The edge detection algorithm followed the outline of the stent and was unable to recognize the stenosis within the stent, giving an MLD of 2.17 mm. A discrepancy between the two functions is present and most notable at the vertical line that denotes the MLCA determined by densitomety. (Reprinted with permission.[76])

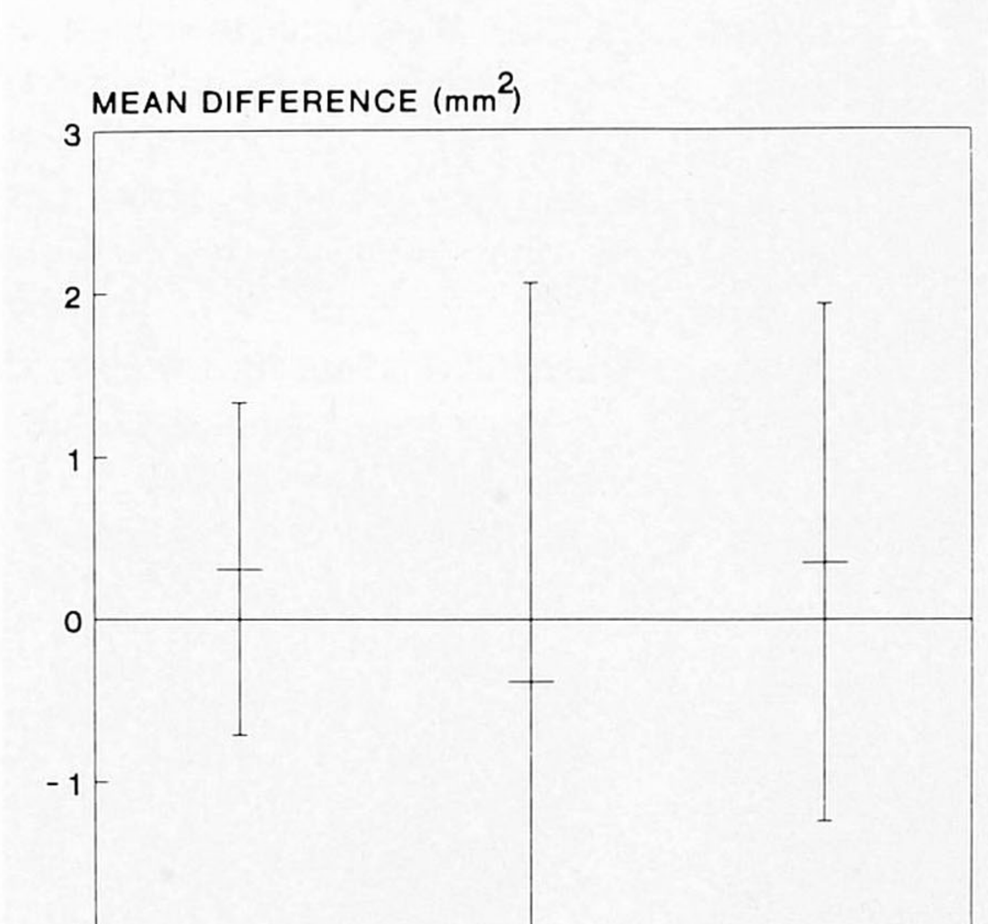


Fig 16. Mean difference (and 95% confidence intervals) between edge detection and densitometry before and after PTCA and after stenting. Mean differences were slightly positive (0.31, 0.35 mm^2) before PTCA and after stenting, respectively, and slightly negative (−0.38 mm^2) after PTCA. The widest 95% confidence interval was in the analysis after PTCA, indicating the poorest association between the two methods, compared with the analysis before PTCA and stenting.

the stent and remodeling of the stented segment into a more circular configuration (Fig 17). Therefore, we believe that both methods are appropriate to assess the immediate results after stenting. In a separate in vitro study in which stents were placed within plexiglass phantoms with known luminal dimensions, the Wallstent and Palmaz-Schatz stents caused minor interference with the densitometric determination of MLCA within the "stenoses" (Figs 18A and B)[76] that probably lack clinical relevance. Conversely, the radiopacity of the tantalum Wiktor stent led to overestimation of MLCA measurements in these same stenoses, which varied from 10% to 56% overestimation depending on the concentration of contrast medium used and on particular features of the stenosis (Fig 18C). Therefore, follow-up quantitative angiographic assessment of a lesion containing a vividly radiopaque stent may be subject to measurement imprecision because of this propensity for error, which appears to be inherent to both the edge detection and videodensitometric methods.

Directional Atherectomy

Few problems have been encountered in the angiographic analysis of lesions treated by directional atherectomy.[77] The radiopacity of the device, particularly when the support balloon is inflated, allows excellent visualization of the position of the eccentric cutting apparatus (Figs 19A and B). The vessel luminal contours are typically smooth and much less ragged than after PTCA, facilitating edge detection analysis. However, despite the apparent smooth contours, a discrepancy exists between analysis performed by edge detection and densitometry, similar to that which occurs after angioplasty (Fig 20),[78] suggesting that the vessel contour after atherectomy may not be as circular as it appears. It has been suggested that this may be caused by preferential expansion of the bases of the atherectomy cuts.[79] Furthermore, QCA of atherectomy-treated lesions has provided some insight into the mechanisms of lesion improvement. Penny et al[79] have shown that an average of approximately 28% of the effect of atherectomy could actually be attributed to tissue removal, although the individual values had a wide range (7% to 92%).[79] The correlation between the volume of tissue retrieved and the change in luminal volume was poor. The investigators concluded that the major component of luminal improvement was caused by "facilitated mechanical angioplasty" resulting from the high profile of the device and the low-pressure balloon inflations. Data from our angiographic core laboratory seem to support this hypothesis. In 10 patients who had angiography (with subsequent quantitative analysis) performed at baseline after the device had been threaded through the stenotic area and, again, immediately after the completion of the atheroma extraction pro-

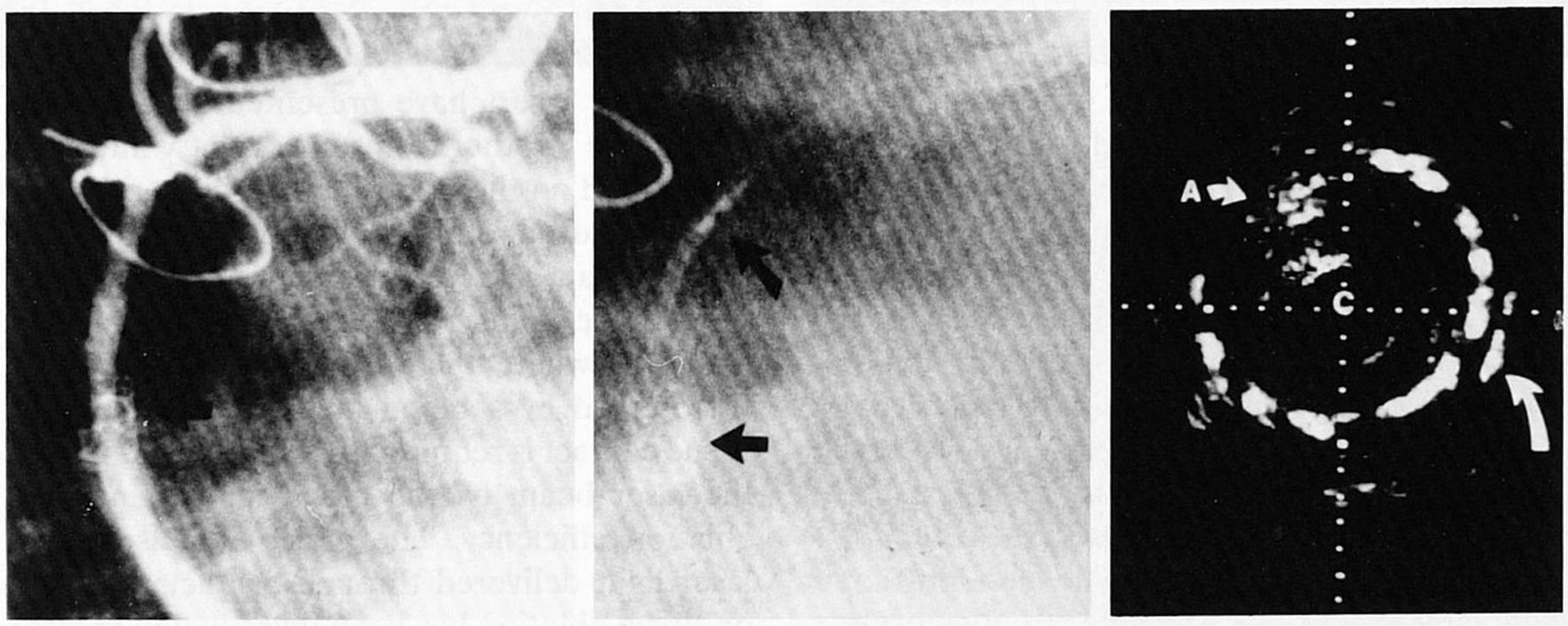


Fig 17. In vitro intravascular ultrasound examination of left anterior descending artery that was stented 24 hours earlier for a severe dissection during PTCA. (The patient died from intracerebral hemorrhage 12 hours after stenting.) The inner circle (c) is the actual intravascular probe itself. The outer echo-dense pattern is caused by the stent wires (large arrow). The lumen is the echo-free space inside the stent. The stent effectively tacked back the dissection and restored the circular configuration of the vessel. (Reprinted with permission.[61])

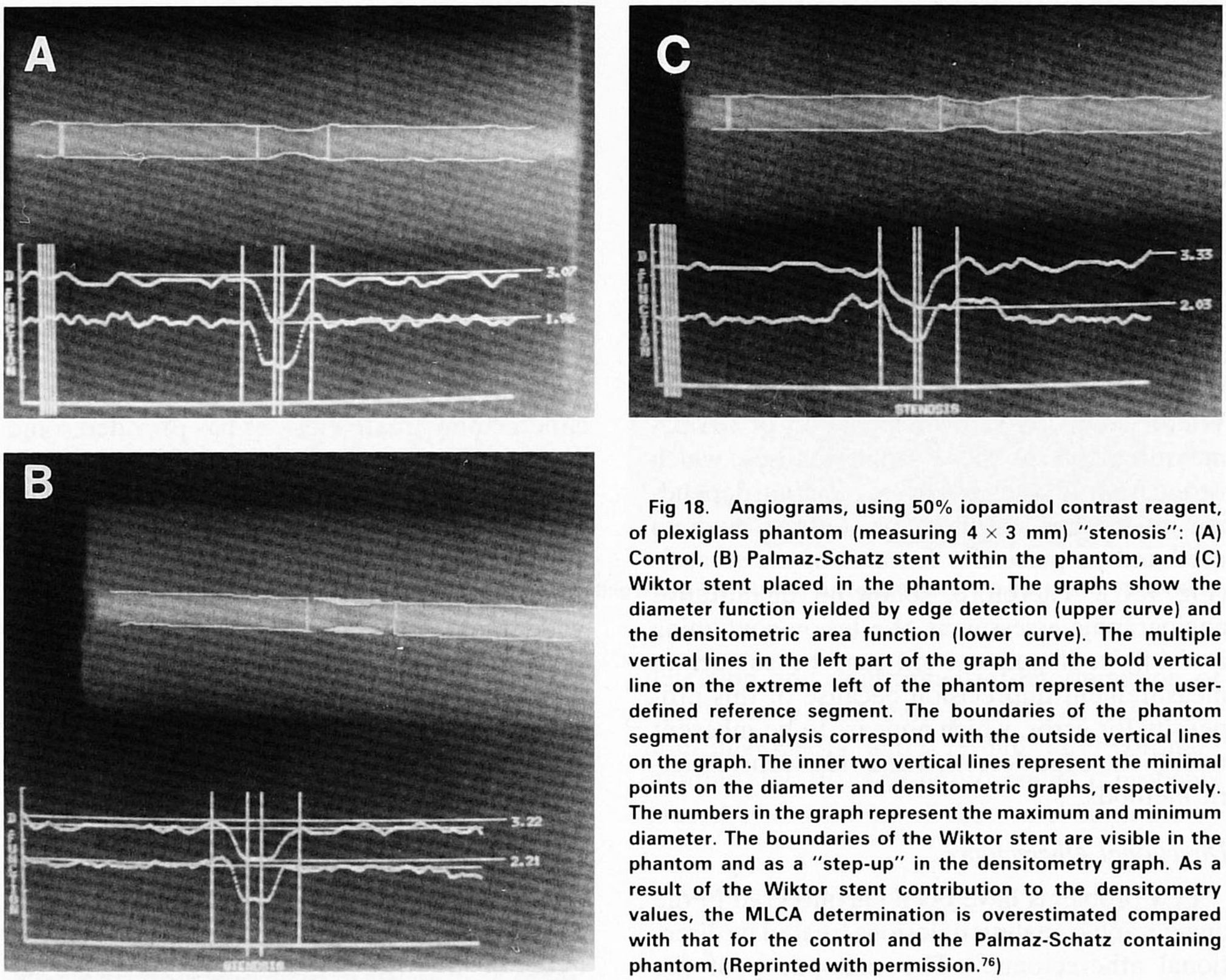


Fig 18. Angiograms, using 50% iopamidol contrast reagent, of plexiglass phantom (measuring 4 × 3 mm) "stenosis": (A) Control, (B) Palmaz-Schatz stent within the phantom, and (C) Wiktor stent placed in the phantom. The graphs show the diameter function yielded by edge detection (upper curve) and the densitometric area function (lower curve). The multiple vertical lines in the left part of the graph and the bold vertical line on the extreme left of the phantom represent the user-defined reference segment. The boundaries of the phantom segment for analysis correspond with the outside vertical lines on the graph. The inner two vertical lines represent the minimal points on the diameter and densitometric graphs, respectively. The numbers in the graph represent the maximum and minimum diameter. The boundaries of the Wiktor stent are visible in the phantom and as a "step-up" in the densitometry graph. As a result of the Wiktor stent contribution to the densitometry values, the MLCA determination is overestimated compared with that for the control and the Palmaz-Schatz containing phantom. (Reprinted with permission.[76])

cedure, the "Dottering effect" of the device accounted for 65% of the luminal improvement.[80]

Rotational Plaque Abrasion

To date, the Thoraxcenter experience with this device has been limited, with only 11 procedures performed.[81] A unique feature of the Rotablator (Biophysics International) is its usefulness as a calibration unit as an alternative to the guiding catheter. The device contains a burr of known size, and there is no question of completeness of expansion as with stents and PTCA catheters of specified sizes (Figs 21A and B). Precise measurement of the device at the lesion site has been useful to assess the extent of elastic recoil, which appears to be an important phenomenon, because the luminal dimension immediately after rotational abrasion is always smaller than the diameter of the burr used.[82] A unique feature of the Rotablator is that the optimal angiographic result is not realized until 24 hours later, because the intense vasoconstriction induced by the burr is largely attenuated at that time (Figs 22A, B, and C).

Excimer Laser

Excimer lasers have presented an attractive alternative to other forms of coronary intervention, based on the experimental finding that, in air, a focused, pulsed, UV laser beam can focally ablate targeted tissue with minimal adjacent tissue injury. However, in the clinical situation, where the vessel luminal surface is surrounded by a blood medium, catheter tip-tissue contact is required to avoid attenuation of the laser beam by the blood and to increase ablation efficiency. The effect of pulsed UV-laser light delivered through contact catheters on tissue ablation has been investigated in vitro and in vivo on human and porcine aorta.[83,84] Considerable temperature accumulation was found, as well as mechanical tissue damage caused by expansion of gaseous debris trapped

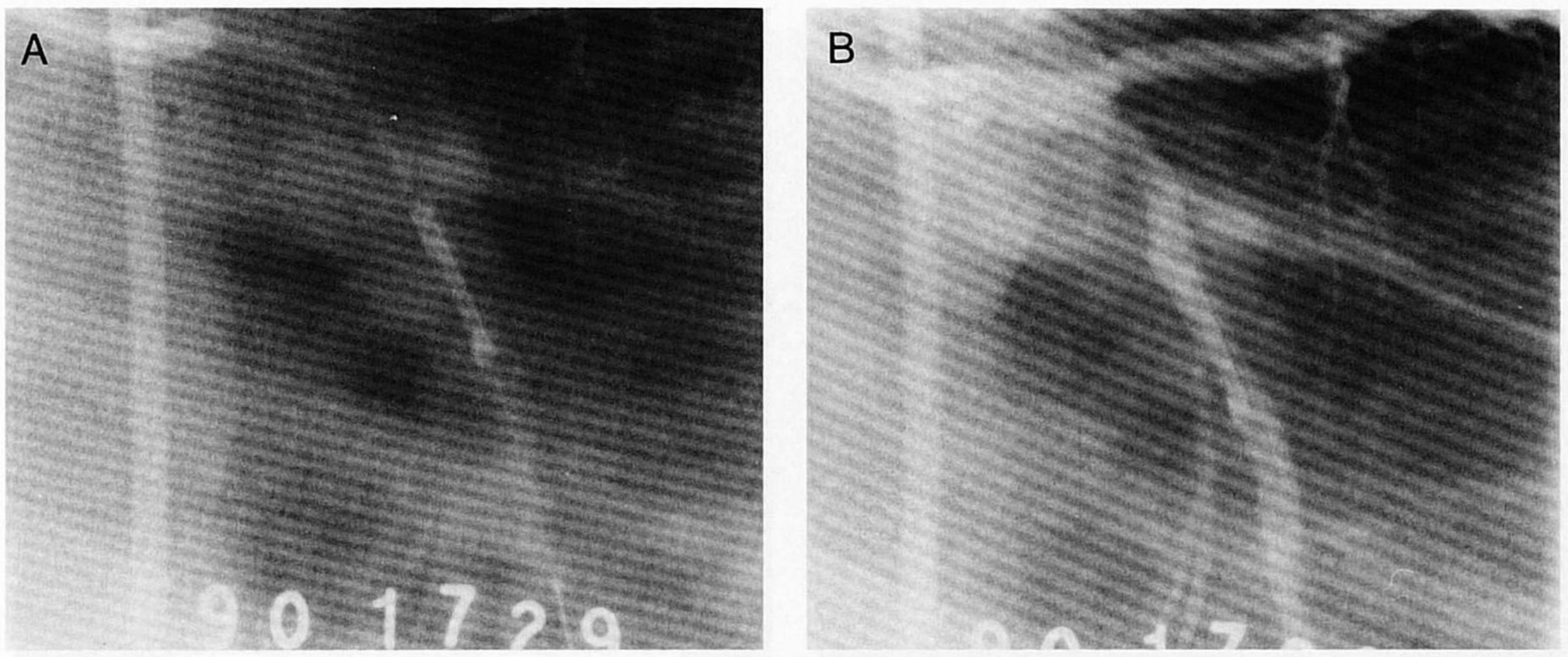


Fig 19. Radiopaque directional atherectomy device (Atherocath; Devices for Vascular Intervention, Redwood, CA) is shown (A) in circumflex artery without contrast and (B) in circumflex artery containing contrast.

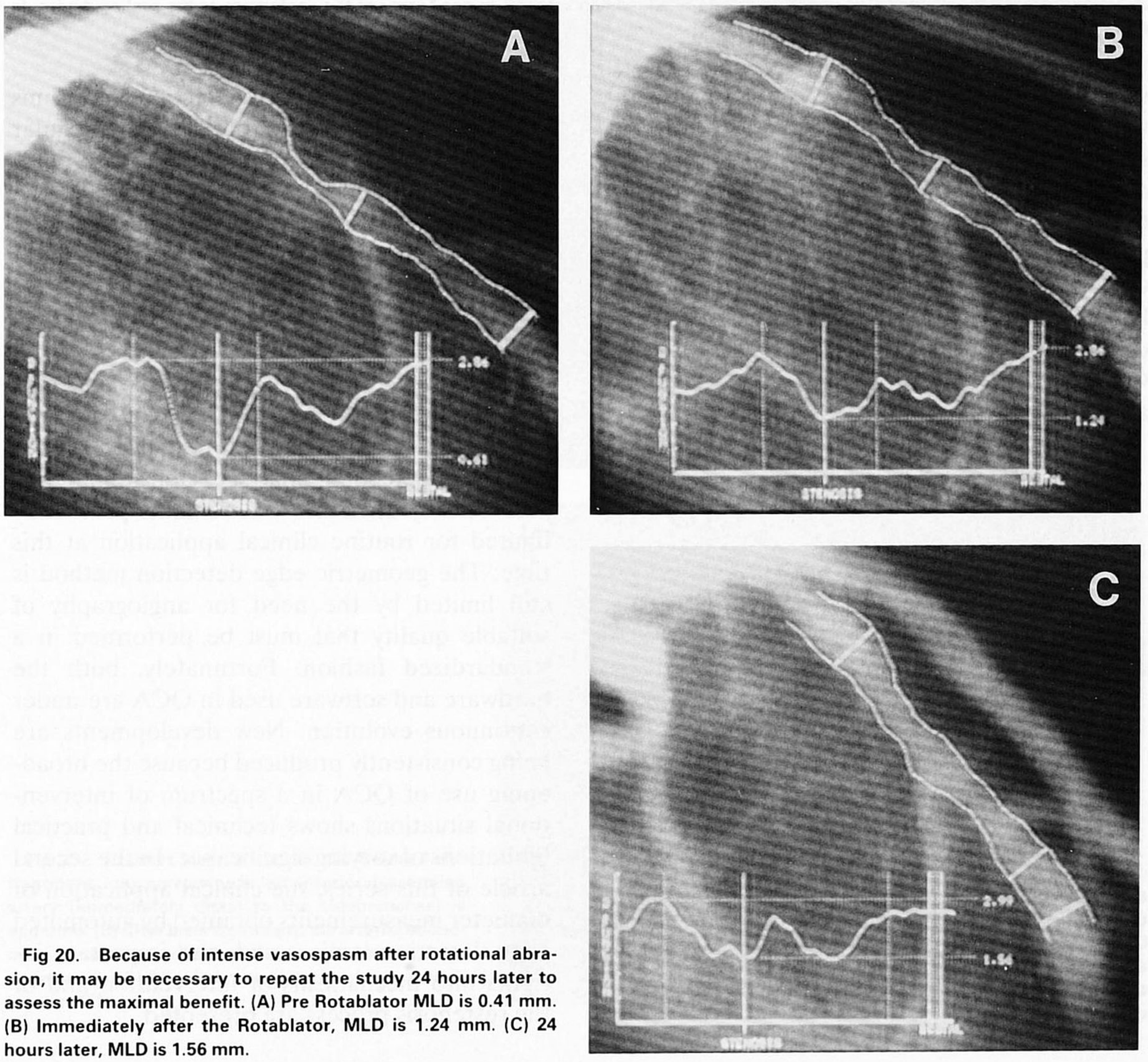


Fig 20. Because of intense vasospasm after rotational abrasion, it may be necessary to repeat the study 24 hours later to assess the maximal benefit. (A) Pre Rotablator MLD is 0.41 mm. (B) Immediately after the Rotablator, MLD is 1.24 mm. (C) 24 hours later, MLD is 1.56 mm.

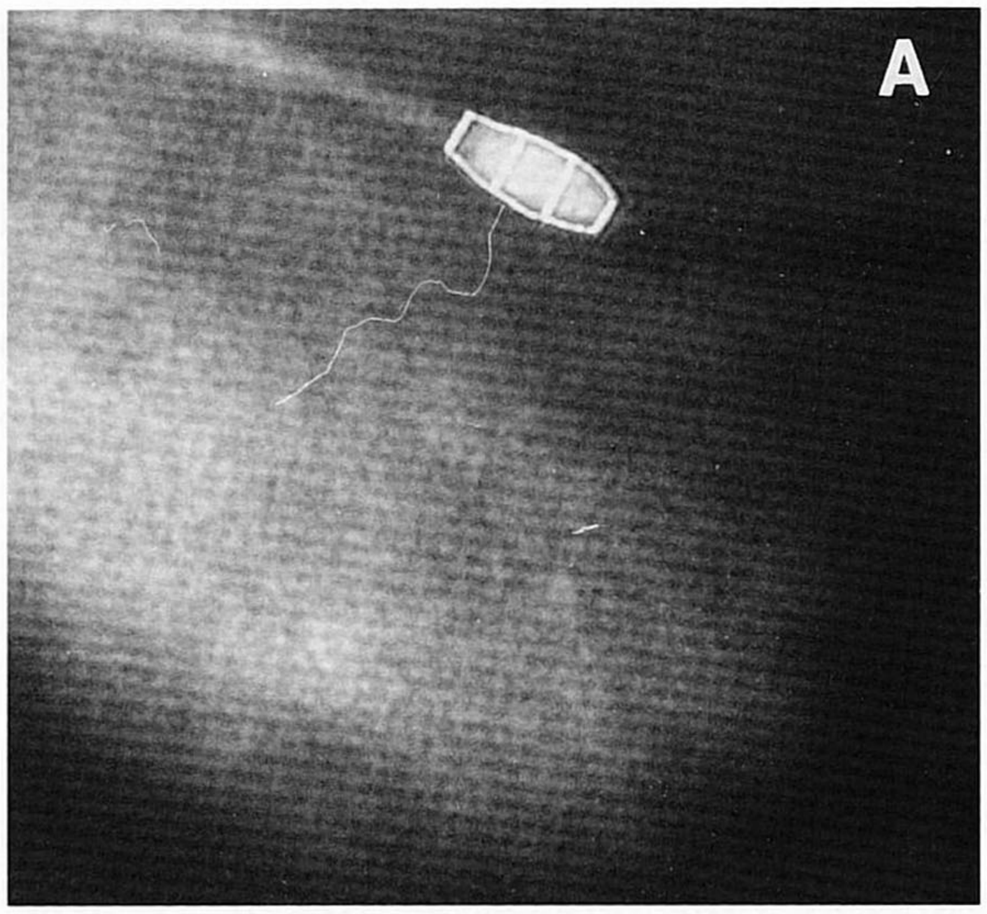


Fig 21. Rotational abrasion (Rotablator) in a coronary artery is shown (A) without contrast. Because the burr is nondeformable and of known diameter, calibration of the angiogram can occur at the site of the procedure in contrast to PTCA, stenting, or directional atherectomy, where we use the contrast-filled guiding catheter in one corner of the angiogram as the scaling device. In this case a 1.50-mm diameter burr was used. (B) In vessel containing contrast, the Rotablator is clearly visible.

under the tip of the delivery system.[83] In addition to thermal injury, dissections were observed that were attributed to pressure build-up and expansion of a vapor cavity within adjacent tissue.[84,85] The angiographic correlate of this phenomenon appears to be haziness of the contours of lesions treated with the excimer laser, with consequent complication of the immediate post-procedure analysis (Figs 23A, B, and C). The lesion has a typically "roughened" appearance and, therefore, may be particularly well-suited to specific edge detection algorithms designed for the evaluation of very irregular luminal contours.[86] Whether densitometry should be preferred to edge detection in the assessment of the specific effects of the excimer laser in coronary interventions remains under investigation.

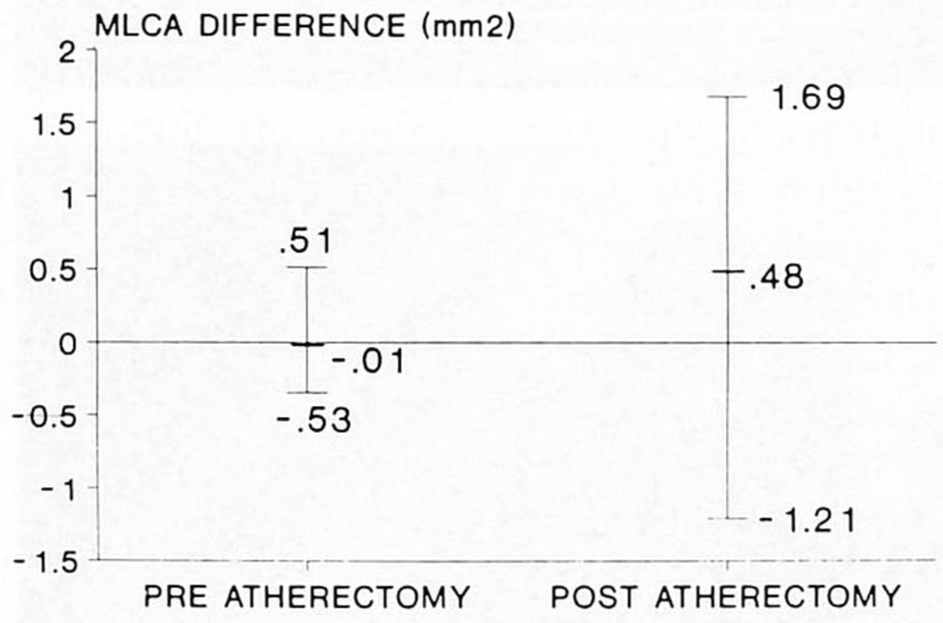


Fig 22. Agreement between densitometric MLCA and the circular (edge detection) MLCA before and after directional atherectomy. Despite apparent smooth contours after atherectomy, similar discrepancy exists between analyses performed by edge detection or densitometry as that which occurs after angioplasty. This may be because of preferential expansion of the bases of the atherectomy cuts, creating a less circular configuration.

CONCLUSIONS

QCA clearly presents an objective and reliable technique to measure coronary luminal dimensions. This has been thoroughly shown for the edge detection analysis. Densitometry is theoretically attractive but remains practically limited for routine clinical application at this time. The geometric edge detection method is still limited by the need for angiography of suitable quality that must be performed in a standardized fashion. Fortunately, both the hardware and software used in QCA are under continuous evolution. New developments are being consistently produced because the broadening use of QCA in a spectrum of interventional situations shows technical and practical limitations of varying significance. In the second article of this series, the clinical application of diameter measurements obtained by automated edge detection is discussed, and important insights into mechanisms of intervention and of the restenosis process are presented.

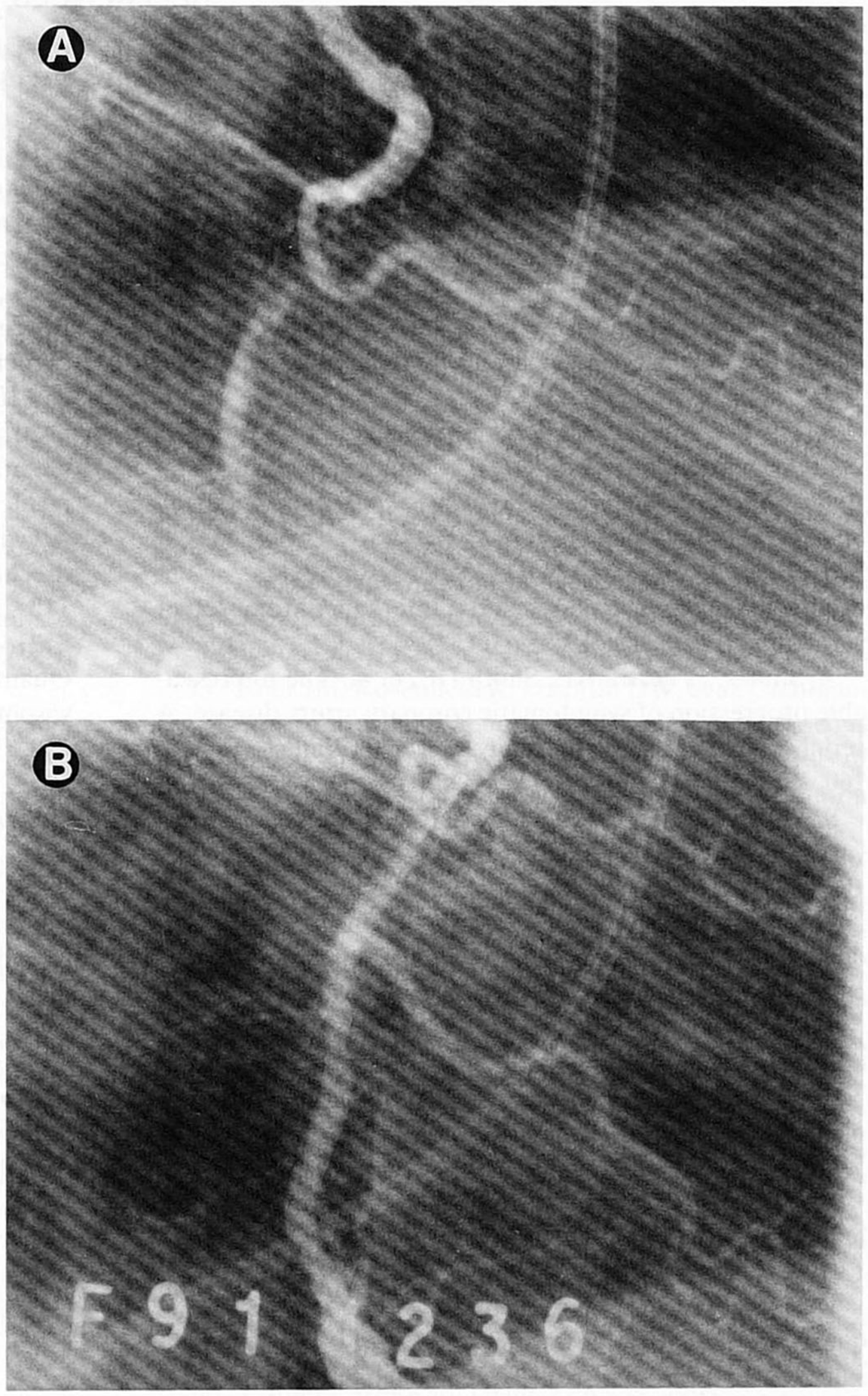


Fig 23. Excimer laser is shown. (A) Before laser treatment, long narrowing in left anterior descending artery (immediately distal to the sidebranches) is apparent. (B) After laser treatment, the arterial boundaries of the treated lesion show a roughened hazy appearance. (C) After balloon dilatation, luminal haziness is still present.

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Quantitative Coronary Angiography (QCA) in Interventional Cardiology: Clinical Application of QCA Measurements

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QUANTITATIVE coronary angiography (QCA) has had a tremendous impact in the field of interventional cardiology. Because of its superior accuracy and objectivity, QCA has supplanted visual and hand-held caliper assessments of coronary arteriograms and has improved interobserver and intraobserver variability.[1-3] QCA is now the "gold standard" for the assessment of the coronary tree in the context of scientific research,[4] although it has not yet gained widespread appeal for routine clinical use.[5] Until very recently, mainly because of the expense and time-consuming aspect involved in routine clinical application of sophisticated computer-based analysis, QCA has only been available for off-line use.[6-9] In addition, the extra precautions that must be taken by the angiographer in obtaining images suitable for quantitative analysis[10] imply that many angiograms routinely performed by busy clinicians or in acute or emergency situations may not be analyzable by an automated computer-based system.[5] However, with the progressively increasing number of clinics involved in multicenter restenosis prevention trials in which QCA plays an integral role,[11-13] perhaps these extra precautions may become routine clinical practice.

QCA has been particularly useful in interventional cardiology as the only objective and reliable means of assessing the immediate and long-term effects of coronary interventions. In particular, the phenomenon of restenosis has primarily been described and researched most extensively on the basis of sequential QCA studies. At the Thoraxcenter (Rotterdam, The Netherlands), we have been advocating the importance of QCA since the first report of its use by our group in 1978[14] and, subsequently, with renewed vigour after our initial experience with QCA in the assessment of coronary interventions, as reported in 1982.[15] The Cardiovascular Angiographic Analysis System (CAAS) has been extensively and rigorously validated,[16-18] and technical aspects are presented in the accompanying report. The entire angiographic database now consists of collected information from more than 5,000 patients who have undergone several different forms of nonoperative coronary revascularization. The principles of QCA, which were initially designed for diagnostic studies of coronary artery disease (CAD), have necessarily been adapted to more complex situations related to either the presence of a device or the effect of an intervention on the angiographic appearance of a damaged vessel. The introduction of several newer devices in the past 7 years, has presented a number of unique and unforeseen problems in image analysis and the subsequent interpretation of important quantitative data, as described in the accompanying report.

The emergence of digital subtraction angiography has allowed on-line performance of QCA measurements in the catheterization laboratory, so that a technique previously confined to research applications has been transformed into a powerful analytic tool, directly applicable to clinical decision making.[7,19] The immediate availability of QCA measurements during interventional procedures provides a unique opportunity for more accurate selection of appropriate interventional devices (eg, balloon, stent, or atherotome dimension) and for continuous monitoring and immediate evaluation of the result obtained. During the last 5 years at the Thoraxcenter, a large clinical experience has been accumulated through the application of the Philips Digital Cardiac Imaging (DCI) Automated Coronary Analysis System.[6,9] In vivo study of stenosis "phantoms" placed in porcine

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coronary arteries has confirmed that the accuracy and precision of the DCI on-line measurements are intimately comparable with those obtained off-line using the CAAS system, with a mean difference between true "phantom" stenosis diameter and DCI minimal luminal diameter (MLD) measurements of 0.08 ± 0.15 mm, for stenosis diameters ranging from 0.5 to 1.9 mm.[8] Therefore, we believe that the information presented here, mainly derived from the analysis of cine-film images, can now be immediately applied to guide the operator during diagnostic and interventional procedures.

In the preceeding article, the process and technical aspects of QCA are explained and described in detail, and it is now (we hope) evident to the reader that QCA analysis is more than just setting up the cine film and returning 20 to 30 minutes later for the data. Only close scrutiny of the analytic results, combined with ongoing communication between the clinician, the analyst, and the programmer, ensures that meaningful and useful data emerge from the use of QCA. The purpose of this review is to describe the insights into the short- and long-term sequelae of the various interventional devices already provided by the use of QCA in interventional cardiology and to explore its current and future applications in the comparative evaluation of interventional devices.

INFORMATION PROVIDED BY THE CAAS SYSTEM

The prime aim of QCA is to provide precise and accurate measurements of coronary anatomy. The CAAS system can provide this information by two different methods, (1) detection of luminal borders (so called "edge detection"), preferably in two (or more) orthogonal projections,[20] to provide a three-dimensional approximation of the diseased segment that can then be converted into absolute values after calibration with an object of known diameter, such as the shaft of the contrast-free guiding catheter and (2) videodensitometry, an approach that describes relative cross-sectional luminal area by measuring and comparing the density of contrast in a diseased and normal segment. The advantage of the information acquired by the densitometric method is that meaningful data can be obtained in a single projection, even if the cross-sectional shape is highly asymmetric or eccentric.[10] In contrast, area measurements derived from edge detection data (and specifically from MLD values), by definition, require an assumption of a circular cross-sectional lumen in the diseased arterial segment, which is at odds with the observations of several pathologic studies.[21,22] The intricacies and limitations of these respective techniques have been described in detail in the accompanying report and will not be discussed further here.

The important parameters which can be obtained by edge detection are listed below:

1. Direct measurements
   a) MLD (Fig 1)
   b) maximal luminal diameter
   c) mean luminal diameter
   d) lesion length
   e) minimal luminal cross-sectional area (MLCA)
   f) reference area

The calculation of cross-sectional area measurements (e, f) from the linear measurements obtained from the diameter function assumes a circular (single-plane view) or elliptic lumen (orthogonal biplane view).

2. Interpolated measurements
   a) reference diameter (RD; automatic computer reconstruction of the assumed disease-free or normal segment of the vessel; Fig 1)
   b) symmetry
   c) plaque area (mm^2)

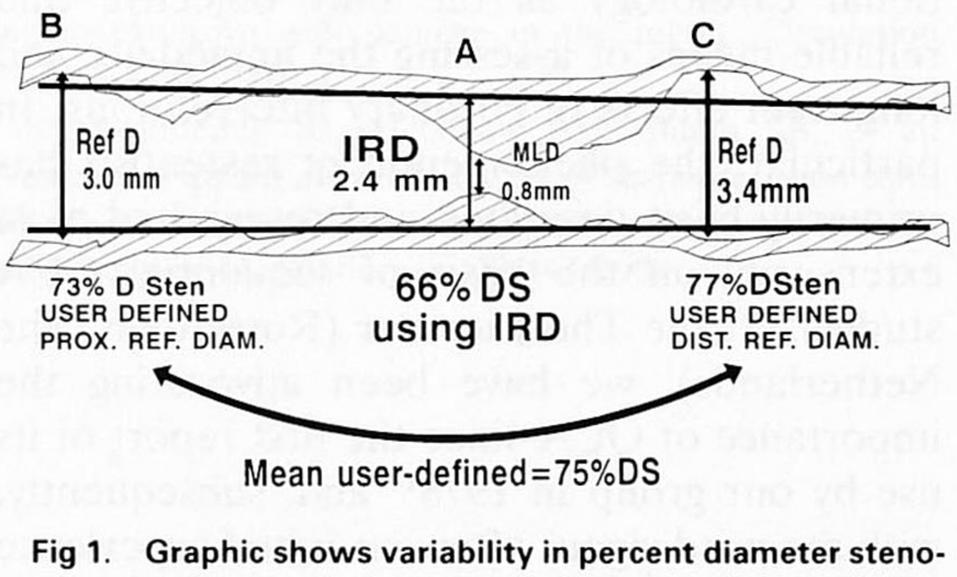

Fig 1. Graphic shows variability in percent diameter stenosis measurements of the same lesion caused by arbitrary selection of the RD by the user and also shows the more objective derivation of percent diameter stenosis by the user-independent method of the interpolated RD. For a stenosis where the MLD is measured at 0.8 mm, if a user-defined proximal or distal reference segment or the mean of both is selected then the resultant measure of percent diameter stenosis for the obstructing lesion is 75%, 77%, or 76%, respectively. If the computer-determined interpolated RD (shown as the upper and lower thick dark lines) is used, a diameter stenosis measurement of 66% is obtained. Prox. ref. diam., proximal reference diameter; dist, distal; MLD, minimal luminal diameter; %DS, percent diameter stenosis.

3. Derived measurements
   a) percent diameter stenosis (calculated from the MLD and RD; Fig 1)
   b) percent area stenosis (calculated from MLCA and reference area)
   c) curvature (calculated from the centerline of the vessel segment)
   d) inflow angle/outflow angle (calculated from the diameter function)
   e) roughness (calculated from the individual contour points, separately for the left- and right-hand vessel contour)
4. Hemodynamic measurements
   a) theoretical transstenotic pressure gradient
   b) calculated Poiseuille resistance
   c) calculated turbulent resistance

A WORD OF CAUTION IN THE INTERPRETATION OF ANGIOGRAPHIC DATA

The limitations of angiographic information in the evaluation of the extent of coronary artery disease have been well-recognized.[23] After all, coronary angiography is really just a two-dimensional profile or "shadowgram" of an opacified vessel lumen; it merely shows the effect of arterial wall disease on the contour of the arterial lumen. Moreover, atherosclerotic changes in the arterial wall are not reliably or precisely reflected by changes in the lumen, as shown by intravascular ultrasound and epicardial high-frequency echocardiography.[24-29] The variability of the atherosclerotic process, which may be smoothly and evenly distributed so that the entire lumen of a segment or vessel may be equally and diffusely reduced,[26] is sometimes beyond the scope of angiography, which may not detect its existence.[30,31] This pathologic fact is reflected in many necropsy studies, where coronary angiography frequently underestimated the severity of coronary artery lesions or even missed significant narrowings in the context of underlying severe diffuse atheromatous CAD.[32-35] Furthermore, elliptic or D-shaped lumens may, depending on the views obtained, be misrepresented on cineangiography, resulting in either underestimation or overestimation of true stenosis severity,[36] particularly if a single angiographic view is used.[10] The CAAS interpolated-measurement approach reconstructs the normal segment of the vessel at the site of the lesion[37] (Fig 1). Although there may be underestimation of the true diameter value by this presumed disease-free vessel contour, this approach is inherently more objective and accurate than the assumption of normality of an arbitrarily selected proximal or distal portion of the vessel as a reference segment.[10] In addition, it is obvious that the dimensions of the RD may change from before to after intervention, as a consequence of any intervention that stretches, dilates, or provokes dissection or coronary vasomotor changes. Moreover, during follow-up, the apparently normal segment adjacent to a treated lesion may be affected by the restenosis process.[38-41]

It is also important for interpreting the results of angiographic studies to know how the actual morphologic characteristics were measured. In a recent study,[42] we found quantitative angiographic morphologic features generally unhelpful in prediction of major procedural and in-hospital adverse cardiac complications among 1,442 patients undergoing balloon angioplasty (BA), in two major European multicenter restenosis prevention trials.[11,12] The only features associated with an increased likelihood of major cardiac complications, according to multivariable logistic regression analysis, were angiographically visible dissection after angioplasty, unstable angina, and lesion location in a tortuous segment, as estimated visually. No quantitative angiographic morphologic characteristics were helpful in this regard.

The predictability of restenosis (at 6-month angiographic follow-up) from baseline angiographic morphology has been widely investigated, and the data are extremely difficult to interpret, because of wide variations in methodological approach. Many studies have reported multiple, differing angiographic risk factors to be associated with a higher restenosis rate.[43-47] Part of the explanation for this diversity is that the definition of restenosis itself has varied widely, and there is still no universal consensus on the best methodological approach.[48] We shall elaborate on this particular application of QCA, as it is of widespread interest because of the exponential increase in the use of percutaneous devices for revascularization and because of the continued persistence of restenosis as the major limitation to maintained long-term success of therapy with these devices. In addition, this is the area to which our group has applied QCA most intensively over the past years.

MEASUREMENT VARIABILITY AND RELIABILITY

Before a discussion of the various devices used for coronary intervention, the utility of the information generated by QCA in general (and the CAAS system specifically) must be addressed. Geometric information, such as MLD, RD, and percent diameter stenosis, represent the most useful and reliable information obtained by this system. Angiographic morphologic features that may be important to the clinical outcome,[49,50] such as ulceration or complex, ragged morphology, have not been a focus of our research, in terms of their natural history in large populations undergoing coronary interventions. The newer intracoronary imaging modalities of intravascular ultrasound and angioscopy are better suited to such study.

The long-term lesion measurement variability of the CAAS system, under "worst case" or nonstandardized acquisition conditions, has previously been validated.[16] More recently, validation studies have been performed for the QCA system operating on-line on the Philips DCI system.[8,51] In addition, lesion measurement variability in the aftermath of coronary BA has also been investigated.[52] Our group has previously reported that a difference in MLD, between two catheterization sessions, of more than 0.72 mm represents an angiographically detectable change.[16] This does not infer physiologic significance. It merely represents twice the standard deviation (ie, the 95% confidence interval [CI]) of the mean difference between MLD measurements performed on angiograms recorded 3 months apart, under angiographic conditions in which no attempt was made to standardize the inspiratory level, the volume and rate of injection of the contrast agent, the vasomotor tone or technical characteristics, and/or the positioning of the x-ray system. Therefore, a measured deterioration in luminal diameter greater than 0.72 mm could be concluded, with 95% confidence, to be a real detectable change and, thus, a definite loss in lumen, under such conditions as prevailed in routine clinical practice at that time (1984). If a more standardized acquisition protocol is followed, the medium-term variability, as reported in that study, would be more applicable, ie, 0.44 mm. To put that index study in its proper perspective, it must be pointed out that the average RD was 3.7 mm, whereas the mean RD of lesions treated by percutaneous transluminal coronary angioplasty (PTCA), during the course of two recent, large multicenter clinical trials, was 2.6 mm.[11,12] Thus, the absolute measurement of 0.72 mm, as an index of detectable luminal change, is no longer relevant in modern studies, which use standardized angiographic protocols and intervene in smaller vessels. For this reason, in addition to the criticized lack of information on the post-BA measurement variability of the CAAS system,[53] our group has recently performed a clinical investigation to clarify these issues.[52] Quantitative analysis was performed on angiograms of 110 patients under optimal angiographic conditions obtained immediately after angioplasty and, again, 24 hours later. Vasomotion was controlled by intracoronary nitrate before each angiographic run, and angiographic projections after angioplasty were exactly repeated at 24 hours. At least two (orthogonal or near orthogonal) views were recorded for right coronary artery lesions, and at least three projections were recorded for left anterior descending or circumflex arteries; all patients were fully anticoagulated for 24 hours. There was no difference in mean MLD or cross-sectional area from postangioplasty to 24-hours postangioplasty, and the variability of the mean difference was 0.20 mm, which is not significantly different from the medium-term (1-hour) variability in the previously described study. This post-PTCA lesion measurement variability is eminently acceptible and shows that quantitative analysis of multiple matched views can provide extremely accurate and precise luminal measurements. RD increased significantly during the 24-hour period (presumably secondary to greater vasodilatory effect of the same dose of intracoronary nitrate at 24 hours relative to that immediately after PTCA); therefore, percent diameter stenosis was also found to increase significantly. This change in percent diameter stenosis without any change in actual MLD shows the limitations of preferential use of percent diameter stenosis measurements in clinical investigation.

LIMITATIONS OF PERCENT DIAMETER STENOSIS MEASUREMENTS AND VISUAL ASSESSMENT OF THE ANGIOGRAM

Percent Diameter Stenosis

As with all new developments, physicians may be somewhat reluctant to abandon the familiar

surroundings of the tried and trusted percent diameter stenosis measurement in favor of the apparently unreal environment of MLD measurement. However, it has long been our contention that percent diameter stenosis measurements are extremely unreliable, and, therefore, we have recommended the use of absolute luminal measurements.[38,54] Use of the term "percent diameter stenosis" connotes the assumption of the conventional measurement approach of selecting a normal-appearing segment, proximal and/or distal to the lesion of interest, as a point of reference. As already described above, this assumption of normality is frequently erroneous, particularly after intervention and at follow-up. Therefore, percent diameter stenosis measurements are prone to considerable variability (Fig 1).

This potential for imprecision and provision of misleading information was shown in the past by Beatt et al[38] and Serruys et al[54] and has been reiterated in two recent studies.[41,52] QCA morphologic features were examined before and after successful BA and at follow-up in 778 lesions in an investigational study (as an ancillary to the Multicenter European Research Trial with Cilazapril after Angioplasty to Prevent Transluminal Coronary Obstruction and Restinosis [MERCATOR][12]) that showed that the restenosis process affects the entire vessel segment which was dilated and not just the target lesion.[41] This finding confirmed the previous findings of Beatt et al,[38] who contended that changes in RD occurring during follow-up invalidated the use of percent diameter stenosis measurements as an accurate estimate of lesion severity. Similarly, the previously mentioned study that used angiography after angioplasty and at 24 hours after angioplasty showed that changes in RD occurring during the 24-hour period had analagous implications for calculation of percent diameter stenosis. The change in percent diameter stenosis from after angioplasty to 24 hours that was observed in this study, if evaluated alone, would have produced the misleading conclusion of significant deterioration in lesion severity during the first day after successful BA. Such a conclusion would have far-reaching consequences. For example, the deterioration could be interpreted as delayed elastic recoil, implying that this might play an important role in the process of restenosis (which is clearly not the case). In addition, the routine application of 24-hour angiography might be recommended in clinical trials to evaluate the true result after angioplasty, after delayed recoil. Use of absolute luminal diameter measurements allowed a clearer and less ambiguous interpretation of the results of this study; no change in lesion severity was detected in the first 24 hours after successful BA, and, therefore, routine angiography at 24 hours is not clinically indicated.

Visual Techniques

Visual and other observer-dependent, nonquantitative approaches of estimating percent luminal obstruction are known to be greatly associated with high intraobserver and interobserver variability.[2-4] In general, visual assessment leads to overestimation of the degree of narrowing in severe lesions and to underestimation of the severity of mild or moderate lesions.[55] Among 1,445 lesions treated by BA during the course of two multicenter European restenosis prevention trials, apart from totally occluded or suboccluded vessels, quantitatively derived percent diameter stenosis measurements greater than 74% were extremely rare and accounted for only 5% of all lesions undergoing PTCA.[56] The most severe lesion encountered had a measured diameter stenosis of 86%. The logic of this is shown in Fig 2, which shows

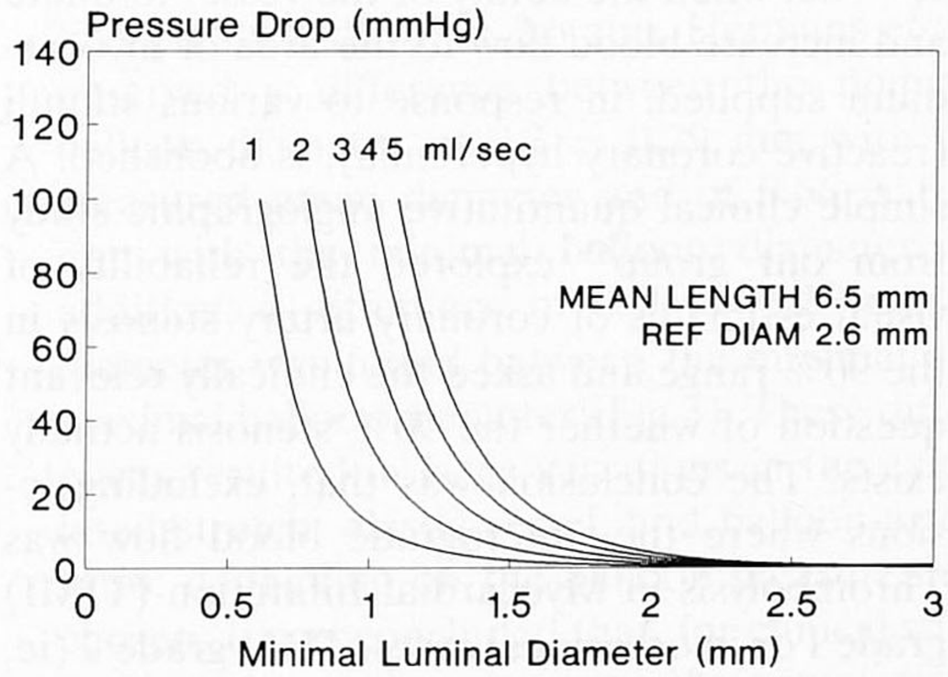

Fig 2. Theoretic pressure gradient calculated from the fluid dynamics equation, derived by Gould et al[59] and Kirkeeide et al,[60] at assumed flow rates of 1 to 5 mL/s is shown. Vessel size (2.6 mm) and lesion length (6.5 mm) were taken as the means for the combined patient populations enrolled in two European multicenter clinical, restenosis prevention trials.[11,12] It is readily appreciated that when MLD is less than 0.5 mm (diameter stenosis more than approximately 81%), the pressure gradient across the stenosis is well beyond the physiologic range at an assumed resting flow rate of 1 mL/s. (Reprinted with permission from the American College of Cardiology.[56])

the pressure gradients (as calculated using the fluid dynamic equations devised in the past by Gould et al,[57] Young et al,[58] Gould et al,[59] and Kirkeeide et al[60]) across a stenosis with a length of 6.5 mm and an interpolated RD of 2.6 mm, the mean values observed during these trials, at assumed flow levels ranging from 1 mL/s at rest to 5 mL/s at maximal hyperemia. It is clear that the pressure gradient necessary to maintain rest flow at 1 mL/s is moving beyond the physiologic range when the MLD is less than 0.5 mm, which, for a 2.6 mm vessel, represents a diameter stenosis value of greater than 80%. Anterograde flow through lesions approaching this severity will tend to decrease below that required to maintain patency, and the lesion becomes occluded, as opposed to a gradual, incremental progression of stenosis over time to eventual occlusion.

To clinicians unfamiliar with QCA, these values for critical lesions may appear low, but in fact, a quantitatively measured diameter stenosis of 74% corresponds with an area stenosis of approximately 93%.[56] Fleming et al[55] have suggested that visual overestimations of percent diameter stenosis arise because of the observer perceiving the area stenosis but calling it diameter stenosis. It has been shown that an area stenosis greater than 70% is associated with a reduction in coronary flow reserve to less than 1,[61,62] ie, when the ability of the vessel to dilate and increase blood flow to the area of myocardium supplied, in response to various stimuli (reactive coronary hyperemia), is abolished. A simple clinical quantitative angiographic study from our group[63] explored the reliability of visual estimates of coronary artery stenosis in the 90% range and asked the clinically relevant question of whether the 90% stenosis actually exists. The conclusion was that, excluding lesions where the anterograde blood flow was Thrombolysis in Myocardial Infarction (TIMI) grade I or in occasional cases, TIMI grade 2 (ie, subtotal or functional occlusions), authentic 90% diameter stenoses probably do not exist. In this study, interventionalists were asked to estimate the percent diameter stenosis of and TIMI grade blood flow through the target lesion before BA. Blood flow was again recorded after guidewire insertion across the target lesion. The likelihood of flow reduction or occlusion after insertion of the guidewire was predicted on the basis of the visual estimation of stenosis severity (percent diameter stenosis) and the quantitatively measured vessel size (interpolated RD) and was compared with actual blood flow. For example, if the observer estimated a 90% diameter stenosis and the vessel diameter was quantitatively measured at 3 mm, the residual lumen diameter, according to the visual estimate, would be 0.3 mm. Thus, introduction of an 0.018-in guidewire (0.48 mm) should cause total occlusion of the vessel, and this stenosis grading was classified as a "predicted occlusion." Although observers frequently provided estimates of stenosis severity corresponding with predicted occlusion, actual occlusion or flow reduction by one or more TIMI grades rarely occurred. In all cases where guide wire insertion across the target lesion caused flow reduction, baseline flow had been classified as TIMI grade 1 or, occasionally, grade 2. Thus, it could be concluded that, where anterograde blood flow is normal, lesion severity never reaches a diameter stenosis of 90%. Therefore, angiographic evaluation systems that allow classification of lesions of such severity do not reflect actual lesion dimensions and describe lesions that are not physiologically possible and, thus, are unsuitable for important studies. Specific training in quantitative coronary analysis can actually improve the discriminant ability of the observer in visual estimation of the severity of coronary stenosis, as observed by Fleming et al[55] and also recently reported by Danchin et al.[64]

PHYSIOLOGIC CORRELATIONS OF MINIMAL LUMINAL DIAMETER

The physiologic significance of a coronary obstruction will depend on a number of factors, but the absolute MLD has been shown to be the most important of these.[60-62,65-68] Rensing et al[69] have reported that recurrence of (or freedom from) angina can be predicted, with 72% accuracy, by MLD threshold of 1.45 mm at 6-month angiographic follow-up after single-lesion BA. Similarly, the likelihood of a positive or negative exercise test by bicycle ergometry could be predicted with 62% certainty by a measured MLD of 1.46 mm. In other words, a patient with MLD at follow-up of greater than 1.45 mm will probably be free from anginal symptoms with 72% certainty, and a symptomatic patient has a 72% chance of having an MLD of less than 1.45 mm. Of course, this measurement will have different relevance in smaller or larger vessels,

and this important aspect was also investigated. It was found that the relevant MLD threshold in smaller vessels (vessels less than the median value of 2.63 mm) that predicted anginal recurrence or ischemia on exercise testing was 1.37 mm and that the corresponding value in larger vessels (> 2.63 mm) was 1.53 mm. Corresponding measures of percent diameter stenosis were also provided, but, considering what has already been stated regarding the reliability of these measurements, they must be cautiously interpreted. Thus, simple quantitative angiographic luminal measurements can provide important and clinically useful, functional information.

The significance of the degree of change in lumen dimensions during follow-up after angioplasty was also investigated in this study but is, however, much more difficult to interpret. Clearly, a deterioration in MLD of 0.72 mm, for example, is likely to have greater functional importance in a 2.6-mm diameter vessel than in a 5-mm diameter vessel, but the functional significance of the change ultimately depends on the final luminal diameter (as well as the amount of myocardium at risk and the level of physical performance required by the individual patient). Thus, loss of as much as 2 mm in MLD may cause no functional deterioration, if the final lumen diameter at follow-up is more than 1.53 mm (obviously such changes would only be possible in vessel larger than 3.5 mm). By contrast, loss of as little as 0.5 mm during follow-up may be of definite clinical relevance, if the final MLD is 1 mm. These findings might reflect either a suboptimal initial angiographic result in a 2.5-mm vessel or a reasonably good, immediate result in a 1.5- to 2-mm vessel.

The degree of absolute luminal change necessary to cause a physiologically significant effect is, therefore, impossible to accurately categorize because of the relative importance of other factors. Thus, the phenomenon of luminal renarrowing after interventions can be most objectively and definitively evaluated using a continuous and purely anatomic approach. Ultimately, the real value of QCA is the provision of objective and reproducible measurements of luminal dimensions, which facilitates the study of the natural history of both atheromatous coronary disease[23] and long-term outcome after interventions,[48] in populations of patients rather than in individual patient management decisions. The impending widespread availability of QCA for routine on-line use in the catheterization room[7,9] may allow such an application.

QCA AND SPECIFIC CORONARY DEVICES

Percutaneous Transluminal Coronary Angioplasty

Insights Into the Therapeutic Mechanism of Balloon Angioplasty

Although our initial analytic approach to serial angiographic studies in patients treated by BA was restricted to repeated measurements of the lesion site, the development of several new concepts related to mechanisms of balloon dilatation required extension of our measurements to include the inflated balloon. These included stretch (theoretic maximal gain in diameter or area during the angioplasty procedure), elastic recoil (which clearly affects the immediate result after angioplasty), and balloon-artery ratio (which affects both the extent of recoil and the likelihood of dissection). Before these assessments, the inflated balloon was used as a scaling device and (incorrectly) assumed to be uniform along the entire balloon length, at a diameter according to the manufacturer's specifications. Monson et al[70] have previously reported that the nominal balloon size is almost never achieved over the entire balloon length. Measuring the balloon diameter over its entire length in 453 patients, during an average inflation pressure of 8.3 ± 2.6 atm, Hermans et al[71] observed a difference between the nominal balloon diameter of 0.3 ± 0.29 mm with the measured mean diameter and of 0.66 ± 0.32 mm with the minimal balloon diameter. In addition, a difference of 0.59 ± 0.23 mm in diameter was found between the minimal and maximal balloon diameter (Fig 3). These differences resulted in large variations in the calculated stretch, elastic recoil, and balloon-artery ratio, depending on the balloon measurement chosen. It was concluded that, for clinical studies, it is essential to measure the actual diameter of the inflated balloon (minimal, mean, and maximal diameter), because the theoretic inflated diameter cannot be assumed and will provide unreliable results. It was recommended that stretch be calculated as the minimal measured diameter (or cross-sectional area) of the largest, fully inflated balloon used during the procedure minus the MLD before angioplasty then corrected for the vessel size, for which

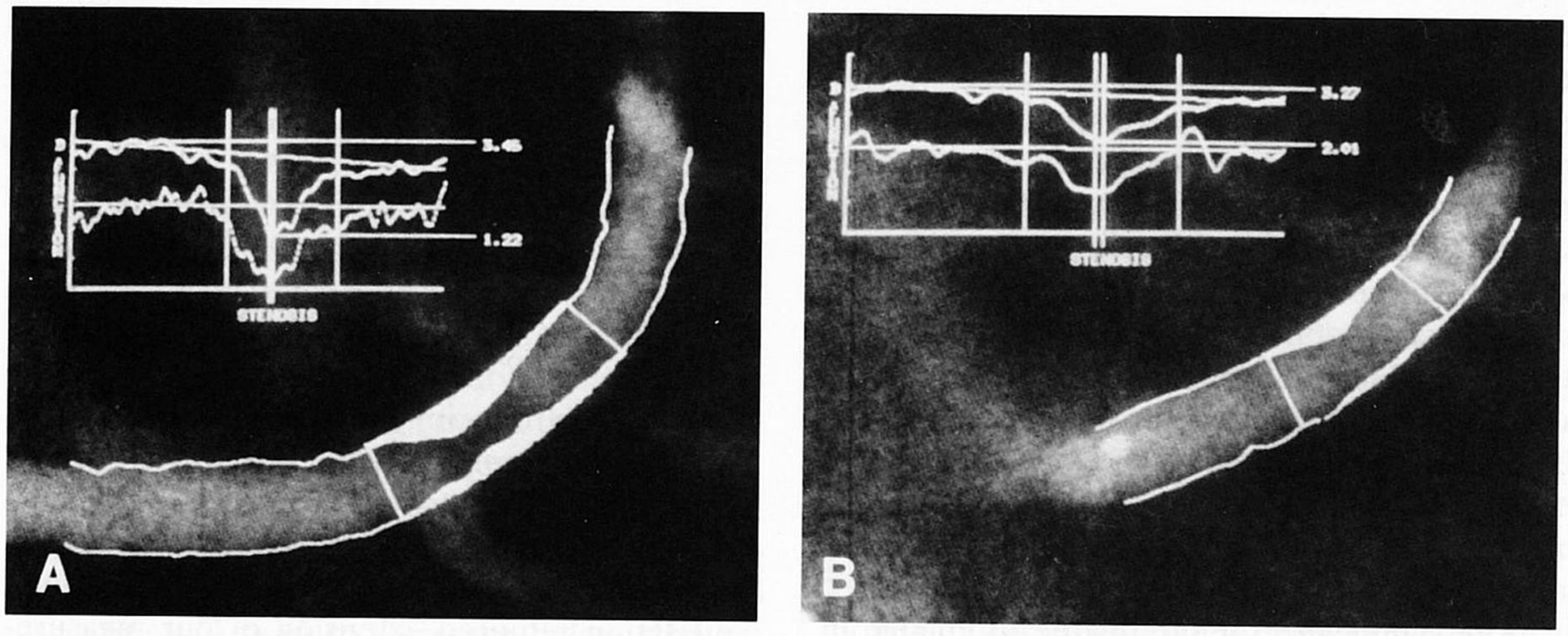

Fig 3. Nonuniform balloon inflation during BA is shown. (A) Pre-PTCA MLD of 1.22 mm is shown. (B) During balloon inflation with a 3.5-mm (manufacturer specification) balloon, the minimal balloon diameter is 2.01 mm, and the maximal balloon diameter is 3.27 mm. (Reprinted with permission.[71])

purpose the interpolated RD before angioplasty should be used. Elastic recoil should be calculated as the difference between the MLD (or cross-sectional area) after angioplasty and the minimal balloon diameter (or cross-sectional area) at the highest inflation pressure, corrected for vessel size, and balloon-artery ratio is best calculated as the ratio of the RD (or reference area) of the inflated balloon (calculated by the automatic contour detection program) and vessel size. The equations used are as follows: stretch = MLD (MLCA) inflated balloon − MLD (MLCA) pre-PTCA/vessel size; recoil = MLD (MLCA) inflated balloon − MLD (MLCA) post-PTCA/vessel size; and balloon/artery ratio = MLD (MLCA) inflated balloon/vessel size where vessel size is the interpolated RD (or reference area) pre-PTCA.

The immediate result of PTCA is influenced by both plastic (dissections, intimal tears) and elastic changes in the vessel wall. Experimental studies have shown that part of the angioplasty mechanism consists of stretching the vessel wall with a resulting fusiform dilation or localized aneurysm formation.[72] However, recent intravascular ultrasound studies have clearly shown that the major effect of balloon dilatation is plaque rupture and compression and vessel wall tearing, with stretching of the nondiseased vessel wall playing only a minor role.[29] This group has also previously reported that, in lesions where no ultrasonographically assessed plaque rupture was produced by angioplasty, a significantly higher restenosis rate, evaluated angiographically using a categoric definition, was subsequently found.[28]

Rensing et al[73] have noted that elastic recoil after coronary angioplasty results in a mean decrease of 50% in luminal cross-sectional area immediately after balloon deflation. A follow-up study showed that asymmetric lesions, lesions located in less angulated parts of the artery, and lesions with a low plaque content showed more elastic recoil.[74] Furthermore, lesions located in distal parts of the coronary tree were also associated with more elastic recoil, probably because of relative balloon oversizing. However, although elastic recoil appears to be an important component of the initial response of the vessel to balloon dilatation, 24-hour angiographic study showed no additional delayed recoil,[52,74] a finding which has been confirmed by other groups.[75-77] More importantly perhaps, multivariate analysis in a large patient group has shown no relationship between the extent of elastic recoil at the time of PTCA and late luminal renarrowing.[78] Conversely, recent preliminary investigations using intravascular ultrasound in small patient groups have concluded that chronic elastic recoil during follow-up after successful transluminal intervention may have a more considerable effect on luminal renarrowing than does intimal hyperplasia,[79,80] and an angiographic study has reported that luminal loss during the first 24 hours is associated with a significantly higher incidence

of late restenosis.[81] However, these studies can be criticized for using a categoric definition of restenosis, therefore, the results are difficult to evaluate in terms of reliability in describing an association between two phenomena. Undoubtedly, some lesions do deteriorate markedly during the first day; however, a similar number undergo additional luminal increase, and the vast majority display minimal change, so that the overall mean change in MLD is essentially zero (Fig 4). It has been shown by Rensing et al[56] and by Kuntz et al[82] that luminal diameter measurements before and after angioplasty and at follow-up, as well as the change in lumen during follow-up, are normally distributed; thus, a continuous statistical approach is appropriate when examining angiographic phenomena. In the 24-hour angiographic study, the combined use of quantitative measurement of the luminal dimensions in millimeters and a continuous statistical approach showed a more complete picture than would have been provided by the use of percentage of diameter stenosis measurements and a categoric analytic approach, permitting a clearer interpretation of the data and a better understanding of the underlying processes. Thus, it could be properly concluded, in agreement with our previous findings[73,74] and those of other investigators,[75,76] that elastic recoil is an instantaneous phenomenon occurring immediately after balloon deflation with no further luminal deterioration within the next 24 hours. Ultimately, these conflicting conclusions need to be further evaluated and reconciled, and serial studies using intravascular ultrasound and quantitative angiography in parallel would be of major interest in laying the matter to rest.

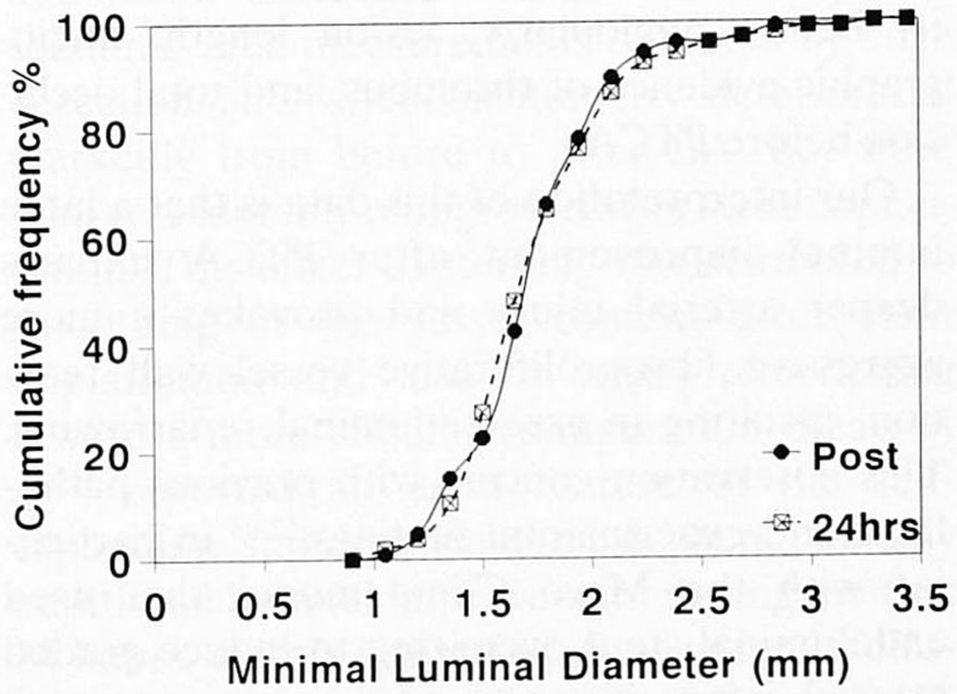

Fig 4. Cumulative distribution curves of MLD immediately after BA and 24 hours later, in 110 successfully dilated lesions, show that there was no deterioration in lesion severity over the 24-hour period.

Insights to the Restenosis Process Through Application of QCA to Clinical Trials

The largest experience in the Thoraxcenter database consists of serial angiographic studies in patients treated by PTCA, which have shown several important aspects of QCA. Firstly, the reproducibility of the CAAS system is extremely high. In several large trials, comparable values have been obtained in the determination of MLD pre-PTCA, post-PTCA, and at 6-month follow-up.[11,12,54,83] Based on data obtained from these QCA studies, a number of important observations on restenosis after BA has been made.

It became apparent that the process of restenosis tends to affect all treated lesions to some degree and that this process could be detected angiographically as progressive luminal renarrowing, which was detectable as early as 1 month post-PTCA and did not appear to advance beyond 4 months after the procedure.[54] These findings were corroborated by Nobuyoshi et al.[39] Restenosis rate was shown to depend most on the actual criterion used and, thus, varied accordingly.[54] In addition, the RD of treated vessels was found to decrease significantly during follow-up after BA, leading to the conclusion that percent diameter stenosis measurements fail to detect true changes in luminal dimensions.[38] Measurements of MLD and RD were noted to be normally distributed,[38] which would justify a continuous rather than categoric approach to description of the long-term outcome. It was recommended that restenosis should be assessed by repeat angiography and ascertained according to the change in absolute quantitative measurements of the luminal diameter.[54] Differences between findings of angiographic restenosis-prevention trials were suggested to arise from three important sources: 1) insufficient patient numbers and incomplete angiographic follow-up; 2) use of inherently variable user-dependent angiographic measurement techniques; and 3) inconsistencies in the approaches used to evaluate restenosis, which do not distinguish between the result of angioplasty and the restenosis process.[84,85] The need for full angiographic follow-up in all clinical studies examining the restenosis issue was advo-

cated,[84] and a continuous rather than categoric statistical approach was recommended[86] to provide a more sensitive evaluation of the effect of a therapeutic agent on the renarrowing process. Moreover, a continuous approach was shown to require considerably fewer patients to reflect a significant treatment effect than would the use of categoric criteria.[86]

Application of a continuous approach to 1,445 lesions treated in the aforementioned European trials confirmed that luminal renarrowing during follow-up is undoubtedly normally distributed in the treated population.[56] This finding contrasts sharply with the conventional clinical belief of an all-or-nothing phenomenon, supported by the findings of King et al[87] through the use of clinical evaluation of angiograms, that luminal renarrowing occurs in some lesions but not in others (ie, a bimodal distribution). In agreement with the report by Rensing et al[56] of a Gaussian distribution for luminal changes after BA, Kuntz et al[82] reported the finding of a normal unimodal distribution for late loss in patients treated by directional coronary atherectomy (DCA) or stent implantation. In addition, contrary to popular belief, Hermans et al[88] found no differences in restenosis between coronary segments, using either a categoric definition of greater than 50% diameter stenosis at follow-up or a continuous approach that compared absolute changes in MLD adjusted for the vessel size. These results collectively show that restenosis is an ubiquitous and normally distributed biologic phenomenon without any predilection for a particular site in the coronary tree and also show the limitations of the use of the term "restenosis rate" to adequately describe long-term outcome after intervention. However, in contrast to the findings of Hermans et al,[88] Kuntz et al[89] have recently reported the finding of a higher restenosis rate and loss index (late loss in lumen diameter divided by acute gain) in left anterior descending compared with right or circumflex artery lesions treated by DCA or stent implantation. The results of this study must be cautiously interpreted because the patient group treated by stent implantation was small (n = 90) compared with that treated by atherectomy (n = 310). The distribution of treated vessels was different in the two groups; lesions were mainly located in the proximal segments, clinical characteristics were not reported or included in the analyses, and angiographic follow-up was incomplete (82%). Although this study raises an interesting question and uses a comprehensive, continuous analytic approach to challenge previous findings by Hermans et al,[88] we believe that the Hermans et al analysis, in a homogenous patient group treated by BA with 94% angiographic follow-up of 1,452 lesions (which were widely distributed throughout the coronary tree), carries more weight at this time. Of course, the conflicting findings of these studies may reflect differing consequences of DCA or stent implantation and BA. Intuitively, it is difficult to reason why one coronary artery should have a greater propensity for neointimal response than another, regardless of how the injury is imparted. Nevertheless, these conflicting conclusions clearly require further study and resolution.

QCA has been useful to clarify conflicting data in the literature regarding angiographic risk factors associated with restenosis. Previous studies using univariate or multivariate analysis with restenosis rate as the dependent factor have provided conflicting reports of risk factors for restenosis.[47,86] Our group has applied a continuous approach to studying the long-term outcome after BA, and we have found, in a number of separate studies, that the proportional luminal increase at angioplasty, or relative gain in MLD (MLD post-PTCA – pre-PTCA, adjusted for vessel size), to be the strongest predictor of absolute luminal loss during follow-up.[78,85,90,91] Other factors were also found to be independently associated with greater lumen renarrowing, namely lesion severity before angioplasty, lesion length, angiographic evidence of thrombus, and total occlusion before PTCA.

Our interpretation of this data is that a large luminal improvement after PTCA imparts deeper arterial injury and provokes a more aggressive fibroproliferative vessel wall reaction, resulting in greater luminal renarrowing. This observation concurs with previous pathologic and experimental findings,[92-98] in particular with the Mayo Clinic model that used endoluminal stent oversizing to induce graded arterial injury in porcine coronary arteries.[99] Other groups, using various methods of quantitation of luminal dimensions, have also reported a direct relationship between angio-

graphic luminal increase at intervention and the subsequent renarrowing.[100-103]

Alternative Devices for Percutaneous Revascularization

QCA Evaluation of the Immediate Therapeutic Effects of Devices

Stent implantation. The ability of an endoluminal prosthesis to maintain luminal patency after failed BA was the original indication for implantation of these devices.[104] Serruys et al[105] investigated serial geometric changes in stenosis morphology in 19 patients after BA and then after stent implantation by quantitative angiographic measurements of luminal dimensions, of the theoretic transstenotic pressure gradient, and of Poiseuille and turbulence resistance. The self-expanding stainless steel mesh stent produced additional immediate luminal dilatation resulting in decrease in both the Poiseuille and the turbulence resistance and in theoretic transstenotic pressure gradient, in addition to the expected scaffolding effect. Puel et al[106] reported a deterioration in MLD and MLCA at 3 months, among 11 patients similarly studied and followed up; however, this change was not associated with any significant increase in transstenotic pressure gradient at assumed flow rates of 1 to 3 cm/s. The conclusion of these studies was that this device had a dilating function, in addition to its stenting role, that might be of value in preventing abrupt closure and restenosis after conventional BA. Further studies of luminal geometry after stent implantation by Strauss et al[107] showed that both the agreement and mean difference between luminal cross-sectional area measurements obtained by edge detection and videodensitometry deteriorated markedly from before to after BA, but were then considerably reimproved after stent implantation. This effect of stenting was attributed to smoothing of the vessel contour after stent implantation and also to vessel remodelling toward a more circular configuration. Beatt et al[108] reported an extra feature of the self-expanding stainless steel mesh stent, namely additional luminal improvement during the first 24 hours, clearly indicating its negation of elastic recoil and justifying its description as self-expanding. However, evaluation of the early clinical experience with this device was unduly disconcerting because of an unacceptably high frequency of acute and subacute stent thrombosis,[109] temporarily quelling the early enthusiasm of some of its proponents.[110] Nevertheless, persistence with the clinical application of endoluminal stents, incorporating increasing attention to control of coagulation, to refinement in stent composition and design, and to deployment techniques has yielded progressive improvements in early clinical success.[111-115]

Morphologic changes brought about by the balloon-expandable tantalum coil (Wiktor) stent were investigated by Serruys et al,[116] with the additional aspect of examining recoil after implantation. This prosthesis was found to produce geometric improvements similar to those previously reported for the self-expanding stainless steel mesh stent. The smaller mean diameter of the stented segment (2.88 ± 0.43 mm) compared with the mean diameter of the fully inflated balloon (2.98 ± 0.44 mm) suggested some minor recoil in the stented segment (3% diameter reduction, compared with a mean of approximately 33% diameter reduction after conventional BA).[73] In addition, it was noted that the balloon did not achieve the diameter specified (3.35 ± 0.36 mm) at the recommended inflation pressures for stent deployment, perhaps because of the opposing forces of both the stent and the arterial wall itself.

Haude et al[117] have recently investigated the occurrence of elastic recoil immediately after sequential BA and Palmaz-Schatz stent implantation and found that this device almost completely eliminated recoil (31% diameter recoil [48% area recoil] for BA, compared with 3.5% [5.1% area] after stent implantation), thus, decreasing the impact of long-term intimal hyperplasia on the residual lumen dimensions.

An experimental in vitro study investigated the interference caused by stainless steel and tantalum stents to the densitometric measurement process and found that only tantalum stents were prone to produce serious overestimation of the MLCA within the stent, which would be accentuated by incomplete vessel opacification by radiographic contrast.[118] For this reason, edge detection has been the preferred quantitative analytic method applied to assessment of angiographic results of stenting with this prosthesis.

Directional coronary atherectomy. DCA may cause luminal improvement by a combination of

dilatation and plaque removal.[119-121] In a cohort of 10 patients (among a total series of 113 patients), Umans et al[119] examined quantitative angiographic lesion morphology before and after passage of the atherectomy device and after activation of the device with plaque retrieval to determine the degree of luminal increase achieved by the procedure, which may be attributed to lesion stretching or dilatation merely by the passage of the device (so called "Dotter" effect). The MLD increased from 0.97 ± 0.32 mm before atherectomy to 1.85 ± 0.37 after crossing the lesion and then to 2.38 ± 0.33 after plaque removal. Among a selected matched patient group undergoing BA, MLD increased from 1.10 ± 0.30 mm to 1.9 ± 0.40 mm, showing that the Dotter effect produced a luminal increase virtually equivalent to that achieved by BA and accounted for 62% of the total luminal increase achieved by DCA. After DCA, the agreement between edge detection and videodensitometry measurements was found to deteriorate somewhat compared with that before DCA, although there was minimal discrepancy between the mean cross-sectional area measurements obtained by each approach (0.28 mm^2), in agreement with previous reports.[120,122] As will be evident from the accompanying report on the technical aspects of these measurement techniques, discrepancy (edge detection/videodensitometry mismatch) is most likely to be explained by the presence of a noncircular lumen morphology. The improved agreement after stent implantation, as described above, is believed to be because of the fashioning of a circular lumen by the device; thus, it was concluded that the finding of a reasonable level of agreement after DCA may imply lumen morphology that is close to circular.[119,122] This interpretation is at variance with the report by Penny et al[121] who postulated a clover-leaf–shaped luminal configuration after DCA. However, the two studies are in accordance regarding the relative contribution of dilatation and plaque removal to the luminal improvement achieved by DCA. Our group has not specifically examined elastic recoil after DCA, but a recent report from Kimball et al[123] suggests significantly less elastic recoil after DCA (23.5% ± 16%) than after BA (41.6% ± 13.8%).

COMPARATIVE EVALUATION OF LONG-TERM THERAPEUTIC EFFICACY OF DEVICES

The safety and immediate efficacy of alternative devices for percutaneous coronary revascularization have now been satisfactorily proven by many investigators. The next logical step is critical evaluation and comparison of the various devices to determine long-term benefit in terms of degree of luminal renarrowing provoked by intervention. Comparison between devices is hampered by a number of clinical and angiographic factors that are most objectively surmounted by randomized clinical trials, a number of which are in progress or are already completed.[124,125]

Because of the difference in vessel size among lesions treated by these respective devices, it has been our contention that direct comparisons could not validly be made without taking this factor into consideration. In fact, comparison of acute and late angiographic results of any intervention between individual patients is similarly ambiguous unless vessel size is comparable. Two possible solutions have been applied by our group to surmount this obstacle. The first involves the selection of lesions; lesions to be compared should be selected according to vessel size and lumen diameter before intervention so that the baseline lesion characteristics are similar, hence the matching process by which unmatchable lesions will be excluded from the comparison. The second approach is to include all patients in the comparison but to adjust or normalize absolute luminal changes at intervention and during follow-up for the individual vessel size for each lesion, as explained further below.

Matching

According to this comparative method, lesions to be compared are selected from baseline angiograms by an independent observer who is unaware of clinical or procedural details or of the 6-month angiographic outcome. The technique[126] is based on three principles. 1) The angiographic dimensions of matched lesions are assumed to be "identical"; 2) the observed difference between the two identical lesions must be within the range of the CAAS analysis reproducibility of 0.1 mm (1 SD); and 3) the size (RD) of the matched vessels are selected within a range of ±0.3 mm (3 SD; ie, 99% CI) (Tables 1

Table 1. Quantitative Comparison of the Immediate and Long-Term Results of DCA Versus BA (Matched Data)

Measurement	DCA	BA	*P* Value
RD (mm)			
Pre	3.03	3.07	NS
MLD (mm)			
Pre	1.08	1.15	NS
Post	2.61	1.92	10^{-5}
F/U	1.69	1.57	NS
ΔIn MLD (mm)			
Post-Pre (gain)	1.53	0.77	10^{-5}
Post-F/U (loss)	0.92	0.35	10^{-3}

Matching of lesions to compare interventions is shown.
Abbreviations: NS, not significant; F/U, follow-up.

and 2). Thus, two comparable groups of lesions treated by different devices are derived. The acute and long-term clinical and angiographic effects of intervention may then be compared. We have, thus far, applied this technique in comparing DCA and stent implantation with conventional BA.[126-128] DCA was found not only to achieve greater luminal increase than BA but also to be attended by greater luminal loss during follow-up, so that the ultimate angiographic outcome was similar in each group (Figs 5A and B). Stent implantation also achieved significantly greater luminal improvement than did BA; however, although attended by greater luminal loss than that for BA, the MLD at follow-up in lesions treated by stent implantation was significantly greater (Figs 5C and D).[127] Important lessons have been learned from these studies that may be considered as surrogates for randomized trials. In fact, the angiographic findings in the matched comparison of DCA and BA could be interpreted as predicting the angiographic outcome of the CAVEAT study.[124]

Table 2. Matched Preprocedural Stenosis Characteristics of Patients With Successful Directional Coronary Atherectomy Versus Balloon Angioplasty

Measurement	DCA	BA	*P* Value
RD (mm)	3.03	3.07	NS
MLD (mm)	1.09	1.15	NS
D-STEN (%)	64	63	NS
A PLAQ (mm^2)	9.5	8.4	NS
Curvature	15.9	22.2	<.02
Symmetry	0.6	0.5	NS
Length (mm)	6.8	6.5	NS

No significant differences exist between the two groups before the procedure except for a lower curvature value for lesions treated by DCA.

Abbreviations: D-STEN, diameter stenosis; A PLAQ, area plaque; Length, length of lesion.

The final results of the Benestent trial[111] are eagerly awaited, and, among the findings, it will be interesting to note whether the matching study mentioned here provided an equally close prediction of the angiographic outcome.

Independent of the vessel size treated, DCA and stent implantation are both clearly capable of greater luminal increase than is conventional BA. Each of these new devices also provokes a greater loss in lumen during follow-up that, according to the injury/hyperplasia hypothesis, is likely to be a direct consequence of the greater luminal increase. Moreover, studies using multivariate analysis techniques in patients treated by stent implantation[129] and DCA[130] have shown the strongest determinant of luminal narrowing during follow-up to be the luminal gain achieved at intervention. Other groups have reported a direct association of luminal gain at intervention with late luminal loss after DCA or stent implantation or after BA.[82,101-103] Greater loss observed after use of the new devices compared with that for conventional BA is generally attributed to the greater luminal increase achieved by these devices, which presumably cause deeper vessel wall injury in the process.

Kuntz et al have gone a step further and concluded that the greatest determinant of long-term angiographic outcome after intervention is the immediate postprocedural result, and this determinant is independent of the device used to achieve this result.[100,101] Our findings in the matching studies would suggest that stent implantation is associated with a better long-term angiographic outcome than BA[127]; however, DCA did not appear to provide a superior long-term benefit.[128] To adequately address the dilemma further, studies matching DCA with stent implantation are underway. In addition, more sophisticated matching techniques may be used to provide specific answers to questions, such as, if the baseline vessel size and lesion severity and the immediate postprocedural result are similar in patients treated by different devices, does the fibroproliferative hyperplastic response vary according to the device used?

Relative Gain, Relative Loss, and Net Gain Index

These indices of luminal change are derived by normalizing absolute gain, loss, and net gain, respectively, for the individual vessel size. To

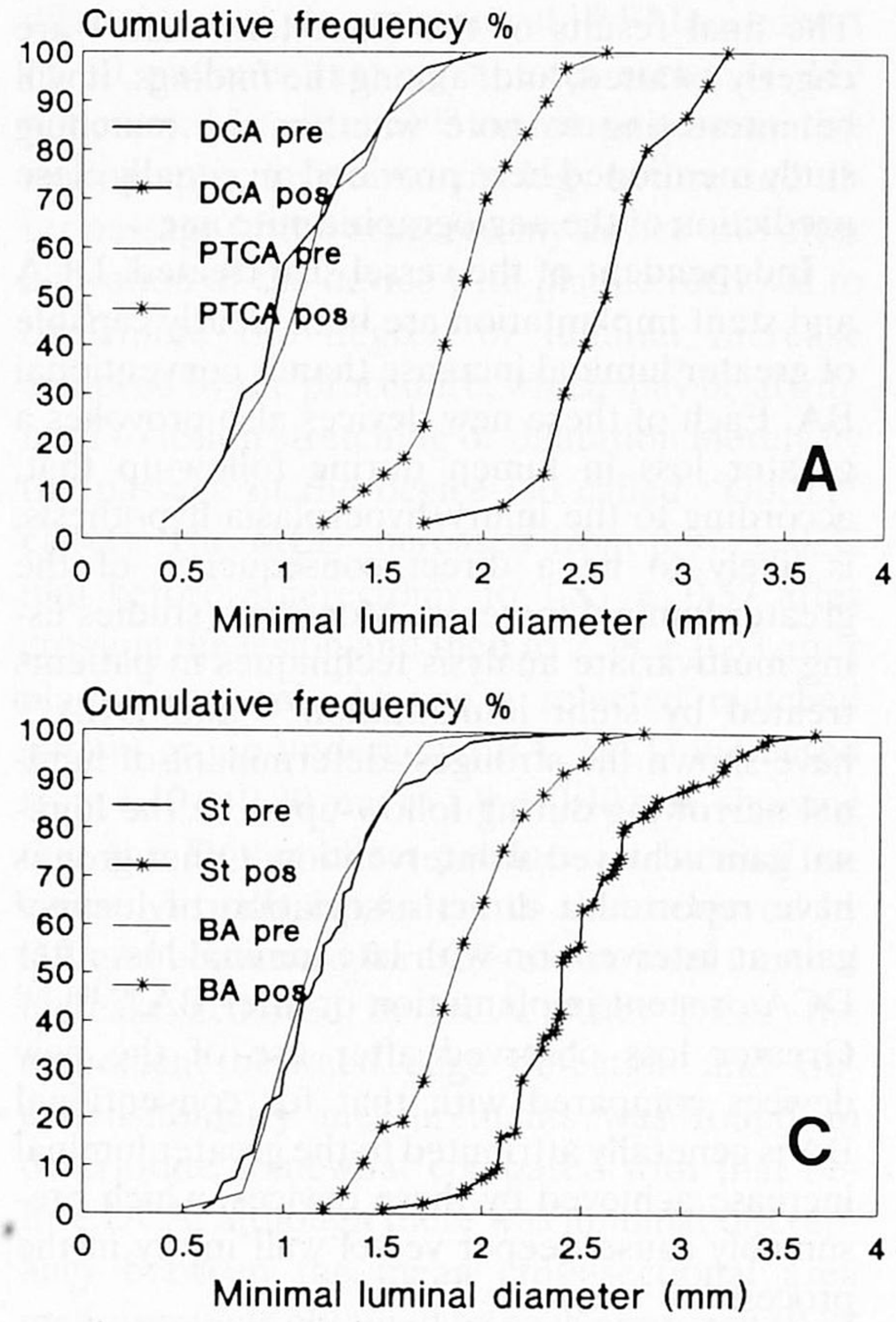

Fig 5. Comparison of immediate and long-term angiographic outcome of BA with DCA and stent implantation using cumulative distribution curves applied to matched patient groups. The x-axis represents the measured MLD, and the y-axis represents the cumulative frequency (in percentage of the total) of lesions corresponding to a given MLD measurement. (A) Preprocedure and immediately postprocedure results for PTCA and DCA (n = 90 lesions); (B) postprocedure and follow-up results for PTCA and DCA; (C) preprocedure and immediately postprocedure for PTCA and the Wallstent (n = 93 lesions); and (D) postprocedure and follow-up for PTCA and the Wallstent.

provide a constant and objective point of reference, the interpolated RD before intervention is used for the vessel size. As mentioned previously, this is the closest angiographic approximation of the disease free or normal vessel diameter. These relative measurements are not interchangable with changes in conventional percent diameter stenosis, because selection of the RD is quite different, as explained earlier (Fig 1). The matching procedure, as described above, is inherently selective, and many lesions cannot be compared because of lack of a suitable partner. However, by normalizing for vessel size, any lesion may be compared with any other with respect to changes at intervention and during follow-up. Using this approach, applied to patient groups treated by DCA, BA, or implantation of a self-expanding stainless steel mesh stent or of a balloon-expandable tantalum coil stent, we have reported, in all of the groups, a direct linear relationship between relative luminal increase at intervention and subsequent deterioration during follow-up; however, this relationship differs considerably among the groups (Fig 6).[131] Although there were definite demographic variations, which may partly explain the observed differences, we believe sufficient evidence was presented to speculate that the findings reflect device-specific variations in the injury/hyperplasia relationship that need to be further investigated. According to these findings, the stainless steel mesh stent and BA display a better profile than DCA or tantalum coil stent implantation, in terms of provoking less relative luminal loss at increasing levels of relative luminal gain. These findings are in conflict with the previously mentioned reports of Kuntz et al,[100,101] perhaps because of differ-

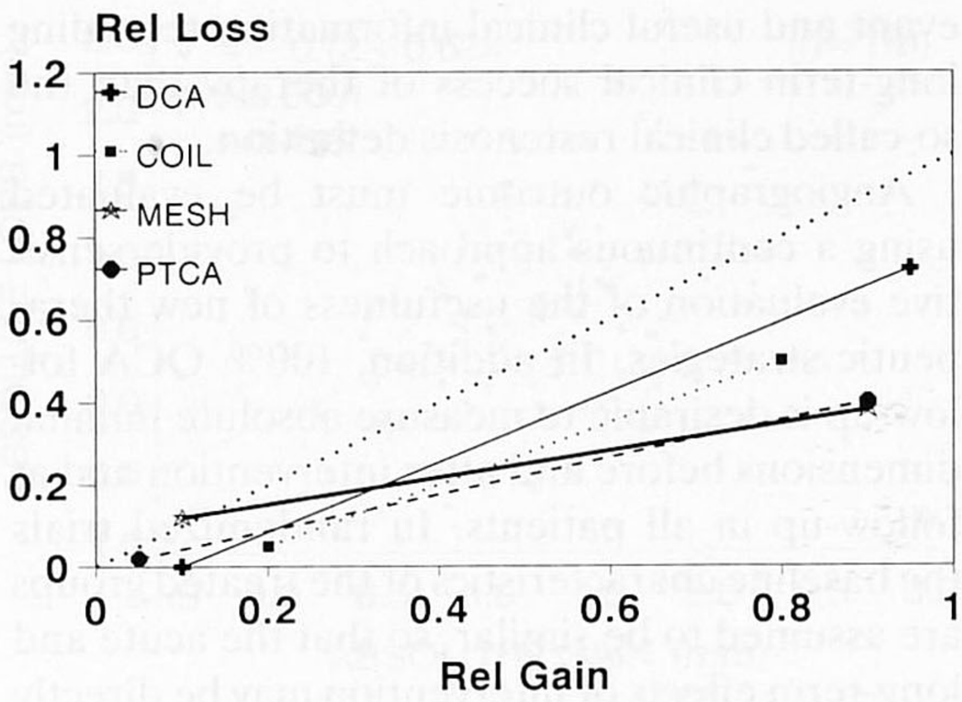

Fig 6. Linear regression relationship of relative gain/relative loss of patients treated by 4 different interventional devices are shown with the line of identity. It can be appreciated that a device whose regression line has a steep slope (eg, DCA) could be considered to be associated with a worse profile than could one with a gentle line-slope (eg, the MESH stent), insofar as a greater relative loss is associated with any given relative gain. It is additionally clear that each device is associated with the achievement of progressively increasing net gain index (the perpendicular distance from the regression line to the identity line) at increasing levels of relative luminal gain. DCA (n = 118 lesions); COIL, balloon-expandable tantalum coil stent (n = 101 lesions); MESH, self-expanding stainless steel mesh stent (n = 110 lesions); PTCA (n = 1435 lesions).

ences in methodological approach, whereby they have used absolute (not adjusted for the vessel size) luminal measurements. In these studies, their conclusion of no difference in proliferative response to the devices is based on the finding of similar loss index for each patient group and of absence of an independent influence of the device used on late loss in multivariate analysis of the patient groups combined. However, possible effects of specific interactions between the individual device and the gain achieved, on the late loss, were not taken into account as independent factors.

Despite these differences in approach and final conclusions, it is clear that the immediate aim of intervention must be to safely achieve as great an angiographic luminal improvement as possible with each device, because it can be extrapolated from Fig 7 that progressively greater, relative luminal gain yields proportionally increasing net gain (each regression line is beneath and diverging from the identity line so that a greater net gain index is associated with increasing relative luminal gain, despite the concomitantly increasing, relative luminal loss). A proviso to this general recommendation is that the achievement of great luminal improvements is obviously more safely possible by stent implantation than by BA or DCA. Aiming to obliterate the target lesion by balloon dilatation is not a legitimate endpoint of intervention with this device, because of the inevitable elastic recoil and the risk of vessel wall dissection. Similarly, by its very nature, aggressive DCA is attended by some risk of vessel perforation. In addition, Umans et al have suggested that DCA should not be used in smaller vessels (<2.5-mm RD), even if smaller cutters are used, because of the apparently aggressive, intimal response as a likely consequence of deeper vessel wall injury in these vessels. However, Kuntz et al[132] have reported a general trend toward an improved long-term angiographic result when medial or adventitial tissue is retrieved; this contrasts with previous reports by Garratt et al.[133] Nevertheless, it is becoming increasingly apparent that, in general, interventions in larger vessels may be associated with a better long-term outcome. Our group has reported that relative luminal deterioration during follow-up after DCA, BA, and balloon-expandable tantalum-coil stent implantation is greater in smaller vessels, which appears to be a consequence of increasing relative luminal gain achieved at intervention (Fig 7).[134] In addition, Kuntz et al

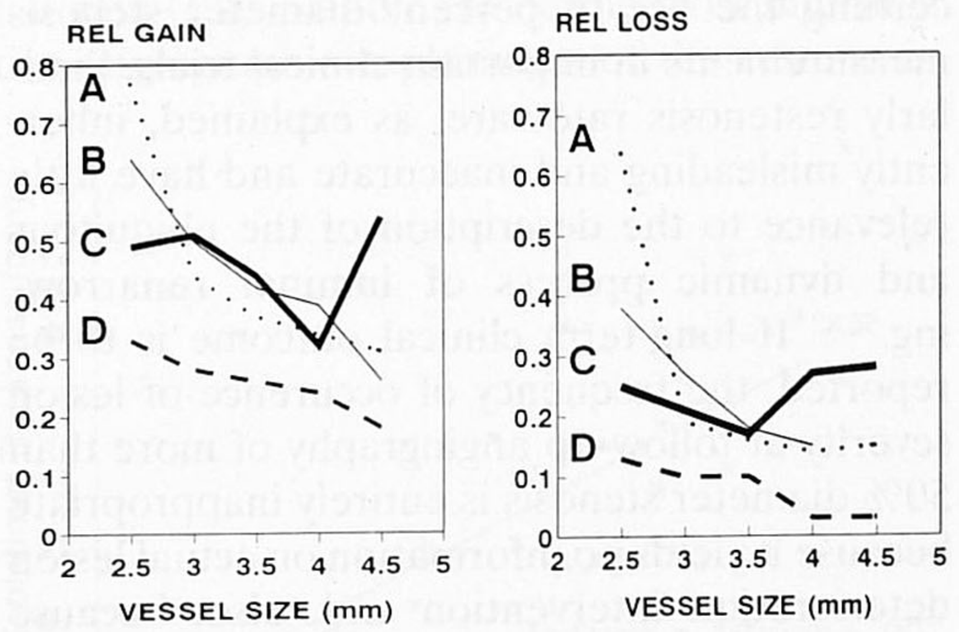

Fig 7. Relative luminal gain (REL GAIN; left panel) and loss (REL LOSS; right panel) according to vessel size in increments of 0.5 mm, for the patient groups described in Fig 6. A pattern of decreasing relative luminal loss with increasing vessel size is apparent for each device except for the MESH stent, and a similar pattern is observed for relative luminal gain. This finding would suggest that previous observations of lower tendency to restenosis in larger vessels is, in fact, a consequence of less relative luminal increase at intervention in these vessels compared with that for smaller vessels. A constant relationship between relative gain and relative loss at all vessel sizes, for each device, can be appreciated. Thus the restenosis process would appear to be independent of vessel size but strongly dictated by the degree of relative luminal gain at intervention, as shown in Fig 6.

have reported lower restenosis rates in larger vessels treated by DCA or stent implantation.[100] Thus, the "bigger is better" philosophy may be more properly interpreted to mean that intervention in a bigger vessel is associated with a better long-term outcome as opposed to the initially reported intention that a bigger lumen after intervention is associated with a better long-term outcome, because larger postprocedural and follow-up lumen are naturally associated with larger vessels.

ANGIOGRAPHIC EVALUATION IN RANDOMIZED TRIALS COMPARING INTERVENTIONAL DEVICES

Important multicenter trials, examining the impact of various pharmacologic agents, or new interventional devices on restenosis are now being assessed in core laboratories[135-137] using quantitatively derived parameters, particularly MLD.[138] In addition, increasing attention is being paid to the use of intracoronary nitrate and replication of the angiographic projections before and after intervention and at follow-up.[115]

However, many studies continue to report results in terms of percent diameter stenosis measurements and restenosis rates. We have already described our strong reservations concerning the use of percent diameter stenosis measurements in important clinical trials. Similarly restenosis rates are, as explained, inherently misleading and inaccurate and have little relevance to the description of the ubiquitous and dynamic process of luminal renarrowing.[56,82] If long-term clinical outcome is to be reported, the frequency of occurence of lesion severity at follow-up angiography of more than 50% diameter stenosis is entirely inappropriate because it yields no information on actual lesion deterioration intervention and, also, because this approach equally categorizes patients with a diameter narrowing of 50% and those with a totally occluded vessel. Similarly, those with a completely normal artery, 0% stenosis, would be classified in the same group as those with a 49% diameter narrowing. Reporting on the occurrence of major cardiac complications or major adverse cardiac events (death, myocardial infarction, coronary artery bypass graft surgery, reintervention[42]) in the follow-up period, a technique used in many current multicenter trials, presents considerably more relevant and useful clinical information regarding long-term clinical success of therapy than the so-called clinical restenosis definition.

Angiographic outcome must be evaluated using a continuous approach to provide sensitive evaluation of the usefulness of new therapeutic strategies. In addition, 100% QCA follow-up is desirable to measure absolute luminal dimensions before and after intervention and at follow-up in all patients. In randomized trials the baseline characteristics of the treated groups are assumed to be similar, so that the acute and long-term effects of intervention may be directly compared, as has been presented in restenosis prevention trials after BA,[11,12,83] in the recently completed CAVEAT,[124] and in the soon-to-be completed Benestent[111] trials. There are three important angiographic aspects of interventional results that need to be considered for thorough comparative evaluation of these trials.

First, the long-term angiographic outcome should reflect patient status at follow-up. To this end, the MLD at follow-up has been shown to have relevant clinical correlations[69] and is the most unambiguous comparative measure of this aspect both for the individual patient and the treated group. Second, the net angiographic benefit of the intervention (the angiographic balance of relative luminal improvement at intervention and relative luminal loss during follow-up) may be considered to convey a comparative measure of the ultimate effectiveness of the device, in providing luminal improvement from before intervention to follow-up. We would suggest that the net angiographic benefit, normalized for the vessel size (what our group has termed the net gain index), is the most useful index in this regard. Finally, the overall effect of the device on the process of restenosis within the treated population may be evaluated using the relative gain/relative loss relationship as an angiographic surrogate for the wall injury/fibroproliferative response relationship and may be compared between groups. Within a randomized trial, whereby all baseline characteristics are comparable, any differences in this relationship may be attributed to real device effects.

Kuntz et al have proposed the use of a loss index[82,89,100,101] (absolute loss corrected for absolute gain) as a measure of the proliferative potential of an instrumented vessel to evaluate the effectiveness of a therapeutic strategy. In essence, this is the regression coefficient of the

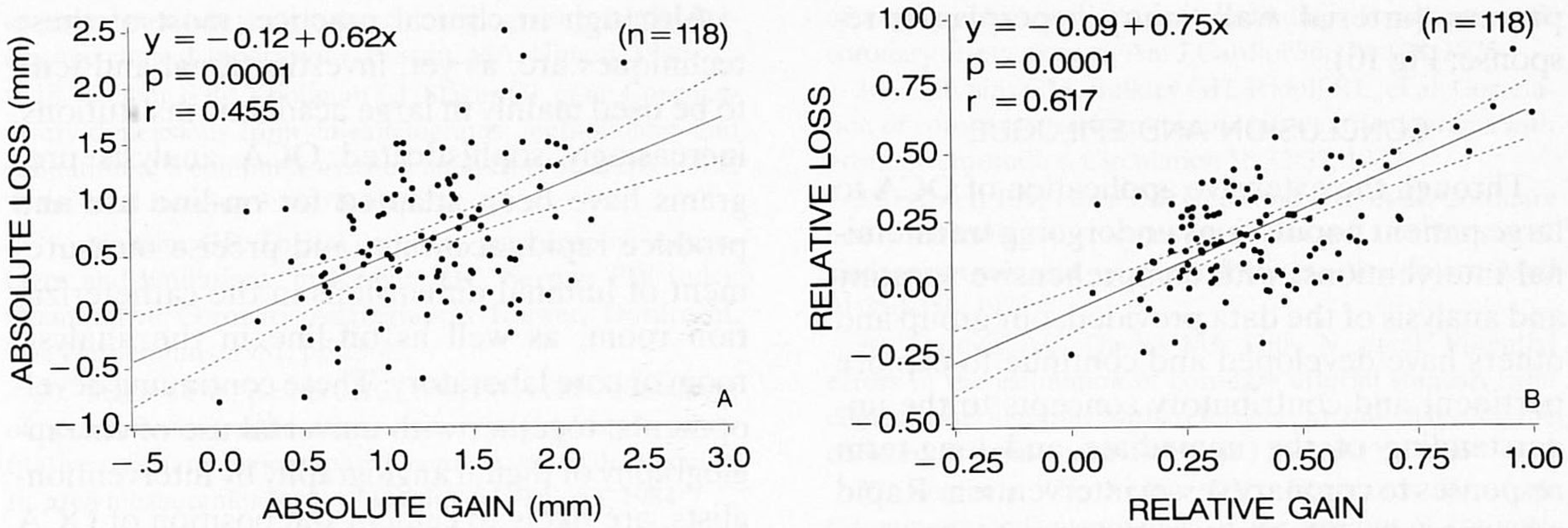

Fig 8. (A) Linear regression (y = a + bx) of absolute loss on absolute gain and relative loss on relative gain for the DCA group shown in Fig 6, with the individual data points included (n = 118), is shown. In the relative gain/relative loss graph (B), the denominator is the same for the calculation of relative measurements (ie, the interpolated RD before DCA), and, thus, the loss/gain relationship will be exactly the same as the relative loss/relative gain, for each lesion; however, the resultant population relationships are clearly not identical. This is because of changes in spatial orientation of individual lesions, with respect to each other, on normalization for the vessel size, as shown. For the reasons given in the text as well as for the obviously stronger correlation (r), we consider the relative loss/relative gain relationship to be more meaningful and useful for comparative purposes between patient groups treated by different interventions. The loss index would be 0.62, whereas a relative loss index would be 0.75. r, Pearson's product moment correlation coefficient; p, statistical certainty of a linear relationship between the dependent (loss, relative loss) and independent (gain, relative loss) variables.

gain/loss relationship, which is similar (but not identical) to the relative gain/relative loss relationship (Fig 8), and may be a useful simple index. However, we have reservations regarding its sensitivity, because two widely separated population responses of luminal loss to luminal gain may be described by the same loss index, which would misleadingly convey similar proliferative response to a given level of injury (Fig 9). In addition, the potentially wide and variable range of individual responses cannot be communicated by the simple loss index. Thus, because we consider normalization of luminal changes for vessel size to be an integral step to comparative evaluation, we believe the linear regression display of relative luminal loss on relative luminal gain (Figs 6 and 8) to be the most informative angiographic exploration of the restenosis

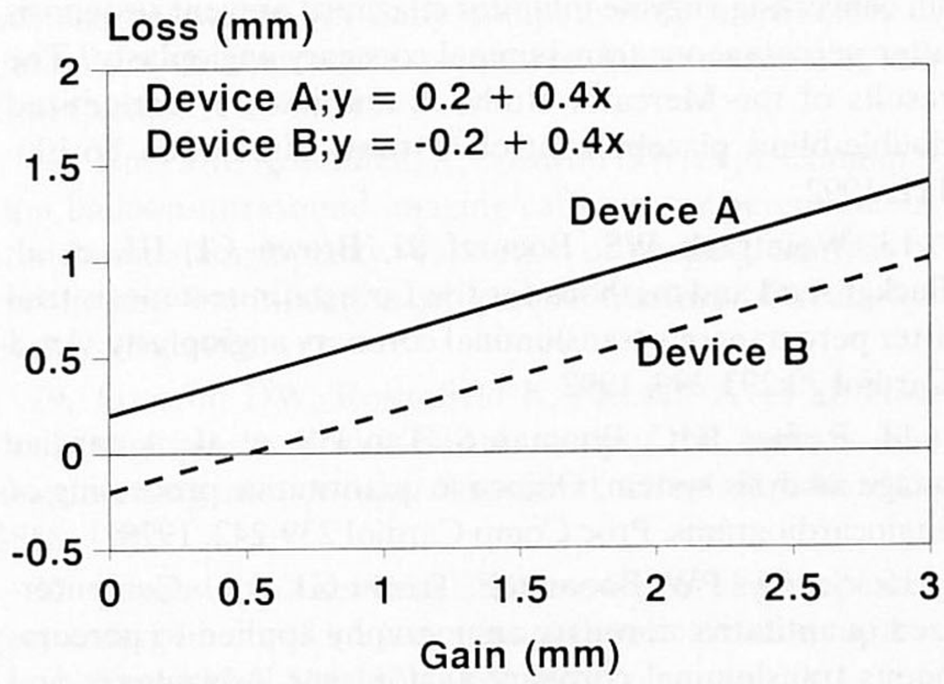

Fig 9. Schematic drawing shows potential limitations of the loss index. Both device A and device B would have a loss index of 0.4, yet it is clear that in the achievement of acute gain of 2 mm, device A would provoke a late loss of 1.2 mm, whereas device B would provoke a loss of 0.8 mm. This is a purely hypothetical example whereby other factors, not considered in the analysis, are likely to explain the different population responses; however, it must be remembered that, in reality, the restenosis phenomenon is clearly multifactorial, and such a scenario may not be completely unrealistic.

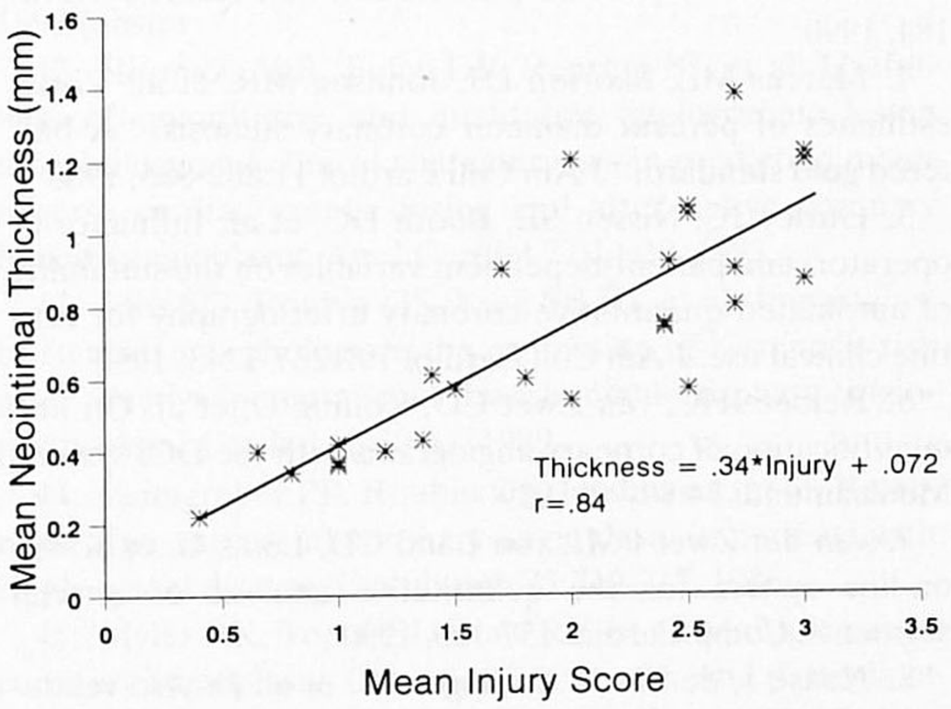

Fig 10. The relationship between wall injury score and measured neointimal thickness, in a stented porcine model, as reported by Schwartz et al,[99] is shown. Compare this with the relative gain/relative loss relationships displayed in Figs 6 and 8. Certain similarities are apparent that stimulate the speculation that these QCA indices may represent relevant correlates of arterial wall injury and neointimal response, which may be of some value for clinical restenosis studies. (Reprinted with permission.[99])

process (arterial wall injury/hyperplastic response; Fig 10).

CONCLUSION AND EPILOGUE

Through the extensive application of QCA to large patient populations undergoing transluminal interventions, with comprehensive scrutiny and analysis of the data provided, our group and others have developed and continue to explore pertinent and contributory concepts to the understanding of the immediate and long-term responses to coronary vessel intervention. Rapid advances in alternative imaging techniques should not be visualized as competing with QCA but, rather, as mutually complementary methods of providing increasingly comprehensive assessment of coronary luminal obstructions and the outcome of therapeutic interventions. Correlations between the information provided by these techniques and quantitatizve angiographic data will be of major clinical interest.

Although in clinical practice, most of these techniques are, as yet, investigational and tend to be used mainly in large academic institutions, increasingly sophisticated QCA analysis programs have been adapted for on-line use and produce rapid, accurate, and precise measurement of luminal dimensions in the catheterization room, as well as off-line in the analysis room or core laboratory. These continuing developments, together with universal use of cineangiography or digital angiography by interventionalists, are likely to cement the position of QCA as the "gold standard" in coronary luminal examination for the forseeable future. Thus, the clinical use of QCA on-line during intervention has barely been explored but presents exciting and fascinating prospects. We hope that this and the accompanying report will provide some general and specific, theoretic and practical guidance for the interventionalist embarking on the fantastic voyage into the realms of QCA.

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