Clinical Investigations

Variability in the Measurement of Intracoronary Ultrasound Images: Implications for the Identification of Atherosclerotic Plaque Regression

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Summary

Background and hypothesis: Serial coronary angiography cannot reliably detect the small changes in arterial dimensions. Measurement of arterial dimensions by intracoronary ultrasound (ICUS) may be a superior method to determine the extent of atherosclerotic burden since it directly images the diseased portion of the vessel.

Methods: To quantify inter- and intraobserver variability of ICUS measurements, 27 images of atherosclerotic coronary lesions were measured by two study physicians and repeated 14 days later.

Results: Interobserver correlation coefficients for external elastic lamina, lumen, and effective plaque area were 0.96, 0.99, and 0.91, respectively. Intraobserver correlation coefficients for external elastic lamina, lumen, and effective plaque area were 0.99, 0.99, and 0.97, respectively. To determine progression or regression in effective plaque area, a minimal difference of 2.77 mm² (which represents a 23% change in plaque area) is needed.

Conclusions: Direct visualization of the extent of atherosclerosis by ICUS can be accomplished with a low degree of inter- and intraobserver variability. ICUS may be a preferable alternative to angiography in atherosclerosis regression trials.

Key words: intracoronary ultrasound, variability, quantitative coronary angiography, atherosclerosis, regression

Introduction

Quantitative coronary angiography (QCA) continues to be the standard method of determining atherosclerotic plaque progression or regression in the majority of clinical trials. Aggressive lipid lowering results in a marked improvement in clinical outcome despite only a minimal degree of atherosclerotic regression seen by QCA.^{1–8} This finding substantiates earlier findings that angiographic stenosis severity alone does not adequately predict future cardiovascular events.⁹ Plaque rupture and thrombosis leading to acute coronary events may be more closely related to plaque composition (soft/lipid rich)¹⁰ and structure (focal areas of high circumferential wall stress).¹¹ The beneficial clinical effects of lipid-lowering agents may be mediated by changes in plaque growth, composition, or remodeling rather than in changes in the degree of luminal narrowing.

Quantitative coronary angiography is limited in the quantitation of plaque burden as it outlines only the lumen and does not directly assess the vessel wall and its pathologic components. This leads to an underestimation of the extent of atherosclerotic involvement, as the degree of compensatory vessel wall enlargement is not taken into account.^{12–16} In addition, atherosclerosis regression trials utilizing QCA rely predominantly on one-dimensional data (i.e., minimal lumen diameter) which may be misleading, especially in eccentric lesions.

More recently, the use of intracoronary ultrasound (ICUS) has been advocated as a superior method in quantifying the extent of atherosclerosis. ICUS provides two-dimensional, cross-sectional views which allow for assessment of both the vessel wall components and lumen. It is superior to angiography in assessing the extent of atherosclerosis as validated by several histologic studies.^{17–20} There is excellent correlation between intravascular ultrasound measurements and histologic cross sections, whereas the correlation between angiographic and histologic measurements is variable. The correlation of angiographic and intravascular ultrasound measurements has thus been inconsistent.^{20–26} Angiographic measurements typically overestimate the lumen cross sectional area, especially in segments with irregular lumen borders. Difficulties with the qualitative and quantitative use of coronary angiography can be overcome with ICUS, making it ide-

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ally suited to assess the extent of atherosclerosis and its response to therapy.

Reproducibility studies have not sufficiently characterized ICUS measurement variability. Procedural and image measurement variabilities are specifically discussed in only a limited number of studies.^{16, 27} The purpose of this study was to determine the variability of ICUS image measurements and to define the degree of change necessary to guarantee a true change in plaque area.

Methods

The methods described are similar to previously described models for the determination of measurement variability.^{28, 29} ICUS data were reviewed for 27 lesions in 13 consecutive patients. All ICUS studies were performed in conjunction with an intracoronary interventional procedure (percutaneous transluminal coronary angioplasty, atherectomy, or laser). Lesions were studied both at the point of maximal stenosis and at adjacent moderately diseased reference sections. No normal areas were measured. Care was taken to maintain coaxial catheter positioning within the artery. Lesions from all three coronary arteries were studied.

A Diasonics Inc. console was used with Boston Scientific #4.8 French intravascular ultrasound catheters transmitting at 20 MHz. All studies were recorded on Super VHS videotapes. Measurements were performed off-line using a Freeland Systems Cardiology Workstation.

Area measurements were made within the external elastic lamina (EEL) and luminal borders. The adventitial-medial border, as defined by the EEL, can be easily identified in all cases and was thus used in our standard measurements. Effective plaque area (EPA) was determined as the difference between the EEL and lumen areas³⁰ (Fig. 1). Exclusion of the EEL from plaque area measurements does not adversely affect our results. Both culprit lesions and diseased reference segments of the vessel were evaluated in assessing the spectrum of atherosclerotic disease. The lesions evaluated from the 13 consecutive patients were chosen randomly, regardless of angiographic appearance, to avoid selection bias.

The lesion to be measured was first identified and the tape time recorded. Experienced readers (GPF, SWZ) of more than 100 prior ICUS studies then selected one image from the 30 frames during the recorded second on the videotape. Thus, the exact image was probably not measured by both investigators. Variability was thus determined within the atherosclerotic segment and not at a single predetermined frame. The ICUS catheter was stationary during all measurements. Three measurements of the EEL and lumen area were performed on each lesion. ICUS measurements were performed blindly and independently by two study physicians. These images were remeasured using the same methods after 14 days.

Statistical Analysis

Standard statistical methods were used to estimate the inter- and intraobserver variability of the EEL area, lumen area, and

FIG. 1 Diagrams of external elastic lamina, lumen, and effective plaque areas.

EPA.³¹ Data are expressed as the mean absolute differences and Pearson's correlation coefficients between pairs of measurements, together with their 95% confidence intervals. A power calculation was used to determine the minimal change required to show a true progression or regression in sequential ICUS measurements. The residual (within-person) component of variance and the standard power formula for comparing two continuous variables with a two-sided test of significance was used for this purpose.³¹

Results

The mean areas, mean absolute differences, and correlation coefficients for EEL, lumen, and EPAs are listed in Table 1. Close interobserver (Fig. 2) and intraobserver (Fig. 3) correlations were found in the measurements of EEL, lumen, and plaque areas with correlation coefficients >0.91 . The small increase in variability in the values calculated for effective plaque area represents the addition of variances of the EEL and lumen area measurements.

Based on the intraobserver data, we estimate that a change of 1.74 mm^2 is necessary to be certain of a true change in luminal area in sequential ICUS studies [85% power ($p < 0.05$)]. This represents an average of a 16% change in lumen area. For a comparable degree of certainty, a 2.77 mm^2 change in plaque area would be required. This represents an average of 23% of change.

Discussion

The variability in the measurement of ICUS images demonstrated in this study was small and compared favorably with a recent ICUS study in which differences between measure-

TABLE I Mean areas, mean absolute differences, and correlation coefficients for measurements of external elastic lamina, lumen, and effective plaque areas

Measurement	Mean area mm ²	Interobserver variability		Intraobserver variability	
		Mean absolute difference (mm ²) (95% CI)	Correlation coefficient (95% CI)	Mean absolute difference (mm ²) (95% CI)	Correlation coefficient (95% CI)
Lumen area	10.55	0.94 (0.77–1.10)	0.96 (0.94–0.98)	0.48 (0.37–0.58)	0.99 (0.98–0.99)
External elastic lamina area	22.36	1.02 (0.81–1.22)	0.99 (0.97–0.99)	0.56 (0.44–0.69)	0.99 (0.99–1.00)
Plaque + media area	11.81	1.52 (1.31–1.73)	0.91 (0.85–0.95)	0.71 (0.52–0.89)	0.97 (0.95–0.98)

Abbreviation: CI = confidence interval.

FIG. 2 Scatter plots with lines of identity demonstrating interobserver variability for measurements of (A) the external elastic lamina, (B) lumen, and (C) effective plaque areas.

FIG. 3 Scatter plots with lines of identity demonstrating intraobserver variability for measurements of (A) external elastic lamina, (B) lumen, and (C) effective plaque areas.

ments were <10%, except for plaque area which was slightly higher.²⁷ Measurement variability studies using QCA and computerized edge detection report the ability to detect 10 to 50% changes in arterial lumen diameter.^{32–35} QCA variability is particularly high when attempting to measure small lumen

diameters.³⁵ Due to the high degree of resolution obtained with ICUS, EPA can be directly measured with a relatively small degree of variability. Theoretically, plaque area (or ideally plaque volume) is a better index for atherosclerotic regression than stenosis severity.

Mechanical pullback of the ICUS catheter allows serial measurements of plaque area along an entire segment of the coronary vessel and subsequent calculation of plaque volume. Although not yet thoroughly validated, three-dimensional reconstruction holds promise in determining plaque volume more accurately over longer segments of coronary arteries. ICUS therefore appears ideally suited to evaluate change in atherosclerotic plaque dimensions over time. A further potential advantage of ICUS in atherosclerosis regression trials is its ability to evaluate plaque composition and the distribution of lipid pools. Recent histologic studies on atherosclerotic samples have correlated ICUS findings with plaque composition.³⁶ Plaque composition by ICUS has also correlated with the presentation of acute coronary syndromes.³⁰ Therefore, ICUS may be useful in assessing plaque vulnerability and the effect of lipid-lowering agents on plaque composition.

No complications occurred during the performance of ICUS in any of the study patients. Pinto *et al.*³⁷ reported their 1-year safety profile with the use of ICUS in which no major complications occurred in 240 procedures. In that study, coronary spasm occurred in 8.3% of the procedures, all of which resolved with nitroglycerin, but it did not occur in the current study. The performance of ICUS is safe and without known long-term untoward effects. Serial ICUS examinations to assess plaque regression appear justified based on this excellent safety profile.

Several components likely added to the variability of measurements in this study. As there are multiple frames per second of videotape, there is no assurance that identical frames were measured. However, once the ICUS catheter is in a stable position, little variability in plaque characteristics is seen. Occasional difficulty in locating the lumen-intimal interface is another element of the measurement variability encountered in the present study. Currently, we are using smaller (#2.9 French) catheters at higher frequency (30 MHz), which markedly improve near-field resolution. The use of smaller catheters also decreases "wedging" in areas of severe stenosis which distorts image resolution and may prevent accurate determination of plaque area.

Although inter- and intraobserver variability is quite small, the use of ICUS in atherosclerosis regression trials may suffer from several limitations. There is difficulty in repeated placement of the ICUS catheter at the identical location in the coronary artery, and this would likely be the principal source of variability in regression trials. Coaxial placement of the catheter in the vessel lumen may be difficult, especially in large vessels. Heavily calcified lesions which cause extensive acoustic shadowing may be difficult to measure accurately. Finally, small distal lesions or severely stenotic lesions cannot always be imaged. However, smaller high-frequency catheters coupled with a mechanized pullback system and three-dimensional reconstruction may help overcome many of these technical difficulties. In addition, the use of calibrated guidewires for the precise location of lesions in relation to adjacent reference points (side branches and bifurcations) may be helpful.

Conclusions

This study demonstrates the exceptional ability of ICUS to detect quantitative changes in the extent of coronary atherosclerosis. The high degree of intra- and interobserver correlation in the measurement of vascular lumen and external elastic lamina area makes ICUS an ideal modality to quantitate the extent of atherosclerosis. These findings support the use of ICUS for the quantitation of vascular dimensions in atherosclerosis regression trials.

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