UCLA

UCLA Previously Published Works

Title

Angle dependence of intravascular ultrasound imaging and its feasibility in tissue characterization of human atherosclerotic tissue.

Permalink

<https://escholarship.org/uc/item/22b3f30z>

Journal

American heart journal, 137(3)

ISSN

0002-8703

Authors

Hiro, T
Leung, CY
Karimi, H
[et al.](#)

Publication Date

1999-03-01

DOI

10.1016/s0002-8703(99)70495-3

Copyright Information

This work is made available under the terms of a Creative Commons Attribution License, available at <https://creativecommons.org/licenses/by/4.0/>

Peer reviewed

Angle dependence of intravascular ultrasound imaging and its feasibility in tissue characterization of human atherosclerotic tissue

Takafumi Hiro, MD, Cyril Y. Leung, MD, Houshang Karimi, BA, Ali R. Farvid, BA, and Jonathan M. Tobis, MD, FACC Orange, Calif

Background Intravascular ultrasound (IVUS) images vary in intensity because of the angle of the transducer relative to the plaque. The purpose of this study was to determine the angle dependence of ultrasound backscatter when the IVUS transducer is aligned coaxially in atherosclerotic arteries and to examine its feasibility in tissue characterization of human atherosclerotic tissue.

Methods and Results Thirty-nine noncalcified regions of interest (ROI, 0.4 to 0.6 mm in diameter) within cross sections of formalin-fixed human iliac arterial plaque were imaged with a 3.9F, 25-MHz IVUS catheter in saline at room temperature. The catheter was moved coaxially from 8 to 16 positions and spanned 50 to 122 degrees relative to the ROI and the lumen center. Echo intensity for each ROI was defined as the videointensity relative to a standard reflector. The angle dependence of echo intensity was defined as the slope of the regression line between the angle of incidence and echo intensity. Each ROI was histologically classified into 4 groups: fibro-acellular (fibrous cap, $n = 7$), fibro-cellular ($n = 9$), fibro-fatty ($n = 13$), or fatty tissue ($n = 10$). The echo intensity of the majority (72%) of plaque components in IVUS images are significantly affected by the angle of incidence of the transducer. The angle dependence of fibro-acellular samples was significantly greater than that of the other 3 groups ($4.69 \pm 3.29 \times 10^{-3} \times$ echo intensity/degree vs 1.06 ± 1.10 in fibro-cellular area, 2.09 ± 1.75 in fibro-fatty area, and 2.16 ± 1.92 in fatty area, $P < .05$).

Conclusions The angle dependence of ultrasound reflections from the fibrous cap of atherosclerotic plaque is another method of tissue characterization in addition to spatial distribution and echo intensity. This technique may be useful in determining the thickness of the fibrous cap, which may be an important predictor of plaque rupture. (Am Heart J 1999;137:476-81.)

Ultrasound backscatter from arterial tissues depends on several factors, including the angle of incidence of the ultrasound beam.^{1,2} Picano et al¹ used an ultrasound frequency of 10 MHz and demonstrated that the backscatter of calcified and fibrous tissue in human aortas is strongly angle dependent, whereas the ultrasound reflections from lipid-laden plaques are influenced less by the beam angle. They concluded that the angle dependence of arterial backscatter may limit the usefulness of ultrasound for

quantitative measurements but that it may be useful for diagnosis of tissue characterization.

Di Mario et al³ studied the effect of the angle of incidence on image quality of arterial specimens by using a 30-MHz transducer intravascular ultrasound (IVUS) catheter. They found significant variability in quality of the ultrasound images when the angle of incidence was approximately 50 degrees. They did not address the hypothesis of Picano et al that differences in ultrasound reflections caused by the angle of incidence could be helpful in tissue characterization. The purpose of this study was (1) to determine the angle dependence of ultrasound backscatter when the IVUS transducer is aligned coaxially in atherosclerotic arteries and (2) to examine the capability of using IVUS beam angle dependence to facilitate tissue characterization of atherosclerotic plaque.

From the Division of Cardiology, University of California, Irvine, and The Orange County Coroner's Office.

Supported in part by NIH grant R01-HL45077-03.

Submitted January 29, 1998; accepted April 22, 1998.

Reprint requests: Jonathan M. Tobis, MD, Department of Medicine/Cardiology, University of California, Irvine, Bldg 53; Route 81; Room 100, 101 The City Dr South, Orange, CA 92668-3298.

Copyright © 1999 by Mosby, Inc.

0002-8703/99/\$8.00 + 0 4/1/91287

Methods

IVUS imaging

Ten formalin-fixed human iliac arteries obtained from necropsy were imaged with a 3.9F, 25-MHz IVUS catheter (InterTherapy/CVIS, model 3003 Sunnyvale, Calif) in saline at room temperature. Thirty-nine regions of interest (ROI) were chosen within arterial plaque cross sections. Each ROI was defined as a circular area with a diameter between 0.4 to 0.6 mm (approximately 0.2 mm²). The ROI was chosen near the middle of the plaque arc, often where the plaque was thickest. Two or three ROIs per plaque were chosen. An acoustic reference point was established by suturing a surgical needle into the wall of the artery perpendicular to the long axis. This technique ensured that the same cross section was imaged for all studies and that the ultrasound images corresponded exactly to the cross section chosen for histologic analysis. The IVUS catheter was inserted into the artery until the surgical needle echo was visualized. The catheter was always kept parallel to the long axis of the artery but was moved coaxially between 8 to 16 positions relative to the lumen center at the same cross section confirmed by identification of the needle echo (Fig 1). The coaxial angular span was determined by the capability of the catheter to move inside the arterial lumen. The gain was manipulated to maximize image morphology without excessive dropout, saturation, or noise. After the first image was optimized, the gain was then fixed for all images within that artery, and these same settings were used for all the other arterial segments studied. The ultrasound images were recorded on super VHS tape. The gain and depth settings of the IVUS machine were kept constant during this study.

Data analysis

The arterial images with the needle acoustic reference was digitized with a frame-grabbing board (RasterOps 24STV with software by MediaGrabber) into a Macintosh IIfx computer. An on-screen image analysis application (NIH Image public domain software) was used to measure an intensity index for each plaque. Because the absolute energy of the reflected ultrasound intensity cannot be obtained with regular IVUS machines, the intensity of each segment was measured with a relative intensity (RI) index calculated as

$$RI = (I_{roi} - I_{bkg}) / (I_{ref} - I_{bkg})$$

where I_{roi} is the echo intensity of the subject region of interest, I_{ref} is the echo intensity of a standard reflector with the same gain settings, and I_{bkg} is the intensity of background of the equivalent region of interest. The background area was chosen from an IVUS image in the water bath before inserting it into the artery. Each ultrasound image had a gray scale of 256 levels on a 640 × 480 pixel display. Tissue paper was placed in the water bath and imaged as the standard reflector. This index is reproducible and varies only 3.0% with changes in the overall gain setting.

The angle of incidence (θ) was measured between the

Figure 1

Determination of angle of incidence of ultrasound in our model. θ is angle between geometric center of lumen and center of IVUS catheter relative to ROI of plaque.

catheter, the ROI within the plaque, and the lumen geometric center (Fig 1). After outlining the lumen boundary, the lumen center was determined automatically by using the NIH Image analysis application. When the transducer was on the lumen geometric center, the angle of incidence was considered as zero. The angle was defined as a positive value on one side of the zero degree incidence line with a minus value on the other side.

In this study, calcified plaques were not used because the intensity of calcium usually saturates the gray scale value and it is difficult to assess the ultrasound intensity because of angle dependence. Calcified tissue is readily identified by visual inspection with high sensitivity and specificity.⁴ The current concern for tissue characterization of plaque is how to discriminate between fibrous and fatty tissue.

Histologic study

After the arteries were imaged by IVUS, the needle was removed and the needle site was marked with india ink. The specimens were processed for histology and were stained with Masson's trichrome and hematoxylin-eosin.

Areas within each plaque cross section were classified into 1 of 4 histologic categories: (1) Fibro-acellular or fibrous hypocellular—hypocellularity was defined as an area of fibromuscular cells that occupied <25% of the collagen matrix portion; (2) fibro-cellular—an area of fibromuscular cells (involving >25% of the area) intermixed with connective tissue matrix; (3) fibro-fatty—fibrous tissue interspersed with lipid-containing cells and vacuoles; (4) fatty—contiguous areas of lipid-containing foam cells, cholesterol crystals, or a lipid pool.

Figure 2

A, Representative examples of angle dependence of IVUS backscatter from same arterial plaque. Each image was created by moving catheter within lumen to alter angle of incidence (θ). *Echo from surgical needle used as acoustic reference to ensure that same cross section was imaged. Small solid circle represents geometric center of lumen. C depicts center of IVUS catheter. ROI is shown as larger open circle. **B**, Histologic specimen of corresponding arterial cross section with Masson's trichrome stain.

Statistics

Values are expressed as mean $\pm$ SD. Analysis of variance with the Bonferroni post hoc test was used to compare the mean values among groups. The least squares method was used to analyze all linear relations. In these analyses, a value of $P < .05$ was considered to be significant.

Results

The transducer was placed in variable positions within the lumen such that the range of θ spanned from 50 to 122 degrees. Representative examples of

the angle dependence of IVUS backscatter from an arterial plaque are shown in Fig 2, A. The part of the plaque that was most sensitive to changes in angle-dependent backscatter corresponded to the fibrous cap as determined from the histologic specimens (Fig 2, B).

Fig 3 illustrates the various relations between the relative intensity index and the angle of incidence of the ultrasound beam. Two patterns were observed: A "directive" pattern (Fig 3, A and B) and a "nondirective" pattern (Fig 3, C and D). The directive pattern is

Figure 3

Representative relations between relative intensity index and angle of incidence of ultrasound beam.

characterized by an angle-dependent echo intensity that is significantly determined (strongly as in Fig 3, *A*, or weakly as in Fig 3, *B*) when the angle of incidence is >10 degrees away from zero. The nondirective patterns are characterized by echo intensities that are not significantly angle dependent. These intensities were either constant (Fig 3, *C*) or fluctuated (Fig 3, *D*) throughout the entire range of θ .

In 28 ROIs in which the echo intensity was angle dependent, the relation between θ and the echo intensity fit 2 linear segments (with the least squares method), with a peak intensity near 0 degrees (Fig 4) as:

$$\begin{aligned} \text{RI} &= a(\theta - \theta_{\max}) + C \text{ (when } \theta < \theta_{\max}) \\ \text{RI} &= -a(\theta - \theta_{\max}) + C \text{ (when } \theta \geq \theta_{\max}) \end{aligned}$$

where RI is the relative intensity and θ is the angle of incidence of the ultrasound beam. The coefficient “a” ($a > 0$) is defined as the slope of the angle dependence of the echo intensity, $\theta_{\max}$ is defined as the angle that provides the peak echo intensity, and C is the peak RI when $\theta = \theta_{\max}$. The peak relative intensity for the 4 histologic subsets varied between 0.43 for fibro-cellular tissue and 0.63 for fibro-acellular areas ($P < .003$), but there was significant overlap with the other tissue types, which indicates that echo intensity above is not an adequate discriminator of tissue types. In this setting, a nondirective but consistent echo-

Figure 4

Method to measure angle dependence of echo intensity. $-a$, Slope of angle dependence of RI.

intensity pattern as in Fig 3, *C*, had a significant correlation coefficient but had a very small value of “a” (close to 0). A fluctuating echo-intensity pattern as in Fig 3, *D*, had a nonsignificant correlation coefficient, and the value of “a” was arbitrarily considered as zero. The angle generating the peak intensity usually did not correspond to $\theta = 0$ as defined in this study. The mean absolute value of $\theta_{\max}$ was 8.0 ± 7.5 degrees.

Table I. Slope of angle dependence of echo intensity for all histologic groups

Histology	Fibro-acellular	Fibro-cellular	Fibro-fatty	Fatty
n	7	9	13	10
Slope, "a" ($10^{-3} \times \text{RI/degree}$)	$4.69 \pm 3.29^*$	1.06 ± 1.10	2.09 ± 1.75	2.16 ± 1.92

* $P < .005$ vs fibro-cellular, * $P < .05$ vs fibro-fatty and fatty tissue.

The mean values of the slopes of "a" from the ultrasound intensity angle dependence curves arranged by histologic groups are shown in Table I. The mean value of the slope from fibro-acellular samples was significantly greater than that of the other 3 groups ($P < .05$). There were no significant differences in any other comparisons such as between fibro-cellular, fibro-fatty, and fatty areas. In 72% of segments (86% of fibro-acellular, 56% of fibro-cellular, 69% of fibro-fatty, 80% of fatty segments) there were significant correlations ($P < .05$, $r = 0.58$ to 0.98) of echo intensity and the angle of incidence. In these segments, the slope varied between -0.05 and -0.51 . In 28% of the segments (14% of fibro-acellular, 44% of fibro-cellular, 31% of fibro-fatty, 20% of fatty segments), a fluctuating nondirective echo intensity pattern was seen.

The distance between the transducer and the tissue did not reveal any significant effect on the echo intensity in the ROI.

Discussion

Tissue characterization of atherosclerotic plaque is usually determined by the spatial distribution and intensity of the ultrasound backscatter. The major finding of this study is that the IVUS intensity of fibro-acellular tissue is more sensitive than other tissue components to the angle of incidence of the ultrasound beam. This finding might be useful as a method of tissue characterization in distinguishing fibrous tissue from other elements. Unfortunately, the angle dependence of the ultrasound intensity did not adequately discriminate fibro-cellular, fibro-fatty, and fatty areas and so would not be useful to make these finer distinctions. However, this method with a commercially available IVUS machine should be useful in determining the thickness of the fibro-acellular component of atherosclerotic plaque. This may have clinical relevance because the fibrous cap is composed of fibro-acellular tissue and the thickness of this capsule may predispose to plaque rupture.⁵⁻¹⁰

A structure that is bigger than the ultrasound wave-

length generates directional backscatter.^{11,12} The direction of the backscatter is determined by the ultrasound beam angle of incidence as well as the shape of the structure. If the shape is a flat surface, the backscatter directed to the transducer reaches a maximum when the ultrasound incidence is perpendicular to the surface.^{11,12} The ultrasound backscatter of some tissue components such as calcium, collagen, or elastic fibers are highly dependent on the angle of incidence of the ultrasound beam compared with other components, for example, lipid-filled cells or the muscular media.¹ Although Picano et al predicted the possibility of ultrasound imaging to discriminate fibrous, fibro-fatty, and fatty areas, in our study only the fibro-acellular component had a greater backscatter directivity than other tissues. This may be caused by the tissue complexity of the plaque. Even in fibrous areas, nondirective patterns were obtained in some cases. These segments were characterized histologically by disarray of the collagen fiber matrix. On the other hand, some fatty areas had a directive pattern, probably because of the orientation of loose collagen fibers or the existence of microcalcifications⁴ within the fatty area. Another reason for differences between these findings and those of Picano et al is that we examined the angle dependence of the echo intensity in small segments within plaques, whereas they examined entire plaques excised from aortas.

The mean value of $\theta_{\max}$ was 8.0 ± 7.5 degrees, which indicates that the maximum reflection of the ultrasound beam from the plaque was slightly displaced from a perpendicular angle of incidence. Although one would expect $\theta_{\max}$ to be 0 degrees when an ultrasound beam reflects off a flat surface, the finding of $\theta_{\max} = 8.0$ degrees is consistent with the mildly irregular geometry of the plaque and the circular orientation of the collagen fibers within the plaque.

The echo-intensity data relative to the angle of incidence fit a curve with 2 linear segments. De Kroon et al² used a gaussian curve to fit their data derived from a 27-MHz acoustic microscope. Our method of fitting

the data to 2 linear segments provides reasonable correlation coefficients and is much easier to use than the previously described method.

There are several limitations of this in vitro study. These experiments were performed after formalin fixation, and we do not know whether these results are transferable to nonfixed living tissue. The number of observations in this study is relatively small, and these measurements need to be corroborated by other experiments. The techniques described in this in vitro study are potentially applicable to tissue characterization in patients; however, these studies need to be repeated in the clinical setting.

In conclusion, the angle dependence of intravascular ultrasound imaging in human atherosclerotic tissue is useful in tissue characterization, particularly for identifying the fibrous cap. This technique may be useful in determining the thickness of the fibrous cap, which may be an important predictor of plaque rupture and acute ischemia syndromes.⁵⁻¹⁰

References

1. Picano E, Landini L, Distanti A, et al. Angle dependence of ultrasonic backscatter in arterial tissues: a study in vitro. *Circulation* 1985;72:572-6.
2. de Kroon MG, van der Wal LF, Gussenhoven WJ, et al. Backscatter directivity and integrated backscatter power of arterial tissue. *Int J Card Imaging* 1991;6:265-75.
3. Di Mario C, Madretsma S, Linker D, et al. The angle of incidence of the ultrasonic beam: a critical factor for the image quality in intravascular ultrasonography. *Am Heart J* 1993;125:442-8.
4. Friedrich GJ, Moes NY, Muhlberger VA, et al. Detection of intraluminal calcium by intracoronary ultrasound depends on the histologic pattern. *Am Heart J* 1994;128:435-41.
5. Cheng GC, Loree HM, Kamm RD, et al. Distribution of circumferential stress in ruptured and stable atherosclerotic lesions: a structural analysis with histopathological correlation. *Circulation* 1993;87:1179-87.
6. Richardson PD, Davies MJ, Born GV. Influence of plaque configuration and stress distribution on fissuring of coronary atherosclerotic plaques [see comments]. *Lancet* 1989;2:941-4.
7. Gertz SD, Roberts WC. Hemodynamic shear force in rupture of coronary arterial atherosclerotic plaques [editorial]. *Am J Cardiol* 1990;66:1368-72.
8. Davies MJ. A macro and micro view of coronary vascular insult in ischemic heart disease. *Circulation* 1990;82:II-38-46.
9. Fuster V, Stein B, Ambrose JA, et al. Atherosclerotic plaque rupture and thrombosis: evolving concepts. *Circulation* 1990;82:II-47-59.
10. MacIsaac AI, Thomas JD, Topol EJ. Toward the quiescent coronary plaque. *J Am Coll Cardiol* 1993;22:1228-41.
11. Curry TS III, Dowdey JE, Murry RC Jr. Ultrasound. In: *Physics of diagnostic radiology*. Philadelphia: Lea & Febiger; 1990. p 323-71.
12. Bushberg JT, Seibert JA, Leidholdt EM Jr, et al. Ultrasound. In: *The essential physics of medical imaging*. Baltimore: Williams & Wilkins; 1994. p 367-416.