Elasticity Imaging of Atheroma With Transcutaneous Ultrasound
Preliminary Study

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Background—Knowledge of the physical properties of atherosclerotic plaque is essential when evaluating its vulnerability in a clinical setting. Such knowledge, however, is still difficult to obtain with the various approaches developed to date.

Methods and Results—This article describes a noninvasive method for evaluating the regional elasticity (the elastic modulus in the circumferential direction) of tissue surrounding atherosclerotic plaque in which a novel phased tracking method is applied to measure minute changes in thickness of each of the multiple layers of the arterial wall during one heartbeat. By comparing the pathological findings with the distribution of elasticity, average elasticity of lipid and that of a mixture of smooth muscle and collagen fiber can be determined. On the basis of these reference parameters, each point is statistically categorized as lipid, mixture, or other. Thus, the plaque is electronically stained using transcutaneous ultrasound. By applying the method to the common carotid arteries, the presence of thin collagen fiber was clarified along the arterial axis for normal subjects, whereas soft inclusion of lipid was found for every plaque in subjects with hyperlipidemia.

Conclusion—This novel method offers potential as a diagnostic technique for detection of plaque vulnerability with high spatial resolution. **(*Circulation*. 2003;107:3018-3021.)**

Key Words: atherosclerosis ■ elasticity ■ plaque ■ ultrasonics

Rupture of atherosclerotic plaque is probably the most important factor underlying the sudden onset of the acute coronary syndrome.[1] Direct characterization of the composition and vulnerability of atherosclerotic plaque, rather than of the angiographic lumen,[2] may offer insight into the mechanisms of plaque regression and progression[3,4] and thereby promote evaluation of cholesterol-lowering therapy[5,6] for reduction of cardiovascular events. MRI and intravascular ultrasound are promising technologies for directly imaging plaque morphology.[7,8] For the evaluation of dynamic mechanics, arterial elasticity has been determined by measuring the pulse wave velocity[9] and rough change in the diameter of the artery.[10,11] However, a method to detect the vulnerability of atherosclerotic plaque with sufficient accuracy has not yet been reported. The purpose of the present study was to determine the cross-sectional distribution of elasticity in the arterial wall using commercially available transcutaneous ultrasound equipment.

Methods

Measurement of Change in Thickness of the Arterial Wall

An ultrasonic beam was sequentially scanned at M ($=60$) positions with a linear-type ultrasonic probe of 7 MHz using conventional ultrasound diagnostic equipment (Toshiba SSH-140A), and multiple (N_m+1) points were preset from the luminal surface to the adventitia along the mth ultrasonic beam ($m=1,\ldots, M$) with constant intervals of $h_0=375$ μm at a time t_0 just before the ejection period. By dividing the arterial wall into multiple layers, we defined the nth layer ($n=1,\ldots, N_m$) as being between two contiguous points, n and $n+1$, along each beam. For measurement of change in thickness of each of the N_m layers, the instantaneous depth $x_{m,n}(t)$ of the nth point along the mth beam was simultaneously tracked by applying the phased tracking method[12,13] to the received ultrasound. The minute decrease of several tenths of a micrometer in wall thickness of the nth layer resulting from the arrival of the pressure wave at the beginning of the ejection period was determined by $\Delta h_{m,n}(t)=x_{m,n+1}(t)-x_{m,n}(t)-h_0$.

In the phased tracking method, for calculation of the autocorrelation function between the quadrature-demodulated signals of sequentially received echoes, minute phase change of $\approx$0.4 degrees caused by movement of the nth point during the pulse transmission interval ΔT ($=200$ μs) can be accurately determined by introducing a constraint, namely, that their waveforms are identical but their phase values change.[12,13] The lowest value of the change in thickness was validated as being $\approx$0.5 μm by expanding a rubber plate in a water tank.[14] Such a minute change in thickness cannot be measured by any other method. This method has already been applied to the in vivo detection of regional instantaneous displacement and change in thickness, with sufficient reproducibility, in the interventricular septum[12,13,15] and in the common carotid artery (CCA).[16]

Elasticity Estimation

From the ratio of the maximum decrease in thickness during one heartbeat, $\Delta h_{m,n,\max}=\max_t|\Delta h_{m,n}(t)|$, to the initial thickness h_0 of the

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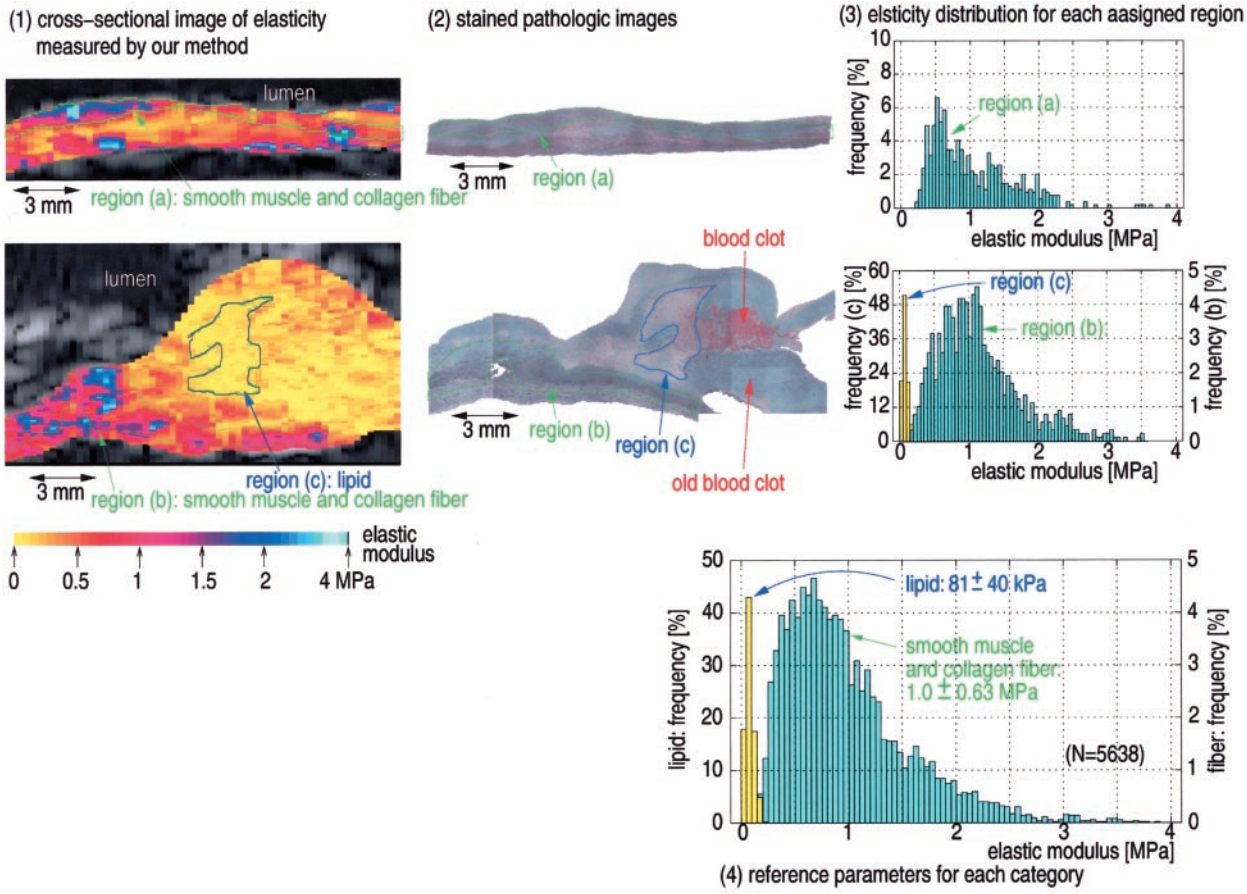

Figure 1. By referring to the stained image (2), the regions of lipid and of the mixture of smooth muscle and collagen fiber were assigned in the spatial distribution of elasticity $E\theta_{,m,n}$ measured in in vitro experiments (1). From the histogram of $E_{\theta,m,n}$ for each region (3), the elasticity for each category was registered as a reference (4), from which each tissue was categorized as belonging to one of the 3 categories.

nth layer, the maximum deformation of the nth layer was obtained by $\Delta\varepsilon_{m,n,\max}=\Delta h_{m,n,\max}/h_0$. Because the deformation was sufficiently small and was in the linear regime, it showed incremental strain in the radial direction. By assuming that the arterial wall is incompressible and that the blood pressure is applied perpendicularly to each layer, the elastic modulus of the nth layer along the mth beam, $E_{\theta,m,n}$, is approximately given by[17]

$$E_{\theta,m,n}\cong\frac{1}{2}\left(\frac{\rho_{m,n,0}}{h_0\cdot N_m}+\frac{N_m-n+1}{N_m}\right)\frac{\Delta p}{\Delta\varepsilon_{m,n,\max}},\quad(1)$$

$$(n=1,\ldots,N_m;\ m=1,\ldots,M)$$

where $\rho_{m,n,0}$ is the initial inner radius of curvature of the nth layer along the mth beam at a time t_0. We assumed that the pressure in the arterial wall decreases linearly with the distance from the intimal side to the adventitia and that the arterial wall is almost isotropic.[18]

For the region with a length of 18 mm along the axis of the artery, the regional elasticity $E_{\theta,m,n}$ was estimated on the cross-sectional image. Because the reflected ultrasound was received at a sampling interval of 100 ns (=75 μm along depth direction) after the quadrature demodulation, we further divided each layer with a thickness of h_0 into 5 points, shifted the initial depth of each layer by one fifth of h_0, and applied the above procedure to each depth. Thus, $E_{\theta,m,n}$ was estimated at intervals of 75 μm in the depth direction and 300 μm in the axial direction. Using a silicone tube with two layers set in an artificial circulation system,[17] the accuracy of the measurement of regional elasticity for each layer has already been validated to be ≈0.1 MPa[17]—that is, the error is ≈8% of the elasticity value obtained by a separate static pressure-diameter test.

In in vivo experiments before the extraction of an iliac artery and in in vitro experiments (described below) after such extraction, the average elasticity was ≈0.96±0.48 MPa and 0.89±0.31 MPa, respectively, the difference between them being ≈8%. Thus, the slight influence of assaying the artery through the skin was eliminated.

In separate in vivo experiments, when the pressure of the ultrasonic probe on the skin surface of a healthy subject was set as 8.0, 14.0, 33.2, 40.7, 54.5, and 74.3 mm Hg, the measured diameter of the same point of the CCA changed as 6.8, 6.8, 6.6, 6.1, 6.0, and 5.4 mm, respectively. For higher pressure, the cross section of the artery changes from a circular to an oval shape. We confirmed that the measured elasticity is not influenced by the pressure on the ultrasonic probe to the skin surface as long as the pressure is ≤30 mm Hg. In our in vivo experiments, the ultrasonic probe was held on the skin surface with a pressure of 30 mm Hg.

Results

Electronic Staining

Immediately after 9 iliac arteries (25 to 40 mm in length and 4 to 24 mm in outer diameter) with plaques were extracted from patients with embolism, cross-sectional elasticity distribution, $E_{\theta,m,n}$, was measured using the above method [Figure 1(1)] under the same artificial circulation system to generate

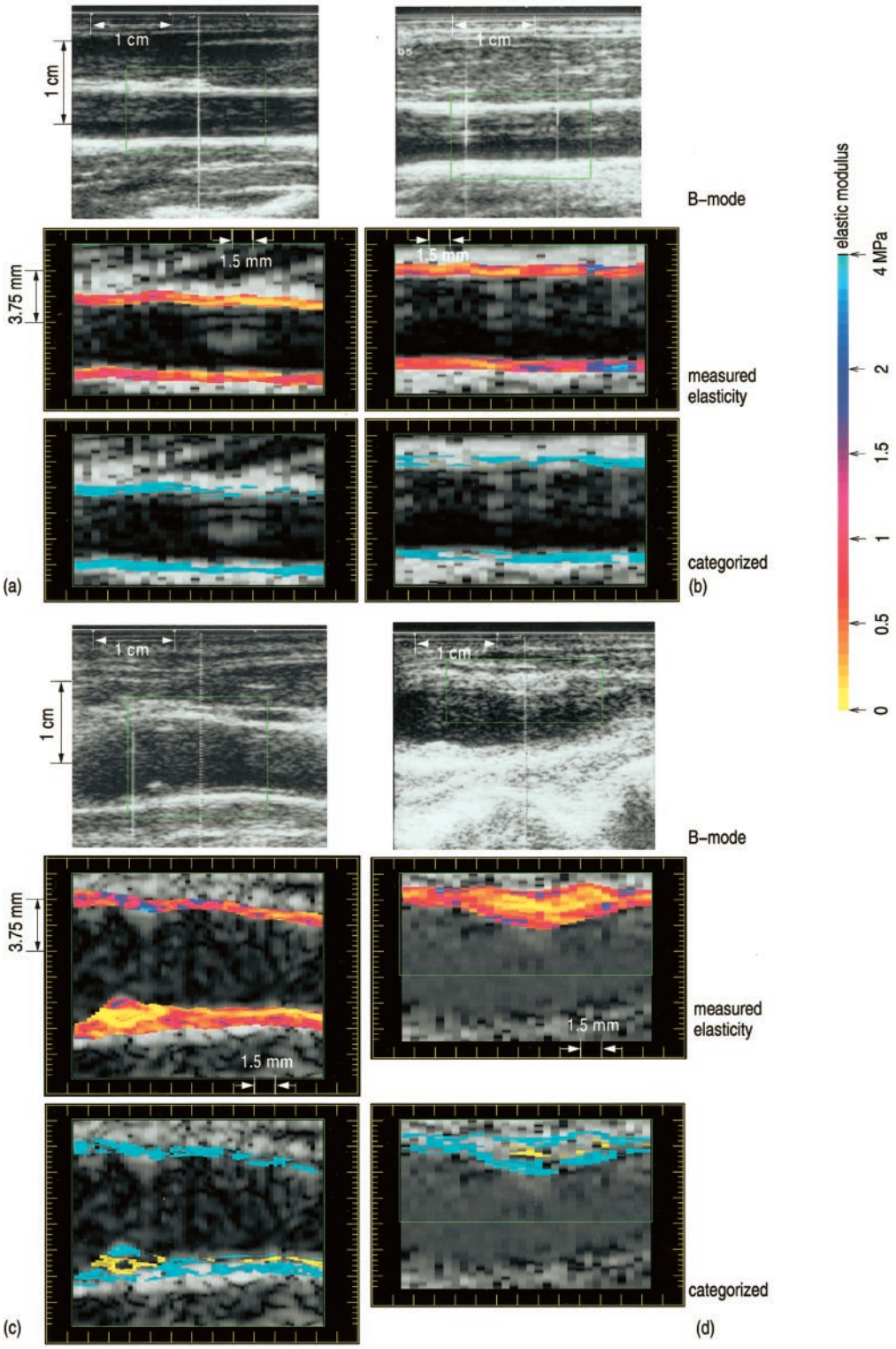

Figure 2. CCAs of 2 healthy male subjects [(a) 24 years old and (b) 25 years old] and 2 male patients with hyperlipidemia [(c) 66 years old and (d) 71 years old)]. The area outlined by green in each uppermost figure was analyzed in the middle and bottom of the figure.

a change in pressure so that it ranged from the diastolic pressure to the systolic pressure of the subjects. After each in vitro measurement, elastica-Masson stain was applied. Two typical results are shown in Figure 1(2). From the stain images, 10 regions with either lipid or a mixture of smooth muscle and collagen fiber were assigned in $E_{\theta,m,n}$ of the 9 specimens. Each histogram of $E_{\theta,m,n}$ in the respective regions is shown in Figure 1(3). For the respective categories of the 9 arteries, the average and the standard deviation in elasticity were determined to be 81 ± 40 kPa and 1.0 ± 0.63 MPa, which were registered as the reference parameters [Figure 1(4)].

On the basis of these reference parameters, each point in the cross-sectional elasticity distribution, which had been noninvasively measured by the above method in separate in vivo experiments, was statistically classified as one of 3 categories (lipid, mixture of smooth muscle and collagen fiber, or other). Thus, the arterial wall and the atherosclerotic plaque were electronically stained.

For CCAs

The proposed method was applied to in vivo measurements of the CCAs of 2 healthy subjects [Figure 2, (a) and (b)] and 2 patients with hyperlipidemia having atherosclerotic plaques [Figure 2, (c) and (d)]. In Figure 2, for each subject, a cross-sectional image obtained by conventional ultrasound diagnostic equipment is shown at the top. The cross-sectional elasticity distribution of $E_{\theta,m,n}$ was color-coded and superimposed on the reconstructed B-mode image as shown in the middle. Finally, at the bottom, the categorized result is shown. The lipid and the mixture of smooth muscle and collagen fiber are shown by yellow and cyan, respectively, and the category of "other" is not colored.

Discussion

For the CCAs of normal subjects, the existence of thin fibrous tissue along the arterial axis was clarified. For the plaque in the subjects, soft inclusions of lipid surrounded by fibrous tissue were found. With extrapolation of the results of an in vitro study,[19] we postulated that a thin layer constitutes a fibrous cap surrounding the plaque. Iliac arteries were used to determine the reference parameters, which were then applied to CCAs in the in vivo experiments. Although the composition of the iliac artery and that of the CCA differ, the characteristics of the collagen fiber itself and the lipid itself do not differ between them. Thus, we employed the approach described above. Whether this composition is closely related to the rupture of atherosclerotic plaque should be investigated. However, the spatial heterogeneity of the elasticity around plaques, where large stress is concentrated, is displayed. These results have not been previously obtained by any other method.

Conclusion

Cross-sectional images of the elasticity around atherosclerotic plaques were transcutaneously obtained in this study. This novel approach offers potential for diagnosis of the vulnerability of plaque in a clinical setting. Further study is being carried out to increase the number of elasticity references.

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