Elasticity Imaging of Atheroma with Transcutaneous Ultrasound -Preliminary Study-

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Abstract

- This paper describes a noninvasive method for evaluating regional elasticity in atheroma in which a novel measurement 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 elasticity distribution, statistic parameters for lipid and a mixture of smooth muscle and collagen fiber can be determined.
- By applying the method to the common carotid arteries (CCAs), thin collagen fiber was clarified and soft inclusion of lipid in plaque was detected.
- This method offers potential for detection of plaque vulnerability in a clinical setting.

Clinical background

- Rupture of atherosclerotic plaque is probably the most important factor underlying the sudden onset of the acute coronary syndrome.
- Direct characterization of the composition and vulnerability of atherosclerotic plaque, rather than of the angiographic lumen, may offer insight into the mechanisms of plaque regression and progression and thereby promote evaluation of cholesterol-lowering therapy for reduction of cardiovascular events.

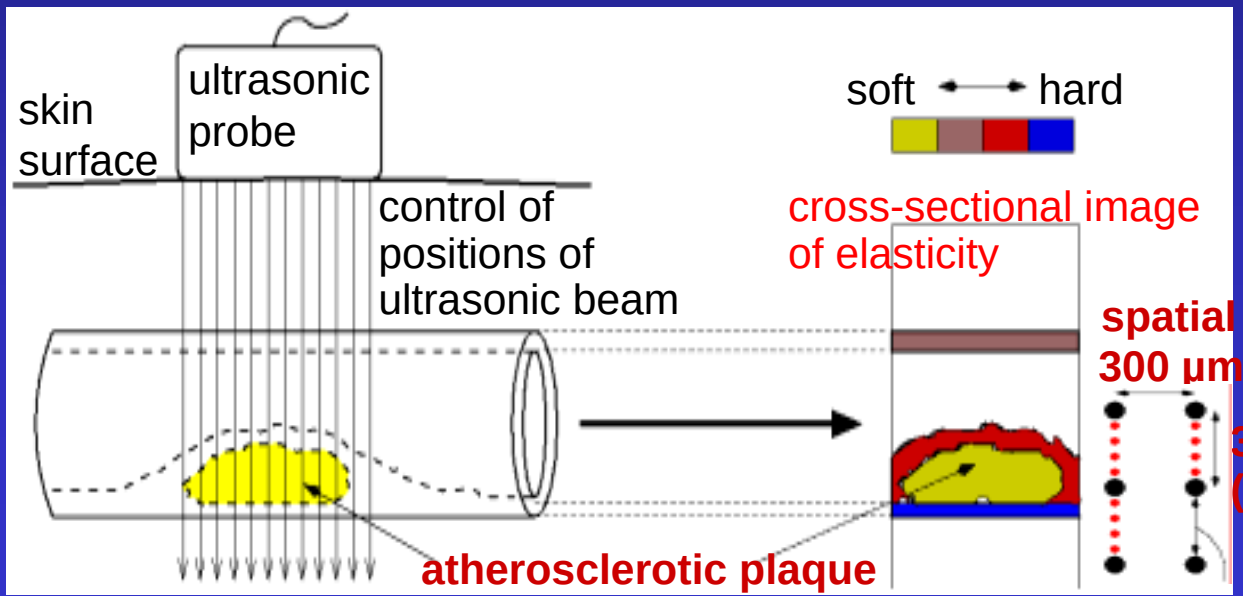
Previous methods and purpose of this study

- MRI and intravascular ultrasound are promising technologies for directly imaging plaque morphology.
- For the evaluation of dynamic mechanics, arterial elasticity has been determined by measuring the pulse wave velocity (PWV) and rough change in the diameter of the artery.
- 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.

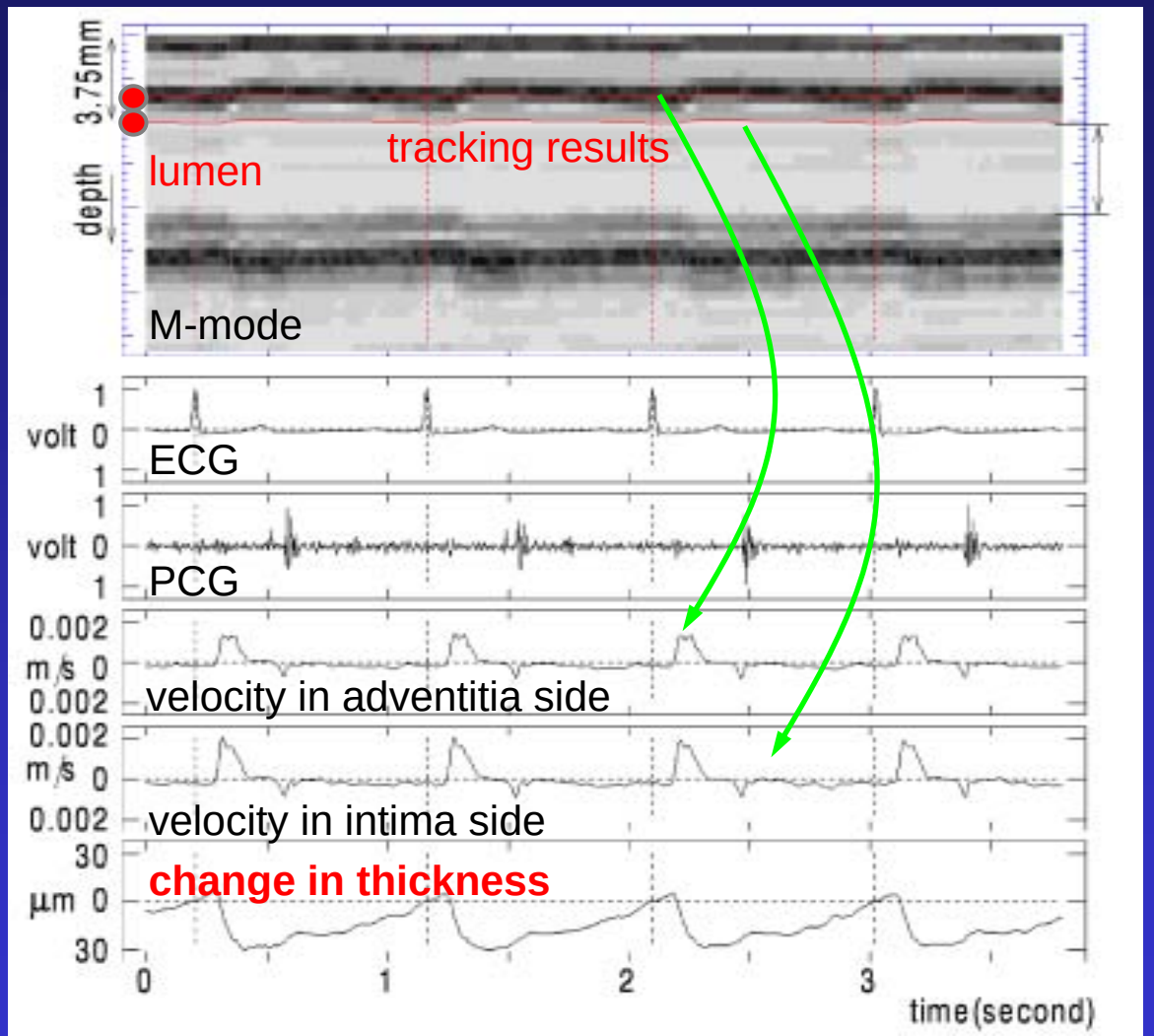
Using conventional ultrasound diagnosis system

- An ultrasonic beam was sequentially scanned at M (=60) positions with a linear-type ultrasonic probe of 7 MHz using conventional ultrasound diagnostic equipment, and multiple (N_m+1) points were preset from the luminal surface to the adventitia along the m-th ultrasonic beam (m=1,…,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 n-th layer (n=1,…,N_m) as being between two contiguous points, n and n+1, along each beam.



Measurement of change in thickness of arterial wall

- For measurement of change in thickness of each of the N_m layers, the instantaneous depth $x_{m,n}(t)$ of the n-th point along the m-th beam was simultaneously tracked by applying the *phased tracking method** to the received ultrasound.
- The minute decrease of several tenths of a micrometer in wall thickness of the n-th layer resulting from the arrival of the pressure wave at the beginning of the ejection period was determined by $\Delta h_{m,n}(t)=x_{m,n+1}(t)-x_{m,n}(t)-h_0$.



(36-year-old, normal, male)

*Kanai H, Hasegawa H, Chubachi N, et al. *IEEE Trans on UFFC*. 1997;44:752-768.

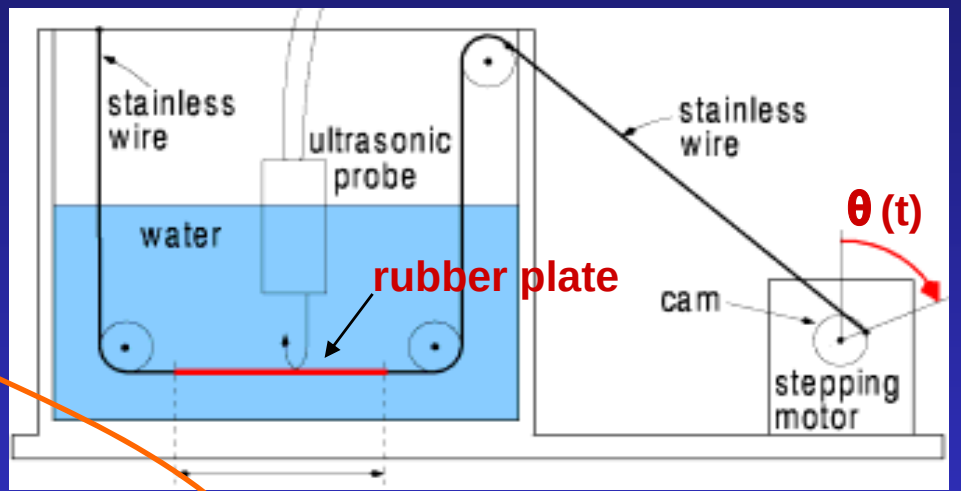
phased tracking method[*1]

- In the *phased tracking method*, for calculation of the auto-correlation function between the quadrature demodulated signals of sequentially received echoes, minute phase change of about 0.4 degrees caused by movement of the *n*-th 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.
- 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[*1,*2,*3,*4] and in the CCA[*5].

*[1]Kanai H, Sato M, Koiwa Y, et al. *IEEE Trans on UFFC*. 1996;43:791-810.
*[2]Kanai H, Hasegawa H, Chubachi N, et al. *IEEE Trans on UFFC*. 1997;44:752-768.
*[3]Kanai H, Koiwa Y. *Ultrasound in Med & Biol*. 2001;27:481-498.
*[4]Koiwa Y, Kanai H, Hasegawa H, et al. *Ultrasound in Med & Biol*. 2002;28:1395-1403.
*[5]Kanai H, Koiwa Y, Zhang J. *IEEE Trans on UFFC*. 1999;46:1229-1241.

Accuracy evaluation* of measurement of change in thickness *by phased tracking method*

- The lowest value of the change in thickness was validated as being about 0.5 μm by expanding a rubber plate in a water tank.* Such a minute change in thickness cannot be measured by any other method.

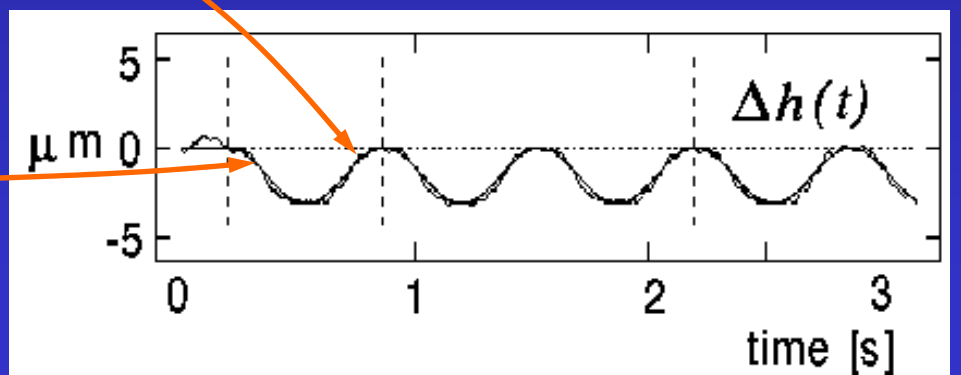


- deciding rubber length from θ (t)
- assuming that Poisson's ratio σ =0.5

Theoretical value of change in thickness

compare

Measured value by the developed method



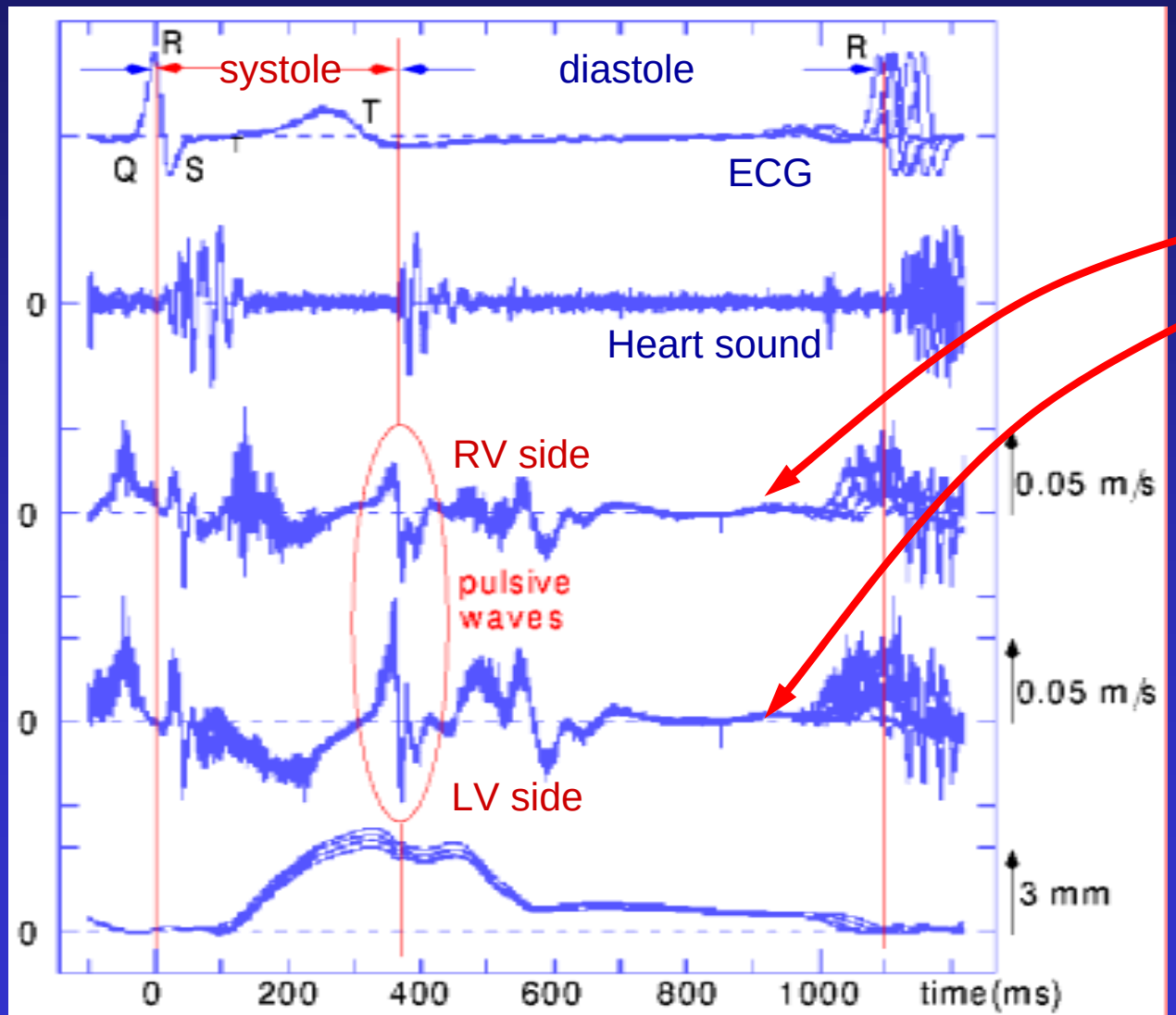
(wavelength: 200 μm, 7.5MHz)

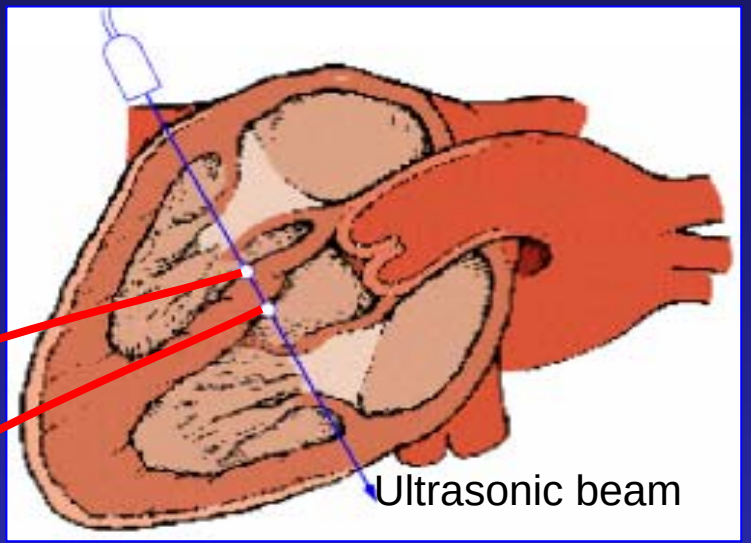
Evaluated accuracy: 0.5 μm

*Kanai H, Sugimura K, Koiwa Y, et al. *Electronics Letters*. 1999;35:949-950.

Application of *phased tracking method* to measurement of heart wall vibrations in IVS

For a healthy subject, 5 heartbeats overlaid





Measurement with reproducibility even for high frequency components (~200 Hz).

Difference between velocity signals

↓ integration

change in thickness (0.5 μm accuracy)

*Kanai H, Hasegawa H, Chubachi N, et al. *IEEE Trans on UFFC*. 1997;44:752-768.

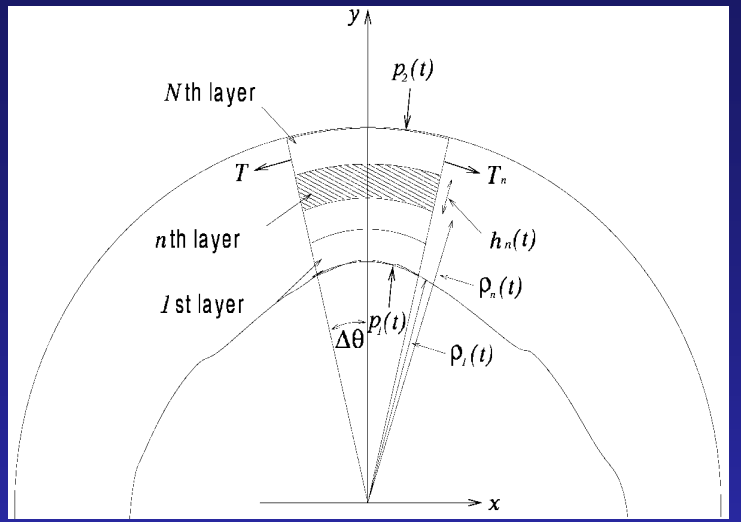
Elasticity estimation

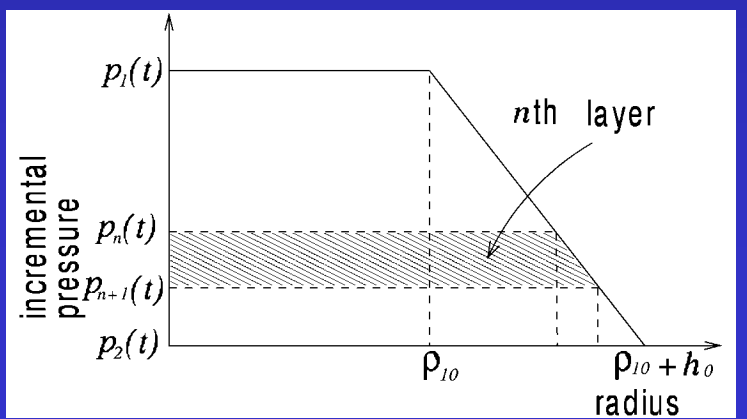
- From the ratio of the maximum decrease in thickness during one heartbeat, $\Delta h_{m,n,\max} = \max_t |\Delta h_{m,n}(t)|$, to the initial thickness h_0 of the n-th layer, the maximum deformation of the n-th layer was obtained by $\Delta \varepsilon_{m,n,\max} = \Delta h_{m,n,\max}/h_0$. Since the 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 normal to each layer, the elastic modulus in the circumferential direction of the n-th layer along the m-th beam, $E_{\theta,m,n}$, is approximately given by*1

$$E_{\theta,m,n} \approx \frac{1}{2}\left(\frac{\rho_{m,n,0}}{h_0 \cdot N_m} + \frac{N_m - n + 1}{N_m}\right)\frac{\Delta p(t)}{\Delta \varepsilon_{m,n,\max}(t)} \qquad (n = 1,\ldots,N_m; m = 1,\ldots,M)$$

where $\rho_{\theta,m,n}$ is the initial radius of curvature of the n-th layer.

- 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.*2

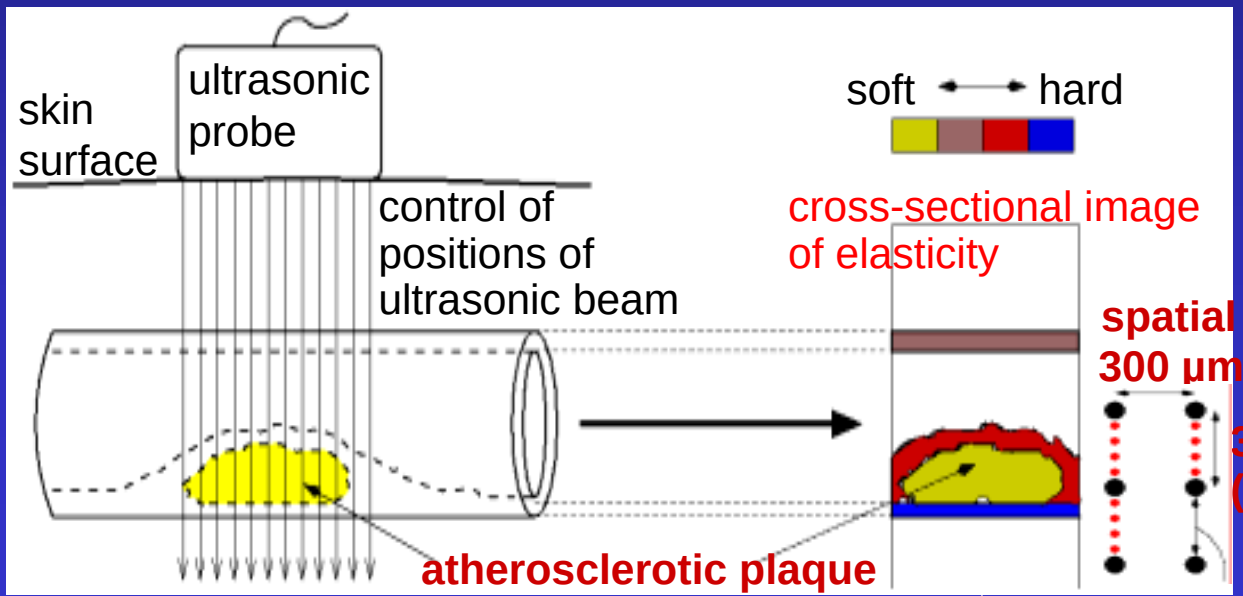




*1 Hasegawa H, Kanai H, Hoshimiya N, et al. *2000 IEEE Ultrason Sympo Proc*. 2000;1829-1832.
*2 Patel DJ, Janicki JS, Vaishnav RN, et al. *Circ Res*. 1973;32:93-107.

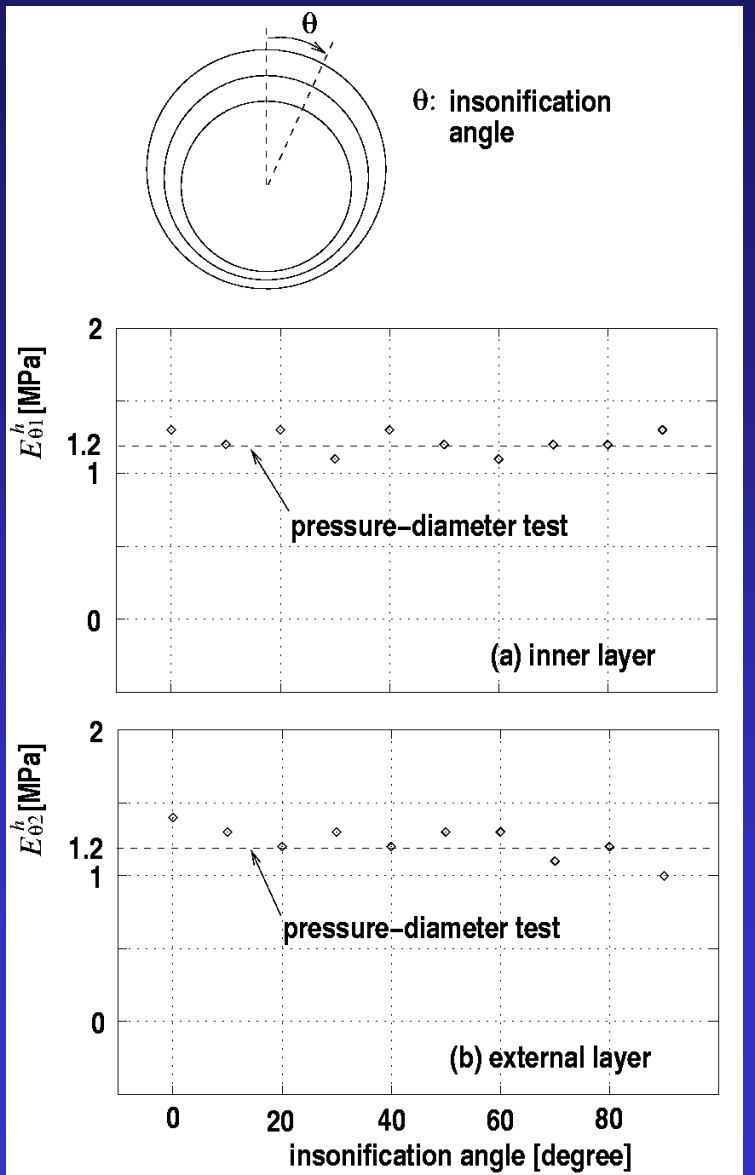
Spatial resolution in elasticity measurement

- 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.
- Since 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 1/5 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.



Accuracy confirmation*

- Using a silicone tube with two layers set in an artificial circulation system, the accuracy of the measurement of regional elasticity for each layer has already been validated to be about 0.1 MPa, that is, the error is about 8% of the elasticity value obtained by a separate static pressure-diameter test.



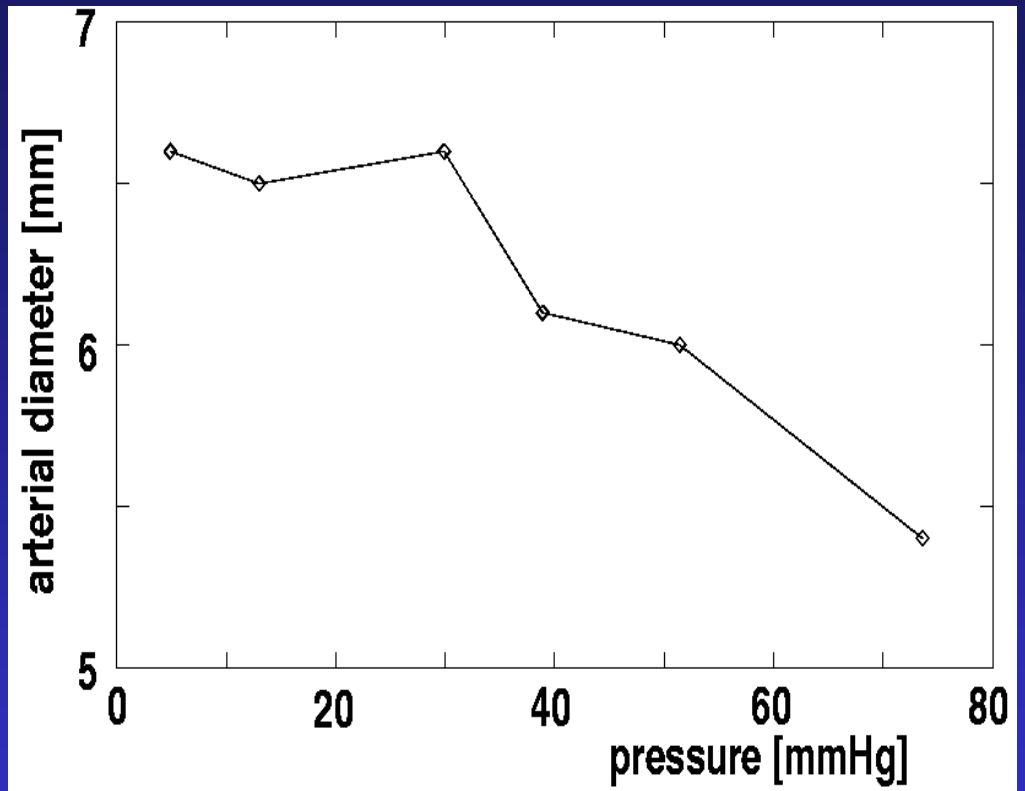
* Hasegawa H, Kanai H, Hoshimiya N, et al. *2000 IEEE Ultrason Sympo Proc*. 2000;1829-1832.

Slight influence of tissue surrounding the artery

- 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 about 0.96 ± 0.48 MPa and 0.89 ± 0.31 MPa, respectively, the difference between them being about 8%.
- Thus, the slight influence of assaying the artery through the skin was eliminated.

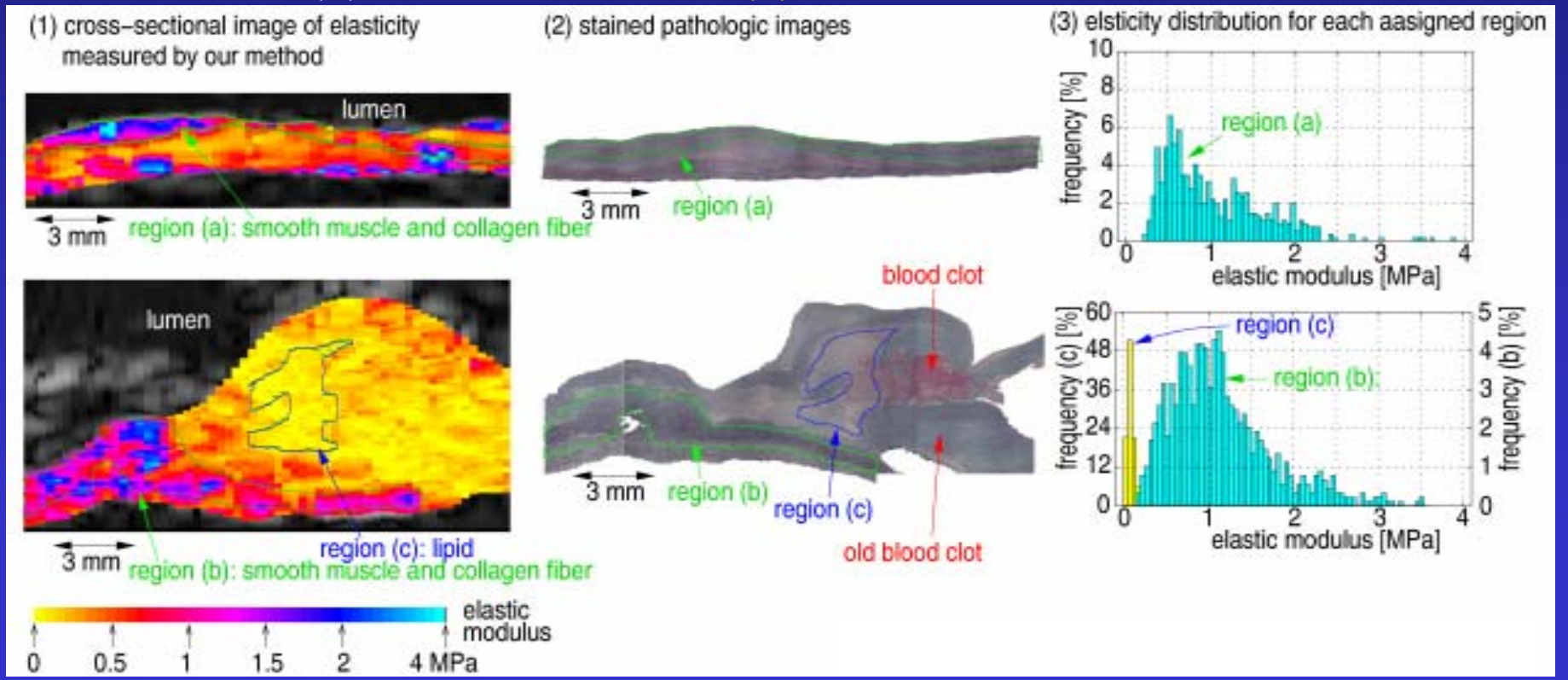
Effect of pressure of ultrasonic probe on skin surface

- 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 mmHg, 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 equal to or less than 30 mmHg. In our *in vivo* experiments, the ultrasonic probe was held on the skin surface with a pressure of 30 mmHg.



In vitro measurements for determination of reference parameters*

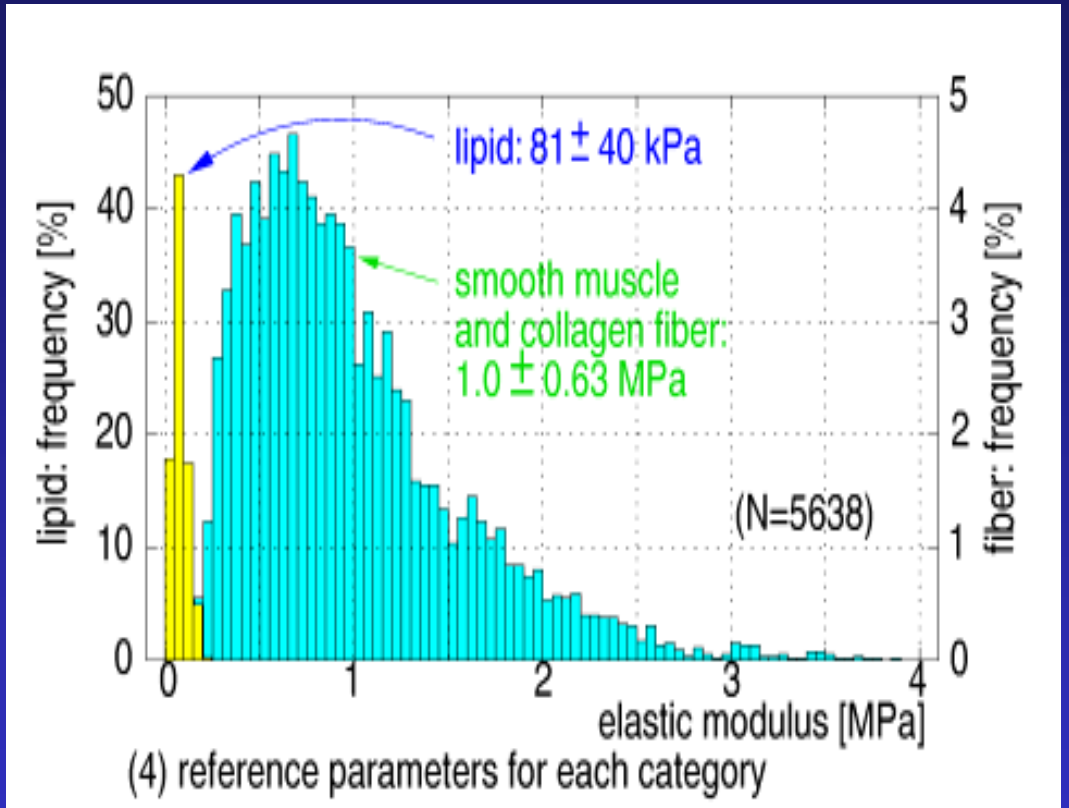
- Immediately after 9 iliac arteries (25-40 mm in length and 4-24 mm in outer diameter) with plaques were extracted from patients with embolism, cross-sectional elasticity distribution, $E_{\theta,m,n}$, was measured using the above method under the same artificial circulation system to generate a change 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.
- From the stain images, each region with either lipid or a mixture of smooth muscle and collagen fiber was assigned in $E_{\theta,m,n}$. Each histogram of $E_{\theta,m,n}$ in the respective regions is shown.



*Kanai H, Hasegawa H, Ichiki M, et al. Circulation 2003;107,3018-3021

Reference parameters for elasticity library*

- For the respective categories of the nine 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.

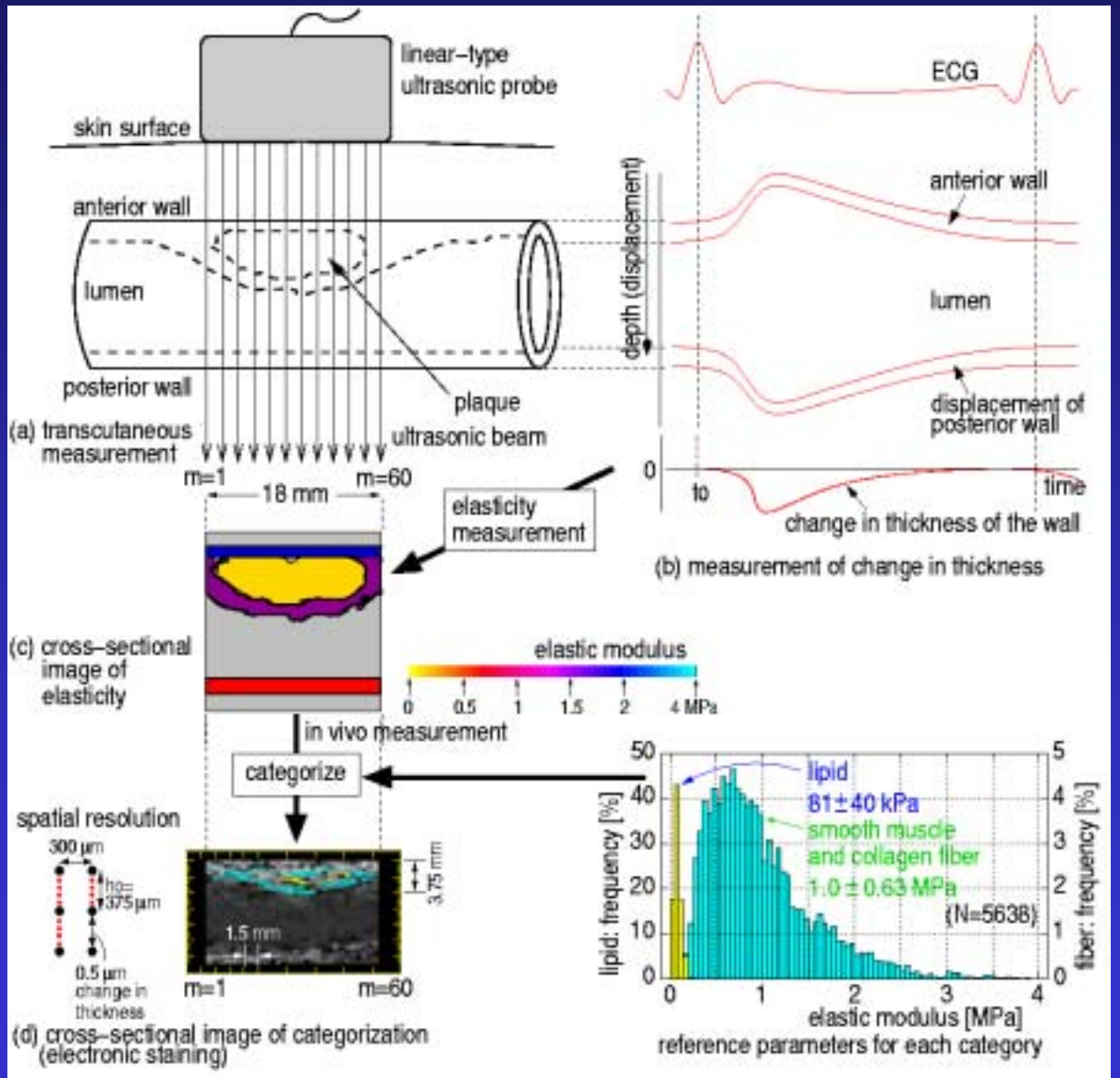


(4) reference parameters for each category

* Kanai H, Hasegawa H, Ichiki M, et al. Circulation 2003;107,3018-3021

*Electronic staining**

- Based on 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 three categories (lipid, mixture of smooth muscle and collagen fiber, or other). Thus, the arterial wall and the atherosclerotic plaque were *electronically stained*.

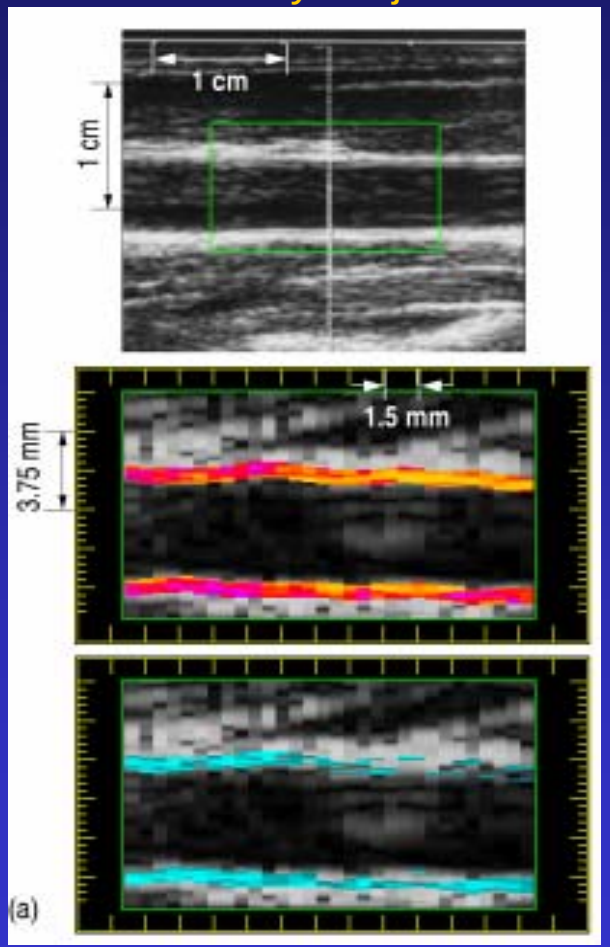


* Kanai H, Hasegawa H, Ichiki M, et al. Circulation 2003;107,3018-3021

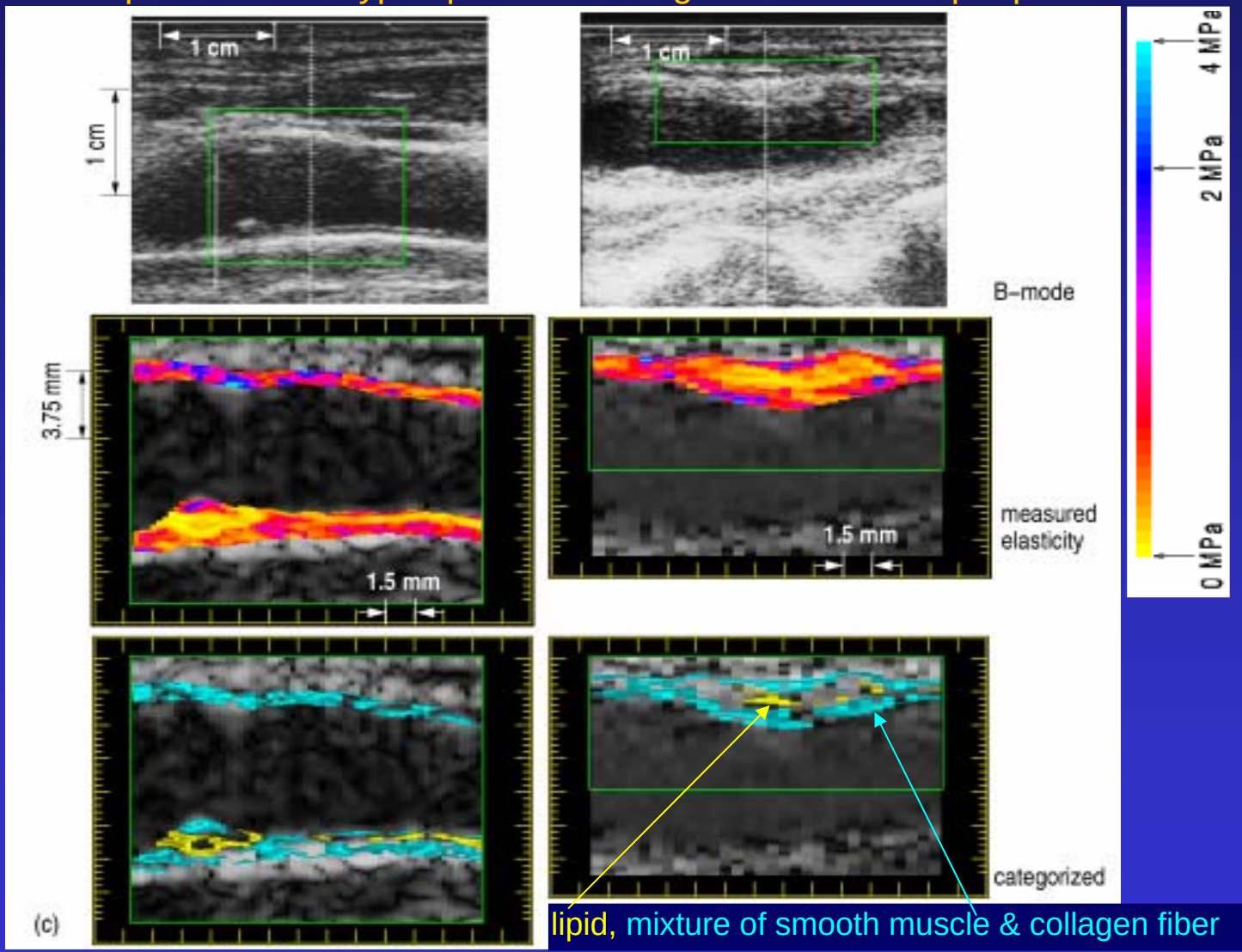
in vivo measurements of the CCAs

- 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.

a healthy subject



two patients with hyperlipidemia having atherosclerotic plaques



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,* 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.

* Lee RT, Grodzinsky AJ, Frank EH, et al. *Circulation.* 1991;83:1764-1770.

Conclusion

- Cross-sectional images of the elasticity around atherosclerotic plaque 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.