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Change in Elasticity Caused by Flow-Mediated Dilation Measured Only for Intima–Media Region of Brachial Artery

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Endothelial dysfunction is considered to be an initial step of arteriosclerosis [R. Ross: N. Engl. J. Med. **340** (2004) 115]. For the assessment of the endothelium function, brachial artery flow-mediated dilation (FMD) caused by increased blood flow has been evaluated with ultrasonic diagnostic equipment. In the case of conventional methods, the change in artery diameter caused by FMD is measured [M. Hashimoto *et al.*: Circulation **92** (1995) 3431]. Although the arterial wall has a layered structure (intima, media, and adventitia), such a structure is not taken into account in conventional methods because the change in diameter depends on the characteristic of the entire wall. However, smooth muscle present only in the media contributes to FMD, whereas the collagen-rich hard adventitia does not contribute. In this study, we measure the change in elasticity of only the intima–media region including smooth muscle using the *phased tracking method* [H. Kanai *et al.*: IEEE Trans. Ultrason. Ferroelectr. Freq. Control **43** (1996) 791]. From the change in elasticity, FMD measured only for the intima–media region by our proposed method was found to be more sensitive than that measured for the entire wall by the conventional method. [DOI: 10.1143/JJAP.44.6297]

KEYWORDS: flow-mediated dilation (FMD), endothelium function, nitric oxide (NO), atherosclerosis

1. Introduction

Endothelial damage is a possible trigger of the development of atherosclerosis.[1] Therefore, it is very important to diagnose endothelial damage at an early stage. In the case of conventional methods, blood flow in the brachial artery is stopped using a cuff at a pressure of 250 mmHg for 5 min.[2] After recirculation, the increase in the diameter of the brachial artery due to flow-mediated dilation (FMD) is measured to evaluate the endothelium function.[2] Smooth muscle only in the media is relaxed by nitric oxide (NO) that is generated in the endothelium in response to increased blood flow, whereas the collagen-rich hard adventitia does not respond to NO. However, the change in diameter, which is used in conventional methods, is dependent on the mechanical properties of the entire wall including the adventitia. Therefore, the sensitivity in FMD detection deteriorates because the layered structure (intima, media and adventitia) is not taken into account in conventional methods. In this study, the change in elasticity of the intima–media region was measured with a high accuracy and a good reproducibility using the *phased tracking method*[3,4] to improve the sensitivity of FMD detection.

2. Principles

2.1 Elasticity estimation of arterial wall

For the measurement of a small change in wall thickness, the phase shift of the echo caused by the displacement of an object is estimated from two consecutive echoes. For this purpose, quadrature demodulation is applied to the received ultrasonic waves reflected by the object, and then the in-phase and the quadrature signals are A/D-converted. From the demodulated signal $z(t; d + x(t))$ reflected at depth $d + x(t)$ at time t, where d and $x(t)$ are the initial depth set at $t = 0$ and the displacement of the object along the direction of depth, respectively, the phase shift $\Delta\theta(t)$ during a pulse repetition interval, ΔT, is obtained from the complex cross correlation function between $z(t; d + x(t))$ and $z(t + \Delta T; d + x(t))$.[3,4]

From the estimated phase shift $\Delta\hat{\theta}(t)$, the velocity $v(t)$ of the object is obtained as follows:

$$\hat{v}(t) = -\frac{c_0}{2\omega_0}\frac{\Delta\hat{\theta}(t)}{\Delta T}, \tag{2.1}$$

where ω_0 and c_0 are the center angular frequency of the ultrasonic pulse and the speed of sound, respectively.

In the velocity estimation, the object position is tracked by integrating the velocity $v(t)$ during the pulse repetition interval ΔT as follows:

$$\begin{aligned}\hat{x}(t + \Delta T) &= \hat{x}(t) + \hat{v}(t) \times \Delta T \\ &= \hat{x}(t) - \frac{c_0}{2\omega_0}\Delta\hat{\theta}(t).\end{aligned} \tag{2.2}$$

From the displacements $x_A(t)$ and $x_B(t)$ of two points (A and B), which are set in the arterial wall along an ultrasonic beam, the small change in thickness $\Delta h(t)$ between these two points is obtained as follows:

$$\begin{aligned}\Delta\hat{h}(t) &= \hat{x}_A(t) - \hat{x}_B(t) \\ &= \int_0^t \{\hat{v}_A(t) - \hat{v}_B(t)\}\,dt.\end{aligned} \tag{2.3}$$

The change in thickness $\Delta h(t)$ corresponds to the strain caused by the change in blood pressure $p(t)$. Therefore, from the maximum change in wall thickness $\Delta h_{max} = \max_t |h(t)|$ and the maximum change in blood pressure Δp_{max} (difference between systolic pressure and diastolic pressure), the approximate circumferential elastic modulus E_θ^h is obtained as follows:[5,6]

$$E_\theta^h \approx \frac{1}{2}\left(\frac{r_0}{h_0} + 1\right)\frac{\Delta p_{max}}{\dfrac{\Delta h_{max}}{h_0}}, \tag{2.4}$$

where r_0 and h_0 are the inner radius and wall thickness at the end diastole, respectively.

2.2 Procedure for in vivo measurement

Blood flow in the brachial artery is blocked by surrounding the forearm with a cuff at a pressure of 250 mmHg for

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5 min. After the release of the cuff, nitric oxide, which is generated in the endothelium in response to shear stress caused by increased blood flow, relaxes the smooth muscle in the media. We measured the change in the elasticity of the intima–media region of the artery due to FMD with a 10 MHz linear-type ultrasonic probe (Aloka, SSD6500) 11 times at an interval of about 10 s. The change in thickness was measured for two consecutive heartbeats in each measurement.

2.3 *Determination of optimum layer for measuring change in thickness*

The change in wall thickness needs to be measured with good reproducibility to detect the change in elasticity. However, it is difficult to measure the change in the wall thickness of the brachial artery in comparison with the carotid artery because the wall of the brachial artery is thinner than that of the carotid artery and the change in thickness is small. Therefore, the optimum layer for measuring the change in thickness is determined as follows: As shown by the data (Fig. 1) measured from a 24-year-old male, when we examine echoes from the lumen to the outside of the posterior wall of the artery along an ultrasonic beam indicated by a vertical arrow with dashed line in Fig. 1(b), firstly, a clear echo, which is reflected from the lumen–intima interface, can be found. Then, the amplitude of the echo slightly decreases in the media region, and that of the echo increases again around the media–adventitia interface.[7] To obtain the change in thickness due to the heartbeat of the intima–media region, two points were designated as the lumen–intima interface and the media–adventitia interface along an ultrasonic beam.

As shown in Fig. 1(c), the echo from the lumen–intima interface can be easily recognized. Therefore, the lumen–intima interface d_{in} is manually set as shown in Fig. 1(b), and the displacement $x_{\mathrm{in}}(t)$ at this point d_{in} is estimated by the *phased tracking method*.[3,4] A slight difference in the manually assigned depth d_{in} does not have serious influences on the estimation of the artery wall elasticity.

To obtain the change in thickness, another point must be set along the same ultrasonic beam to determine the layer to be analyzed. However, as shown in Fig. 1(c), the beginning of the echo from the media–adventitia interface is not very clear in comparison with that from the lumen–intima interface because there are weak echoes from the inside of the wall. Therefore, the optimum layer for the measurement of the change in thickness is determined as follows. Although it is difficult to clearly differentiate the echo from the media–adventitia interface from echoes from scatterers in the media, the amplitude of the echo from the media–adventitia interface is larger than those of other echoes. Therefore, with respect to measured RF data showing a typical pattern of echoes from the lumen–intima and media–adventitia interfaces (as shown in Fig. 1), the beginning of the echo from the media–adventitia interface is approximately assigned manually as the first candidate point d_1. Then, multiple candidate points d_{in} $(k = 1, 2, \ldots, 9)$ are assigned along the ultrasonic beam at a pitch of 19.25 μm. The distance from d_1 to d_k is set at 154 μm in consideration of the half-value width of an employed ultrasonic pulse of 122 μm. Then, the displacement $x_k(t)$ $(k = 1, 2, \ldots, 9)$ of each point, d_k, is estimated, and the change in thickness $\Delta h_k(t)$ between two points, d_{in} and d_k, is obtained by

$$\Delta h_k(t) = x_k(t) - x_{\mathrm{in}}(t) \quad (k = 1, 2, \ldots, 9). \tag{2.5}$$

The change in thickness $\Delta h_k(t)$ is measured for each of two consecutive heartbeats in one measurement, and the maximum $\Delta H_{k,1}$ and $\Delta H_{k,2}$ of the measured change in thickness $\Delta h_k(t)$ are determined for both heartbeats. From $\Delta H_{k,1}$ and $\Delta H_{k,2}$, the reproducibility between two heartbeats is evaluated by the normalized standard deviation α_k $(k = 1, 2, \ldots, 9)$ of the maximum change in thickness defined by

$$\alpha_k = \frac{\sqrt{\dfrac{1}{N}\displaystyle\sum_{i=1}^{N} |\Delta H_{k,i} - \Delta \bar{H}|^2}}{\Delta \bar{H}} \quad (k = 1, 2, \ldots, 9). \tag{2.6}$$

$$\Delta \bar{H} = \frac{1}{N}\sum_{i=1}^{N} \Delta H_{k,i}, \tag{2.7}$$

where N is the number of heartbeats (in this study, $N = 2$). The distance from d_{in} to d_1 is set to be larger than pulse width.

In Fig. 2, α_k obtained for RF data showing a typical pattern of echoes (the same data shown in Fig. 1) is plotted as a function of distance, $d_k - d_{\mathrm{in}}$. From the point d_{min} which gives the minimum of α_k, the thickness of the layer to be

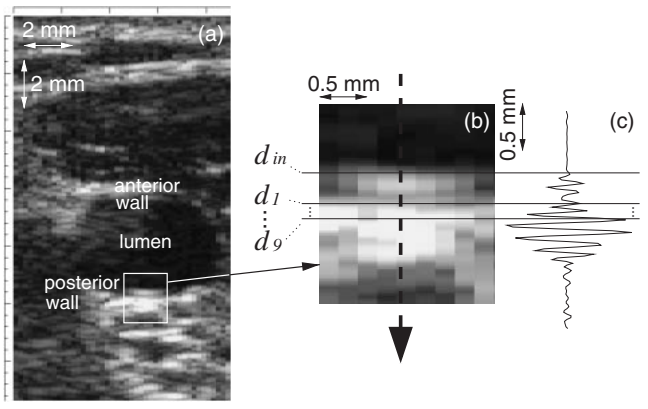

Fig. 1. (a) B-mode image of brachial artery of 24-year-old male along plane perpendicular to axis of artery. (b) Enlarged view of region surrounded by white line in (a). (c) Received RF signal along ultrasonic beam indicated by vertical arrow with dashed line in (b).

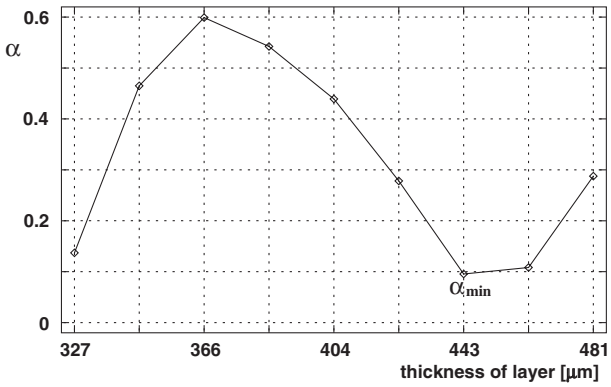

Fig. 2. Determination of optimum layer corresponding to intima–media region from normalized standard deviation, α_{min}, of maximum change in thickness.

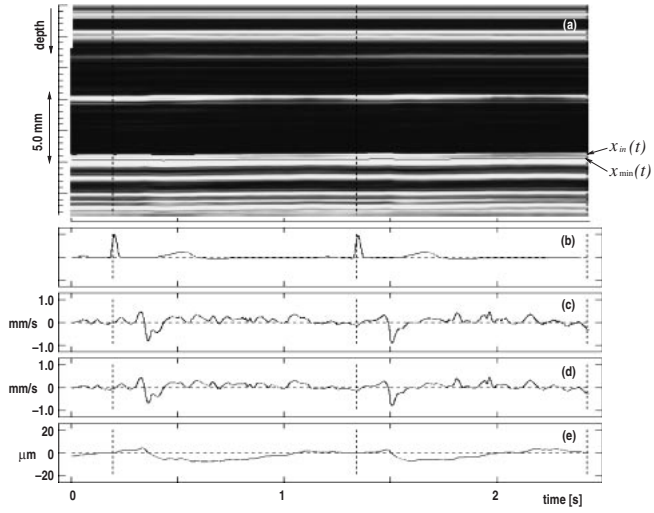

Fig. 3. (a) M-mode image of brachial artery (24-year-old male). (b) Electrocardiogram. (c) Velocity at point designated as lumen–intima interface. (d) Velocity at point designated as media–adventitia interface. (e) Change in thickness.

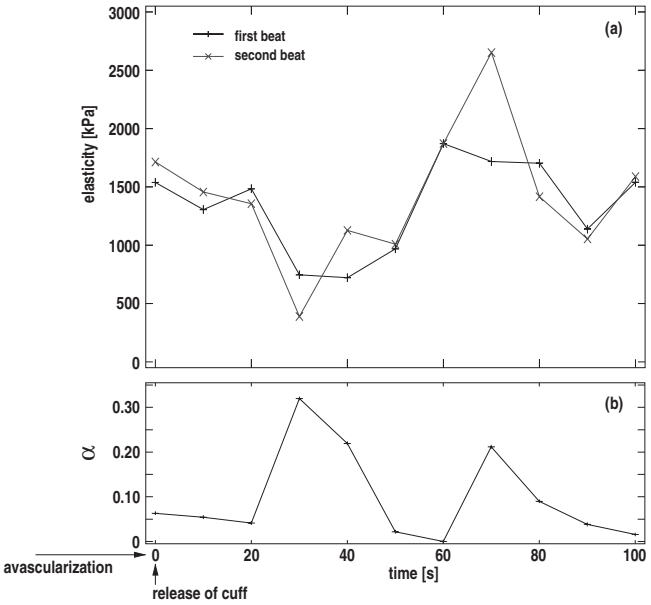

Fig. 4. (a) Changes in elasticity for intima–media region after recirculation (24-year-old male). (b) Change in α obtained with respect to optimum layer, $d_{min} - d_{in}$.

analyzed is determined to be $d_{min} - d_{in}$. d_{in} and d_{min} are set at echoes from the lumen–intima and media–adventitia interfaces, respectively. Therefore, the change in the thickness of the intima–media region can be obtained.

3. *In Vivo* Experimental Results

Figure 3(a) shows an M-mode image of the brachial artery of the same subject shown in Fig. 1 immediately after release of the cuff ($t = 0$). By determining the optimum layer as described in §2.3, the change in the thickness of the layer corresponding to the intima–media region is obtained as shown in Fig. 3(e) by measuring velocities at two points, d_{in} and d_{min}, as shown in Figs. 3(c) and 3(d). Changes in the thickness and elasticity of the intima–media region were determined for other successive measurements.

Figure 4 shows the change in elasticity of the intima–media region. Around 30 s after the release of the cuff, the discriminate decrease was found in the measured elasticity. From the mean elasticity between two heartbeats, the normalized maximum decrease in the elastic modulus compared with the elastic modulus at $t = 0$ was determined to be 65.1%.

Figure 5(a) shows the change in elasticity of the brachial artery of the same subject shown in Fig. 4 obtained by setting d_{in} to be deeper by one point than that in Fig. 4. From the results shown in Fig. 5, a slight difference in setting d_{in} does not have serious influences.

Figures 6 and 7 show changes in elasticity measured for a 25-year-old male and a 31-year-old male, respectively. The maximum decreases in the elastic modulus compared with the elastic modulus at $t = 0$ were 42.7 and 52.5%, respectively.

These FMD% values evaluated from elasticity were compared with those obtained by the conventional artery diameter measurements. Figures 8(a), 9(a), and 10(a) show RF echoes obtained at R-waves (first beat) of the electrocardiogram during successive measurements. From Figs. 8(a), 9(a), and 10(a), artery diameter at each measurement was measured as shown in Figs. 8(b), 9(b), and 10(b).

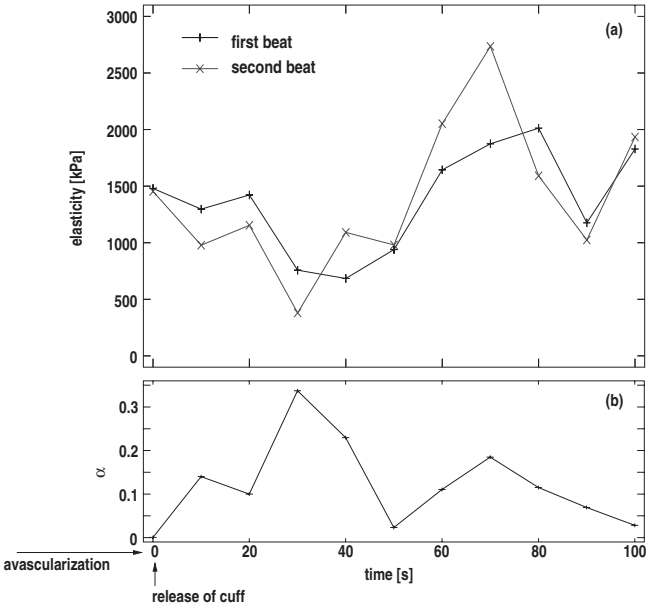

Fig. 5. Changes in (a) elasticity and (b) α for intima–media region after recirculation (24-year-old male). Intima–media interface, d_{in}, shifted in the depth direction by one point in comparison with that shown in Fig. 4.

FMD% values obtained from artery diameter were 6.7, 1.4, and 11.0% for the 24-year-old male, the 25-year-old male, and the 31-year-old male, respectively. These values were comparable to those reported in literature,[2)] and it was found that FMD% obtained by the proposed method is much larger than that obtained by the conventional diameter measurement. These results can be well explained by the finding that nitric oxide generated in the endothelium specifically relaxes smooth muscle in the media. From these results, for the evaluation of endothelium function, the measurement of the decrease in the elasticity of the intima–media region is considered to be more effective than the measurement of the increase in diameter by conventional methods.

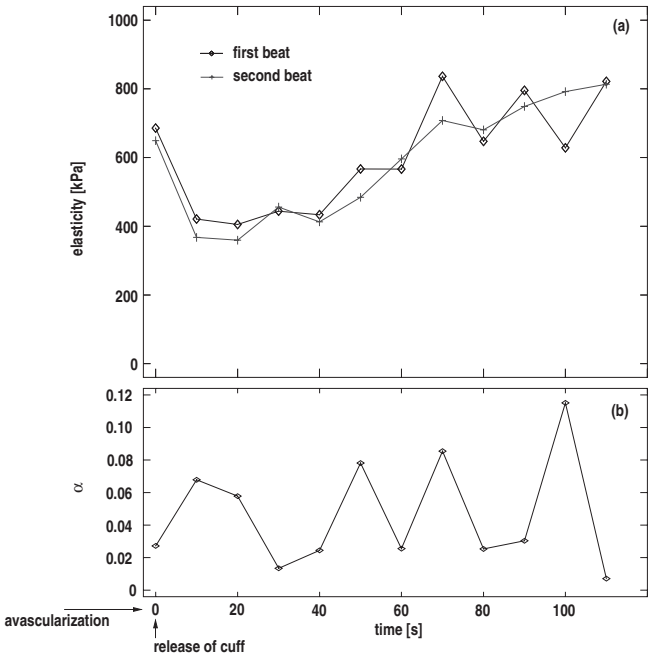

Fig. 6. Changes in (a) elasticity and (b) α for intima–media region after recirculation (25-year-old male).

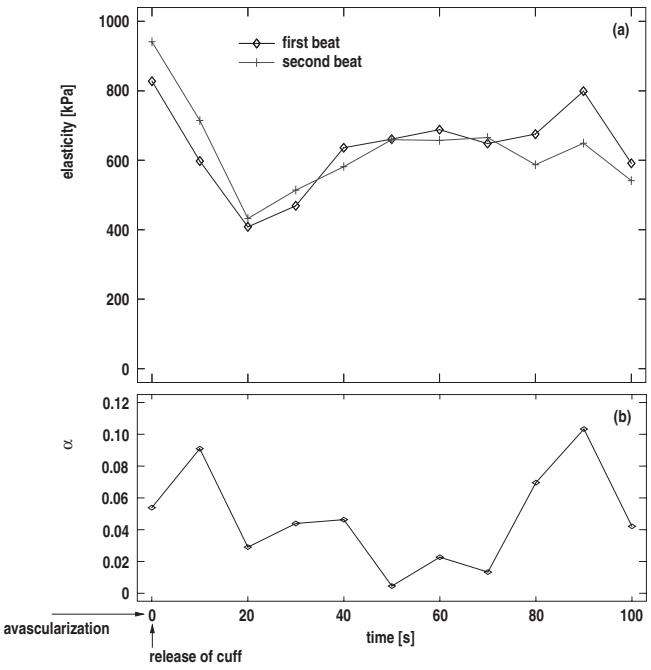

Fig. 7. Changes in (a) elasticity and (b) α for intima–media region after recirculation (31-year-old male).

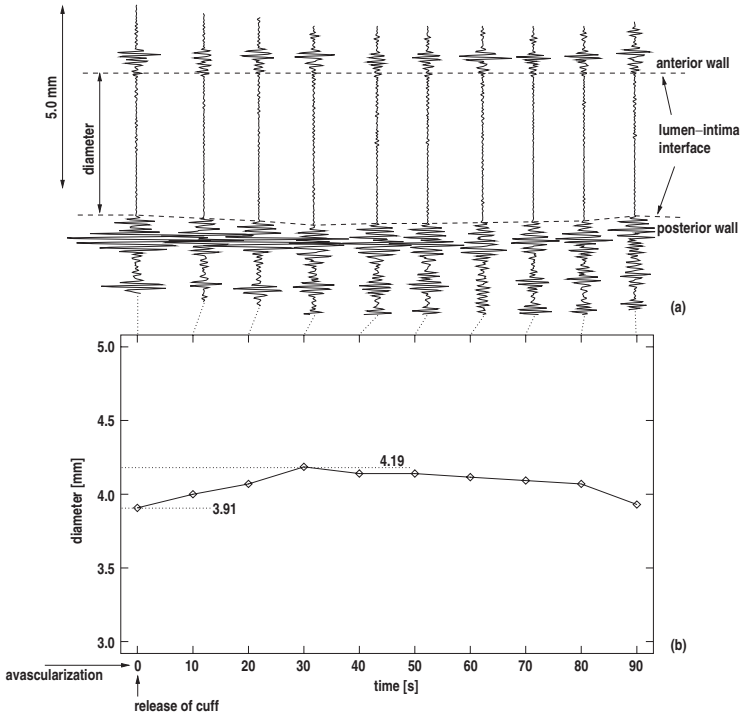

Fig. 8. (a) RF signal obtained at each measurement after release of cuff (24-year-old male). (b) Change in inner diameter obtained from distance between lumen–intima interfaces of anterior and posterior walls indicated by dashed lines in (a).

4. Conclusions

We measured the change in elasticity only in the intima–media region. The layer, in which elasticity was obtained, was determined on the basis of the reproducibility of the change in thickness measured for two heartbeats. The normalized change in elasticity measured by the proposed method was much larger than the normalized change in diameter measured by conventional methods because the conventional methods evaluate the mechanical property of the entire wall. From these results, the proposed method has a potential for improving the sensitivity of noninvasive evaluation of the endothelium function by measuring the change in elasticity due to FMD only for the intima–media region including smooth muscle.

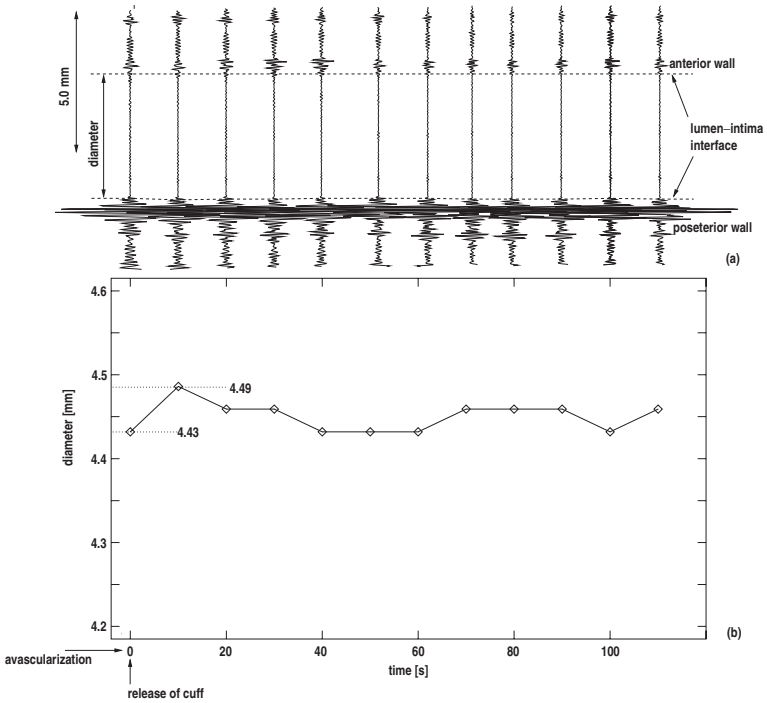

Fig. 9. (a) RF signal obtained at each measurement after release of cuff (25-year-old male). (b) Change in inner diameter obtained from distance between lumen–intima interfaces of anterior and posterior walls indicated by dashed lines in (a).

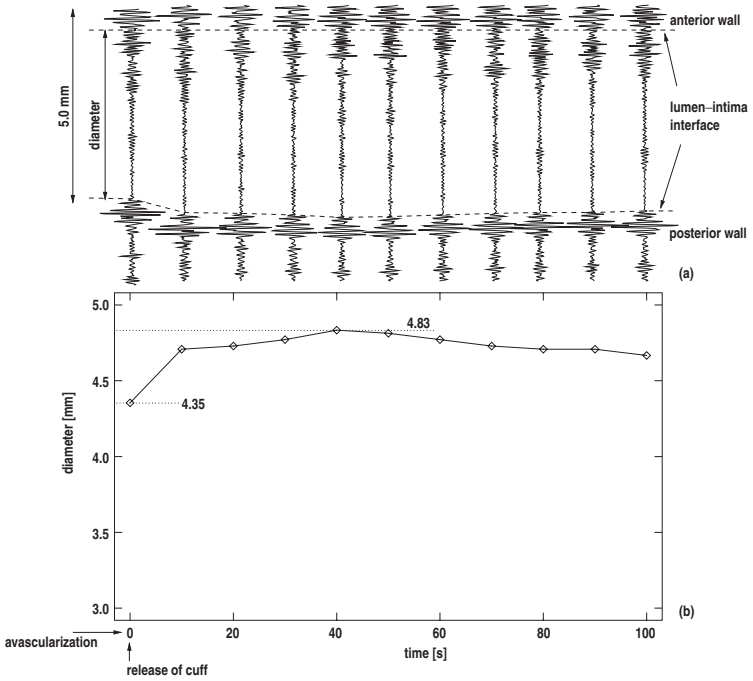

Fig. 10. (a) RF signal obtained at each measurement after release of cuff (31-year-old male). (b) Change in inner diameter obtained from distance between lumen–intima interfaces of anterior and posterior walls indicated by dashed lines in (a).

1) R. Ross: N. Engl. J. Med. **340** (2004) 115.
2) M. Hashimoto, M. Akishita, M. Sato, M. Eto, M. Ishikawa, K. Kozaki, K. Toba, Y. Sagara, Y. Taketani, H. Orimo and Y. Ouchi: Circulation **92** (1995) 3431.
3) H. Kanai, M. Sato, Y. Koiwa and N. Chubachi: IEEE Trans. Ultrason. Ferroelectr. Freq. Control **43** (1996) 791.
4) H. Kanai, H. Hasegawa, N. Chubachi, Y. Koiwa and M. Tanaka: IEEE Trans. Ultrason. Ferroelectr. Freq. Control **44** (1997) 752.
5) H. Hasegawa, H. Kanai, N. Hoshimiya and Y. Koiwa: Jpn. J. Med. Ultrason. **31** (2004) 81.
6) H. Kanai, H. Hasegawa, M. Ichiki, F. Tezuka and Y. Koiwa: Circulation **107** (2003) 3018.
7) A. D. M. Swijndregt, S. H. K. The, E. J. Gussenhoven, C. T. Lanée, H. Rijsterborgh, E. Groot, A. F. W. Steen, N. Bom and R. G. A. Ackerstaff: Ulitrasound Med. Biol. **22** (1996) 1007.