

# Flow-Mediated Change in Viscoelastic Property of Radial Arterial Wall Measured by 22 MHz Ultrasound

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The endothelial dysfunction is considered to be an initial step in atherosclerosis. Additionally, it was reported that the smooth muscle, which constructs the media of the artery, changes its characteristics owing to atherosclerosis. Therefore, it is essential to develop a method of assessing the regional endothelial function and mechanical properties of the arterial wall. To evaluate the endothelial function, a conventional technique of measuring the transient change in the diameter of the brachial artery caused by flow-mediated dilation (FMD) after the release of avascularization is used. However, this method can not evaluate the mechanical properties of the wall. We previously developed a method for the simultaneous measurements of waveforms of radial strain and blood pressure in the radial artery. In this study, the viscoelasticity of the arterial wall was estimated from the measured stress–strain relationship using the least-squares method and the transient changes in the mechanical properties of the arterial wall were revealed. From *in vivo* experimental results, the stress–strain relationship showed a hysteresis loop and viscoelasticity was estimated by the proposed method. The slope of the loop decreased owing to FMD, which resulted in the decrease in estimated *elastic modulus*. The increase in the area of the loop occurred after recirculation, which corresponds to the increase in the ratio of the loss modulus (depends on *viscosity*) to the elastic modulus when the Voigt model is assumed. In this study, the variance in estimates was evaluated by *in vivo* measurement for 10 min. The temporal decrease in static elasticity after recirculation due to FMD was much larger than the evaluated variance. These results show a potential of the proposed method for the thorough analysis of the *transient change in viscoelasticity* due to FMD. © 2009 The Japan Society of Applied Physics

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## 1. Introduction

The main cause of circulatory diseases is considered to be atherosclerosis. Therefore, the quantitative assessment of atherosclerosis is essential for making an early diagnosis of these diseases.

The endothelial dysfunction is considered to be an initial step in atherosclerosis.<sup>1)</sup> Additionally, it was reported that the smooth muscle, which constructs the media of the artery, changes its characteristics owing to atherosclerosis.<sup>2)</sup> Consequently, it is important for an early preventive treatment to noninvasively assess the endothelial function and mechanical properties of the media mainly composed of smooth muscle.

Endothelial cells react to the shear stress caused by blood flow and produce nitric oxide (NO), which is known as a vasodepressor material. The smooth muscle is relaxed as a result of the response to the produced NO. This function is important for maintaining the homeostasis of the vascular system. Smooth muscle cells in the media are classified into two types with different functionalities.<sup>3)</sup> The composite type is proliferative, and the contractional type contracts and relaxes as responses to chemical and mechanical stimuli. When the blood vessel is initially formed, smooth muscle cells change their type from composite to contractional and control blood flow and blood pressure. On the other hand, after the vascular system is established, smooth muscle cells change their characteristics from contractional to composite owing to atherosclerosis. The composite type is related to the growth factor and accelerates the migration of smooth muscle cells to the intimal layer. Therefore, as described above, the evaluation of the endothelial function and characteristics of smooth muscle cells is important for the early diagnosis of atherosclerosis.

For the evaluation of the endothelial function, there is a conventional technique of measuring the transient change

in the inner diameter of the brachial artery caused by flow-mediated dilation (FMD) after the release of avascularization.<sup>4)</sup> For a more sensitive and regional evaluation, we developed a method of directly measuring the change in the elasticity of the intima–media region due to FMD.<sup>5)</sup>

We propose a method for the evaluation of FMD, which was previously applied to the measurement of the radial artery. There is an inversely proportional relationship between the percent change in inner diameter due to FMD and that in the inner diameter of the artery at rest because the flow velocity, which affects the shear stress, is inversely proportional to the square of the inner diameter when the pressure and flow volume are constant.<sup>6)</sup> Additionally, the blood pressure (stress) waveform can be continuously measured in the radial artery, together with the minute change in thickness (radial strain), which is measured using the ultrasonic *phased tracking method*.<sup>7)</sup> From such measurements, we could determine the stress–strain relationship during each heartbeat.<sup>8)</sup> Therefore, the radial artery would be a more suitable site for the measurement of FMD.

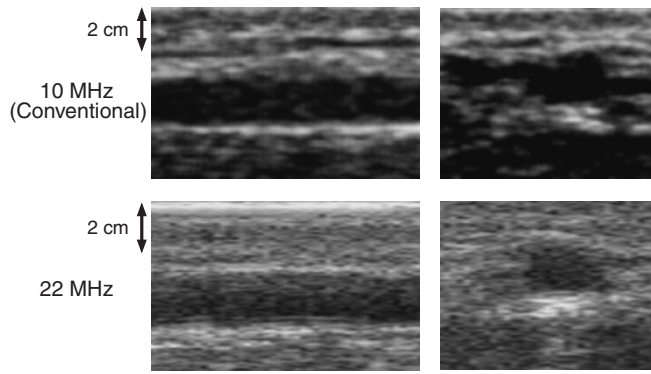
In this study, from the stress–strain relationship during each heartbeat, the viscoelasticity of the intima–media region was estimated using the least-squares method, and the transient change in viscoelasticity due to FMD was estimated. In addition, the viscoelasticity at rest was measured for 10 min to evaluate the variance in measurements.

## 2. Principles and Experimental Methods

### 2.1 Estimation of minute change in thickness of arterial wall for measuring stress–strain relationship

The arterial wall is composed of three layers, namely, intima, media and adventitia. The smooth muscle, which constructs the media, is the main source of the viscoelasticity of the vessel wall. Therefore, the dilation and contraction of the artery depend on the characteristics of the media. The detailed analysis of the change in the

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**Fig. 1.** B-mode images of the radial artery along the longitudinal axis (left) and in the plane perpendicular to the arterial longitudinal direction (right).

viscoelasticity of the arterial wall due to FMD requires the *in vivo* measurement of the stress–strain relationship, which has not been measured noninvasively thus far.

The blood pressure waveform can only be measured noninvasively *in vivo* at the radial artery. However, it is impossible to measure the strain of the radial arterial wall by ultrasound at a typical frequency (10 MHz) in conventional equipment. Therefore, we constructed an acquisition system for high-frequency ultrasound.<sup>8)</sup> This system improved the spatial resolution in the axial direction. Therefore, this system allows more detailed measurements and analyses. Figure 1 shows the B-mode images of the radial artery along the longitudinal axis and in the plane perpendicular to the axis of the artery.

To determine the stress–strain relationship, the minute change in the thickness (strain)  $\Delta h(t)$  of the right radial arterial wall during a cardiac cycle was measured using the *phased tracking method*.<sup>7)</sup> Together with the measurement of RF signals for the estimation of  $\Delta h(t)$ , the waveform of blood pressure (stress)  $p(t)$  in the left radial artery was continuously measured with a sphygmometer.

To obtain the change in thickness, the velocities of artery-wall boundaries (lumen-intima and media-adventitia) were estimated. The velocity  $v(t)$  was estimated from the phase shift  $\widehat{\Delta\theta}(t)$  of echoes in two consecutive frames. The phase shift  $\widehat{\Delta\theta}(t)$  was obtained using the complex cross-correlation applied to the demodulated signals of RF echoes.

From the estimated phase shift  $\widehat{\Delta\theta}(t)$ , the average velocity  $\widehat{v}(t)$  of the arterial wall at the pulse repetition interval  $T$  was obtained as

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

where  $\omega_0$  and  $c_0$  are the center angular frequency of the ultrasound wave and the speed of sound, respectively. The change in thickness,  $\Delta h(t)$ , between two different depths,  $A$  and  $B$  (corresponding to the boundaries of the arterial wall), in the arterial wall along an ultrasonic beam was obtained from the difference between displacements,  $x_A(t)$  and  $x_B(t)$ , at these two positions as

$$\begin{aligned} \Delta \widehat{h}(t) &= \widehat{x}_A(t) - \widehat{x}_B(t) \\ &= \int_0^t [\widehat{v}_A(t) - \widehat{v}_B(t)] dt. \end{aligned} \quad (2.2)$$

The change in thickness,  $\Delta h(t)$ , corresponds to the incremental strain in the arterial radial direction at the time  $t$  due to the pressure increment  $\Delta p(t)$  from the diastolic pressure.

## 2.2 Viscoelasticity estimation of arterial wall using least-squares method

The smooth muscle constructs the media and is the main source of the viscoelasticity of the arterial wall. We assumed a viscoelastic model as a mechanical model of the arterial wall to estimate its viscoelasticity.

There are many types of models for describing the viscoelasticity of the arterial wall. We selected a viscoelastic model with two components to simply understand the viscoelastic behavior of the arterial wall; one component corresponds to elasticity and the other to viscosity. In this study, the Voigt model was used because the deformation of the arterial wall during one cardiac cycle is reproducible among cardiac cycles, and there is no permanent deformation. The Maxwell model, which is another model with two components, was not used because it should be used for viscoelastic materials showing a permanent deformation.

By assuming the Voigt model as a viscoelastic model of the intima–media region, the stress–strain relationship is given by

$$\widehat{\tau}(t) = E_s \gamma(t) + \eta \dot{\gamma}(t) + \tau_0, \quad (2.3)$$

where  $\widehat{\tau}(t)$  is the stress modeled by the Voigt model and  $\gamma(t)$ ,  $\dot{\gamma}(t)$ ,  $E_s$ , and  $\eta$  are the strain, strain rate, static elasticity, and viscosity, respectively. In the *in vivo* measurement, the measured strain  $\tau(t)$  is the incremental strain due to the pulse pressure, whereas the measured stress includes the bias stress (diastolic blood pressure). Therefore,  $\tau_0$  is added to the right-hand side of eq. (2.3) as the bias stress corresponding to diastolic pressure.

The parameters in eq. (2.3),  $E_s$ ,  $\eta$ , and  $\tau_0$ , are estimated using the least-squares method by minimizing the mean squared error  $\alpha$  between the measured  $\tau(t)$  and model  $\widehat{\tau}(t)$  stresses and defined by

$$\alpha = E_r\{[\tau(t) - \widehat{\tau}(t)]^2\}, \quad (2.4)$$

where  $E_r[\dots]$  indicates the averaging operation during a cardiac cycle. The parameters  $\widehat{E}_s$ ,  $\widehat{\eta}$ , and  $\widehat{\tau}_0$  that minimize  $\alpha$  are determined by setting the partial derivatives of  $\alpha$  with respect to  $E_s$ ,  $\eta$ , and  $\tau_0$  to zero as

$$\frac{\partial \alpha}{\partial E_s} = 0, \quad \frac{\partial \alpha}{\partial \eta} = 0, \quad \frac{\partial \alpha}{\partial \tau_0} = 0. \quad (2.5)$$

To solve the simultaneous equations, the optimum parameters that minimize  $\alpha$  are determined.

## 2.3 Procedure for *in vivo* measurement

The right radial arteries of two healthy male subjects (subject A: 35 years old and subject B: 22 years old) were measured. In these measurements, ultrasonic RF echoes (transmit: 22 MHz) were acquired at a sampling frequency of 66.5 MHz for 2 s and the frame rate was about 160 Hz.<sup>8)</sup> The acquisition for the evaluation of FMD was repeated every 20 s for 2 min at rest before avascularization and every 12 s for 3 min after recirculation. Together with the measurement of RF signals, the waveform of blood pressure  $p(t)$  in

the left radial artery was continuously measured with a sphygmometer (Colin Jentow-7700). Additionally, for the evaluation of reproducibility, RF data and the blood pressure waveform at rest were measured every 1 min for 10 min. In this study, a sphygmometer, which automatically optimizes the position of the sensor for blood pressure measurement by detecting the regional pulsation of the radial artery, was used for the continuous measurement of the blood pressure waveform  $p(t)$  for about 10 min. However, the sphygmometer always requires the arterial pulsation to optimize the position of the sensor. In this measurement, therefore, the sensor of the sphygmometer was placed in the left arm, in which avascularization was not induced.

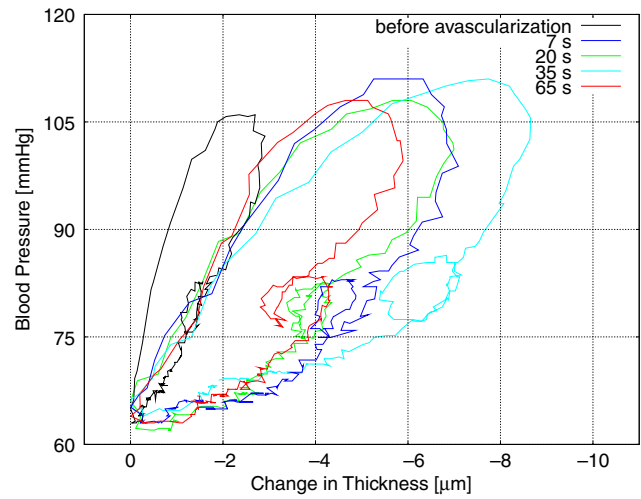
The experimental apparatus employed in this study showed undesirable time delays. We corrected the time delay between stress and strain to determine the stress–strain relationship that depended on only the viscoelasticity of the arterial wall.<sup>8)</sup> The transient change in stress–strain relationship during a cardiac cycle due to FMD was obtained from the measured change in the thickness  $\Delta h(t)$  of the arterial wall and from the blood pressure  $\Delta p(t)$ .

### 3. Results

#### 3.1 *In vivo* experimental results for two healthy subjects

RF data for 2 s obtained by each acquisition included at least an entire cardiac cycle. Therefore, the changes in thickness  $\Delta h(t)$  and blood pressure  $p(t)$  were obtained for at least one cardiac cycle in each measurement for estimating the viscoelastic parameters of the radial arterial wall.

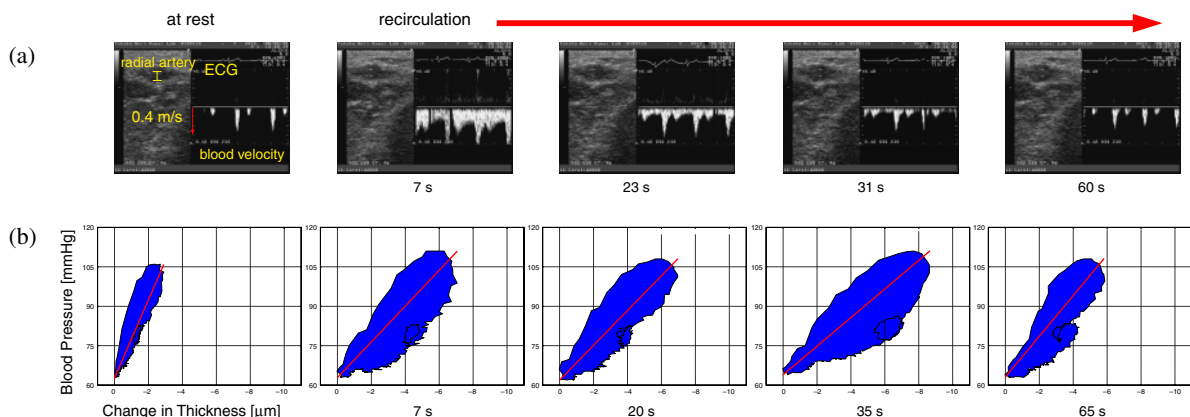
To reveal the change in the stress–strain relationship of the arterial wall due to FMD, the blood pressure  $p(t)$  and the change in the thickness of the intima–media region  $\Delta h(t)$  during a cardiac cycle during FMD were measured. Figure 2 shows the transient change in stress–strain relationship between the change in thickness and the blood pressure of subject A. The stress–strain relationship showed hysteresis property and gradually changed its shape. The slope of the hysteresis loop decreased owing to FMD, which shows that the elastic modulus decreased. In addition to the change in slope, the area of the loop clearly increased after recirculation. The area of the loop depended on the ratio of the loss modulus  $\omega\eta$  ( $\omega$ : angular frequency of strain,  $\eta$ : viscosity) to the static elastic modulus  $E_s$  when the Voigt model was assumed.



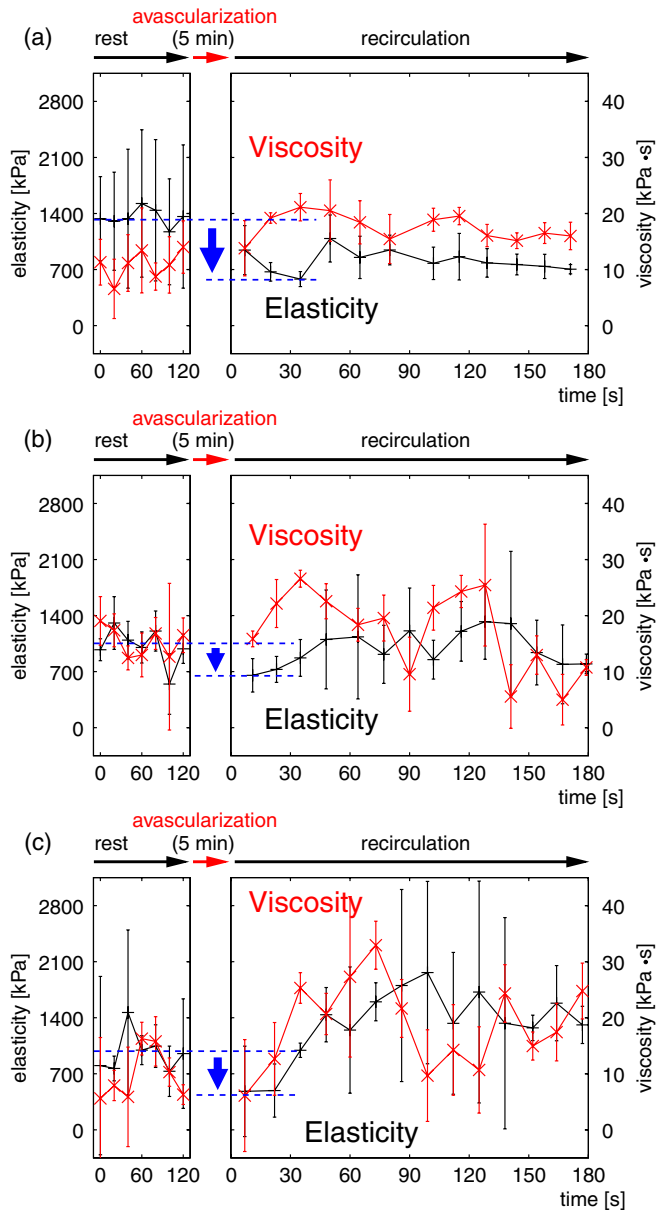
**Fig. 2.** (Color online) Transient change in relationship (hysteresis) between blood pressure  $p(t)$  and change in thickness  $\Delta h(t)$  measured in the radial artery *in vivo*.

Figures 3(a) and 3(b) show the time sequence of the blood flow velocities and stress–strain relationships of subject A, respectively. Blood velocity clearly increased immediately after recirculation and the stress–strain relationship started to change. Sixty seconds after recirculation, blood velocity returned to its original value and the stress–strain relationship also came around gradually.

Figure 4(a) shows the transient changes in the means and standard deviations (SDs) of the static elasticity  $E_s$  and viscosity  $\eta$  averaged by 5 ultrasonic beams. These parameters were estimated from the stress–strain relationships obtained from subject A (the first measurement). The transient change in static elasticity  $E_s$  was similar to that in a different elastic parameter reported in the literature.<sup>5)</sup> The minimum static elasticity  $E_s$  was measured at 35 s after the release of the cuff. The maximum percentage change in static elasticity  $E_s$  was about 57% (770 kPa). Moreover, the viscosity  $\eta$ , which was evaluated noninvasively by the proposed method, increased after recirculation. The measured viscosity was in the same range as the viscosity at the carotid artery reported in the literature (*in vitro* measurement).<sup>9)</sup> The maximum viscosity  $\eta$  at 35 s after recirculation was about 21 kPa·s, which was about 94% (10 kPa·s) larger than the mean at rest.



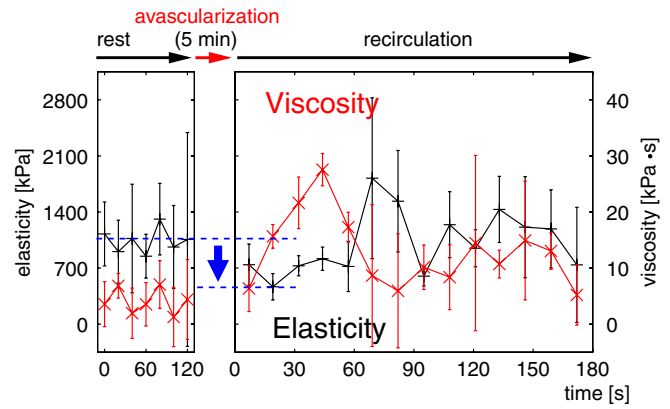
**Fig. 3.** (Color online) Time sequence of transient change in the blood velocity (a) and stress–strain hysteresis (b).



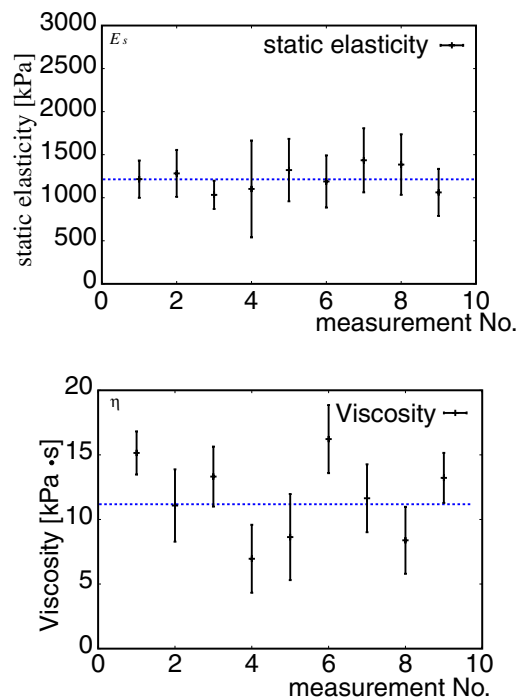
**Fig. 4.** (Color online) Transient change in means and SDs of estimated static elasticity  $E_s$  and viscosity  $\eta$  measured in subject A: (a) first, (b) second, and (c) third measurements.

Figures 4(b) and 4(c) show the transient changes in the means and SDs of the static elasticity  $E_s$  and viscosity  $\eta$  measured in the same subject on other days (the second and third measurements in subject A). The maximum percentage change in static elasticity  $E_s$  observed at 11 s after recirculation was about 36% (360 kPa) in the second measurement, and that at 7 s after recirculation was about 50% (490 kPa) in the third measurement. The maximum increase in viscosity  $\eta$  at 35 s after recirculation was about 73% (11 kPa·s) in the second measurement and that at 73 s after recirculation was about 240% (23 kPa·s) in the third measurement from the means at rest.

Figure 5 shows the transient change in the means and SDs of the static elasticity  $E_s$  and viscosity  $\eta$  measured in another subject (subject B). The maximum percentage change in static elasticity  $E_s$  at 19 s after recirculation was about 55% (570 kPa). The maximum increase in viscosity  $\eta$  at 44 s after recirculation was about 571% (23 kPa·s) from the mean at



**Fig. 5.** (Color online) Transient change in means and SDs of estimated static elasticity  $E_s$  and viscosity  $\eta$  measured in another subject (subject B).



**Fig. 6.** (Color online) Means and SDs of static elasticity  $E_s$  and viscosity  $\eta$  for 10 min *in vivo* measurements.

rest. The temporal decrease in elasticity  $E_s$  and the increase in viscosity  $\eta$  were observed also in the another subject.

For the evaluation of reproducibility, RF data and the blood pressure waveform at rest were measured every 1 min for 10 min. Figure 6 shows the means and SDs of the measured static elasticity  $E_s$  and viscosity  $\eta$ . The SDs were obtained from 30 ultrasonic beams. Horizontal dashed lines show the means of the parameters.

Figure 6 shows the means and SDs of the parameters. Table I shows the means and SDs of the parameters averaged for 10 min. For the static elasticity  $E_s$ , the maximum difference from the mean was about 200 kPa (17% of mean). The maximum change in static elasticity due to FMD (770, 360, 490, and 570 kPa) was much larger than this value. For the viscosity  $\eta$ , the variation in mean was 5 kPa·s. The maximum change in viscosity due to FMD (10, 11, 23, and 23 kPa·s) was also much larger

**Table I.** Means and SDs of parameters for 10 min *in vivo* measurements.

	Static elasticity $E_s$ (kPa)	Viscosity $\eta$ (kPa·s)
Average	1225.1	11.6
SD	640.1	5.0

than this value. However, the patterns of the changes in the static elasticity  $E_s$  and viscosity  $\eta$  after recirculation, and the time for observing the maximal changes in these parameters were different among these measurements.

#### 4. Discussion

To reveal the change in the stress–strain relationship of the arterial wall due to FMD, as shown in Figs. 2 and 3, the transient change in the relationship between the blood pressure and the change in the thickness of the intima–media region (correspond to the stress and strain, respectively) during a cardiac cycle and the time sequence of the hysteresis loop and blood velocity were obtained. Figures 4 and 5 show the viscoelasticity estimated by the least-squares method.

Figure 2 shows the gradual transient change in stress–strain relationship due to FMD. The relationship shows hysteresis property, which is caused by the viscoelasticity of the arterial wall. Figures 3–5 show the gradual changes in shape and area of the loop, and the parameters ( $E_s$  and  $\eta$ ), immediately measured after recirculation together with the increase in blood velocity. The temporal increase in blood flow velocity indicates the temporal increase in shear stress on the arterial wall. After the blood flow velocity came around, the stress–strain relationship and estimated parameters gradually came around. These results suggest that the transient change in viscoelasticity was caused by FMD.

Figure 6 shows the mean and SD of each parameter measured every 1 min for 10 min at rest. The maximum changes in static elasticity  $E_s$  (770, 360, and 490 kPa) and viscosity  $\eta$  (10, 11, and 23 kPa·s) due to FMD obtained from subject A were much larger than their fluctuations at rest. The maximum changes in these parameters measured in subject B (static elasticity  $E_s$ : 570 kPa and viscosity  $\eta$ :

23 kPa·s) were also much larger than their fluctuations. However, the fluctuation in the mean of the estimated viscosity  $\eta$  was large even at rest in the same subject Fig. 6. One of the reasons for this is the noise contained in the strain rate that is amplified by the temporal differentiation of the measured strain. Therefore, it is necessary to improve the precision in the measurement of strain rate by further investigation for the reduction in variance in the estimated viscosity. As described above, although there are many aspects of this study that should be further investigated, the obtained results show that the method described in this paper can detect the changes in the viscoelastic properties of the arterial wall due to FMD. Such a method would be beneficial for the detection of early-stage atherosclerosis.

#### 5. Conclusions

In this study, we measured the transient change in the stress–strain relationship of the intima–media region of the radial artery due to FMD. From the measured stress–strain relationship, we estimated the viscoelasticity of the artery wall noninvasively. The proposed method showed a potential for the thorough analysis of the transient changes in the mechanical properties of the intima–media region caused by FMD in addition to the evaluation of the endothelial function.

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