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Flow-mediated change in viscoelasticity of radial arterial wall measured by 22-MHz ultrasound

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The endothelial dysfunction is considered to be an initial step of atherosclerosis. Moreover, it was reported that the smooth muscle, which constructs the media of the artery, changes its characteristics due to early-stage atherosclerosis. Therefore, it is essential to develop a method for assessing the *regional* endothelial function and mechanical property of the arterial wall. There is an ultrasound-based conventional technique to measure the change in inner diameter of the brachial artery caused by flow-mediated dilation (FMD) after release of avascularization. In this study, the transient change in the mechanical property of the arterial wall was further revealed by measuring the stress-strain relationship during each heartbeat. For this measurement, the minute change in thickness (strain) of the radial artery was measured using the ultrasonic *phased tracking method*, together with the waveform of blood pressure (stress) which was continuously measured at the radial artery. From *in vivo* experiments, it was found the slope of the stress-strain hysteresis loop decreased due to FMD and the area, which depends on the ratio of *elastic modulus* and loss modulus (depends on *viscosity*), increased. These results show a potential of the proposed method for thorough analysis of the *transient change in viscoelasticity* due to FMD.

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 of atherosclerosis [1]. Additionally, it was reported that the smooth muscle, which constructs the media of the artery, changes its characteristics owing to atherosclerosis [2]. Consequently, it is important for early preventive treatment to noninvasively assess the endothelial function and the mechanical property of the media which is mainly composed of smooth muscle.

Endothelial cells react to the shear stress caused by the blood flow and produce nitric oxide (NO), which is known as a vasodepressor material. The smooth muscle is relaxed by 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. The composite type is proliferative, and the contractional type contracts and relaxes as responses to chemical and mechanical stimuli. When the blood vessel has 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 [3]. For 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 [4]. In this study, the proposed method was 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 [5]. Therefore, the radial artery would be a more suitable site for the measurement of FMD.

Furthermore, the blood pressure can be measured continuously at the radial artery, which realizes the noninvasive evaluation of the stress-strain relationship during each heartbeat. We estimate the viscoelasticity of the intima-media region using the least-square method, and investigate the transient change in the viscoelasticity due to FMD.

2 Experimental methods

2.1 Estimation of minute change in thickness of arterial wall

The minute change in the thickness of the radial arterial wall, $(\Delta h(t))$, at time t during a cardiac cycle was measured by the *phased-tracking method* [6].

To obtain the change in thickness, the velocities of the artery wall boundaries were estimated. The velocity $v(t;d)$ at the depth d (d: initial depth at $t = 0$) was estimated from the phase shift $\Delta\theta(t;d)$ of echoes in two consecutive frames. The phase shift $\Delta\theta(t;d)$ was obtained using the complex cross-correlation function $r(t;d)$ applied to the demodulated signal $z(t;d)$ of the RF echo as

$$\exp\{j\widehat{\Delta\theta}(t;d)\} = \frac{r(t;d)}{|r(t;d)|}, \tag{1}$$

$$r(t;d)=\sum_{m=-M}^{M} z^*(t;d+x(t;d)+mD)\cdot z(t+T;d+x(t;d)+mD),$$

where $x(t;d)$, D, $*$ and M are the displacement of the object at the depth d in the depth direction, the sampling interval in the depth direction, a complex conjugate, and a half width of the correlation window, respectively. From the estimated phase shift $\Delta\theta(t;d)$, the

average velocity $\hat{v}(t;d)$ of the arterial wall at the pulse repetition interval T was obtained by

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

where ω_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, d_A and d_B, in the arterial wall along an ultrasonic beam was obtained from the difference between displacements, $x(t;d_A)$ and $x(t;d_B)$, at these two positions as

$$\begin{aligned}\Delta\hat{h}(t) &= \hat{x}(t;d_A) - \hat{x}(t;d_B) \\ &= \int_0^t \{\hat{v}(t;d_A) - \hat{v}(t;d_B)\}\mathrm{d}t. \end{aligned} \tag{3}$$

where $\hat{}$ means an estimate. 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. Therefore, from the maximum changes in wall thickness $\Delta h_{max} = \max_t |\Delta h(t)|$ and pulse pressure $\Delta p_{max} = \max_t |\Delta p(t)|$, which is the difference between the systolic and diastolic pressures, the approximate circumferential dynamic elastic modulus E_θ^h [Pa] was obtained as

$$E_\theta^h \approx \frac{1}{2}\left(\frac{r_0}{h_0}+1\right)\frac{\Delta p_{max}}{\frac{\Delta h_{max}}{h_0}}, \tag{4}$$

where r_0 and h_0 are the internal radius and wall thickness at the end diastole, respectively [7].

2.2 Viscoelasticity estimation of arterial wall using least-square method

The smooth muscle constructs the media and is the main source of the viscoelasticity of the vessel wall [8]. By assuming the Voigt model as a viscoelastic model of the intima-media region, the stress-strain relationship is expressed as

$$\hat{\tau}(t) = E_s\gamma(t) + \eta\dot{\gamma}(t) + \tau_0, \tag{5}$$

where $\hat{\tau}(t)$ is the stress modeled by the Voigt model and $\gamma(t)$, $\dot{\gamma}(t)$, E_s, and η are strain, strain rate, static elasticity, and viscosity, respectively. The measured strain is the incremental strain due to the pulse pressure whereas the measured stress includes the bias stress (diastolic blood pressure). Therefore, τ_0 is added to the right-hand side of eq. (5) as the bias stress corresponding to diastolic pressure.

The parameters in eq. (5), E_s, η, and τ_0, are estimated using the least-square method by minimizing the mean squared error, α_t, between the measured and model stresses $\tau(t)$ and $\hat{\tau}(t)$ defined by

$$\alpha_t = \frac{E_t[\{\tau-\hat{\tau}\}^2]}{E_t[\{\tau-\bar{\tau}\}^2]}, \tag{6}$$

where $E_t[\cdot]$ and $\bar{\tau}(t)$ means the averaging operation and the average of measured blood pressure during a cardiac cycle. Parameters, $\hat{E}_s$, $\hat{\eta}$, and $\hat{\tau}_0$ which minimize α_t are determined by setting the partial derivatives of α with respect to E_s, η, and τ_0, to zero [9] as

$$\frac{\partial\alpha}{\partial E_s} = 0,\ \frac{\partial\alpha}{\partial\eta} = 0,\ \frac{\partial\alpha}{\partial\tau_0} = 0 \tag{7}$$

To solve the simultaneous equations, the optimum parameters which minimize α are determined.

2.3 Evaluation of estimated stress waveform

In this study, the reliability of the estimated viscoelastic constants were evaluated using the minimum value, α and the determination coefficient, R^2, between the stress measured by ultrasound and that modelled by the estimated viscoelastic constants.

$$R^2 = \left(\frac{E_t[\{\tau(t)-\overline{\hat{\tau}}\}\{\tau(t)-\bar{\tau}\}]}{\sqrt{E_t[\{\tau(t)-\overline{\hat{\tau}}\}^2]}\sqrt{E_t[\{\tau(t)-\bar{\tau}\}^2]}}\right)^2, \tag{8}$$

where $\overline{\hat{\tau}}$ is the average of the model stresses. This equation means the correlation coefficient between the estimated and measured waveform.

2.4 Procedure for *in vivo* measurement

The right radial artery of a healthy male subject (33 years old) was measured. In the measurement of the radial artery (Fig. 1), ultrasonic RF echoes (transmit: 22 MHz) were acquired at a sampling frequency of 66.5 MHz for 2 s and a frame rate was 165 Hz. This acquisition 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

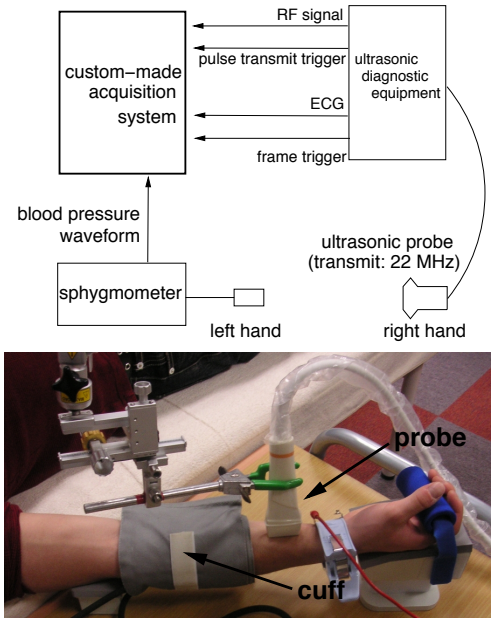

Figure 1: Ultrasonic measurement of radial artery.

waveform of blood pressure $p(t)$ in the left radial artery was continuously measured with a sphygmometer. In this study, a sphygmometer (COLIN, JENTOW-7700), 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 transient change in stress-strain relationship during a cardiac cycle due to FMD was obtained from the measured change in thickness, $\Delta h(t)$, the arterial wall and the blood pressure $\Delta p(t)$.

3 Results

3.1 Calibration of time delay

The delay of the strain from the applied stress is determined on the basis of the viscoelasticity of the material. The experimental apparatus employed in this study has two factors, which lead to undesirable time delays.

(1) The sphygmometer incorporates a low pass filter (LPF), which leads to a time delay in the output of the waveform of blood pressure. The time delay of the analog LPF depends on the inverse of the cutoff frequency.

(2) The blood pressure is measured in the left radial artery, whereas the strain is measured in the right radial artery.

In this study, the time delay τ_1 due to factor (1) is evaluated by simultaneously measuring the pulsation of the left radial artery using the sphygmometer and a pressure sensor with a much smaller time delay (maximum frequency response: 20 kHz). The pressure sensor was manually placed and used for measurement during a short period (2 s) at almost the same place as the sphygmometer on the skin surface over the radial artery. The time delay τ_2 due to factor (2) is evaluated by measuring the waveforms of velocities of the left and right radial arterial walls by the ultrasonic *phased-tracking method*.

Figure 2(1-a) shows the waveforms measured using the sphygmometer and the pressure sensor. The waveform measured using the sphygmometer was delayed by about 25 ms from that measured using the pressure sensor. Thus, $\tau_1 \approx 2525ms$.

Figures 2(2-a) and 2(3-a) show the wall velocities $v_i(t)$ of the left and right radial arteries, respectively, for seven and eight cardiac cycles i consecutively measured using ultrasound. The waveforms are ECG-triggered.

Figures 2(2-b) and 2(3-b) show the correlation functions between the waveforms of the wall velocities $v_i(t)$ (i=1, 2, . . ., 7 or 8) of seven or eight heartbeats and the

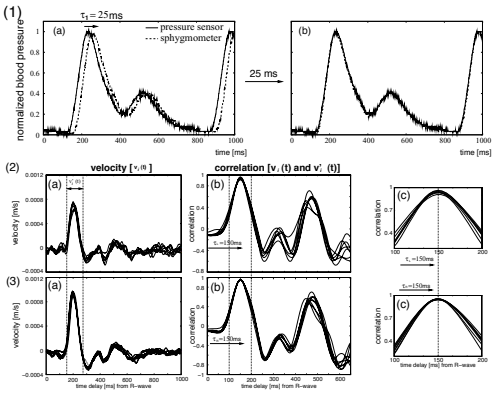

Figure 2: (1) Correction of delay caused by experimental system. For (2) left and (3) right radial arteries, (a) velocities of arterial walls, (b) correlation functions, and (c) enlarged views of (b).

waveforms $v'_i(t)$ during the period indicated by the dotted lines in Figs. 2(2-a) and 2(3-a). Figures 2(2-c) and 2(3-c) show the enlarged views of the periods between the dotted lines in Figs. 2(2-b) and 2(3-b). As shown in Figs. 2(2-c) and 2(3-c), there is almost no difference between the time delay from the R-wave in the left arm τ_L and that in the right arm τ_R when the sampling intervals T_s of velocity waveforms are 0.33 ms, because the time delay τ_2 means the difference between τ_L and τ_R, that is, $\tau_2 < Ts \ll \tau_1$. The same procedure can be applied to other subjects to evaluate the difference in the arrival time of the pulse wave between the left and right arms prior to the measurement of FMD.

3.2 *In vivo* experimental results for healthy subjects

RF data for 2 s obtained by each acquisition included at least an entire cardiac cycle. Consequently, the changes in thickness $\Delta h(t)$ and blood pressure $p(t)$ were obtained for at least one cardiac cycle in each measurement to estimate the elasticity E^h_θ of the radial arterial wall.

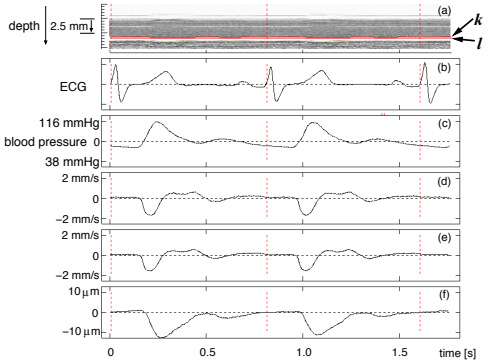

Figure 3: (a) M-mode image of radial artery (healthy 33-year-old male). (b) Electrocardiogram. (c) Blood pressure $p(t)$. (d) Velocity at the lumen-intima boundary (LIB). (e) Velocity at media-adventitia boundary (MAB). (f) Change in intima-media thickness of posterior wall, $\Delta h(t)$.

Figure 3 shows the results of the measurement of the change $\Delta h(t)$ in the intima-media thickness of the right radial artery in a healthy 33-year-old male for 2 s. As shown in Fig. 3(a), the initial positions k and l of the lumen-intima and media-adventitia boundaries of the posterior wall were determined manually on the M-mode image by referring to the RF echo from the posterior wall sampled at 66.5 MHz. Then, the instantaneous positions of these points were automatically tracked, as shown by the red lines, by the *phased tracking method*. Figures 3(b) and 3(c) show the electrocardiogram and blood pressure waveform $p(t)$, respectively. The time delay τ_1 in the waveform of the blood pressure $p(t)$ was corrected, as described in the previous section. Figures 3(d) and 3(e) show the estimated velocities at k and l, respectively. The change in the thickness of the intima-media region, $\Delta h(t)$, was calculated by the temporal integration of the difference between these velocities, as shown in Fig. 3(f). The minute change in thickness, $\Delta h(t)$, for two cardiac cycles was measured with sufficient reproducibility. The stress-strain characteristics of the intima-media region of the radial artery for each measurement were obtained using the measured blood pressure waveform [Fig. 3(c)] and the change in thickness [Fig. 3(f)].

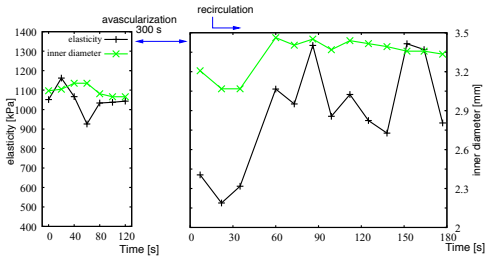

Figure 4: Transient change in elasticity E_θ^h of intima-media region and inner diameter d of radial artery.

Fig. 4 Transient change in elasticity E_θ^h of intima-media region and inner diameter d of radial artery. Figure 4 shows the transient change in inner diameter d, which was manually determined by referring to the RF echo obtained at each R-wave of ECG, and that in the elasticity E_θ^h of the intima-media region. Figure 4 shows that the percent change in measured elasticity, E_θ^h is much larger than that in diameter d measured by the conventional method. Moreover, the increase in inner diameter was measured after the decrease in elasticity, and a difference was observed between the time of the maximum increase in inner diameter d and that of the maximum decrease in elasticity E_θ^h. The elasticity E_θ^h began to recover to its original value before avascularization when the diameter began to increase. The time and magnitude of these percent changes are comparable to those reported in the literature.

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 5 shows the transient change in stress-strain relationship during FMD. The slope and area of the hysteresis loop changed gradually. The slope of the loop decreased owing to FMD, which shows that the elastic modulus decreased.

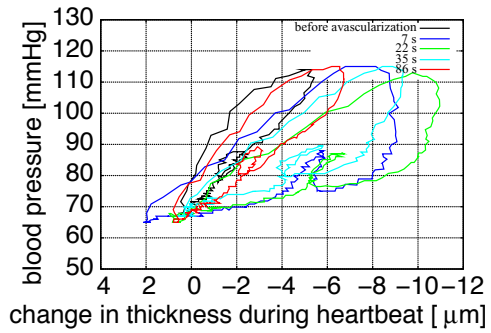

Figure 5: Transient change in stress-strain relationship of radial artery during FMD.

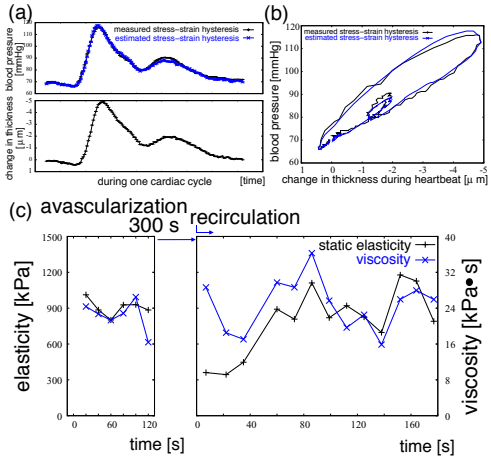

Figure 6: (a) Measured and estimated blood pressure waveforms and the change in thickness during a cardiac cycle. (b) Stress-strain relationships obtained by measured and estimated blood pressure. (c) Transient changes static elasticity E_s and viscosity η, during FMD.

By using the stress-strain relationship, we estimated the viscoelasticity of the arterial wall. To suppress the high frequency noise contained in the strain rate, a low-pass filtration was applied to the waveform of strain rate. Figure 6(a) shows the measured and estimated blood pressure waveforms and the change in thickness during a cardiac cycle. The minimum mean squared error, $\alpha_m in$, between the measured and model blood pressure was 3%. As shown in Fig. 6(b), the stress-strain relationship obtained by measured blood pressure was in good agreement with that by model blood pressure. Figure 6(c) shows the transient changes in estimated parameters, static elasticity E_s and viscosity, η, during FMD.

Figure 7 shows the transient changes in the determination coefficient $R^2$and the minimum mean squared

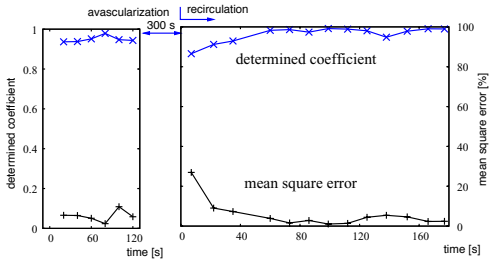

Figure 7: Transient change in determination coefficient R^2 and minimum mean squared error $alpha_m in$.

error $alpha_m in$. The determination coefficient R^2 were totally strong. But the mean squared error varied point to point. beginfigure

4 Discussion

Figure 4 shows the transient changes in the inner diameter d and elasticity E_θ^h of the intima-media region of the radial artery due to FMD. Furthermore, to reveal the change in the stress-strain relationship of the arterial wall due to FMD, the transient change in the relationship between the change in the blood pressure $p(t)$ and the change in the thickness of the intima-media region, $\Delta h(t)$, (respectively correspond to the stress and strain) during a cardiac cycle was measured.

Figure 5 shows the gradual transient change in stress-strain relationship. The relationship shows the hysteresis property, and it is caused by the viscoelasticity of the arterial wall. By defining the applied stress as $\tau = \tau_0 \cos \omega t$, the strain of a viscoelastic material explained using the Voigt model can be expressed as

$$\begin{aligned} \gamma &= \gamma_0 \cos(\omega t - \theta), \\ \theta &= \tan^{-1} \frac{\omega \eta}{E_s}. \end{aligned} \tag{9}$$

By assuming that E_s and η are independent of the magnitude of stress, the area of the hysteresis loop is calculated as

$$A = \oint \tau d\gamma = \tau_0 \gamma_0 \sin \theta. \tag{10}$$

Actually, the stress should be expressed as $\tau = \sum_\omega \tau_0 \cos \omega t$. Therefore, the area of the hysteresis loop depends on the phase lags θ of strains γ from stresses τ, at multiple frequencies $\{f = \omega/2\pi\}$.

Figure 6(c) shows the transient change in viscoelasticity due to FMD. The viscosity increased totally after recirculation, which corresponds to the increase of the area of loop after recirculation. This result shows the potential of the measurement of change the characteristics of the smooth muscle in media.

The reliability of estimated viscoelastic constants were evaluated as shown by Fig. 6(a), 6(b) and Fig. 7. The determination coefficient R^2, which shows the similarity between the measured and model stress waveforms, was totally high during whole measurement. However, the minimum mean squared error $\alpha_m in$ was over 10% at some time moments. It was supposed that the error in the measured strain rate led to such large error in the estimated viscoelastic constants. In this study, the high frequency noise contained in the strain rate was suppressed by low-pass filtration. However, methods for improvement of the accuracy in estimation of strain rate should be developed in future work.

5 Conclusion

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 of the thorough analysis of the transient change in mechanical property of the intima-media region caused by FMD in addition to the evaluation of the endothelial function.

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