Transient Change in the Hysteresis Property of the Arterial Wall due to Flow-Mediated Dilation

Kazuki Ikeshita, Hideyuki Hasegawa, Hiroshi Kanai
Graduate School of Engineering, Tohoku University,
Sendai 980-8579, Japan
E-mail: ikeshita@ee.c.uhs.tohoku.ac.jp

Abstract—The endothelial dysfunction is considered to be an initial step of atherosclerosis. Additionally, it was reported that the smooth muscle, which constructs the media of the artery, changes its characteristics due to atherosclerosis. Therefore, it is essential to develop a method for assessing regional endothelial function and mechanical property of arterial wall. There is a technique to measure the transient change in diameter of the brachial artery caused by flow-mediated dilation (FMD) after release of avascularization. For more sensitive and regional evaluation, we developed a method to measure the change in elasticity of the radial artery due to FMD. 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. The minute change in thickness (strain) of the radial arterial wall during a cardiac cycle was measured using the phased tracking method. At the same time, the waveform of blood pressure at the radial artery was continuously measured with a sphygmometer. Transient change due to FMD in the stress-strain relationship during a cardiac cycle was obtained from the measured strain and blood pressure to show instantaneous viscoelasticity. From the results, the stress-strain relationship shows the hysteresis loop. The slope of the loop decreased due to FMD, which shows that the elastic modulus became lower, and the increasing area of the loop depends on the ratio of the loss modulus (depends on viscosity) to the elastic modulus when the Voigt model is assumed. These results show a potential of the proposed method for thorough analysis of the transient change of viscoelasticity due to FMD.

I. INTRODUCTION

A main cause of circulatory diseases is considered to be atherosclerosis. Therefore, the quantitative assessment of atherosclerosis is essential to make 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 due to atherosclerosis [2]. Consequently, it is important for early preventive treatment to non-invasively assess the endothelial function and the mechanical property of the media composed of smooth muscle.

The endothelial cells react to the shear stress caused by the blood flow and generate the nitric oxide (NO) which is known as vasodepressor material. The smooth muscle is relaxed as a result of the response to produced NO. This function is important to maintain the homeostasis of the vascular system. Smooth muscle cells in the media are classified into two types with different functionalities [3]. 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 type to contractional type, and control blood flow and blood pressure. On the other hand, after the vascular system is completed, smooth muscle cells change their characteristics from contractional type to composite type due to atherosclerosis. The composite type is related to the growth factor and increases the migration of smooth muscle cells to the intimal layer. As described above, the evaluation of endothelial function and characteristics of smooth muscle cells are important to early diagnosis of atherosclerosis.

For evaluation of the endothelial function, there is a technique to measure the transient change in inner diameter of the brachial artery caused by flow-mediated dilation (FMD) after the release of avascularization [4]. For more sensitive and regional evaluation, we developed a method to directly measure the change in elasticity of the intima-media region due to FMD [5]. In this study, the proposed method was applied to the measurement of the radial artery. Furthermore, the stress-strain relationship during each heartbeat was non-invasively measured. We estimate the viscoelasticity of the intima-media region using the least-square method [6], and assess the transient change in the viscoelasticity due to FMD.

II. METHODS

A. Estimation of minute change in thickness of arterial wall

The minute change in thickness Δh(t) of the radial arterial wall during a cardiac cycle was measured using the phased tracking method [7].

To obtain the change in thickness, the velocities of the artery-wall boundaries were estimated. Velocity v(t) is estimated from phase shift Δθ(t) of echoes in two consecutive frames. Phase shift Δθ(t) is obtained based on the complex cross-correlation function r applied to the demodulated signal, z*(t; d + x(t)), of RF echo reflected at depth d + x(t) at time t as follows:

\[ \exp \{ j \Delta \theta(t) \} = \frac{r}{|r|}, \]

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

where d and x(t) are the initial depth set at t = 0 and the displacement of the arterial wall in the direction of depth, respectively. From the estimated phase shift Δθ(t), the average...
velocity \( \dot{v}(t) \) of the arterial wall during one pulse repetition interval \( \Delta T \) is obtained as follows:

\[
\dot{v}(t) = -\frac{c_0}{2\omega_0} \frac{\Delta \theta(t)}{\Delta T},
\]

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 positions, \( A \) and \( B \), in the arterial wall along an ultrasonic beam is obtained from the difference between displacements, \( x_A(t) \) and \( x_B(t) \), at these two positions as follows:

\[
\Delta \dot{h}(t) = \dot{x}_A(t) - \dot{x}_B(t) = \int_0^t \{ \dot{v}_A(t) - \dot{v}_B(t) \} \, dt.
\]

The change in thickness, \( \Delta h(t) \), which corresponds to the incremental strain in the radial direction at a time \( t \) due to the pressure increment, \( \Delta p(t) \), from the diastolic pressure. Therefore, from the maximum change in wall thickness \( \Delta h_{\text{max}} = \max_t [\Delta h(t)] \) and the pulse pressure, \( \Delta p_{\text{max}} = \max_t [\Delta p(t)] \), which is the difference between the systolic and diastolic pressures, the approximate circumferential dynamic elastic modulus \( E_h^s [\text{Pa}] \) which is derived by the conventional approach [5] is obtained as follows [8]:

\[
E_h^s \approx \frac{1}{2} \left( \frac{r_0}{h_0} + 1 \right) \frac{\Delta p_{\text{max}}}{\Delta h_{\text{max}}},
\]

where \( r_0 \) and \( h_0 \) are the internal radius and wall thickness at the end diastole, respectively.

B. 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 [9]. By assuming the Voigt model as a viscoelastic model of the intima-media region, the stress-strain relationship is expressed as follows:

\[
\tau(t) = E_s \gamma(t) + \eta \dot{\gamma}(t) + \tau_0,
\]

where \( \tau(t) \) is the stress modeled by the Voigt model and \( \gamma(t) \), \( \dot{\gamma}(t) \), \( E_s \), and \( \eta \) 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, \( \tau_0 \) is added to the right-hand side of eq. (5) as the bias stress corresponding to diastolic pressure.

The parameters in eq. (5), \( E_s \), \( \eta \), and \( \tau_0 \), are estimated using the least-square method by minimizing the mean squared error, \( \alpha \), between the measured and model stresses \( \tau(t) \) and \( \hat{\tau}(t) \) defined by

\[
\alpha = E_i \{ \tau - \hat{\tau} \}^2,
\]

where \( E_i [\cdot] \) means the averaging operation during a cardiac cycle. Parameters \( E_s \), \( \eta \), and \( \tau_0 \) which minimize \( \alpha \) are determined by setting the partial derivatives of \( \alpha \) with respect to \( E_s \), \( \eta \), and \( \tau_0 \) to zero as follows:

\[
\frac{\partial \alpha}{\partial E_s} = 0, \quad \frac{\partial \alpha}{\partial \eta} = 0, \quad \frac{\partial \alpha}{\partial \tau_0} = 0
\]

To solve the simultaneous equations, the optimum parameters which minimize \( \alpha \) are determined.

C. Procedure for in vivo measurement

In this study, the right radial artery of a healthy subject 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 seconds. This acquisition was repeated every 20 seconds for 2 minutes at rest before avascularization and every 12 seconds for 3 minutes after recirculation. At the same time, the waveform of blood pressure in the left radial artery was continuously measured with a sphygmometer. The transient change in the stress-strain relationship during a cardiac cycle due to FMD was obtained from the measured strain and blood pressure.

III. RESULTS

RF data for 2 seconds obtained by each acquisition included at least an entire cardiac cycle. We measured the change in thickness, blood pressure, and elasticity of the radial artery wall for at least one cardiac cycle in each measurement.

Figure 2 shows the results of measurement of the change in intima-media thickness in a healthy 33-year-old male for 2 seconds. As shown in Fig. 2(a), the initial positions, \( k \) and \( l \), of the lumen-intima and media-adventitia boundaries of the posterior wall on the M-mode image were determined manually 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 using the phased tracking method. Figures 2(b) and (c) shows the electrocardiogram and blood pressure waveform, respectively. Figures 2(d) and (e) show the estimated velocities at \( k \) and \( l \), respectively. The change in thickness of the intima-media region was calculated by temporal integration of the difference between these velocities as shown in Fig. 2(f). It shows that the minute change in thickness for 2 cardiac cycles was measured with high reproducibility. The static elasticity and viscosity of the intima-media region of the radial artery for each measurement was estimated by the least-square method, with the measured blood pressure waveform (Fig. 2(e)), strain (obtained from Fig. 2(f)), and strain rate which is obtained by differentiating the strain with respect to time as described in
the previous section. Figure 3(a) shows the transient change in
the inner diameter manually determined by referring to the RF
echo obtained at each R-wave of ECG and that in elasticity $E^h$
of the intima-media region. Figure 3(a) shows that % change
in the measured elasticity $E^h$ is much larger than % change in
diameter measured by the conventional method, and there is a
difference between the time of the maximum increase of inner
diameter and that of the maximum decrease of elasticity $E^h$.
The time and magnitude of these % changes are comparable
with those reported in literature [5].

To reveal the change in the stress-strain relationship of the
arterial wall due to FMD, the blood pressure and the change
in thickness of the intima-media region during a cardiac cycle
during FMD were measured. Figure 3(b) shows the transient change
in the relationship of the change in thickness and blood
pressure. The change in the stress-strain relationship shows
the hysteresis loop. The time when each hysteresis loop was
obtained is indicated by the red circle in Fig. 3(a).

The hysteresis loop is considered to be caused by the time
delay between blood pressure and change in thickness due to
the viscoelasticity of the arterial wall. Therefore, the correction
of time is very important to evaluate the viscoelasticity from
the hysteresis loop because the change in thickness and blood
pressure were measured in the right and left arms, respectively.
In this study, the time delays due to the measurement system
and the difference between the propagation time of the pulse
wave along the left and right arms.

The time delay due to the sphygmometer was evaluated by
measuring the blood pressure waveform simultaneously and in
the almost same place on the skin surface over the radial artery
using the sphygmometer and a pressure sensor with much
smaller time delay (about 0.5 ms). Figure 4(1-a) shows the
waveforms measured by the sphygmometer and the pressure
sensor. The waveform measured by the sphygmometer was
delayed by about 25 ms from that measured by the pressure
sensor.

Figures 4(2-a) and 4(3-a) show the wall velocities of the left
and right radial arteries respectively for 7 and 8 cardiac cycles
consecutively measured using ultrasound. The waveforms are
ECG-triggered. Figures 4(2-b) and 4(3-b) show their autocor-
relation functions, and Figs. 4(2-c) and 4(3-c) are the enlarged
views of the periods between the dotted lines in Figs. 4(2-b)
and 4(3-b). As shown in Figs. 4(2-c) and 4(3-c), there is almost
no time delay. In the same manner, the difference between the
left and right arms can be evaluated for other subjects prior
to the measurement of FMD.
follow the recirculation and the area of loop came around gradually. The area of the loop depends on the ratio of the loss modulus $\omega \eta$ ($\omega$: angular frequency of strain) to the static elastic modulus $E_s$ when the Voigt model is assumed.

The transient change of static elasticity $E_s$ and viscosity $\eta$ estimated using the least-square method. The transient change of the static elasticity $E_s$ was similar to that of elasticity $E_s^h$ estimated by eq. (4). Moreover, the viscosity $\eta$, which was evaluated noninvasively measured by the proposed method, increased totally after recirculation. The maximum decrease of static elasticity was measured at 22 s after release of the cuff and the maximum area of the loop was found immediately following recirculation (7 s), which results from the decreasing elastic modulus and the increasing viscosity.

IV. DISCUSSION

Figure 2 shows the transient change in the inner diameter and the elasticity 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, Figs. 3, 5, and 6 show the transient change in the relationship between the change in the blood pressure and the change in thickness of the intima-media region (correspond the stress and strain respectively) during a cardiac cycle, the area of hysteresis loop, and viscoelasticity estimated by the least-square method.

In Fig. 2, there is difference between the time of the maximum increase of inner diameter and the maximum decrease of elasticity $E_s^h$. This is considered to be caused by the nonlinearity in the stress-strain relationship of the arterial wall. Additionally, Fig. 3 shows the gradual transient change in the 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 $\tau = \tau_0 e^{j\omega t}$, the strain of a viscoelastic material explained by the Voigt model can be expressed as follows:

$$\gamma = \gamma_0 e^{j(\omega t + \theta)}, \quad \theta = \tan^{-1} \frac{\omega \eta}{E_s}.$$  \hspace{1cm} (8)

By assuming the independence of the stress from $E_s$ and $\eta$, the area of hysteresis loop is calculated as follows:

$$S = \int_0^T \tau d\gamma = \tau_0 \gamma_0 e^{-j\theta}.$$  \hspace{1cm} (9)

Actually, the stress should be expressed as $\tau = \sum \tau_0 e^{j\omega t}$. Therefore, the area of hysteresis loop depend on the phase-lag $\theta$ from stress $\tau$, which results in the dependence on the area of loop on the ratio of viscous term $\omega \eta$ to static elasticity $E_s$.

Figure 5 shows the maximum area of the loop was found immediately following recirculation (7 s) because viscosity $\eta$ at 7 s is larger than that at 22 s whereas static elasticity $E_s$ at these time points are similar. After 22 s, the area of loop was changed depending mainly on static elasticity $E_s$ because static elasticity $E_s$ is larger than that immediately after recirculation. The measurement of the transient change in stress-strain relationship by the proposed method showed its potential for clarification of the transient change in the functional and mechanical characteristics of the intima-media region due to FMD.

V. 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. The proposed method showed a potential of the thorough analysis of the transient change in viscoelasticity caused by FMD.

REFERENCES