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Evaluation of Arterial Stiffness During the Flow-Mediated Dilation Test

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***Abstract*—The paper discusses the arterial stiffness during the flow-mediated dilation (FMD) test. The FMD test is a method of evaluating the vascular endothelial function and has been popular as it is non-invasive and readily performed by a skillful ultrasound technician. The FMD test, however, evaluates only the maximal increase in vascular diameter mediated by the increases in blood flow after the release of the occlusive cuff and does not evaluate the arterial viscoelastic properties. This paper thus estimates the log-linearlized stiffness, to evaluate the arterial stiffness properties using the arterial diameter and blood pressure measured in a beat-to-beat manner during the FMD test. To six healthy volunteers, we performed the FMD test to measure the arterial diameter and blood pressure with ultrasound diagnostic imaging equipment and non-invasive continuous arterial blood pressure monitor, respectively. As a result, the maximal vasodilatation ratio of FMD (*FMD*) was obtained after cuff occlusion. In comparison with the arterial stiffness before the FMD test, the stiffness of the arterial wall is temporarily decrease and increase. It was concluded the the arterial stiffness can be estimated on a beat-to-beat basis during the FMD test.**

I. Introduction

The arterial wall can be divided into three layers: the tunica intima, consisting of the vascular endothelium; the tunica media, consisting of smooth muscle; and the tunica adventitia, consisting of connective tissue, collagen and elastic fibers. Vascular endothelial cells produce various vasodilators such as nitric oxide (NO), which adjusts the coarctation and ectasia of vascular vessels to maintain their flexibility [1]. When risk factors such as diabetes and hypertension impair vascular endothelial function, the likelihood of arteriosclerosis is increased. In addition, significant cardiovascular events such as myocardial infarction are caused by the development and progression of arterioselerosis [2]. Accordingly, it is expected that the ability to quantitatively evaluate endothelial function will support the early recognition of arteriosclerosis.

Recently, numerous methods for evaluating endothelial function have been proposed, including an invasive approach that involves measuring blood flow variation via plethysmography [3] or another based on the use of flow wire [4] before/after the administration of a vasodilator substance agonist and antagonist into the artery via a catheter. However, these invasive techniques impose a physical burden on patients. Meanwhile, flow-mediated dilation (FMD) [5] has been proposed as a non-invasive method. The FMD test is performed to evaluate vascular endothelial function based on diameter variations as measured with an ultrasound device before and after avascularization in the brachial artery or the forearm arteries [5]. However, it has been reported that the viscoelastic characteristics of smooth muscle change due to organic changes [6], so that, when smooth muscle is damaged, vasodilator response decreases even if vascular endothelial function is normal [7]. Accordingly, the FMD test can potentially be used to evaluate vascular endothelial dysfunction separately from the presence or absence of vascular smooth muscle dysfunction by identifying arterial viscoelastic characteristics associated with normal endothelial function during the test.

Some researchers have studied the arterial viscoelastic characteristics observed during the FMD test [8]–[11]. For example, Ikeshita *et al.* estimated the viscoelasticity of the radial artery in a test situation based on arterial wall thickness variations (measured using ultrasonic echo) and continuous arterial pressure [8]. However, viscoelasticity in the study was evaluated only at intervals of about twelve seconds, meaning that arterial viscoelastic variations were not continuously monitored during the FMD test. In addition, the experiment was performed with only two subjects, and the relationship between arterial viscoelastic characteristics and the FMD test results was not discussed. Meanwhile, Kutluk *et al.* estimated arterial viscoelasticity based on the arterial wall mechanical impedance model [9] using measured forearm plethysmogram data from strain-gauge plethysmography[10], and also measured continuous arterial pressure [11]. However, the plethysmogram signals measured were affected by disturbances such as arteriolar vasodilatation because they represented the volume variation of the entire arm.

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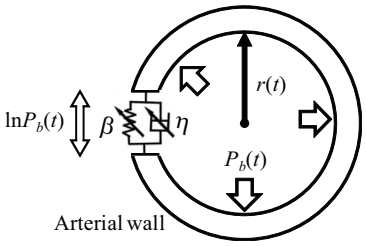

Fig. 1. Model of arterial dynamics (schematic representation)

Against such a background, this paper proposes a novel FMD measuring system to support the estimation of arterial stiffness on a beat-to-beat basis and the evaluation of variations in arterial stiffness characteristics observed during the FMD test. The paper also highlights the relationship between the FMD test results and arterial stiffness characteristics.

II. Method for evaluation of arterial stiffness observed during FMD test

When the vascular vessel is released after an avascularization using a pressure higher than the patient's systolic blood pressure for the predetermined time, a blood flow rapidly-increases compared with before the avascularization. Increase in blood flow stimulates vascular endothelial cells as shear stress and the vascular endothelial cells release various vasodilators such as NO [1]. The released NO makes the vascular smooth muscle relax and makes the vascular diameter dilate. The FMD evaluates the vascular endothelial function using rate of the vascular diameter dilation before/after the artery occlusion [5]. In the FMD test, the diameter of the brachial artery is measured with an ultrasound device. The avascularization of the arterial vessel is accomplished using a cuff attached to the forearm. A pressure which is added 50 [mmHg] to the patient's systolic blood pressure is applied to the cuff for five minutes to stop the arterial flow, and the change in the vascular diameter is continuously measured after releasing the cuff occlusion. It is known that the diastolic vascular diameter of the brachial artery is typically maximized between 45 [s] to 60 [s] after releasing the cuff occlusion. The $\%FMD$, which is the maximum dilation rate of the vascular diameter calculated using the measurement results for the vascular diameter before/after cuff occlusion, is evaluated following Equation:

$$\%FMD = \frac{d_{peak} - d_{base}}{d_{base}} \times 100, \tag{1}$$

where d_{base} is the diastolic vascular diameter at rest and d_{peak} is the maximum diastolic vascular diameter after cuff occlusion. In general, higher $\%FMD$ values indicate more normal vascular endothelial function.

In this study, arterial stiffness observed during the FMD test were evaluated using the arterial viscoelastic indices [12] based on the pulsation element of heartbeats. The arterial viscoelastic indices were considered non-linear based on the logarithm of blood pressure, as Hayashi *et al.* demonstrated a non-linear relationship between intravascular pressure and vascular diameter [13]. It is assumed that the cross-section of the arterial short axis is perfectly circular, and that blood pressure is uniformly dispersed in all directions. The log-linearized arterial viscoelastic model is represented in Fig. 1, and the arterial mechanical characteristics of the model are expressed by

$$\ln\left(\frac{P_b(t)}{P_b(t_0)}\right) = \beta\varepsilon(t) + \eta\dot{\varepsilon}(t), \tag{2}$$

where t_0 is the initial time of the R wave for each cardiac cycle, $P_b(t)$ is the arterial blood pressure at time t, $\varepsilon(t)$ and $\dot{\varepsilon}(t)$ are distortion in the arterial circumference direction and distortion velocity in the same direction, respectively, and β and η are the stiffness and viscosity of the arterial wall, respectively. $\varepsilon(t)$ is given by

$$\varepsilon(t) = \frac{r(t) - r(t_0)}{r(t_0)}, \tag{3}$$

where $r(t)$ is the arterial radius at time t. Stiffness β and viscosity η were estimated using the least-squares method for each cardiac cycle based on Equation (2). The stiffness β is the log-linearized arterial stiffness index evaluated in this paper.

III. Experiments

To evaluate arterial stiffness characteristic observed during the FMD test, evaluation of arterial stiffness for the periods before and after the five-minute period of avascularization and clarification of related variations need to be examined experimentally. Below is an outline of the experiment performed to examine the above point.

Experiments on the evaluation of arterial stiffness during the FMD test were performed using the method described in Section II. Figure 2 shows an overview of the measurement system. The subject was in a resting supine position during the experiment. Electrocardiogram signals and the arterial diameter of the right brachial artery were measured with an ultrasound system (UNEXEF-18G, Unex Co.) with a sampling period of 13 [ms]. Avascularization of the right brachial artery was performed using a cuff blown up with a rapid cuff inflator (E20 Rapid cuff inflator, Hokanson). In addition, electrocardiogram signals and the pressure of the left radial artery were simultaneously measured using a bedside monitor (BSS-9800, Nihon Kohden Corp.) with a sampling period of 4 [ms]. The arterial diameter and arterial pressure values obtained were resampled with a period of 1 [ms], and index values were estimated using the least-squares method for each cardiac cycle after biological signal filtering using a second-order IIR low-pass filter with a cut-off frequency of 10 [Hz].

Six healthy male subjects (mean age $\pm$ S.D.: 33 ± 15.4 [yrs]) were chosen for the study. Biological signals from 10 heartbeats were measured before and after a three-minute period of cuff occlusion. During the FMD test, arterial stiffness β was calculated, and the stiffness β for the periods before and after cuff occlusion was compared for cases when the coefficient of determination R^2 between the estimated arterial pressure as found using Equation (2) (as described in Section II) and the measured arterial pressure was more than 0.80. The mean value and the minimum values of arterial stiffness β for the period before cuff occlusion was calculated for evaluation. Paired t-test was used to determine the significance of differences between index values for the periods before and

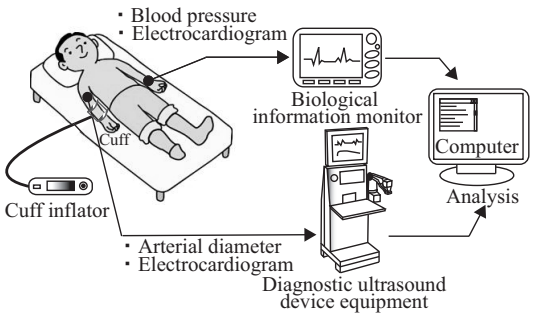

Fig. 2. Experimental equipment for measurement of FMD and biological signals

after cuff occlusion. Differences were considered significant when results showing $p < 0.05$ were seen.

Informed consent was obtained from all study subjects before the experiments were performed based on the Declaration of Helsinki, and the study was approved by the Nihon Kohden Corporation Ethics Committee.

IV. Results

Figure 3 shows signals measured before and after cuff occlusion during the FMD test. Its individual parts show electrocardiogram signals, arterial diameter and arterial pressure, respectively. Figure 4 shows arterial diameter, left radial artery pressure, mean arterial pressure, and arterial stiffness β as observed during the FMD test for Subject E. The dotted line in Fig. 4 (A) shows the timing at which maximum index values were observed for arterial diameter d and the dotted line in Fig. 4 (B) shows the timing at which the minimum stiffness β was observed. Figure 4 indicates that the artery was more dilated after release from avascularization than before cuff occlusion, and that the value of $\%FMD$ was 8.5 [%]. It can also be seen that the measured arterial stiffness β followed a downward convex path after cuff occlusion. The rates of change in stiffness β between before and after the cuff occlusion was -18.9 [%]. Figure 5 shows the mean values and standard deviations of the measured mean arterial pressure and pulse pressure for the periods before and after cuff occlusion for all subjects. It can be seen that the values did not differ significantly between before and after cuff occlusion.

Figure 6 (a) and (b) show the estimated stiffness β described in Section II for all subjects. These were calculated using estimated stiffness β between before and after cuff occlusion. Figure 6 (c) shows stiffness β_n for all subjects the periods before and after cuff occlusion. It can be seen that stiffness β was significantly lower after cuff occlusion.

Figure 7 shows the scatter diagram between the normalized arterial stiffness $\beta_n = \beta_{bottom}/\beta_{base}$ and the normalized vascular diameter $d_n = d_{peak}/d_{base}$. where β_{bottom} and d_{peak} are the minimum and the maximum values of each index, and β_{base} and d_{base} are the mean index values for the period before cuff occlusions, respectively. The correlation coefficient for β_n and d_n was 0.242. Figure 7 indicated stiffness β of the all subjects decreased after the cull occlusion and vascular

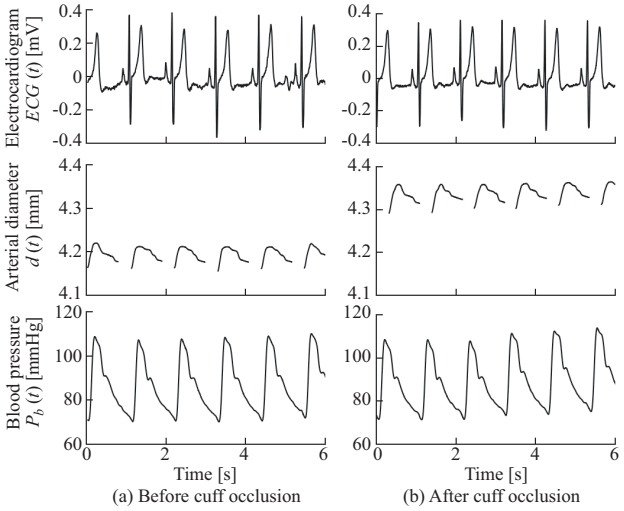

Fig. 3. Measured biological signals for the periods before and after cuff occlusion (Sub. E)

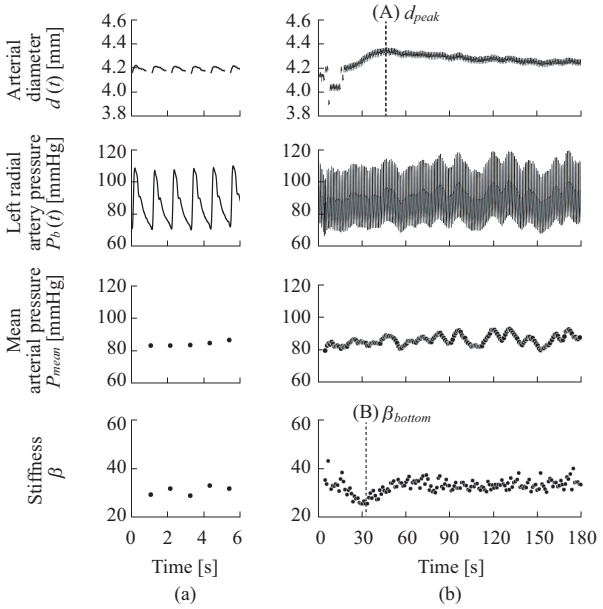

Fig. 4. Measured biological signals and estimated stiffness of Sub. E: (a) the period before cuff occlusion, (b) the period after cuff occlusion

diameter d of the all subjects increased compared with the period for before cuff occlusion.

V. Discussion

Figures 4 and 6 show that stiffness β tended to be lower after cuff occlusion on a temporary basis. This is because the NO produced and released as a result of increased blood flow after cuff deflation caused the smooth muscle to relax. Figure 3, 5, and 6 indicated the change of arterial stiffness β during the FMD test depended on only the variation of arterial diameter because the arterial pressure values did not

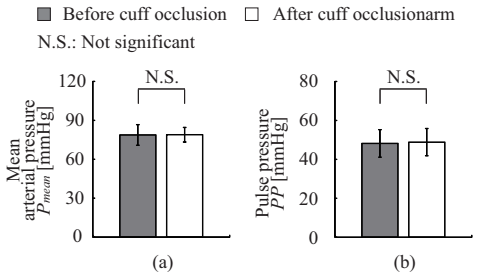

Fig. 5. Comparison of measurement left radial artery pressures for the periods before and after cuff occlusion: (a) mean arterial pressure; (b) pulse pressure

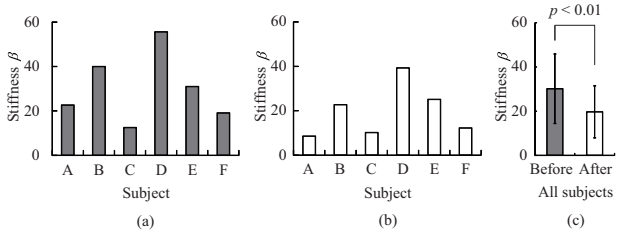

Fig. 6. Calculated and estimated indices: (a) estimated β for the period before cuff occlusion, (b) estimated β for the period after cuff occlusion, (c) comparison of stiffness β between before and after cuff occlusion

differ significantly between before and after cuff occlusion. Figure 7 indicated the relation between the normalized vascular diameter d_n and the normalized stiffness β_n was weakly-correlated. These result thus indicated a part of the cause of β decline between the period before and after cull occlusion may include the effect in the change of vascular endothelial function. In future, the possibility that the estimated index may provide other biological information (such as the presence or absence of vascular smooth muscle dysfunction) should be considered and the relationship between arterial mechanical characteristics and the vascular endothelial function need to be considered. The results of the study thus revealed that arterial wall characteristics can be evaluated using arterial pressure and vascular diameter values measured during the FMD testing, and that the arterial wall state change associated with the release of NO after cuff occlusion can be evaluated quantitatively.

VI. Conclusion

This paper outlined the development of a system for measuring arterial diameter and arterial pressure continuously during the FMD test and the evaluation of arterial stiffness characteristics for the periods before and after cuff occlusion. The results showed no difference in measured arterial pressure waveforms observed at both times. In addition, stiffness β was significantly lower thereafter. It can therefore be concluded that the proposed method enables quantitative evaluation of the arterial wall state change associated with the release of NO after cuff occlusion.

In future work, the proposed method needs to be applied to a wide variety of patients to examine the validity of its viscoelastic indices, and the reproducibility of the proposed indices need to be verified.

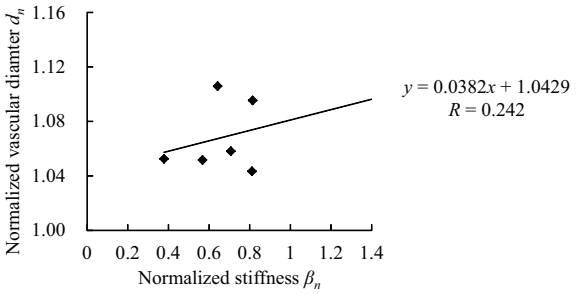

Fig. 7. Relationship between the normalized stiffness β_n and the normalized vascular diamter d_n

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