# A New Approach to Evaluation of Reactive Hyperemia Based on Strain-gauge Plethysmography Measurements and Viscoelastic Indices

Abdugheni Kutluk[1], Takahiro Minari[1], Kenji Shiba[1], Toshio Tsuji[1], Ryuji Nakamura[2], Noboru Saeki[3], Masashi Kawamoto[3], Hidemitsu Miyahara[3], Yukihito Higashi[3], Masao Yoshizumi[3]

[1] Graduate School of Engineering, Hiroshima University, Higashi-Hiroshima, Japan
[2] Hiroshima University Hospital, Hiroshima, Japan
[3] Graduate School of Biomedical Sciences, Hiroshima University, Hiroshima, Japan

*Abstract* — **Endothelial dysfunction is an initial step of atherosclerosis and is associated with cardiovascular diseases. Measurement of flow-mediated vasodilation in the brachial artery using ultrasound is noninvasive and an accurate indicator of nitric oxide production. However, ultrasound based measurement sometimes depends on the observer's skill. The purpose of this study was to evaluate response in reactive hyperemia employing viscoelastic indices, including stiffness and viscosity measured by strain-gauge plethysmography (SPG) in beat-to-beat. We measured viscoelastic parameters and pulse wave velocity (PWV) in 4 young (23±1 years) and 3 elderly (55±4 years) subjects. Our results showed that there were significant differences in viscosity after cuff deflation (0 to 100 sec) between the young and the elderly (p<0.001). However, there was no significant difference in PWV after cuff deflation between the young and the elderly (P=0.11). These findings suggest that the proposed viscoelastic indices represent the changes of arterial mechanical properties, which might be derived from flow-mediated vasodilation.**

*Keywords* — **atherosclerosis, reactive hyperemia, strain-gauge plethysmography, viscoelastic indices, PWV.**

## I. INTRODUCTION

Cardiovascular and cerebral vascular diseases are the major cause of mortality in Japan. These conditions are strongly associated with atherosclerosis [1]. Previous studies have evaluated arteriosclerosis using arterial elastic properties such as pulse wave velocity (PWV) [2], arterial elasticity [3] and arterial compliance [4]. However, arterial elasticity is useful for the quantification of arterial sclerosis rather than of atherosclerosis.

Endothelial dysfunction is thought to be an important factor in the development of atherosclerosis [5], [6]. It is well known that endothelium function plays a role in releasing nitric oxide to regulate the relaxation of smooth muscle cells within the vascular wall. The function can be evaluated from endothelial-mediated dilatory response, and two methods that evaluate this response are known. One involves measuring forearm blood flow after the administration of an NO agonist and antagonist [7]. These vasoactive substances must be administered via a catheter inserted into the brachial artery, and the method may become invasive and includes potential risk and discomfort. The other method involves a reactive hyperemia test that evaluates flow-mediated dilation promoted by increasing blood flow created by cuff inflation to suprasystolic pressure. This method is widely used because it is noninvasive and allows repeated measurement [8], [9]. However, its drawbacks include the high cost of ultrasound devices and the fact that measurement depends on the observer's skill.

To address the problem, Baldassarre *et al.* assessed endothelial function during reactive hyperemia using strain-gauge plethysmography [10]. This study takes into account only the compliance component between the strain-gauge plethysmogram (representing the strain) and blood pressure (representing the stress). However, it is important for precise estimation of mechanical dynamics to consider the viscous component as well as the compliance component.

We therefore propose a new method to evaluate response in reactive hyperemia using viscoelastic indices measured by strain-gauge plethysmography. In this paper, the proposed indices are measured during a reactive hyperemia experiment, and we assess whether response in reactive hyperemia differs between the young and the elderly subjects.

## II. ARTERIAL WALL IMPEDANCE MODEL

Fig. 1 illustrates the proposed impedance model of the arterial wall. This model represents only the characteristics of the wall in an arbitrary radius direction. The impedance characteristic can be described using the stress $F(t)$ and the displacement $r(t)$ of the arterial wall as follows [11]:

$$dF(t) = B\dot{r}(t) + K(r(t) - r_e) \tag{1}$$

where $B$ and $K$ are the coefficients of viscosity and the elastic modulus respectively, $\dot{r}(t)$ is the first derivative of strain in the arterial wall, and $r_e$ is the equilibrium point of the arte-

Chwee Teck Lim, James C.H. Goh (Eds.): ICBME 2008, Proceedings 23, pp. 2059–2063, 2009
www.springerlink.com

rial wall without internal pressure. Here, the dynamic characteristic on the basis of $t_0$ is described as follows:

$$dF(t) = Bd\dot{r}(t) + Kdr(t) \tag{2}$$

where $dF(t) = F(t) - F(t_0)$ and $dr(t) = r(t) - r(t_0)$. To estimate the impedance parameters given in (2), it is necessary to measure $F(t)$ and $r(t)$. The stress exerted on the arterial wall is equal to the arterial pressure. This stress can be given as follows:

$$F(t) = k_f P_b(t) \tag{3}$$

where $P_b(t)$ is the arterial pressure, and $k_f$ is the constant.

On the other hand, the strain of the blood vessel in the radius direction is recorded using strain-gauge plethysmography, which can measure changes in limb volume. The vascular volume change measured by the strain-gauge plethysmogram is represented as follows [12]:

$$r(t) = k_l P_l(t) \tag{4}$$

where $P_l(t)$ is the strain-gauge plethysmogram and $k_l$ is the constant.

The stress exerted on the arterial wall $F(t)$ is expressed by the arterial pressure $P_b(t)$ given by equation (3). And the displacement of the arterial wall $r(t)$ is represented by the strain-gauge plethysmogram $P_l(t)$ in (4). The arterial wall impedance parameters can be estimated by using the least square method from the measured $P_b(t)$ and $P_l(t)$. the vascular dynamic characteristics can be derived as follows:

$$dP_b(t) = \tilde{B} d\dot{P}_l(t) + \tilde{K} dP_l(t) \tag{5}$$

where the parameters, stiffness $\tilde{K}$ and viscosity $\tilde{B}$ correspond to the viscoelastic properties of the arterial wall in the measured part.

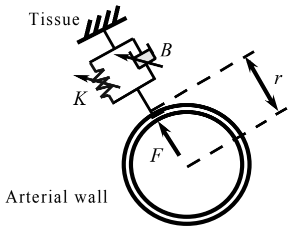

Fig. 1 Arterial impedance model

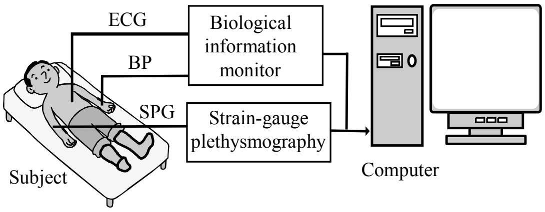

Fig. 2 Experimental setup for measurement

## III. REACTIVE HYPEREMIA EXPERIMENTS

In order to investigate the validity of the proposed method, we conducted reactive hyperemia experiments. Endothelial dysfunction is a major risk factor for atherosclerosis, and endothelial function in aging tends to be impaired [13]. We therefore attempted to assess the difference in response during reactive hyperemia between the young and the elderly, and Fig. 2 illustrates the experimental setup. A blood pressure cuff was placed around the upper right arm, and inflated to 50 mmHg above systolic pressure by a rapid cuff inflator (E20, DE Hokanson). The strain-gauge connec- ted to a plethysmograph (EC6, DE Hokanson) was placed around the right forearm, and continuous blood pressure was measured from the left arm using a biological information monitor (BP-608, Omron Healthcare). The forearm was then elevated 10 cm above the heart level as necessary to facilitate venous drainage, and electrocardiogram (*ECG*) was measured to recognize the cardiac cycle. All signals were stored on a personal computer after AD transformation with a sampling time of 10 ms. In total, 4 young (22-24 years) and 3 elderly (50-59 years) healthy subjects were recruited. The measurements, which were repeated three times, were performed in a resting state and in an ischemic state by inflation of the brachial cuff and after cuff deflation, each for five minutes. All subjects rested for at least 10 minutes prior to the measurement. After reactive hyperemia measurement, PWV was assessed with an automatic pulse wave analysis device (BP-203 RPEII, Colin Co). The measured values of each subject were taken as the average of the three reactive hyperemia trials.

## IV. EXPERIMENTAL RESULTS

In the experiment, *ECG*, $P_b$ and strain-gauge plethysmogram signals were measured. Since factors such as motion of the patient's hand may affect the measured signals, digital filters were used to regulate the frequency characteristics of the signals. The electrocardiogram was filtered out through a second-order infinite impulse response (IIR) band-pass filter (5-40 Hz), the blood pressure was filtered through a second-order IIR band-pass filter (0.5-8 Hz), and the strain-gauge plethysmogram was filtered through a second-order IIR band-pass filter (0.5-8 Hz).

Fig. 3 shows an example of the experimental results for Subject A, plotting the arterial pressure $P_b$, the amplitude of

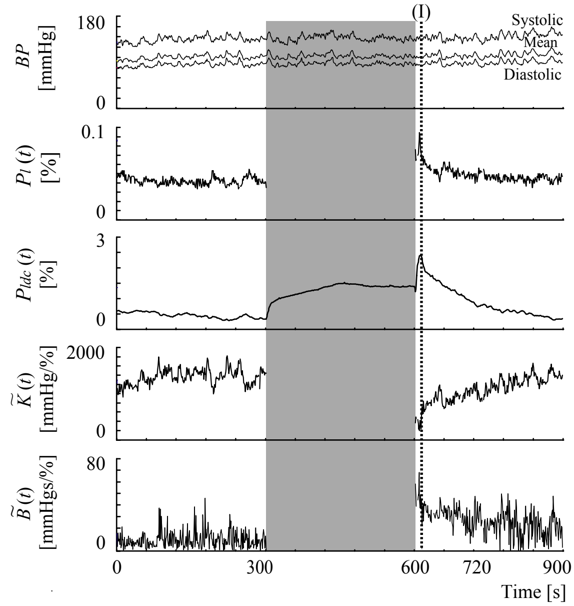

Fig. 3 An example of results in reactive hyperemia

strain-gauge plethysmogram $P_{lac}$, the direct component of strain-gauge plethysmogram $P_{ldc}$, stiffness $\widetilde{K}$ and viscosity $\widetilde{B}$ in order from the top. The shaded areas correspond to the ischemic period. The results show no remarkable change in the blood pressure, but both the amplitude and the direct component of strain-gauge plethysmogram ($P_{lac}$, $P_{ldc}$), increased relative to resting values 10-15 s after cuff deflation ((I) in Fig. 3) and gradually returned to the resting value. On the other hand, $\widetilde{K}$ decreased to the minimum relative to the resting value 10-15 s after cuff deflation ((I) in Fig. 3) and gradually returned to the resting value. $\widetilde{B}$ increased to the peak relative to the resting value about 5 s after cuff deflation ((I) in Fig. 3) and gradually returned to the resting value.

Fig. 4 and Fig. 5 shows the results for the 4 young and 3 elderly with figures (a) and (b) representing the time course of $\widetilde{K}$ and $\widetilde{B}$ respectively. Each time-course curve is the mean value for the three trials of each subject. In the graph, the baseline is the average of the resting values (0-300 s), and each value after cuff deflation (600-900 s) is the average during 5 s. The results show that each $\widetilde{K}$ reached the minimum about 10 s after cuff deflation ((I) in Fig. 4(a) and Fig. 5(a)) and then returned to the baseline. Each $\widetilde{B}$ reached the maximum about 5 s after cuff deflation ((II) in Fig. 4(b) and Fig. 5(b)) and then returned to the baseline. This change was consistent for all subjects.

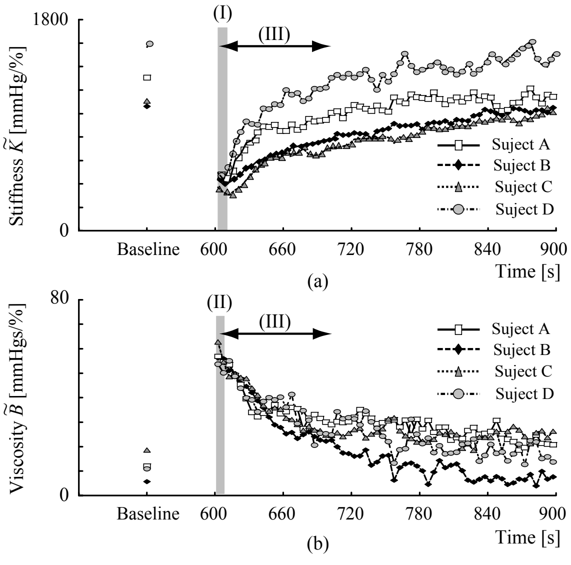

Fig. 4 Time courses of (a) Stiffness and (b) Viscosity in young

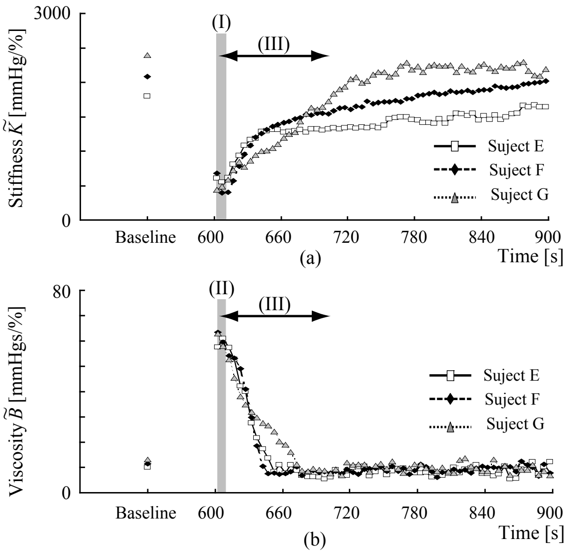

Fig. 5 Time courses of (a) Stiffness and (b) Viscosity in elderly

From the Fig. 4(a) and Fig. 5(a)), $\widetilde{K}$ shows similar changes between the young and the elderly. By contrast, $\widetilde{B}$ shows greater values for young than for elderly after cuff deflation 600 to 700 s area ((III) in Fig. 4(b) and Fig. 5(b)). Therefore, in order to investigate the difference between the young and the elderly were compared with two paired t-tests, and the values $\widetilde{B}$ for young were significantly higher than for elderly from 600 to 700 s ($P < 0.001$).

Table 1 Differences between young and elderly subjects

| | Young (Mean ± SD) | Elderly (Mean ± SD) | P * |
|---|---|---|---|
| Age [years] | 23 ± 1 | 55 ± 4 | 0.001 |
| Area of normalized $\widetilde{K}$ | 195 ± 25 | 268 ± 53 | 0.058 |
| Area of normalized $\widetilde{B}$ | 64.1 ± 4.5 | 37.7 ± 3.6 | 0.001 |
| PWV [cm/s] | 1112 ± 112 | 1607 ± 499 | 0.11 |

* Significance level for two-tailed paired *t*-test of young and elderly

## V. DISCUSSION

The results of Figs. 5 and 6 confirm a consistent change with all subjects. They also show that, before returning to the baseline, $\widetilde{K}$ reached the minimum 10 s after cuff deflation, $\widetilde{B}$ reached the maximum 5 s after cuff deflation. In conventional studies, the changes during reactive hyperemia are increased blood flow (10 s after cuff deflation) and flow-mediated dilation (about 50 s after cuff deflation) [9]. Here, the period with the maximum change in the proposed method ((I) and (II) in Figs. 5 and 6) corresponds to the period with the maximum increased blood flow reported in previous studies. Moreover, the proposed method measures the characteristics of vessels presented in the forearm.

The comparison using the two-tailed paired t-test between the young and the elderly of the viscoelastic indices and PWV are shown in Table 1. The difference between the young and the elderly for the time course after cuff deflation, the areas of $\widetilde{K}_{rate}$ and $\widetilde{B}_{rate}$ are defined by calculating their integrals between 600 and 700 s. The results show a significant difference ($P < 0.001$) in viscosity. For this reason, the proposed viscoelastic indices represent the modification of arterial mechanical properties derived from flow-mediated dilation, and the strain-gauge plethysmogram represents the increase of the forearm circumference derived from flow-mediated dilation. On the other hand, PWV showed no significant difference ($P = 0.11$).

From these results, viscosity and the strain-gauge plethysmogram show a significant difference between the young and the elderly. It is thought that the changes in these proposed indices after cuff deflation represent the flow-mediated dilation response because previous studies [13] showed that flow-mediated dilation was significantly impaired in the group of the elderly as a whole compared with the young. It was therefore confirmed that the proposed method has the potential to evaluate endothelial function.

## VI. CONCLUSIONS

In this study, we proposed the new method to evaluate response in reactive hyperemia using viscoelastic indices measured by strain-gauge plethysmography, and then conducted reactive hyperemia experiments to investigate the validity of the proposed method. The results show that, before returning to resting values, $\widetilde{K}$ reached the minimum 10 s after cuff deflation, $\widetilde{B}$ reached the maximum 5 s after cuff deflation with the consistent tendency through all subjects. Additionally, we attempt to assess the difference in response during reactive hyperemia between the young and the elderly, and confirmed the significant difference with time courses of proposed stiffness $\widetilde{K}$ and viscosity $\widetilde{B}$. Our proposed technique is definitely less expensive both from hardware and manpower points of view.

Future research will be directed to assess the additional availability of the proposed method to evaluate the endothelium function by the comparison with an ultrasonic method and the measurement with subjects of various ages. Furthermore, measurement setup will be improved for the robust and comfortable measurement of reactive hyperemia using the strain-gauge plethysmography.

## REFERENCES

1. R.Ross: Atherosclerosis-an inflammatory disease. N Engl J Med, Vol. 340, pp.115-126, 1999.
2. J C, Bramwell, A V. Hill: Velocity of transmission of the pulse wave and elasticity of arteries. Lancet, Vol.1, pp.891-892, 1922.
3. Blacher J, Pannier B, Guerin AP, et al: Carotid arterial stiffness as a predictor of cardiovascular and all-cause mortality in end-stage renal disease. Hypertension, Vol.32, pp.570-574, 1998.
4. C. Giannattasio, M. Failla, A A. Mangoni, L Scandola, N Fraschini, G Mancia: Evaluation of arterial compliance in humans. Clin Exp Hypertens, Vol. 18, pp.347-362, 1996.
5. P.M.Vanhoutte: Endothelium and control of vascular function. Hypertension, Vol.13, pp.658-667, 1989.
6. T.F.Lucher: Imbalance of endothelium-derived relaxing and contracting factors. Am J Hypertens, 3(4), pp.317-330, 1990.
7. Y.Higashi, S.Sasaki, K.Nakagawa, et al: Endothelial function and oxidative stress in renovascular hypertension. N Engl J Med, Vol.346, pp.1954-1962, 2002.
8. E.A.Anderson, A.L.Mark: Flow-mediated and reflex changes in large peripheral artery tone in humans. Circulation, Vol.79, pp.93-100, 1989.
9. M C. Corretti, T J. Anderson, et al: Guidelines for the ultrasound assessment of endothelial-dependent flow-mediated vasodilation of the brachial artery. J Am Coll Cardiol, Vol.39, pp. 257-265, 2002.
10. D. Baldassarre, M. Amato, C. Palombo, C. Morizzo, et al: Time course of forearm arterial compliance changes during reactive hyperemia. Am J Physiol Heart Circ Physiol, Vol.281, pp. H1093-H1103, 2001.
11. A.Sakane, K.Shiba, T.Tsuji, et al: Non-invasive monitoring of arterial wall impedance. Proc. of the First International Conference on Complex Medical Engineering, pp. 984-989, 2005.

12. K Shiba, U Terao, T Tsuji, M Yoshizumi, Y Higashi, K Nishioka: Estimation Arterial Wall Impedance using a Strain-gauge Plethysmogram. Transaction of the Japanese Society for Medical and Biological Engineering, Vol. 45, No. 1, pp. 55-62, 2007.
13. D S.Celermajer, K E. Sorensen, et al: Non-invasive detection of endothelial dysfunction in children and adults at risk of atherosclerosis. Lancet, Vol. 340, Issue. 8828, pp. 1111-1115, 1992.

Author: ABDUGHENI KUTLUK
Institute: Hiroshima University
Street: 4 - 1 Kagamiyama 1-chome
City: Higashi-Hiroshima City
Country: Japan
Email: akutluk@bsys.hiroshima-u.ac.jp