Simultaneous Ultrasonic Measurement of Vascular Flow-mediated Dilation and Quantitative Wall Shear Stress for Endothelium Function Assessments

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***Abstract*— For early detection of arteriosclerosis, the evaluation of endothelium function has attracted attention in recent years. Flow-mediated dilation (FMD) is the blood vessel dilation due to the smooth muscle relaxation, which is caused by the effect that the wall shear stress (WSS) on the endothelium induces the nitric oxide (NO) production. Therefore, for accurately evaluating the endothelial function, the quantitative %FMD and WSS must be measured simultaneously. In this study, with the aim of assessing the endothelium function accurately, a novel ultrasound system for simultaneous measurements of %FMD and quantitative WSS is presented. A feature of this system is to combine the %FMD and the WSS obtained by considering the ultrasonically-estimated blood viscosity. The system performance was verified through in vitro experiment using bovine blood and in vivo measurement for healthy volunteers. These results revealed the effectiveness of developed system.**

Keywords - flow-mediated dilation; wall shear stress; blood viscosity; ultrasound; endothelium function

I. INTRODUCTION

For early detection of arteriosclerosis, the evaluation of endothelium function has attracted attention in recent years. One method for evaluating endothelium function is the flow-mediated dilation (FMD) measurement, as shown in Fig. 1(a). In the typical FMD measurement, blood vessel diameters dilating after avascularization during 5 minutes are measured (Fig. 1(c)), and compared with that before avascularization (resting phase; Fig. 1(b)). This dilating rate is referred to as %FMD, which is an evaluation index for the endothelium function. Here, one of stimulus sources for activating endothelium function is the wall shear stress (WSS). The WSS applied on the endothelium induces nitric oxide (NO) production, and the NO relaxes smooth muscle. Thus, the WSS is an important parameter for evaluating endothelium function. However, conventional equipments for the %FMD measurement measure only the blood vessel dilation.

Therefore, for accurate evaluation of endothelial function, quantitative WSS and %FMD must be measured simultaneously. In this study, a novel ultrasonic evaluation system of endothelium function based on simultaneous measurements of %FMD and WSS is presented. The system performance was verified through in vitro experiment using bovine blood and in vivo measurement for healthy volunteers.

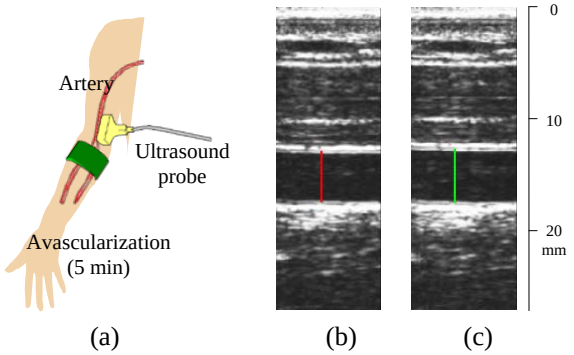

Figure 1. Ultrasonic FMD measurement. (a) A scheme of ultrasonic FMD measurement, (b) blood vessel diameter in resting phase, and (c) blood vessel diameter after releasing avascularization.

II. A DEVELOPED SYSTEM

In the developed system, it is important to simultaneously measure the %FMD and WSS on the central sagittal section of blood vessel. Therefore, we used a H letter-typed ultrasound probe connected to the ultrasound diagnosis equipment (UNEXEF, UNEX, Japan), as shown in Fig. 2. This probe has center frequencies of 8 MHz for blood flow measurement and 10 MHz for vessel imaging and diameter measurement. Moreover, in order to identify the central sagittal section, three apertures for two short axis views and one sagittal view are mounted on the probe. By this configuration, precise positioning of the probe on the central sagittal section, and accurate measurements of %FMD and WSS are available. In the %FMD measurement, forearm artery parallel to the probe surface is often the target for measurement. Therefore, the oblique-incidence beam is available for blood flow measurement in the forearm artery, by using the beam steering technique. Here, the beam steering angle is fixed to 15 degrees.

In the following subsections, methods for measuring %FMD and WSS are described.

A. %FMD measurement

Blood vessel diameter is detected as the inner diameter of blood vessel. Fig. 3 shows the echo signals from the vessel walls. Thus, the vessel walls can easily be detected as echoes with high intensity in the ultrasound image. Therefore, by tracking the high intensity part, the temporal trend of blood vessel diameter can be measured and %FMD is calculated.

 ISBN: 978-1-61208-260-8

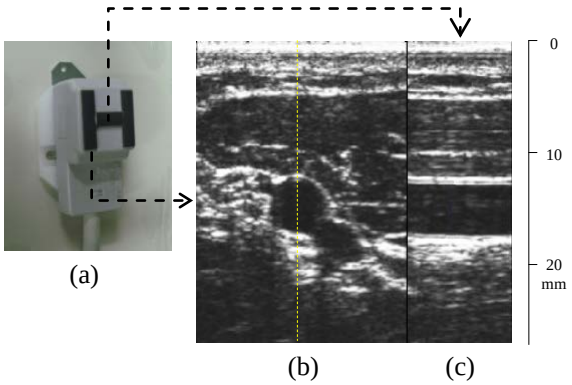

Figure 2. Ultrasound probe for FMD diagnosis. (a) H letter-typed ultrasound probe, (b) short axis view and (c) sagittal view of forearm artery.

B. *Wall shear stress measurement*

Shear stress is defined as a product of viscosity and shear rate. Therefore, the viscosity and shear rate are necessary for obtaining the quantitative shear stress.

1) SV curve: Fig. 4 shows an example of shear rate-viscosity (SV) curve in whole blood [1]. Since the whole blood is the non-Newtonian fluid, viscosity is higher in the lower range of shear rate and lower in the higher range of shear rate, as shown in Fig. 4. Although a set of methods for obtaining SV curve has presented in the past works [2-4], the methods are described briefly as follows. The 2-D velocity vector distribution is obtained by Doppler measurement and incompressible condition, and the viscosity coefficient is estimated by substituting the velocity vector distribution into the Navier-Stokes equations. In this methodology, non-Newtonian property of blood should be considered. First, to consider this property, intravascular area is divided into several ROIs. Next, in each ROI, kinematic viscosity coefficient is calculated, based on Navier-Stokes equations [2].

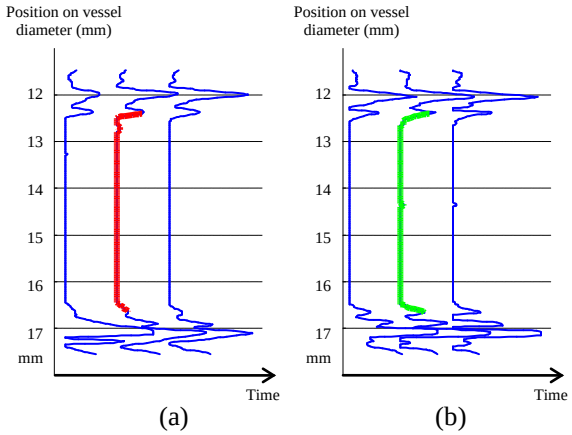

Figure 3. Inner diameter measurements of forearm artery using echoes. (a) Thick solid line indicates the diameter in resting phase. (b) Thick solid line indicates the maximum diameter after releasing avascularization.

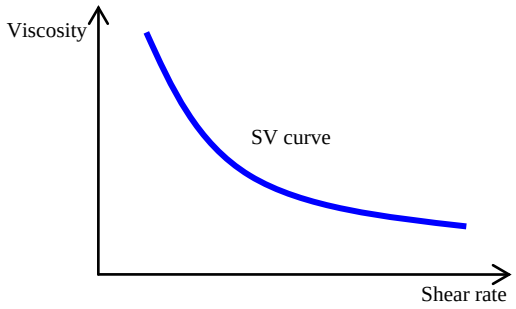

Figure 4. SV curve for obtaining quantitative wall shear stress.

Thirdly, in each ROI, shear rate is also calculated by spatially-differentiating the 2-D velocity vector distribution in blood flow [3]. Finally, shear stress is calculated in each ROI. Viscosity, shear rate and shear stress can be estimated by using only the 2-D velocity vector distribution in each ROI. Therefore, for gathering all ROIs, a SV curve is reconstructed [4].

2) Wall shear stress calculation using SV curve: The SV curve can be modeled as follows.

$$\mu = \alpha \cdot e^{\beta} \qquad (1)$$

Here, μ and e indicate viscosity and shear rate. α and β are regarded as constants determined by only the hematocrit. Based on Eq.(1), WSS σ_{wall} can be obtained as follows.

$$\sigma_{wall} = \alpha \cdot (e_{wall})^{\beta+1} \qquad (2)$$

where e_{wall} indicates the wall shear rate (WSR), that is, the shear rate on the vessel wall. If α and β have already calculated by modeling the SV curve using viscosity and shear rate data in resting phase, the WSS trend can be calculated by measuring the only WSR e_{wall}. Therefore, the WSS can be obtained in real time, if Eq.(2) is used.

III. In Vitro Experiments

Fig. 5 shows an in vitro experimental setup for verifying the system performance. Circulation system using silicone tube with a diameter of 4 mm was constructed. Mean velocity of flow is adjusted by a pump (31.6 cm/s). Fresh bovine blood with non-Newtonian property was circulated in the silicone tube at 37 degrees C. Hematocrit of the blood was 25 %.

Fig. 6(a) shows the comparison between results of ultrasonic measurement and viscometer in the SV curve reconstructions. Both plots exhibited similar property. Fig. 6(b) shows the comparison between the reference (true) shear stress and the measured shear stress. Here, the reference shear stress was obtained by multiplying viscosity by shear rate measured by the viscometer.

As the result, the shear stress obtained by the developed system coincides well with that obtained by the viscometer.

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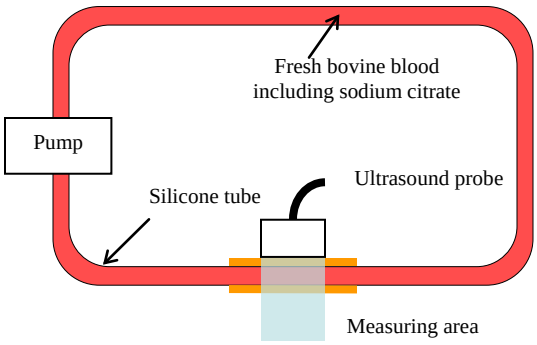

Figure 5. Experimental setup using fresh bovine blood.

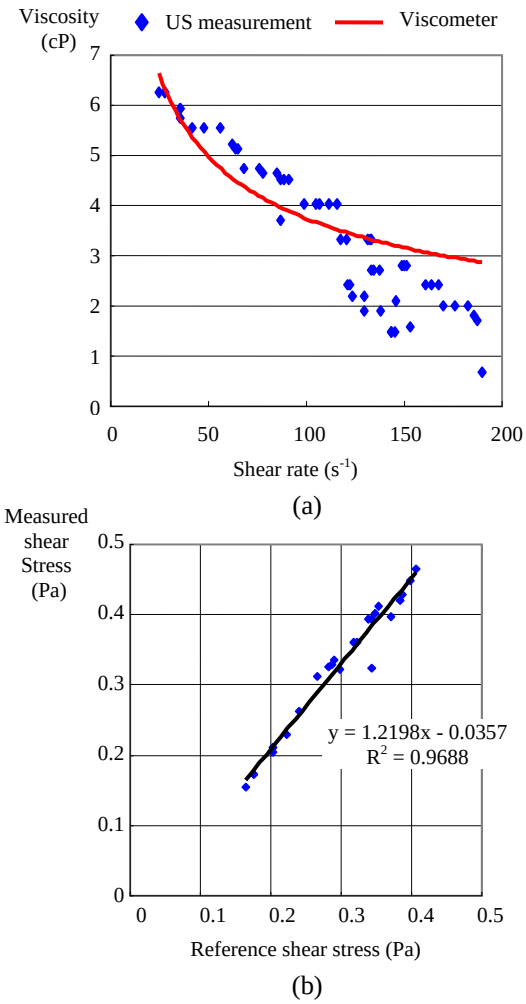

Figure 6. Experimental results using bovine blood. (a) Reconstructed SV curve, and (b) comparison between measured and reference shear stresses.

IV. In Vivo Measurement

As the next verification, in vivo measurements with the healthy male subjects were conducted. The echo data were acquired by using the developed system, and the temporal trends of blood vessel diameter and WSS were obtained.

A. Protocol

The measurement protocol is described as follows.

The simultaneous trends of the vessel diameter and WSS were acquired during 10 seconds in resting phase, and then the trends were acquired during 5 minutes at the avascularization phase. Finally, the trends were acquired during about 2 minutes after releasing the avascularization.

B. Results

Fig. 7 shows the intravascular imaging of shear rate, viscosity, and shear stress, respectively. Fig. 7(a)-(c) indicate images in resting phase and Fig. 7(d)-(f) indicate images after releasing avascularization. While the shear rate exhibits the maximum values near the tube wall, the viscosity at the tube center shows the maximum value because the shear rate at the tube center is close to zero. In addition, obviously, the WSS after releasing avascularization is larger than that before avascularization.

Fig. 8(a) and (b) show the examples of inner diameter and WSS trends, respectively. Left plots indicate the trends in resting phase, and right plots indicate the trends after releasing the avascularization. After releasing avascularization, the vessel diameter gradually expands and exhibits the maximum value after about 60 seconds in the post-avascularization phase. On the other hand, the WSS exhibits the maximum value immediately after releasing avascularization.

In order to characterize these properties, the following %FMD and IR_{SS} were introduced on a trial basis.

$$\%FMD = 100 \times \frac{\Delta d}{d_{rest}} \quad (3)$$

$$IR_{SS} = \frac{SS_{max}}{SS_{rest}} \quad (4)$$

where Δd indicates the difference between the mean diameter d_{rest} in resting phase and the maximum diameter in the post-avascularization phase. The IR_{SS} (Increasing rate of shear stress) means the ratio of the maximum value SS_{max} in the post-avascularization phase to the mean value SS_{rest} in resting phase.

The correlation between %FMD and IR_{SS} for 4 subjects is presented in Fig. 9. High correlation between them was observed. Similarly, IR can also be calculated for mean velocity (MV), maximum velocity (MAXV), flow volume (FV), wall shear rate (WSR), and viscosity (VSC). Therefore, the result of each IR is also presented in Fig. 9. Based on this comparison, the highest correlation between the %FMD and WSS is suggested. Although this suggestion is still preliminary, it is expected that the quantitative WSS is available based on the SV curve in resting phase, and a quantitative evaluation of endothelial function is possible based on the relationship between the flow-mediated dilation and wall shear stress measured by the developed system.

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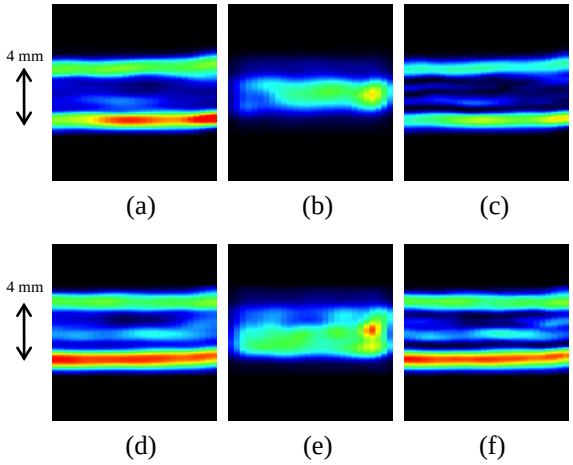

Figure 7. Intravascular imaging of shear rate ((a) and (d)), viscosity ((b) and (e)), and shear stress ((c) and (f)), respectively. (a)-(c) indicate images at rest phase and (d)-(f) indicate images after releasing avascularization.

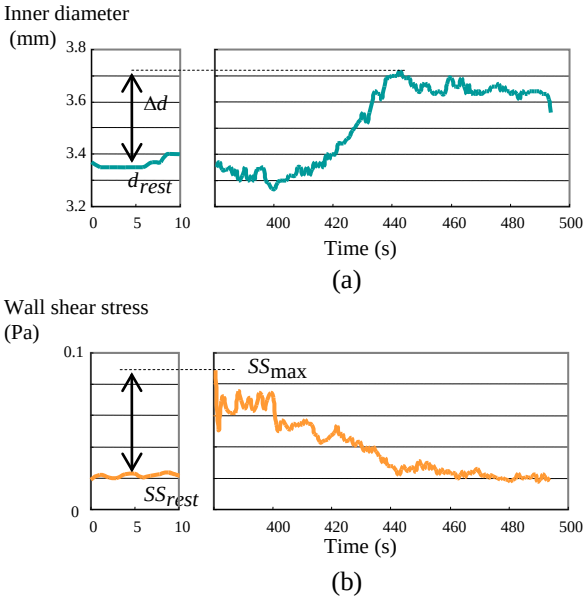

Figure 8. Examples of (a)vessel diameter and (b)WSS trends.

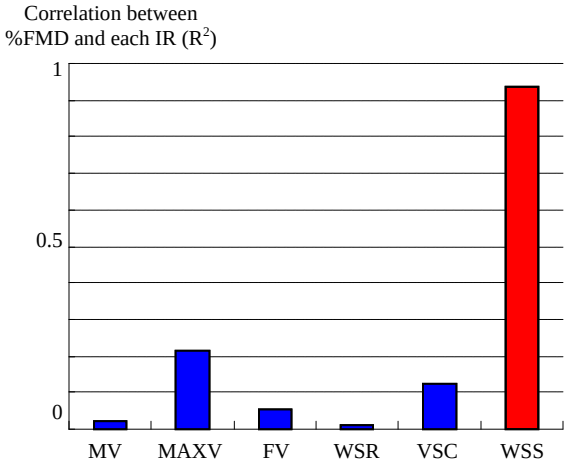

Figure 9. Correlation between %FMD and each IR.

V. CONCLUSIONS

In this study, a novel ultrasound system for evaluating endothelial function based on simultaneous measurements of flow-mediated dilation and wall shear stress was developed. In vitro experiment using fresh bovine blood and in vivo measurement for healthy volunteers revealed the effectiveness of the developed system.

In future work, the feasibility in clinical use will be investigated by increasing the number of cases.

ACKNOWLEDGMENT

This work was supported by a Grant-in-Aid for Scientific Research C (22500449) from Japan Society for the Promotion of Science.

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 ISBN: 978-1-61208-260-8