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The Importance of Assessment of Endothelial Function According to the Time Course of Flow-mediated Dilation of the Brachial Artery

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Ultrasonography is widely used to evaluate atherosclerosis. Therefore, many ultrasound parameters exist, each with its own clinical implications. Many reports have shown that these ultrasound parameters are useful for evaluating the progression of atherosclerosis or the risk of cardiovascular disease in healthy persons and in persons with cardiovascular risk factors. Ultrasound parameters are categorized as either structural or functional parameters. Particularly in the early stage of atherosclerosis, functional parameters are useful for evaluating the risk of the further development of atherosclerosis. We have also reported that the pulsatility index of the brachial artery is related to atherothrombotic infarctions in high-risk elderly subjects[1].

Next, we studied flow-mediated dilation (FMD) as a functional parameter in the early stage of atherosclerosis. FMD is believed to be associated with endothelial nitric oxide (NO) synthesis. Furthermore, NO has the ability to prevent progression in the early stage of atherosclerosis. Guideline for FMD measurement have already been established[2]. FMD has been defined as the rate of brachial artery vasodilation 60 seconds after a sphygmomanometric cuff is deflated after being inflated for 5 minutes to a pressure 50 mmHg greater than the systolic blood pressure. In several prospective studies, FMD measured according to these guidelines was shown to be a predictor of cardiovascular disease[3,4]. We have also already reported a cross-sectional study in which FMD of the brachial artery based on this guideline was found to be associated with diabetic retinopathy in elderly persons who had diabetes but no cardiovascular disease[5]. However, because these guidelines are based on the results of a study of healthy young adults, it remains to be seen whether these guidelines can be applied to elderly persons or persons with cardiovascular risk factors such as diabetes, hypertension, and dyslipidemia. Furthermore, because vasodilation occurred continuously for several minutes after sphygmomanometric cuff deflation, the time course of FMD of the brachial artery must be assessed.

Therefore, we evaluated the time course of flow-mediated dilation of the brachial artery with a UNEXEF18G (UNEX Corp., Nagoya, Japan), which can continuously measure brachial artery vasodilation. Vasodilation measured 60 seconds after sphygmomanometric cuff deflation on the basis of the International Brachial Artery Reactivity Task Force guidelines designated FMD60[2], and the maximum vasodilation obtained during continuous measurement of the brachial artery was designated MaxFMD. Furthermore, the elapsed time from sphygmomanometric cuff deflation to MaxFMD was designated peak time (PT). Using these parameters, we evaluated the relationship between the time course of flow-mediated dilation of the brachial artery and aging, diabetes, hypertension, and dyslipidemia.

Regarding the effect of age-related alteration of the time course of FMD of the brachial artery, we showed in

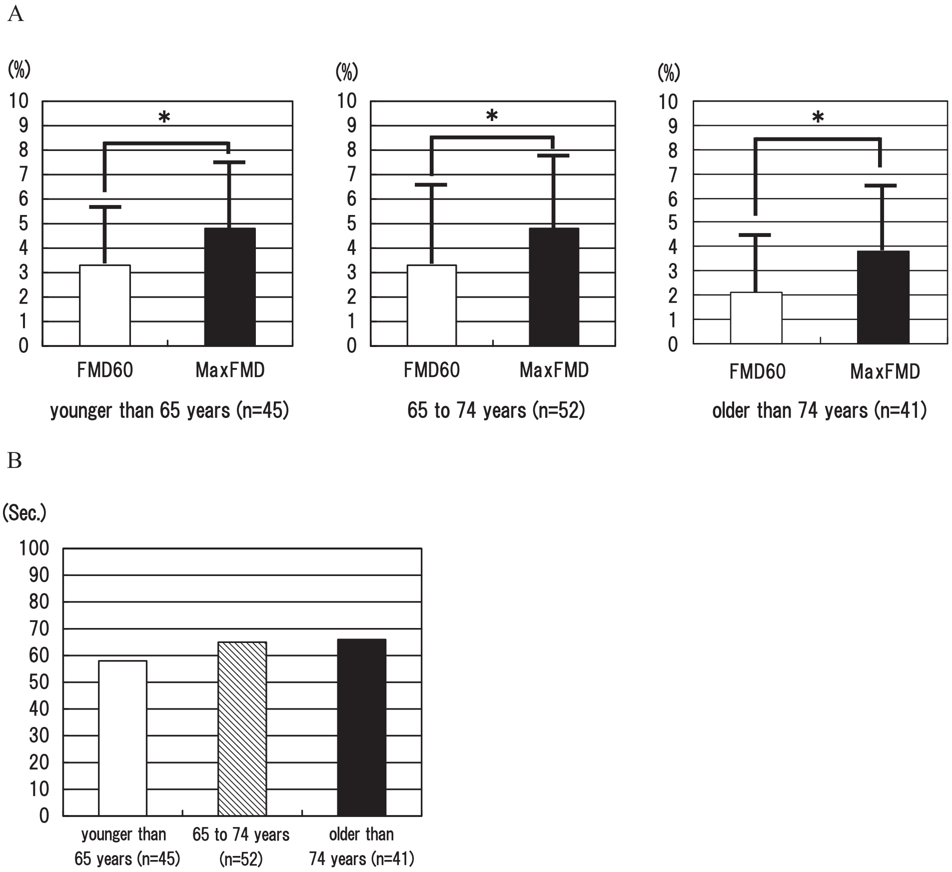

Fig. 1 Comparison of FMD60, MaxFMD, and PT between each pair age groups. There were significant differences between FMD60 and MaxFMD in each age group (A) . It was also shown that PT became longer, but not significantly, correlation with aging (B). *: P<0.001 by Student's t-test.

a cross-sectional study that MaxFMD was significantly higher than FMD60 **(Fig. 1A)** in people younger than 65 years (n=45), 65 to 74 years (n=52), or older than 74 years of age (n=41) with diabetes, hypertension, or dyslipidemia. This result suggests that MaxFMD can be used to evaluate endothelial function more accurately in both young adults and the elderly than FMD60 can. Furthermore, it was also shown that PT was prolonged, but not significantly, in correlation with aging **(Fig. 1B)**.

Regarding gender difference in relation to changes in FMD resulting from aging (younger than 65 years, 65 to 74 years, or older than 74 years), the decrease in MaxFMD in women (6.79 ± 2.81% vs. 5.26 ± 2.79% vs. 4.41 ± 2.54%; $P<0.01$) was more affected by aging than that in men. Moreover, changes in PT in men seemed to be more affected by aging (59.7 ± 19.3 seconds vs. 63.3 ± 21.4 seconds vs. 79.8 ± 21.7 seconds; $P<0.01$) than those in women (52.0 ± 14.0 seconds vs. 65.5 ± 24.5 seconds vs. 67.3 ± 20.7 seconds; $P<0.05$). These results suggest that age-related alterations of endothelial function differ between men and women in terms of the time course of flow-mediated dilation of the brachial artery.

Concerning the relationship between the time course of flow-mediated dilation of the brachial artery and the clustering of diabetes and hypertension, we showed that MaxFMD showed a significantly higher correlation with the number of these complications than FMD60 (**Table 1** and **Fig. 2**). Furthermore, concerning the effect of statin use on endothelial function in a patient with dyslipidemia, MaxFMD was significantly improved (3.13 ± 1.48% vs. 6.37 ± 4.06%; $P<0.05$) and PT at an average of 4 months after statin use (93.7 ± 36.8 seconds) was significantly longer than that at baseline (59.0 ± 34.4 seconds; $P<0.05$).

On the basis of these results, we intend to establish methods of improving endothelial function, and we aim to establish an effective method for preventing cardiovascular disease.

Table 1 t-value, β Co-efficient, and P-value of group number for predicting FMD60 and MaxFMD adjusted for clinical characteristics

	FMD60			MaxFMD		
	t-value	β Co-efficient (95%CI)	P-value	t-value	β Co-efficient (95%CI)	P-value
Group number						
univariate	− 1.671	− 0.157 (− 0.803 − 0.068)	0.098	− 2.183	− 0.203 (− 0.960 − − 0.046)	0.031
multivariate	− 2.112	− 0.215 (− 0.988 − − 0.031)	0.037	− 2.769	− 0.268 (− 1.154 − − 0.191)	0.007

multivariate; adjusted for gender, age, body mass index, smoking habit, systolic blood pressure, statin use, T-CHOL, uric acid, serum creatinine, and HbA_{1c}.

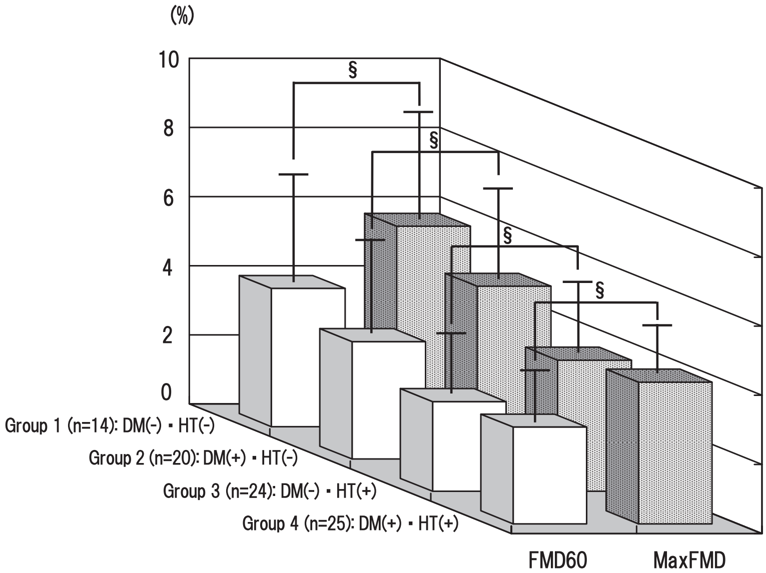

Fig. 2 Comparison of FMD60 and Max FMD of groups with and without diabetes or hypertension. There were significant differences between FMD 60 and MaxFMD in every group. §: P<0.01 by Wilcoxon test.

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