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Reliability of measurement of endothelial function across multiple institutions and establishment of reference values in Japanese

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ABSTRACT

Aims: For the standardization of flow-mediated vasodilatation (FMD) assessment as a clinical tool, validation of its reliability across multiple institutions and the establishment of normal/reference values based on reliable data from multiple institutions are needed.
Methods and results: In Study 1, assessment of FMD (scan recording and analysis) using an ultrasonographic semi-automatic measuring system (sFMD) was conducted at 18 participating institutions (sFMD-INST) (n = 981). All of the brachial arterial scans were also analyzed at a core laboratory (sFMD-COLB). After 111 subjects with inadequate sFMD recordings were excluded (n = 880), the correlation between the sFMD-INST and sFMD-COLB improved from R = 0.725 to R = 0.838 ($p < 0.001$). In Study 2, based on good-quality sFMD data obtained from 6660 subjects without cardiovascular disease (CVD) and 729 subjects with CVD from 27 institutions, reference values of sFMD are proposed by the Framingham risk score (FRS)-based risk categories and according to gender and age. The receiver-operating characteristic curve analysis revealed a significant power of sFMD values in reference ranges to discriminate between subjects with and without CVD (e.g., area under curve = 0.64 in the FRS-low risk group).

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Conclusions: When the analysis was limited to cases with clear sFMD recordings, the reliability of the sFMD assessment (scan and its analysis) conducted in individual institutions appeared to be acceptable. Reference sFMD values (lower cuff occlusion) for the Japanese population are proposed based on reliable data derived from multiple institutions, and the reference values may identify patients without advanced vascular damage.

1. Introduction

Although assessment of flow-mediated vasodilatation of the brachial artery (FMD) has potential as a useful clinical tool in the clinical management of patients with cardiovascular (CV) disease and/or its risk factors [1–5], highly skilled sonographers are required for the accurate assessment of FMD (brachial artery scan recording and analysis) [6–8]. Therefore, in most multi-center studies conducted to date, the brachial artery scans obtained in each participating institution have been analyzed at a core laboratory (COLB) [4,5,7,8]. For the standardization of FMD assessment as a clinical tool, validation of the FMD assessment method across multiple institutions and the establishment of normal/reference FMD values based on reliable data obtained from multiple institutions fulfilling the criteria for reliability of the assessment method are needed.

Recently, an ultrasound instrument dedicated to FMD assessment, equipped with both an on-line computer-assisted semi-automatic analysis software to measure the FMD and accessories for fixing the measured arm and ultrasound probe, has been introduced for commercial use [9–12]. A major advantage of this device is that it allows automatic direct A-mode signal analysis of changes of the vessel diameter during the FMD assessment procedure in real time under stereotaxic guidance based on 2-dimensional B-mode images for maintenance of the appropriate position for the vessel interfaces recording [9–12]. Thus, this device might be helpful for the standardization of FMD assessment via facilitating the assessment at individual institutions and improving the quality of analysis of the FMD scan records at each institution.

The FMD-J study was a prospective multicenter study conducted to examine the usefulness of FMD assessment using a semi-automatic device at individual institutions in the management of patients at risk for CV disease [9]. The present study was conducted as an extension of the FMD-J study to examine the following for the standardization of FMD assessment; Study 1) To validate the reliability of FMD assessment (scan and its analysis) using the aforementioned semi-automatic device at individual participant institutions as compared to analysis of the brachial artery scans at a COLB; Study 2) if the reliability was found to be acceptable, the FMD data obtained in the FMD-J study and in the previously reported Flow-mediated Dilatation Japan Registry study (FDR study) [11,12], in which the FMD assessment was conducted using the same protocol as that in the FMD-J study, would be collected to obtain the reference values of FMD. In addition, a receiver-operating-characteristic curve (ROC) analysis was carried out to evaluate the discriminative power of FMD in the reference ranges for the presence of CV disease (i.e., to discriminate between subjects with and without CV disease).

2. Methods

The study protocols conform to the principles of the Declaration of Helsinki, and have been approved by the Ethics Committee of Tokyo Medical University (The core center of FMD-J study) (No. 2456) and also by the Ethics Committees of other each of the participating institutions. The written informed consent was obtained from all of the study participants before participation in the FMD-J study or the FDR study.

2.1. Study cohorts

The present studies were conducted in subjects derived from study cohorts of the FMD-J study (2 study cohorts for Study 1 and 4 study cohorts for Study 2) (Fig. 1). The FMD-J study included 3 study arms (Study A, Study B, and Study C) (Fig. 1).

The details of the study protocols and the subjects are described in Supplement file 1 and Reference 9. In the FDR study, all of the participants underwent annual health check-ups and assessment of FMD at one of 4 institutions (clinics/hospitals) affiliated to the following 3 institutions participating in the FMD-J study {Tokyo Medical University (COLB for the FMD-J study), National Defense Medical College, and Hiroshima University}. Some parts of the data from the FDR study have already been reported elsewhere [11,12]. The protocol for the assessment of FMD was the same in the FDR study as that in the FMD-J study, and the aforementioned semi-automatic device was used for the FMD assessment in all the subjects of the FDR study. In Study C (an arm of FMD-J study) and the FDR study, the FMD was measured at the time of the annual health check-up in the subjects, and the presence/absence of CV disease in the subjects (heart disease and/or cerebrovascular disease: the details were not described) was confirmed by a questionnaire.

2.2. Study design

2.2.1. Study 1: examination of the reliability of assessment of FMD at individual participant institutions

Some of the study subjects in Study A and Study B (arms of FMD-J study) (from 18 participating institutions) participated in Study 1 (Fig. 1). The results of assessment of the quality of the brachial artery scans and of the data analyses conducted at each institution were registered on the WEB. Each participant institution (18 institutions) was instructed to send the USB devices containing the brachial artery scans obtained during the assessment of FMD without the results of the data analysis to the COLB located in Tokyo Medical University, and the recordings were individually analyzed by a well-experienced reader at the COLB (FMD-COLB) without any information concerning the FMD data assessment at the participant institution. This well-experienced reader (T.S.) had the experience of conducting this analysis in more than 500 cases (as at the end of December 2010). Then, the results of the FMD assessment at each of the institutions registered on the WEB, and the FMD-COLB were compared (Study 1-1, Study 1-2, and 1-3).

2.2.2. Study 2: establishment of reference values of FMD and evaluation of the discriminative power of FMD for the presence of CV disease

In addition to the subjects from Study B, subjects without CV disease from Study C and the FDR study [11,12] were enrolled for