Low-flow mediated constriction incorporated indices as indicators of cardiovascular risk in smokers

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A B S T R A C T

Background and aims: Low-flow-mediated constriction (L-FMC), the endothelial response to reduced blood flow by forearm compression, is present in some smokers. The differences between smokers with and without L-FMC are unclear. It is also unknown whether flow-mediated total dilation (FMTD) or modified flow-mediated dilation (mFMD), both of which incorporate information concerning L-FMC, could be used to estimate cardiovascular risk. We sought to clarify the clinical factors associated with the presence of L-FMC in smokers according to sex and examine whether L-FMC incorporated indices would be better than a conventional index to estimate cardiovascular risk in smokers.
Methods: In total, 140 consecutive smokers (58 ± 13 years old) with no coronary heart disease and 48 non-smokers, who comprised the age- and sex-matched control group, were enrolled.
Results: L-FMC was demonstrated in 33.6% (47/140) and 25% (12/48) of the smokers and non-smokers, respectively. In male smokers, the predictors of the presence of L-FMC were age ($p = 0.014$), body mass index (BMI) ($p = 0.045$), and baseline brachial arterial diameter (D_{base}) ($p = 0.048$). In female smokers, there were no predictors of the presence of L-FMC. The correlations between the Framingham risk score (FRS) and %FMTD ($r = -0.34$) and between FRS and %mFMD ($r = -0.33$) were stronger than that between FRS and conventional flow-mediated dilation (%cFMD) ($r = -0.20$).
Conclusions: Independent predictors of the presence of L-FMC were age, BMI, and D_{base} in male smokers. L-FMC incorporated indices may be good alternatives to cFMD to estimate cardiovascular risk.

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1. Introduction

Conventional flow-mediated dilation (cFMD) has been widely accepted as an indicator of cardiovascular risk [1—3], and its validity in predicting cardiovascular events has been described in many

previous studies [4—11]. Vasoconstriction during the low flow state, known as low-flow-mediated constriction (L-FMC), has been recently introduced, and its usefulness has been demonstrated in patients with cardiovascular risk [12]. Diminished L-FMC responses have been observed in patients with coronary artery disease [13] and heart failure [14]. Therefore, L-FMC is thought to reflect vascular health. cFMD is associated with endothelial nitric oxide production [15] and measures the ability of the endothelium to dilate when stimulated by an increase in shear stress. However, cFMD does not provide information regarding the vascular response to resting levels of shear stress [14]. L-FMC is the endothelial response to reduced blood flow by forearm compression, that is, resting levels of shear stress. L-FMC is induced by several factors such as the release of endothelin-1 or the inhibition of the

release of cyclooxygenase-dependent products and is an indicator of endothelial function [13,16,17]. Thus, novel indices such as flow-mediated total dilation (FMTD), which is the sum of cFMD and L-FMC, and the modified FMD (mFMD), both of which incorporate information concerning L-FMC, have been proposed, and their associations with cardiovascular risk have been examined [12,13].

Smoking causes ischemic heart disease as well as impairment of endothelial function in the general circulation, including the coronary circulation. Ischemic heart disease accounts for about 40% of all smoking-related deaths [18]. Therefore, smoking cessation remains the most important intervention in preventive and pre-emptive medicine [19]. Although constriction of the brachial artery during the low flow period of cuff occlusion has been demonstrated in smokers [20], vasomotor responses are influenced by many factors [13,16,17,21], and L-FMC has not been observed in all smokers [14,20]. The differences between smokers with L-FMC and those without L-FMC have not been fully investigated. It is also unknown whether L-FMC incorporated indices such as FMTD or mFMD should be applied in estimating cardiovascular risk in smokers.

The present study aimed to clarify the clinical factors associated with the presence of L-FMC in smokers according to sex and examine whether L-FMC incorporated indices, FMTD or mFMD, would be better than a conventional index, cFMD, to evaluate cardiovascular risk in smokers.

2. Materials and methods

2.1. Study population

From April 2010 to March 2014, a total of 140 consecutive smokers (mean ± SD age, 58 ± 13 years) with no evident coronary heart disease (CHD) who were all current smokers and visited our smoking cessation outpatient department were enrolled in this study. In addition, a total of 48 age- and sex-matched non-smokers were also enrolled. Those who had never used cigarettes were defined as non-smokers.

The study protocols adhered to the Declaration of Helsinki, and were approved by the ethics committee of Osaka City University. Written informed consents were obtained from all 188 subjects.

2.2. Conventional flow-mediated dilation, low-flow-mediated constriction, flow-mediated total dilation, and modified flow-mediated dilation

The FMD measurements were performed once before smoking cessation according to the guidelines for FMD assessment [15]. All subjects were required to fast for at least 12 h; avoid heavy exercise for at least 24 h; not take caffeine containing products, alcohol, and antioxidant vitamins for at least 6 h; withhold all drugs for at least 12 h; and sleep soundly for at least 6 h the night before the measurement. Among premenopausal women, the examinations were performed during the menstrual cycle. All subjects were rested in the sitting position in a quiet temperature-controlled room (22–25 °C) for 15 min, and then placed in the supine position for 15 min. The measurement of the brachial artery was performed between 7:00 a.m. and 11:59 a.m.

We used a 10 MHz H-type probe that was equipped with a semiautomatic vessel wall tracking software and provided one longitudinal, two short-axis B mode images, and one processed A-mode lines-image of the brachial artery as previously described (UNEXEF; UNEX, Nagoya, Japan) [15]. Each B-mode vessel image was detected and tracked automatically from the two short-axis images, respectively, to select the most likely position of the brachial artery and to maintain positional stability of the A-mode

lines. Measurements of the vessel lumen on the longitudinal image were automatically performed using the A-mode lines. A total of 20 bilateral points on a designated position on a total of 41 A-mode lines were measured at every 0.15-mm interval. The measured values were averaged and demonstrated on the image. A B-mode edge detection method was designed to automatically maintain the same position of the brachial artery by adjusting the deviation of the probe position before and after compression at the forearm to achieve a precise measurement of the vessel lumen [15]. After determining the probe position where the clear baseline image was obtained, the forearm cuff was inflated up to at least 50 mmHg above the systolic blood pressure for 5 min. Longitudinal images of the brachial artery were continuously recorded from 0 s after the cuff inflation to 5 min after the cuff release.

L-FMC was defined as vasoconstriction during the last 30 s before the cuff release as previously described [13] (Fig. 1B). The presence of L-FMC in this study was defined as L-FMC ≥0.05 mm, based on our previous study, which demonstrated that the intra-observer mean difference for lumen diameter measurements was 0.021 ± 0.016 mm using the same ultrasound system [22]. %L-FMC was defined as the change from the resting baseline lumen diameter (D_{base}) to the minimum lumen diameter during the last 30 s before the cuff release (D_{min}) divided by D_{base}. %L-FMC was calculated using the following formula:

$$\%L - FMC = \frac{D_{min} - D_{base}}{D_{base}} \times 100$$

The percentage of the maximum change from the resting baseline lumen diameter (D_{base}) to that of the hyperemic state (D_{max}) divided by D_{base} was defined as %cFMD (Fig. 1A) [13]. The sum of %cFMD and the absolute value of %L-FMC was defined as %FMTD, calculated as the percentage of the maximum change from the minimum lumen diameter during the last 30 s before the cuff release (D_{min}) to D_{max} divided by D_{base} (Fig. 1B). The percentage of the maximum change from D_{min} to D_{max} divided by D_{min} was defined as %mFMD [12] (Fig. 1B). These indices were calculated using the following formulae:

$$\%cFMD = \frac{D_{max} - D_{base}}{D_{base}} \times 100$$

$$\%FMTD = \frac{D_{max} - D_{min}}{D_{base}} \times 100$$

$$\%mFMD = \frac{D_{max} - D_{min}}{D_{min}} \times 100$$

2.3. Clinical data and Framingham risk score

The Brinkman index (cigarettes per day × years smoked) was used to indicate the smoking burden. The expired carbon monoxide level and the FMD measurements were assessed simultaneously. Laboratory data from blood samples on the same day of the FMD measurement were obtained. Clinical data were obtained from the medical records of each of the 188 subjects and comprehensively reviewed. The Framingham risk score (FRS) of all the participants aged 30–74 years was calculated to determine their risk of CHD according to the score sheet for men and women [23,24].

2.4. Statistical analysis

Clinical characteristics are presented as mean ± SD for