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Original Article

Seasonal variation of endothelium-dependent flow-mediated vasodilation measured in the same subjects

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Abstract: Background: Seasonal variation of flow-mediated vasodilation (FMD) remains controversial. A large cohort study showing that FMD was highest in summer and lowest in winter has been performed in a cross-sectional manner on different populations in different seasons, and the results for the same population were not compared. Methods: FMD was compared between the cool season (14.4 ± 4.4°C) and warm season (28.8 ± 1.0°C) in the same 27 outpatients with hypertension, diabetes mellitus and/or hyperlipidemia. Results: The mean resting brachial artery diameter was significantly larger in the warm season than in the cool season. The maximal post-deflation brachial artery diameter was also significantly larger in the warm season than in the cool season. FMD, which was calculated from the resting diameter and the maximal diameter, was significantly higher in the warm season than in the cool season even when expressed as the relative value (4.74 ± 2.15 vs. 5.71 ± 2.17%, p=0.03) or absolute value (0.18 ± 0.08 vs, 0.23 ± 0.07 mm, p=0.008). Conclusions: FMD was significantly higher in the warm season than in the cool season when the measurements were performed on the same subjects and a paired comparison was made.

Keywords: Flow-mediated vasodilation, seasonal variation

Introduction

Assessing the flow-mediated dilation (FMD) of the brachial artery by high-resolution sonography is widely used as a non-invasive method determining the endothelial function. The technique for measuring FMD has been significantly improved by the efforts of many researchers since it was firstly introduced by Celermajer et al. [1]. The first guideline published in 2002 summarized the development of FMD measurement and contributed to standardizing the methodology [2]. Many important physiological issues that affect FMD assessment have since been identified and are described in recently published guidelines [3, 4]. Suitable preparation of the subject and adequate acclimatization are necessary factors before FMD measurements to ensure accuracy. These factors include dietary intake, vitamin supplementation, medications, smoking, caffeine and alcohol ingestion, menstrual phase, previous exercise and environmental conditions [3].

Climatic change is an important factor influencing blood circulation. Similar to the seasonal variation of blood pressure [5-7], the FMD value may be influenced by season and temperature. Several studies have examined the seasonal variation of FMD, but exhibited inconsistent findings. Two studies failed to show any seasonal variation of FMD; one in young adults with Raynaud's syndrome and healthy controls [8], and the other in lean and obese subjects [9]. In a relatively larger study, Nawrot et al. examined FMD in a random population sample (n=273) of the Flemish Study on Environment, Genes and Health Outcomes and unexpectedly showed that FMD was negatively associated with the mean daily temperature [10]. In contrast, Widlansky et al. have demonstrated that FMD was highest in the summer and lowest in the winter in a large population (n=2587) of the Framingham Offspring cohort [11]. They suggested that the increased incidence of cardiovascular events during the winter might be partly associated with a decline of the vascular endothelial function. However, these measurements were performed in a cross-sectional manner with different populations during different seasons and were not compared for the same population of subjects.

We attempt in the present study to compare FMD between cool and warm seasons for the same subjects and investigate the seasonal variation of FMD.

Materials and methods

Twenty-seven subjects were recruited from outpatients who regularly visited the Miyashita clinic in Shizuoka-city (Shizuoka, Japan) suffering from hypertension, diabetes mellitus and hyperlipidemia. The patients' characteristics are shown in Table 1. Most of these patients were receiving medication and were in a stable condition throughout the study period. Antihypertensive drugs were counted from medical records and classified according to the number of drugs taken. The participants were instructed to be fast overnight and not to drink caffeine-containing beverages and alcohol before the examination. Smoking was also prohibited on the day of the examination. The study protocol was approved by the Ethics Committee at University of Shizuoka, and informed consent was obtained from all participants before the examination.

Table 1. Patients' characteristics

Male/ female	14/13
Age, yrs	60.4 ± 10.1
Height, cm	160.3 ± 9.6
Body weight, kg	59.9 ± 11.7
BMI, kg/m^2	23.1 ± 2.8
Smoking	
Never smoker, n (%)	19 (70%)
Past smoker, n (%)	5 (19%)
Current smoker, n (%)	3 (11%)
Alcohol	
Never drinker, n (%)	16 (57%)
Past drinker, n (%)	1 (4%)
Current drinker, n (%)	10 (37%)
Hypertension, n (%)	23 (85%)
Diabetes, n (%)	7 (26%)
Hyperlipidemia, n (%)	20 (74%)

BMI: body mass index

All participants were examined twice for FMD; once in the cool season between November and March and once in the warm season between July and September. The outdoor temperature in Shizuoka city on the day of FMD measurement was obtained from data recorded by Japan Meteorological Agency, the mean daily temperature being used for the analysis. The temperature in the clinic was maintained at 25°C throughout the year by the air-conditioning system. Each participant entered in the examination room at least 30 min before FMD measurements were started. The blood pressure and heart rate were measured before measuring FMD, and the blood pressure measured at home in the morning was recorded for most of the participants.

Flow-mediated dilation was assessed by using EF18G equipment (UNEX, Nagoya, Japan) as previously described [12]. Briefly, FMD was measured in the brachial artery according to the guidelines in the supine position after resting for 15 min. All measurements were taken by one trained examiner. The brachial artery was scanned by an ultrasound probe at 10 MHz for longitudinal and transverse windows, and the digitized image was continuously captured by a computer. After recording the base-line image, the cuff placed distal to the ultrasound probe was inflated to 50 mmHg above systolic blood pressure for 5 min and then deflated. The post-deflation arterial image was recorded for 2 min. The pre-occlusion diameter and maximal post-deflation diameter of the brachial artery were measured, and the difference between both values was calculated. FMD was calculated as the maximal post-deflation diameter relative to the averaged pre-occlusion diameter. The reproducibility of the brachial artery diameter during a session had a coefficient of variation of 1.37% with this equipment.

Statistical analysis

Data are presented as the mean ± SD. The significance of differences between groups was examined by a paired Student's t-test, and the correlation between groups was assessed by the Pearson correlation coefficient. A p-value of less than 0.05 was considered significant. All statistical analyses were performed with GB-

Table 2. Seasonal variation of hemodynamic parameters

	Cool season	Warm season	*P* value
Blood pressure at office			
Systolic, mmHg	132.5 ± 14.6	124.7 ± 15.6	0.02
Diastolic, mmHg	80.1 ± 13.9	76.0 ± 10.3	0.07
Blood pressure at home			
Systolic, mmHg	124.5 ± 15.6	116.7 ± 8.9	0.02
Diastolic, mmHg	76.0 ± 10.3	71.9 ± 10.2	0.04
Heart rate, beats/min	68.6 ± 9.2	69.0 ± 8.3	NS
Antihypertensive drugs, n	2.0 ± 1.2	2.0 ± 1.2	NS
Brachial artery diameter			
Resting, mm	3.96 ± 0.63	4.08 ± 0.59	0.04
Maximal, mm	4.14 ± 0.62	4.31 ± 0.57	0.006
FMD			
Relative, %	4.74 ± 2.15	5.71 ± 2.17	0.03
Absolute, mm	0.18 ± 0.08	0.23 ± 0.07	0.008

Data are mean ± SD. FMD: flow-mediated dilation.

STAT software (version 10; Dynamic Microsystems, Silver Spring, MD, USA).

Results

The outdoor temperature was significantly higher in the warm season (28.8 ± 1.0°C) than in the cool season (14.4 ± 4.4°C, $p<0.001$). The mean systolic blood pressure of the participants was significantly lower in the warm season than in the cool season when measured both in the office and at home (Table 2). A similar trend was shown in diastolic blood pressure, while there was no difference in heart rate between the two seasons. The number of antihypertensive medications administered to these patients did not differ between the two seasons.

The mean resting brachial artery diameter was significantly larger in the warm season than in the cool season. The maximal post-deflation brachial artery diameter was also significantly larger in the warm season than in the cool season. FMD that was calculated from the resting diameter, and the maximal diameter was significantly higher in the warm season than in the cool season, even when expressed as the relative value (%) or absolute value (mm). The change in FMD for each participant is shown in Figure 1. Twenty-one participants demonstrated an increase in FMD during the warm season, while the remaining six subjects exhibited paradoxical changes. No specific characteristics were found in these six participants.

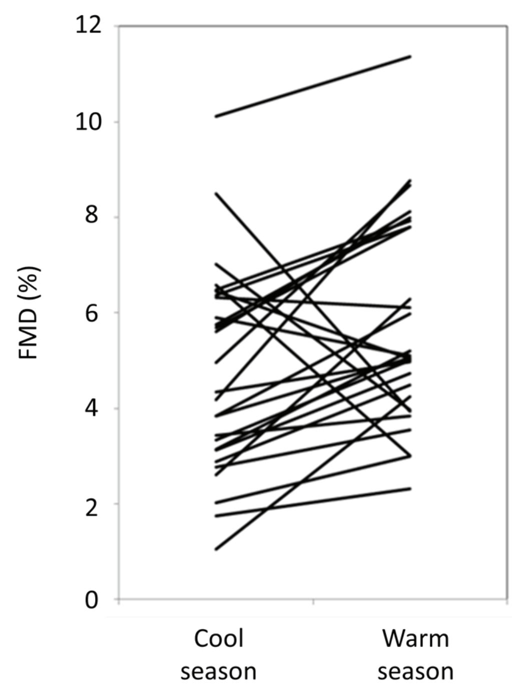

Figure 1. Comparison of FMD between cool and warm season. FMDs for each participant are shown in this figure. Mean ± SD is shown in Table 2.

The change in FMD value with seasonal variation was not associated with gender, age, body mass index, smoking or alcohol consumption.

There was no association between the seasonal change in FMD and the seasonal change of blood pressure in this study.

Discussion

The results of this study demonstrate that FMD, a marker of the vascular endothelial function, had a significant seasonal variation in which FMD was higher in the warm season than in the cool season. This result is consistent with that of a previous study performed with a large cohort in the Framingham Heart Study [11]. Although that study dealt with more than 2000 participants, the study population was different between the seasons and no paired comparison was performed. Those authors pointed out that the subjects examined during the cold season were younger than those examined in the warm season, because elderly participants were likely to refuse winter appointments. This limitation was avoided in the present study since we evaluated the seasonal variation of FMD in the same subjects. This trend of seasonal variation in FMD is supported by the results that the cold pressure test induced impaired FMD [13] and that the sauna treatment improved the vascular endothelial function [14].

The resting brachial artery diameter was significantly larger in the warm season than in the cool season during the present study. If the maximal post-deflation artery diameter were to remain unchanged by season, the calculation indicates that the effect of temperature on the resting brachial artery diameter would make the FMD value smaller in the warm season than in the cool season. However, since the maximal post-deflation diameter was much more enlarged in the warm season, FMD became, as a result, higher in the warm season than in the cool season. Several factors including sympathetic nervous activity, systemic vascular resistance and nitric oxide could be associated with these vascular responses to the environmental temperature [15]. A warm temperature would suppress sympathetic nervous activity leading to peripheral vasodilation and an increase resting blood flow. The dilation of the resting brachial artery can be explained by this scenario, although the increase in FMD by a warm temperature may have been caused by another mechanism. Nitric oxide (NO) plays an important role in the vasodilator response to such a stimulus as heat exposure. Endothelial nitric oxide synthase activation has been reported to be stimulated by a combination of shear stress and heat stress [16]. These facts suggest the possibility that a warm temperature can enhance NO secretion and increase FMD response after vascular obstruction and deflation.

Although a seasonal variation of blood pressure was also apparent in the present study, there was no direct association between the change of blood pressure and the change of FMD. In terms of this dissociation, the influence of hypertension treatment might have been involved, as many participants were receiving antihypertensive medications. The influence of diabetes, which sometimes induces an autonomic dysfunction, might also need to be considered.

FMD measurements were performed in a room where the temperature was kept constant at 25°C throughout the year. Nevertheless, FMD seemed to be principally influenced by the outdoor temperature for reasons remaining unknown in this and other studies. A similar finding has been reported for the seasonal variation of blood pressure in many studies [5-7, 17, 18] and the consensus has been that the effect of indoor temperature had limited influence on blood pressure. A few studies have examined the association of indoor temperature with blood pressure, but showed inconsistent findings [17, 18]. The outdoor temperature probably had a long-lasting effect on FMD and blood pressure, irrespective of the mechanisms involved.

There were some limitations in this study. First, the sample size was so small that analyses could not be separated by gender, age and BMI, although these factors might be associated with the FMD response. Second, the equipment used in this study was first-generation, and was not able to measure shear stress after the cuff's deflation. Since FMD is closely associated with shear stress, the simultaneous measurement of both FMD and shear stress may provide a potential clue to analyzing the mechanism for the seasonal variation of FMD.

In summary, FMD was significantly higher in the warm season than in the cool season when the measurements were performed on the same participants and a paired comparison was made. Since the difference in FMD value between both seasons should not be ignored, attention should be paid to seasonal change for interpreting the FMD data.

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