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Assessment of chilly sensation in Japanese women with Laser Doppler Fluxmetry and Acceleration Plethysmogram with Respect to Peripheral Circulation

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ABSTRACT

To investigate the relationship between peripheral blood flow and chilly sensation in women. Peripheral blood flow was measured by laser Doppler fluxmetry and acceleration plethysmography in 1,624 women. Of these, 458 women who visited the outpatient menopausal and endocrine clinic and gave informed consent to blood flow measurement (284 women for whom chilly sensation was one of the chief complaints and 174 women free of chilly sensation) underwent laser Doppler fluxmetry (TBF-LN1, Unique Medical Co., Ltd., Osaka, Japan) to measure tissue blood flow in the middle finger and the third toe. The same women then received acceleration plethysmography (CP-3166, Fukuda Denshi Co., Ltd., Tokyo, Japan) to measure blood flow in the index finger.

Chilly sensation was complained by 52.0% of all patients (1,624/3,124). The blood flow as measured by laser Doppler fluxmetry and fingertip acceleration plethysmography reflected the chilly sensation well. The blood flow by laser Doppler fluxmetry and the fingertip acceleration plethysmogram index (APG-I) showed significantly lower and higher data, respectively, in the women with chilly sensation than in women free of the chilly sensation.

The chilly sensation is partially attributable to reduced skin blood flow at the periphery of the extremities and the hardness of the vascular wall in these areas. Measurement of the peripheral tissue blood flow in patients complaining of chilly sensation seems to be clinically significant as a means of evaluating this sensation.

Introduction

Chilly sensation is an unexplained complaint. It usually assumes the form of hot flush and chill.

Some cases complain only of uncomfortable chill, not accompanied by hot flush. If the person with this sensation does not feel any inconvenience related to the sensation in daily living, this

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sensation is deemed as a nonpathologic event associated with the individual constitution that does not require medical intervention. However, if the sensation forms an unexplained complaint syndrome and restricts the daily activity of the individual, it is deemed as a pathologic chilly sensation, i.e., a disease entity that requires medical intervention. In Western medicine, chilly sensation is not usually deemed as a disease entity, and this term is only used as an idea generally accepted in the society. In the literature, chilly sensation has been reported only as an unusual brain injury symptom (EAMES, 1997; SILVER and ANDERSON, 1999), a symptom of brucellosis (*Brucella* infection) (TRIFILETTI et al, 2000), a symptom of nonocclusive mesenteric ischemia (NOMI) (HAN et al, 2000) or as a cold feeling or chilly sensation associated with sensory features of variant Creutzfeld-Jacob disease (MACLEOD et al, 2002). However, some investigators pointed out that the cold feeling that appears as an unexplained complaint in elderly people and the mild vasoconstriction and cold feeling seen in cases of inadvertent hypothermia require prophylactic treatment (BERNTHAL, 1999; JENSEN et al, 1998).

Within the framework of our series of study to investigate the actual state of chilly sensation among women and to elucidate the pathophysiology of this sensation, the present study was undertaken to examine chilly sensation by laser Doppler fluxmetric analysis of tissue blood flow and fingertip acceleration plethysmographic evaluation of peripheral blood flow kinetics.

MATERIALS and METHODS

Materials

The subjects included a total of 3,124 women between 15 and 74 years of age who visited the Department of Obstetrics and Gynecology at Osaka Medical College Hospital for regular gynecological checkups, several gynecological complaints, and menopausal complaints. Of these, 458 women who visited the outpatient menopausal and endocrine clinic and gave informed consent to blood flow measurement (284 women for whom chilly sensation was one of the chief complaints and 174 women free of chilly sensation) underwent laser Doppler fluxmetry (TBF-LN1, Unique Medical Co., Ltd., Osaka, Japan) to measure tissue blood flow in the middle finger and the third toe. The same women then received acceleration plethysmography (CP-3166,

Fukuda Denshi Co., Ltd., Tokyo, Japan) to measure blood flow in the index finger. The mean age of the 458 women was 36.3 ± 8.76 years (range: 22-52 years). There were no patients with diabetes mellitus, neuromuscular disease, Berger disease, leprosy, and reflex sympathetic dystrophy. Underlying conditions of the women studied were unexplained menopausal complaints, infertility and abnormal menstrual cycle. Women with organic diseases were excluded from this study.

Measurement with the laser Doppler fluxmeter

The laser Doppler fluxmeter and its measuring principle are outlined below.

The laser, generated from a light-emitting photo-fiber, is scattered within the tissue and due to the erythrocytes within the capillaries, resulting in Doppler shifts. The Doppler signals are received by the light-receiving fibers and recorded by the detector as frequency spectra. These spectra have no particular frequency. Their mean frequency is proportional to the mean flow rate of erythrocytes, and their mean amplitude is proportional to the density of erythrocytes.

Therefore, processing these signals can determine tissue blood flow, tissue blood volume and blood velocity. Skin blood flow is measured continuously under this principle.

Tissue blood volume was calculated using the following equation:

$$\text{Tissue blood volume} = k_1 \int \omega P(\omega) d\omega / 12$$

where k_1 is the proportional constant, ω denotes the angular frequency ($2\pi f$), $P(\omega)$ is the power spectrum of signals and l is the amount of light received.

As the measurements differed between right and left extremities, they were averaged to yield a value for each patient.

Measurement with the fingertip acceleration plethysmogram

The principle for obtaining the fingertip acceleration plethysmogram is shown below.

The acceleration plethysmogram (APG) is a double differential wave. The secondary differential wave of plethysmogram (PTG) begins with upward wave (a), followed by downward wave (b) and upward wave (c). Then, its amplitude gradually decreases to become downward wave (d). From the poles of these 4 waves (a, b, c and d), the accelerated plethysmogram index (PTGA-Index) was calculated using the following equation:

$$\text{PTGA-Index} = [b - (c + d)] / a$$

Statistical analysis

The significance of differences was tested by Wilcoxon signed-rank test and chi-square test. $P < 0.05$ was regarded statistically significant.

RESULTS

1. Prevalence and severity of chilly sensation among the women visiting our hospital

Of the 3,124 women who visited our Department of Obstetrics and Gynecology, 1,624 women (52.0%) complained of chilly sensation. A

difference in the thermal sensation was noted between right and left extremities in some of these women. Women complaining of chilly sensation on either side were judged as having chilly sensation. The prevalence of this sensation in each age group is shown in Fig. 1. The prevalence of this sensation was less than 30% for women in the first half of the 40s or below 40, while it was over 40% for women in the perimenopausal period and over 50% for women over 55 years of age. Of the 1,624 women complaining of chilly sensation, 547 (33.7%) had the sensation on both the upper and lower extremities. In 235 women (14.5%), the sensation was always present (Table 1).

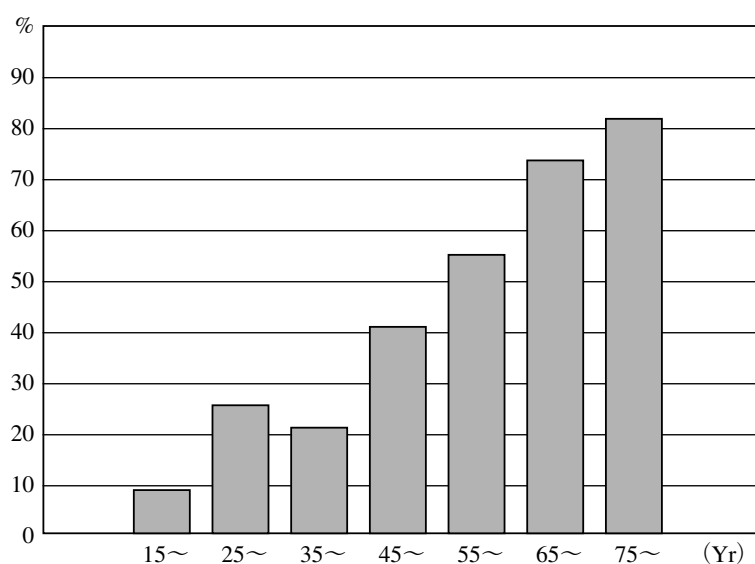


Fig. 1. Percentage of women complaining of chilly sensation on the extremities among all women visiting a hospital (n = 3124)

Table 1. The incidence and severity of chilly sensation on extremities (n=1,624)

Variety of chilly sensation	Incidence	%
Localization		
all extremities	547/1,624	33.7
lower extremities alone	1,018/1,624	62.7
upper extremities alone	59/1,624	3.6
Severity		
always	235/1,624	14.5
sometimes	843/1,624	51.9
occasionally	546/1,624	33.6

2. Evaluation of the chilly sensation by peripheral blood flow of the extremities

We examined whether or not chilly sensation could be evaluated by peripheral blood flow in the extremities. The blood flow in the upper extremities did not differ significantly between the 174 women free of chilly sensation and the 176 women complaining of chilly sensation on the lower extremities alone, while 108 women with chilly sensation on both the upper and lower extremities had a significantly lower blood flow in

the upper extremities as compared to the group without chilly sensation ($P = 0.0093$). The blood flow in the lower extremities was significantly lower in the women complaining of the sensation on the lower extremities alone than in women free of the sensation ($P = 0.036$), and it was also significantly lower in the women complaining of the sensation on both the upper and lower extremities than in the group without chilly sensation ($P = 0.0384$) (Fig. 2).

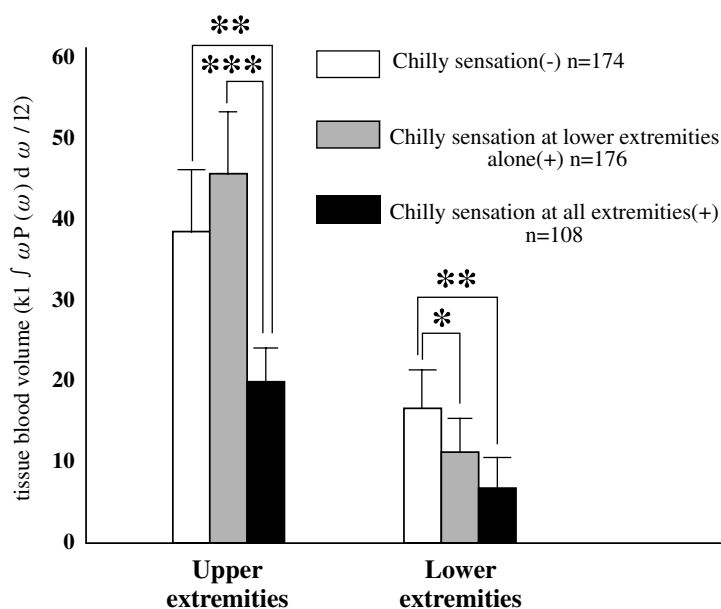


Fig. 2. Severity of chilly sensation and tissue blood volume in the upper and lower extremities as measured by laser Doppler fluxmetry

*: $P < 0.05$, **: $P < 0.01$, ***: $P < 0.001$

3. Assessment of chilly sensation by acceleration plethysmogram index (APG-I)

The presence/absence and severity of chilly sensation were analyzed in relation to APG-I. The APG-I for the group with chilly sensation on the lower extremities alone (1.181 ± 0.205) and that for the group with chilly sensation on both the upper and lower extremities (1.193 ± 0.231) were significantly higher than that for the group without chilly sensation (1.111 ± 0.255) ($P < 0.05$), as shown in Fig. 3.

DISCUSSION

Chilly sensation is more frequently seen in females than in males. There are women who complain of chill or numbness as symptoms of autonomic imbalance in the absence of organic

disease, occasionally reducing the quality of life. During active daytime, the sympathetic nerves are predominant over the parasympathetic nerves, making the individual provocative. At night or when the individual is relaxed, the parasympathetic nerves are predominant, causing the peripheral blood vessels dilated and making the individual feel warm in extremities, relaxed and sleepy. In the presence of autonomic imbalance, switching from predominance by sympathetic or parasympathetic nerves is disturbed, causing the individual to become irritable or have palpitation, facial hot flush, sleeplessness and/or chilly sensation on the extremities (JHA and HAG, 1995; KOMAN et al, 1995; WIART et al, 1998; HOSONO et al, 2001; EDELL-GUSTAFSSON, 2002).

It is said that disturbed peripheral circulation underlies pathologic chilly sensation. Pathologic chilly sensation can be caused by various factors

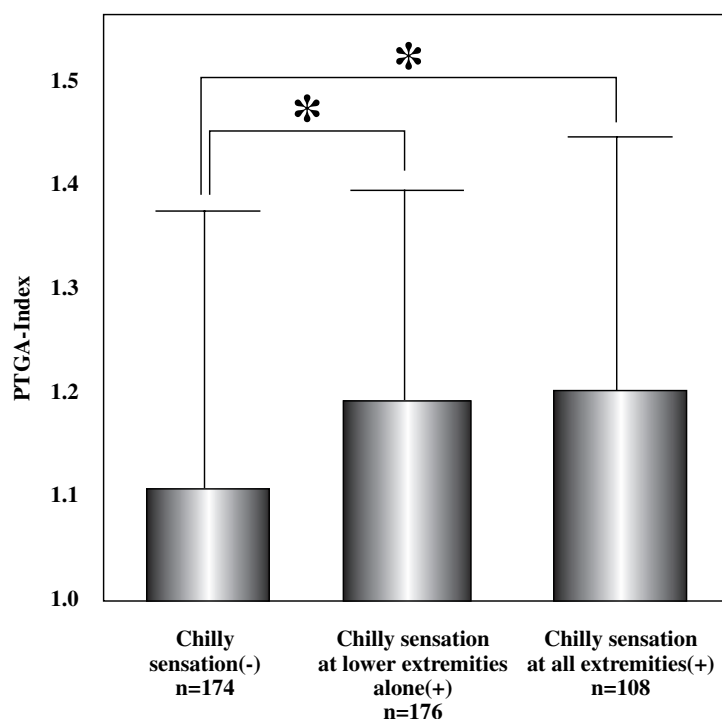


Fig. 3. Presence/absence of chilly sensation and fingertip acceleration plethysmogram index (secondary differential wave: PTGA-index)

*: $P < 0.05$

including arterial or venous disturbances and disturbances of microcirculation (e.g., capillaries). Representative disorders of peripheral circulation responsible for chilly sensation include obstructive arteriosclerosis, thromboangiitis obliterans (Buerger's disease), Raynaud's phenomenon (VAN DEN WAL et al, 1987; FRANSSEN et al, 1992), angiopathy associated with collagen disease, diabetic peripheral angiopathy (WILSON et al, 1992), leprosy (ABOOT et al, 1992) and reflex sympathetic dystrophy (RSD) (KURVERS et al, 1995). Frostbite is also a disorder of peripheral circulation. Chilly sensation is one of the symptoms that patients with these diseases complain of. Systemic diseases are also associated with chilly sensation. For example, it has been reported that 45.2% of all patients with NIDDM had cold sensation on the lower extremities (OGAWA et al, 1999) and that most patients with decubitus ulcer had cold feeling and cyanosis on the lower extremities (MIYAJIMA et al, 2000).

Additional factors which can affect the sensation at the periphery of extremities include sensory nerve function, autonomic nerve function and skin temperature. Whole body cold-air exposure in laboratory conditions has been used previously in several studies on human cold

adaptation. It has been observed that the decrease in deep body temperature was greater after cold-air exposures than before them (DAVIS, 1961; THE EUROWINTER GROUP, 1997; KREIDER et al, 1959), but decreases in mean skin temperature remained unchanged (DAVIS, 1961). Only a few studies have reported peripheral skin temperatures or cold sensations during repeated cold-air exposures (KREIDER et al, 1959; KEATINGE, 1961; KEATINGE et al, 1984). In these foreign studies, cold air exposure, repeated cold stress or whole body cryotherapy induced temporary chilly sensation, but it seemed likely that at least under laboratory conditions, the chilly sensations were reduced by adaptive changes. LEPPALUOTO et al. (2001) demonstrated that the skin thermal sensations became habituated after the first or second cold-air exposure in the clinical study with healthy Finlander men. The Different cold and warmth perception mapped for age, gender, and body area have been reported by researcher of Sweden (HARJU, 2002). The findings from these experimental studies cannot be viewed as giving adequate accounts of the pathogenesis and frequency of chilly sensation common among Japanese women. In our clinical study, treatment with a herbal preparation Toki-shigyaku-ka-

goshuyu-shokyo-to resulted in an increase in skin surface temperature, accompanied by an increase in blood flow volume, over a certain period of time (data not shown). It can be speculated that surface blood flow is closely related to skin surface temperature and that sympathetic nerve function is involved in these changes. Adrenal medullary and thyroid hormones and brown adipose tissue are crucial in maintaining body temperature in experimental animals, but their role in humans is less well known (LEPPLUOTO et al, 2001). A single, whole body cold-air exposure leads to increased plasma norepinephrine levels, but epinephrine levels remain unchanged (HESSLINK et al, 1992; LEPPLUOTO et al, 1988; RAVEN et al, 1975; THOMAS et al, 1990), suggesting an activation of the sympathetic nervous system.

The present study of the prevalence of chilly sensation among Japanese people revealed that approximately 50% of perimenopausal women under non-repeated cold-air exposures had chilly sensation and that the prevalence gradually rose at higher ages after menopause. A previous study of Chinese population revealed that 87.9% of women with recurrent cystitis had chilly sensation (ALRAEK et al, 2000). These findings suggest that Oriental people is susceptible to chilly sensation. Many years ago, So (1975) argued about the possibility of the presence of genetic components in the physiological adjustments to cold stress on the basis of a finding that recovery in skin temperature following exposure to cold stress differed between Chinese people living in north China and those living in south China. This suggests an ethnic difference in the cold sensation. It seems advisable to compare thermal perception by skin and the chilly sensation between Japanese and Western people on the basis of analysis of blood flow.

In the present study, analysis of the blood flow in the periphery of extremities by means of laser Doppler fluxmetry revealed that the severity of chilly sensation correlated with the peripheral tissue blood flow of the lower extremities. Laser Doppler fluxmetry is a means of evaluating total capillary circulation on the basis of a general assessment of many factors including cutaneous perfusion, capillary blood flow, blood cell flow velocity and total skin microcirculation (JORNESKOG et al, 1995; NILSSON et al, 1998). KOMAN et al. (1995) reported that isolated cold stress testing demonstrated abnormalities in temperature and laser Doppler fluxmetry response between patients with refractory pain or

ulceration of extremities and controls, and peripheral artery sympathectomy appear to be related to postsurgical correction of abnormal arteriovenous shunting and to improved nutritional blood flow to ischemic areas. In the present study, the blood flow as measured by laser Doppler fluxmetry in women complaining of chilly sensation on the extremities was significantly lower than that in women without the sensation. This may be attributable to reduced capillary blood flow volume, reduced blood cell flow velocity or increased resistance of the capillary microcirculation network.

Plethysmogram has been widely known as a conventional non-invasive simple method to obtain information on peripheral circulatory kinetics, baroreflex sensitivity, cardiovascular variability, and sympathetic nervous system response (MINAMI et al, 1993; RINALDI et al, 2000; GMTROV and ANDREJKO, 2000). Especially, the ratio of two wave component (magnitude of b/a constituting the second derivative of the plethysmogram) was correlated with arterial distensibility (blood vessel extensibility), hardness, and vascular ageing, and the ratio of d/a values was correlated to peripheral circulatory kinetics (i.e., late systolic pressure augmentation) (IMANAGA et al, 1998; TAKAZAWA et al, 1998; OHI et al, 2002).

The acceleration plethysmogram (APG) is a double differential wave of plethysmogram (PTG). It represents capillary blood flow kinetics of peripheral circulation and reflects the physical properties of proximal elastic arterial wall. It is used as an objective indicator of afterload. In the past, APG was used clinically as an arteriosclerosis index (KATSUKI et al, 1994). An experimental study of vascular dynamics using an artificial circulation device also demonstrated that APG (b/a ratio) can serve as an indicator of blood vessel extensibility (OHI et al, 2002). Recently, APG is applied as the factor of non-fractal in fractal (EEG, Plethysmogram, respiratory curves and EMG) and non-fractal dimension analysis to evaluate anxiety-affinitive constitution in psychosomatic medicine (TAKEICHI et al, 2001). Sato and Agishi demonstrated that improvement of intermittent claudication of arteriosclerotic patients was related to improvement in plethysmogram suggesting an increased circulation in lower extremities (SATO and AGISHI, 1996). In our study, the APG-I score became greater as chilly sensation became severer. This relationship indicates that one of the factors responsible for

chilly sensation is reduced blood vessel extensibility. This suggests the presence of reduced cutaneous perfusion due to micro-circulatory failure caused by sympathetic nervous stimulation. Because the severity of chilly sensation on the extremities correlated well with deterioration of cutaneous perfusion or capillary blood flow and with reduced compliance of the arterial system, it is advisable that when dealing with patients complaining of chilly sensation, the condition be evaluated thoroughly and active treatment be provided to avoid reducing the quality of life.

On the basis of the data yielded from the present study alone, it is not possible to conclude that the women having chilly sensation of both upper and lower extremities differ from women having chilly sensation of only upper or lower extremities in terms of the sympathetic nerve function or involvement of some extra-circulatory function. Regulation by sympathetic and parasympathetic nerve systems is not always a major factor determining the appearance of the subjective symptom "chilly sensation". It is possible that a variety of other factors (e.g., function of sensory organs and inter-individual variance in the threshold level for perception of cold) are also involved in the chilly sensation. Depending on the degree to which these factors are involved, some individuals may complain of chilly sensation of lower extremities alone whereas others may complain of such sensation in both upper and lower extremities. We may at least say that superficial local skin blood flow and predominance of the sympathetic nerve system in the regulation of superficial local skin blood flow serve as one of the factors responsible for the chilly sensation.

Chilly sensation is often viewed as a symptom but has not yet been widely accepted as a disease entity. Because many women are suffering from chilly sensation, clinicians should pay more attention to chilly sensation to improve women's quality of life. It is desirable that criteria are established for evaluating the severity of chilly sensation and defining treatment-requiring cases of chilly sensation, using laser Doppler fluxmetry score and acceleration plethysmogram index as biological indicators. We will continue our study towards this goal.

Study limitations

The first limitation of this study is that this study did not use a comparative examination

between peripheral blood flow and skin temperature in women with chilly sensation, because we did not have convenient thermography. Second, we could not perform an examination among women with chilly sensation in all extremities, in upper limbs alone, and lower limbs alone. Future study should address the detailed mechanisms of change in peripheral blood flow in relation to thermal sensation.

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