Sex Differences in Control of Cutaneous Blood Flow

John P. Cooke, MD, PhD, Mark A. Creager, MD, Philip J. Osmundson, MD, and John T. Shepherd, MD, DSc

Women are far more likely than men to suffer from Raynaud’s disease. The purpose of this study was to determine whether there are gender differences in local or central control of cutaneous blood flow that could account for the increased incidence of Raynaud’s disease in women. To assess cutaneous blood flow, hand blood flow (HBF), finger blood flow (FBF), or skin perfusion (SP) was measured by fluid plethysmography, mercury strain-gauge plethysmography, or laser Doppler spectroscopy, respectively, in 47 volunteers. Basal HBF in men exceeded that of women (12.1±2.0 versus 6.2±1.5 ml/100 ml/min). Likewise, FBF in men surpassed that of women (19.5±4.1 versus 7.7±1.8 ml/100 ml/min). Similarly, SP in men was greater than that of women (270±42 versus 81±16 perfusion units). However, after total body warming (to induce a thermal sympatholysis), HBF in women exceeded that of men, suggesting that the lower basal HBF in women was due to increased sympathetic outflow to the extremities. Mental stress and deep inspiration reduced HBF and SP in men. Paradoxically, both of these maneuvers increased HBF and SP in women. To determine whether these paradoxical responses in women were due to the women’s elevated basal sympathetic tone, these experiments were repeated after total body cooling in men to increase sympathetic tone and after total body warming in women to reduce sympathetic tone. Total body cooling reduced HBF and SP in men. Under these conditions, mental stress and deep inspiration induced vasodilation. In women, total body warming for 10 minutes increased HBF. Under these conditions, mental stress and deep inspiration induced vasoconstriction. In conclusion, basal cutaneous blood flow is reduced in women. This appears to be due to a basal increase in sympathetic tone rather than to a local structural or functional difference in the cutaneous circulation. In addition, a paradoxical vasodilation in response to mental arithmetic and deep inspiration is unmasked at high levels of sympathetic tone. The gender differences in cutaneous blood flow may account for the increased incidence of Raynaud’s disease in young women. (Circulation 1990;82:1607–1615)

Raynaud’s disease is a vasospastic disorder characterized by excessive vasoconstriction of the cutaneous circulation of the extremities.1 Attacks of Raynaud’s disease are precipitated by ambient cold or mental stress and are thought to be mediated by increases in sympathetic nervous outflow to the cutaneous vasculature. A “local fault” in the digital circulation is thought to predispose subjects to excessive vasoconstriction during elevations in sympathetic tone. Women are far more likely than men to suffer from Raynaud’s disease.2 It is not known if this increased incidence in women is due to local structural or functional differences in the cutaneous circulation or if increased sympathetic tone to the limbs predisposes women to this disorder. Thus, the purpose of this study was to determine if there are gender differences in local or central control of cutaneous blood flow that could account for the increased incidence of Raynaud’s disease in women.

Methods

Subjects

Informed consent was obtained from the 23 men and 26 women who participated in this investigation, which was approved by the institutional review board of the Mayo Clinic. The participants (age range, 22–38 years) were in good health and, with one
exception, did not use tobacco. On the day of the study, they were asked to refrain from consuming vasoactive substances, including caffeine. Subjects were studied in a postprandial state and were lightly clothed in hospital scrub suits. Subjects rested quietly in a supine position in the laboratory (room temperature, 23°C) for 20 minutes before data were collected. External stimuli were reduced to a minimum.

Techniques

Three complementary techniques were used to assess cutaneous blood flow: 1) volume plethysmography of the hand, 2) mercury strain-gauge plethysmography of the finger, and 3) laser Doppler spectroscopy of the finger. Volume plethysmography of the hand provides highly accurate and reproducible measurements of hand blood flow over a wide range of flow. A disadvantage of this technique is that although hand blood flow predominantly reflects cutaneous blood flow, a portion of the total value is contributed by skeletal muscle. Conversely, finger blood flow almost exclusively represents cutaneous blood flow, and this is the strength of using finger plethysmography. However, mercury strain-gauge plethysmography of the finger is not as accurate or reliable as the former technique, particularly at higher values of flow. Laser Doppler spectroscopy measures skin perfusion of a small volume of tissue (a hemisphere with a radius of 1 mm) beneath the probe head. It therefore exclusively reflects cutaneous blood flow. An additional advantage is the short time constant of this technique; however, measurements are only semiquantitative.

To measure hand blood flow, a water-filled plethysmograph was used. The water temperature of the plethysmograph was thermostatically controlled and continuously monitored and could be adjusted to warm or cool the hand. The outlet of the plethysmographic chamber was connected by stiff plastic tubing to a pressure transducer. Before each experiment, the transducer was calibrated volumetrically. With the subject supine, the hand was inserted into a loosely fitting surgical glove affixed to the plethysmograph. The position of the plethysmograph was then adjusted to maintain the hand at a level above the right atrium. The upper extremity was supported by a padded arm board, and the patient’s position was adjusted to maximize comfort and minimize respiratory artifact. A collecting cuff was applied to the wrist, and its position was adjusted to reduce inflation artifact; pressures of 40–70 mm Hg were used to impede venous return, and were delivered automatically by a servosystem (Periflow, Janssen Scientific Instruments). The minimal pressure evoking the greatest rate of increase in hand volume was determined for each subject. Hand volume was determined volumetrically, and hand blood flow was expressed in milliliters per 100 milliliters of tissue per minute. Each blood flow determination is the average of five successive blood flow recordings made at 10-second intervals. The effect of a deep inspiration on hand blood flow is transitory, and only the first recording of hand blood flow after this maneuver was analyzed.

To measure finger blood flow, mercury strain-gauge plethysmography was used. The strain gauge was calibrated, placed circumferentially around the distal phalanx of the second or third digit, and connected to a Hokansen plethysmograph. A 2.5-cm cuff was placed at the base of the finger and inflated to the lowest venous occlusion pressure (30–50 mm Hg) required to produce the maximum increase in finger circumference for each subject. Finger blood flow was derived from the rate of change in finger circumference during acute venous occlusion and was expressed in milliliters per 100 milliliters of tissue per minute. Each measurement of finger blood flow comprised 10 serial blood flow determinations.

Skin perfusion was assessed by laser Doppler spectroscopy (laser Doppler Flowmeter Periflux 3). The probe head was fixed to the volar aspect of the thumb by an adhesive ring. Movement artifact was made negligible by the use of a rigid arm support. The analog output from the flowmeter (as well as that from the plethysmograph) was continuously monitored with a strip-chart recorder. A reference baseline for the flowmeter recordings corresponding to zero perfusion was obtained by inflating an arm cuff to supraphysiological pressures and recording the Doppler signal during this time. Each skin perfusion value is the average of 10 measurements at 5-second intervals. In some experiments, blood pressure was measured by sphygmomanometry.

Specific Protocols

Changes in cutaneous blood flow in response to regional temperature changes may be under central control (i.e., changes in sympathetic nervous activity) or local control (i.e., changes in affinity of the adrenoceptors in the vessel wall). To study the gender differences in local and central control of cutaneous blood flow, the following protocols were followed.

Gender differences in basal cutaneous blood flow. To determine if there were gender differences in basal cutaneous blood flow at room temperature (23°C), hand blood flow, finger blood flow, or finger skin perfusion was measured in 49 subjects (23 men and 26 women).

Gender differences in the interaction of central and local control. To study the interaction of central and local control of cutaneous blood flow in response to local temperature changes, the following study was performed. Hand blood flow was measured simultaneously in both extremities at 32°C. The temperature in one plethysmograph was maintained at 32°C.
The temperature in the other plethysmograph was increased to 42°C (local warming) and thereafter reduced by decrements of 4°C every 5 minutes to a final temperature of 22°C (local cooling) while continuously monitoring flow in both hands. Any changes occurring in flow to the hand maintained at 32°C are due to central effects (i.e., changes in sympathetic outflow to the extremities). Any additional change in flow of the warmed or cooled hand is then due to local superimposed effects of the temperature change.

**Gender differences in local control.** The following experiment was performed to examine local control of cutaneous blood flow in the absence of central control. Hand blood flow was measured simultaneously in both extremities at 32°C. One plethysmograph was then heated to 42°C (local warming), and the other was cooled to 22°C (regional cooling). Subsequently, subjects were placed between two hypothermia blankets with fluid inflow temperatures of 45°C. Total body warming was performed for 40 minutes to abolish sympathetic tone ("thermal sympatholysis"). This way, the local control of cutaneous blood flow in response to regional temperature changes could be evaluated in the absence of sympathetic tone. Hand blood flow, blood pressure, and oral temperature were measured every 10 minutes.

To determine the effectiveness of the thermal sympatholysis, the flow responses to mental stress as well as to deep inspiration were observed at 10-minute intervals. Mental stress was induced by asking subjects to perform mental arithmetic using standardized sums. After performing mental arithmetic, the subjects were asked to take a deep breath to maximal inspiratory capacity and then exhale passively.

**Gender differences in central control.** First, the initial protocol was designed to assess central control of cutaneous blood flow in the absence of local changes in temperature that might affect local control. Therefore, while local temperature was held constant (plethysmograph temperature, 32°C), hand blood flow was examined during reflex activation of sympathetic tone (mental stress and deep inspiration).

Second, the above protocol revealed paradoxical vasodilation to mental stress and deep inspiration in women. To determine if the paradoxical responses were associated with an elevated basal sympathetic tone, the following experiment was performed. Hand blood flow and skin perfusion were measured in five men at rest and during mental stress and deep breath. Subsequently, the men were placed between hypothermia blankets for 5 minutes of total body cooling (inflow temperature, 5°C) to elevate sympathetic tone, and the flow measurements were repeated. Similarly, eight women were placed between hypothermia blankets (inflow temperature, 45°C), and hand blood flow response to mental arithmetic (n=8) and deep inspiration (n=5) were assessed before and after total body warming (to reduce sympathetic tone).

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<thead>
<tr>
<th>Table 1. Effect of Deep Inspiration on Skin Perfusion</th>
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<td>Subjects</td>
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<td><strong>Men</strong></td>
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<td>Basal</td>
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<td>After deep inspiration</td>
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<td><strong>Cooled men</strong></td>
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<td>Basal</td>
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<td>After deep inspiration</td>
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*Arbitrary perfusion units, as measured by laser Doppler spectroscopy. ‡p<0.05, significantly different from basal value obtained under standard environmental conditions. †p<0.05, significantly different from value observed in men. §Men were subjected to total body cooling for 5 minutes.

**Hormonal effects on control of cutaneous blood flow.** To determine if the gender differences were phasically affected by the estrous cycle, the following experiments were performed. Oral temperature, blood pressure, and hand blood flow were measured twice weekly for 1 month in six women and three men. The female volunteers recorded their rectal temperature daily as well as the onset and duration of menses. After completing the hand blood flow measurements, 7 ml of venous blood was obtained on each experimental day from each female subject for measurement of estradiol and progesterone.

**Statistics**

Most of the 49 subjects participated in several of the experimental protocols during a period of 6 months and had measurements obtained on as many as 12 different occasions.

Values are given as mean±SEM. Statistical evaluation of the data was by Student's t test for paired or unpaired observations. Where multiple comparisons were made, an analysis of variance was used, followed by a Newman-Keuls test. A p value of less than 0.05 was considered significantly different.

**Results**

**Basal Cutaneous Blood Flow**

Basal hand blood flow in men (n=13) exceeded that of women (n=14) at a plethysmograph temperature of 32°C (12.1±2.0 versus 6.2±1.5 ml/100 ml/min, p<0.02).† Likewise, at room temperature, basal finger blood flow in men (n=8) exceeded that of women (n=11) (16.9±4.8 versus 7.7±1.8 ml/100 ml/min). Similarly, skin perfusion in men was greater than that in women under standard environmental conditions (Table 1). These differences in cutaneous blood flow were due to differences in vascular resistance; hand vascular resistance in men (n=8) was less than that in women (n=8) (4.7±0.6 versus 21.4±6.8 Wood units, p=0.02).

**Interaction of Central and Local Control**

Warming the hand (plethysmograph temperature, 42°C) caused hand blood flow to increase in both
Local to greater women (n=9), induced by tone is elevated in response to blood flow (cooled hand) causes a greater reduction in HBF in men than in women (p=0.04). During local cooling, flow also drops in the contralateral hand maintained at 32°C (control hand) to a greater degree in men (p=0.007).

Cooling the hand (plethysmograph temperature, 22°C) caused blood flow to decrease significantly in both groups (men: 15.6±1.9 to 20.7±1.9 ml/100 ml/min, n=9, p=0.04; women: 9.2±2.7 to 16.9±2.5 ml/100 ml/min, n=9, p=0.03). During local warming, blood flow in the contralateral hand (control, maintained at 32°C) did not change in either group (Figure 1). Therefore, the increased flow in the warmed hand is not due to withdrawal of sympathetic tone to the extremity but probably is due to local antagonism of adrenergic responsiveness.

During local cooling, blood flow in the contralateral hand (control, maintained at 32°C) decreased in each of the men (n=9) (15.6±1.9 to 6.7±1.3 ml/100 ml/min, p=0.009). Paradoxically, in three of the women (n=9), the contralateral hand vasodilated; for this reason, in women the reduction in flow in the contralateral (control) hand did not reach significance (8.9±2.2 to 6.8±1.4 ml/100 ml/min, p=NS). The reduction in hand blood flow in the contralateral (control) hand was greater in men than in women (Figure 1).

Local Control of Hand Blood Flow

Total body warming induced a significant and identical increase in core temperature in both groups (men: 36.8±0.1°C to 37.7±0.1°C, n=8, p=0.03; women: 36.9±0.1°C to 37.7±0.2°C, n=8, p=0.04). In both groups, this increase in core temperature induced a "thermal sympatholysis" as evidenced by an increase in hand blood flow (Figure 2) and abolition of the vasoconstriction with mental stress after 40 minutes of body warming (data not shown). After total body warming, hand blood flow in women (n=9) exceeded that of men (n=9) (54.2±4.2 vs 42.8±3.2 ml/100 ml/min, p<0.001).

Despite the attenuation of central control, there remained a persistent difference in flow between the
warmed and the cooled hands (46.5±1.6 versus 34.4±2.4 ml/100 ml/min, p<0.001, n=15). The difference in flow between warmed and cooled hands was similar in men and women (men: 12.6±1.7 ml/100 ml/min, n=8; women: 11.6±5.1 ml/100 ml/min, n=7) after total body warming for 40 minutes (Figures 2A and 2B).

These experiments suggest that in both men and women, there appear to be local mechanisms mediating hand blood flow responses to temperature changes in the absence of sympathetic control. Furthermore, the lower basal hand blood flow in women appears to be due to enhanced sympathetic activity rather than to local functional or structural differences in the vascular bed. The subsequent experimental protocol was designed to determine whether the increase in basal sympathetic tone to the cutaneous vasculature altered reflex vasomotor responses.

Central Control of Hand Blood Flow

Mental stress reduced hand blood flow and skin perfusion in men (Figures 3 and 4A). Deep inspiration had the same effect in men (Figure 5A and Table 1). Paradoxically, both of these maneuvers caused an increase in hand blood flow and skin perfusion in women (Figures 3, 4B, and 5B and Tables 1 and 2).

In a subset of subjects, measurements of arterial pressure were also obtained during these maneuvers to calculate hand vascular resistance. These measurements revealed that during these maneuvers, the observed decrease in hand blood flow in men was due to increased hand vascular resistance (Table 2). Conversely, the increase in hand blood flow in women was due to a decrease in hand vascular resistance (Table 2).

To determine if these paradoxical responses in women were due to their elevated basal sympathetic tone, these experiments were repeated after total body cooling in men (for 5 minutes) to increase sympathetic tone and total body warming (for 10 minutes) in women to reduce sympathetic tone. Total body cooling caused a reduction in hand blood flow and skin perfusion in men. Under these conditions, the responses to mental stress and deep inspiration were qualitatively different from those in men during basal conditions. Mental stress now increased hand blood flow (Figure 4C). Similarly, deep inspiration increased skin perfusion (Table 1).
In women, total body warming for 10 minutes increased hand blood flow. Under these conditions, the responses to mental stress and deep inspiration were qualitatively different from those of women during basal conditions. Deep inspiration now reduced hand blood flow, and mental stress no longer induced vasodilation (Figures 4D and 5D). To summarize, in a setting of reduced sympathetic tone (basal conditions for men, or warmed women), vasoconstriction is observed during deep inspiration.

Conversely, with increased sympathetic tone (basal conditions for women, or cooled men), a paradoxical vasodilation is observed during deep inspiration and mental arithmetic.

**Hormonal Effects on Control of Hand Blood Flow**

Basal hand blood flow and the response to mental stress or deep inspiration remained stable in men and women over time (Figures 6A and 6B). There was no
TABLE 2. Hemodynamic Effects of Mental Stress or Deep Inspiration

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<th>Basal</th>
<th>During mental arithmetic</th>
<th>During deep inspiration</th>
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<tbody>
<tr>
<td></td>
<td>HBF</td>
<td>HVR</td>
<td>MAP</td>
</tr>
<tr>
<td>Men (n=4)</td>
<td>20±4</td>
<td>5.2±1</td>
<td>92±4</td>
</tr>
<tr>
<td>Women (n=5)</td>
<td>2.9±0.8</td>
<td>40±11</td>
<td>84±2</td>
</tr>
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HBF, hand blood flow; HVR, hand vascular resistance; MAP, mean arterial pressure; HR, heart rate.

*Significantly different from basal value.

correlation between female hand blood flow and levels of serum estrogen or progesterone (Figure 7).

Discussion

The major findings of this study were that 1) cutaneous blood flow in women is less than that in men, 2) this gender difference is due to differences in central, rather than local, control mechanisms, 3) maneuvers generally believed to increase sympathetic outflow to the extremities induce cutaneous vasoconstriction in men but a paradoxical vasodilation in women, and 4) this paradoxical vasodilation is unmasked in men under conditions in which sympathetic tone is elevated.

The control of hand blood flow is complex, and both local and central forces are operative. Mental stress, deep inspiration, or local cooling are generally believed to increase sympathetic outflow, resulting in cutaneous vasoconstriction. Conversely, elevation of core temperature reduces basal sympathetic outflow and attenuates the vasoconstriction to mental stress and deep inspiration—thermal sympatholysis.5 Thus, the central nervous system, through sympathetic effects, exerts a strong influence on cutaneous vasoemotion.

The cutaneous vasoconstriction induced by increased sympathetic tone is due in part to the release of norepinephrine from sympathetic nerve endings. More recently, it has become apparent that other cotransmitters may be released with norepinephrine from sympathetic nerve endings, including neuropeptide Y, ATP, and 5-hydroxytryptamine.7-9 Both ATP and norepinephrine are released from sympathetic nerve endings in canine cutaneous vessels, and together they are responsible for cold-induced vasoconstriction.8 In humans, 5-hydroxytryptamine probably plays a significant role in cold-induced vasoconstriction. Serotonergic receptors have been demonstrated in human digital arteries.10 Furthermore, the reflex reduction in finger blood flow induced by body cooling is attenuated but not abolished by α-adrenergic antagonists; the remaining vasoconstriction is reversed by ketanserin, the 5-HT₆ antagonist.11

However, local changes in the temperature of the hand also induce regional effects that are not mediated by the central nervous system.12 Local changes in temperature alter vascular smooth muscle contractility through effects on calcium permeability and by

![Figure 6](http://circ.ahajournals.org/)

**Figure 6.** Plots of hand blood flow (HBF) over the course of 1 month under basal conditions and after (top panel) mental arithmetic (MA) or (bottom panel) deep inspiration (DI). HBF under basal conditions and the response to MA or DI are fairly stable over the course of 1 month in male (n=3) and female (n=6) subjects. Note that the HBF response to MA and DI is qualitatively different between the two groups.

![Figure 7](http://circ.ahajournals.org/)

**Figure 7.** Plot of hand blood flow (HBF, Δ), serum estradiol (○), and serum progesterone (●) levels over the course of 1 month in one representative female subject. There was no cyclic fluctuation in HBF related to hormonal levels in the six women studied.
influencing the sequestration, release, and disposition of endogenous norepinephrine. Furthermore, temperature may influence receptor-agonist interactions to augment the vascular response to adrenergic or serotoninergic stimulation. Therefore, the predisposition of women to Raynaud's disease could be due to gender differences in central control of hand blood flow (i.e., elevated sympathetic tone) or differences in local effects of temperature. Thus, the purpose of this study was to determine if there are gender differences in local or central control of hand blood flow that might account for the increased incidence of Raynaud's disease in women.

This investigation uncovered gender differences in control of cutaneous blood flow. Under standard environmental conditions, hand blood flow, finger blood flow, and skin perfusion in women were half those of men. This difference appears to be due to an increase in sympathetic outflow to the cutaneous circulation in women. This is suggested by the observation that after total body warming (to induce thermal sympatholysis), hand blood flow increased to a greater degree in women.

In fact, after abrogation of sympathetic tone, hand blood flow in women exceeded that of men. Therefore, local structural or functional differences in the cutaneous circulation cannot account for the reduced basal cutaneous blood flow in women. Results of this study suggest that maximal achievable hand blood flow is greater in women. This observation parallels that made in the forearm, in which hyperemic blood flow is greater in women. Thus, maximal blood flow in both the cutaneous and muscular circulations of the upper extremity appears to be greater in women.

If basal sympathetic outflow to the extremities is tonically increased in women, one might expect a downregulation of postjunctional \( \alpha \)-adrenoceptors. In women, there is a reduced response of finger blood flow to intra-arterial infusion of adrenergic agonists. One might also expect maneuvers that further increase sympathetic tone to have less effect on men. In the present study, maneuvers to increase sympathetic tone caused blood flow to decrease to a greater degree in men. For example, cooling the hand activates sympathetic nervous outflow. This maneuver induced a greater reduction in blood flow in the contralateral hand in men. In three of the nine women, this maneuver paradoxically induced vasodilation in the contralateral hand.

Mental stress and deep inspiration are also known to activate sympathetic nervous outflow. Under standard environmental conditions, men responded to these maneuvers with a cutaneous vasoconstriction. Paradoxically, in women these maneuvers increased hand blood flow. Hand blood flow primarily reflects cutaneous blood flow, but a smaller fraction of the total value is secondary to skeletal muscle blood flow. Thus, a possible explanation of the paradoxical increase in hand blood flow is an augmentation of skeletal muscle blood flow. However, the increase in skin perfusion detected by laser Doppler spectros-
vasodilation may be to preserve episodic nutritive flow during states of excessive vasoconstriction. Cold-induced vasodilation may be due to opposing neurogenic impulses, intermittent abrogation of local adrenergic neurotransmission, or direct effects of cold on the vascular smooth muscle.\textsuperscript{6,13–19,27–29}

To determine if the elevated sympathetic tone in women was plausibly influenced by the estrous cycle, we made serial measurements of hand blood flow as well as of plasma estradiol and progesterone. There was no apparent relation between hormonal changes and hand blood flow. It is therefore more likely that the gender differences in sympathetic control of hand blood flow are due to a tonic effect of estrogen and/or progesterone. This is supported by the observation that finger blood flow in women increases after menopause.\textsuperscript{30} Furthermore, the manifestations of Raynaud’s disease are also attenuated with aging.\textsuperscript{31} Finally, a reduction in estrogenic influence (as evidenced by increases in levels of luteinizing hormone) is associated with the vasomotor phenomenon (“hot flashes”) of menopause.\textsuperscript{32}

\section*{Conclusion}

We found that basal hand blood flow is reduced in women. This appears to be due to a basal increase in sympathetic tone. Furthermore, we describe a paradoxical neurogenic vasodilation to mental arithmetic and deep inspiration that is unmasked at high levels of sympathetic tone. The gender differences in control of hand blood flow may account for the increased incidence of Raynaud’s disease in young women.

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\textbf{Key Words} • thermoregulation • Raynaud’s disease • vasospasm • autonomic control
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