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RESEARCH ARTICLE

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Gender differences in cutaneous vascular and autonomic nervous response to local cooling

Abstract To investigate gender differences in cutaneous vascular reactivity to local cooling we performed cold exposure of one hand and measured laser Doppler (LD) flux on fingers ipsilaterally and contralaterally in a group of 10 healthy females and a group of 10 healthy males. The females were tested twice: in the early follicular and in the mid-luteal phase of the menstrual cycle. We related the characteristics of cutaneous vascular responses to indices of autonomic nervous system activity (heart rate, blood pressure, heart rate variability) at rest and during the cold challenge. In our experimental settings females exhibited greater cutaneous vascular response to local cooling at the ipsilateral site (LD flux decreased to 48.6 ± 6.2 % of the resting value), as compared to males (LD flux decreased to 71.9 ± 6.2 % of the resting value) as well as at the contralateral site (LD flux decreased to 68.2 ± 6.1 % in females and to 85.6 ± 3.8 % in males) ($p < 0.05$, Dunnett's test). The more pronounced cutaneous vascular response in females seems consistent with the finding of their lower sympathetic activity at rest as well as with their heart rate variability indices of greater sympathetic system reactivity to local cold exposure. Correspondingly, males showed a higher level of sympathetic nervous system activity at rest and a predominant reactivity of the parasympathetic system during local cooling at 15 °C. The females in our study, all of whom were premenopausal, exhibited intra-menstrual cycle variability only in cutaneous vascular response at the site of local cooling (LD flux decreased during the early follicular phase to 48.6 ± 6.2 % and during the mid-luteal phase to 29.2 ± 3.2 % of the resting value, $p < 0.05$, paired t-test), but not contralaterally. In addition, we found no intra-menstrual cycle differences in the indices of autonomic nervous system reactivity.

Key words microcirculation · skin · gender · laser-Doppler fluxmetry · cold · heart rate variability

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Introduction

Physiological cutaneous vascular response to local cooling is typically a vasoconstriction that is functionally a part of a thermoregulatory homeostatic response. The impact of local cold exposure is not a simple phenomenon. Local cooling evokes a complex response of skin microcirculation with several underlying components and mechanisms. At the cooling site, the response reflects the effect of cold on alpha-adrenergic receptors [14, 34], on smooth muscle contractility [16], and on the endothelium-dependent local vascular mechanism [3], as well as the contribution of sympathetic vasomotor reflexes [19].

Ample evidence exists supporting the hypothesis that there are gender differences in vascular reactivity to local cold exposure. Most investigators have focused their studies at the level of local vascular response. Bartelink and associates measured laser-Doppler (LD) flux response to local cooling and found significant gender differences in the response; however, their study did not address the possible role of the autonomic nervous system in the gender characteristics of the response [4].

Other investigators focused their studies on clarifying sex differences in autonomic nervous system reactivity using "cold pressor tests" or face immersion tests with the local cold challenge near 0 °C. Their findings are not unequivocal, with some authors having reported the existence of differences in blood pressure and heart rate response to local cold exposure [17, 32, 35], but others not [10, 15, 29, 30]. Very cold stimulus has also been proven to stimulate pain receptors, which can potentate the autonomic nervous response [27]. On the other hand, very little is known about the systemic effect of a local cold stimulus at 15 °C, which would be expected to stimulate primarily skin thermoreceptors and which is routinely used to provoke cold-induced vasospasms. Although direct evidence is lacking, it is very likely that due to its complex nature local vascular cold response is significantly affected by sympathetic nervous activity.

So far only a few studies have been designed to study both local control on microcirculatory blood flow as well as central (sympathetic) control of heart rate variability simultaneously [9, 20]. Cooke and associates have addressed this issue with the use of a protocol to study local control of cutaneous blood flow in response to regional temperature changes in the absence of sympathetic tone induced by thermal sympatholysis [9]. They obtained evidence suggesting that the gender difference of cutaneous blood flow is due to differences in central rather than local control mechanisms. However, their study was based on forearm plethysmography and did not account for microvascular skin response during local cooling, nor did it include the measurement of indices of sympathetic activity.

Our study was therefore aimed at investigating gender specificity of cutaneous microcirculatory response to local cooling as measured by laser-Doppler fluxmetry. We made an effort to associate gender specificity of local vascular responses to indices of the central autonomic nervous reactivity as reflected in heart rate, arterial blood pressure, and heart rate variability during local cooling with a cold stimulus at 15 °C.

Subjects and methods

Subjects

We measured LD flux, heart rate, and arterial blood pressure changes as a result of local cooling in 10 healthy males (age 32.6 ± 3.3 SEM) and age-matched 10 healthy females (34.9 ± 2.4 SEM) with a regular menstrual cycle. None of the subjects used any medication, and none had any symptoms of even mild Raynaud's phenomenon. The National Ethics Committee approved the study, and informed consent was obtained from each subject.

Methods

The subjects were asked not to smoke or to drink coffee or tea for at least 8 hours before the experiments. The measurements were performed from 9 a. m. to 12 a. m. at a room temperature kept between 23 and 25 °C, 30 minutes after acclimatization. The subjects lay in supine position and were instructed not to move during the measurements in order to avoid movement artifacts as much as possible.

LD flux

LD flux was measured with a Periflux P4001 Master/4002 Satellite LD monitor (Perimed, Sweden). The principle governing the measurement of skin perfusion with this technique has been described elsewhere [25]. In brief, the method uses the frequency shift of laser light caused by reflection on moving cells to measure red cell flux. The readings are expressed in perfusion units (PU) related to the Brownian motion in motility standard (emulsion of latex particles) provided by the manufacturer. The LD probes (PF401) were attached to the pulp of the index finger of both hands, and the measurements were done on both hands simultaneously. We refer to the LD flux changes obtained from the cooled hand (always left) as the ipsilateral response and LD flux changes from the right hand as the contralateral response.

Noninvasive measurement of arterial pressure in digital arteries

The 2300 Finapress monitor (Ohmeda, USA) was used for a continuous measurement of finger arterial blood pressure. It provides digital values of systolic, diastolic, and mean arterial pressure. The cuff was attached to the third finger of the right hand.

Standard electrocardiogram with heart rate variability analysis

The surface electrocardiogram was continuously monitored through the standard second lead with the use of a conventional ECG apparatus to determine the average heart rate and R-R intervals before and during the cooling period. A spectral analysis of R-R intervals obtained during two 5-minute recordings (one before and the other during cold exposure) was done by the Fast Fourier Transform (FFT) using Hanning's window. The sampling rate was 500 per second. The results are expressed in Power Spectral Density, the squared amplitude calculated for each frequency. We determined the area under the power spectrum curves over the high frequency (HF) band (0.15–0.4 Hz), which is reported by most authors to be an indicator of parasympathetic nervous system activity [2, 18, 26], and the low frequency (LF) band (0.04–0.15 Hz). From the obtained values, we also calculated LF/HF and LF/(LF + HF) coefficients. The former reflects "sympathovagal balance" and the latter, primary sympathetic modulation of heart rate [31].

Measurement of skin temperature

Skin temperature was measured ipsilaterally with the PeriTemp 4005 Heater (Perimed, Sweden) before the experiments. The probe was put on a fingertip at the site of subsequent LD flux measurements.

Protocol

We measured LD flux, arterial blood pressure, and ECG for 6 minutes before and for 6 minutes during the local cooling of the left hand. The cooling was achieved with flexible cold packs (Comfort Pack, 3M USA, 200 x 300 mm) at 15 °C. The hand was placed between the two packs so that both volar and dorsal side of the hand was cooled. The packs were arranged in a way that the LD probe was not disturbed during the measurements except for the movement artifact at the moment of the placing of the packs. The movement artifact duration was from approx. 10 to maximum 15 seconds and it was excluded from the analysis.

All measurements for female subjects were done twice: on the third to the fifth day after the start of menstrual bleeding – early follicular phase (low hormonal state) and in the mid-luteal phase (high hormonal state). To estimate the time of ovulation as well as the mid-luteal phase in female subjects, body temperature was measured sublingually in the morning. Oral temperatures in females increased from 36.1 ± 0.1 °C in the follicular phase to 36.5 ± 0.1 °C in mid-luteal phase ($p < 0.05$, paired t-test).

Statistics

Mean LD flux, arterial blood pressure, and heart rate values during 6 minutes of cooling were compared to the resting LD flux (average value of 6 minutes recorded immediately before the cooling) in males and in females in both phases of the menstrual cycle by a paired t-test. LD flux changes were expressed as a percentage of resting LD flux. The area under the power spectrum curves over the HF and LF bands as well as the LF/HF and LF/(LF + HF) coefficients during cooling were also compared by a paired t-test to the values obtained before stimulation.

We performed a one-way ANOVA (Dunnett's test) to test the differences between males and females in the relative changes of LD flux, arterial blood pressure, heart rate, and heart rate variability values during cooling. A paired t-test was used to assess the difference in the cold response measured during the early follicular and the mid-luteal phases of the menstrual cycle.

All results are expressed as mean values and standard error of means (SEM).

Results

Resting values

Skin temperatures before the experiments are shown in Table 1. We found no significant differences between the males and the females. Our data showed no statistical difference in resting LD flux (Table 1), blood pressure, and heart rate (Table 2) values between the group of males (n = 10) and the group of females (n = 10), irrespective of the phase of the menstrual cycle (one-way ANOVA).

Table 1 Resting LD flux and local skin temperature values. Data are shown as means ± SEM

	Females early follicular phase	Females mid-luteal phase	Males
LD flux (PU)	223 ± 37	200 ± 43	210 ± 32
Local skin temperature (°C)	33.4 ± 0.6	32.5 ± 0.8	33.9 ± 0.4

PU perfusion units

In contrast, the males had a significantly lower value of the HF component of heart rate variability and a significantly higher value of the LF component with respect to the females in both phases of the menstrual cycle ($p < 0.05$, one way ANOVA). A significantly higher value for males was found also for the LF/HF and the LF/(LF + HF) coefficient values ($p < 0.05$). The values for the HF and the LF components of heart rate variability did not differ between the two phases of the menstrual cycle, nor did the LF/HF and LF/(LF + HF) coefficient values (Table 3).

Effect of cooling on LD flux, blood pressure, heart rate, and heart rate variability

LD flux response

LD flux changes during cooling are shown in Fig. 1. The LD flux in the males and in the females during both phases of the menstrual cycle decreased significantly

Table 2 Systolic (SAP) and diastolic arterial blood pressure (DAP), and heart rate (HR) values before and during cold exposure. Data are shown as means ± SEM

	Females early follicular phase		Females mid-luteal phase		Males	
	rest	cooling	rest	cooling	rest	cooling
SAP (mmHg)	114.4 ± 4.3	118.5 ± 4.2*	117.2 ± 8.3	122.6 ± 7.1*	105.8 ± 3.1	110.3 ± 2.4*
DAP (mmHg)	74.3 ± 3.0	76.3 ± 3.1*	76.3 ± 4.2	79.7 ± 4.3*	73.8 ± 2.4	74.8 ± 2.0
HR (beats/min)	66.9 ± 3.4	65.3 ± 3.1	69.7 ± 3.6	67.5 ± 2.4	65.6 ± 2.0	62.9 ± 2.1*

* Statistically significant difference ($p < 0.05$) compared with the value before cooling

Table 3 Resting heart variability values. Data are shown as means ± SEM

	Females early follicular phase	Females mid-luteal phase	Males
HF (s^2/Hz)	$1.0x10^{-3} \pm 2.8x10^{-4}$*	$1.0x10^{-3} \pm 2.2x10^{-4}$*	$0.5x10^{-3} \pm 1.6x10^{-4}$
LF (s^2/Hz)	$0.6x10^{-3} \pm 1.2x10^{-4}$*	$0.4x10^{-3} \pm 0.6x10^{-4}$*	$1.6x10^{-3} \pm 1.0x10^{-4}$
LF/HF	0.8 ± 0.2*	0.7 ± 0.1*	2.9 ± 0.9
LF/(LF + HF)	0.43 ± 0.05*	0.37 ± 0.05*	0.60 ± 0.07

* Statistically significant difference ($p < 0.05$) when compared to the group of males

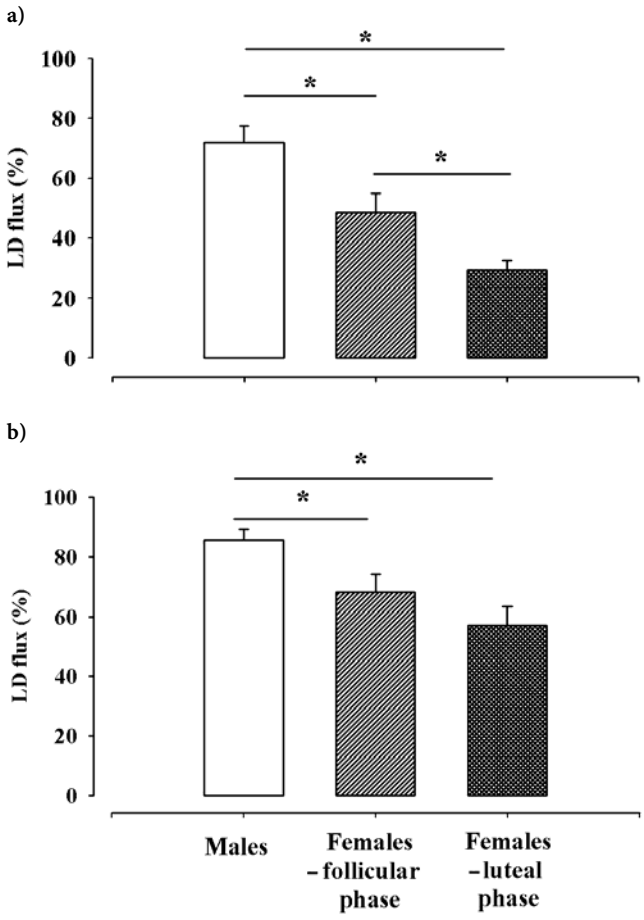

Fig. 1 Relative LD flux changes during local cooling (expressed as a percentage of resting LD flux) measured on the cooled hand (direct response) (**a**) and relative LD flux changes measured on the contralateral hand (indirect response) (**b**). Data are shown as means ± SEM. * Statistically significant difference ($p < 0.05$) between the groups

($p < 0.05$, paired t-test) with the respect to the resting LD flux for both the ipsilateral and the contralateral site.

The females during both phases of the menstrual cycle exhibited significantly greater relative LD flux decrease ipsilaterally and contralaterally compared to the males ($p < 0.05$, Dunnett's test).

We found no significant difference in the LD flux decrease measured contralaterally when comparing the two phases of the menstrual cycle but the females had a significantly greater response to cooling ipsilaterally (the relative LD flux decreased more) during the mid-luteal phase as compared to the early follicular phase ($p < 0.05$, paired t-test).

Systolic and diastolic pressure

Systolic blood pressure values increased significantly in response to local cold exposure in both the males and in the females irrespective of the menstrual cycle phase (Table 2). Diastolic blood pressure values increased only in the females during both phases of the menstrual cycle ($p < 0.05$, paired t-test).

Heart rate

The heart rate decreased significantly during cooling only in the group of males ($p < 0.05$, paired t-test) (Table 2).

Heart rate variability

In the males, the HF component of heart rate variability increased significantly during cooling ($p < 0.05$, paired t-test), while the LF component (Fig. 2) and both coefficients did not change significantly (Fig. 3). On the contrary, in the females during both phases of the menstrual cycle all of the heart rate variability parameters measured increased significantly ($p < 0.05$, paired t-test) as compared to the resting levels. However, for females we observed no differences in the heart rate vari-

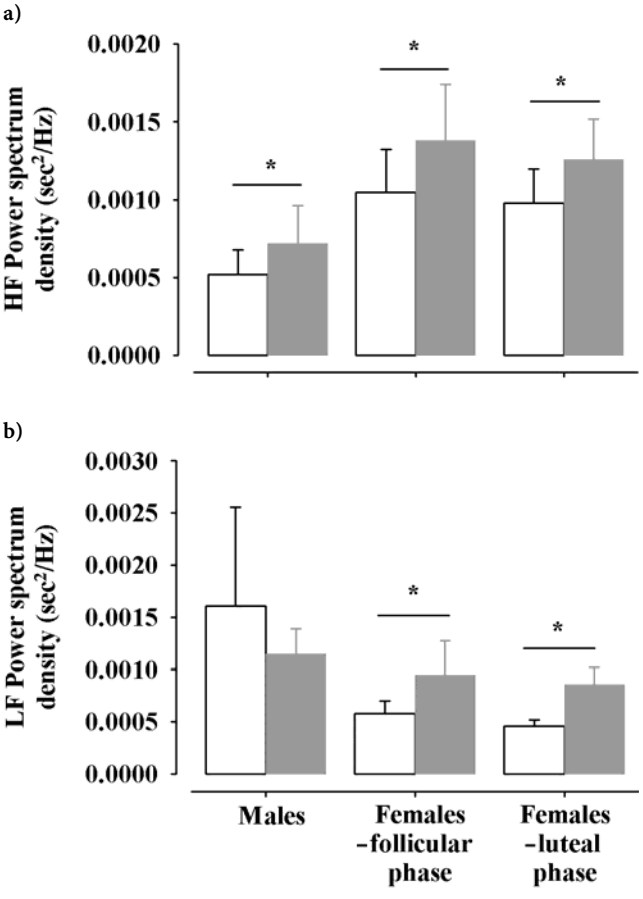

Fig. 2 High frequency (HF) (**a**) and low frequency (LF) (**b**) values measured before (white bars) and during (grey bars) local cooling. Data are shown as means ± SEM. * Statistically significant difference ($p < 0.05$) compared with the value before cooling

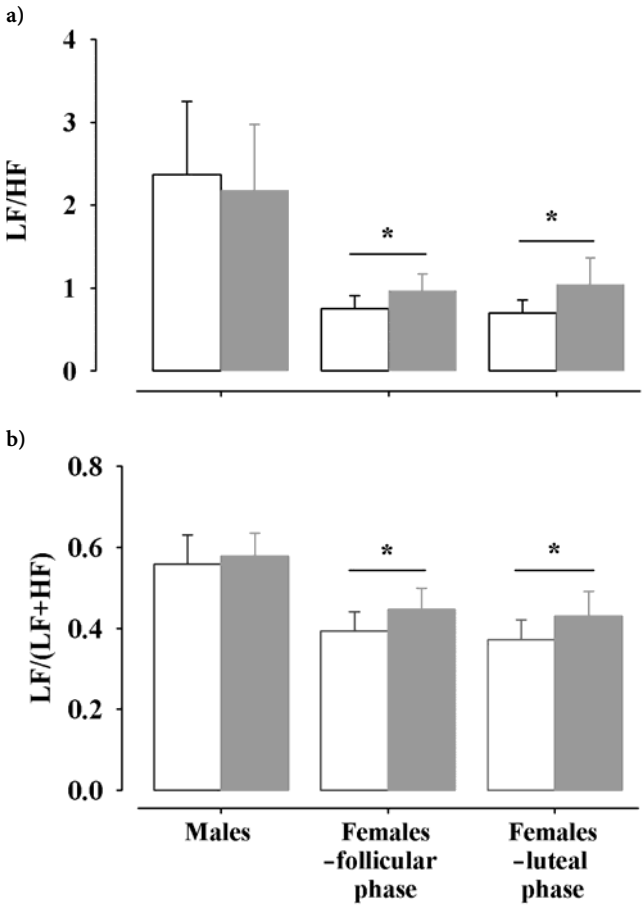

Fig. 3 LF/HF (**a**) and LF/(LF + HF) (**b**) values measured before (white bars) and during (grey bars) local cooling. Data are shown as means ± SEM. * Statistically significant difference ($p < 0.05$) compared with the value before cooling

ability parameters between the two phases of the menstrual cycle.

Discussion

Major findings of the present study are that the females exhibited greater response (LD flux decreased significantly more) to local cooling ipsilaterally and contralaterally, compared to the males, irrespective of the phase of the menstrual cycle. We obtained intra-menstrual difference in the LD flux cold response ipsilaterally, but not contralaterally. At rest, our heart rate variability data indicated that the females expressed a predominance of parasympathetic while the males showed a predominance of sympathetic cardiac control. The heart rate variability data obtained during cooling indicate increased both sympathetic and parasympathetic activity in the females regardless of the menstrual cycle phase and increased parasympathetic activity in the males.

We found no statistically significant difference in resting skin LD flux between the males and females. This is consistent with the study of Bartelink et al. who also found a greater cold-induced decrease of cutaneous LD flow in premenopausal women than in men [4, 5]. In both studies the experimental setting was similar to ours. LD probe was attached to the volar fingertip and hand and fingers were immersed in 15 or 16 °C water bath. Gender differences could be explained by several mechanisms. One of the most plausible explanations is the effect of hormonal status on the peripheral adrenergic synapses. It has been shown that estrogens induce an increase in the sensitivity of vasoconstrictive alpha 2 adrenoceptors [8]. The estrogen-induced increase in either their affinity to catecholamines or the density of adrenergic alpha 2 receptors could lead to an enhanced response to cold in premenopausal women. There is also evidence that progesterone [22] and estrogen [33] could affect peripheral vascular responsiveness acting via endothelium-dependent mechanisms.

In contrast to our study, Charkoudian et al. found no difference in the vasoconstrictor response to local cooling between women in high-hormone and low-hormone phases of oral contraceptive use [7]. However, they measured LD skin flux on the volar side of the forearm after cooling much smaller area of the skin to different temperature (20 °C) which makes their results not directly comparable to ours.

We found a significantly greater LD flux response in the mid-luteal phase when compared to the early follicular phase at the site of cooling but not contralaterally. This seems to rule out female hormonal influence on reflex sympathetic vascular activity. Our finding is in accordance with the study of Minson et al. [23], who were not able to show the influence of normal menstrual cycle on the transduction of sympathetic activity into vascular resistance. These results seem to indicate that the intra-menstrual cycle variability observed in the vascular response to cold is due mainly to local vascular mechanisms.

Besides local vascular mechanisms, gender characteristics could also influence vasculature through the modulation of central autonomic nervous system activity. One of our goals was therefore to establish how cutaneous vascular response to local cooling is related to indices of autonomic nervous system reactivity. Except for the studies of cardiovascular responses to cold pressor test or face cooling [10, 17, 28–30] no comparable data on cardiovascular reactivity have been obtained regarding gender differences in response to local cooling. The results of these studies are inconsistent possibly due to the use of different populations and protocols. There is no comparable study involving the quantitative aspect of local cold challenge. Our study indicates that local cold challenge at 15 °C significantly influences the indices of autonomic nervous activity. Our results show that heart rate decreased significantly during cooling in

males, while females showed no heart rate response, irrespective of the menstrual cycle phase. In contrast, there was a comparable increase in the systolic blood pressure in both males and females, while diastolic blood pressure increased only in females. These results are in accordance with the heart rate and arterial blood pressure adjustments obtained after whole body cold exposure at similar temperatures in the study of Wagner et al. [35].

We also found that the females at rest expressed a predominance of vagal control of the heart as indicated by a higher proportion of HF, while the males showed a predominance of sympathetic cardiac control as indicated by a greater LF, LF/HF and also LF/(LF + HF) coefficient, which is in agreement with previous studies [2, 18, 26, 28, 30]. During cooling, the females showed an increase of LF/(LF + HF) (indicating increased sympathetic activity) and HF (indicating increased parasympathetic activity) regardless of the menstrual cycle phase, while the males showed increased HF value.

Sympathetic neural activity plays a significant role in peripheral vascular responsiveness and was found to be responsible for sex differences in blood flow [9, 21]. Reflex thermoregulatory control of cutaneous vasoconstrictor system was also found to be influenced by female reproductive hormone status [6]· There are numerous studies showing gender differences in autonomic nervous system output [1, 11, 13, 36]. Furthermore, sympathetic (as revealed by microneurography) and cardiovagal baroreflex sensitivities were shown to change during menstrual cycle [23, 24].

The HRV analysis made in our study could not be directly related to the sympathetic control of blood vessels. Nevertheless, the LD flux changes during cooling seem to parallel changes in HRV parameters: the increase of the LF/(LF + HF) in the females is consistent with the greater LD flux decrease compared with the males. Correspondingly, the indices of a predominantly parasympathetic response and lower sympathetic reactivity are consistent with the smaller cutaneous vascular cold response in males.

In our experiments we observed no differences in the heart rate variability parameters between the two phases of the menstrual cycle. This finding also seems to go along with our observation that LD flux response to cooling was significantly greater only ipsilaterally, but not contralaterally, when comparing the mid-luteal phase to the early follicular phase of the menstrual cycle.

Several mechanisms could be responsible for the difference in responses to local cooling in males and females, and also in females during different phases of the menstrual cycle. Our study does not allow us to evaluate the relevance of alpha1, alpha2 and beta2 receptors to local cold response. However, according to the study by Ekenwall et al. vasoconstriction on local cooling in human finger skin microcirculation is mediated predominantly by adrenoceptors of alpha2 subtype [12].

Another limitation of our study is also the fact that we measured only oral temperature changes to estimate the menstrual cycle phase. With such measurements it is possible to estimate the phases of the menstrual cycle reasonably well [23]. Nevertheless, this could mean that our experiments were not performed exactly in the lowest and in the highest hormone phases.

Conclusion

In our experimental setting females, compared to males, exhibited greater cutaneous vascular response to local cooling of a hand ipsilaterally and contralaterally, as measured by LD fluxmetry in glabrous skin area. The more pronounced vascular response in females seems to be consistent with our HRV data suggesting a gender difference in autonomic control of the heart.

The premenopausal females in our study exhibited intra-menstrual cycle variability only in the cutaneous vascular response at the site of local cooling but not contralaterally. Furthermore, we obtained no intra-menstrual cycle differences in the indices of autonomic nervous system reactivity. This seems to be consistent with the hypothesis that intra-menstrual variation of cutaneous vascular reactivity to cold in glabrous skin area is due mainly to local vascular mechanisms.

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