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Exercise hyperpnea and hypercapnic ventilatory responses in women

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Summary
We studied the relationship between exercise hyperpnea (i.e., ventilatory dynamics) at the onset of exercise and hypercapnic ventilatory response (HCVR), and their differences between the follicular (FP) and luteal (LP) phases of the menstrual cycle in six healthy females. HCVR was tested under three O_2 conditions: hyperoxia ($FiO_2 = 1.0$), normoxia (0.21), and hypoxia (0.12). HCVR was defined as the relationship between the end-tidal P_{CO_2} and minute ventilation ($\dot{V}_E$) using the regression line of the CO_2 slope and a mimetically apneic threshold of CO_2. HCVR provocation and measurements were conducted using an inspired CO_2 concentration of up to approximately 8 mmHg higher than the end-tidal P_{CO_2} level of basal isocapnic the end-tidal P_{CO_2} at each menstrual both the slope and threshold in HCVR showed no statistically significant difference between LP and FP under any inspired FiO_2 conditions. In the case of exercise hyperpnea during the onset of submaximal exercise, the mean response time (MRT) in $\dot{V}_E$ dynamics showed no significant difference between LP and FP. Consequently, MRT in $\dot{V}_E$ response was not related to the slope in HCVR. During steady-state exercise, even though the $\dot{V}_E/\dot{V}_{CO_2}$ showed no significance between LP and FP, $\dot{V}_E/\dot{V}_{CO_2}$ was significantly related to the slope in HCVR ($r = 0.59$, $P < 0.05$). Exercise ventilation (i.e., $\dot{V}_E/\dot{V}_{CO_2}$) would partly be adjusted by the enhancement of the chemoreflex drive to CO_2 only during the steady-state exercise.

Introduction

The apneic threshold and the sensitivity of ventilatory response to carbon dioxide (CO_2), mediated by the central

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chemoreflex, are unchanged between the follicular (FP) and luteal (LP) phases.[1–3] White et al.[3], Takano et al.[4] and Slatkovska et al.[5] have demonstrated that the different phases of the menstrual cycle have no effect on ventilatory responses to hypercapnia (HCVR), while some studies reported that ventilatory responses to hypercapnia increase during LP.[6–8] Thus, studies of ventilatory responses to higher CO_2 have produced conflicting results. Morelli et al.[1] reported that the sensitivities in HCVR under hyperoxia, attributed to central chemoreflex drive, were similar between LP and FP. In the present study, we measured the threshold and sensitivity of HCVR, under hypoxia, mediated by the sum of both central and peripheral chemoreflexes.

From another point of view, we also examined the relationship between exercise hyperpnea at the onset of exercise (i.e., ventilatory dynamics) and alterations in HCVR between the FP and the LP of the menstrual cycle. This approach was informed by our previous observations that HCVR accounts for 9% of the variance of hypoxic exercise hyperpnea at the onset of exercise,[9] which provided evidence that HCVR might contribute less to exercise hyperpnea at the onset of exercise. However, under normoxic conditions, it is unclear to what degree HCVR contributes to exercise hyperpnea during submaximal exercise. In addition, the relationship between the characteristics of HCVR and exercise hyperpnea under normoxic conditions in women has yet to be determined.

Thus, the present investigation was undertaken in order to examine the hypothesis that menstrual cycle phase has significant effect on the chemoreflex drive to CO_2 under any FiO_2 condition, and leads to steeper ventilatory dynamics and greater ventilation during exercise in the luteal phase.

Methods

Subjects

Six untrained females (age, 21.2±0.4 years; height, 160.5±3.6 cm; weight, 51.8±4.1 kg; mean±SD) participated in the present study. None had any experience of smoking during at least the preceding 2 years, and none had cardiovascular diseases, as determined by a written medical history and a 12-lead resting electrocardiogram. All subjects gave their informed consent to participate prior to beginning the experiment, which was approved by the ethics committee of the Institutional Review Board of Prefectural University of Kumamoto. All experimental procedures and protocols confounded to the Declaration of Helsinki. Each subject underwent tests during the period 4–10 days after the start of FP and LP. The subjects' resting body temperatures were significantly higher during LP (36.5±0.2 °C) than during FP (36.2±0.2 °C) ($P<0.01$). No pregnant women were participated in this investigation.

HCVR test

The first test measured isocapnic ventilatory response during each menstrual phase as the subject breathed spontaneously under three different conditions: normoxia (FiO_2 of 0.21), hyperoxia (FiO_2 of 1.00), and hypoxia (FiO_2 of 0.12), for 2 min of continuous exposure in each case. In the second test, HCVR was tested as PET_{CO_2} underwent a controlled increase of approximately 1.0% (~8 mmHg) to a level higher than that attained in isocapnic ventilatory response under FiO_2 levels of 1.0, 0.21 and 0.12. The subjects performed at the same level as they did in the first test. Measurements of ventilatory parameters were collected during a 2-min period of steady-state ventilation after exposure to an FiO_2 of 0.21 for 4 min.

Exercise test

Exercise tests were carried out under close medical supervision, and the subjects were continuously monitored by 12-lead electrocardiography (ECG). The tests were carried out in the afternoon, a few hours after a light meal. The subjects underwent an incremental bicycle exercise (*incremental exercise*: starting from rest, with 20 W added every 2 min) to voluntary exhaustion, which was defined as the inability to sustain the recommended pedaling frequency of 40–60 revolutions/min (rpm) despite vigorous encouragement by the operators. An electromagnetically braked cycle ergometer (RS-232c, Combi, Tokyo, Japan) was utilized, and pedaling frequency was digitally displayed to the subjects throughout the tests. Subsequently, we determined the ventilatory threshold (VTh) at which the ratio of ventilation to oxygen uptake (i.e., $\dot{V}_E/\dot{V}_{O_2}$) and the end-tidal P_{O_2} start to increase without any increase or decrease in end-tidal P_{CO_2}, and at which time we see the point of a nonlinear increase in $\dot{V}_E$.[10]

On the day following the incremental test, the subjects performed two repetitions of a square-wave exercise (*constant load exercise*) on the same cycle ergometer, at a workload corresponding to 60% of the VTh power output determined the day before. Pedaling frequency was maintained at ~60 rpm throughout the experiment. On-transitions were from unloading work (i.e., 0 W) for 3 min to the imposed load, which was attained in ~3 s, and off-transitions were from the imposed load to 0 W of work for 3 min work, which was then continued for 3 min. Unloaded cycling might cause neurological factors to contribute slightly to exercise hyperpnea at the onset of exercise (i.e., phase I).[9,11]

Measurements

Expiratory flow measurement was performed using a mass flow sensor (hot wire anemometer, RF-H, Minato Medical Science, Osaka, Japan), calibrated before each experiment by a 3-L syringe at three different flow rates in which its accuracy was regulated automatically within ±1.0%. Tidal volume (VT), breathing frequency (fR), and $\dot{V}_E$ were calculated by integrating the flow tracings recorded at the mouth of the subject. The O_2, CO_2, and N_2 concentrations in the expired gas were continuously drawn from the mouth piece and analyzed by mass spectrometry (WSMR-1400, Arco System, Chiba, Japan). Precision-analyzed gas mixtures were used for calibration of the mass spectrometer before each experiment. Oxygen uptake ($\dot{V}_{O_2}$) and carbon dioxide output ($\dot{V}_{CO_2}$) were determined by continuously monitoring PO_2 and P_{CO_2} at the mouth of the subject throughout the respiratory cycle, and from established mass balance

equations after alignment of the expiratory volume and expiratory gas tracings and A/D conversion. The digital data were transmitted to a personal computer, and stored on disk. $\dot{V}_{O_2}$ and $\dot{V}_{CO_2}$ were expressed in standard temperature, pressure, dry (STPD) units, and $\dot{V}_E$ in body temperature and pressure saturated (BTPS) units. The gas exchange ratio (R) was calculated as $\dot{V}_{CO_2}/\dot{V}_{O_2}$. End-tidal PO_2 (PET_{O_2}) and PET_{CO_2} were determined from PO_2 and P_{CO_2} gas tracings, respectively. Cardiac frequency (fH) was determined beat-by-beat from R–R intervals by a cardiotachometer coupler (AG901, Nihon-Koden, Tokyo, Japan).

Data analysis

The average values of individual ventilatory and metabolic variables were calculated using breath-by-breath data obtained during the last 30 s of each test. The linear part of the curve relating $\dot{V}_E$ to PET_{CO_2} was analyzed by the least-squares linear regression equation $\dot{V}_E = S(PET_{CO_2} - B)$, where S is the slope, that is, a measure of ventilatory sensitivity to hypercapnia, and B is the x-intercept, that is, the PET_{CO_2} level at which the regression line crosses the CO_2 axis.

Resting values were obtained by calculating averages during the last 60 s of rest while undergoing the incremental exercise test. Values obtained during the last 30 s of the incremental exercise were considered to be the "*peak*" values of the work rate ($\dot{W}$), $\dot{V}_{O_2}$, and fH. During the constant load exercise, $\dot{V}_E$ data obtained during the two repetitions were time-aligned and superimposed for each subject. Steady-state values, defined as "ss", and recovery resting values were calculated over 60 s intervals during the last minute of constant exercise, and between the fourth and fifth minutes of recovery. For on- (0 W-to-exercise) and off- (exercise-to-0 W) $\dot{V}_E$ kinetics analysis, data smoothing was obtained by calculating a three-point moving average.[12] $\dot{V}_E$ on-kinetics during the transient phase of exercise was evaluated by fitting an exponential function of the type.

$$y = a + b[1 - e^{-(t-c)/d}] \quad (1)$$

and the parameter values (c and d) were determined to yield the lowest sum of squared residuals. In Eq. (1), a indicates the baseline value, b the amplitude between a and the new steady state value (a+b), c is the time delay (TD), and d is the time constant of the variable. Mean response time (MRT) was defined as c+d.

For the purposes of the present study, we were not interested in discriminating between the different components of phase I, II, and III.[13] Thus, we decided to utilize MRT which would allow the evaluation of the overall rate of adjustment of the $\dot{V}_E$, such as time of response, by utilizing a monoexponential function equivalent to that presented as Eq. (1).

Statistical analysis

Data were evaluated for differences between menstrual cycle and the three FiO_2 conditions using analysis of variance (ANOVA) procedures. Two-factor ANOVAs were utilized with repeated measures as necessary to determine whether a significant difference existed between LP and FP phases and the three FiO_2 conditions. When significant differences were found, a post-hoc Tukey's test was used to discriminate exactly where they occurred. Linear regression analysis was employed for each experiment in order to obtain the threshold and slope of the $\dot{V}_E$ vs. PET_{CO_2} relationship. A probability level of $P<0.05$ was accepted as significant. Data are presented as the mean$\pm$standard deviation ($x \pm$ SD). In addition, as a method to partially circumvent the likelihood of a type II error as a consequence of our small sample size, the effect size ES $=$ (mean$_1$–mean$_2$)/SD was calculated for selected results that did not achieve significance and the pooled SD was calculated when SDs were unequal.[14] Cohen's conventions for effect size were adopted for interpretation, where ES $= 0.2$, 0.5, and 0.8 are considered small, medium, and large, respectively.

Results

Ventilatory responses to hypercapnia in both LP and FP phases

The data regarding changing $\dot{V}_E$ responses in a typical subject are shown in Fig. 1. The $\dot{V}_E - PET_{CO_2}$ response line shifted to the left by 2 Torr in PET_{CO_2} from FP to LP (Fig. 2). However, although the slope (parameter S) in HCVR showed no statistical significance between LP and FP under any test conditions, the S in HCVR tended to be higher in LP under normoxic (ES: 0.59) and hypoxic conditions (ES: 0.55) as compared to that in FP. The CO_2 thresholds (parameter B) also tended to be lower in LP under all FiO_2 conditions (Table 1), but they did not show a statistical significance between LP and FP. Interestingly, the B values indicating the apneic threshold were closely linked to the resting PET_{CO_2} under normoxic conditions ($r = 0.79$, $P<0.01$), independent of the menstrual cycle.

Ventilatory and gas exchange parameters during maximal and submaximal exercise

At peak performance, the $\dot{V}_{O_2}$ peaks were 29.8 ± 7.8 ml kg^{-1} min^{-1} in LP and 30.7 ± 10.3 ml kg^{-1} min^{-1} in FP, which shows no significant difference. Other metabolic parameters at peak exercise also failed to achieve statistical significance between the LP and FP (Table 2). During submaximal 60%VTh exercise, some parameters also tended to be greater in LP than in FP (ES: $\dot{V}_E$; 0.72, fH; 0.52, $\dot{V}_{O_2}$; 0.80, $\dot{V}_{CO_2}$; 0.65, PET_{CO_2}; 0.53), but we did not observe a statistical significance in these parameters between LP and FP. For the transient phase of 60%VTh exercise, $\dot{V}_E$ dynamics could be fitted by mono-exponential treatment of each individual's data (Fig. 3). As the MRT values in $\dot{V}_E$ dynamics were 90.1 ± 18.7 and 91.2 ± 25.8 s in LP and FP, respectively, they showed no significant difference between phases.

Relationship between MRT in $\dot{V}_E$ dynamics or $\dot{V}_E/\dot{V}_{CO_2}$ and HCVR under normoxic condition

To what degree HCVR contributes to exercise hyperpnea during submaximal exercise, the relationships between

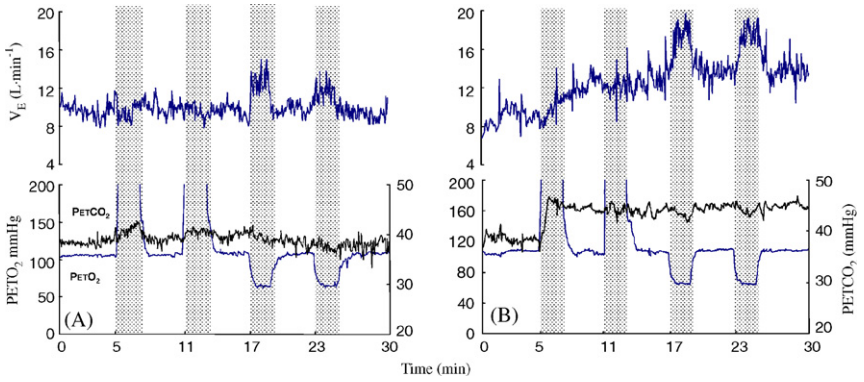

Figure 1 Typical results from an isocapnic (A) and hypercapnic (B) experiment in one subject. Upper panel shows ventilation. Lower panel shows end-tidal P_{CO_2} and P_{O_2}. The shadow areas indicate abrupt changes in the concentrations of inhaled O_2 (FiO_2: 1.0, and 0.12), which was duplicately repeated. PET_{CO_2} was maintained mostly constant throughout the isocapnic experiment (A). During hypercapnic experiment (B), HCVR was tested as PET_{CO_2} underwent a controlled increase of approximately 1.0% (~8 mmHg) to a level higher than that attained in isocapnic ventilatory response.

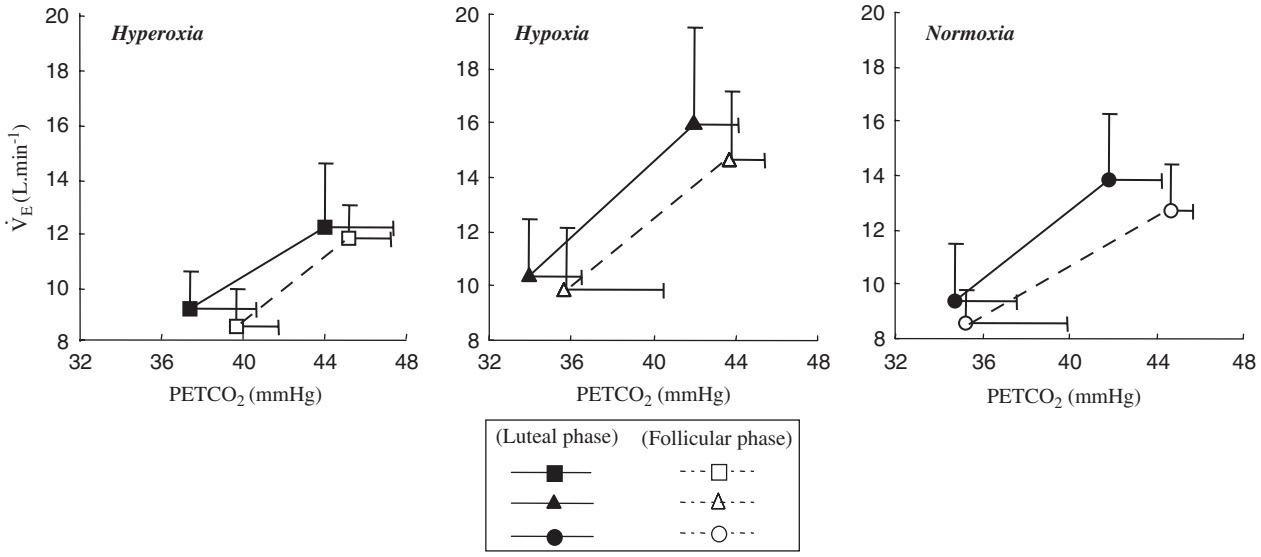

Figure 2 Mean $\dot{V}_E - PET_{CO_2}$ plots in each menstrual phase, luteal phase (LP; solid line) and follicular phase (FP; dotted line) in different FiO_2 conditions.

Table 1 HCVR under any FiO_2 conditions between LP and FP.

	FP	LP
HCVR		
Normoxia		
S	0.49±0.09	0.62±0.30
B	33.8±10.9	29.5±10.8
Hypoxia		
S	0.69±0.18	0.80±0.21
B	30.6±7.8	27.4±7.5
Hyperoxia		
S	0.74±0.33	0.61±0.27
B	36.0±6.3	31.5±11.7

S (L min^{-1} mmHg^{-1}): slope in HCVR, *B* (mmHg): threshold in HCVR.

changes in the response time of $\dot{V}_E$ dynamics or steady-state $\dot{V}_E/\dot{V}_{CO_2}$ and the *S* in HCVR were analyzed. As shown in Fig. 4A, the MRT in $\dot{V}_E$ dynamics was not related to the *S* ($r = 0.15$, n.s.) for pooled data from both LP and FP under normoxic conditions; the alteration in MRT thus was unaffected by the increase of the *S* in HCVR. In contrast, during steady-state exercise, $\dot{V}_E/\dot{V}_{CO_2}$ was also found to be significantly related to the *S* ($r = 0.59$, $P < 0.05$) in HCVR (Fig. 4B).

Discussion

In order to examine the relationship between exercise hyperpnea at the onset of exercise and alterations in HCVR between the FP and LP of the menstrual cycle, we studied differences in ventilation to hypercapnia and exercise in six healthy females with the following results: (1) menstrual cycle did not occur in the alternations in PET_{CO_2} and PET_{O_2}

Table 2 Ventilatory and gas exchange parameters at resting, during submaximal and peak exercise.

	$\dot{V}_T$ (mL)	fR (n min^{-1})	$\dot{V}_E$ (L min^{-1})	fH (beats min^{-1})	$\dot{V}_{O_2}$ (mL min^{-1})	mL min^{-1} kg^{-1}	$\dot{V}_{O_2}$ (mL min^{-1})	*R*	PET_{CO_2} (mmHg)	PET_{O_2} (mmHg)	WR (W)	$\dot{V}_E/\dot{V}_{CO_2}$
Resting												
FP	580±97	16.0±3.3	8.95±0.78	82±15	209±19	(4.0±0.4)	174±20	0.83±0.03	36±3	109±3	—	53.8±9.8
LP	643±121	15.3±4.1	9.49±1.85	82±10	207±14	(4.1±0.6)	175±29	0.84±0.09	35±3	111±6	—	54.9±5.7
60%VTh												
FP	1196±296	23.1±7.7	25.46±4.14	120±11	841±76	(16.2±1.0)	815±81	0.97±0.04	42±3	107±5	50±6	31.1±3.5
LP	1262±372	24.8±7.3	28.51±3.89	125±8	911±84	(17.8±1.2)	872±87	0.95±0.05	40±4	109±5	54±7	32.8±4.4
Peak exercise												
FP	1649±198	47.6±12.1	76.80±15.68	189±6	1816±348	(30.7±10.3)	2315±441	1.28±0.04	37±4	121±4	153±19	33.2±3.3
LP	1585±147	49.8±10.9	77.59±13.75	187±7	1797±296	(29.8±7.8)	2286±407	1.27±0.04	36±3	121±3	153±21	33.8±3.5

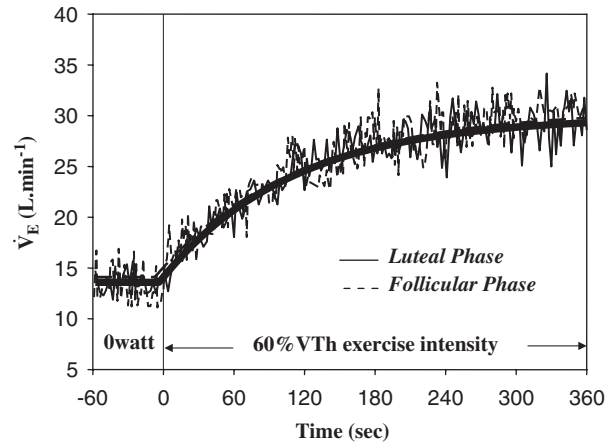

Figure 3 The representative data of $\dot{V}_E$ on-kinetics during submaximal exercise for a typical subject in LP (solid line) and FP (dotted line). Overlaid exponential line was fitted on breath-by-breath $\dot{V}_E$ data at each menstrual phase, which was very similar trend at both LP and FP.

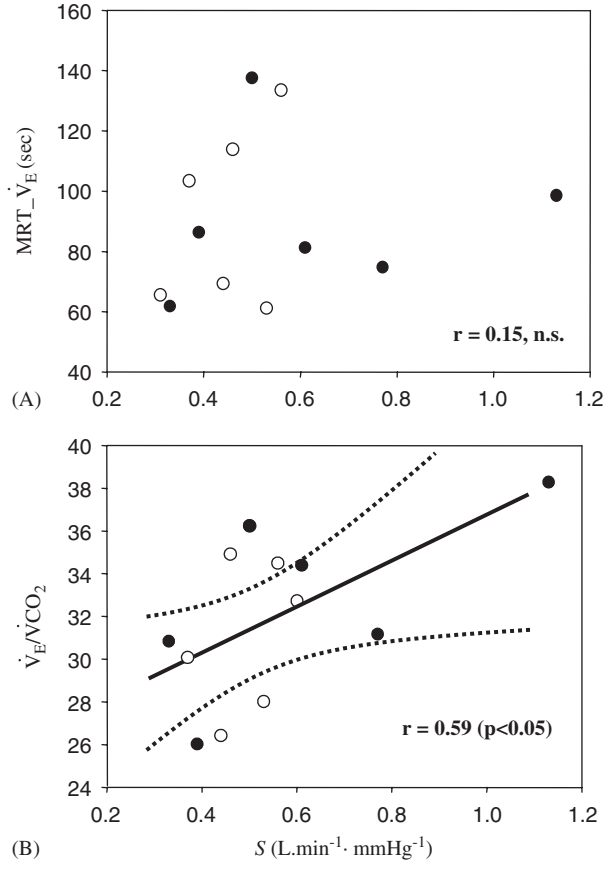

Figure 4 The relationships between MRT of $\dot{V}_E$ on-kinetics (A) or $\dot{V}_E/\dot{V}_{CO_2}$ (B) during submaximal exercise and the *S* in HCVR under normoxia using individual data. Regression line was applied using all data. LP (●), FP (○). Significant correlations were found at the relationships of $\dot{V}_E/\dot{V}_{CO_2}$ and *S* in HCVR.

repsonses at rest and during exercise, (2) the line of HCVR in LP was found to be slightly steeper and shifted to the left to a lower PET_{CO_2} compared to FP, (3) for exercise hyperpnea at

the onset of submaximal exercise, the MRT values in $\dot{V}_E$ were not closely associated with the *S* in HCVR and were independent of the menstrual cycle, (4) greater $\dot{V}_E/\dot{V}_{CO_2}$ values were found to be significantly correlated to an increase in the *S* in HCVR. Exercise ventilation (i.e., $\dot{V}_E/\dot{V}_{CO_2}$) would be adjusted by the enhancement of the chemoreflex drive to CO_2 only during the steady-state exercise.

HCVR and the menstrual cycle

Hyperoxia inhibits actions in the peripheral chemoreceptor, and *S* values of HCVR under hyperoxia have been attributed to the central chemoreflex drive to CO_2. Although in the present study we observed no difference in CO_2 sensitivity between LP and FP under hyperoxia, the *S* in LP showed a tendency to increase under normoxia and hypoxia, suggesting a proclivity toward hypoventilation under hyperoxia in LP. Morelli et al.[1] reported no difference in the central chemoreflex drive to CO_2 between LP and FP. Otherwise, *S* values were found in the present study to be somewhat higher in LP than in FP under hypoxic (ES: 0.55) and normoxic (ES: 0.59) conditions, even though there were no significant differences. Some studies have identified an augmented parameter *S*,[6,15–17] while others have not.[18–20] In the present study, HCVR was found to be slightly steeper and shifted to the left to a lower PET_{CO_2}. The augmentation in chemosensitivity found with progesterone could be accounted for by an effect either on the carotid body or areas of the central nervous system that receive carotid body impulses, although a cross-circulation study in dogs suggested that peripheral chemoreceptors are not necessary for the acute hyperventilation induced by progesterone.[21] Based on the above considerations, we believe that ventilatory stimulation with progesterone in LP is unlikely to be exerted directly on the brainstem via the central and peripheral chemoreflex drives but rather via some higher centers, such as the hypothalamic area.[22] Although we did not address the administration of sexual hormones, combined progesterone and estrogen treatment has a greater impact on ventilatory control than does progesterone alone.[2,23]

$\dot{V}_E$ dynamics at the transient phase of exercise

Considering the increased HCVR in LP, it would appear surprising that the MRT values in $\dot{V}_E$ dynamics at the onset of exercise were similar between LP and FP, which does not provide evidence of progesterone-induced hyperpnea in LP during the transient of exercise.

The carotid bodies are considered to be the primary mediators of $\dot{V}_E$ dynamics at the transient phase in response to work rate.[13,24,25] Reduced carotid-body gain in response to induced hyperoxia[26–28] and carotid-body resection[29] result in slowed $\dot{V}_E$ dynamics. The lack of difference in MRT in $\dot{V}_E$ dynamics between LP and FP in women in the present study would support a similarity in the peripheral chemoreflex drive via the carotid body during menstrual cycle. Ventilatory response to progesterone does not require input from the carotid body,[21] and its occurrence after the central administration of progesterone implicates a central site of action. This supports the explanation that the ventilatory response to progesterone is mediated through an estrogen-dependent progesterone receptor-mediated genomic mechanism at the level of the hypothalamus.[30] Serotonin (5HT) release in the hypothalamus is at least partially dependent upon circulating levels of estrogen and progesterone.[31,32]

In another aspect of related $\dot{V}_E$ dynamics, the lowering of body CO_2 stores before main exercise may in part explain the slower $\dot{V}_{CO_2}$ dynamics and, subsequently, the slower $\dot{V}_E$ dynamics.[33] Judging from our results, the difference in CO_2 stores between LP and FP could not be identified, even though resting PET_{CO_2} tended to be lower in LP compared to FP. If CO_2 stores might vary between LP and FP, it will be important to consider the influence of CO_2 stores on $\dot{V}_E$ dynamics at the onset of exercise.

$\dot{V}_E$ response during exercise related to CO_2 chemoreflex drive

In a previous study we observed that HCVR during exercise varying exercise intensities was unaltered and that HCVR accounts for 9% of the variance of hypoxic exercise hyperpnea at the onset of exercise.[9] Therefore, hypoxic ventilatory responsiveness rather than HVCR would contribute greatly to exercise hyperpnea. Even though the *S* in HCVR tended to be apparently higher in LP under normoxia (ES: 0.59) compared to FP, the *S* would not lead to an increase in the rate of $\dot{V}_E$ dynamics (Fig. 4A). HCVR's action exerted mostly on a central site due to an increase in progesterone in LP as described above consequently contributed less to exercise hyperpnea at the onset of exercise.

By contrast, $\dot{V}_E/\dot{V}_{CO_2}$ during the steady-state of exercise was related to the *S* in HCVR ($r = 0.59$, $P<0.05$, seen in Fig. 4B). Rebuck et al.[34] and Martin et al.[35] found a similar close relationship between HCVR and exercise $\dot{V}_E$ below the anaerobic threshold. Consequently, HCVR corresponded with $\dot{V}_E/\dot{V}_{CO_2}$, which could be attributed to merely chemoreflex sensitivity to CO_2 via a mostly central site, while progesterone's effects on ventilatory stimulation may be easily verified only during steady-state exercise. Therefore, the values of the ventilator equivalents to CO_2 ($\dot{V}_E/\dot{V}_{CO_2}$) and $\dot{V}_E$ dynamics might be differentially regulated by the chemoreflex drive to CO_2 between centrally and peripherally located sites.

In summary, the present study reached the following conclusions: (1) menstrual cycle did not occur in the alteration in PET_{CO_2} and PET_{O_2} repsonses at rest and during exercise, (2) the regression lines between PET_{CO_2} and $\dot{V}_E$ moved upwards in LP compared to those in FP, but these lines showed no significant difference, (3) for exercise hyperpnoea at the onset of submaximal exercise, MRT values in $\dot{V}_E$ were not associated with the alteration of the *S* in HCVR, (4) during steady-state submaximal 60% VTh exercise, greater $\dot{V}_E/\dot{V}_{CO_2}$ was closely related to an increase in the *S* in HCVR. These findings provide evidence that HCVR contributes relatively less to exercise hyperpnoea at the onset of exercise, while it is related to exercise ventilation during steady-state exercise. Both exercise hyperpnoea and exercise ventilation were independent of the menstrual cycle.

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Conflict of interest

The authors declare that they have no competing interests.

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