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Research article

Effects of the menstrual cycle on expiratory resistance during whole body exercise in females.

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Abstract
Our objective was to determine if the menstrual cycle affected expiratory resistance developed during progressive incremental exercise in females. Eleven females (age = 19.7 ± 1.1 yr., body mass = 58.9 ± 8.8 Kg, height = 1.65 ± 0.3 m) gave consent to participate in the study. Participants were studied during the follicular (day 7 ±2 days following onset of menses) and luteal (day 21 ±2 days following onset of menses) phases of their menstrual cycle. The expiratory resistance was significantly higher during the follicular phase at maximal workload versus the luteal phase (1.0 ± 0.06 cm H_2O/L/sec vs. 0.9 ±0.07 cm H_2O/L/sec.: $p< 0.05$). No other differences were found in expiratory resistance, oxygen uptake or maximal heart rate during exercise. Results showed that the increase in expiratory resistance during the follicular phase of the menstrual cycle may be contributing to the changes in the pulmonary system of females as reported by other authors.

Key words: airway resistance, female, menstrual cycle, exercise.

Introduction

Exercise-induced pulmonary limitations occur more frequently in healthy females compared to age- and height-matched male subjects (Harms et al., 1998; McClaran et al., 1998). McClaran et al. (1998) reported that female subjects (88% of the subjects tested) exhibited expiratory flow limitation (EFL) during moderate as well as intense workloads. The females represented a broad spectrum of fitness levels from moderately to highly fit. In contrast only about 50% of elite endurance trained male subjects were found to experience limitation of their expiratory tidal volume at maximal exercise loads (Johnson et al., 1992). There are limited data examining these differences in females so a larger number of subjects need to be studied in order to determine if these limitations occur in a wider range of female subjects.

Gender differences as noted above may be due to two factors: hormonal differences with progesterone and oestrogen being most important (Harms, 2006), and structural / morphological differences. Most of the hormonal effects on ventilation appear to be due to elevated levels of progesterone (see Harms, 2006). Serum progesterone was found in higher concentrations in the luteal portion of the normal menstrual cycle (Dombovy et al., 1987). Inspiratory muscle endurance has been reported to be greater during the mid-luteal phase (progesterone concentration increasing) compared to mid-follicular phase (Chen and Tang, 1989). There does not appear to be a consensus with regard to the idea that progesterone alters the ventilatory response to exercise but more studies need to be done in order to clarify this.

Differences in lung structure have been reported in females versus male subjects. Males have larger airways (Mead, 1980), lung volumes, and diffusion surfaces (Schwartz et al., 1988) compared to female subjects. In addition, it has been reported that females have smaller lung volumes and lower maximal expiratory flow rates, corrected for sitting height (Crapo et al., 1982). These structural differences in the female pulmonary system may impede their ventilatory response to exercise and exactly how remains to be determined.

The flow-interruption method for measuring airway resistance has been extensively tested for its reliability and was a non-invasive test for providing valuable data about respiratory functions. The flow-interruption method was based on the idea that during the transient interruption of expired airflow, alveolar pressure would equilibrate with mouth pressure (Chowienczyk et *al*, 1991). Airway resistance was defined as the pressure difference between the alveoli and the external environment divided by the expired flow measured at the mouth (Oswald-Mammosser et al., 1997). Although body plethsmography methods have traditionally been used for collection of such data, measurement of airway resistance was not possible during exercise if individuals are confined to such an area (Van Altena and Gimeno, 1994). For preliminary testing, however, the interrupter method was sufficient and provided a simple means for measuring airway resistance during exercise.

As noted above female subjects experience EFL during moderate as well as intense exercise levels (McClaran et al., 1999). These female subjects were studied during the follicular phase of their menstrual cycle when progesterone was low. Since progesterone has been suggested to affect the pulmonary system we wondered if the sex hormones might affect the flow characteristic in female subjects. Therefore, the purpose of this study was to examine if differences occurred in exercise expiratory flow resistance between the two phases of the menstrual cycle (follicular versus luteal).

Methods

Subjects

Eleven female subjects gave informed consent to participate in this study. The Wilfrid Laurier University ethics committee had given prior approval of all study proce-

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dures. The young women were between the ages of eighteen to twenty-four and from various levels of physical fitness (Table 1). The only criteria required was that the subjects were not taking any oral contraceptives or other hormone therapies that may have affected normal hormone levels throughout the menstrual cycle of the subject during the test period. None of the subjects were smokers.

Expiratory occlusion

The expiratory port of a Hans Rudolph (3700) one-way breathing valve was equipped with a modified Hans Rudolph occlusion pressure valve automated large inflatable balloon-type (Series 9300-1 balloon). The method used to measure airway resistance was based on the detection of transient interruption in airflow. The balloon within the interrupter device was inflated, during the expiratory phase, 4-6 times during each workload for a 100 ms occlusion. Mouth pressure was recorded during airway occlusion under the assumption that mouth pressure equilibrates with alveolar pressure during transient interruption of airflow (Chowienczyk et al., 1991). The expiratory flow rate recorded immediately prior to each occlusion was used in the calculation of expiratory resistance (see below).

Data collection

During the exercises tests (outlined below) the subjects breathed through a Hans Rudolph one-way valve (Hans Rudolph 3700). The inspired airflow was measured by pneumotach (Hans Rudolph-3813 Series) that was connected to a differential pressure transducer (Validyne MP45); the pressure transducer was connected to a sine wave carrier demodulator (Validyne CD15A). The expired airflow passed through a similar setup to determine expired flow rates. Mouth pressure was measured using a differential pressure transducer (Validyne DP 15A) and sampling was done via a port in the mouthpiece.

Expired oxygen (O_2) and carbon dioxide (CO_2) percentages were determined using a paramagnetic analyzer (O_2; AEI S-3A/1) and an infrared analyzer (CO_2; AEI CD-3A) from samples drawn from a mixing box connected to the expired side of the breathing valve. Heart rate was measured using a standard V5 lead configuration. The oxygen saturation of haemoglobin (SaO_2) was estimated using an ear oximeter probe (AD Instruments ML 320 oximeter pod with Nonin ear probe).

Protocol

Maximal oxygen uptake test

An incremental exercise test was performed by each subject to determine maximal aerobic capacity (VO_2max) values and to establish the workloads to be used for subsequent exercise tests. The subjects were required to stand at rest for 5-6 minutes before beginning a warm-up on the treadmill (Preform AV.2/i) so that resting data could be collected. The subjects then walked on the treadmill at increasingly higher speeds, for 1-2 minutes at each speed, until they reached a speed at which they were comfortable running. This was the first workload, at which they ran for 2.5 minutes. By increasing the grade of the treadmill by 2% every 2.5 minutes, the workloads were increased incrementally until the subject reached volitional fatigue. Data were collected using a Power Lab 16 SP data acquisition system. Included in data files were inspired and expired flow rates, SaO_2, heart rate, expired O_2 concentration, expired CO_2 concentration, mouth pressure, and the calculated inspired-expired volumes using the integral of their respective flow rate. The VO_2 at each work load was calculated using 30 sec averaged data and standard equations (Powers and Howley, 2007).

Expiratory resistance tests

Each subject completed the subsequent exercise tests; visits 2 and 3 were within two days of the peak of their respective follicular and luteal phases (i.e. ± 2 days of day 7 and day 21 respectively). All procedures were the same as described above except that during these test sessions the expiratory port of the mouthpiece was attached to a flow-interruption device used for measuring airway resistance. The flow-interruption device was controlled manually from the control box. Airway resistance was measured at each progressive workload, as was heart rate and VO_2 in order to monitor the intensity of work.

Calculating airway resistance

The airway resistance at each workload was calculated for each subject using the following equation: Expiratory Resistance = Transpulmonary Pressure ÷ Expired Flow Rate

During the transient interruption of expiratory flow, the mouth pressure was assumed to equilibrate to the transpulmonary pressure and so it was used in the above equation together with the expiratory flow rate recorded just prior to occlusion. For the purposes of the

Table 1. Anthropometric and physiological characteristics of the subjects who participated in the study.

Subject	Age (years)	Height (m)	Weight (kg)	BMI	VO_2 max (ml/kg/min)	Max HR (bpm)
1	21	1.65	50.5	22.44	48.9	181
2	20	1.65	55.5	24.67	64.0	189
3	20	1.59	66.8	31.97	40.3	188
4	21	1.66	55.0	24.15	42.0	165
5	18	1.63	47.7	21.72	47.1	198
6	20	1.64	53.2	23.93	54.7	200
7	20	1.65	65.0	29.06	49.1	190
8	18	1.67	56.8	24.64	43.5	184
9	19	1.69	65.0	27.54	38.2	168
10	20	1.65	73.6	32.71	55.4	178
Mean	**19.7**	**1.65**	**58.9**	**26.28**	**48.3**	**184**
Std. Error	**1.1**	**.02**	**8.8**	**3.67**	**7.68**	**12**

study, the atmospheric pressure was assumed to equal 0 torr.

Statistical analysis

Paired t-tests (Graph Pad Prism 4) were used to determine if a significant difference in airway resistance at the same workload during a progressive whole body exercise test existed between the follicular and luteal phase of each subject's menstrual cycle. Values from each subject's final and second last workload were used for the analysis.

The expiratory resistance data from each menstrual cycle phase were analyzed with a repeated measures one-way analysis of variance (Graph Pad Prism 4) to determine if airway resistance changed from workload to workload during the progressive incremental tests. Only subjects with three or more workloads were included in this analysis. The significance level was set at $p \leq 0.05$. Values are reported as Group mean ±SEM.

Results

Ten subjects completed all aspects of the study. One subject had an irregular menstrual cycle and was excluded from the study. The maximal heart rate (HR_{max}) and the VO_2max values recorded during the three exercise tests were not different between the tests. The mean VO_2 max was 48.3 ± 7.7 $ml \cdot min^{-1} \cdot kg^{-1}$. The difference between the VO_2 max during the follicular and the luteal phases was insignificant (p = 0.91, Figure 1). The mean maximal heart rate during the follicular phase was 182.3 ± 4.3 bpm. For the luteal phase, the mean HR_{max} was 180.6 ± 5.7 bpm. These values were compared to the initial VO_2 max test (181.5 ± 3.9 bpm) to show that subjects were exercising at a similar intensity during all of the exercise tests. The difference in HR_{max} between the VO_2 max, the follicular and luteal phase tests were insignificant (p = 0.90).

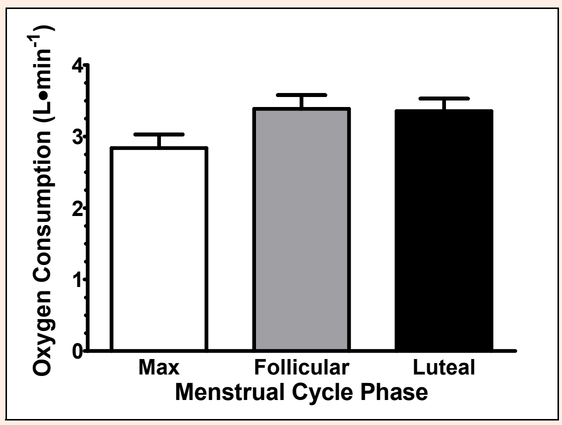

Figure 1. Oxygen uptake levels of final workload for the initial maximum test and for follicular and luteal phases.

Expiratory resistance

The expiratory resistances were recorded during the follicular and luteal phases. A mean value for expiratory resistance (cm $H_2O \cdot L^{-1} \cdot sec^{-1}$) was calculated for each subject for the last and second last workloads during each phase. As shown in Figure 2, the mean expiratory resistance for the final workload was found to be substantially higher for the follicular phase compared to the luteal phase (1.1 ± 0.06 cm $H_2O \cdot L^{-1} \cdot sec^{-1}$ vs. 0.91 ± 0.07 $H_2O \cdot L^{-1} \cdot sec^{-1}$; p = 0.006). At the sub maximal workload, the mean expiratory resistance was 1.0 ± 0.05 cm $H_2O \cdot L^{-1} \cdot sec^{-1}$ for the follicular phase and 0.9 ± 0.07 $H_2O \cdot L^{-1} \cdot sec^{-1}$ for the luteal phase, which were not different (p = 0.1865).

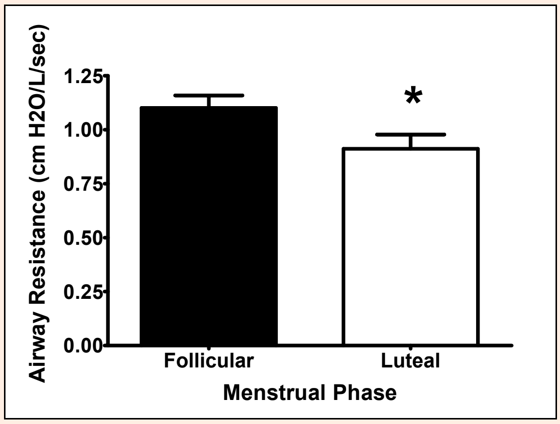

Figure 2. Oxygen uptake levels of final workload for the initial maximum test and for follicular and luteal phases. * p≤0.05.

The differences in R_{exp} between each workload in the follicular and in the luteal phases were not significant.

Discussion

The purpose of the study was to determine if the expiratory resistance during progressive whole body exercise in healthy female subjects was different between the follicular and luteal phases of the menstrual cycle. Results showed that a significant difference in expiratory resistance calculated during the final workload was found between the follicular phase and the luteal phase of the menstrual cycle of young females.

Limitations

Expiratory resistance was measured using the flow interrupter technique (Chowienczyk et al., 1991) during a brief occlusion. This was done under the assumption that during the transient interruption of airflow, mouth pressure equilibrates with alveolar pressure. The mouth pressure can then be substituted in the calculation for transpulmonary pressure as follows: Expiratory Resistance (R_{exp}) = Mouth (Transpulmonary) Pressure ÷ Expired Flow Rate. For accuracy and precision, a balloon tipped oesophageal catheter would allow for the resistance calculation to be performed without the use of an occlusion. But the use of an oesophageal catheter is a more invasive process and requires the presence of trained individuals and special permission from the ethics committee. Since the purpose of this preliminary experiment was to ascertain if any changes occurred in expiratory resistance between phases of the menstrual cycle, the use of mouth pressure in the

R_{exp} equation was acceptable. Previously this technique has been found to be reliable (Chan et al., 2003).

Another limitation of the occlusion technique was the fact that the inflatable balloon in the expiratory port of the one-way breathing valve was controlled manually. Ideally, the balloon would have been inflated automatically for 100 ms after receiving a signal from the computer. Technical difficulties made this impossible to set up and so the balloon was inflated manually from the control box for as short a time as possible. The mouth pressure reported was the plateau in mouth pressure immediately following cessation of expiratory air flow to ensure accurate readings.

Finally, each individual was tested only during one follicular phase and one luteal phase. Preferably, testing would have been completed during two or more menstrual cycles in order to provide evidence that the results were in fact representative of all follicular and all luteal phases of the menstrual cycle. The study was very much dependent on the menstrual cycle of the individual; there was not enough time to test the subjects during the two phases of another menstrual cycle.

Expiratory resistance

We have found a higher expiratory resistance during the maximal workload in female subjects during the follicular phase of the menstrual cycle compared to what was measured exercising at the same workload during the subject's luteal phase. Previous studies have been done mostly using male subjects and children but very few studies have been done involving female subjects during exercise. In the studies done previously using adult subjects performing a bout of moderate exercise (workload required 60-65% of maximal oxygen uptake) the R_{exp} was reported to 2.01±0.4 cm $H_2O \cdot L^{-1} \cdot sec^{-1}$ and this value was maintained throughout the exercise (Beck et al., 1999). Normal resting R_{exp} values in adults, measured using the interrupter technique, were found to be in the range of 0.91 – 2.4 cm $H_2O \cdot L^{-1} \cdot sec^{-1}$ (Vooren and van Zomeren, 1989). These values are close to what was found here.

One explanation for the differences in R_{exp} between the follicular and luteal phases of the menstrual cycle could be the fluctuations in hormones, specifically progesterone and /or oestrogen, which occur over the course of the menstrual cycle. These two hormones have been shown to have an effect on exercise ventilation in female subjects. Progesterone has been shown to stimulate exercise ventilation and ventilatory drive in both athletes and non-athletes (Schoene et al., 1981). During the luteal phase, when circulating levels of progesterone are at their highest, females experience an enhanced hypoxic ventilatory response (Schoene et al., 1981; White et al., 1983). Therefore, the possibility that progesterone while stimulating ventilation was also acting to decrease R_{exp} during the luteal phase. The actual mechanism of how progesterone decreases R_{exp} remains to be determined.

A stimulatory effect of oestrogen cannot however, be ruled out. Another explanation for the results observed in the present data was that high oestrogen concentrations caused increased expiratory resistance. This possibility seems unlikely as it has been shown that oestrogen may be intensifying the effects of progesterone on respiration in humans (Bruno da Silva et al., 2006; Regensteiner et al., 1990). Oestrogen has been shown to increase progesterone receptor numbers in rats (MacLusky and McEven, 1978). Whether this occurs in humans has not been shown.

In order to determine the exact effects of the ovarian hormones on ventilation and airway resistance, exercise tests should be done during menses as well as the follicular and luteal phases. Oestrogen and progesterone concentrations are both low during menses and by determining expiratory resistance during this phase of the menstrual cycle it may indicate whether it is oestrogen, progesterone, or neither hormone affecting expiratory resistance. If oestrogen was in fact causing an increase in expiratory resistance, then R_{exp} would be lower during menses and the luteal phase. On the other hand, if progesterone was alleviating R_{exp}, it will be lower during the luteal phase verses during menses and the follicular phase.

Physiological significance

Does the difference in the expiratory resistance found here during the follicular phase of the menstrual cycle have any physiological consequence? By it self, we do not think that the increased R_{exp} would have a physiological consequence on exercise performance as shown by the fact that the subjects tested here showed similar values for VO_2 at the same workloads during both cycle phases. The increase in R_{exp} found during the follicular phase may be one of many factors contributing to the increase in occurrence of expiratory flow limitation in exercising females during the follicular phase (Guenette et al., 2007; McClaran et al., 1998). As the expiratory resistance increased expiratory effort would increase which may cause small airways to collapse leading to flow limitation. Further study is necessary to confirm if this does occur in females during exercise.

Finally, it was difficult to compare these results with other studies because there was no literature published regarding ovarian hormones and expiratory resistance. A larger sample size, measurement of circulating levels of progesterone and oestrogen in arterial blood and using a more robust method to determine R_{exp} would help confirm or disprove the present results, giving more insight into the effects of progesterone and/or oestrogen on the changes in expiratory resistance during exercise.

Conclusion

The results of this study have shown that expiratory resistance was significantly increased during the maximal exercise workload in female subjects during the follicular phase of their menstrual cycle compared to values recorded at the same workload during the luteal phase. Further work is required to ascertain if the changes in expiratory resistance contribute to the occurrence of expiratory flow limitation in female subjects.

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Key points

- During maximal exercise there was a significantly larger expiratory resistance during the follicular phase versus luteal phase of the female subjects menstrual cycle.
- Fluctuation in hormones (especially progesterone and/ or oestrogen) may contribute to changes in expiratory resistance.
- The increased expiratory resistance may be a contributing factor to the increased occurrence of expiratory flow limitation in female subjects.

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