Influence of Body Mass Index and Ovarian Cycle on Metaboreflex

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ABSTRACT

Background: Sustained isometric (static) exercise followed by a period of post-exercise vascular occlusion and consequent skeletal muscles ischemia allows the preservation of sympatho-excitation (pressor effect) induced by skeletal metaboreceptors. Direct evidences of the effect of body mass index and phases of ovarian cycle on the contribution of metaboreflex on the pressor effect of metaboreflex were provided.

Objectives: To provide a comprehensive and optimized protocol for the assessment of metaboreflex activity and to provide evidences for the contribution of phases of ovarian cycle and the body mass index on the metaboreflex activity.

Methods: Seventeen males and 7 females were recruited in the present study. The male subjects were divided according to their body mass index (BMI) into normal weight and overweight subjects. The female subjects were tested in two sessions, one during mid-luteal phase of ovarian cycle and the second session was during early follicular phase of ovarian cycle. The metaboreflex pressor response during post exercise vascular occlusion was isolated from pressor response of hand grip static exercise by recording blood pressure during exercise and during post exercise vascular occlusion. Metaboreflex contribution to the pressor effect on cardiovascular system (CVS) was calculated.

Results: In males, the mean blood pressure (MBP) and heart rate (HR) were increased during isometric hand grip exercise by 24% and 21% respectively. During post exercise vascular occlusion, MBP was maintained at a higher level (by 12%) relative to base level while HR was returned to base level. In male subjects, metaboreflex contribution to the pressor effect on CVS was found to be significantly and inversely correlated with the BMI and metaboreflex contribution tends to be significantly lower (by 37%) in overweight relative to normal weight subjects. In female subjects, No significant effect was observed of ovarian phases on the metaboreflex pressor response to sustained hand grip muscle exercise.

Conclusion: Body mass index affects metaboreflex activity while phases of ovarian cycle have no such effect.

Keywords: Metaboreflex, Body mass index, Menstrual cycle.

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Exercising skeletal muscle requires a constant source of energy. The CVS copes with an increase in skeletal muscle metabolic needs by increasing blood flow to the working muscle through an increase in the cardiac output and vascular resistance to the less metabolically demanding organs, or varying levels of both. A feedback mechanism must exist to match oxygen availability to the demand of the exercising muscle.

Three main neural control mechanisms are essential for appropriate CV response to exercise: central command (descending neural input), afferent feedback (metabo- and mechanoreflex) from skeletal muscle and the baroreflex evoked from arterial side of circulation. These neural control mechanisms converge at CV centers in the brain and modulate the autonomic nervous effect on the CV system[1-7].

Sustained isometric (static) exercise followed by a period of post-exercise vascular occlusion and consequent skeletal muscles ischemia allows the preservation of sympatho-excitation

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(pressor effect) induced by metaboreceptors (chemoreceptors) stimulation during the post-exercise phase without the confounding influence of central command and mechanoreceptor effects. This technique enables the separation of the pressor effect of metabreceptors from the pressor effects of the central command and stimulation of mechanoreceptors.

The findings regarding the effects of sex hormones on sympathetic metaboreflex activity during static exercise in humans are few and are inconsistent. Ettinger et al [8] reported an increase in MSNA during menstrual phase of the ovarian cycle in static handgrip is higher than during the follicular phase of the ovarian cycle. Jarvis et al[9] showed that the low versus high hormone status during ovarian cycle did not affect the responses to either static handgrip or post exercise vascular occlusion in women. It was found that both genders responded with comparable increases in muscle sympathetic nerve activity (MSNA) that reflects metaboreflex activity during 1 min of static handgrip exercise[10]. In contrast, Ettinger et al[11] demonstrated that CV response to sympathetic activity due to static handgrip was attenuated in women compared with men. Furthermore, Greaney et al[12] demonstrated that postmenopausal women, compared to young women, exhibited an exaggerated MSNA response to isolated muscle metaboreflex activation.

Previous studies were able to show that obesity is positively correlated with the MSNA[13,14]. It has been demonstrated that the mean blood pressure were significantly higher in obese women compared with lean women during static handgrip exercise associated with a blunted muscle metaboreflex control of MSNA [15]. Furthermore, Trombetta et al[16] showed that weight loss improves muscle metaboreflex control in obese women.

The aim of the present research is to provide a comprehensive and optimized protocol for the assessment of metaboreflex activity that was collected from various publications and to provide evidences for the contribution of phases of ovarian cycle and the body mass index on the metaboreflex activity.

Methods

The recruited volunteered subjects (17 males, 7 females) in this study were normotensive and were free from major medical illness or taking medications for a major illness. This is assessed by a medical history questionnaire, and resting brachial BP. Subjects did not smoke or drink coffee for overnight. All subjects provided verbal informed consent. All procedures and protocols were approved by the ethical committee in the Department of physiology, College of Medicine, Al-Mustansiriya University and the study followed the standards principles in the Declaration of Helsinki.

The female subjects (age 38.6 ± 5.6 years; BMI = 27.4 ± 3.3 kg/m^2) were tested in two sessions, one during mid-luteal phase (days 19-22 after the onset of menstruation) of their menstrual cycle when both estrogen and progesterone are high. The second session was during early follicular phase (1 to 4 days after the onset of menstruation) of their menstrual cycle when both sex hormones are low. The started session was chosen randomly. Hormonal analysis in these two phases was confirmed by Jarvis et al[9] and Ettinger[8].

The male subjects (BMI = 24.9 ± 5.8 kg/m^2, n = 17) were mainly of young age group (21.2 ± 4.1 years) and were divided according to their body mass index into normal weight subjects (BMI = 20-25 kg/m^2, n =9) and overweight subjects (BMI > 25 kg/m^2, n = 8). 15 of male subjects were at an age range between 18-24 years, two of the whole male volunteers having an age of 30 and 32 years.

Protocol of muscle metaboreflex: On the experimental day, subjects entered the test room, which was maintained around 25°C. Each subject was asked to rest on the couch in supine position with the head slightly flexed and completely supported by

the couch surface, and keep the visual contact with the digital screen of the handgrip dynamometer. The exercising dominant arm was flexed at about 90 degree and was supported so that no upper limb muscles (except the forearm muscles) are in any state of contraction and was kept close to the body[17]. Using the dominant arm, the maximal voluntary contraction (MVC) was determined by a handgrip dynamometer (Lafayette Instrument Company, Lafayette, IN, USA), by asking him to squeeze maximally on the dynamometer and to maintain this squeeze for at least 3 seconds. After MVC was determined, 30% of MVC was calculated. Thereafter, the participants asked to rest for 10 min before measurements started. During this time, repeated BP and HR measurements were done by automated sphygmomanometer (OMRON HEALTHCARE Co., Ltd. Kytoto, JAPAN) on brachial artery of non-dominant arm until stable values for both of these parameters were obtained and were considered them the basal resting period levels (BRP), i.e. BP and HR at rest, (Figure 1).

Subjects were instructed to maintain a constant respiratory rate throughout the protocol, and to remain quiet and try to avoid performing Valsalva manoeuvres during measurements. A pneumatic mercury sphygmomanometer cuff was wrapped around the dominant arm before starting the exercise protocol. Next, the participant was asked to squeeze the handgrip dynamometer to 30% of the MVC[18] and to keep the squeeze for 2 min [17] and maintains his hand grip force in a steady state as possible as he can by observing the target force as it is displayed on the digital screen of the handgrip dynamometer. Verbal encouragement was given to the subject to maintain 30% MVC value. Forty seconds before the end of 2 min contraction period, automated sphygmomanometer on non-dominant arm was operated to give enough time for the device to inflate and deflate the cuff for BP and HR measurements. This time is enough to record these parameters and coincide with end of 2 min contraction of forearm muscles. The BP and HR values at the end of 2 min contraction time represent exercise period (EP) measurement. Five seconds before the cessation of this 2 min period, a pneumatic mercury sphygmomanometer cuff around the exercising dominant arm was rapidly inflated to 250 mm Hg and this was maintained for a further 2 min, this period is called post exercise vascular occlusion period (PEVOP). The pressure was topped up if necessary using the hand bulb. Forty seconds before the end of 2 min of post exercise vascular occlusion period, automated sphygmomanometer on non-dominant arm was operated again to record BP and HR. After the end of 2 min post exercise vascular occlusion period, the pneumatic cuff around the dominant exercising arm was deflated, the BP and HR were measured after 1 min period. These measurements were considered as a recovery period (RP) values. Mean blood pressure (MBP) was calculated from systolic and diastolic BP. Metaboreflex contribution (MC) to the pressor effect on CV system was calculated as follow:

100 X (MBP after 2 min PEVOP – MBP after BRP) / (MBP after 2 min EP – MBP after BRP). Where BRP = Basal resting period. EP = Exercise period. PEVOP = Post exercise vascular occlusion period.

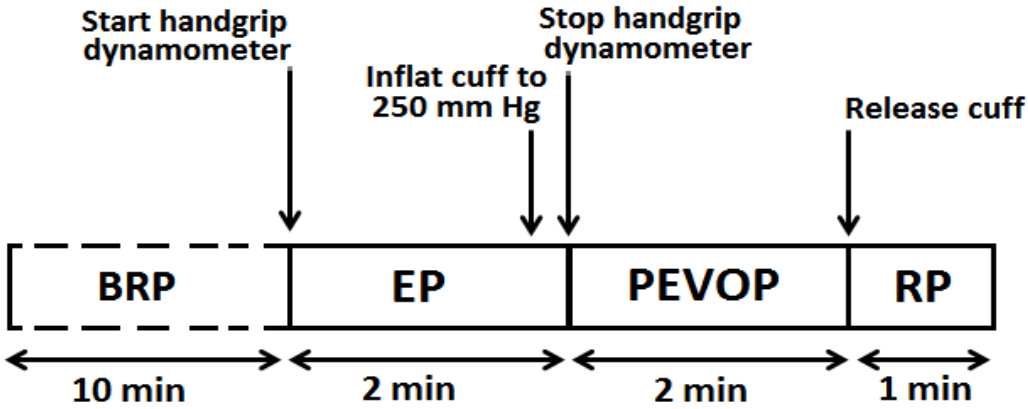

Figure 1: Schematic representation of the experimental protocol. BRP = Basal resting period. EP = Exercise period. PEVOP = Post exercise vascular occlusion period. RP = Recovery period.

Values are reported as means ± SD. Differences between variables were calculated by Paired or Unpaired Student`s *t-test*. Statistical significance was accepted when $P < 0.05$. For Normality test of the data for Gaussian distribution, Graphpad Instat version 3.06 software was used. If the paired data did not pass the normality test, then Wilcoxon test is used. If the unpaired data did not pass the normality test, then Mann-Whitney test is used.

Results

The MVC of normal weight male subjects (55.1 ± 26.9 kg) tends to be higher, although not significantly, than overweight subjects (38.8 ± 9.7 kg). MVC of females was 29.3 ± 15.5 kg.

During BRP, Systolic BP, diastolic BP, MBP, and HR of normal weight subjects (129.3 ± 12.8 mm Hg, 72.9 ± 9.0 mm Hg, 91.7 ± 8.4 mm Hg, and 80.3 ± 6.1 beat/min respectively) tend to be lower, although not significantly, from those of overweight subjects (132.5 ± 10.1 mm Hg, 76.8 ± 4.8 mm Hg, 95.3 ± 5.2 mm Hg, and 81.8 ± 10.6 beat/min respectively).

During EP, Systolic BP, diastolic BP, MBP, and HR of normal weight subjects (156.4 ± 20.2 mm Hg, 98.1 ± 18.0 mm Hg, 117.6 ± 17.1 mm Hg, and 104.0 ± 13.8 beat/min respectively) tend to be higher, although not significantly differ, from those of overweight subjects (150.3 ± 13.1 mm Hg, 94.8 ± 9.7 mm Hg, 113.3 ± 9.9 mm Hg, and 91.6 ± 14.3 beat/min respectively).

The general trend of changes regarding the measured cardiovascular parameters was maintained During PEVOP, in which Systolic BP, and diastolic BP, MBP, and HR of normal weight subjects (144.8 ± 17.1 mm Hg, 87.6 ± 10.9 mm Hg, 106.6 ± 11.2 mm Hg, and 87.0 ± 15.2 beat/min respectively) tend to be higher, although not significantly differ, from those of overweight subjects (139.3 ± 11.0 mm Hg, 84.6 ± 9.8 mm Hg, 102.8 ± 9.2 mm Hg, and 79.4 ± 10.0 beat/min respectively).

After 1 min of RP, the Systolic BP, diastolic BP, MBP, and HR was returned almost to the levels recorded during BRP.

During the basal resting period, MBP and HR were 93.4 ± 7.1 mm Hg, and 81.1 ± 8.2 beat/min respectively. Upon 2 min of isometric hand grip exercise period, the MBP was increased significantly by 24% relative to base level value (figure 2). During 2 min of post exercise vascular occlusion period, where the metaboreflex pressor effect operated alone, the MPB was still significantly higher by 12% relative to the basal value during basal resting period. After 1 min of recovery period, MBP return almost to the resting basal level.

After 2 min period of static hand grip exercise, the HR was increased significantly by 21% relative to base level value (figure 3). In contrast to the MBP, after 2 min of post exercise vascular occlusion period, the HR was return to the basal value reported during basal resting period and was maintained at the same level after 1 min of recovery period (figure 3).

Metaboreflex contribution (MC) to the pressor effect on CVS was found to be significantly and inversely correlated with the BMI (figure 4) and MC tends to be significantly lower (by 37%) in overweight subjects (figure 5).

Neither MBP nor HR is affected by the phases of ovarian cycle, (Table 1). In addition, metaboreflex contribution to the pressor effect of exercise did not changed with the phases of ovarian cycle.

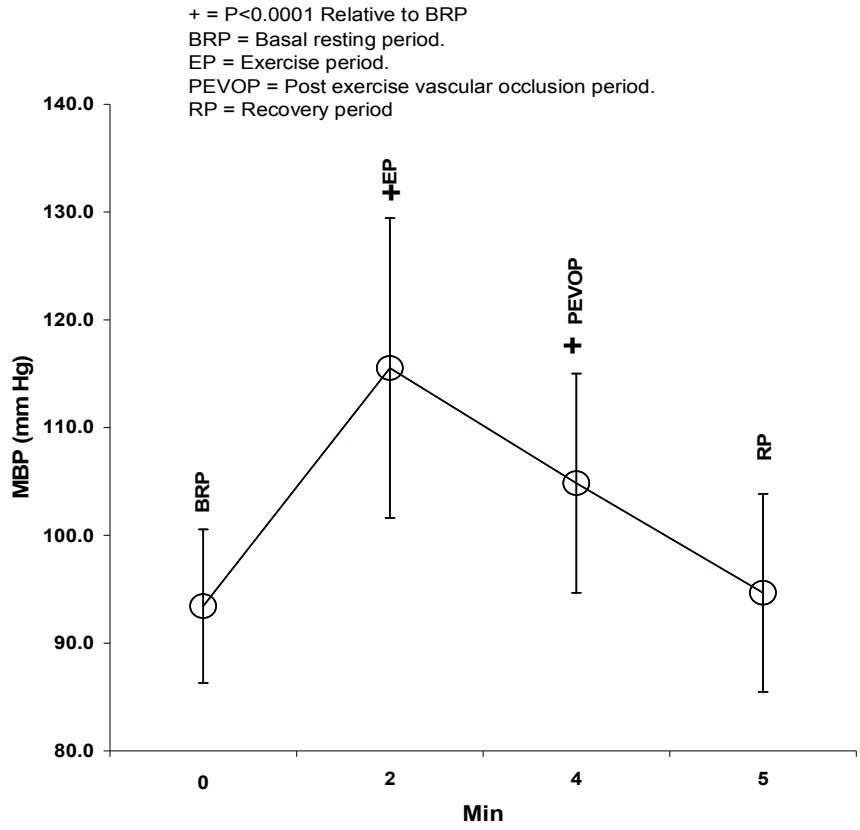

Figure 2: Mean blood pressure (MBP) response in static hand grip exercise (n = 17).

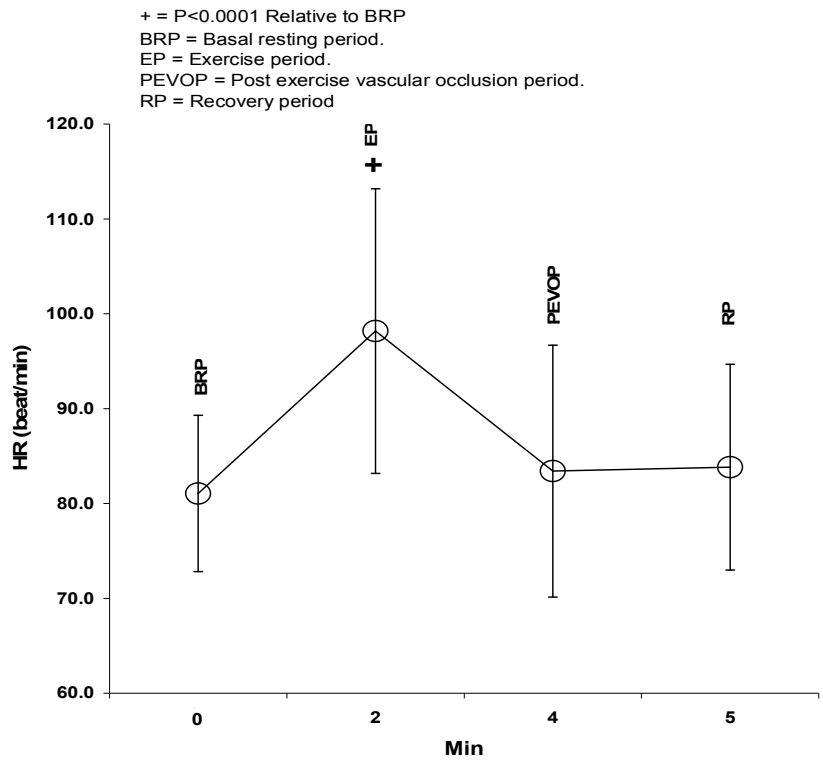

Figure 3: Heart rate (HR) response in static hand grip exercise (n = 17).

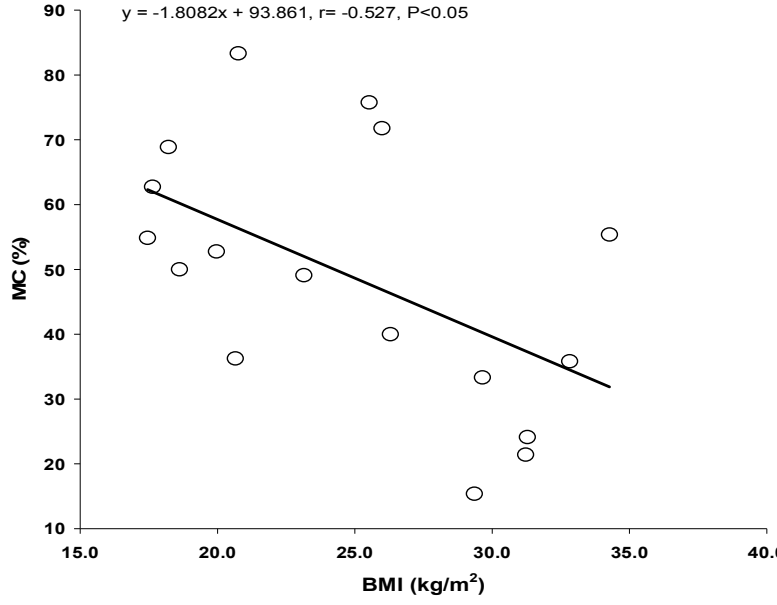

Figure 4: Correlation between BMI and metaboreflex contribution (MC) in pressor response in static hand grip exercise (n = 17).

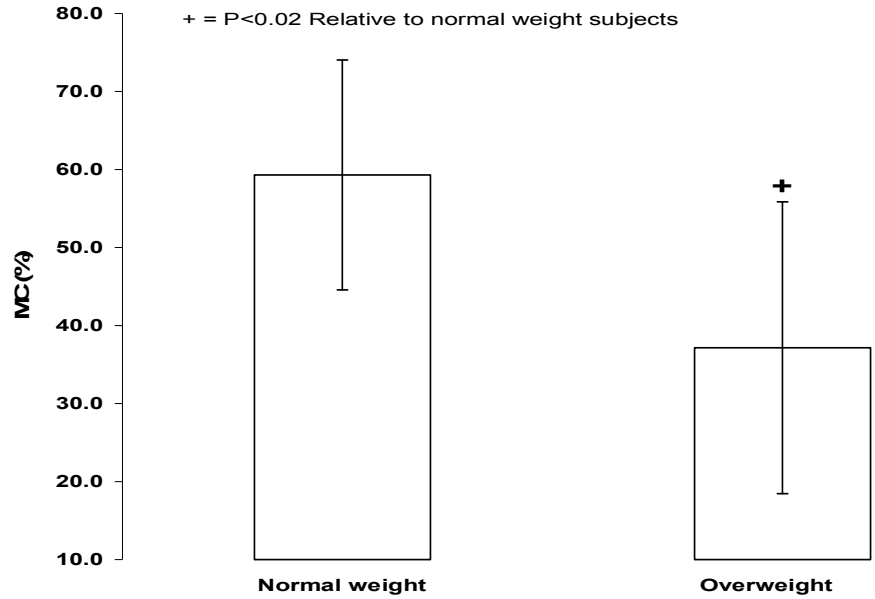

Figure 5: Metaboreflex contribution (MC) in pressor response in static hand grip exercise in normal weight (n = 9) and overweight subjects (n = 8).

Table 1: Comparison of MBP and HR during mid-luteal phase and early follicular phase of ovarian cycle through the whole hand grip protocol (n = 7).

	BRP	EP	PEVOP	RP	MC
MBP during Mid-luteal phase (mm Hg)	87.8 ± 7.9	105.6 ± 7.5	99.2 ± 6.9	87.6 ± 9.7	65.5 ± 16.5
MBP during Early follicular phase (mm Hg)	91.5 ± 6.1	111.6 ± 18.0	103.6 ± 9.5	92.1 ± 6.1	65.2 ± 22.3
P	NS	NS	NS	NS	NS
HR during Mid-luteal phase (beat/min)	79.9 ± 8.6	91.4 ± 11.8	83.3 ± 12.8	77.9 ± 11.6	
HR during Early follicular phase (beat/min)	77.3 ± 8.5	86.6 ± 12.0	73.9 ± 9.2	74.0 ± 8.6	
P	NS	NS	NS	NS	

BRP = Basal resting period. EP = Exercise period. PEVOP = Post exercise vascular occlusion period. RP = Recovery period. MBP = Mean blood pressure. HR = Heart rate. MC = Metaboreflex contribution.

Discussion

The number of recruited subjects in the current research was comparable to those reported else[9,19-21]. Under the present experimental conditions, a one minute of recovery period after exercise was enough to normalize the measured parameters back to normal RBP levels. The CV system responses during static exercise include a small increase in cardiac output caused by an increase in heart rate and a large increase in arterial blood pressure due to sympathetic vasoconstriction. This is due to integrated signals that converge on the medullary cardiovascular control center from higher motor centers, afferent feedback (metabo- and mechanoreflex) from skeletal muscle and from the baroreflex evoked from large arteries. The metabolic reflex can be isolated and studied separately by occlusion of blood flow of an exercising limb muscle through inflation of a cuff placed around the limb above the systolic pressure and asked the subject to relax his limb muscles. In this case, the muscles are no longer contracting (no mechanoreflex) and no central command. Therefore, the metabolites produced by the contracting muscles that are trapped within the circulation of limb muscle exert its stimulatory effect on the muscle afferent nerve fibers and evoking the metabolic component of the exercise pressor reflex.

In the present study, the CV responses in terms of MBP and HR changes during static (isometric) hand grip muscle exercise and during post exercise vascular occlusion period were completely in agreement with those reported by Jarvis et al[9], Fisher et al[20], and Trombetta et al[16].

The increase in MBP during exercise period is due to the pressor combined effects of central command, metaboreflex and mechanoreflex from skeletal muscle on CV center. The efferent sympathetic outflow from cardiovascular center increases MBP via vasoconstriction and to an increase in cardiac output (due to an increase in HR). The increase of MBP during post exercise vascular occlusion period is less than MBP increase during exercise period. This is probably due to metaboreflex pressor effect per se without the contribution of the other pressor factors (i.e. central command and mechanoreceptors). Additional possible cause for the less increment of MBP during post exercise vascular occlusion period relative to high increment in MBP during exercise period is the normal cardiac output due to normal heart rate during isolated metaboreflex activation. Accordind to Iellamo et al [21] study, the muscle metaboreflex affect heart rate during static hand grip exercise via a sympathetic activation. The normal HR (or bradycardia) that occurs during post exercise muscle ischemia may be explained by an increase in parasympathetic outflow to the sinoatrial node by baroreflex that overrides the metaboreflex-induced cardiac sympathetic activation[21]. This suggestion was supported by Fisher el al[20] who was able to demonstrate that the increase in parasympathetic outflow to the sinoatrial node by baroreflex was clear only at intensity of isometric hand grip performed of 40% maximum voluntary contraction and was not clear at 25% maximum voluntary contraction. In addition, Watanabe et al[22] showed that the HR response to post exercise vascular occlusion -induced activation of muscle metaboreflex varies among individuals and that these differences reflect changes in parasympathetic tone to the heart and spontaneous baroreceptor sensitivity during post exercise ischemia. Trombetta et al[16] were able to show that weight reduction of obese women was associated with improvement of metaboreflex control.

The results of latter authors are supported by the current findings that show the inverse correlation between BMI and MC which tends to be lower in overweight subjects. Furthermore, the narrow range of age for the recruited subjects in the present study excludes the age as a cofounding factor for such differences. In addition, Negrão et al[15] were also showed that muscle metaboreflex control of muscle sympathetic nerve activity is blunted in obese women during static exercise at 10 and 30% of maximal voluntary contraction. Pramita et al[23] suggested that in subjects with higher BMI, accumulation of the excessive fat in the in the skeletal muscle may desensitize the metaboreceptors, and consequently reducing the metaboreflex-

mediated muscle sympathetic nerve activity and, therefore, would impair vasoconstriction mediated pressor response.

The result of the current work support the hypothesis that the contribution of the metaboreflex pressor response during static hand grip exercise does not affected by the phases of ovarian cycle. These results are parallel with those reported by Jarvis et al[9]. In contrast, Greaney et al[12] demonstrated that metaboreflex activation elicits a higher sympathetic nervous system response in postmenopausal women relative young women, and consequently contributing to the exaggerated blood pressure response during exercise. The discrepancies between the result of the present work and the latter authors may be due to different sample type.

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