Spectral Analysis of Heart Rate Variability: Gender-Related Differences and Fitness Status

A thesis
submitted to the Faculty of Graduate Studies and Research
in partial fulfillment of the requirements
for the Degree of Master of Arts.

Department of Physical Education
Faculty of Education
McGill University
Montreal, Quebec, Canada

August, 1997

ABSTRACT

Recent observations indicate that gender-related differences may exist in the control of blood pressure. This study utilized spectral analysis of R-R interval (HRV) and blood pressure variability (BPV) to examine the effects of gender and fitness status on sympathovagal balance. Subjects were 46 age-matched, control (C) and athletic (A), men (M) and women (F) (VO_2 max (ml/kg/min): MA: 71.4±4.65 vs. MC: 43.6±7.27; FA: 57.6±3.72 vs. FC: 42.3±4.29). Continuous electrocardiogram (ECG) recordings were obtained during supine rest, sitting, controlled respiration, standing, exercise at 100 and 130 bpm, and following 5 and 15 minutes of seated recovery. Standing and exercise resulted in similar decreases in the high frequency (HF) component and increases in the low to high frequency (LF/HF) ratio in all subjects. No differences were observed between athletes and controls of either gender in any of the HRV spectral components at rest or under any testing condition despite significantly lower heart rates (bpm) in the athletic subjects (MA:53.1±1.95 vs. MC:63.3±2.43; FA:55.5±2.12 vs. FC:60.4±2.74). Pooled data revealed a significant effect of gender on HRV such that, overall, females experienced higher vagal tone (high frequency (HF) component) than male subjects during baseline (M:42.2±3.74 nu, F:55.2±2.68 nu), standing (M:15.1±1.75, F:21.7±2.53), exercise at 130 bpm (M:37.3±2.95, F:43.2±3.05), and 15 minutes recovery (M:24.5±2.75, F:31.8±2.82). Controlled breathing (0,20 Hz) resulted in a similar increase in the HF component of HRV in both M (1.5 fold) and F (1.3 fold) suggesting a similar sensitivity of response to respiratory sinus arrhythmia. No gender- or fitness-related differences were observed for the HF or the LF components of systolic or diastolic BPV. Results from cardiopulmonary baroreflex function assessment using application of lower body negative pressure to -40 mmHg in a small subset of subjects (n = 8) revealed no gender-related differences in circulatory responses. In conclusion, despite

similar heart rates, results of this study indicate a predomint vagal spectral component of HRV in female subjects, potentially implying a higher spontaneous discharge rate of the SA node.

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Finally, to my husband Lee, I will always appreciate your never ending patience and motivational speeches. It was your confidence in me that allowed me to reach my goal.....I love you.

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ABSTRACT

Recent observations indicate that gender-related differences may exist in the control of blood pressure. This study utilized spectral analysis of R-R interval (HRV) and blood pressure variability (BPV) to examine the effects of gender and fitness status on sympathovagal balance. Subjects were 46 age-matched, control (C) and athletic (A), men (M) and women (F) (VO_2 max (ml/kg/min): MA: 71.4±4.65 vs. MC: 43.6±7.27; FA: 57.6±3.72 vs. FC: 42.3±4.29). Continuous electrocardiogram (ECG) recordings were obtained during supine rest, sitting, controlled respiration, standing, exercise at 100 and 130 bpm, and following 5 and 15 minutes of seated recovery. Standing and exercise resulted in similar decreases in the high frequency (HF) component and increases in the low to high frequency (LF/HF) ratio in all subjects. No differences were observed between athletes and controls of either gender in any of the HRV spectral components at rest or under any testing condition despite significantly lower heart rates (bpm) in the athletic subjects (MA:53.1±1.95 vs. MC:63.3±2.43; FA:55.5±2.12 vs. FC:60.4±2.74). Pooled data revealed a significant effect of gender on HRV such that, overall, females experienced higher vagal tone (high frequency (HF) component) than male subjects during baseline (M:42.2±3.74 nu, F:55.2±2.68 nu), standing (M:15.1±1.75, F:21.7±2.53), exercise at 130 bpm (M:37.3±2.95, F:43.2±3.05), and 15 minutes recovery (M:24.5±2.75, F:31.8±2.82). Controlled breathing (0,20 Hz) resulted in a similar increase in the HF component of HRV in both M (1.5 fold) and F (1.3 fold) suggesting a similar sensitivity of response to respiratory sinus arrhythmia. No gender- or fitness-related differences were observed for the HF or the LF components of systolic or diastolic BPV. Results from cardiopulmonary baroreflex function assessment using application of lower body negative pressure to -40 mmHg in a small subset of subjects (n = 8) revealed no gender-related differences in circulatory responses. In conclusion, despite

similar heart rates, results of this study indicate a predomint vagal spectral component of HRV in female subjects, potentially implying a higher spontaneous discharge rate of the SA node.

RÉSUMÉ

Certaines évidence expérimentales suggèrent l'existence de différences reliées au sexe dans le contrôle de la pression artérielle. Cette étude utilise l'analyse spectrale de la variabilité sinusale de l'electrocardiogramme (ECG) et de la variabilité de la pression artérielle pour évaluer l'influence de la condition physique et du sexe sur la balance sympathoadrénergique. Un enregistrement continu de l'ECG a été obtenu en décubitus dorsal ainsi qu'en position assise, avec respiration spontanée ou imposée, en orthostation, ainsi qu'au cours d'exercices sur ergocycle effectués à une fréquence cardiaque de 100 et 130 batt/min et après 5 et 15 minutes de récupération assise chez 46 sujets assignés aux groupes masculin (M), féminin (F), entraîné (A), et sédentaire (C) (VO_2 max (ml/kg/min): MA: 71.4 ± 4.65, MC: 43.6 ± 7.27; FA: 57.6 ± 3.72, FC: 42.3 ± 4.29). Une augmentation similaire de la composante spectrale de haute (HF) et du rapport de la composante de basse et de haute fréquence a été observée chez tous les sujets. Aucune différence n'est apparu entre les sujets A et C aussi bien F que M pour les composantes spectrales de l'ECG bien que les sujets A présentent une fréquence cardiaque de repos plus basse (MA:53.1 ± 1.95, MC:63.3 ± 2.43; FA:55.5 ± 2.12, FC:60.4 ± 2.74). L'analyse statistique révèle cependant une composante HF de l'ECG (n.u.) plus importante dans toutes les conditions: repos (M:42.2 ± 3.74 vs. F:55.2 ± 2.68), orthostation (M:15.1 ± 1.75 vs. F:21.7 ± 2.53), exercice (130 batt/min) (M:37.3 ± 2.95 vs. F:43.2 ± 3.05), et récupération (15 min) (M:24.5 ± 2.75 vs. F:31.8 ± 2.82). Une augmentation similaire de la composante HF a été observée chez les sujets M (1.5 x) et F (1.3 x) en réponse à une fréquence respiratoire imposée à 0,20 Hz. Ces résultats suggèrent que les hommes et les femmes présentent une sensibilité comparable en ce qui a trait a la réponse associée à l'arythmie sinusale respiratoire. Aucune différence reliée au sexe ou à la condition physique n'a

été observée pour la variabilité de la pression artérielle. Par ailleurs, les résultats de l'évaluation de la fonction baroréflexe cardiopulmonaire effectué chez un faible nombre de sujets (n = 8) n'a pas permis de mettre en évidence des effets reliés au sexe ou à la condition physique. En conclusion ces résultats indiquent une composante vagale du noeud sinusal plus importante chez la F malgré une fréquence cardiaque similaire à celle de l'H, ce qui pourrait suggérer un rythme sinusal spontané plus élevé chez la F jeune.

Part I: Review of Literature

Comparative physiology has generally, readily acknowledged species differences in circulatory physiology. It was not until recently, however, that attention has turned to within species differences related to gender. This is certainly true for the human species.

1.0 Evidence for Gender-Related Differences in Circulatory Parameters Under Resting Conditions

It has been observed that, at rest, females have significantly higher heart rates than age-matched males when measured in either the upright or supine positions. Results from national samples of men and women ages 18 to 95 found that females have resting heart rates ranging from 6 to 14 beats per minute higher than age- and race-matched males (Gillum et al., 1988; Kannel et al., 1987; Persky et al., 1979; Sutliff and Holt, 1925). Similar results were observed for baseline heart rate values in studies of even small groups of men and women (Table 1) (Abdel-Rahman et al., 1994; Collins and Frankenhaeuser, 1978; Gotshall et al., 1991; Hanley et al., 1989; Matthews and Stoney, 1988; Montgomery et al., 1977; Rahman et al., 1991; Sagiv et al., 1991).

This gender-related difference seen in resting heart rate seems to exist only before menopause which typically occurs around the age of 52 in North American women. The Chicago Heart Association's Detection Project in Industry surveyed 30,665 men and women ages 18 to 64 and found that

females exhibited a 5 beat per minute greater resting heart rate than males, but that this difference disappeared after the age of 45. (Persky et al., 1979)

Similarly, studies of post-menopausal women and age-matched men, as well as those studies looking at a mixture of young and old subjects found no significant gender difference in resting heart rate for all of the ages pooled, (Adams et al., 1987; Frey and Hoffler, 1988; Hinderliter et al., 1992) or among the older subjects alone (Iwasaka et al., 1994; Matthews and Stoney, 1988; Ryan et al., 1994).

On the contrary, Gotshall et al. (1991) reported that their female subjects (20-30 yrs.) exhibited significantly lower resting heart rates than their age-matched male counterparts. Because fitness level was not controlled for in this or any of the other studies, and because resting heart rate is reduced with exercise training, it is apparent that it could act as a confounding factor. Whether or not a true gender-related difference exists in resting heart rate, regardless of age, remains controversial. Differences in heart rate could, however, reflect differences in the autonomic balance to the sinus node. Heart rate variability was found to be different between males and females at rest (Ryan et al., 1994). In brief, spectral analysis of heart rate variability allows the quantification of sympathetic and parasympathetic influence on the sinus node, or more specifically the R-R interval. In general, the high frequency oscillations are due to vagal tone associated with respiratory sinus arrhythmia, while low frequency oscillations are associated

Table 1. Brief summary of the literature examining gender differences in heart rate and systolic blood pressure under resting conditions (n < 30).

STUDY	AGE	Δ FEMALE-MALE	
		RESTING HR (BPM)	SYSTOLIC BP (MMHG)
Matthews and Stoney (1988)	7-18 31-62	+3.8 +2.7	-4.7 -14.5
Sagiv et al. (1991)	≈30	+11	-8.0
Hanley et al. (1989)	< 50	+8	-2.0
Ryan et al. (1994)	20-39 40-64	+3 +2	-16 -13
Kilgour et al. (1994)	≈25	+5	-16
Adams et al. (1993)	18-56		-5
Allen et al. (1993)	no age		-11.3
Hinderliter et al. (1992)	18-49		-6
Frey and Hoffler (1988)	29-56		-9.2
Girdler et al. (1990)	≈26		-15.5
Moore and Newton (1986)	25-35		-7.5
Martin III et al. (1991)	18-35		-13
Rahman et al. (1991)	19-21	+15	
Collins and Frankenhaeuser (1978)	≈23	+7	
Abdel-Rahman et al. (1994)	≈25	+18	
Montgomery et al. (1977)	20-36	+11.5	

with both sympathetic and parasympathetic influences. A ratio of the two will provide an overall picture of sympatho-vagal balance at the sinus node. In a recent study, Ryan et al. (1994) found that women have a significantly greater high frequency power during both spontaneous and metronomic breathing than men. The results of this study suggest that women experience a greater parasympathetic influence at the sinus node.

In contrast, cardiac output at rest appears to be similar among males and females in both children (Bar-Or, 1983); and adults (Gotshall et al., 1994; Sullivan et al., 1991; Younis et al., 1990). However, in a recent study, Kilgour and Carvalho (1994) reported that resting cardiac output as well as resting stroke volume were roughly 13% greater in males (age 25 yrs) than females of similar age and training status. A similar gender-related difference in stroke volume was reported by Sagiv et al. (1991) although cardiac output data were not significantly different between males and females, presumably due to the significantly higher resting heart rates of their female subjects.

Further evidence has shown that there exists a significant effect of gender on resting systolic blood pressure. More specifically, it has been shown that young and middle-aged males have a resting systolic blood pressure ranging from 5 to 20 mmHg higher than same aged females. (Adams et al., 1987; Allen et al., 1993; Frey and Hoffler, 1988; Girdler et al., 1990; Gotshall et al., 1994; Hanley et al., 1989; Hinderliter et al., 1992;

Kilgour and Carvalho, 1994; Martin et al., 1991; Matthews and Stoney, 1988; Moore and Newton, 1986; Ryan et al., 1994; Sagiv et al., 1991).

It is generally accepted that there exists an age-related increase in systolic blood pressure (Folkow and Svanborg, 1993; Ganong, 1991). Interestingly, however, longitudinal research has demonstrated an interaction between gender and these age-related increases such that the increase in systolic blood pressure occurs faster in females than in males, particularly around menopause (Folkow and Svanborg, 1993). In fact, by age 65-70, research has shown that the systolic blood pressures of females may be approximately 10 mmHg higher than males (Folkow and Svanborg, 1993). The gender-related differences in systolic blood pressure observed in young adults however, are generally not observed in small groups of older adults (greater than 60 yrs of age). Consequently, Ryan et al. (1994) found significant gender-related differences in resting systolic blood pressure among both young (20-39 yrs) and middle-aged (40-64 yrs) subjects but not for the older group of subjects (65-90 yrs). Similarly, Iwasaka et al. (1994) reported that the mean arterial pressure was not found to be significantly different between post-menopausal females and age-matched males.

Concerning diastolic blood pressure at rest, a recent study by Kilgour and Carvalho (1994) showed that males have a significantly greater diastolic blood pressure at rest than females of the same age. This result has yet to be supported by a national sample.

As with systolic blood pressure, diastolic blood pressure shows a gradual increase with age in both males and females, with the slope of the rise being a function of gender. More specifically, the rise in diastolic blood pressure reaches a plateau at the age of 70 in females, whereas the plateau is reached in males at the age of 50 (Folkow and Svanborg, 1993).

As has been shown, it is typical in "westernized societies" to see an increase in both systolic and diastolic blood pressures with age. Research in this area, however, has suggested that the increase may not be purely age-related. Timio et al. (1988), in a 20-year follow-up study of 144 white Italian secluded, monastic nuns and 133 laywomen, who served as controls, found that while the control women experienced the typical age-related increases in both systolic and diastolic blood pressures, the nuns maintained the same systolic and diastolic pressures throughout the 20 years. The groups were closely similar in every aspect except drastic differences in psychosocial environments; that of the nuns consisting of intense daily meditation and introspection. The results of Timio et al.'s research suggest that the influence of the environment on the age-related increase in blood pressure may be immense. The question thus arises whether the greater age-related increase in systolic blood pressure seen in females could be related to a greater reactivity to environmental stressors in women.

Using a variety of mental and behavioral stressors, such as arithmetic, speech, coordination, and the Stroop Color-Word interference task,

researchers were able to compare differences in cardiovascular reactivity between males and females (Allen et al., 1993; Collins and Frankenhaeuser, 1978; Frey et al., 1987; Girdler et al., 1990; Matthews and Stoney, 1988). In general both males and females responded with increases in blood pressure, heart rate, and total peripheral resistance, but to differing extents. Males clearly responded to these stressors with greater increases in blood pressure (systolic, diastolic and mean arterial) (Allen et al., 1993; Frey et al., 1987; Matthews and Stoney, 1988) and total peripheral resistance (Allen et al., 1993; Girdler et al., 1990). In contrast, female subjects exhibited a greater heart rate response to the behavioral stressors (Allen et al., 1993; Collins and Frankenhaeuser, 1978; Frey et al., 1987; Girdler et al., 1990; Matthews and Stoney, 1988). The difference in the responses of males and females was so distinct that Girdler et al. (1990) labeled their male subjects "vascular hyperreactors", while their female subjects were labeled "cardiac hyperreactors".

Interestingly, early research by Collins and Frankenhaeuser (1978) found the females greater heart rate response as a result of the stressor to be accompanied by lower levels of plasma epinephrine as compared to males. These results suggest that the mechanism of heart rate increase in females may therefore be related to vagal withdrawal rather than sympathetic activation. This theory remains controversial, however. In relation to age, a cross-sectional comparison of children (7-18 yrs) and adults (31-62 yrs) by

Matthews and Stoney (1988) found increasing age to be associated with greater blood pressure response and attenuated heart rate response to laboratory stressors as well.

Similar to research using laboratory stress, researchers have found that in response to a cold-hand pressor test or facial cooling, males respond with greater increases in blood pressure than do females exposed to similar stresses (Graham, 1988; Le Blanc et al., 1978; McLean et al., 1992). The elevation in blood pressure observed in males was also maintained in these males following removal of the stressor, but not in females, whose blood pressure values returned to at or below resting levels (Kilgour and Carvalho, 1994; Le Blanc et al., 1978). Kilgour and Carvalho (1994) reported that the maintenance of blood pressure observed in their male subjects was due to a large rise in systemic vascular resistance in only the male subjects during minutes 4 to 6 of a six minute facial cooling protocol.

Although Graham (1988) reports that males typically respond to cold air stress with bradycardia and increased stroke volume, while women do not, both males and females generally responded to the cold stimulus with increased heart rate. However, in cold hand pressor and facial cooling studies, Kilgour and Carvalho (1994), and Le Blanc et al. (1978), found that the heart rate response of young and middle-aged females was significantly greater than that of age-matched males in the studies. Treiber et al. (1993) found similar results for male and female children (6-8 yrs). As well, females

experienced a quicker recovery of heart rate to below resting levels following removal of the stimulus in all three studies.

2.0 Evidence for Gender-Related Differences in Circulatory Parameters under Exercising Conditions

It is generally accepted that there is an exercise-induced increase in stroke volume from resting levels in healthy males and females, although the majority of research has used only male subjects. In general, it is thought that the increase results from both an enhanced left ventricular inotropic state, as well as heterometric regulation via Frank Starling's Law of the Heart (Ganong, 1991). Recent research has focussed on potential gender-related differences in the regulation of stroke volume, via these two mechanisms.

2.1 Response to Dynamic Exercise

By definition, stroke volume is the difference between end-diastolic volume (EDV) and end-systolic volume (ESV). An increase in stroke volume, therefore, could occur either by increasing EDV, decreasing ESV, or through a combination of both. It is generally known that in response to progressive, dynamic exercise up to approximately 40-50% VO. max, stroke volume is increased mainly due to an exercise-induced increase in ventricular diastolic filling; at greater exercise intensities a plateau in stroke volume is reached on account of a decline in ventricular end-diastolic volume coupled with a continuous decline in end-systolic volume (Ganong, 1991; Higginbotham et

al., 1986; Plotnik et al., 1986; Poliner et al., 1980; Sullivan et al., 1991).

Potential gender-related differences in the extent of the exercise-induced increase in end-diastolic volume were observed by Higginbotham et al. (1984). Using radionuclide angiography during upright, progressive cycling exercise, the researchers found the relative contribution of the Frank-Starling mechanism to the exercise-induced increase in stroke volume to be significantly more important in women than in men. Under maximal exercise conditions, women showed a 30% increase in end-diastolic counts, whereas no significant difference from rest was found in the men. Within the past decade, many researchers have addressed the gender-related differences in the regulation of exercise-induced increases in stroke volume, particularly concerning the relative contributions of enhanced ventricular contractility and the Frank-Starling mechanism.

Using radionuclide angiography, the responses of male and females subjects to maximal ergometer exercise in an upright (Higginbotham et al., 1984; Sullivan et al., 1991;, Younis et al., 1990) or supine position (Adams et al., 1987; Hanley et al., 1989; Pfisterer et al., 1985; Spina et al., 1993a; Spina et al., 1993b) were assessed. In contrast to the original findings of Higginbotham et al. (1984) in the upright position, Sullivan et al. (1991) and Younis et al. (1990) found similar increases in end-diastolic volume from rest to maximal exercise in male and female subjects suggesting that gender does not significantly influence left ventricular end-diastolic volume.

Data recorded in the supine position strongly suggest an influence of gender on the exercise-induced increase in end-diastolic volume. As Figure 1 illustrates, in all four investigations, a 5-10% increase in end-diastolic dimensions from rest to maximal exercise was observed in women; this in excess of the increased dimensions inherent to the supine position. On the contrary, data for age-matched males showed either a decrease (Adams et al., 1987; Hanley et al., 1989) or no change from rest in end-diastolic volume (Spina et al., 1993a; Spina et al., 1993b).

Similar to an increase in end-diastolic volume, it is generally accepted that, like men, women experience an increase in ventricular contractility from rest to maximal exercise. Although contractility is difficult to measure, ejection fraction, the ratio of stroke volume to end-diastolic volume, is generally taken as an acceptable index of contractility. Data from research over the last ten years, however, has indicated that independent of body position, exercise-induced changes in ventricular ejection fraction from rest to maximal exercise appears to be less in females than in males . Results from a few of these studies are presented in Figure 2 (Adams et al., 1987; Hanley et al., 1989; Higginbotham et al., 1984; Pfisterer et al., 1985; Younis et al., 1990). There are two exceptions to this general observation. Sullivan et al. (1991) reported only a tendency ($p = 0.06$) toward a gender-related difference in ejection fraction, while Younis et al. (1990) only found a

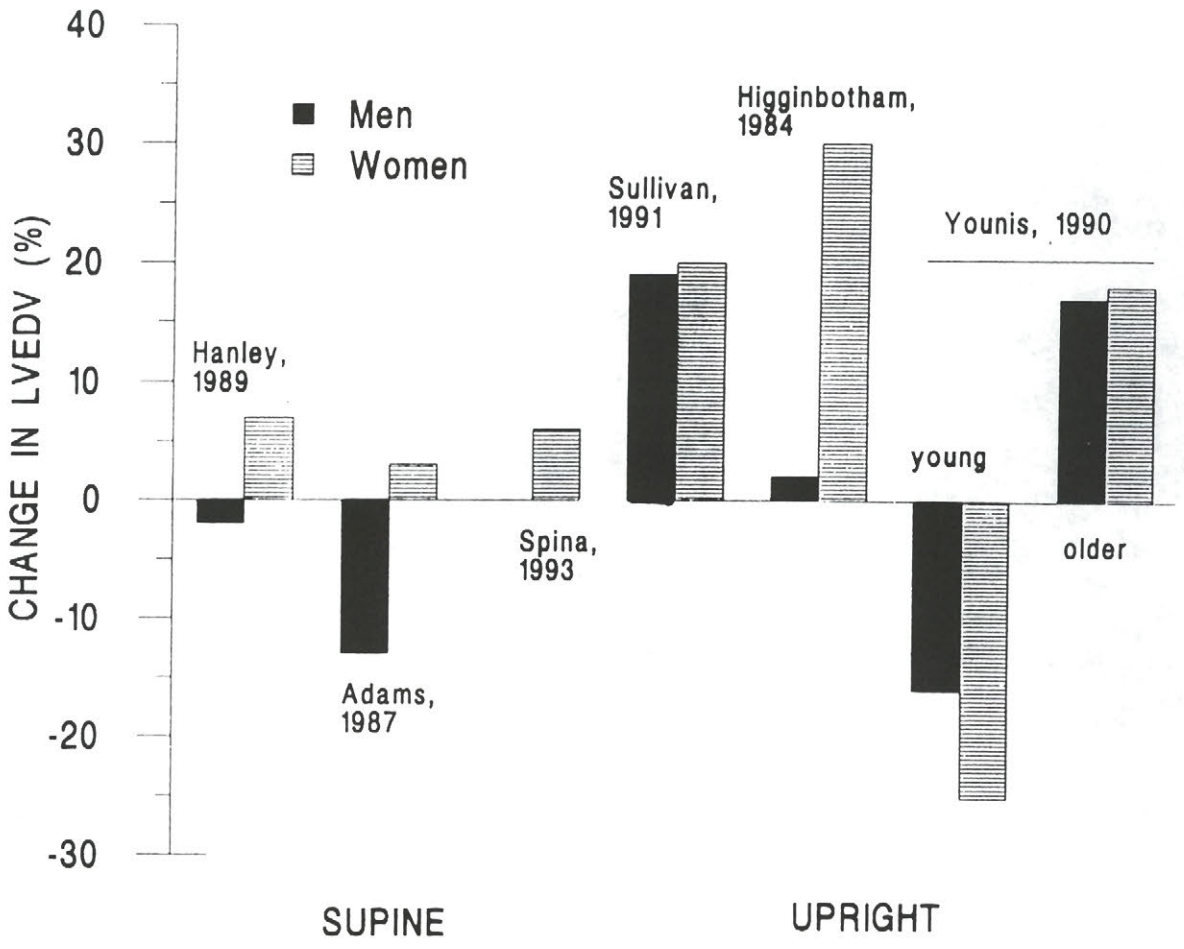

Figure 1. Brief summary of the literature examining the change in left ventricular end-diastolic volume (LVEDV) in men and women during upright and supine exercise.

From Perrault, H. Cardiorespiratory function and exercise. In: Perspectives in Exercise Science and Sports Medicine, vol. 9: Exercise and the Female: A Life Span Approach, 1996, 215-247.

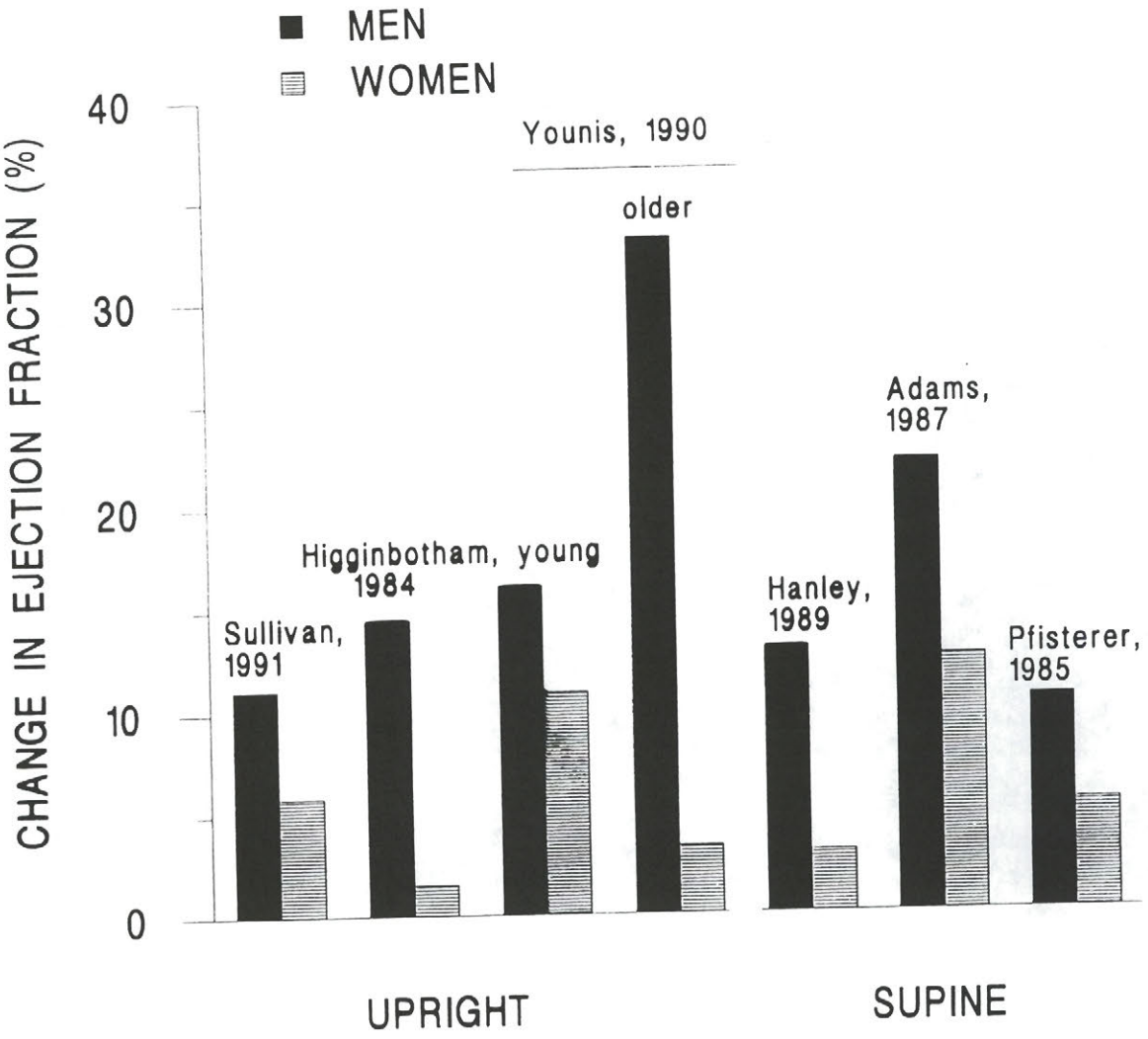

Figure 2. Brief summary of the literature examining the change in ejection fraction (EF) in men and women during upright and supine exercise.

From Perrault, H. Cardiorespiratory function and exercise. In: Perspectives in Exercise Science and Sports Medicine, vol. 9: Exercise and the Female: A Life Span Approach, 1996, 215-247.

significant influence of gender in a group of older women (52±2.5 yrs). Nevertheless, in an attempt to determine factors that would best predict the change in left ventricular ejection fraction with exercise, multiple regression analysis found only gender to be a significant predictor of left ventricular ejection fraction (Adams et al., 1987).

It is clear that a gender-related difference in the regulation of dynamic exercise-induced increases in stroke volume may exist. However the influence of age and fitness level on the gender-related differences is not clear. Perhaps the gender-related difference in ejection fraction is a function of age as Younis et al. (1990) found significant differences in the only a group of post-menopausal women. As well, fitness status may act as a confounding factor in these studies as endurance trained individuals benefit from higher resting blood volumes, which could contribute to higher end-diastolic and stroke volumes in such individuals (Convertino et al., 1990).

2.2 Response to Isometric Exercise

Under isometric exercising conditions, gender-related differences in circulatory parameters have also been observed. Sagiv et al. (1991) reported that young men experienced significant increases in ejection fraction and fractional shortening in response to 30% MVC isometric deadlift, while young women did not. Further research by Iwasaka et al. (1994) investigated left ventricular diastolic function in post-menopausal women and

age-matched men in response to isometric handgrip. They observed that women had a lower rapid atrial filling fraction than their male counterparts. This suggests that women have lesser, not greater, left ventricular compliance than men. Whether this would be true for younger men and women is not known. The overall picture of gender-related differences in the regulation of exercise-induced increases in stroke volume indeed remains controversial.

3.0 Factors in the Control of Circulation

The evidence presented thus far suggests significant gender-related differences in circulatory parameters at rest, and in response to stress and exercise. Are these differences true differences or are they artificial? If they are true differences, what are the mechanisms behind them? These questions have yet to be answered. It has been suggested though, that the gender-related differences are due to differences in the cardiovascular control of circulation.

A variety of homeostatic mechanisms exist within the body to regulate blood pressure about a given set point. It has been suggested that the major function of cardiovascular control is to maintain arterial blood pressure. Thus by looking at the response to perturbations in blood pressure, it is possible to look at the mechanisms involved in the control of circulation.

Briefly, arterial pressure is a function of both cardiac output and total

peripheral resistance (MAP = Q x TPR). Because cardiac output is determined by the product of heart rate and stroke volume (ie. MAP = (HR x SV) x TPR), a disturbance in either of these factors, or total peripheral resistance will, in turn, cause a change in arterial pressure. Two types of control systems, neural and hormonal, exist to regulate deviations in blood pressure. It is the responsibility of the autonomic nervous system and the baroreflexes to control blood pressure over the short term. It is primarily through autonomic adjustments to heart rate and peripheral resistance that arterial blood pressure is regulated.

Reflex control of blood pressure involves a negative feedback loop consisting of receptor, integrator, and effector components. As early as 1866 it was observed that stimulation of the carotid sinus and the "Aortennerv", more commonly referred to as the aortic arch, resulted in hypotension and bradycardia (Koushanpour, 1991). Today it is widely recognized that peripheral arterial baroreceptors of the carotid sinus and aortic arch play an important role in the reflex regulation of blood pressure. Though tonically active at rest, the arterial baroreceptors are activated by static changes in mean arterial pressure as well as the rate of change in pressure (Ganong, 1991; Koushanpour, 1991). Afferent impulses from the carotid sinus baroreceptors are carried via the glossopharyngeal nerve, while the aortic arch receptors are innervated by myelinated and unmyelinated fibers of the vagus nerve (Koushanpour, 1991). Both afferent systems

terminate in the medullary cardiovascular centers of the brainstem. It is through the arterial baroreceptor reflex that modulation of autonomic influence on the sinus node will occur and help to restore blood pressure.

Additionally, the existence of mechanically sensitive receptors in the atria and ventricles have been identified within the past 20 years. These cardiopulmonary receptors tonically inhibit vasomotor tone, but may be further activated by changes in blood volume, ventricular loading conditions, or changes in venous or pulmonary vascular pressure (Persson, 1991). Primarily found in the endocardium, ventricular receptors discharge in response to stretch that differs from an optimal length, such as that caused by distension or severe volume unloading (Persson, 1991). More recently, atrial receptors have been described in the venoatrial junctions ie. the right atrium/ vena cavae and left atrium/ pulmonary veins. As in the ventricles, distension of the atrial walls as a result of increased venous return and/or increased blood volume will activate the atrial receptors and increase afferent impulses to the medulla via myelinated branches of the cervical vagi (Persson, 1991). The combined afferent impulses from peripheral arterial baroreceptors and cardiopulmonary receptors converge on the hypothalamic centers and determine the balance between sympathetic and parasympathetic efferent outflow to cardiac and vascular tissue.

The primary efferent response of arterial baroreceptor stimulation is via sympathetic and parasympathetic divisions of autonomic nervous system and

is on the sinoatrial node. Sympathetic efferent pre-ganglionic neurons, originating in the intermediolateral cell column, and parasympathetic pre-ganglionic neurons originating in the nucleus ambiguus, reach the heart and vessels via fibers contained in the cardiac and vascular nerves innervating the atria and ventricles, and smooth muscle of arterioles, respectively (Persson, 1991). In general, it is thought that reflex control of blood pressure by the arterial baroreceptors occurs primarily through the action on the sinoatrial node (Minisi and Thames, 1991). The importance of a change in myocardial contractility as an effector mechanism in baroreceptor reflexes remains controversial (Scher, O'Leary and Sheriff, 1991).

In contrast to the arterial baroreflexes of the carotid sinus and aortic arch, studies in conscious humans and animals have shown that afferent stimuli from cardiopulmonary receptors rarely contribute to reflex control of heart rate (Minisi and Thames, 1991). In fact, when the low-pressure receptors are unloaded, no changes are observed in arterial pressure and there are no reflex responses in heart rate. However, the unloading results in reflex increases in vascular smooth muscle sympathetic nerve activity resulting in an increased vascular resistance (Minisi and Thames, 1991). It is suggested that stimulation of cardiopulmonary receptors by low-pressure volume unloading releases the tonic inhibitory vasomotor afferent input from the cardiopulmonary receptors, causing reflex vasoconstriction of vascular beds of skeletal muscle primarily but also perhaps of splanchnic areas (Minisi

and Thames, 1991).

It is clear that the arterial and cardiopulmonary baroreflexes play an integral part in the short-term regulation of blood pressure, through reflex alterations in heart rate and peripheral resistance. Are the gender-related differences seen during rest, stress, and exercise due to differences in cardiovascular control and baroreflex function?

3.1 Non-Invasive Techniques to Investigate the Control of Circulation

Control of circulation is, in fact, accomplished by arterial and cardiopulmonary baroreflex control of blood pressure. Several techniques have allowed for non-invasive investigations into control by these reflex mechanisms.

Heart Rate Variability Approach Heart rate variability (HRV) is the cyclic changes or fluctuations in heart period (R-R Interval) over time (Cowan, 1995). The use of the heart rate variability approach in research allows for the non-invasive assessment of the autonomic nervous system influences on the sinoatrial node, and therefore provides a measure of the control of heart rate.

Measurement and analysis of heart rate variability can be classified into time domain and frequency domain analyses. In its simplest form, time domain analysis is a general measure of autonomic nervous system balance based on measurement of the mean and standard deviation of the heart

period. In contrast, frequency domain analysis, or power spectral analysis, separates the heart rate signal into its frequency components, allowing for the delineation of parasympathetic from sympathetic components of heart rate control. Following application of a mathematical algorithm, such as the Fast Fourier Transform, to an ECG signal, three peaks are typically observed. High frequency (HF) components (0.15-0.4 Hz) are related to respiratory sinus arrhythmia, the oscillations in autonomic activity due to normal inspiration and expiration, and are thus an index of parasympathetic neural activity (Akselrod et al., 1981; Cowan, 1995; Pomeranz et al., 1985). Low frequency (LF) components are generally observed between 0.05 and 0.15 Hz and are mediated by both the parasympathetic and sympathetic nervous systems (Akselrod et al., 1981; Cowan, 1995; Pagani et al., 1986; Pomeranz et al., 1985). The low frequency component of the power spectrum is also strongly affected by the oscillatory rhythm of the baroreceptors (Stein et al., 1994). A third, very low frequency (VLF) component may be observed around 0.04 Hz and is thought to be related to peripheral vasomotor regulation (Saul et al., 1990; Stein et al., 1994), thermoregulation, and the Renin-Angiotensin system (Stein et al., 1994). The amount of the total signal variance explained by each frequency is represented by the area under each of the power spectral peaks. Additionally, the ratio of low to high frequency variations (LF/HF) may be used to express overall sympathovagal balance at the sinoatrial node (Malliani

et al., 1991; Pagani et al., 1986; Pomeranz et al., 1985)

In previous research, the analysis of heart rate variability has been used to examine the shift in autonomic balance, toward either sympathetic or parasympathetic predominance, in response to various hemodynamic stressors. It is through studies of this type that analysis of heart rate variability and the significance of the peaks have been validated. In studies of human subjects, gravitational, or orthostatic and stressors are commonly used to activate the sympathetic nervous system and thus change the autonomic balance in favor of the sympathetic side. One of the most frequently performed maneuvers of this type is passive tilt. The physiological response to tilting of any degree includes a shift of the blood volume from the upper body into the legs, thereby decreasing blood pressure. However, in response to this slight drop in blood pressure, the baroreflexes act to stimulate the sympathetic nervous system, which in turn increases outflow to the sinoatrial node. in an effort to increase heart rate, thereby increasing blood pressure. As the autonomic nervous system functions to balance the opposing forces of the sympathetic and parasympathetic systems, it follows that along with an increase in sympathetic outflow, a drop in blood pressure initiates a withdrawal of vagal influence as well. Considering the heart rate variability response to tilting, Malliani et al. (1990) found that from supine rest to 90° tilt, along with a decrease in total variance of the R-R intervals, there was a significant increase in the low frequency component of the

power spectrum, with a concomitant decrease in the high frequency component. As the maneuver activated the sympathetic nervous system, it would seem that the low frequency component was primarily mediated by sympathetic activity, while the high frequency component primarily vagally mediated. Subjects of Furlan et al. (1993) were tilted to 90° and maintained there for 15 minutes before recordings were taken. As in the study by Malliani et al. (1991), the researchers found a significant increase in the low frequency component with a decrease in the high frequency component. However, these results were only significant when expressed in normalized units. Vybiral et al. (1989) and Montano et al. (1994) found similar results at lower tilt inclines. In fact, subjects of Montano et al. (1994) found that the heart rate variability technique was sensitive enough to induce graded changes in autonomic balance. The researchers tilted their subjects to a level chosen at random from 15, 30, 45, 60 and 90 °. Along with an increase in LF, decrease in HF, and decrease in total variance, the researchers found that the low and high frequency components, when expressed in normalized units, were significantly correlated with table incline ($r = 0.78$ and $r = -0.72$, respectively).

Similar trends in heart rate variability analysis were observed upon standing, a less stressful orthostatic challenge. More specifically, Pomeranz et al. (1985) found that with standing, the high frequency component of HRV was decreased while the low frequency component was increased ten-

fold.

Exercise, although not an orthostatic stress, is another stressor which shifts the autonomic balance. In general, with exercise there is an increase in heart rate and blood pressure due to an overall increase in sympathetic nervous system activity. When looking at heart rate variability analysis during submaximal exercise, an increase in relative low frequency and decrease in high frequency have been observed in both humans (Bernardi et al., 1990; Furlan et al., 1993) and conscious dogs (Rimoldi et al., 1990).

Maneuvers which increase parasympathetic outflow have also been used OT validate the heart rate variability approach. Specifically, the technique of controlled respiration, metronomic breathing at frequencies within the physiological range, has provided a convenient tool to enhance vagal modulation of heart rate, achieved through the synchronization of respiratory components (Malliani et al.,1991). In general, controlled breathing leads to increased power in the high frequency range of the HRV power spectrum with a decrease in the LF/HF ratio, usually to less than 1.0, and an overall shift in sympathovagal balance in favor of the vagal component. Pomeranz et al. (1985) found that subjects controlling their breathing at 0.25 Hz, which falls in the HF range, increased the portion of total variance that was found in the high frequency component. Hayano et al. (1994) observed similar results in healthy males under beta-adrenergic blockade. The researchers found that compared with spontaneous breathing,

paced breathing at the same frequency revealed no significant differences in high frequency power spectral peaks in either the supine or tilt positions although low frequency peaks were lower in both positions. However, when the respiratory interval was increase from 3 to 6 seconds, the high frequency peak showed a progressive increase in both positions, while no changes were observed in the low frequency powers.

Lower Body Negative Pressure Application In investigating the cardiovascular responses to changes in blood pressure, a technique that is often used is lower body negative pressure (LBNP). LBNP is a controllable and reproducible technique to induce graded levels of fluid redistribution from the central circulation to the lower body. Cardiovascular effects and reflex responses mimic those during a true orthostatic stress, but are studied more easily, because the subject is supine, relaxed, and passive (Frey and Hoffler, 1988). LBNP deactivates cardiopulmonary receptors which induces reflex vasoconstriction of smooth muscle. Through measurements of vascular resistance at varying levels of LBNP, it is possible to evaluate the sensitivity of cardiopulmonary baroreceptors in the control of arterial blood pressure.

The lower body negative pressure technique consists of placing the subjects lower body in a Plexiglas box which is sealed at the level of the iliac crest. Pressure within the box is reduced by a large commercial vacuum cleaner creating blood volume shifts from the upper to the lower half of the body; the magnitude of the shift depending on how negative the pressure in

the box (Rowell,1986). In response to mild lower body suction (up to -20 mmHg), a small decrease in central venous pressure is observed, although mean arterial pressure is unchanged. With higher levels of LBNP (-40 to -60 mmHg), the shift in blood volume, and therefore the fall in central venous pressure, is greater. On account of reflex blood pressure regulatory mechanisms, mean arterial pressure is usually maintained even at these high levels of LBNP. However, at very high levels of LBNP (at or above -60 mmHg) blood pressure regulatory mechanisms eventually fail and arterial pressure falls rapidly (Rowell, 1986).

The physiological responses to LBNP in both men and women include a decreases central blood flow, decreased systolic and pulse pressures, increased pooling of blood in the lower extremities, and decreased cardiac output (Montgomery et al., 1977). In response to minor shifts in blood pressure (ie. LBNP -15) the cardiopulmonary baroreceptors are stimulated and respond with reflex adjustments in peripheral vascular resistance and thus peripheral blood flows. With greater shifts, such as that caused by LBNP -40, the arterial baroreceptors are stimulated, causing reflex changes in heart rate in an attempt to restore blood pressure. During the LBNP protocol, simultaneous and continuous ECG, arterial blood pressure, and forearm blood flow (FBF) measurements are recorded. As well, a venous catheter and/or echocardiography are used to determine central venous pressure (CVP), or left ventricular internal diastolic dimensions (an index of CVP), respectively.

Baroreceptor reflex control of forearm blood flow (or Forearm Vascular Resistance, FVR, it's inverse) may be examined from the slope of the relationship between FBF or FVR and central venous pressure (CVP), or an index of CVP such as left ventricular internal diastolic diameter (LVIDD). In general, it is thought that the steeper the slope, ie. the greater change in vascular resistance per unit change in central venous pressure or end-diastolic dimension, the tighter the reflex control of blood pressure (Kouame et al. 1995). Conversely, because the arterial baroreflex acts to regulate blood pressure through the moderation of heart rate, the change in heart rate per unit change in blood pressure can provide an indication of arterial baroreflex sensitivity.

3.2 Evidence of Gender-Related Differences in the Control of Circulation

It is through understanding the non-invasive techniques such as Heart Rate Variability and Lower Body Negative Pressure and the typical responses to different stressors, such as orthostatic challenges, that reactivity of the cardiovascular control systems can be measured. Interestingly, it has been found that the cardiovascular control systems of males and females respond differently to certain stressors.

The most simple of the orthostatic stressors is the stand test. This test consists of five minutes supine rest followed by five minutes of back-

supported standing. As discussed previously, the change in posture causes fluid shifts into the legs eliciting reflex mechanisms to maintain blood pressure. In response to five minutes of standing stress, Gotshall et al. (1991) reported that male and female subjects experienced similar changes in heart rate, but men had significantly greater decreases in stroke volume, cardiac output, and pulse pressure, and greater increases in mean arterial pressure and total peripheral resistance than female subjects. A similar gender-related blood pressure response was observed by Moore et al. (1986), although females in this study also showed a tendency toward a higher heart rate response from supine to standing. As well, young women had higher orthostatic heart rates and lower orthostatic blood pressures than young men in response to 20 minutes of 70 degree head-up tilt (Shvartz and Meyerstein, 1970).

In a follow-up to their standing study, Gotshall et al. (1994) observed similar gender-related responses to 2 hours of prolonged sitting. More specifically, they observed similar heart rate responses between males and females, while males exhibited greater increases in mean arterial pressure (+9% M vs. no change F) and total peripheral resistance (+54% M vs. +17% F) and greater decreases in cardiac index (-27% M vs. -12% F). Because these differences were maintained throughout the 2 hour period, it was suggested that a gender-related difference in baroreflex response exists both in the acute and chronic phases of orthostatic stress.

The LBNP technique has also been used to measure baroreceptor sensitivity in males and females. In general, it has been observed that men and women respond qualitatively the same to high levels of LBNP in that they exhibit the same net capacity to respond to the decrease in blood pressure. However, it is becoming increasingly apparent that the mechanisms of their responses may be different (Frey and Hoffler, 1986; Raven et al., 1984). As shown in Figure 3, in response to graded lower body negative pressure to a peak of -50 or -60 mmHg, women exhibited greater increases in heart rate (Montgomery et al., 1977) while men had greater increases in peripheral resistance (Frey and Hoffler, 1986; Frey and Hoffler, 1988) and blood pressure (Montgomery et al., 1977). As well, men showed greater pooling of blood in the legs than did the women in response to similar levels of LBNP application (Frey and Hoffler, 1986; Frey and Hoffler, 1988; Montgomery et al., 1977). Furthermore, Montgomery et al. (1977) found that females were less tolerant of high levels of LBNP than their male counterparts. Of the 12 tests with female subjects at -60 mmHg, only 2 were completed whereas all of the 18 tests on males at these high levels were completed without initial signs of syncope.

In studying responses to very low levels of lower body negative pressure (-1 to -4 mmHg) Rahman et al. (1991) found that males and females do not respond differently to the stress, although females exhibited a tendency toward tachycardia while males did not. These results, taken

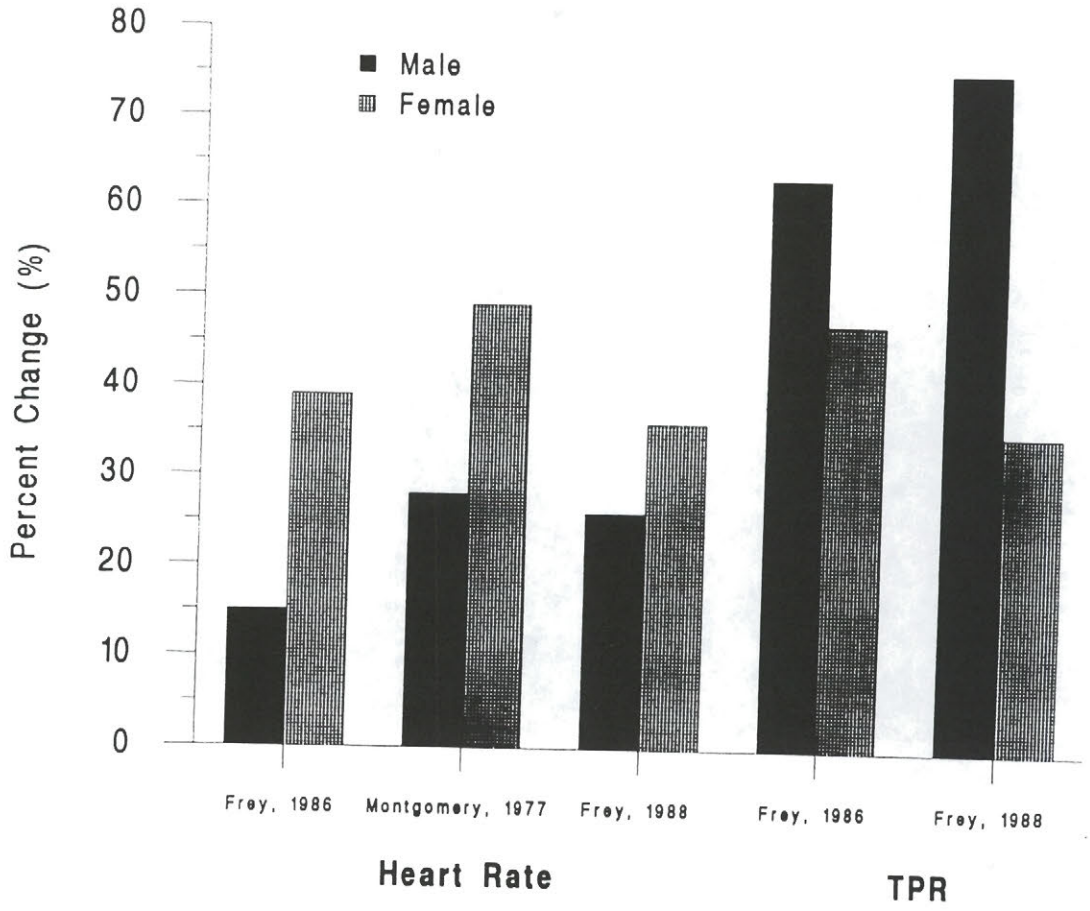

Figure 3. Brief summary of the literature examining changes in heart rate (HR) and total peripheral resistance (TPR) in men and women in response to application of lower body negative pressure to -50 or -60 mmHg.

together, suggest that in response to low, non-hypotensive levels of LBNP, the low-pressure cardiopulmonary receptors function independent of gender. However, in response to high levels of LBNP where fluid shifts cause decreases in arterial pressure, the reflex response is in fact dependent upon gender.

Gender-related differences have also been observed using the heart rate variability approach. In a large study of Atherosclerotic Risk in the Community (ARIC), researchers investigated heart rate spectral power of 1,984 healthy persons during supine rest (Liao et al., 1995). Their results showed that women have both a lower LF power and a higher HF/LF ratio than men. It was not clear, however, if the higher ratio was also a result of a higher high frequency power as well. A recent study by Gregoire et al. (1996) found the same to be true for young and middle aged, trained and untrained female subjects. Similarly, Cowan et al. (1994) found that heart rate variability was significantly lower in healthy women compared with healthy men in all time-domain and frequency-domain variables except for the high frequency components. Ryan et al. (1994) supported this idea, as they observed that high frequency heart rate spectral power is higher in women than in men. In general, the results of these studies suggest that women's heart rate dynamics may be associated with greater vagal and lesser sympathetic tone than that of men. These findings indicate the need to account for gender-related differences in heart rate dynamics.

Using an invasive pharmacological approach to activate the arterial baroreflex, Abdel-Rahman et al. (1994) measured the reflex control of heart rate following bolus-evoked elevations in blood pressure by intravenous administration of phenylephrine. In response to the abrupt pressure stimulus, women demonstrated a 50% lower baroreflex-mediated bradycardia than males. This gender-related difference was maintained when subjects were matched for basal heart rate. In a separate study, Freedman et al. (1987) used a pharmacological approach to investigate sex differences in peripheral vascular adrenergic receptors. In comparing finger blood flow responses of men and women, they found that men showed greater dose-related vasoconstriction to brachial artery infusion of phenylephrine and clonidine, selective alpha1 and alpha2-agonists, while women did not. Similarly, in response to the beta-agonist isoproterenol, men showed dose-related vasodilation but again women did not. Taken together, the results of both invasive and non-invasive investigations suggest that gender-related differences in arterial baroreflex control of blood pressure may exist.

3.3 Influence of Fitness on Gender-Related Differences

The previous research strongly suggests the existence of gender-related differences in the response to orthostatic stress as well as differences in orthostatic tolerance. However, recent research has indicated that tolerance to orthostatic stress may be inversely related to aerobic fitness,

thereby presenting a confounding factor in these studies.

Early research by Stegemann et al. (1974) found baroreflex gains were significantly smaller in male athletes than non-athletes following alterations in transmural pressure across the carotid artery (-60 to +60 mmHg). As well, heart rate responses to low pressure changes were less marked in the athlete group than in the untrained group. Similarly, young, endurance-trained males (VO. max = 70.2 ml/kg/min) exhibited less tachycardic response to lower body negative pressure at -50 mmHg, along with lesser increases in peripheral vascular resistance than average fit (41.3 ml/kg/min) males (Raven et al., 1984). In a study of young females, Hudson et al. (1987) found no significant overall differences in hemodynamic variables between trained and untrained subjects in response to progressive lower body negative pressure to -50 mmHg. However, at -50 mmHg, trained females showed significantly lower vascular resistance and diastolic blood pressure than the untrained subjects.

In contrast, research by Frey et al. (1987) found that the incidence of syncopal episodes and hemodynamic response to graded LBNP to -50 mmHg were not related to peak VO. of young female subjects. Aerobically fit subjects did, however, respond with greater pooling of blood in the legs. Similarly, in two studies by Convertino et al. (1984, 1986) using lower body negative pressure and head-up tilt as orthostatic stresses, data indicate that body fluid dynamics, not aerobic capacity may be the critical factor

associated with orthostatic intolerance in men.

Because the influence of fitness on blood pressure control remains controversial, it appears that fitness may have acted as a confounding factor in previous research concerning gender-related differences in the control of blood pressure.

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Part II: Experimental Study

It has become increasingly apparent that gender-related differences exist in the circulatory physiology of humans. In general, it has been observed that females have both a higher heart rate (Gillum et al., 1988; Kannel et al., 1987; Persky et al., 1979; Sutliff and Holt, 1925) and lower systolic blood pressure at rest,(Adams et al., 1987; Allen et al., 1993; Frey and Hoffler, 1988; Girdler et al., 1990; Gotshall et al., 1994; Hanley et al., 1989; Hinderliter et al., 1992; Kilgour and Carvalho, 1994; Martin et al., 1991; Matthews and Stoney, 1988; Moore and Newton, 1986; Ryan et al., 1994; Sagiv et al., 1991) than their male counterparts. In studies of both national samples and those using smaller sample sizes, researchers observed that female subjects experienced heart rates 2-15 beats per minute higher than and systolic blood pressures 2-15 mmHg lower than age-matched males. However, this gender-related difference appears to exist before the age of menopause as researchers have found no difference in resting heart rates (Iwasaka et al., 1994; Matthews and Stoney, 1988; Ryan et al., 1994) or systolic blood pressures (Iwasaka et al., 1994; Ryan et al., 1994) among samples of male and female subjects over the age of 60. The researchers in previous studies did not control for the effect of fitness on resting circulatory parameters, and since exercise training may result in an exercise-induced reduction in resting heart rate, it appears that fitness status could act as a potential confounding factor in these studies.

In addition to differences in resting parameters, results from studies

using mental (Allen et al., 1993; Collins and Frankenhaeuser, 1978; Girdler et al., 1990; Matthews and Stoney, 1988) and cold-pressor stressors (Graham, 1988; LeBlanc et al., 1978; McLean et al., 1992) show that the circulatory responses to these stressors is different in men and women. The data revealed that, although they respond qualitatively the same to these stressors, males respond with significantly greater increases in vascular resistance, whereas females respond with significantly greater increases in heart rate.

Similarly, within the past decade, researchers have addressed potential gender-related differences in the regulation of exercise-induced increases in stroke volume, particularly concerning the relative contributions of enhanced ventricular contractility and the Frank-Starling mechanism. Using radionuclide angiography, researchers have shown that in response to maximal exercise in the supine position, female subjects experience a 5-10% increase in end-diastolic dimension from rest to maximal exercise, while age-matched males showed wither a decrease (Adams et al., 1987; Hanley et al., 1989) or no change from rest in end-diastolic volume (Spina et al., 1993a; Spina et al., 1993b). Furthermore, studies have generally indicated that exercise-induced changes in ventricular ejection fraction from rest to maximal exercise appears to be less in females than in males (Adams et al., 1987; Hanley et al., 1989; Higginbotham et al., 1984; Pfisterer et al., 1985; Younis et al., 1990). However, Younis et al. (1990) only found a significant

influence of gender in a group of post-menopausal women. Again, the influence of fitness level in these studies is not clear, as endurance-trained individuals may benefit from higher resting blood volumes which could contribute to higher end-diastolic and stroke volumes in these individuals (Convertino et al., 1990).

A gender-related difference in circulatory parameters, however, may be related to a difference in autonomic nervous system activity. A relatively recently developed, non-invasive technique quantifying autonomic control to the sinus node is heart rate, or R-R interval, variability. By decomposing the variability in the R-R interval into frequency components, two specific frequency peaks may be identified. High frequency (HF) variations (0.16 Hz or greater) are related to respiratory sinus arrhythmia and are essentially due to vagal influence on the sinus node (Akselrod et al., 1981; Pomeranz et al., 1985). Variations occurring with a low frequency (LF) (0.05-0.15Hz) have been attributed to a combination of sympathetic and parasympathetic influences on the sinus node (Akselrod et al., 1981; Cowan et al., 1995; Pomeranz et al., 1985). The LF/HF ratio has been suggested to be a useful index for expressing overall sympathovagal balance at the sinus node (Malliani et al., 1991; Pagani et al., 1986). Only a few authors have used this technique to examine the effect of gender on sympathovagal balance at the sinus node. In general, data indicate that under resting conditions, pre-menopausal women experience a lower LF spectral component of R-R

interval variability than age-matched males (Liao et al., 1995; Madden and Savard, 1995; Ryan et al., 1994). However, again, fitness status was not controlled for in these studies. In the one study examining the effect of exercise on gender-related differences in R-R interval variability, it is reported that although females experiences greater total R-R interval variability, along with lower calculated indicators of sympathetic nervous system activity and higher calculated indicators of parasympathetic nervous system activity, these differences were not maintained with exercise (Gregoire et al., 1996).

The purpose of this study is to examine gender-related differences, and the influence of fitness status, in R-R interval variability between age-matched male and female, sedentary and endurance-trained, subjects at rest, during orthostatic stress, exercise, and recovery from exercise.

Methodology

Subjects

Heart Rate Variability The study population consisted of two groups of healthy male and female volunteers ranging in age from 17 to 35 years (mean 23.8 ± 3.71). The athletic group consisted of 22 highly trained endurance athletes, 11 male and 11 female, (mean VO_2 max ± SD: 71.4 ± 4.65 and 57.6 ± 3.72 ml/kg·min for males and females, respectively), who trained an average of 12-20 hours per week. The sedentary control group consisted of 24 age- and sex-matched healthy subjects (n = 14 male, n = 10 female) who had not engaged in regular physical activity (less than three times per week) for a period of at least one year (mean VO_2 max: 43.6 ± 7.27 and 42.3 ± 4.29 ml/kg·min for males and females, respectively). All subjects were normotensive and were not taking any medication. The subjects were asked to refrain from ingesting any alcohol or caffeine-containing beverages on the day of testing, although it was recommended that a light meal be eaten prior to the session. All subjects were instructed to refrain from engaging in physical activity within the 12 hour period prior to their scheduled testing session. Written informed consent was obtained from all participants prior to the testing session. Approval for this protocol was obtained from the Ethics Committee of the Faculty of Education, McGill University as well as from the ethics review board of Sacre-Coeur Hospital, Montreal.

Lower Body Negative Pressure A small subset of subjects also participated in a protocol assessing baroreflex function. The subject population consisted of 8 sedentary volunteers (n = 4 male) ranging in age from 19 to 27 years (mean±SD: 21.5±3.56). At the time of testing all subjects had not participated in regular physical activity (less than three times per week) for a period of at least one year. All subjects were normotensive and not taking any medications. Written informed consent was obtained from all participants prior to testing. Approval for this protocol was obtained from the Ethics Committee of the Faculty of Education, McGill University, as well as from the ethics review board of Sainte Justine Hospital, Montreal.

Experimental Protocol

Heart Rate Variability The experiment was carried out in the morning or early afternoon in a semi-dark, temperature-controlled room (19-22°C). Subjects were asked to relax and to remain quiet and awake for the duration of the testing procedure. Care was taken to ensure that both auditory and visual stimuli were kept to a minimum. As shown in Figure 1, a total of nine recordings were obtained for each subject: 2 supine, 1 standing, 2 seated, 2 exercise, and 2 recovery. Prior to the first recording, each subject rested in a supine position on a bed for 20 minutes. Following this adaptation period, continuous ECG, blood pressure, and respiratory signals were recorded

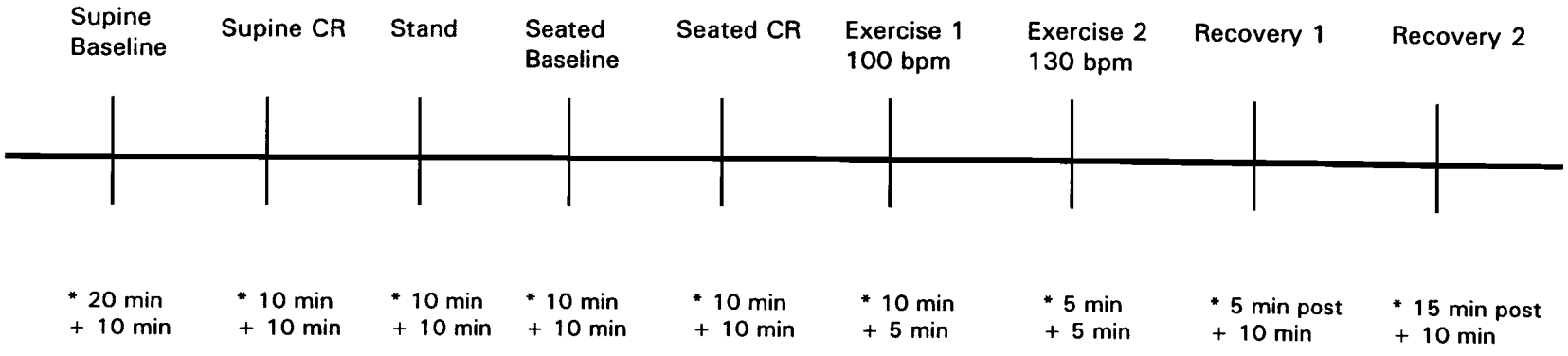


Figure 1 . Experimental Protocol. CR = Controlled respiration at 12 breaths/min, Rec 1 and Rec 2 = seated recovery 5 and 15 minutes post-exercise, * duration of adaptation period, + approximate length of recording

simultaneously. Data acquisition time varied according to the heart rate of the subject, such that no less than 532 beats were recorded for each subject at each stage. Following the supine rest recording, subjects were instructed to control their respiration rate by breathing in synchrony with a metronome set at 12 breaths per minute (0.2 Hz). This rate was selected as it would not overlap with the low frequency variability range. To observe the effects of orthostatic stress, subjects were asked to maintain a free standing position. Signals were recorded following a 10 minute adaptation to the orthostasis. Subjects were then seated and recordings taken following a 10 minute adaptation period to this position. Recordings were then repeated with subjects seated upright while controlling their breathing at the rate of 12 breaths/min. Following adjustment of the seat to an appropriate height, subjects were exercised on a cycle ergometer (Monark) at two different submaximal intensity levels. With a pedal rate of 70 RPM, the resistance of the ergometer was increased until a steady state heart rate of 100 beats/min was maintained. Signal recordings were only taken during steady state exercise defined as variations in heart rate of less than five beats/min. The resistance of the ergometer was then increased until the subject reached a steady state heart rate of 130 bpm and signals recorded. Two recovery recordings were taken after 5 and 15 minutes of passive recovery in the seated position following cessation of exercise at the second intensity level.

Lower Body Negative Pressure This experiment was carried out in the afternoon, in a lighted, temperature-controlled room (19-22°C) at Sainte Justine Pediatric Hospital. Lying in a supine position on a bed, the lower limbs of the subjects were placed in a Plexiglas box, sealed at the iliac crest with a neoprene skirt. Following a thirty minute adaptation to the supine position, the protocol was begun. The pressure within the box was continuously monitored with a pressure transducer (P23 Id, Gould). Using a commercial vacuum, the pressure within the box was decreased to 0, 15, and 40 mmHg (LBNP -40) below atmospheric pressure. Each level of LBNP was maintained for five minutes, during which recordings were taken. Following LBNP -40, pressure within the box was returned to atmospheric pressure (LBNP 0) and recordings taken within the first two minutes at this level. Continuous ECG recordings were taken throughout the LBNP procedure, while blood pressure was measured on the right arm during the last minute of each stage. Left forearm blood flow (FBF) response to the change in pressure was recorded at each level with care being taken to ensure that movement of the arm during blood flow measurements was kept to a minimum.

The LBNP sequence was then repeated to allow estimation of changes in central venous pressure (CVP) via an antecubital vein catheter ($n = 6$) and/or measurement of left ventricular internal diastolic dimension (LVIDD) by echocardiography ($n = 7$), in place of the forearm blood flow measurements.

As before, ECG and blood pressure values were recorded at each level of LBNP.

Instrumentation

Heart Rate Variability Five adhesive ECG electrodes were firmly attached to the anterior chest. Care was taken to ensure that a prominent R-wave was obtained for data processing, while avoiding any movement artifact. Continuous ECG (modified Lead III) signals were obtained with a physiograph (model 974429, Electronics for Medicine). Respiratory frequencies were recorded using a thermistor probe placed subadjacent to the nares. Non-invasive beat-to-beat arterial blood pressure was recorded using a photoplethsmographic transducer (Ohmeda Finapres, model 2300) and a small cuff placed around the third finger of the left hand. Blood pressure was also taken via conventional sphygmomanometry following each recording.

Continuous data acquisition was performed at a sampling rate of 250 samples/second for each experimental condition. This sampling rate was adequate to maintain the accuracy of the R-wave, systolic and diastolic blood pressure algorithms, and time interval measurements. ECG, respiratory, and systolic and diastolic blood pressure signals were recorded and stored on a personal computer-based system equipped with an eight channel analog-to-digital acquisition card (Data Translation model DT 2801). All tapes analyzed

were in normal sinus rhythm. Time domain analysis of successive R-R intervals was performed to determine the mean and standard deviation of the R-R intervals. Recordings containing 532 sample points (QRS complexes) were selected from each condition and analyzed, separately, using power spectral analysis. The software used was custom-designed for use in our laboratory. As equidistant time sampling of all times series is required for a spectral estimation, R-R intervals, respiration, and systolic and diastolic blood pressure values were linearly interpolated at 0.8 s intervals. A moving fourth order polynomial was used to remove the baseline trend from all signals which includes the very low frequency component below 0.005 Hz (Lepicovska et al., 1992). A Fast Fourier Transform (FFT), using the Fourier algorithm (Oppenheim and Schafer, 1985), was performed on the R-R interval segments to obtain a frequency domain analysis. Spectral powers were averaged across low frequency (0.05-0.15 Hz) and high frequency (0.16-0.5 Hz) ranges.

Lower Body Negative Pressure Five adhesive ECG electrodes were firmly attached to the anterior chest. Heart rate was measured with a tachograph triggered by the R-wave of the electrocardiogram recorded in Lead III (7P4, Grass Instruments) with a continuous tachogram recorded on polygraph paper. Mean, systolic, and diastolic blood pressures were measured using a Dinamap monitor and cuff of appropriate size. Forearm blood flow (FBF) was measured by venous occlusion plethysmography

(Hokanson EC-4) using a mercury-in-Silastic strain gauge placed around the arm contralateral to that used for blood pressure measurements. Appropriate strain gauge size was determined by measuring the left forearm at the largest circumference and choosing a strain gauge 2 cm shorter. The strain gauge was placed 4-5 cm distal to the antecubital crease and the forearm elevated to heart level. Two inflatable cuffs were placed on the left arm to isolate the forearm. One cuff was placed on the upper arm and automatically inflated to 40 mmHg to inhibit venous return. A second cuff was inflated around the wrist to suprasystolic pressure (200 mmHg) thereby arresting blood flow to the hand. The wrist cuff was manually inflated during the last two minutes of each level of LBNP, although FBF was continuously recorded on polygraph paper throughout the protocol. FBF was calculated by averaging the slopes of at least six blood flow curves recorded while hand blood flow was occluded. Central venous pressure (CVP) was estimated by measuring venous pressure from a small antecubital vein catheter (20g, 32 mm, Cathlon IV, Critikon, Canada) connected via a saline-filled line to a pressure transducer (P23 Id, Gould). Continuous tracings were recorded on polygraph paper. Echocardiography (ATL-Mark III Ultrasonograph) was performed in a left lateral decubitus position simultaneously with CVP estimation (in # subjects). For each level of LBNP, LVIDD was determined in M-mode after locating the parasternal long-axis in two-dimensional mode when heart rate was stable.

Treatment of the Data

Heart Rate Variability Time domain analysis of the R-R interval, systolic and diastolic blood pressure variabilities provided mean and standard deviations of these values under each experimental condition. The standard deviations were then squared to determine the total variance as SD^2 = Variance. The results of power spectral analysis of the R-R intervals (as well as systolic and diastolic blood pressures), provided low and high frequency powers expressed as a *percentage of total variance*. By multiplying total variance (SD^2) by the percent of total variance represented by the high frequency, the high frequency component may be expressed in **absolute units (ms^2)**. This calculation was performed for both high and low frequencies for each variable in all nine experimental conditions. The values of each power component were then converted from absolute units (ms^2) to normalized units (nu). Normalized units represent the relative value of each power component in proportion to the total power minus the very low frequency (VLF) component (ie. HF (nu) = (HF/ (HF + LF + VLF) - VLF) x 100). Moreover, the normalization of units tends to minimize the effect of changes in total power, due to changes in autonomic activity, on the values of the high and low frequency components. Thus, in order to standardize values relative to total power, and to allow for comparison to literature values, only normalized units will be presented. As well, because the interpretation of the

low frequency component remains controversial, the LF/HF ratios were calculated to reflect sympathovagal balance during each of the experimental conditions.

Lower Body Negative Pressure In order to determine the sensitivity of the cardiopulmonary baroreflex, the slope of the relationship between CVP and FBF (n = 6) and/or LVIDD and FBF (n = 7) were determined for each subject from a computer-derived regression line. In addition, both absolute and relative changes in heart rate, between LBNP 0 and LBNP -40 were calculated to provide an indication of arterial baroreflex sensitivity. The change in heart rate following the return from LBNP -40 to LBNP 0 was also calculated as a reflection of arterial baroreflex sensitivity.

Statistical Analysis

Heart Rate Variability Results of time domain analysis of heart rate and blood pressure variabilities are expressed as mean ± SD. Analysis of gender, fitness, and condition effects on LF, HF and LF/HF ratios was achieved through a two-factor analysis of variance (ANOVA) with repeated measures (condition effect) using SYSTAT statistics software. When a significant F-ratio was observed for a main effect of either gender or fitness, post-hoc Student's t-tests were used to locate significant differences, applying the Bonferroni correction factor to all probabilities. When a significant within-groups factor main effect was observed, planned comparisons were

performed using a C-matrix. A p-value of ≤ 0.05 was considered statistically significant.

Lower Body Negative Pressure Results are expressed as mean $\pm$ SE. The effects of gender and level of LBNP on HR, SBP, DBP, MAP, FBF, and LVIDD were examined with separate two-way (male and female) ANOVAs for repeated measures (LBNP conditions). The slopes of least-square regression equations calculated individually for each subject between FBF and CVP, as well as between FBF and LVIDD were also compared with two-way ANOVAs for repeated measures. A repeated measures ANOVA was also performed to determine the effect of gender and LBNP level on arterial baroreflex sensitivity [(HRLBNP-40 - HRLBNP 0)/HRLBNP 0] When a significant F-ratio was observed for a main effect of gender, Student's t-tests were performed to locate significant differences, applying the Bonferroni correction where appropriate.

Results

Subject Characteristics Subjects characteristics are presented in Table 1. Subjects in all groups were of similar age and height. Athletic subjects exhibited lower body weights than gender-matched controls and in general, males weighed more than their female counterparts, though neither reached statistical significance. As shown in Table 1, VO_2 max ($ml/kg \cdot min^{-1}$) values were higher in athletes than non-athletes for both male and female subjects. However, no significant differences were found between male and female, control or athletic subjects (CM: 43.6 ± 7.27; CF: 42.3 ± 4.29; AM: 71.4 ± 4.65; AF: 57.6 ± 3.72).

As seen in Tables 2 a. and b., mean values $\pm$ SD are presented for baseline, standing, sitting, exercise and recovery conditions. As expected, heart rate, systolic, and diastolic blood pressures increased or remained the same with orthostasis and exercise, and returned toward baseline with 5 and 15 minutes of recovery. As can be seen in Table 2 a, athletic subjects had generally lower heart rates than sedentary subjects under all testing conditions with the exception of exercise at 100 and 130 beats/min when heart rate was controlled for all groups. During 5 and 15 minutes of seated recovery, heart rates of athletic subjects were generally lower than control subjects with the difference reaching statistical significance for only male subjects (Table 2b.). Following 15 minutes of recovery, the heart rates of both the male and female athletes had returned to seated baseline values;

this was not found in the sedentary subjects of either gender. There were no gender differences observed in heart rate during any of the testing conditions. Mean systolic blood pressures were significantly higher in male athletes than in their sedentary counterparts under supine and sitting baseline conditions as well as during standing, during exercise at the second intensity level, and 5 and 15 minutes of seated recovery. This difference, however, was not generally observed between female athletes and controls. Systolic blood pressure values of male athletes were also significantly greater than female athletes, although this gender-related difference was not found in the sedentary subjects. Diastolic blood pressure values were similar for male and female subjects and were not found to be affected be fitness status, although athletes generally exhibited somewhat lower diastolic blood pressures than control subjects during exercise. This difference, however, was not found to be significant.

R-R Interval Variability

Baseline, orthostasis, exercise, and recovery. Means ± SD for R-R interval (ms) and total variance (ms^2) for male and female athletes and controls are presented in Table 3. Both male and female athletes exhibited greater R-R interval (ms) and total R-R interval variance (ms^2) at rest than their sedentary counterparts (Table 3) although differences in R-R interval approached statistical significance in only the male subjects, $p<0.10$. R-R

Table 1. Subjects Characteristics----Heart Rate Variability.

Parameter	Fitness State	Gender	
		Male	Female
N	C	14	10
	A	11	11
Age (yrs)	C	24.1(3.77)	23.5(3.75)
	A	24.6(3.17)	25.8(4.53)
Height (m)	C	1.77(0.07)	1.67(0.09)
	A	1.72(0.06)	1.68(0.05)
Weight (kg)	C	78.1(11.18)	65.0(12.15)
	A	65.1(9.12)	56.6(3.86)
VO_2 max ($ml/kg \cdot min^{-1}$)	C	43.6(7.27)	42.3(4.29)
	A	71.4(4.65)*	57.6(3.72)*+

Values are mean(SD). C = Control; A = Athlete
* significantly different from control values ($p < 0.05$)
+ significantly different from corresponding male group ($p < 0.05$)

Table 2a. Circulatory Parameters during Orthostatic Stress and Exercise

Subject		Baseline			Stand			Seated			Exercise 1			Exercise 2		
		HR (bpm)	SBP (mmHg)	DBP (mmHg)	HR (bpm)	SBP (mmHg)	DBP (mmHg)	HR (bpm)	SBP (mmHg)	DBP (mmHg)	HR (bpm)	SBP (mmHg)	DBP (mmHg)	HR (bpm)	SBP (mmHg)	DBP (mmHg)
C	M	63.3 (2.43)	116.9 (3.36)	58.9 (2.23)	82.1 (3.20)	112.5 (3.31)	68.9 (1.97)	68.5 (2.62)	114.5 (3.90)	65.8 (2.57)	103.5 (3.76)	144.6 (3.91)	77.4 (2.46)	127.7 (0.99)	146.5 (4.04)	79.4 (3.95)
	F	60.4 (2.74)	106.3^{+} (4.44)	56.7 (2.95)	82.3 (3.61	107.7 (4.38)	70.0 (2.61)	67.5 (3.12)	117.9 (5.17)	71.3 (3.41)	104.4 (4.31)	146.4 (5.18)	76.2 (3.25)	125.6 (1.12)	147.5 (5.34)	78.4 (5.22)
A	M	53.1** (1.95)	136.3** (3.97)	67.1 (2.64)	67.5** (2.46)	130.5** (3.92)	72.7 (2.33)	55.6** (1.97)	131.9** (4.61)	69.5 (3.05)	102.5 (4.18)	148.5 (4.63)	68.9 (2.91)	131.8 (1.25)	166.6** (4.78)	67.9 (4.67)
	F	55.5$\cdot$ (2.12)	112.2^{+} (4.44)	54.9 (2.95)	69.6** (2.59)	123.3** (4.38)	70.8 (2.61)	57.0** (2.05)	117.8^{+} (5.17)	62.3 (3.41)	114.2 (5.16)	148.7 (5.18)	71.7 (3.25)	133.9 (1.23)	168.3** (5.34)	78.9 (5.22)

Values are Mean(SD)
HR = Heart rate; SBP = Systolic Blood Pressure; DBP = Diastolic Blood Pressure; Exercise 1 and Exercise 2 = Submaximal exercise at steady-state heart rates of 100 and 130 beats/min, respectively.
Significantly different from Control values, $^{**}p<0.05$, $^{*}p<0.10$
Significantly different from Male values, $^{+}p<0.05$

Table 2b. Circulatory Parameters during Recovery from Exercise

Subject		Recovery 1			Recovery 2		
		HR (bpm)	SBP (mmHg)	DBP (mmHg)	HR (bpm)	SBP (mmHg)	DBP (mmHg)
C	M	85.6 (7.56)	114.7 (3.32)	67.0 (2.43)	81.9 (8.05)	115.5 (3.10)	66.9 (2.31)
	F	86.0 (10.8)	115.0 (4.44)	71.8 (3.22)	81.9 (9.36)	114.9 (4.09)	70.3 (3.06)
A	M	65.1** (6.08)	125.7** (3.93)	69.0 (2.88)	62.8** (5.85)	125.0** (3.66)	67.5 (2.73)
	F	70.5 (8.26)	116.5 (4.39)	63.4 (3.22)	66.7** (8.71)	117.9 (4.09)	64.0 (3.06)

Values are Mean(SD)
HR = Heart rate; SBP = Systolic Blood Pressure; DBP = Diastolic Blood Pressure;
Recovery 1 and Recovery 2 = upright, seated passive recovery at 5 and 15 minutes post-exercise, respectively.
Significantly different from Control values, **$p < 0.05$

Table 3. R-R Interval (ms) and Total Variance (ms^2) for male and female athletes and controls under supine baseline condition.

Subject		R-R Interval (ms)	Total Variance (ms^2)
Control			
	Male	949.6 ± 36.2	4316.2 ± 3161.7
	Female	1005.2 ± 45.2	3943.1 ± 1433.5
Athlete			
	Male	1131.6 ± 42.8*	8520.9 ± 7242.3
	Female	1099.2 ± 42.8	5699.2 ± 5079.3

Values are mean ± SD.
Significantly different from control values, * $p < 0.10$

interval variance (ms^2) was not significantly different between male and female subjects.

The mean high frequency (HF) spectral component and ratio of low to high frequencies (LF/HF) are shown for female athletes and controls (Figure 1a.) and male athletes and controls (Figure 1b.). As expected, both standing and submaximal exercise resulted in a decrease in the high frequency spectral component of heart rate variability from baseline values. As can be seen in Figures 1 a. and b., athletes and controls responded similarly to each of the testing conditions in both males and females. However, under the standing condition, female athletes had a significantly greater high frequency component than their sedentary counterparts. Because no main effect of fitness status, nor an interaction between gender and fitness status, was observed, data from athletes and non-athletes of both genders were pooled to examine specifically the gender-related effects on heart rate variability. Figure 2 (a,b,c) illustrates the results of pooled data from athletes and non-athletes of each gender, for high frequency (HF) and low frequency (LF) spectral components of R-R interval variability and the ratio of LF/HF components under supine baseline conditions, standing, seated rest, and during exercise at 100 and 130 beats/min. As can be seen in Figure 2, results generally indicate a higher high frequency spectral component and thus a lower low frequency spectral component in female subjects compared to male subjects under all experimental conditions. However, no significant

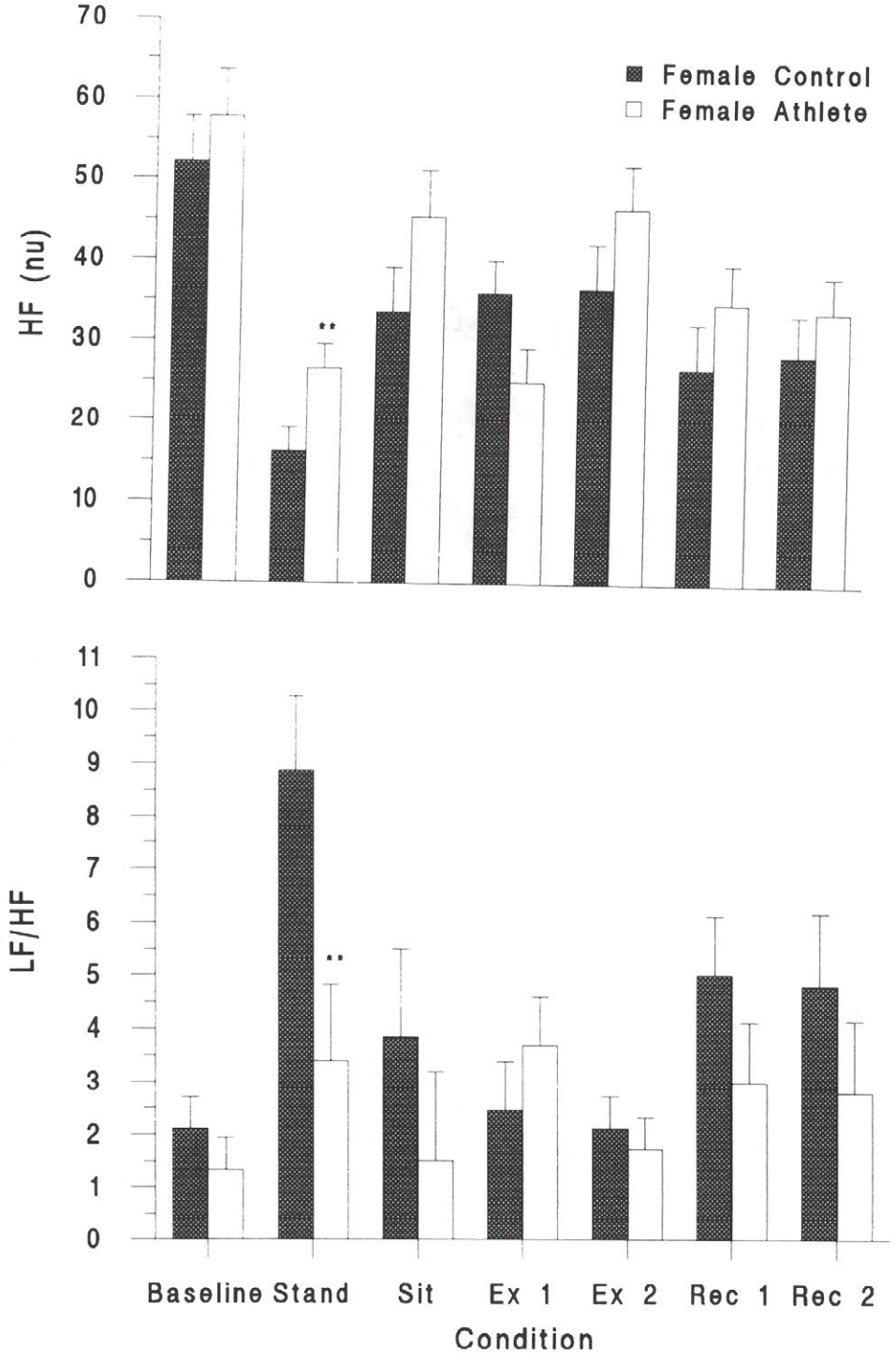


Figure 1. a. and b. High frequency (HF) and the ratio of Low frequency (LF) and high frequency (LF/HF) spectral components of R-R interval variability at rest (baseline) and during orthostatic challenge, exercise and recovery in (a) female athletes and controls, and (b) male athletes and controls. Sit = Seated baseline; Ex1 and Ex2 = submaximal steady-state exercise at heart rates of 100 and 130 beats/min, respectively, Rec 1 and Rec 2 = upright, seated recovery 5 and 15 minutes post-exercise 2, respectively; nu = normalized units. Data are expressed as means and SD. Significantly different from control value, $**p < 0.05$.

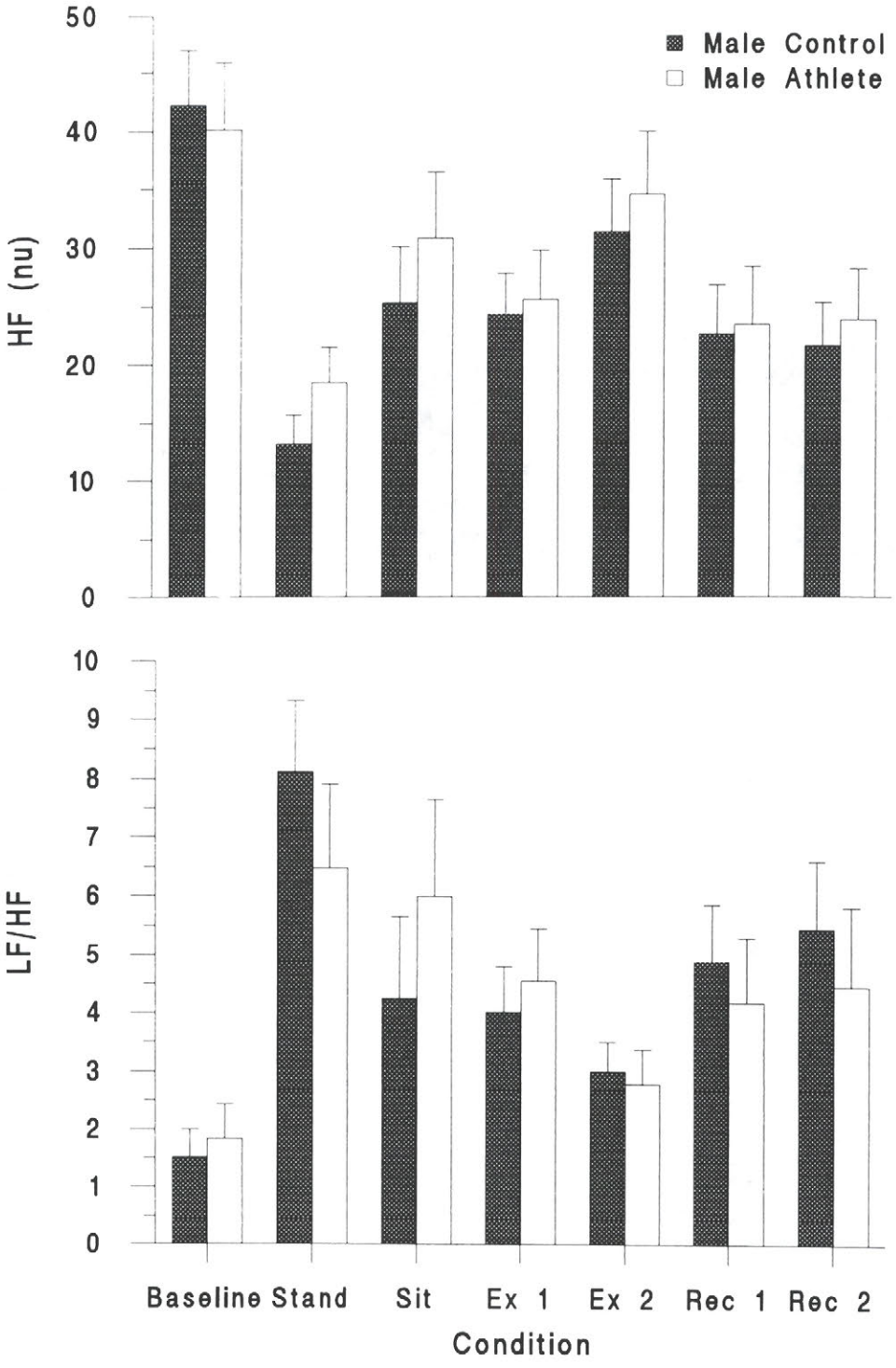

Male Control
Male Athlete
HF (nu)
50
40
30
20
10
0
LF/HF
10
9
8
7
6
5
4
3
2
1
0
Baseline
Stand
Sit
Ex 1
Ex 2
Rec 1
Rec 2
Condition

Figure 1b.

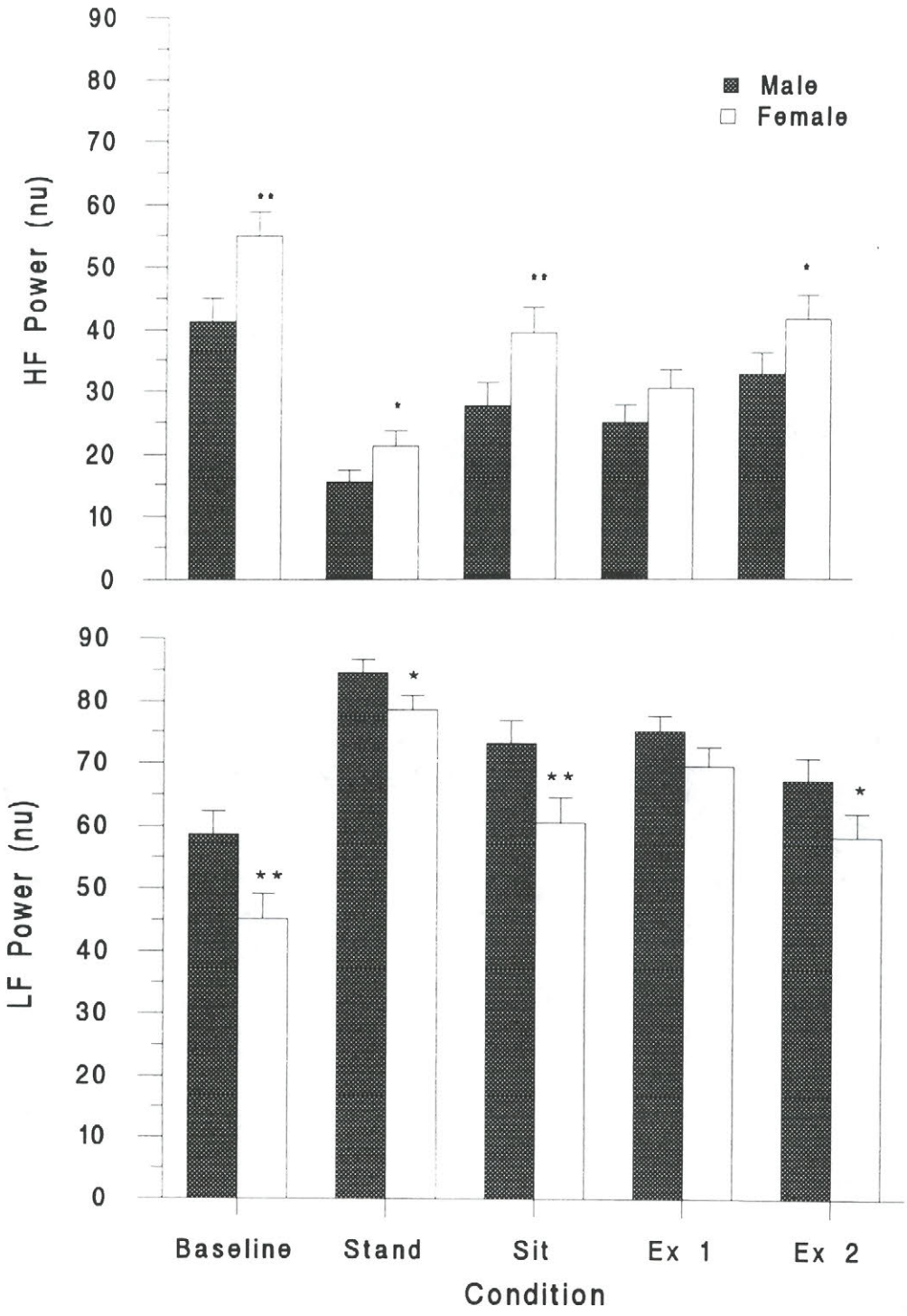


Figure 2. a. High frequency (HF) and b. Low frequency (LF) spectral components and c. LF/HF ratio of R-R interval variability at rest (baseline) and during orthostatic challenge and exercise in males (solid bars) and females (open bars). Sit = Seated baseline; Ex1 and Ex2 = submaximal steady-state exercise at heart rates of 100 and 130 beats/min, respectively; nu = normalized units. Data are expressed as means and SD. All conditions are significantly different from baseline, $p < 0.05$. Significantly different from male value, $^{**}p < 0.05$, $^{*}p < 0.10$.

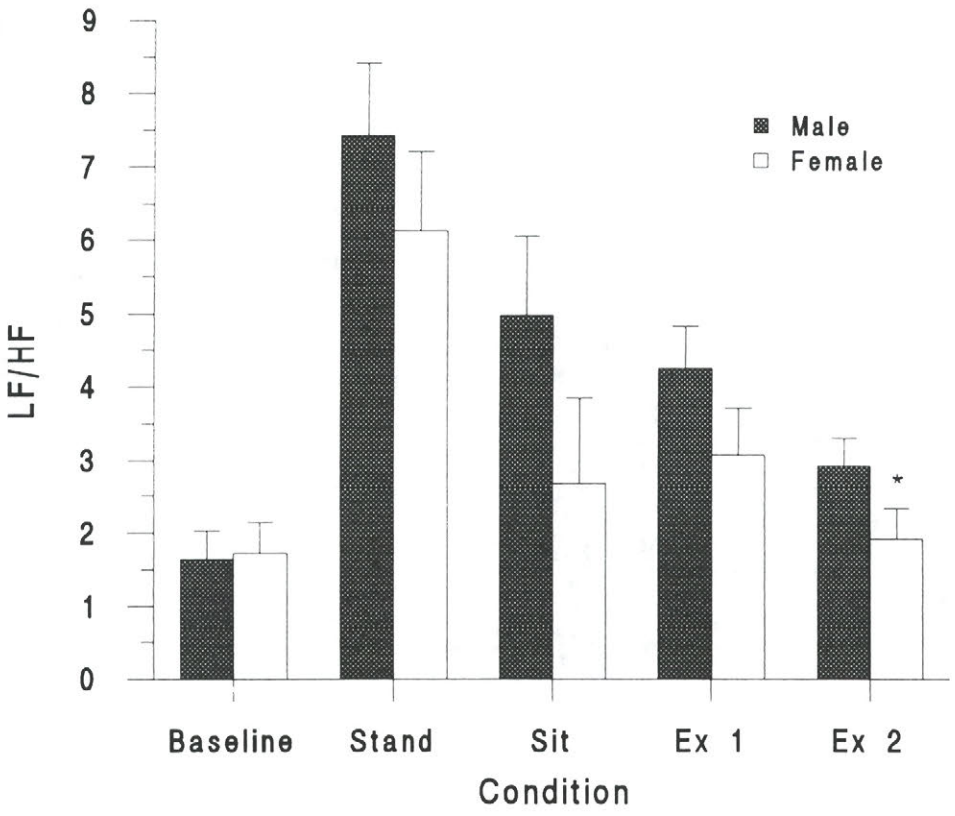

9
8
7
6
5
4
3
2
1
0
LF/HF
Male
Female
*
Baseline
Stand
Sit
Ex 1
Ex 2
Condition

Figure 2c.

differences were found in the ratio between LF and HF. As expected, sitting, standing, and exercise significantly decreased the HF component and inversely increased the LF component compared to supine baseline leading to a higher LF/HF ratio. However, there were no statistical differences observed in the HF, LF, or ratio of LF/HF components from seated rest to either intensity level of exercise, although a slight, but non-significant increase was observed in both males and females at the second intensity level. Recovery values are shown in Figure 3 in comparison to the upright seated condition and exercise at 130 bpm (ex 2). Results are again indicative of a predominance of HF in females compared to male subjects. As can be seen, the HF spectral component measured after 5 (rec 1) and 15 minutes (rec 2) of passive seated recovery was found to be significantly lower than that under seated baseline and exercise at 130 bpm.

Effects of controlled respiration Figure 4 illustrates the effect of controlled respiration on the spectral components of R-R interval variability for pooled data from athletes and non-athletes of both genders. As seen previously under baseline conditions, women exhibited a greater HF than male subjects during controlled respiration under both the supine and seated conditions. As expected, controlled respiration resulted in a significant increase in the HF component from the supine baseline condition. Similar results were obtained for controlled respiration in the seated condition. The increase in the high frequency component was of a similar magnitude for male (1.5 fold) and

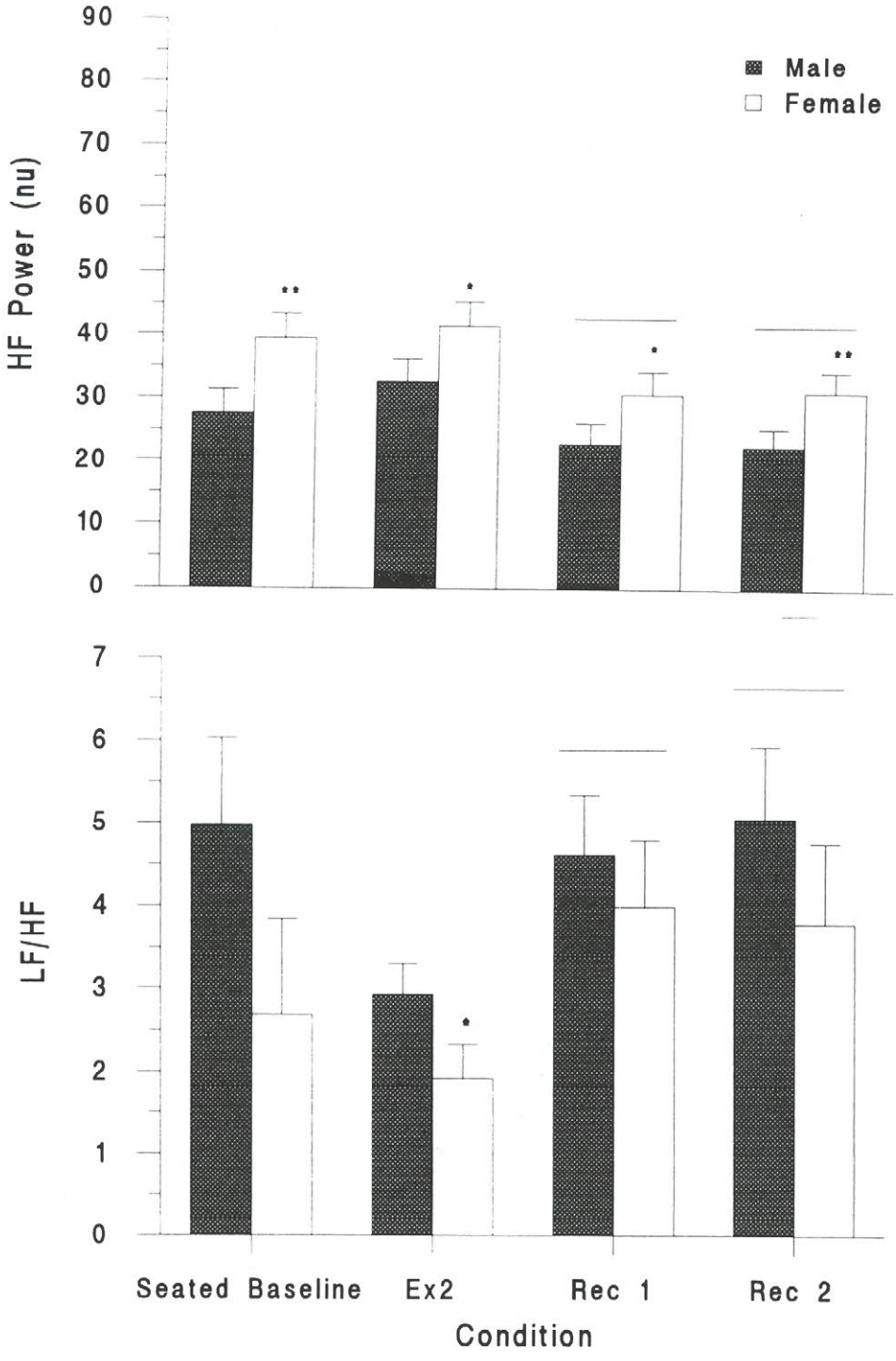


Figure 3. Spectral power of the High Frequency component of R-R interval variability and LF/HF ratio at rest (seated baseline), during exercise, and recovery from exercise in males (solid bars) and females (open bars). Ex2 = submaximal steady-state exercise at a heart rate of 130 beats/min; Rec 1 and Rec 2 = recovery periods 5 and 15 minutes post-exercise; nu = normalized units. Data are expressed as means and SD. Significantly different from male value, $**p < 0.05$, $*p < 0.10$. Horizontal line indicates significant difference from exercise 2 condition.

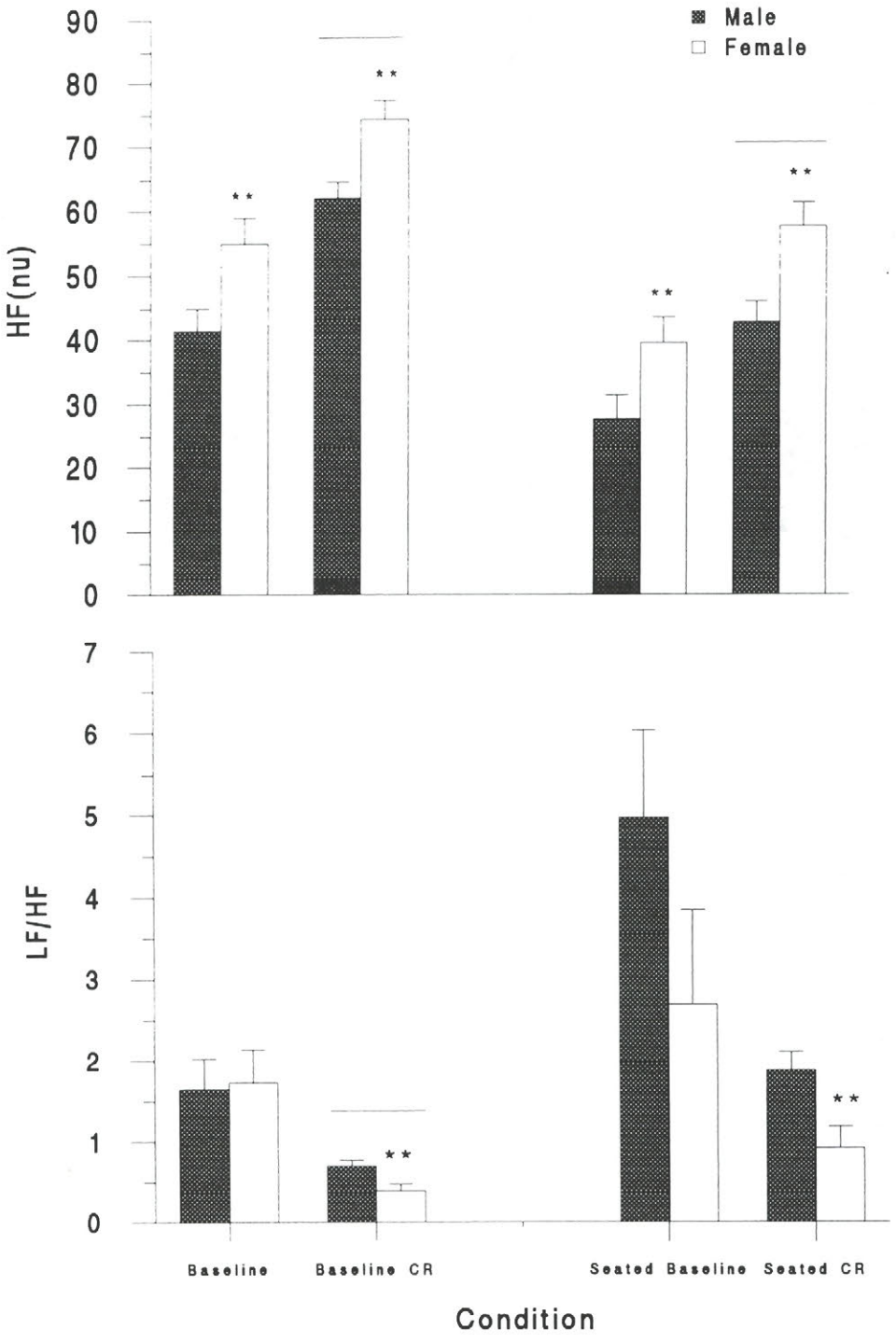


Figure 4. Spectral power of the High Frequency (HF) component of R-R interval variability and LF/HF ratio during spontaneous and controlled respiration in supine (baseline) and seated positions in males (solid bars) and females (open bars). CR = controlled respiration at 12 breaths/min; nu = normalized units. Data are expressed as means and SD. ** Significantly different from male value, $p < 0.05$; horizontal line indicates significant difference from corresponding spontaneous breathing condition, $p < 0.05$.

female (1.3 fold) subjects in both conditions leading to a concomitant decrease in the LF/HF component ratio.

Beat-to-beat Systolic and Diastolic Blood Pressure Variability

Baseline, orthostasis, exercise, and recovery Figures 5 and 6 illustrate the spectral power components of systolic and diastolic blood pressure variability for male and female athletes and control subjects. Analysis of variance revealed no main effect of either gender nor fitness status, therefore results of pooled data for males and females of both fitness states in normalized units are presented. As can be seen in Figure 5, sitting and standing had no effect on the HF component or on the LF/HF ratio of systolic blood pressure variability, while exercise at the second level elicited a significant increase in the HF component, and a concomitant decrease in the LF/HF ratio in both groups. During immediate recovery, the HF component returned to seated baseline values and was maintained through further seated recovery. Beat-to-beat diastolic blood pressure variability is shown in Figure 6. Similar to systolic blood pressure variability, there were no significant group differences in either the HF component or LF/HF component ratio of diastolic blood pressure variability. Results again indicate a significant exercise-induced increase in the HF component and a concomitant decrease in the LF/HF ratio in all groups.

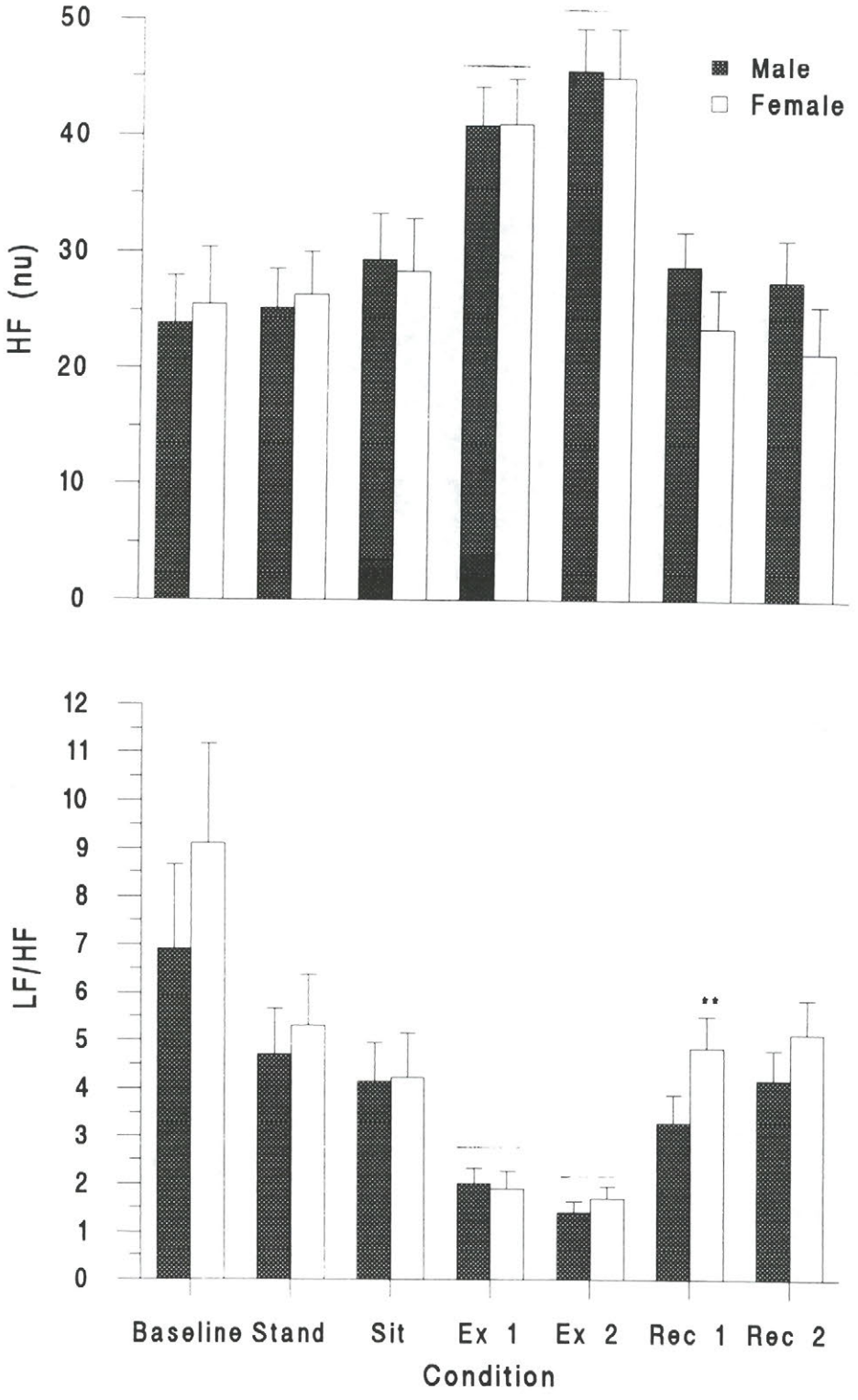


Figure 5. Spectral power of the High Frequency (HF) component of Systolic Blood Pressure variability and LF/HF ratio during rest (baseline), orthostatic challenge, and recovery from exercise in male and female athletes and controls. Sit = seated rest; Ex1 and Ex2 = steady-state exercise at heart rates of 100 and 130 beats/min, respectively; Rec1 and Rec 2 = recovery periods 5 and 15 minutes post-exercise at 130 bpm; Ctrl = Control; Ath = Athlete; nu = normalized units. Data are expressed as means and SD. Horizontal line indicates significant difference from baseline condition, $p < 0.05$.

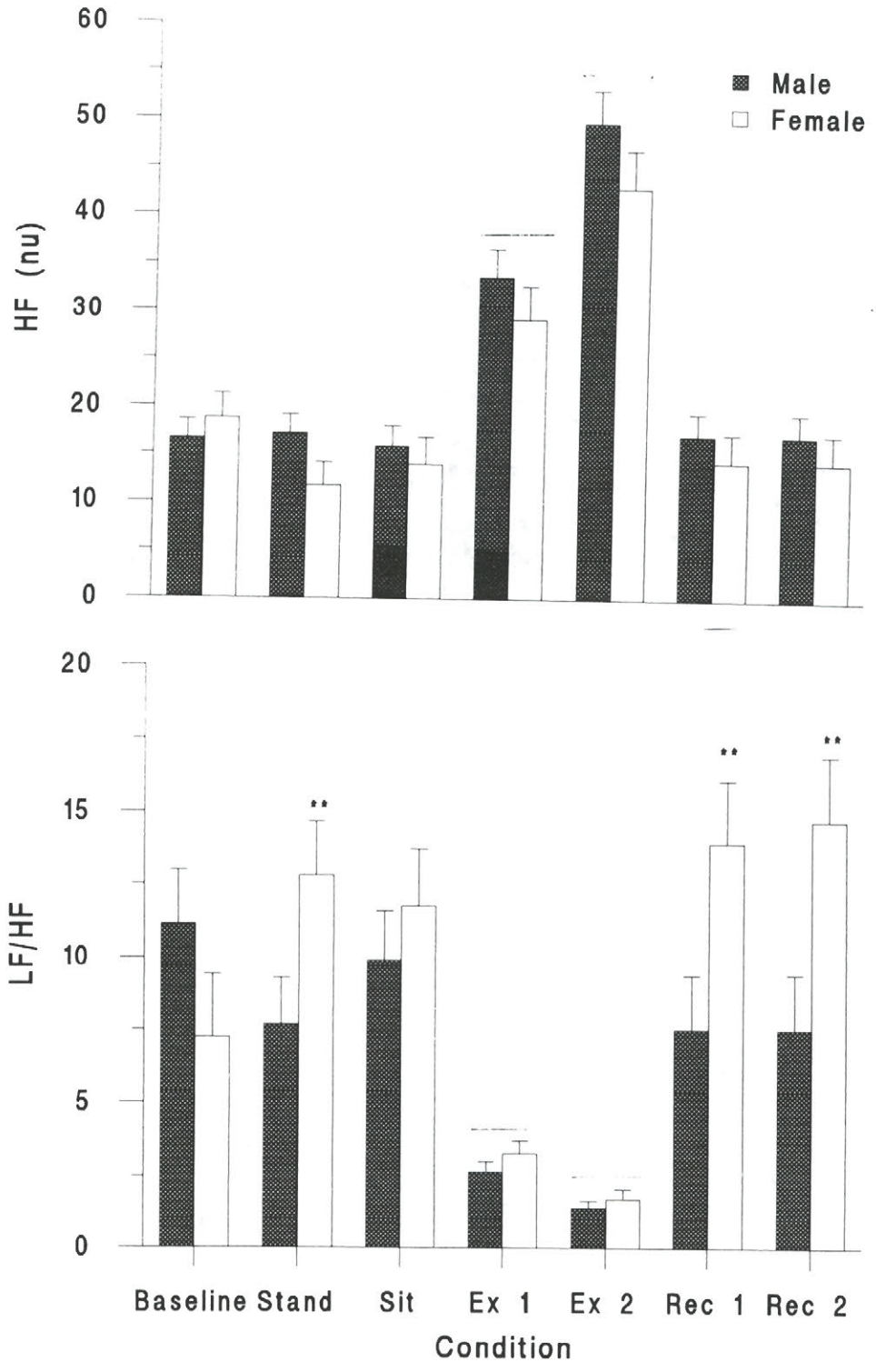


Figure 6. Spectral power of the High Frequency (HF) component of Diastolic Blood Pressure variability and LF/HF ratio during rest (baseline), orthostatic challenge, and recovery from exercise in male and female athletes and controls. Sit = seated rest; Ex1 and Ex2 = steady-state exercise at heart rates of 100 and 130 beats/min, respectively; Rec1 and Rec 2 = recovery periods 5 and 15 minutes post-exercise at 130 bpm; Ctrl = Control; Ath = Athlete; nu = normalized units. Data are expressed as means and SD. Horizontal line indicates significant difference from seated baseline condition, $p < 0.05$.

Effects of controlled respiration The effects of controlled breathing on beat-to-beat systolic and diastolic blood pressure variability are shown in Figures 7 and 8, respectively. Results again indicate no significant group differences in either the HF component or ratio of LF/HF spectral components. As for the R-R interval variability, controlled respiration resulted in significant increases in the HF spectral component of both systolic and diastolic blood pressure variability of a similar magnitude in males and females, resulting in a decrease in the LF/HF ratio.

BAROREFLEX RESPONSES TO THE APPLICATION OF LOWER BODY NEGATIVE PRESSURE

Subjects Characteristics Subjects characteristics are presented in Table 4. All subjects were of similar age, though the male subjects were significantly taller and weighed more than females. All subjects were of average fitness level.

Circulatory parameters during application of LBNP Circulatory parameters for all subjects are presented in Table 4. As expected, with increasing levels of LBNP application (ie. LBNP 0 to -40), subjects experienced decreases in systolic, diastolic, and mean arterial blood pressures. Significant decreases in central venous pressure, left ventricular end-diastolic dimension and forearm bloodflow were also noted in all subjects, concomitant with increases in heart rate and forearm vascular resistance. Significant gender-related differences were noted at baseline

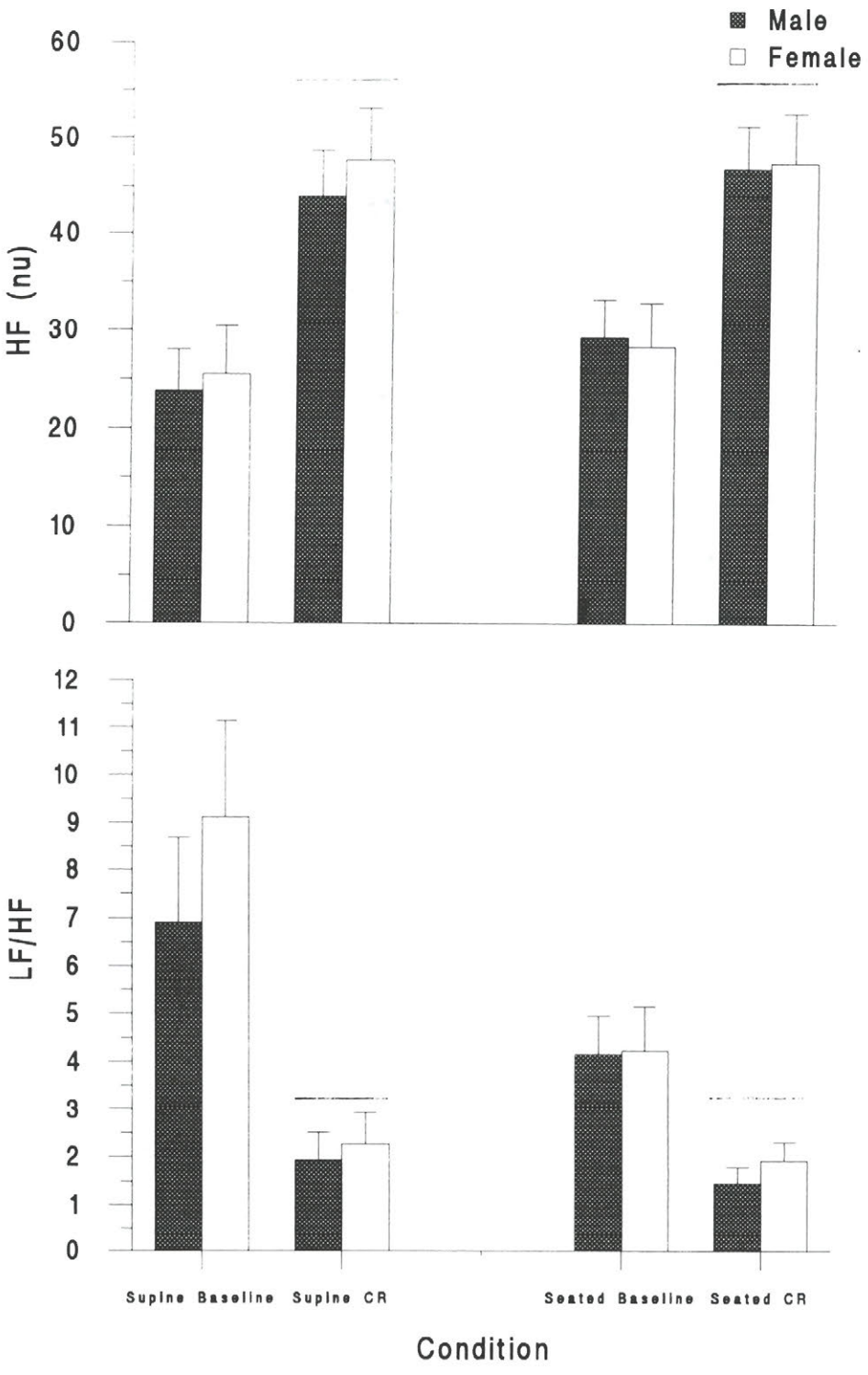


Figure 7. Spectral power of the High Frequency (HF) component of Systolic Blood Pressure variability and LF/HF ratio during spontaneous and controlled respiration in the supine and seated positions in male and female controls and athletes. Sup CR and Sit CR = controlled respiration at 12 breaths/min in the supine and seated positions, respectively; Ctrl = Controls; Ath = Athletes; nu = normalized units. Data are expressed as means and SD. Horizontal line indicates significant difference from corresponding spontaneous breathing condition, $p < 0.05$.

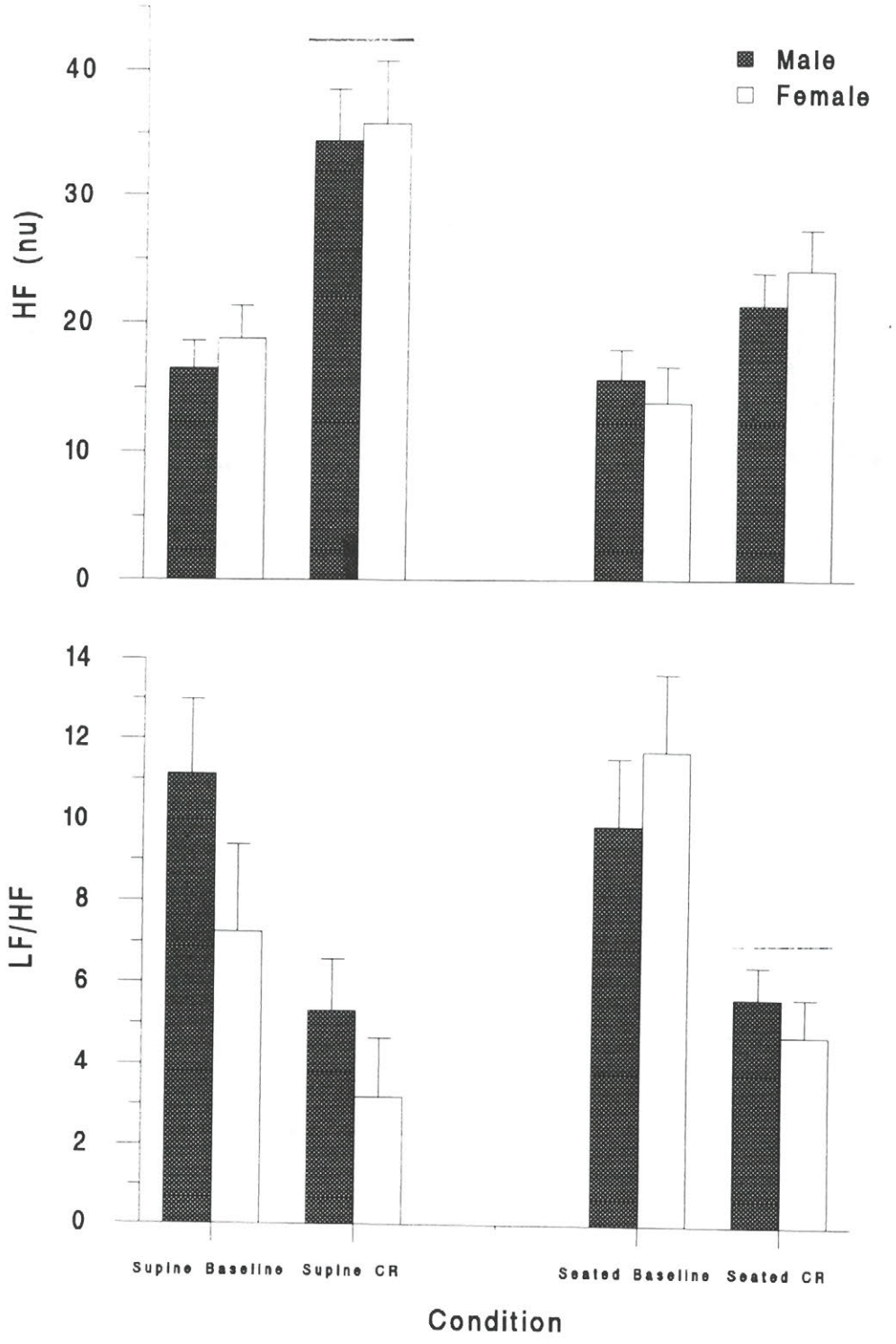


Figure 8. Spectral power of the High Frequency (HF) component of Diastolic Blood Pressure variability and LF/HF ratio during spontaneous and controlled respiration in the supine and seated positions in male and female controls and athletes. Sup CR and Sit CR = controlled respiration at 12 breaths/min in the supine and seated positions, respectively; Ctrl = Controls; Ath = Athletes; nu = normalized units. Data are expressed as means and SD. Horizontal line indicates significant difference from corresponding spontaneous breathing condition, $p < 0.05$.

Table 4. Subjects Characteristics---Baroreflex responses to Lower Body Negative Pressure

Parameter	Gender	
	Male	Female
N	4	4
Age (yrs)	22.2(3.27)	20.0(3.74)
Height (m)	1.79(0.03)	1.65(0.03)*
Weight (kg)	75.7(6.73)	59.6(3.34)*

Values are Mean(SD)
* significantly different from male values, $p<0.05$

Table 5. Circulatory Parameters During Application of Lower Body Negative Pressure.

Parameter	Gender	Baseline LBNP 0	LBNP -15	LBNP -40	Release of LBNP
SBP (mmHg)	M	124.8(7.36)	123.4(4.98)	115.8(8.98)	121.0(6.16)
	F	111.4(6.88)**	110.2(6.98)**	109.4(2.41)	113.6(12.95)
DBP (mmHg)	M	70.4(8.74)	66.0(11.11)	66.6(10.50)	64.4(5.98)
	F	64.2(10.16)	60.6(4.40)	62.8(5.45)	67.8(2.49)
MAP (mmHg)	M	88.5(7.76)	85.1(7.72)	83.0(8.22)	83.3(4.97)
	F	79.9(7.76)	77.1(4.68)*	78.3(3.62)	83.1(5.80)
HR (bpm)	M	62.4(7.93)	63.8(8.26)	69.0(9.03)	65.2(9.37)
	F	71.2(10.73)	74.2(12.38)	83.8(13.35)*	73.8(7.76)
CVP (mmHg)	M	7.7(2.48)	5.9(2.90)	4.5(3.37)	7.0(1.66)
	F	7.8(2.77)	4.9(2.93)	3.5(4.22)	8.4(3.44)
LVIDD (cm)	M	5.1(0.50)	5.1(0.68)	4.7(0.54)	5.2(0.69)
	F	4.7(0.32)	4.5(0.28)	4.1(0.38)	4.7(0.37)
FBF ($ml \cdot 100cc^{-1} \cdot min^{-1}$)	M	2.3(1.24)	1.9(1.00)	1.7(0.89)	4.2(0.81)
	F	2.1(0.61)	1.7(0.39)	1.3(0.43)	3.8(1.27)
FVR (units)	M	48.5(28.02)	55.9(33.67)	63.2(37.21)	20.3(5.25)
	F	44.3(17.12)	48.9(11.85)	69.1(33.06)	24.3(7.54)

Values are Mean(SD).
M = Male; F = Female; SBP = Systolic Blood Pressure; DBP = Diastolic Blood Pressure; MAP = Mean Arterial Blood Pressure; HR = Heart Rate; CVP = Central Venous Pressure; LVIDD = Left Ventricular Internal Diastolic Dimension; FBF = Forearm Blood Flow; FVR = Forearm Vascular Resistance, calculated as MAP/FBF.
Significantly different from male values, ** $p<0.05$, * $p<0.10$

(LBNP 0), such that females had significantly lower systolic blood pressures than males ($p<0.05$) while values for all other hemodynamic variables were not significantly different. This gender difference was maintained with application of LBNP -15. However, with LBNP -15 females generally also exhibited lower mean arterial pressures than males, ($p<0.10$). At LBNP -40 these gender differences in blood pressure were no longer observed though females had a significantly greater heart rate response to this higher level (M: +10.6% F: +17.9%; $p<0.05$). Following return from LBNP -40 to LBNP 0, there were no significant differences observed between males and females in any of the parameters. The relative changes in all of the circulatory parameters with application and release of LBNP -40 mmHg are illustrated in figures 9 and 10.

Sensitivity of the Arterial Baroreflex Figure 11 a. and b. illustrates the relationships between central venous pressure and both forearm blood flow and forearm vascular resistance. The slope of the relationship between FBF and CVP as well as FVR and CVP was not significantly different for male and female subjects, suggesting no difference in the sensitivity of the arterial baroreflex between genders.

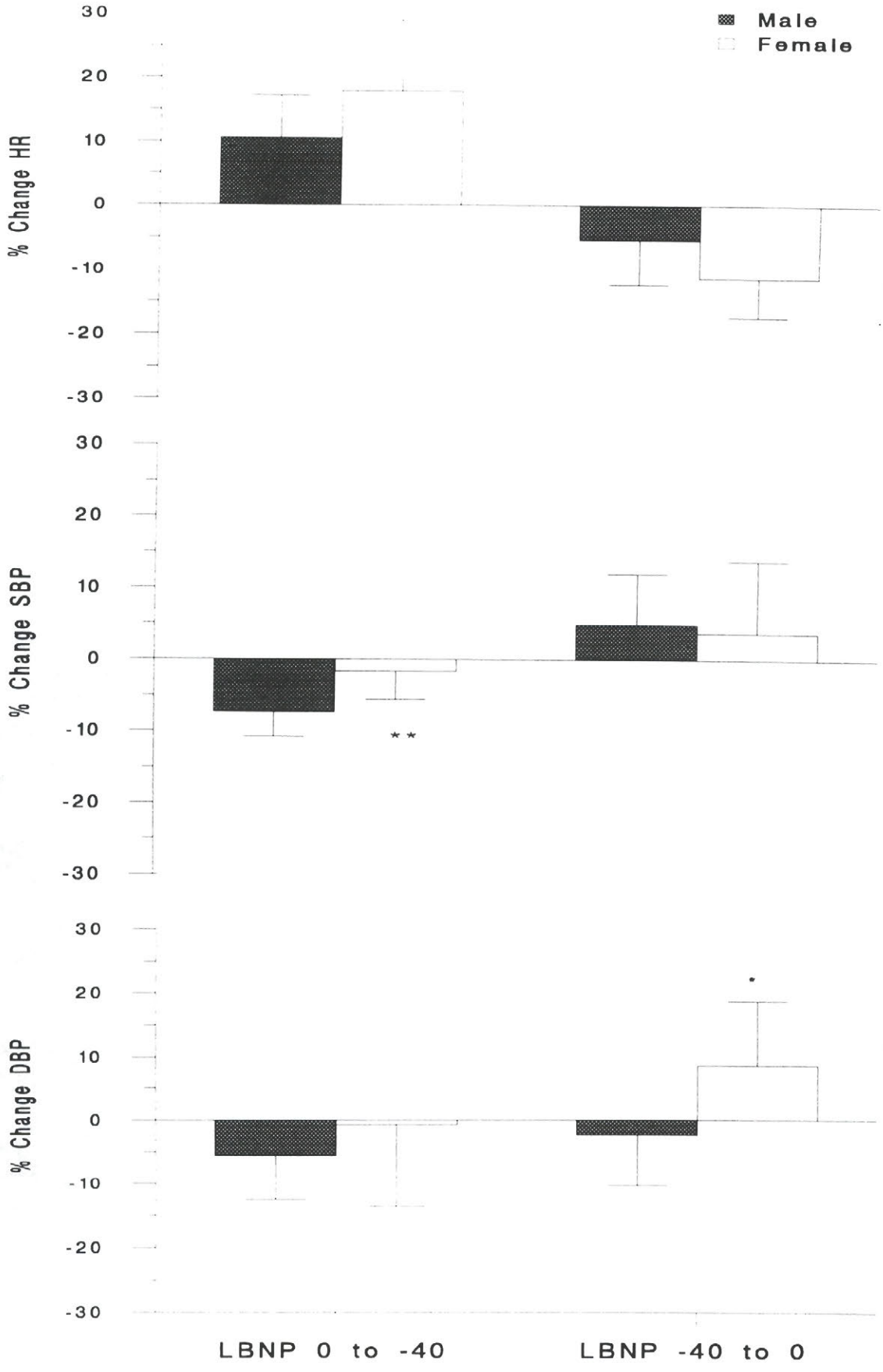


Figure 9. a, b, c. Relative changes in a. Heart Rate (HR), b. Systolic Blood Pressure (SBP), and c. Diastolic Blood Pressure (DBP) during application of lower body negative pressure (LBNP) to -40 mmHg and following return to LBNP 0. Data are expressed as means and SD. Significantly different from male value, $**p<0.05$, $*p<0.10$.

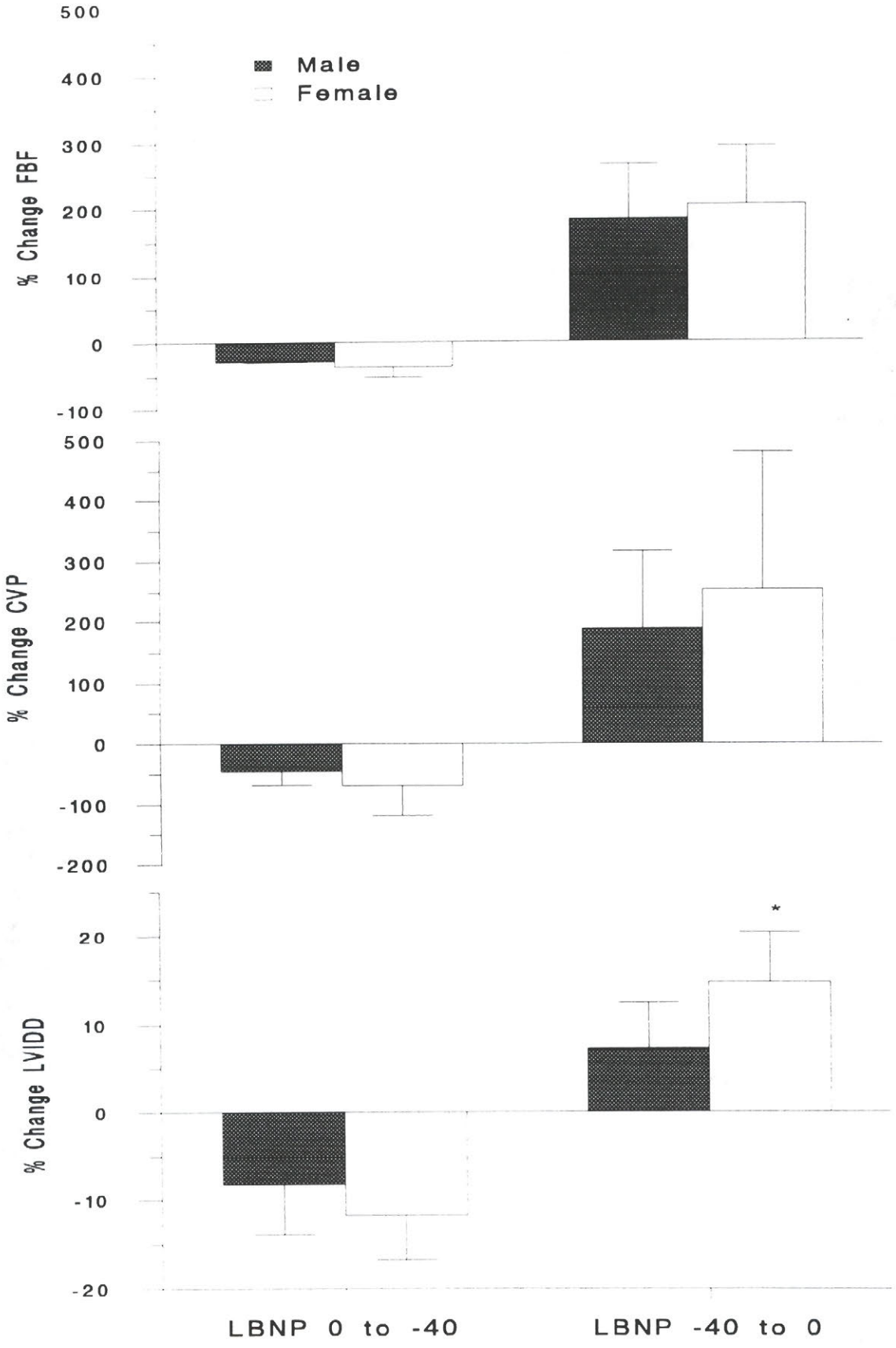
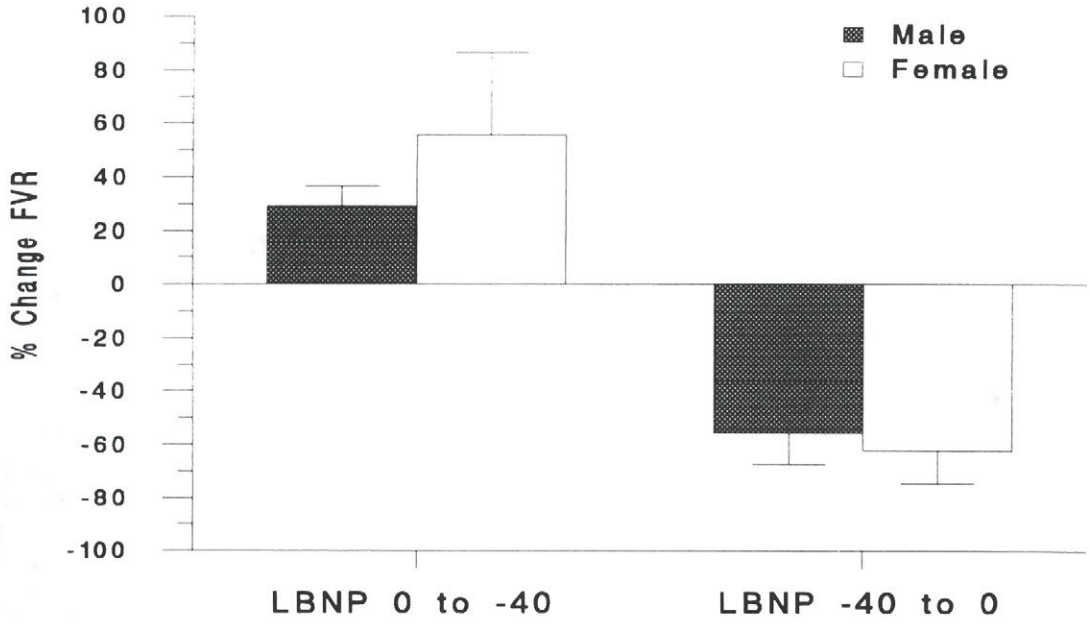


Figure 10. a, b, c, d. Relative changes in a. Forearm Blood Flow (FBF), b. Central Venous Pressure (CVP), c. Left Ventricular Internal Diastolic Dimension (LVIDD), and d. Forearm Vascular Resistance (FVR) in males and females during application of lower body negative pressure to -40 mmHg and following return to LBNP 0. Data are expressed as means and SD. Significantly different from male value, $**p<0.05$, $*p<0.10$.


100
80
60
40
20
0
-20
-40
-60
-80
-100
% Change FVR
Male
Female
LBNP 0 to -40
LBNP -40 to 0

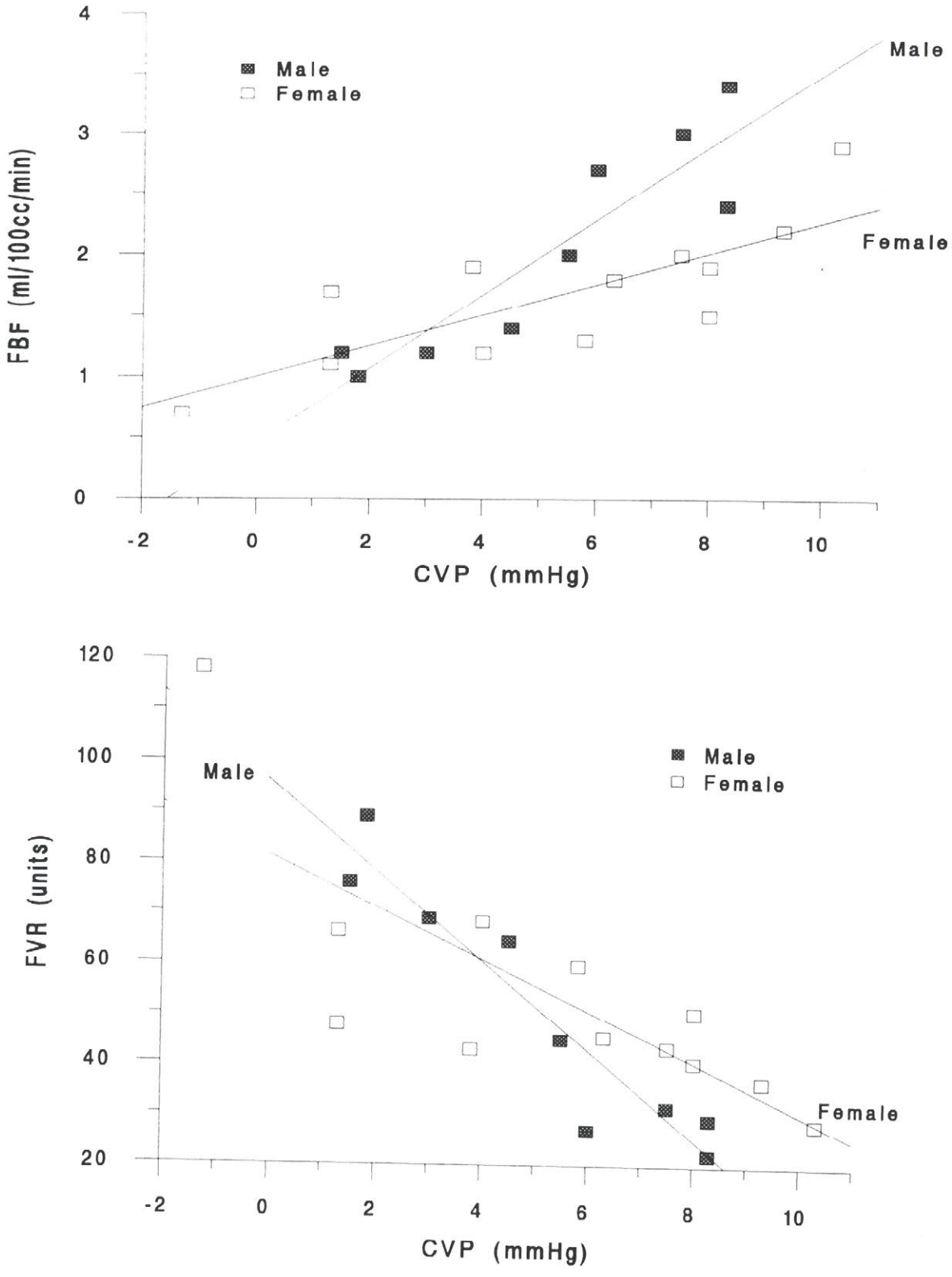


Figure 11. a, b. The sensitivity of the arterial baroreflex as illustrated by the relationship between Central Venous Pressure (CVP) and a. Forearm Blood Flow (FBF) and b. Forearm Vascular Resistance in males and females.

Discussion

The main finding from this study was a higher HF spectral component of the heart rate variability in female subjects compared to age-matched male subjects despite findings of a similar heart rate in both groups. Similar observations were made under all conditions including rest, standing, exercise, and recovery from exercise. The sensitivity of the response, assessed through changes due to controlled respiration, showed similar increases in HF power, suggesting that the sensitivity is also similar in males and females.

Evidence exist that suggest fitness related differences in the control of blood pressure. For example, investigations of arterial baroreflex sensitivity using application of negative and/or positive pressure to the carotid arteries as well assessment of cardiopulmonary baroreflex function using lower body negative pressure indicate a lower baroreflex gain in endurance athletes versus non-atheltes (Stegemann et al., 1974; Raven et al., 1984). In the present study, assessment of cardiopulmonary baroreflex sensitivity in a small subset of male and female subjects revealed no gender-related differences nor apparent fitness-related differences in blood flow response to lower body negative pressure application up to -40mmHg. However because testing was achieved on only 8 subjects and fitness was assessed only through self-report, no definite conclusion can be reached from these observations. On the other hand, spectral analysis of blood pressure

variability also revealed no differences in HF or LF spectral components between athletes and non-athletes under any testing condition. Similarly, no differences between gender-groups were found under resting, exercise or recovery conditions. A similar increase in the HF spectral component of the BP variability was observed with exercise in all groups which can probably be explained by an associated increase in the breathing frequency. Indeed results from an extensive review on blood pressure variability indicate that the HF component of blood pressure variability to be mainly related to mechanical repercussions on BP of the changes in intrathoracic pressure related to breathing (Parati et al.,1995).

In the present study, regular training practice rather than performance criteria was used to categorize subjects into either the athlete or control group. In fact, a significantlty lower resting heart rate ($p<0.05$), presumably due to training bradycardia, was only found between male athletes and non-athletes, whereas female athletes showed only a tendency toward lower resting heart rates than female controls, $p<0.10$. In any case, results from spectral analysis of heart rate variability showed no differences in any of the spectral components between athletes or non-athletes. These observations are in agreement with previous findings of a similar HF component in endurance athletes compared to sedentary controls (Bernardi et al. 1990; Lazoglu et al. 1996; Gregoire et al., 1996). Findings of a higher HF component have also been reported (Dixon et al.,1992; Goldsmith et al.,

1992; Al-Ani et al.,1996) but the fact that HF component values were reported in absolute rather than normalized units may explain the discrepancy in findings, since a lower heart rate in athletes will necessarily translate into lower heart rate variance when expressed in absolute units. Observations from studies reporting values in normalized units thus suggest that regular physical activity, while potentially causing training bradycardia does not lead to an increase in the parasympathetic indicator of sinus node activity.

On the other hand, in the present study a significant gender effect on the HF and LF spectral indicators of heart rate variability was observed. Results indicate a higher HF and a lower LF spectral component in female subjects under all testing conditions regardless of fitness status. Upon standing and exercise under spontaneous breathing conditions, a decrease in the HF and an increase in the LF spectral components was observed of a similar magnitude in both male and female subjects. Moreover, when breathing frequency was increased to 0.20Hz a similar increase in the HF respiratory spectral component of heart rate variability was observed in both male (1.5 fold) and female (1.3 fold) subjects under both supine and seated conditions. This observation may thus be taken to suggest a similar respiratory sinus arrhythmia sensitivity between genders despite a greater initial respiratory component of heart rate variability.

There exists limited data on gender-related comparisons of heart rate variability. Assessment of heart rate variability under resting conditions in

pre-menopausal women and age-matched men using spectral analysis generally indicate a lower LF spectral component in normalized units in the female subjects, when heart rates are similar between the groups (Ryan et al.,1994; Madden and Savard, 1995; Liao et al., 1995). To my knowledge, there exists only one study addressing the issue of spectral analysis of heart rate variability in male and female subjects during exercise. As in the present study, Gregoire et al. (1996) report that young and middle-aged females of varying fitness status experience greater total R-R interval variability, along with lower calculated indicators of sympathetic nervous system activity, and greater calculated indicators of parasympathetic nervous system activity at rest. However, this gender-related difference was not maintained with exercise at 50 or 100 watts. In the present study, during orthostatic stress and exercise, all subjects experienced a decrease in the HF component of heart rate variability in accordance with previously published reports (Cassadei et al., 1995; Kamath et al., 1991). This change was both quantitatively and qualitatively similar in the male and female subjects, such that the gender-related difference in spectral components was maintained throughout the exercise conditions. The discrepancy in findings may be related to the fact that although absolute work intensities were identical in men and women in the study by Gregoire et al. (1996), these intensities would correspond to different relative intensities between men and women if expressed in terms of percentage maximal heart rate. In the present study,

the exercise intensity was selected to represent similar relative intensities, although absolute workload achieved was significantly higher in male subjects. Findings of a higher HF spectral or respiratory component could also be related to differences in breathing frequencies between groups. However, in the present study, during conditions of spontaneous and controlled breathing there were no significant differences in respiratory frequencies between male and female subjects. The present observations may thus be taken to suggest that female subjects experience a greater parasympathetic influence at the sinus node than age-matched males despite similar heart rates. These differences can not be explained by differences in breathing frequency and thus may be a function of the spontaneous discharge rate of the sinus node. To my knowledge, there is no research to date that supports this suggestion.

It is clear that, based on results of the present and previous studies, further research is warranted examining the gender-related differences in the control of heart rate and blood pressure at rest and during exercise.

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