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Exercise Blood Pressure Response and Cardiometabolic Risk Factors in Middle Aged Women: A MONET Group Study

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Abstract

Objective: To investigate if an exaggerated peak exercise systolic blood pressure (peak ESBP) is associated with alteration of cardiometabolic risk factors and predict future resting hypertension in middle aged women. Methods: Data analysis was performed in 95 healthy normotensive premenopausal women at baseline and 84 after 5-year follow-up (age, 49.9 ± 1.9 years; BMI, 23.3 ± 2.2 kg/m^2; resting BP, 117/73 ± 11.8/7.6 mmHg). Blood pressure was measured at rest and during a progressive exercise test on treadmill. Women were divided into two groups according to their peak ESBP <190 mmHg *vs.* ≥190 mmHg. Other outcome measures were: cardiorespiratory fitness (VO_2 peak), body composition, body fat distribution and fasting plasma lipids, glucose and insulin levels. Results: 15% and 27% of women presented an exaggerated peak ESBP response (≥190 mmHg) at baseline and year 5 respectively. Linear mixed model repeated measures analysis revealed higher values of fasting glucose, resting systolic and diastolic BP in women with an exaggerated peak ESBP (≥190 mmHg) compared to women with a peak ESBP (<190 mmHg). No significant difference was observed between the two groups for VO_2 peak, body composition and body fat distribution indices and other cardiometabolic risk factors. Finally, baseline peak ESBP was not a significant risk factor for future resting hypertension (OR: 2.96, 95%CI [0.48 - 18.12]; P = 0.24). Conclusion: Our results, despite being non significant, are of great interest because in healthy and active premenopausal women, exaggerated peak ESBP is not predictive of future hypertension af-

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ter 5-year follow-up throughout menopause transition.

Keywords

Blood pressure, Exercise Blood Pressure, Exaggerated Peak Exercise Systolic Blood Pressure, Hypertension, Cardiometabolic Risk Factors

1. Introduction

Hypertension (HT) is one of the major risk factors for cardiovascular diseases (CVD) [1]. The exact causes of essential HT are not identified, but several factors appear to be highly correlated with this clinical condition, including age, family history of HT, smoking, obesity, diabetes, sedentary lifestyle, high sodium intake, high alcohol consumption and stress [2]. Approximately 19% of Canadians over the age of 20 years have HT and its prevalence is constantly on the rise [3]. According to the 2013 Canadian Community Health Survey, the prevalence of HT during mid-life (45 - 54 years old) is higher in men (20.5%) than in women (15.2%) [4]. However, it is important to note that the prevalence of the HT is under-estimated because of the absence of symptoms in the majority of individuals [4] [5].

Moreover, an exaggerated peak exercise blood pressure (peak EBP) is defined as an abnormally elevated systolic (S) and/or diastolic (D) BP response during exercise testing in individuals with a normal resting BP [6]. Exaggerate EBP response is diagnosed when peak ESBP is ≥190 and/or peak EDBP ≥ 105 mmHg in women and peak ESBP ≥ 210 and/or peak EDBP ≥ 105 mmHg in men [7] [8]. This phenotype has been suggested to be a risk factor for future development of HT at rest in asymptomatic individuals [9] [10]. Some researchers have documented various characteristics that are specific to such a phenotype. Among these, the most common are high values of resting systolic and diastolic BP [6] [11], body mass index (BMI) [12] [13], waist circumference [13], fasting glucose [11] [13] and insulin levels, as well as insulin resistance [11] [13] and abnormal lipid profile [14] [15].

Most studies that investigated the exaggerated peak EBP in association with cardiometabolic risk factors were cross-sectional [6] [9] [11]-[16] and included either only men [10]-[12] [14] or consisted mostly of men [6] [9] [13] [15]. One study appears to have included middle-aged obese premenopausal women in their analysis on the clinical implications of exaggerated peak EBP response [16]. None of the studies appear to have included non-obese premenopausal women and followed them through the menopause transition. Therefore the objective of this study was to investigate if an exaggerated peak EBP is associated with alteration of cardiometabolic risk factors and predict future resting HT in premenopausal women. We hypothesized that women with an exaggerated peak EBP response would 1) have higher resting SBP and DBP, adiposity and cardiometabolic risk factors, and 2) predict future resting HT in healthy normotensive middle-age women in transition to menopause.

2. Methods

2.1. Subjects

The study is a secondary data analysis of 102 healthy normotensive premenopausal women aged between 47 and 55 years who participated in a 5-year longitudinal study on the effect of the menopause transition on body composition and CVD risk factors (MONET project, Montreal Ottawa New Emerging Team) [17]. For the purpose of this study, only data from year 1 and year 5 were included in the analysis. Participants were recruited using: 1) community advertising and 2) referrals from the obstetrics and gynaecology clinics.

Premenopausal women were included if they met the following criteria: 1) premenopausal status (two menstruations in the last three months, no increase in cycle irregularity in the 12 months preceding testing, and a plasma follicular-stimulating hormone level <30 IU/liter); 2) no surgically-induced menopause; 3) non-smoking; 4) BMI between 20 and 29 kg/m^2; and 5) reported weight stability (±2 kg) for ≥6 months before enrolment in the study. Exclusion criteria were: 1) pregnant women or planned to become pregnant; 2) had medical problems that could have interfered with outcome variables including cardiovascular and/or metabolic disease; 3) were taking oral contraceptives or hormone replacement therapy; 4) had high risk for hysterectomy; and 5) had a history of

drug and/or alcohol abuse. This study received approval from the University of Ottawa and the Montfort Hospital Ethics committees, and written consent was obtained from each participant.

2.2. Cardiorespiratory Fitness

A progressive exercise test on a treadmill was performed to measure participants' peak maximal oxygen uptake (VO_2 peak). Participants were asked to refrain from any vigorous exercise for 24 hours and consumption of alcoholic beverages for 6 hours before the test. They were also asked to abstain from eating and drinking coffee for 2 hours prior to the test. The progressive test consisted of 3-minute stages starting with a speed of 3.4 mph and a slope of 0% with an increasing workload to the point of participant exhaustion (speed increased to 4.0 mph by stage 6, 5.2 mph by stage 8 and 6.0 mph by stage 10; slope increased by 4% at every stage). Heart rate, BP and the rate of perceived exertion (Borg scale) [18] were taken at rest and at the end of each stage during the test. Breath-by-breath samples of expired air were collected through a mouthpiece throughout the test, and measurements of VO_2 and CO_2 were made automatically using a Vmax 229 series metabolic cart (SensorMedics Corporation, Yorba Linda, CA). The indirect calorimetry unit was calibrated according to the manufacturer's specifications.

After a brief warm up on the treadmill, subjects performed the exercise test. The test was considered maximal when at least 2 of the following criteria were achieved [19]: 1) predicted maximal heart rate for age reached, 2) respiratory exchange ratio > 1.1, 3) oxygen uptake remained stable or decreased with an increase in workload, or 4) rate of perceived exertion reached ≥19 (15 points Borg scale). Peak VO_2 was considered as the highest 30 seconds average VO_2 reached during the test.

2.3. Blood Pressure

Qualified research assistants measured supine resting blood pressure manually from the left arm after participants had been resting quietly for 5 minutes using a standard stethoscope and a mercury sphygmomanometer. For this measurement, an appropriate cuff size was selected for each participant based on arm circumference. Assessment of resting blood pressure was standardized according to the American College of Sport Medicine [19]. SBP was considered as the first detectable Korotkoff sound (phase 1) and DBP was considered as the last detectable Korotkoff sound (phase 5) [20]. Blood pressure during exercise was measured and recorded manually by a trained exercise physiologist using the same equipment, while the subject was being tested on the treadmill. Blood pressure was measured at every stage during the last minute of exercise until the test was stopped. The highest SBP and DBP achieved during the exercise test were defined as the peak ESBP and peak EDBP respectively. An exaggerated BP response to exercise is defined as a peak ESBP response of ≥190 mmHg and/or peak EDBP response of ≥105 mmHg as previously described [7] [8]. Because none of the participants presented an exaggerated peak EDBP, we focused only on exaggerated peak ESBP.

2.4. Anthropometric Assessment

Body weight and height were measured with a BWB-800AS digital scale and a Tanita HR-100 height rod, respectively (Tanita Corporation of America, Inc.) and BMI was calculated [body weight kg/height (m^2)]. Waist circumference (mean of two measures) was determined using a Gulick tape at the mid-distance between the lowest rib and the iliac crest.

Fat mass, percent body fat (% BF), lean body mass and trunk fat mass were measured using dual-energy X-ray absorptiometry (DEXA) (GE-LUNAR Prodigy module, GE Medical Systems, Madison, WI, USA) as previously described [17]. Subjects wore a light hospital gown without shoes for these measurements.

2.5. Blood Sampling

Samples were taken after a 12-h overnight. Plasma insulin concentrations were determined in duplicate by radioimmunoassay using ^{125}I-labeled Human Insulin and a Human Insulin antiserum (Millipore, St. Charles, MO, USA). Plasma glucose levels were determined using spectrophotometric analysis after conversion of glucose to glucose-6-phosphate by hexokinase (Sigma-Aldrich Canada Ltd., Oakville, ON, CAN; Fisher Scientific Limited, Nepean, ON, CAN). Fasting insulin resistance was also estimated using the homeostasis model assessment (HOMA-IR) equation: HOMA-IR = (fasting glucose × fasting insulin)/22.5. Total cholesterol (TC), high-density-

lipoproteins cholesterol (HDL-C), and triglycerides (TG) were analyzed using the Vitros 950 immunoassay analyzer (Ortho Clinical Diagnostics, Johnson & Johnson Company, Markham, ON, CAN) at a wavelength of 540 nm. TC, HDL-C, and TG were used in the Friedewald [21] formula to calculate low-density-lipoproteins cholesterol (LDL-C) concentration. Finally, FSH was measured using an automated immunoassay analyzer, the Beckman Coulter DxI Unicell 800 (Beckman Coulter, Brea, CA, USA).

2.6. Statistical Analysis

SPSS 17.0 for windows (SPSS Inc., Chicago, IL, USA) was used to perform the secondary statistical analysis. Variables were verified for normality, consequently, only TG was log-transformed to normalize the distribution. The women were divided into two groups: those with a peak ESBP response (<190 mmHg) and those with and exaggerated peak ESBP response (≥190 mmHg). A linear mixed model repeated measures analysis was then performed for determination of main effects on various variables of interest. Time (baseline and year 5) was considered as a *within-subject* factor; and the peak SBP response to exercise was considered as *between-subject* factor. Two-sided Pearson correlations were done to assess the associations between peak ESBP response and cardiometabolic risk factors of interest at baseline. Further associations were done between the changes (year 5 - year 1) in peak ESBP response and the changes in various variables of interest. Finally, a binary logistic regression was performed, with peak ESBP response as an independent factor, to assess whether or not it predicts future resting hypertension. Results are expressed as the mean ± standard deviation (Mean ± SD) and odds ratio (OR) with 95% confidence intervals. A P value ≤ 0.05 was considered as significant.

3. Results

3.1. Subjects' Characteristics

Subjects' characteristics based on time and peak ESBP responses are presented in Table 1. Based on resting and exercise BP availability, data analysis was performed in 95 women at baseline and 84 at year 5, respectively. There were no significant differences in the women characteristics and cardiometabolic risk factors between the original cohort and the sub-sample. To the exception of age, our cohort displayed a broad range of values for the variables of interest. Women presented a mean peak ESBP and EDBP of 171 ± 18.1 mmHg (range: 134 to 248 mmHg) and 72.8 ± 8.7 mmHg (range: 56 to 98 mmHg), respectively.

Fourteen women presented an exaggerated peak ESBP response (≥190 mmHg), which represents 15% of the whole cohort at baseline. Nine out of the 14 women and an additional 13 women presented an exaggerated peak ESBP response at year 5 for a total of 22 women (27%).

3.2. Independent and Interaction Effects of Peak ESBP Response

Linear mixed model repeated measures were performed (**Table 1**) to determine the main effect of time and peak ESBP response (normal vs. exaggerated) on cardiometabolic risk factors. As a result, a significant main effect of peak ESBP response was observed for fasting plasma glucose and resting systolic and diastolic BP. These variables were significantly higher in participants with an exaggerated peak ESBP response (≥190 mmHg) compared to those with a peak ESBP response (<190 mmHg). Finally, no significant effect of *time* × *peak* ESBP interaction was observed.

3.3. Association between Peak Exercise Blood Pressure and Cardiometabolic Risk Factors

Pearson correlation analyses were performed between peak ESBP and EDBP and cardiometabolic risk factors at baseline (**Table 2**). A significant positive correlation was observed between peak systolic and diastolic EBP and resting SBP and DBP, and a trend between peak ESBP and VO_2 peak ($p = 0.052$). No associations were observed for all other cardiometabolic risk factors. Finally, no significant correlations were observed between the changes in peak ESBP and changes in resting BP, body composition and body fat distribution indices and cardiometabolic risk factors.

3.4. Associations between Peak ESBP and Hypertension at Year 5

Finally, only 2 (14%) of the women with an exaggerated peak ESBP response at baseline presented high resting

Table 1. Comparison of baseline and year 5 cardiometabolic risk factors between women with normal and exaggereated peak exercise systolic blood pressure response.

Variables	Peak Exercise Systolic Blood Pressure				Independent Effects (P value)		
	Normal (<190 mmHg)	Exaggerated (≥190 mmHg)	Normal (<190 mmHg)	Exaggerated (≥190 mmHg)			
N	Baseline		Year 5		Time	Peak SBP	Interaction
	81	14	61	22			
Body mass index	23.2 ± 2.3	23.6 ± 1.7	23.4 ± 2.8	23.4 ± 2.7	NS	NS	NS
% Body fat	31.4 ± 6.7	29.6 ± 5.5	33.7 ± 7.6	31.8 ± 7.8	<0.001	NS	NS
Fat mass (kg)	19.2 ± 5.5	17.9 ± 4.1	21.1 ± 6.4	19.1 ± 6.5	<0.01	NS	NS
Lean body mass (kg)	38.9 ± 4.1	38.1 ± 5.1	38.1 ± 4.1	37.6 ± 3.2	NS	NS	NS
Trunk fat mass (kg)	9.3 ± 3.2	8.5 ± 2.3	9.7 ± 4.0	8.4 ± 3.4	NS	NS	NS
Waist circumference (cm)	77.8 ± 7.0	78.6 ± 5.2	78.6 ± 6.9	72.2 ± 6.7	NS	NS	NS
N	82	14	62	22			
VO_2 peak (ml $O_2 \cdot kg^{-1} \cdot min^{-1}$)	33.4 ± 6.0[a]	35.3 ± 6.1	31.8 ± 5.8[b]	35.1 ± 7.7[c]	< 0.05	NS	NS
Resting BP (mmHg)							
Systolic	114.7 ± 10.9	124.6 ± 14.1	116.6 ± 10.6	127.1 ± 10.9	NS	<0.001	NS
Diastolic	72.6 ± 7.5	77.1 ± 7.6	72.9 ± 7.1	77.6 ± 5.7	NS	<0.01	NS
N	81	14	56	22			
Triglycerides (mmol/l)	0.88 ± 0.34	0.76 ± 0.22	0.92 ± 0.50	0.84 ± 0.35	NS	NS	NS
Total cholesterol (mmol/l)	4.46 ± 0.70	4.40 ± 0.63	5.01 ± 0.79	4.77 ± 0.82	<0.001	NS	NS
HDL-C (mmol/l)	1.57 ± 0.36	1.59 ± 0.34	1.77 ± 0.39	1.77 ± 0.35	<0.001	NS	NS
LDL-C (mmol/l)	2.49 ± 0.60	2.46 ± 0.68	2.82 ± 0.60	2.62 ± 0.77	<0.01	NS	NS
TC/HDL-C	2.96 ± 0.73[d]	2.87 ± 0.71	2.91 ± 0.69[e]	2.80 ± 0.69	NS	NS	NS
Fasting glucose (mmol/l)	4.78 ± 0.37	5.02 ± 0.34[**]	4.56 ± 0.41	4.63 ± 0.32	<0.001	<0.05	NS
Fasting insulin (µU/ml)	11.97 ± 5.52[d]	9.84 ± 2.31	11.19 ± 4.20[f]	10.20 ± 2.17[g]	NS	NS	NS
HOMA-IR	2.56 ± 1.30[h]	2.21 ± 0.57	2.35 ± 0.96[e]	2.13 ± 0.53[g]	NS	NS	NS

[**]P ≤ 0.01; [*]P ≤ 0.05. Values are mean ± standard deviation. N: number of subjects; HDL-C: high-density-lipoproteins cholesterol; HOMA-IR: homeostasis model assessment; LDL-C: low-density-lipoproteins cholesterol; TC: total cholesterol; VO_2 peak: peak oxygen uptake. Triglycerides values were log-converted for statistical analysis and reconverted for presentation in table format. [a]N = 81; [b]N = 59; [c]N = 20; [d]N = 80; [e]N = 52; [f]N = 57; [g]N = 21; [h]N = 79. Linear mixed model repeated measures: Independent effect of time (within subject factor); Independent effect of peak systolic blood pressure (between subject factor).

SBP (≥140 mmHg) 5 years later. However according to the binary logistic regression, exaggerated peak ESBP response was not a significant predictor of future resting hypertension (OR: 2.96, CI 95% [0.48 - 18.12; P = 0.24]) (**Table 3**).

4. Discussion

Hypertension is one of the most prevalent CVD and the least diagnosed in clinical setting because patients are asymptomatic most of the times [5]. Exaggerated peak ESBP and/or peak EDPB response have been previously suggested to be a predictor of a future resting HT as well as an early signs of future CVD in normotensive men and women [10] [22] [23]. In this study, as previously mentioned, none of the women presented an exaggerated peak EDBP. However, 15% of women at baseline and 26% at year 5 presented an exaggerated peak ESBP. Interestingly, those percentage are lower compared to the prevalence reported between 30% and 50%, in published

Table 2. Pearson correlations between baseline peak exercise blood pressure and anthropometric and anthropometric and cardiometabolic indices.

	Peak exercise systolic BP	Peak exercise diastolic BP
Weight	−0.02	0.03
Body mass index	0.05	0.17
% Body fat	−0.11	0.02
Fat mass	−0.09	0.02
Lean body mass	−0.09	0.02
Trunk fat mass	−0.08	0.06
Waist circumference	−0.04	0.13
Triglycerides	−0.14	0.06
Total cholesterol	−0.15	−0.12
HDL-C	−0.07	−0.03
LDL-C	−0.09	−0.13
TC/HDL-C	−0.03	−0.04
Fasting glucose	0.17	0.16
Fasting insulin	−0.09	−0.07
HOMA-IR	−0.06	−0.06
VO_2 peak	0.20	0.05
Heart rate max	−0.10	0.10
Resting blood pressure		
Systolic	0.44**	0.54**
Diastolic	0.27**	0.52**

**$P \leq 0.01$. BP: blood pressure; VO_2 peak: peak oxygen uptake ($mlO_2 \cdot kg^{-1} \cdot min^{-1}$); HDL-C: high-density-lipoproteins cholesterol; LDL-C: low-density-lipoproteins cholesterol; TC: total cholesterol; HOMA-IR: homeostasis model assessment.

Table 3. Odds ratio associations between peak exercise blood pressure (peak ESBP) response and hypertension at year 5 in women.

	Resting blood pressure		Odds ratio	95% confidence interval	P value
	Normotensive (<140 mmHg)	Hypertensive (≥140 mmHg)			
Peak ESBP response					
<190 mmHg	65	4			
≥190 mmHg	11	2	2.96	0.48 – 18.12	0.24

Dependent variable: presence of hypertension.

studies [6] [9]-[11] [13] [24]. Possible reason behind such difference in the prevalence of exaggerated peak ESBP is likely explained by study participants. More specifically these studies were cross-sectional; which included middle-aged (range: 30 - 66 years) men only [10] [11], or mostly of men [6] [9] [13] [25] with an average BMI ranging between 26 kg/m^2 and 33 kg/m^2. Only one study was done in premenopausal women [13], the others have no mention on the menopausal status of the women. Furthermore, not all studies used the same cri-

teria for exaggerated ESBP. One study used ≥220 mmHg [11], while the others have used ≥200 mmHg [6] [10] and ≥230 mmHg [26]. However, it should be noted that we observed a significantly higher resting systolic and diastolic BP in participants that presented an exaggerated peak ESBP response, which is consistent with our hypothesis and results reported in literature [6] [8] [10] [11]. Out of those that presented an exaggerated peak ESBP response at baseline, 2 participants (14%) presented resting HT (SBP ≥ 140 mmHg) 5 years later. Yet, baseline peak ESBP was not a significant predictor of future resting hypertension, nor was it a significant predictor of pre-hypertension [3] (data not shown). Previous studies have shown that within a 5-year follow-up at least 33% of patients with an exaggerated peak EBP response developed resting HT [10] [26]. However, the latter studies were performed mostly in men and using different cut-offs for exaggerated peak ESBP response, where one defined peak ESBP as ≥200 mmHg [10], and the other ≥230 mmHg [26]. Whereas, in our study the cut-off value for an exaggerated peak ESBP was ≥190 mmHg, has previously used in the Framingham study [7]-[9]. Furthermore, at baseline our sample was specifically composed of healthy and fit normotensive premenopausal women followed for 5 years.

Our results also revealed higher fasting plasma glucose levels in women displaying an exaggerated peak ESBP response. High plasma glucose was previously reported to be correlated with elevated BP [27], a relationship which might be mediated by hyperinsulinemia [28] and/or insulin resistance [13] [29]. The results of our study, up against literature data, showed that despite the fact that fasting glucose was significantly higher in participants with an exaggerated peak ESBP response, fasting insulin values as well as HOMA-IR index were not significantly different than those with a normal ESBP. Furthermore, BMI, waist circumference, body composition indices and trunk fat mass were not significantly higher among participants with exaggerated peak ESBP responses; which is the opposite of what was previously reported [9] [11]-[13] [16]. These observations can be partly explained by the normal values of fasting plasma glucose; which are in the normal glucose tolerance category. Moreover, our participants were leaner compared to previous studies [9] [11]-[13] [16], based on our cohort's BMI. Also the participants' baseline mean WC value is lower (78.0 ± 6.6 cm) than the reported thresholds of 88.0 cm; which has been associated with an increased risk of cardiometabolic disturbance in women [30].

Our study presents certain limitations. First the population consisted of healthy fit middle-aged women with a BMI < 30 kg/m^2. Therefore our findings cannot be generalized to the whole population. Second, only a small number of participants presented an exaggerated peak ESBP response, while none presented an exaggerated peak EDBP. Third, the small number of women who became hypertensive in follow-up was very low; which most likely decreased statistical power. Fourth, due to the duration of the study BP was not measured by the same person for all women at all time points. In fact, several studies, such as Pickering (2002), noted the importance of having a single person measuring the BP to reduce the inter-individual variation. However, BP was measured using standardized procedure [31] and by qualified and well trained research assistants. Finally, because we worked on a low risk group of women, the study duration might be insufficient to capture the magnitude of the risk. Despite these limitations, the well-characterized cohort of women followed for 5 years strengthens the present study. We used gold standard measures methods (DEXA) for the measurement of body composition and body fat distribution. Second, direct measurement of VO_2 peak is a valid and highly reproducible measure of cardiorespiratory fitness [32]. Finally, to the exception of age, our cohort displayed a broad range of values for the variables of interest.

5. Conclusion

Our results, despite being non-significant, are of great interest because in healthy and active premenopausal women, exaggerated peak ESBP is not predictive of future hypertension after 5-years follow-up throughout menopause transition. However, future studies are needed to validate our results.

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Conflict of Interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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