Original Article

Increased Rate Pressure Product is Linked to Sympathovagal Imbalance in Indian Obese Postmenopausal Women

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Abstract

Background and Aim: Postmenopausal women experience changes in cardiovascular (CV) system and autonomic functions. Increased body mass index (BMI) alters the autonomic discharge pattern. Rate pressure product (RPP) is linked to autonomic imbalance. However, the autonomic functions status and its link to RPP in Indian obese postmenopausal women are not yet known. The present study was designed to assess sympathovagal imbalance (SVI) and its link to RPP in Indian obese postmenopausal women. **Methods:** In 104 postmenopausal women of 40–55 years of age, anthropometric indices such as age, height, body weight, waist-hip ratio, waist-height ratio, and CV parameters such as heart rate, systolic, and diastolic blood pressure were recorded. BMI, mean arterial pressure and RPP were calculated. Resting heart rate variability was recorded for 5 min in the supine position. Data were compared between obese (BMI >25) and nonobese (BMI 18.5–24.99) women and the link of low frequency to high frequency (LF-HF) ratio with RPP was assessed by Pearson's correlation analysis. **Results:** RPP was increased, sympathetic drive (low-frequency component expressed as normalized unit) was increased, vagal drive (high-frequency component expressed as normalized unit) was decreased, and LF-HF ratio, the marker of SVI was found to be increased in high BMI postmenopausal women. In addition, LF-HF ratio was significantly associated with RPP. **Conclusion:** There was SVI with increased sympathetic and decreased vagal function in high BMI postmenopausal women. RPP, the marker of myocardial work stress was associated with SVI.

Keywords: Cardiovascular risk, obese postmenopausal women, rate-pressure product, sympathovagal imbalance

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Introduction

The world health organization defines menopause as the permanent cessation of menstruation that occurs due to a decreased level of female sex hormones mainly estrogen and progesterone in the blood, and this can be confirmed after 12 months of amenorrhea.[1] Menopause usually occurs at the age of fourth to fifth decade of life. The postmenopausal life describes years that follows the menopause. In India, the women on an average live for 65 years, whereas it is much more in case of women in developed countries, which is about 80 years. This shows the poor health status of women in India, emphasizing the need of special healthcare for women especially in their postmenopausal life.[2] The research data derived from epidemiological studies reveal that the incidence of cardiovascular disease (CVD) is very less in younger women that is in women who are <50 years of age. However, the incidence of CVD rises to a greater extent in women once menopause is attained.[3]

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Menopausal status is accompanied by unfavorable levels of cardiovascular (CV) risk factors, such as changes from gynecoid to android body pattern, dyslipidemia, insulin resistance, increased sympathetic tone, endothelial dysfunction, vascular inflammation, and increased blood pressure.[4] Following menopause, several hormonal as well as metabolic changes in the body occur over a period of many years. However, it is not clear whether all the postmenopausal women or only women with central adiposity have increased CVD risk.[5]

Anthropometric parameters such as body mass index (BMI), waist circumference (WC), waist-to-height ratio (WHtR), and

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waist-to-hip ratio (WHR) have a close relationship with CV risk.[6] Increase in BMI has been reported to be an important risk factor for adverse CV event.[7]

In normal individual, the sympathetic and parasympathetic functions remain in a balanced state, and the imbalance among them is known as sympathovagal imbalance (SVI).[8] Power spectral analysis of heart rate variability (HRV) is a noninvasive and useful tool to assess cardiac autonomic activity and sympathovagal balance.[9] Reduced HRV is observed to increase the CVD risk.[10] Subjects with High BMI tend to have increased sympathetic and decreased parasympathetic activity.[11] Autonomic imbalance was reported in postmenopausal women compared to premenopausal women.[12] Although both BMI and autonomic imbalance act as CV risk factors, there are very few reports available on resting autonomic function in postmenopausal women with high BMI. Moreover, the reports are conflicting on the activity of autonomic nervous system in postmenopausal obese women. While one study reported that autonomic function was not different in postmenopausal lean and obese women,[13] another study reported that autonomic functions differed significantly[14] in them. Therefore, we planned to compare the autonomic functions in normal and high BMI postmenopausal women. Rate pressure product, an indirect measure of myocardial workload, has been linked to SVI in obesity.[11] Therefore, we also studied the association of RPP to low frequency to high frequency (LF-HF) ratio, the marker of SVI in obese postmenopausal women.

Materials and Methods

The present study was conducted in the Department of Physiology, JIPMER, Puducherry, India. After obtaining approval of the project plan from the JIPMER Scientific Advisory Committee and the Institutional Ethics Committee for human studies, 104 apparently healthy postmenopausal women of 45–60 years were recruited from among the staff and their relatives residing in JIPMER campus and from the Obstetrics and Gynecology OPD of JIPMER. The subjects were divided into two groups. Group 1 having normal BMI (18.50–24.99) and Group 2 having high BMI >25.00 based on Asian's classification for BMI.[15] Individuals were evenly matched for age and menopausal duration.

Written informed consent was obtained from all postmenopausal women participating in this study before the initiation of any study procedure. Participants were asked not to participate in any strenuous exercises, drinking, smoking, drinking caffeinated beverages, at least 12 h before the recording. Participants were advised not to take sleeping pills or tranquilizers at least 48 h before the recordings. They were instructed to report to the AFT laboratory of Physiology Department at 8 am, about 2 h after a light breakfast.

Brief procedure

The physical and physiological parameters were recorded using weighting machine, height strands. Participants were assessed with minimal clothing and barefoot for their height in centimeters using a stadiometer (BHH6, Easy Care, Mumbai, India), weight in kilogram using a digital weighing machine (MS 4900, Charder Electronics Co. Ltd., Taichung, Taiwan) to its nearest value. In this machine, the minimum recordable reading was 0.1 kg. BMI was calculated using Quetlet index[16] as per the formula weight in kilogram/square of height in meter. Circumferences were measured using nonelastic steel tape (CESCORF, Brazil, South America). WC was measured between lower costal border and top of the iliac crest, and hip circumference was measured at the level of greatest posterior protuberance of the buttocks. The indices like WHR and WHtR were calculated.

Short-term HRV was measured in each participant, by connecting lead II ECG in BIOPAC MP 100 data acquisition system (BIOPAC Inc., USA). A 5 min of resting R-R intervals was recorded as per the standard procedures recommended by Task Force on HRV.[17] Using the R wave detector in the Acqknowledge software, the R-R tachogram was extracted from the edited 256 s ECG. HRV was analyzed using HRV analysis software (Version 2.0., Bio-signal analysis group, University of Kuopio, Finland). Various frequency domain indices such as total power (TP), low-frequency component expressed as normalized unit (LFnu), high-frequency component expressed as normalized unit (HFnu), and ratio of low-frequency to high-frequency power ratio were calculated. In addition, the time domain indices such as Mean RR, standard deviation of normal to normal R-R interval (SDNN), square root of the mean squared differences of successive normal to normal RR intervals (RMSSD), the number of interval differences of successive normal to normal RR (NN) intervals greater than 50 ms (NN50), and the proportion obtained by dividing NN50 by the total number of NN intervals (pNN50) were calculated.

Statistical analysis of data

SPSS version 19 (SPSS software Inc., Chicago, IL, USA) was used for statistical analysis. All the data were presented as mean ± standard deviation. Normality of the data was tested by Kolmogorov–Smirnov test. The level of significance between the groups was tested by Student's unpaired *t*-test for the normally distributed data. The association between LF-HF ratio and RPP was done by Pearson's correlation analysis.

Results

In high BMI postmenopausal women, body weight and BMI were significantly higher ($P < 0.001$); and all the anthropometric indices such as WC, hip circumference, WHR, waist height ratio were significantly high ($P < 0.05$) [Table 1]. The CV parameters, such as BHR ($P = 0.009$), SBP ($P = 0.002$), DBP ($P < 0.0001$), and RPP ($P < 0.0001$), were significantly high [Table 2] in high BMI postmenopausal women. In frequency domain HRV parameters, TP and HFnu were significantly less ($P < 0.0001$) and LFnu and LF-HF ratio were significantly high ($P < 0.0001$) [Table 3], whereas all

Table 1: Age and anthropometric indices in normal and high body mass index postmenopausal women

Variables	Normal BMI (n=50)	High BMI (n=54)	P
Age	51.68±4.96	50.46±5.05	0.219
Weight	52.44±7.29	67.17±8.46	<0.0001
Height	153.56±6.23	151.98±6.00	0.192
BMI	22.16±2.08	29.06±3.18	<0.000
Waist circumference	81.19±7.91	87.94±9.35	<0.000
Hip circumference	94.80±7.76	100.25±10.20	0.003
Waist: Hip ratio	0.85±0.41	0.87±0.04	0.037
Waist: Height ratio	0.52±0.57	0.57±0.06	<0.000

Variables are expressed as mean±SD; analysis is done by student unpaired t-test. P<0.05 was considered statistically significant. BMI: Body mass index, SD: Standard deviation

Table 2: Comparison of cardiovascular parameters between normal and high body mass index postmenopausal women

Parameters	Normal BMI (n=50)	High BMI (n=54)	P
BHR (per min)	75.72±10.13	79.85±4.84	0.009
SBP (mmHg)	116.37±7.18	121.41±9.07	<0.002
DBP (mmHg)	67.90±7.40	76.60±6.83	<0.0001
MAP	84.10±7.84	91.50±9.48	<0.000
RPP (mmHg/min)	88.11±14.02	96.94±12.31	<0.000

The values are expressed as Mean±SD; Statistical analysis was done by student unpaired t-test. The P<0.05 was considered statistically significant. BHR: Basal heart rate, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, RPP: Rate pressure product, BMI: Body mass index, SD: Standard deviation, MAP: Mean arterial pressure

the time domain indices of HRV such as RMSSD, SDNN, NN50, and pNN50 were significantly decreased (P < 0.0001) in high BMI postmenopausal women compared to normal BMI group [Table 3]. LF-HF ratio was significantly correlated with RPP (P = 0.003) [Table 4].

Discussion

In menopausal women, studies have concluded that the annual weight gain of about 0.5 kg/year is due to the age rather than the presence of menopause itself.[18,19] However, in the present study, there was no significant difference in age between the normal BMI and high BMI group. All the anthropometric parameters, such as BMI, WC, hip circumference, WHR, and WHtR, were significantly more in high-BMI postmenopausal women compared to normal BMI group. The parameters such as BMI, WC, WHR, and WHtR were observed to have a close association with CV morbidity and mortality.[6] Indicators of abdominal obesity such as WC and WHR were found to be better predictors of CV health risk compared to overall obesity.[20,21] In addition, WHtR has been noted as the effective prognosticator of CVD risk.[22] The possible pathophysiological mechanism contributing to CV risk could be due to deposition of fat in the central regions of the body associated with lack of estrogen.[4,5]

Table 3: Comparison of heart rate variability indices in normal and high body mass index postmenopausal women

Variables	Normal BMI (n=50)	High BMI (n=54)	P
TP (ms^2)	1585.28±739.28	871.93±422.54	<0.0001
LFnu	36.09±13.84	76.61±34.65	<0.000
HFnu	63.17±19.84	23.08±10.65	<0.000
LF: HF	0.57±0.28	3.31±1.50	<0.000
Mean RR	956.72±470.14	793.74±177.26	0.019
SDNN (m)	40.47±19.85	25.27±8.92	<0.000
RMSSD (m)	26.32±11.84	17.83±9.15	<0.000
NN50	24.22±11.17	18.14±7.24	<0.001
pNN50 (%)	6.66±2.78	2.04±0.99	<0.000

The values are expressed as Mean±SD; Statistical analysis was done by student unpaired t-test. The P<0.05 was considered statistically significant. TP: Total power, LFnu: Normalized low frequency component, HFnu: Normalized high frequency component, LF-HF ratio: Ratio of low-frequency to high-frequency power, SDNN: Standard deviation of normal to normal R-R interval, RMSSD: Square root of the mean squared differences of successive normal to normal RR intervals, NN50: The number of interval differences of successive normal to normal RR (NN) intervals>50 m, pNN50: the proportion obtained by dividing NN50 by the total number of NN intervals, SD: Standard deviation, BMI: Body mass index

Table 4: Correlation of low frequency to high-frequency ratio with rate pressure product in high body mass index postmenopausal women

Variable	r	P
RPP	0.362	0.003

P<0.05 was considered statistically significant. RPP: Rate pressure product

In the postmenopausal women, LF-HF ratio was increased in high-BMI group compared to normal BMI group [Table 1]. At supine rest, increased LF-HF ratio depicts elevated sympathetic and declined parasympathetic tone indicating a state of SVI. This autonomic dysfunction was further supported by the significant rise in LFnu and fall in HFnu values in the high-BMI postmenopausal women. Increased LFnu depicts increased sympathetic activity and decreased HFnu suggests reduced parasympathetic activity. In the high-BMI group, decrease in the activity of parasympathetic drive was further appreciated by a drop in the Mean RR, RMSSD, SDNN, NN50, and pNN50 of time domain indices HRV.[9,23] Moreover, the TP of HRV was significantly reduced in high-BMI postmenopausal women. Decreased TP suggests reduced parasympathetic activity and it is associated with cardiac mortality and morbidity.[24,25] This was further supported by the increased resting HR in high-BMI postmenopausal women indicating vagal withdrawal in these participants, as resting HR is the index of vagal tone.[26] Increased resting HR has been reported to be associated with increased CV morbidities.[27] In addition, SBP, DBP, and MAP were significantly more in high-BMI postmenopausal women highlighting increased sympathetic activity in these participants. Our reports are in agreement with other studies that narrated the autonomic dysfunctions in the obese women in the form of sympathetic overactivity and parasympathetic underactivity.[28] Our findings of increased sympathetic tone and reduced parasympathetic tone in postmenopausal obese women compared to postmenopausal nonobese women are similar with the report of Franz R,[14] but not in agreement with Monda *et al*.,[13] who reported no difference in autonomic function in lean and obese postmenopausal women. However, the sample size was less in the study by Monda *et al*. ($n = 10$ in each group), which could be the reason for lack of any difference between the two groups. Kimura *et al*.[29] found both the LF and HF powers were reduced in obese postmenopausal women. This could be due to the fact that he grouped the participants based on TP of HRV (<220 ms or >220 ms) and not based on BMI and low TP group had greater BMI, ($P < 0.05$). Thus, in his study, the difference in significance in BMI was less compared to ours ($P < 0.0001$), as the high TP group might be having participants with higher BMI. As both BMI and SVI are CV risk factors,[30] postmenopausal women having high BMI are more prone to CV risk. Our report of HRV in Indian obese and nonobese postmenopausal women is the first of its kind.

RPP is used to measure the workload or oxygen demand of the heart, and it depicts the hemodynamic stress. RPP is calculated using the formula: RPP = HR (in beats per minute) × SBP (in mm/Hg) × 10^{-2}. Increased RPP has been reported as an established risk of CVD.[31] It was found that women who have undergone a state of natural or surgical menopause aged 35–55 had 2 times greater coronary risk when compared to premenopausal women of the same age group.[32] In the present study, RPP was increased in high BMI postmenopausal women when compared to normal BMI group indicating that the workload by the heart was more in the high-BMI group. Moreover, RPP showed a significant correlation with LF-HF ratio in the high-BMI postmenopausal women. Hence, it is proposed that the SVI in high-BMI postmenopausal women is linked to the enhanced myocardial energy load and expenditure, which could be a potential CVD risk.[33,34]

Conclusion

This study demonstrates the presence of SVI in the form of enhanced sympathetic and reduced parasympathetic drive in obese postmenopausal women. Increased WC, WHR, WHtR, HR, BP, RPP and LF-HF ratio and decreased TP in these groups of women predisposes them to CVD risk. RPP showed positive correlation with SVI, indicating that the myocardial work load increases with increase in SVI.

Limitations of the study

The study has a modest sample size. In addition, the classical autonomic function tests and direct measurement of cardiac functions were not performed in postmenopausal women.

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Conflicts of interest

There are no conflicts of interest.

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