A Comparative Study of Heart Rate Variability between Young Premenopausal and Postmenopausal Female Medical Professionals at Rest Using Frequency Domain Spectral Components

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Abstract: ***Background**: Heart rate variability (HRV) is a non-invasive index of cardiac autonomic modulation. Menopause causes poor sympathovagal balance that shifts toward sympathetic hyperactivity. Present study compared HRV between young premenopausal and postmenopausal medical professional women at rest using frequency domain spectral components. **Materials and Methods**: It was a comparative, cross-sectional, observational study. After obtaining ethics committee approval, the study population divided into two groups as per inclusion and exclusion criteria. One group included 40 young premenopausal women aged 18-24 years and the other group included 40 postmenopausal women aged 45-55 years. The power spectrum density for the HRV was calculated in frequency domain by the traditional Fast Fourier transform (FFT) based method. **Results**: 'Total Power' was significantly lower (p-value< 0.001) in postmenopausal women (917.89+647.67 ms^2) as compared to young premenopausal women (4900.82+2876.29 ms^2). 'LF Power' was significantly higher in postmenopausal women (693.14+271.21 ms^2) as compared to young premenopausal women (141.60+107.49 ms^2). 'HF Power' was significantly higher in young premenopausal women (1186.65+783.73 ms^2) as compared to postmenopausal women (134.97+109.85 ms^2). 'LF/HF ratio' was significantly higher in postmenopausal women (8.95+2.47) as compared to young premenopausal women (0.22+0.14). Serum estradiol level was significantly lower in postmenopausal women while 'body fat percentage' was significantly higher in postmenopausal women. **Conclusion**: Postmenopausal women have overall reduced parasympathetic drive and poor sympathovagal balance. Further, decreased level of serum estradiol and increased body fat percentage indicates sympathetic predominance that may lead to higher risk of cardiovascular morbidity and mortality in postmenopausal women.***

Keywords: Heart rate variability, Sympathovagal balance, Total Power, LF/HF ratio

1. Introduction

Heart rate variability (HRV) is a non-invasive index of neuronal activity of heart[1]**.** It is defined as the cyclic fluctuations of heart periods (R-R intervals) over time at rest. HRV reflects spontaneous changes in autonomic activity as it is regulated by sympathetic as well as parasympathetic activity. HRV is a good predictor of cardiovascular morbidity and mortality as it measures the degree of autonomic modulation. HRV depends on the rate of discharge of SA node, which is mainly controlled by parasympathetic activity. During inspiration and expiration, variations in vagal tone occur, which may lead to respiratory sinus arrhythmia.

Heart rate variability estimates the 'sympathovagal balance'. There are two components of the power spectrum analysis of HRV. They are high frequency (HF) component and low frequency (LF) component. Parasympathetic activity is indicated by HF component, while sympathetic activity is expressed by LF component. LF/HF ratio reflects sympathovagal balance. 'Total Power' also reflects the parasympathetic activity. Increased HF, reduced LF, and reduced LF/HF ratio indicate parasympathetic predominance, whereas reduced HF, increased LF, and increased LF/HF ratio indicate sympathetic predominance. Predominant parasympathetic activity favours good cardiovascular health. Predominant sympathetic activity is an important cardiovascular risk factor.

Menstrual phase, luteal phase and follicular phase, are the three phases of the menstrual cycle in a young reproductive woman. Due to cessation of ovarian function, menstrual cycle ceases at an approximate age of 45 to 50 years which is commonly termed as menopause. The termination of menstruation continuously longer than 12 months is a postmenopausal state. Many physiological changes occur during the menstrual cycle and postmenopausal period in women. These changes affect the cardiac functioning of the heart[2]. The risk towards the cardiovascular diseases increases after menopause and extensive fluctuation in HRV, are seen during the menopause and even after the menopause. Postmenopausal women had lower total power, lower HF in absolute power, higher relative power of LF, and higher LF/HF ratio[3]. Menopause causes an imbalance of the autonomic nervous control of the cardiovascular system that shifts toward sympathetic hyperactivity[4].

Various previous epidemiological studies have indicated that postmenopausal women had alteration in their autonomic status with higher sympathetic and lower vagal tone compared to premenopausal women[5]. A significant hypoestrogenism state occurs during postmenopausal period which promotes modifications in the autonomic control of heart rate. These modifications induce changes in sympathetic activity and vagal regulation of cardiovascular system. Akiyoshi et al[6]observed that cardiac parasympathetic function is decreased in postmenopausal women, which is related associated to aging and hormone level. Schillaci G et al[7] evaluated that vasomotor symptoms are associated with sympathetic predominance during postmenopausal period. The menopaused women have an imbalance of autonomic control of cardiovascular system. Various techniques and maneuvers have been developed to detect the integrity of autonomic nervous system. Bannister R et al[8]studied that most of the techniques such as cold pressure test, Valsalva maneuver and tilting table test have focused on the evoked response of autonomic nervous system. After an extensive literature survey, it has been observed that there is no substantial work that delves down to the details of HRV analysis using frequency domain method of HRV, in young and postmenopausal female medical professionals at the resting supine posture. Besides being a non-invasive study procedure, an important advantage of frequency domain analysis of HRV is that it utilizes spontaneous fluctuations in the heart rate to estimate autonomic functions.

The present study was conducted to evaluate the difference in HRV between young premenopausal women and postmenopausal women from medical profession at rest using frequency domain method and to find out the possible role of confounding factors of HRV like serum estradiol level, serum triglycerides level and body fat percentage.

2. Materials and Methods

It was a comparative, cross-sectional, observational study. After obtaining approval from the institutional ethics committee, the present study was carried out at Index Medical College Hospital and Research Centre, Indore (Madhya Pradesh). All the young premenopausal and postmenopausal subjects were medical professionals working at the same medical institute. In this study total sample size was 80 having power of study 80% and significant p-value<0.05 as per online statistical software for sample size calculation. The study population was divided into two groups as per inclusion and exclusion criteria. One group included 40 young premenopausal women aged 18-24 years and the other group included 40 postmenopausal women aged 45-55 years who had attained menopause naturally at least 1 years ago. Data collection for proposed study was conducted within six months from January 2020 to July 2020. Any known case of acute or chronic illness, subjects taking any medicine that modulates autonomic nervous system; subjects taking any oral contraceptives pills or any hormonal replacement therapy were excluded from the study.

Patient preparation-Experimental protocol was maintained by explaining the study protocol in detail to the participants of the study and written informed consent was taken from the participants. A thorough history was taken and general physical examinations were done to screen out the subjects for exclusion. After explaining exact experimental procedure, the procedures were performed at resting supine posture in our physiology research laboratory, in the morning time (room temperature was maintained at 20-25°C) in the fasting state. In premenopausal group, it was carried out only in the follicular phase of menstrual cycle. Subjects were refrained from caffeinated beverages for at least 12 hours prior to the experiment. The height and weight of all subjects were screened. After 15 min of rest, basal heart rate, basal blood pressure, and ECG were recorded at supine posture. The basal recording of blood pressure was done using sphygmomanometer by standard Riva-Rocci method. ECG recording was performed at resting supine posture using BIOPAC® MP150 system at sampling frequency of 500Hz. Software Acknowledge 4.2 was used for acquisition of HRV signals of all subjects. All the subjects were instructed to breathe quietly during the entire recording period with closed eyes and to avoid talking, moving limbs and body, coughing, and sleeping.

All the subjects underwent the different tests in following order –

1. Serum Estradiol Level: 5 ml venous blood sample was withdrawn from antecubital vein and serum was separated. This sample was stored at 2-8^{0}C. Further analysis and serum estradiol assay was performed by chemiluminescence immunoassay (CLIA) method. In premenopausal group, it was carried out only in the follicular phase of menstrual cycle.

2. Body Fat percentage-Includes the measurement of skin fold thickness at triceps, sub scapular and supra-iliac sites by skin fold caliper. The sum of three skin folds was used in age and gender specific equation to obtain an estimate of body fat percentage (Edwards K. D. G. et al.1962).

Body fat percentage = 0.29 SF*+ 3.9 (Weight in Kg.)

(SF*: sum of Skin Fold thickness)

3. Heart Rate Variability (HRV)-HRV was recorded by medical analyzer module (based on principle of impedance plethysmography) of NIVOMON, L & T and analysis of signal was done in frequency domain measures. In the frequency domain analysis, traditional Fast Fourier transform (FFT) based method was used to calculate the power spectrum for the HRV. Data were edited manually for artefacts and ectopic beats. Frequency domain measurement including Total Power, HF Power (0.15-0.40 Hz), LF Power (0.04-0.15Hz) and LF/HF ratio was calculated to assess sympathetic/parasympathetic modulation. 'Total Power' and 'HF Power', HF_{nu} (normalised units) are measures of parasympathetic activity and 'LF Power', LF_{nu} and 'LF/HF ratio' are measures of the sympathetic activity.

Statistical analysis: The data was expressed as mean+SD. Analysis was conducted by using Microsoft excel software, Microsoft Corporation USA, 2003. To find the

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statistical difference between young premenopausal and postmenopausal groups, we used Student's unpaired t-test in this study. We considered our findings statistically significant, if p-value < 0.05.

3. Results

In the present study, we analysed various anthropometric data (age, height, and weight) and vitals (Systolic B. P., Diastolic B. P. and heart rate) of all the subjects in both the groups (Table 1).

The results of our study showed (Table 2; Fig.1) that the 'Total Power' was lower in postmenopausal women (917.89+647.67 ms^2) as compared to young premenopausal women (4900.82+2876.29 ms^2). This difference was statistically highly significant (p-value< 0.001) between the two groups.

In the present study, we observed (Table2; Fig.2) that the 'LF Power' was significantly higher in postmenopausal women (693.14+271.21 ms^2) as compared to young premenopausal women (141.60+107.49 ms^2). On the other hand, we found (Table 2; Fig.3) that the 'HF Power' was significantly lower in postmenopausal women (134.97+109.85 ms^2) as compared to young premenopausal women (1186.65+783.73 ms^2).

In this study (Table 2; Fig.4), 'LF/HF ratio' was higher in postmenopausal women (8.95+2.47) as compared to young premenopausal women (0.22+0.14). This difference was statistically highly significant (p-value< 0.001) between the two groups.

In the present study, we analysed various confounding factors which affect the heart rate variability (Table 3). Our study results showed that serum estradiol level was lower in postmenopausal women (19.04+7.87 Pg/ml) as compared to young premenopausal women (195.53+77.18 Pg/ml). This difference was statistically highly significant (p-value< 0.001) between the two groups. We observed that serum triglyceride level was significantly higher in postmenopausal women (127.10+12.61 mg/dl) as compared to young premenopausal women (98.84+7.57 mg/dl). Similarly, 'body fat percentage' was also significantly higher in postmenopausal women (18.55+2.13%) as compared to young premenopausal women (17.04+1.07 %) (Table 3).

Table 1: Shows the various anthropometric data, and general physical & vital findings

Parameters	Group (n=40)	
	Young Premenopausal (Mean+SD)	**Postmenopausal (Mean+SD)**
Age (Years)	20.70+2.69	50.67+3.42
Height (cm)	158.66+2.57	156.97+2.61
Weight (Kg)	56.42+3.84	62.34+6.27
Systolic B. P. (mm of Hg)	121.15+4.79	127.60+7.35
Diastolic B. P. (mm of Hg)	78.05+1.65	79.70+3.11
Heart Rate (per minute)	74.45+3.69	76.25+4.21

Data expressed as mean+SD.

Table 2: Shows the various frequency domain parameters of HRV between Young Premenopausal and Postmenopausal women group by Unpaired 't' Test

Parameters	Group (n=40)		p-value
	Young Premenopausal (Mean+SD)	**Postmenopausal (Mean+SD)**	
Total Power (ms^2)	4900.82+2876.29	917.89+647.67	<0.001**
LF Power (ms^2)	141.60+107.49	693.14+271.21	<0.001**
LF_{nu} (%)	21.24+10.21	71.76+14.57	<0.001**
HF Power (ms^2)	1186.65+783.73	134.97+109.85	<0.001**
HF_{nu} (%)	66.97+15.87	19.11+9.75	<0.001**
LF/HF ratio	0.22+0.14	8.95+2.47	<0.001**

Data expressed as mean+SD; *p<0.05 (Significant); **p<0.001 (Highly Significant); LF= Low Frequency, HF= High Frequency, and n. u. = normalized units.

Table 3: Shows various confounding factors of Heart Rate Variability

Parameters	Group (n=40)		p-value
	Young Premenopausal (Mean+SD)	**Postmenopausal (Mean+SD)**	
Serum Estradiol level (Pg/ml)	195.53+77.18	19.04+7.87	<0.001**
Serum Triglycerides level (mg/dl)	98.84+7.57	127.10+12.61	<0.001**
Body Fat Percentage (%)	17.04+1.07	18.55+2.13	<0.001**

Data expressed as mean+SD; *p<0.05 (Significant); **p<0.001 (Highly Significant).

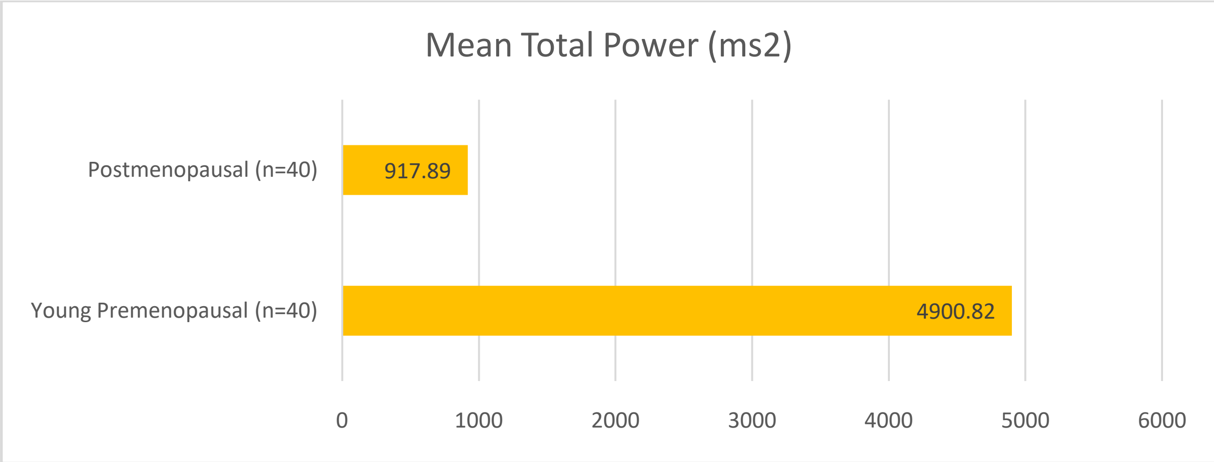

Figure 1: Shows Power Spectral Density in terms of 'Total Power' in Young Premenopausal and Postmenopausal women group

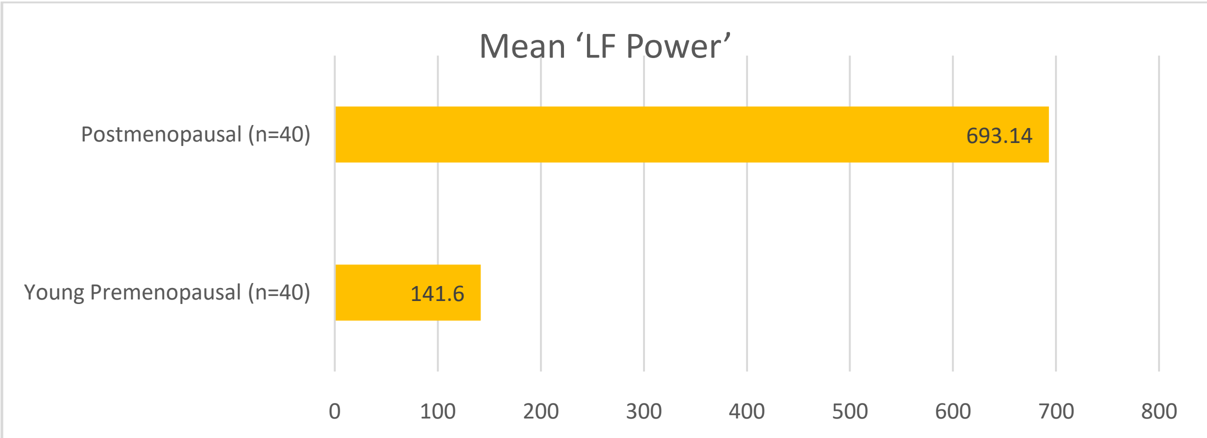

Figure 2: Shows Power Spectral Density in terms of 'LF Power' in Young Premenopausal and Postmenopausal women group

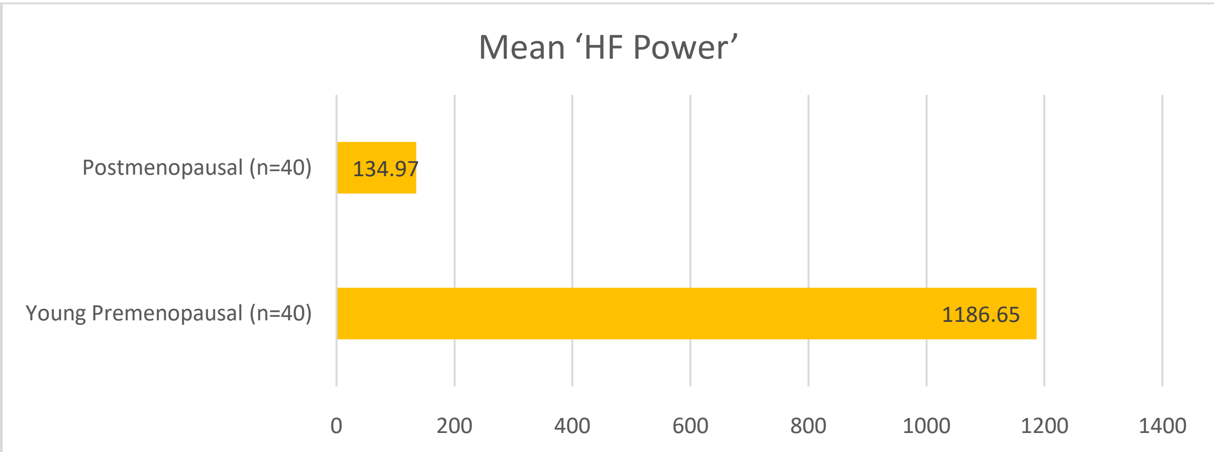

Figure 3: Shows Power Spectral Density in terms of 'HF Power' in Young Premenopausal and Postmenopausal women group

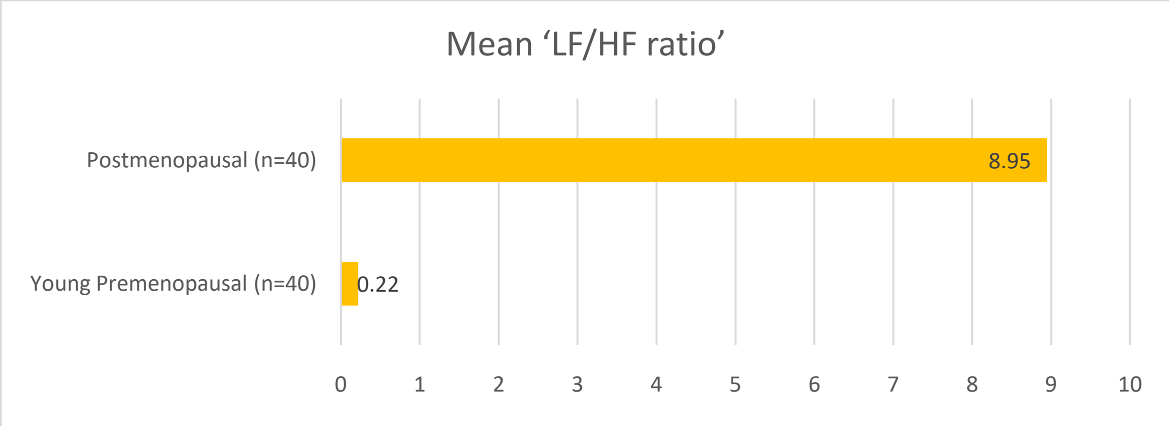

Figure 4: Showing Power Spectral Density (PSD) in terms of 'LF/HF ratio' in Young Premenopausal and Postmenopausal women group

4. Discussion

Due to loss of ovarian follicular activity, a phase develops at the end of reproductive life of each woman, in which there is permanent cessation of menstruation occurs. This phase is known as menopause. It's a gradual transition from reproductive to non-reproductive phase of life. Menopause is associated with decreased HRV, which is due to increased sympathetic or reduced parasympathetic out flow to the heart (Sherwood A et al[9]).

Daily physical activity level is considered one of the potential confounders in the measurement of autonomic activity. In the present study, we used spectral analysis of HRV using frequency domain parameters, while subjects were in relaxing and resting supine posture. All premenopausal subjects were studied only during their follicular phase of menstruation cycle to find out the contribution of estradiol for the difference in HRV between the study groups. Previous studies on comparison of HRV of premenopausal women using time domain indexes had not controlled for phases of menstrual cycle during subject recruitment, despite the possibility of ovarian hormonal influences on ANS function.

Hence, on the basis of results of our study, we evaluated that the higher LF Power, increased LF/HF ratio, and lower HF Power components of HRV in postmenopausal women suggest shifting of cardiac autonomic balance towards sympathetic hyperactivity in postmenopausal women even at resting supine posture. Such physiological changes may be confounded by age, declined serum estradiol level, increased serum triglycerides level, and increased body fat percentage as the status changes from premenopausal to postmenopausal. All these observations are well comparable with the study findings of Moodithaya S et al[3], Neves VF et al[4], and Davy KP et al[10].

5. Conclusion

On the basis of our present study findings, it can be concluded that HRV is a good tool to measure the degree of autonomic modulation. 'Total Power', and 'HF Power' is significantly lower, while 'LF Power' and 'LF/HF ratio' is significantly higher in postmenopausal women as compared to young premenopausal women, which suggests overall reduced parasympathetic drive and poor vasovagal balance in postmenopausal women. Further, decreased level of serum estradiol, increased serum triglycerides level and increased body fat percentage indicate sympathetic dominance in postmenopausal women that may lead to higher risk of cardiovascular morbidity and mortality. It is important to analyse and detect the variations in HRV between the young premenopausal and postmenopausal female, so that affected women can be instructed for proper precautions and timely interventions of many related diseases.

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Declarations:

Source (s) of funding: None

Conflict of interest: None.

Ethical approval: This study was approved by the institutional ethics committee.

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