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COMPARISON OF CARDIAC AUTONOMIC FUNCTIONS AMONG POSTMENOPAUSAL WOMEN WITH AND WITHOUT HORMONE REPLACEMENT THERAPY, AND PREMENOPAUSAL WOMEN

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Abstract : The aim of present study was comparison of cardiac autonomic status during different phases of reproductive life in women – in premenopausal women between proliferative and secretory phase, in postmenopausal women and in postmenopausal women receiving hormone replacement therapy (HRT). The study included 30 premenopausal women (Group 1) who were assessed in both proliferative (Group 1A) and secretory phase (Group 1B) of menstrual cycle, 30 postmenopausal women (Group 2) and 30 postmenopausal women on HRT (Group 3). Various autonomic function tests were done to assess parasympathetic and sympathetic functions. Results were obtained by ANOVA followed by Tukey test. The postmenopausal women (Group 2) showed increased sympathetic and decreased parasympathetic tone compared to premenopausal women (Groupl). The women on HRT (Group 3) showed parasympathetic dominance and decrease in sympathetic activity compared to postmenopausal women (Group 2). Across the menstrual cycle, increased parasympathetic activity was seen in secretory phase while no change was observed in the sympathetic activity in the two phases.

Key words : premenopausal women, postmenopausal women, hormone replacement therapy, autonomic function tests

INTRODUCTION

Changes in the neuroendocrine system due to the loss of ovarian function at menopause have an important bearing in the control of reproductive and nonreproductive functions, and cause changes in mood, memory, cognition, behaviour, immune function, locomotor system, and cardiovascular functions. The high incidence of ischemic heart disease after menopause suggests a close association between ovarian hormone levels and the cardiovascular system (1). In addition, there are several lines of evidence connecting symptoms and illnesses such as idiopathic orthostatic intolerance and

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syncope to the hormonal alterations along the menstrual cycle (2, 3, 4). Also, the presence of estrogen receptors in the heart, vascular smooth muscle, and autonomic brain stem centers (e.g. nucleus tractus solitarius, ventrolateral medulla) suggest a possible involvement in the regulation of the cardiovascular system (5).

Hormone replacement therapy (HRT) supplements exogenous ovarian hormones to the postmenopausal women where these hormones have decreased in amount. This therapy introduced decades ago for the treatment of postmenopausal symptoms still continues despite a lot of controversies. The purpose of this study was to evaluate the influence of ovarian hormone fluctuations in women as they pass through the various phases of reproductive life and following the use of HRT in postmenopausal women, on cardiac autonomic nervous system (ANS) reflected by parameters of heart rate variability (HRV), E: I ratio, 30:15 ratio and blood pressure (BP) tests. Heart rate variability, that is, the amount of heart rate fluctuations around the mean heart rate is a valuable tool to investigate the ANS. Reduced HRV has been reported to predict increased risk for subsequent mortality of all causes and sudden cardiac death (6). Lower HRV was also proven to be associated with a greater risk for developing hypertension among normotensive men; and hypertension is one of the major risk factors of congestive heart disease (7). Acute myocardial infractions are accompanied by a decreased HRV, which is due to reduced vagal or increased sympathetic outflow to the heart (8).

In this present study, non-invasive methods of ANS parameter measurements were practised. A combination of these was employed as some of these tests give information about the cardiac sympathetic functions (postural challenge test, sustained handgrip test) whereas others give information about the cardiac parasympathetic functions (basal heart rate variability, E:l ratio, 30:15 ratio) (9)

MATERIALS AND METHODS

The study was conducted in the Department of Physiology, University College of Medical Sciences and GTB Hospital, Delhi. The ethical committee of the institution cleared the project. The subjects were informed about the project both in written and in person and written consent was obtained from all subjects. The study included 90 adult female subjects. The postmenopausal subjects were recruited from the HRT clinic of Department of Obstetrics and Gynaecology, GTB hospital. All the postmenopausal women included had cessation of menstruation atleast one year before. The premenopausal women were recruited from the relatives of the postmenopausal women attending the HRT clinic. Subjects on oral contraceptive pills and drugs that alter the cardiovascular functions were also excluded from the study. All those women with history of diabetes mellitus, hypertension, heart disease, history of smoking and alcoholism were excluded. There were the following groups :

Group I (n=30) : Premenopausal women in the age group of 30 to 45 years having a regular menstrual cycle. The subjects in the Groupl were investigated twice :

Group 1A In proliferative phase of menstrual cycle

Group 1B In secretory phase of menstrual cycle

Group 2 (n=30) : Postmenopausal women in age group of 45 to 55 years who had not yet been put on HRT.

Group 3 (n=30) : Postmenopausal women in age group of 45 to 55 years on HRT who were on oral HRT for the last three months or more in the form of continuous combined regimen. (conjugated equine estrogen 0.625 mg and medroxyprogesterone acetate 2.5 mg daily).

Experimental protocol

All the subjects were tested under similar laboratory conditions. The tests were conducted according to the recommended protocol used in clinical studies (10, 11). The subjects abstained from coffee, tea or cola for 12 hours before the measurement. A light breakfast was allowed 2 hours before the study. All the measurements were performed between 10.30 am to 12.30 pm in an isolated examination room the temperature of which was maintained between 25°C and 27°C. They were allowed to get familiar with the experimental and environmental condition of the laboratory and procedures were explained to them. For time domain analysis of HRV, E:l ratio and 30:15 ratio lead-II EGG was recorded using the student physiograph machine (INCO), while Postural Challenge Test and Sustained Handgrip Test were performed using a mercury sphygmomanometer by the standard Riva-Roci method.

Statistical Analysis : All the results were obtained by SPSS-13 for windows using one-way ANOVA followed by Tukey test at 5% level of significance.

RESULTS

The age (in years) and BMI (in kg/m^2) in mean±SD of groups were: Group 1 (premenopausal women) age 33.83±2.44 and BMI 21.28±2.78, Group 2 (postmenopausal women) age 51.03±3.28 and BMI 24.73±3.12, Group 3 (postmenopausal women on HRT) age 52.53±2.87and BMI 24.33±2.31.

Table I shows the cardiac autonomic activity of Group 2 (postmenopausal women), Groupl A (premenopausal women in proliferative phase of menstrual cycle) and Group 1B (premenopausal women in secretory phase of menstrual cycle) and their intercomparison. BHRV, E:l ratio & 30:15 ratio was significantly lower in postmenopausal women (Group 2) as compared to premenopausal women both in the proliferative phase (Group 1A) and secretory phase (Group 1B). BHRV, E: I ratio and 30:15 ratio were significantly higher in secretory phase (Group 1B) compared to proliferative phase (Group 1A). The basal systolic and diastolic blood pressures were significantly higher in postmenopausal women (Group 2) compared to proliferative phase (Group 1A) & secretory phase (Group 1B). There were no significant difference in basal BP between Group 1A & 1B. The changes in systolic BP in postural challenge test and changes in diastolic BP in sustained handgrip test were insignificant.

Table II shows the comparison of cardiac autonomic activity of postmenopausal women

TABLE I: Showing cardiac autonomic activity of Group 1A (premenopausal women in proliferative phase), Group 1B (premenopausal women in secretory phase), & Group 2 (postmenopausal women).

Parameters	*Group 1A Mean±SD*	*Group 2 Mean±SD*	*Tukey test (group 1A & 2) P value*	*Group 1B Mean±SD*	*Tukey test (group 1B & 2) P value*	*Tukey test (group 1A & 1B) P value*
BHRV (beat/min)	16.57±5.52	11.13±3.50	<0.001	20.50±4.22	<0.001	0.009
E:l Ratio	1.34±0.14	1.18±0.07	<0.001	1.42±0.12	<0.001	0.047
30:15 Ratio	1.25±0.14	1.15±0.10	0.037	1.34±0.16	<0.001	0.046
SSBP (mm Hg)	111.2±6.27	124.2±6.88	<0.001	111.07±5.55	<0.001	1.00
SDBP (mm Hg)	73.13±4.51	83.33±5.93	<0.001	74.27±5.80	<0.001	0.833
CSBP (mm Hg)	4.33±4.36	4.27±5.08	1.000	3.67±4.20	0.954	0.938
CDBP (mm Hg)	27.00±4.66	23.47±4.33	0.110	25.60±8.01	0.519	0.804

SSBP – supine systolic BP, SDBP – supine diastolic BP, CSBP – change in systolic BP in postural challenge test, CDBP – change in diastolic BP in sustained handgrip test.

TABLE II: Showing cardiac autonomic activity of Group 2 (postmenopausal women) and Group 3 (postmenopausal women on HRT).

Parameters	*Group 2 Mean±SD*	*Group 3 Mean±SD*	*Tukey test (Group 2 & 3) P-value*
BHRV (beats/min)	11.13±3.50	17.43±5.39	<0.001
E:1 Ratio	1.18±0.07	1.26±0.10	0.018
30:15 Ratio	1.15±0.10	1.25±0.14	0.032
SSBP (mm Hg)	124.2±6.88	115.33±7.07	<0.001
SDBP (mm Hg)	83.33±5.93	76.4±4.34	<0.001
CSBP (mm Hg)	4.27±5.08	3.47±4.07	0.898
CDBP (mm Hg)	23.47±4.33	26.13±6.34	0.32

SSBP – supine systolic BP, SDBP – supine diastolic BP, CSBP – change in systolic BP in postural challenge test, CDBP – change in diastolic BP in sustained handgrip test.

(Group 2) & postmenopausal women on HRT (Group 3). BHRV, E:l ratio and 30:15 ratio were significantly higher in postmenopausal women on HRT compared to the other postmenopausal women. Values of supine systolic and diastolic BP were significantly higher in Group 2 compared to Group 3 while the changes in systolic BP in postural challenge test and changes in diastolic BP in sustained handgrip test were insignificant.

DISCUSSION

In this study the age of postmenopausal women was kept in the range of early menopausal years. The premenopausal women were kept in the age group of 30-45 years to make them more comparable to postmenopausal women. Still, the comparison of parameters between premenopausal and postmenopausal women reflects the affect of sex hormones as well as age. However, the

postmenopausal women on HRT are in the same age range as the postmenopausal women without HRT and thus the comparison between postmenopausal women with or without HRT reflects only the variation in the level of female gonadal hormones.

High frequency oscillations in HRV (HF, 0.15–0.40 Hz), which are related to respiration, provide a marker of vagal input to the heart. Low frequency oscillations (LF, 0.04–0.15 Hz) reflect the fluctuations in sympathetic tone and LF/HF ratio (0.01–0.40 Hz) is a marker of sympathovagal balance (12). In time domain, standard deviation of normal RR intervals (SDNN) and root mean square of differences of successive normal RR intervals (rMSSD) are believed to be expression of vagal tone (13). According to Conny, HRV can be assessed in two ways: by calculation of indices based on statistical operation on R-R intervals (time domain) or by spectral (frequency domain) analysis of an array of R-R intervals. These analysis can be performed on short ECG segments (lasting from 0.5 to 5 minutes) or on 24 hour ECG recordings (14).

BHRV, E:l ratio & 30: 15 ratio which reflect the parasympathetic tone found significantly lower values in postmenopausal women compared to premenopausal women. (Table I) This can be attributed to increased age and decreased sex hormones in postmenopausal women. We have not come across any study that has used 30:15 ratio and E: I ratio to compare the autonomic status of pre and postmenopausal women. In a previous study of HRV in pre and postmenopausal women it was found that total power, HF and LF of HRV were significantly lower in postmenopausal women suggesting decreased parasympathetic tone (15). In postural challenge test and sustained handgrip test, systolic and diastolic blood pressure of the postmenopausal women showed significantly higher absolute values of BP during baseline supine recording compared to premenopausal women (Table I). These findings suggest an elevated sympathetic tone in postmenopausal women. Similarly, Zanchetti et al found that systolic and diastolic BP is significantly higher in postmenopausal than in the premenopausal and perimenopausal women (16).

Across the menstrual cycle, significantly higher BHRV, E:l ratio & 30:15 ratio was found in secretory phase indicating parasympathetic dominance in secretory phase (Table I). In contrast, Yildirir et al who investigated the power spectral analysis of HRV during menstrual cycle found increased sympathetic activity in luteal phase (17). Mehta et al documented significantly higher systolic BP and increased sympathetic activity in the pre-menstrual phase compared to post- menstrual & menstrual phases; without significant difference in the parasympathetic activity (18). No significant changes were seen in postural challenge test and in sustained handgrip test across the menstrual cycle; indicating that sympathetic activity remains the same across the menstrual cycle (Table I). Similarly, Matsumoto et al who studied the activity of ANS during the menstrual cycle by means of power spectral analysis of HRV found no intramenstrual cycle differences (19). In contrast, Ettinger et al have suggested that during static handgrip exercise, muscle sympathetic nerve activity is increased more during the menstrual phase compared with

the follicular phase of the ovarian cycle (20).

The postmenopausal women on HRT had significantly higher BHRV, E:l & 30:15 ratio compared to postmenopausal women without HRT (Table II); this suggest that parasympathetic tone was higher in the postmenopausal women on HRT. E:l and 30:15 ratio have not been used by previous researchers in studying the effect of HRT. Previous research that compared the effect of HRT found LF/HF ratio and LF normalized unit significantly decreased after HRT with a significant increase in the HF component of HRV (21). However, some other researchers have documented lack of protective cardiovascular effect of HRT (22). The postmenopausal women on HRT had significantly lower values of systolic and diastolic BP compared to postmenopausal women not on HRT (Table II). This suggests that there was lower sympathetic activity in women on HRT. In normotensive populations, even small reductions in diastolic BP are postulated to prevent incident hypertension, coronary heart disease, and stroke and suggest decreased cardiac risk (23). An earlier study has also shown that elevation of low postmenopausal hormone levels to physiological premenopausal levels by HRT suppresses sympathetic activity (24).

In conclusion this study found that postmenopausal women had alteration in their autonomic status with higher sympathetic and lower vagal tone compared to premenopausal women. In women on HRT, the sympathovagal balance was shifted towards parasympathetic dominance. Across the menstrual cycle, higher parasympathetic activity was seen in the secretory phase while no change was observed in the sympathetic activity in the two phases.

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