ORIGINAL ARTICLE

Autonomic Functions in Postmenopausal Women

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Abstract

The study was undertaken on 24 human female postmenopausal subjects above the age of 50 years, to test the hypothesis that estrogen exerts regulatory influence on the autonomic nervous system in postmenopausal women. The parameters recorded and the test used were- pulse, blood pressure, orthostasis, cold pressor test, mental arithmetic and QTc interval for assessment of sympathetic activity and valsalva ratio, heart rate response, expiratory-inspiratory ratio (E.I. Ratio), standing-lying ratio (S.L. Ratio) and 30:15 ratio for assessment of parasympathetic activity. Our findings show that the changes in sex hormone levels, after menopause may affect the autonomic system response, with increase in reactivity of both sympathetic and parasympathetic systems.

Key Words

Autonomic nervous system, Parasympathetic reactivity, Sympathetic reactivity, Postmenopause

Introduction

Menopause, a normal aging phenomenon in women, consists of gradual transition from the reproductive to the non-reproductive phase of life. The median age of menopause is currently around 50 years. As a result of increasing life expectancy in the first and second worlds, many women will be post menopausal for over one third of their lives (1).

Menopause is a normal biological event marked for most women by the end of menstrual periods and it signifies the depletion of functional ovarian follicies that are responsible for estradiol production. Though technically it is the last menstrual period but clinically it is the months or years surrounding this marker event (2).

Much contemporary interest in menopause is actually directed at the postmenopause and the medical illness common to postmenopausal women that may be affected by endogenous/exogenous hormones eg. osteoporosis, coronary heart disease, endometrial cancer, Alzheimer's disease and mood symptoms. The changes in spontaneous ovarian function that precede the last menstrual period occur gradually, typically over a period of several years, referred to as menopause transition. Common clinical characteristics of the transition are a change in the women's usual menstrual periods and the beginning of the vasomotor symptoms like hot flushes and night sweats. These climacteric vasomotor symptoms suggest an alteration of either cardiovascular reflexes or the local control of blood flow to skin i.e. on alteration of autonomic haemodynamic control.

Thus, the present investigation has been done to evaluate and carry out a comprehensive study of autonomic functions in postmenopausal women to assess if there are any significant deviations from normal in sympathetic as well as parasympathetic reactivity.

Material and Methods

The study was conducted on 24 postmenopausal female subjects above the age of 50 years. Mean age+S.D= 55.5+7.39. Age of onset of menopause was between 45 to 50 years.

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Selection of the subjects was done on the basis of a detailed medical, menstrual history and general physical examination. Each subject was in good physical and mental state of well being. None reported hypertension, diabetes or cardiovascular, renal, hepatic or psychiatric disorders. No subject was using medications on a routine basis nor had used any hormonal preparations. Number of years a subject had experienced menopause varied from 2 years to 20 years. All tests were conducted at the same time in all subjects- between 10 a.m and 11 a.m. Pulse and B.P were recorded by palpatory method and auscultatory method, respectively. E.C.G was recorded by a simple compact electrocardiograph (BPL-Cardiart) unit. All the E.C.G recordings were carried out with lead II.

For assessing sympathetic system activity, the parameters recorded and tests used were:

1. Basal pulse rate - by palpatory method.
2. Blood Pressure - by auscultatory method.
3. Orthostasis - change in B.P being determined as the difference between the reading while supine and standing (3).
4. Cold-pressor test - the maximal B.P reading obtained with a hand in 4 degree C water being taken as the index of response. Blood pressure recorded at the end of 30 seconds of immersion and at the end of 60 seconds there-after in the opposite arm (4).
5. Mental arithmetic - with blood pressure being recorded after the subject is made to solve some mathematical problem (5).
6. Corrected QT interval - (QTc)-QT interval was measured from the ECG and then standardizedby converting it to QTc. For this Bazett's formula was used (6).

$$QTc = \frac{QT\ INTERVAL}{\sqrt{R - R\ INTERVAL}}$$

QT interval and R-R interval and QTc were expressed in seconds.

For assessing parasympathetic activity, parameters were used:

1. Pulse rate - it can be used for assessing both parasympathetic and sympathetic reactivity because of dual innervation of heart.
2. Valsalva ratio - calculated as ratio between maximal R-R interval after release of strain and maximal R-R interval during the strain (7).
3. Heart rate response- the response being taken as the difference in heart rate in supine and erect positions (8).
4. Expiratory-Inspiratory ratio - taken as the ratio of the longest R-R interval during expiration to shortest R-R interval during inspiration (9,10).
5. Heart rate variability - is the maximum and minimum heart rate during quiet breathing (10).
6. Standing-Lying ratio - being the ratio of longest R-R interval during 5 beats before lying down to shortest interval during 10 beats after lying down (11).
7. 30:15 ratio- being ratio of R-R interval at beat 30 to R-R interval at beat 15 after standing up from supine position.

Statistical analysis was carried out by "unpaired student 't' test", where the mean values of all parameters tested in postmenopausal subjects were compared with established normal values and $p<0.05$ was considered significant (10).

To substantiate findings of altered vasomotor functions in post menopausal women with diminished oestrogen levels - (to exclude the diminished arterial bororeflex sensitivity and vagal cardiac dys function per se due to aging), oestrogen levels were determined in all subjects - by the method of electro-chemiluminescence immunoassay-

E 2 levels were 34.8 + 2.2 (Mean + S.D)

Results

In our study, we observed that there were significant alterations in sympathetic as well as parasympathetic reactivity in postmenopausal period, when compared with normal established range of response to various tests of autonomic reactivity (10).

The parameters reflecting predominantly sympathetic activity show significant or highly significant variations when the data obtained in postmenopausal women is compared with normal established range of responses in case of recording of pulse, basal systolic B.P, orthostasis (systolic B.P as well as diastolic B.P), cold pressor test (diastolic B.P), mental arithmetic (systolic B.P and

diastolic B.P) and Q-Tc. Variations in basal diastolic B.P and systolic B.P response with cold-pressor test were insignificant (As depicted in Table 1).

Table 1. Parameters reflecting predominantly sympathetic activity

PARAMETER					
Pulse					

The parameters reflecting predominantly parasympathetic activity i.e. valvalva ratio, heart rate response, expiratory-inspiratory ratio, heart rate variability and 30:15 ratio also show significant variations when the results obtained in postmenopausal women were compared with normal established range of responses. But the variation in sitting lying ratio was insignificant as depicted in table 2.

Table 2. Parameters reflecting parasympathetic activity

PARAMETER				
VALSALVA				

Discussion

Estrogens are believed to be potent regulators of mind and body.

The generally accepted explanation for normally timed spontaneous menopause is that the ovaries begin with a finite number of follicles and these atrophy at a steady rate throughout the reproductive years. And at some point, there are two few functional follicles to produce meaningful amounts of estradiol.

The primary peripheral hormone change that occurs as a result of menopause is a marked reduction of estradiol, the principal product of the ovarian follicle, from the normal levels of between 70-100 pg/dl during reproductive years to a level below 20 pg/dl.

The endocrinologic changes underlying the menopausal transition have been discussed during the 10th World Congress on Menopause, 2002 where it was shown that FSH begins to rise during the early menopausal transition with steepest rise occurring about one year before last menopausal transition.

The rise in FSH seems to be driven by a fall in the level of inhibin B and to some extent estradiol with which FSH has an inverse correlation. FSH levels stabilize at an elevated level during the early postmenopause, while estradiol levels stabilize at low levels during the same phase.

It is also well known that total testosterone levels do not change with menopausal transition. However, the amount of bioavailable testosterone (free testosterone index) increase as a result of corresponding fall in sex hormone binding globulin (SHBG).

Dehydroepiandrosterone sulphate (DHEAS) is not affected by the menopausal transition but show a steady decline with age.

The use of estrogen/hormone replacement therapy in preventing disease in menopausal women has been well documented.

Less attention has been paid to the menopausal symptoms that can impair the quality of life of menopausal women- such as hot flushes, sleep disorders and alterations in mood. Also premenopausal women and postmenopausal differ in their cardiovascular and neuroendocrine responses to behavioural stress- which suggest that reproductive hormones influence stress responses. The mechanism of this influence may be linked to estrogens and their haemopdynamic effects.

Hormone/estrogen replacement therapy in postmenopausal subjects has a sympatho-inhibitory effect, which could be important for beneficial cardiovascular effects of estrogen replacement therapy in postmenopausal women.

The present study tested the hypothesis that estrogen exerts regulatory influence on autonomic nervous system in postmenopausal women.

Our results show an increased reactivity of both sympathetic and parasympathetic components of the autonomic nervous system in postmenopausal period.

Weitz et al (12) have shown that the activity of sympathetic nervous system shows gender specific differences with lower sympathoneural activity to the muscle vascular bed in women, as compared with men, with this difference vanishing after menopause. Our study also shows similar results.

Mercuro et al (13) show that surgical menopause (oophorectomy) induce a decline in cardiac vagal modulation with a shift towards sympathetic hyperactivity. But they recorded only a single parameter i.e. heart rate variability, whereas we have used multiple parameters to assess both sympathetic and parasympathetic activity and both show an increase in postmenopausal subjects.

Staessen et al (1) studied the epidemiology of association between hypertension and menopause and observed that estrogen deficiency in postmenopausal subjects may induce endothelial and vascular dysfunction and potentiate the age related increase in systolic pressure. This may be because of the sympatho-inhibitory effect of estrogen.

Du et al (14) have also shown that cardiovascular protection by estrogen is partly mediated through modulation of autonomic nervous system.

Ettinger et al (15) and Matsukawa et al (16) have studied sympathetic nerve activity in males and females - in relation to static exercise and in relation to age respectively and observed that sympathetic neural outflow is less in women as compared with men and that muscle sympathetic nerve activity increases with age in women and men that the activity is markedly lower in young women than in men, but is markedly accelerated with age. Our study also shows increased sympathetic activity in postmenopausal women.

Saab et al (17) have studied cardiovascular and neuroendocrine responses to behavioural stressors in premenopausal and postmenopausal women. Their results show exaggerated cardiovascular and neuroendocrine responses in postmenopausal women and they also link the mechanisms of these influences to estrogens and their haemodynamic effects.

Behavioural stress responses in premenopausal and postmenopausal women have also been studied by Lindheim et al (18) who demonstrated increased baseline blood pressure in pulse in postmenopausal women and also showed greater responses to psychologic stress tests- which could be modified by estrogen.

Sherwood (19) observed a blunting of nightime B.P dipping in postmenopausal women. Waking B.P did not differ by menopausal status. But nocturnal systolic and diastolic blood pressure were both higher during nightime sleep in postmenopausal women than in premenopausal women. This also reflects an increased sympathetic reactivity in postmenopausal women.

At variance with our results are two studies by Virtanen et al (20) and Saeki et al (21).

Virtanen et al performed autonomic nerves system tests in healthy postmenopausal women, who were both on and off estrogen replacement therapy. Their results showed autonomic nervous function normal for age. But in their work, the authors did observe a highly sensitive baroreflex and a strong 30 mm Hg blood pressure rise in the orthostatic test after administration of estrogen- which they attributed to the fact that, in general women with menopausal symptoms do not have impaired haemodynamic control.

Saeki et al studied the difference in autonomic regulation induced by posture change between postmenopausal and young women. Their results suggested that cardiac parasympathetic tone may be reduced in older persons in comparison with young women. This variance may be because they have carried out only a single test of recording heart rate variability to assess parasympathetic reactivity.

Conclusion

Hot flushes and sweating, both symptoms mediated by the autonomic nervous system, are believed to be a consequence of the decreased production of estrogen after menopause. Estrogen replacement therapy is widely used because estrogen changes extreme autonomic responses. And estrogen may play a role in cardiovascular protection in postmenopausal women by stabilising autonomic dysfunction (22).

Observations in animals suggests that the normalisation of cardiac autonomic control partly accounts for the cadio-protective effect of estrogen.

Therefore, we carried out autonomic nervous system tests in healthy postmenopausal women who were off estrogen replacement therapy and we observed an increase in both sympathetic and parasympathetic reactivity in our subjects. Further studies are warranted-especially in women with cardiovascular disease, diabetes or hypertension, who may benefit from treatment.

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ERRATUM

Kindly read N. Mittal as Vimla N. in the Case Report ''Hyper-reactio Luteinalis associated with Hypothyroidism'' published in Vol. 7 No. 2 (2005), Page No, 104-106. Printing error is highly regretted.