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RESEARCH ARTICLE

Influence of menopause on cardiovascular responses to behavioral stressors: A comparative study

Ashwini N Patil[1], Sunita M Handergulle[2]

[1]Department of Physiology, Dr. DY Patil Medical College, Hospital and Research Center, Pune, Maharashtra, India, [2]Department of Physiology, Swami Ramanand Teerth Rural Government Medical College, Ambajogai, Maharashtra, India

Correspondence to: Ashwini N Patil, E-mail: sony.patil.85@gmail.com

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ABSTRACT

Background: There is increased cardiovascular morbidity and mortality in post-menopausal women as compared to pre-menopausal women. There is an altered autonomic control with a shift toward sympathetic hyperactivity in menopause. Abnormal autonomic activity, behavioral stressors, and estrogen deficiency are related with increased cardiovascular risk. However, the underlying cardiovascular mechanisms in menopause still remain unclear. **Aims and Objectives:** The aim of this study is to determine and compare the following parameters indicating cardiovascular sympathetic function status in pre-menopausal and post-menopausal women subjected to three behavioral stress tests: (i) Blood pressure (BP) response to sustained isometric handgrip test, (ii) BP response to cold pressor test, and (iii) BP response to standing from supine position (orthostasis). **Materials and Methods:** This was a cross-sectional study for which 150 pre-menopausal and 150 post-menopausal women were selected. They underwent three behavioral stress tests of sustained isometric handgrip test, cold pressor test, and orthostatic test. The parameters indicating cardiovascular sympathetic function status were determined. Statistical analysis was performed using *Z*-test. **Results:** Diastolic BP (DBP) response to sustained isometric handgrip and systolic BP (SBP) and DBP response to the cold pressor test showed statistically highly significant ($P < 0.001$) greater rise in post-menopausal women as compared to pre-menopausal women. SBP response to standing from the supine position showed statistically insignificant ($P > 0.05$) greater fall in post-menopausal women. **Conclusion:** Sympathetic hyperactivity in response to behavioral stressors seen in post-menopausal women as compared to pre-menopausal women, suggests that the cardiovascular changes related to estrogen deficiency occurring in menopause may trigger adverse cardiovascular events.

KEY WORDS: Menopause; Behavioral Stress; Cardiovascular Response; Estrogen

INTRODUCTION

The menopause is that point in a woman's life when permanent cessation of menstruation occurs following the loss of ovarian activity.[1] By the year 2025, 23% of the population will be aged 60 or above.[2] Mean age at menopause ranges in Indian women from 40.32 to 48.84 years and in developed countries from 48 to 51 years.[3] Although the age of onset of menopause has remained constant, life expectancy in women has increased substantially. Currently, a woman can expect to live a third of her life after attaining menopause, in a state of estrogen deficiency.[4]

At menopause, changes in the neuroendocrine system due to the loss of ovarian function cause changes in mood, memory, cognition, behavior, immune function, locomotor system,

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and cardiovascular functions.[5] Pre-menopausal women have a lower incidence of cardiovascular diseases than age-matched men. However, after menopause, the incidence of cardiovascular diseases in women is similar to that in men.[6]

Much of the focus of investigation to explain the increased risk of cardiovascular disease in post-menopausal women has been on estrogen-induced effects producing a more beneficial lipid profile in the pre-menopausal women. However, beneficial changes in lipid profiles appear to account for only 25-50% of the cardiovascular benefit seen in pre-menopausal women, thereby raising the question of other estrogen-induced cardiovascular benefits that may be lost at menopause.[6]

Groups that differ in reproductive hormone status differ in the magnitude of their cardiovascular responses to psychosocial stress as well as their risk for atherosclerosis.[7] Post-menopausal women have elevated cardiovascular and neuroendocrine responses to stress relative to pre-menopausal women.[8] Women who undergo bilateral oophorectomy are at elevated risk for coronary heart disease or extensive atherosclerosis.[9] Women who undergo bilateral salpingo-oophorectomy tend to show larger increases in blood pressure (BP) responses to stress after surgery relative to those exhibited by women who underwent hysterectomy with ovarian conservation.[10] The activity of the sympathetic nervous system shows gender-specific differences with lower sympathoneural activity to the muscle vascular bed in women compared with men, with this difference vanishing after menopause.[11]

In menopause, there is an altered control of the cardiovascular system with a shift toward increased sympathetic activity.[12] Estrogen is cardio protective for women. Furthermore, cardiovascular mortality rate of post-menopausal women receiving hormone replacement therapy is decreased by approximately one-half.[13] Abnormal autonomic activity[14] and behavioral stressors[4] are related with increased cardiovascular risk.

Hence, the present research was conducted to study the underlying physiology governing the cardiovascular responses to behavioral stressors in healthy Indian pre-menopausal and post-menopausal women. This might help the physicians to take early appropriate measures to prevent complications in post-menopausal women, thus giving them both good quality and quantity of life.

The aims and objectives of our study were to determine and compare the following parameters indicating cardiovascular sympathetic function status in pre-menopausal and post-menopausal women subjected to three behavioral stress tests: (i) BP response to sustained isometric handgrip test, (ii) BP response to cold pressor test, and (iii) BP response to standing from supine position (orthostasis).

MATERIALS AND METHODS

This cross-sectional study was carried out in 150 pre-menopausal and 150 post-menopausal women selected from the general population of town area. They all belonged to middle socioeconomic class. The approval from the Institutional Ethics Committee was obtained.

Selection Criteria

Inclusion criteria

A. Pre-menopausal women:
   1. Age group: 25-35 years
   2. They had regular menstrual cycles with an average length of 28 days
   3. They were in the follicular phase of their menstrual cycle.
B. Post-menopausal women:
   1. Age group: 45-55 years
   2. They had completed a period of atleast 12 months since their last menstrual period.

Exclusion criteria

The following women were excluded from this study:
1. Those on oral contraceptive pills or hormonal therapy in any form
2. Those consuming drugs that alter the cardiovascular functions
3. Those having any history of diabetes, cardiovascular disease, surgical menopause, or history of addiction to tobacco, alcohol, and smoking
4. Those suffering from any other disease or complication.

All the participants were explained the procedure to alleviate any fear or apprehension. Before starting the procedure, physical examination of all the participants was done with the help of a predesigned pro forma and a written informed consent form was signed by all of them. The participants were asked to abstain from tea or coffee for 12 h before the procedure. All observations were made between 8.30 am and 9.30 am.

Procedure

The apparatus used was mercury sphygmomanometer, isometric handgrip dynamometer, stethoscope, and stopwatch. The participants were asked to perform three behavioral stress tests:[4,8,15]
1. Sustained isometric handgrip test,
2. Cold pressor test, and
3. Orthostatic test.

The following parameters indicating cardiovascular sympathetic function status were recorded in all the participants:

1. BP response to sustained isometric handgrip test
2. BP response to cold pressor test
3. BP response to standing from supine position (orthostasis).

BP response to sustained isometric handgrip test[16]

The participant was asked to sit comfortably in a chair. The baseline BP was measured from the left arm with the help of sphygmomanometer by the standard Riva-Rocci method. Three such readings were taken. Then, the cuff was deflated completely. The participant was then asked to hold the dynamometer in the right hand and compress it with maximum effort, to determine the maximum voluntary contraction. Handgrip is then maintained at 30% of that maximum for as long as possible up to 5 min. BP is measured from the left arm at 1 min intervals during handgrip. The result is expressed as the difference between the highest diastolic BP (DBP) during handgrip exercise and the mean of the three DBP readings before handgrip began. The value of more than 15 mmHg rise in DBP is taken as normal response; 11-15 mmHg as borderline; and 10 mmHg or less is abnormal, as an indicator of sympathetic insufficiency.

BP response to cold pressor test[17]

The participant was asked to sit comfortably in a chair for 5 min. The baseline BP was measured from the left arm with the help of sphygmomanometer by the standard Riva-Rocci method. BP was taken two to three times to determine normal levels. The deflated cuff was left on the arm. Then, the participant was asked to immerse her right hand in cold water maintained at 4-6°C for 1 min. The BP was determined every 30 s for 1 min. She was asked to remove her hand from the water at the end of 1 min. Immediately, the BPs were recorded at 30 s intervals until the BP returned to normal. The average baseline systolic BP (SBP) and DBP were calculated from the data obtained before immersion. These average pre-immersion pressures were subtracted from the highest readings obtained during or after immersion. Participants whose SBP increases by 25 or more mmHg or whose DBP increases by 20 or more mmHg are considered to be hyperreactive.

BP response to standing from supine position (orthostasis)[16]

The participant was asked to lie supine on the examination table for 5 min. The baseline BP was recorded from the left arm with the help of sphygmomanometer by the standard Riva-Rocci method. Then, the cuff was deflated completely and the participant was asked to stand up and lean against the wall for support. Immediately after the participant stood up, the BP was recorded again from the same arm. The difference between the baseline SBP and the SBP after standing was noted. The value of <10 mmHg fall in SBP is taken as normal response; 11-29 mmHg as borderline; and 30 mmHg or more is abnormal, as an indicator of sympathetic insufficiency. A rest period of 15 min was given to the participant in between each test.

Statistical Analysis

Z-test for testing difference between two sample means was applied to compare the different parameters between the two groups and the software used was http://in-silico.net/tools/statistics/ztest.

RESULTS

The DBP response to sustained isometric handgrip test shows higher rise in post-menopausal women as compared to pre-menopausal women, which is statistically highly significant ($Z = -11.90$, $P < 0.001$) (Table 1). The SBP response to the cold pressor test shows higher rise in post-menopausal women as compared to pre-menopausal women, which is statistically highly significant ($Z = -9.15$, $P < 0.001$) (Table 2). The DBP response to the cold pressor test shows higher rise in post-menopausal women as compared to pre-menopausal women, which is statistically highly significant ($Z= -6.79$, $P < 0.001$) (Table 3). The SBP response to standing from the supine position shows higher fall in post-menopausal women as compared to pre-menopausal women, which is statistically insignificant ($Z = -0.52$, $P > 0.05$) (Table 4).

DISCUSSION

The mean age of pre-menopausal women was 29.04 ± 2.7 years and that of post-menopausal women was 47.45 ± 2.42 years. The mean body mass index of pre-menopausal women was 24.77 ± 3.93 kg/m^2 and that of post-menopausal women was 24.82 ± 3.24 kg/m^2 and the difference between these values was statistically insignificant. Almost all the studies have attributed the effects seen on the autonomic system in the post-menopausal phase to estrogen deficiency.[11,12,14]

Comparison of BP Response to Sustained Isometric Handgrip

In the present study, the DBP response to sustained handgrip test showed greater rise in post-menopausal women as compared to pre-menopausal women, which was statistically highly significant (Table 1). During sustained isometric muscular exercise, for example, during sustained handgrip, there is normally a heart rate-dependent increase in cardiac output with no change in peripheral vascular resistance and a consequent increase in systemic BP. The initial heart rate rise is due to vagal withdrawal, but if this is inoperative, increased cardiac sympathetic stimulation may occur to cause tachycardia, and the BP can also be increased by peripheral vasoconstriction.[18] During exercise, the skeletal muscle afferents are stimulated evoking sympathoexcitation. This has been termed as the exercise pressor reflex and explained

Table 1: Comparison of diastolic blood pressure rise in response to sustained isometric handgrip test

Group	Mean±SD			Z value	*P* value	95% CI
	Sitting DBP‡ (mmHg)	DBP after 1 min of sustained handgrip (mmHg)	Change in DBP (mmHg)			
Pre-menopausal women (*n*=150)	76.83±6.19	92.41±7.15	15.59±3.73	−11.90	<0.001*	−5.40 to−3.87
Post-menopausal women (*n*=150)	80.29±5.30	100.5±6.06	20.23±2.98			

*Significant at *P*<0.001. DBP: Diastolic blood pressure; SD: Standard deviation, CI: Confidence interval

Table 2: Comparison of systolic blood pressure rise in cold pressor test

Group	Mean±SD			Z value	*P* value	95%CI
	Sitting SBP (mmHg)	SBP after 1 min of cold immersion (mmHg)	Change in SBP (mmHg)			
Pre-menopausal women (*n*=150)	116±9.21	133.3±9.56	17.21±2.82	−9.15	<0.001*	−3.71 to−2.40
Post-menopausal women (*n*=150)	120.1±9.24	140.4±9.06	20.27±2.97			

*Significant at *P*<0.001. SBP: Systolic blood pressure; SD: Standard deviation, CI: Confidence interval

Table 3: Comparison of diastolic blood pressure rise in cold pressor test

Group	Mean±SD			Z value	*P* value	95% CI
	Sitting DBP (mmHg)	DBP after 1 min of cold immersion (mmHg)	Change in DBP (mmHg)			
Pre-menopausal women (*n*=150)	76.83±6.19	86.41±7.18	9.58±3.73	−6.79	<0.001*	−3.41 to−1.88
Post-menopausal women (*n*=150)	80.29±5.30	92.52±6.06	12.23±2.98			

*Significant at *P*<0.001. DBP: Diastolic blood pressure, SD: Standard deviation, CI: Confidence interval

Table 4: Comparison of SBP fall in orthostatic test

Group	Mean±SD			Z value	*P* value	95%CI
	Supine SBP (mmHg)	SBP immediately after standing (mmHg)	Change in SBP (mmHg)			
Pre-menopausal women (*n*=150)	116.9±9.27	108.7±9.50	8.22±2.98	−0.52	0.59 NS*	−0.84 to 0.48
Post-menopausal women (*n*=150)	121.1±9.28	112.6±10.4	8.4±2.93			

*Non-significant at *P*>0.05. SBP: Systolic blood pressure, SD: Standard deviation, CI: Confidence interval

as follows: [19] Two types of stimuli, mechanical and chemical, are thought to activate these muscle nerve fiber endings and trigger this reflex.[19] Chemical stimulation of both finely myelinated and unmyelinated fibers (i.e. metaboreceptors) is likely to play a crucial role in evoking this reflex in humans.[19] Lactic acid is one of the chemical substances released by muscle cells during contraction and thought to play an important role in stimulating these metabolite-sensitive afferents.[19] Lactic acid is produced by the breakdown of glucose. In response, the body mobilizes free fatty acids as an additional source of energy. An increase of free fatty acids suppresses the oxidation of glucose. (This is called the Randle effect, glucose-fatty acid cycle, substrate-competition cycle, etc.). Women, with higher estrogen, usually have more free fatty acids than men, and during exercise, oxidize a higher proportion of fatty acids than men do.[20] In animal models, estrogen promotes lipolysis and increases fatty acid availability while decreasing the rate of gluconeogenesis and sparing muscle and liver glycogen use. Estrogen upregulates mitochondrial enzymes favoring fat oxidation.[21] Hence, estrogen might decrease the levels of lactic acid produced during exercise. All this could lead to less metaboreceptor activation in pre-menopausal women who have higher estrogen levels, hence causing less sympathetic neural outflow, which in turn causes a decreased BP rise in response to the handgrip test. Since there are reduced estrogen levels in post-menopausal women, this may lead to an increased metaboreflex causing increased sympathetic neural outflow, which in turn causes greater BP rises in response to the handgrip test. Estrogen may decrease the number of alpha-1 adrenergic receptors.[22] Estrogen lowers vascular resistance. Thus, with lower estrogen levels in post-menopausal women, BP responses during stress may increase.[8] Thus, in our study, the DBP rise in response to sustained handgrip was greater in post-menopausal women as compared to pre-menopausal women.

Comparison of BP Response to Cold Pressor Test

In our study, post-menopausal women showed statistically highly significant greater SBP and DBP rise in response to cold pressor test as compared to pre-menopausal women (Tables 2 and 3). The observed greater SBP and DBP responses to cold immersion in post-menopausal women as compared to pre-menopausal women are explained as follows: A number of studies have been performed to identify the mechanisms leading to elevations in BP during the cold pressor test. For example, the cold pressor test increases plasma norepinephrine and muscle sympathetic nerve activity.[23] The activation of sympathetic vasoconstrictor outflow to skeletal muscle is an important component of the pressor response to the cold pressor test[24] and it is an alpha-adrenoceptor-mediated vasoconstriction.[25] The role of muscle sympathetic nerve activity and alpha-adrenoceptor-mediated vasoconstriction is the same here also as explained for the handgrip test. Estrogen may reduce the circulating norepinephrine levels by the following mechanisms: (i) Estrogen may have a direct effect on the adrenal gland and at the central or peripheral nervous system;[26] (ii) estrogen may inhibit adrenomedullary secretion and probably blunt chromaffin cells reactivity;[26] (iii) estrogen may influence catecholamine synthesis, catecholamine metabolism, and affect beta-2 adrenergic receptor number;[26] (iv) estrogen may influence cell membrane reactivity by acting through the calcium channel;[26] (v) alpha-2 adrenergic receptors located presynaptically are inhibitory to neurotransmitter release.[27] Estrogen increases the density and enhances the function of pre-synaptic alpha-2 adrenoceptors, resulting in a significant decrease of norepinephrine-induced responses;[28] and (vi) there may also be a role for nitric oxide (NO) which is produced in response to estrogen and is known to inhibit norepinephrine release presynaptically.[27] Estrogen increases low-density lipoprotein (LDL) receptors in the liver. Hence, deficiency of estrogen in post-menopausal women may cause atherosclerosis due to increased LDL cholesterol in the circulation.[29] The process of atherosclerosis may decrease the production of endothelial-derived releasing factors, that is, NO[30] and vessels are likely to exhibit greater constrictor response.

Comparison of BP Response to Standing from the Supine Position (Orthostasis)

In our study, the SBP response to standing from the supine position showed greater fall in post-menopausal women as compared to pre-menopausal women, which was statistically insignificant (Table 4). In our study, although the SBP response to standing from the supine position showed insignificantly greater fall in post-menopausal women, the DBP response to sustained handgrip and SBP and DBP response to the cold pressor test showed significantly greater rise in post-menopausal women as compared to pre-menopausal women.

Implications

This study indicates that further research is needed to find out if clinical use of hormone replacement therapy in post-menopausal women can help to decrease the incidence of cardiovascular diseases in them, thus improving their quality and quantity of life.

Limitations

Although the large sample size is very supportive to the study, additional testing of hormonal assays in the women and their correlation with the behavioral stress tests can provide confirmatory evidence to the role of reproductive hormones.

CONCLUSION

There is sympathetic hyperactivity in response to behavioral stressors seen in post-menopausal women as compared to pre-menopausal women. This suggests that the cardiovascular changes related to estrogen deficiency occurring in healthy women after menopause may be involved in triggering adverse cardiovascular events.

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