

Comparative Analysis of Autonomic Function Tests in Normotensive Premenopausal and Postmenopausal Women

Uppalapadu Sudarsana^{1*}, Shailaza Shrestha², Praveen Kumar³

^{1*}Tutor, Department of Physiology, FH Medical College, Tundla, Uttar Pradesh, India.

²Tutor, Department of Biochemistry, Heritage Institute of Medical Sciences, Varanasi Uttar Pradesh, India. ³Assistant Professor, Department of Anatomy, Fathima Medical College, Kadapa, Andhra Pradesh, India.

ABSTRACT

Aims: The aim of this study was to assess the physiological changes in the autonomic function tests in post-menopausal women.

Materials & Methods: 70 normal females (30 premenopausal and 40 post-menopausal) were included in the study. The parasympathetic function tests included pulse rate, heart rate response, heart rate variability, E:I ratio, 30:15 ratio and the valsalva ratio whereas the sympathetic function tests included systolic and diastolic blood pressure, orthostatic tolerance test, isometric handgrip (IHG) test and cold pressor test.

Results: HRV, EI ratio, IHG, cold pressor SBP and cold pressor DBP were significantly lower whereas HRR, VR, SBP, DBP, OTT significantly higher in postmenopausal women (p<0.05). When the autonomic function parameters were compared among non-obese and obese post-menopausal women, we found that functions like HRV, VR, EI ratio, IHG, cold pressor SBP were significantly lower whereas functions like HRR, DBP, OTT were significantly higher in the obese post-menopausal women in comparison to non-obese postmenopausal females (p<0.05). BMI was correlated positively with PR, HRR, SBP, DBP, OTT, cold pressor SBP and cold pressor DBP and negatively with HRV, VR, EI, 30:15 and IHG, all of which were statistically significant (p < 0.05). In case of WHR (Waist Hip Ratio), we found significant correlation with HRR, DBP and OTT (p<0.05) and significant negative correlation with HRV, VR, EI, 30:15, and IHG (p<0.05).

Conclusion: Obesity, physical inactivity, and altered estrogen metabolism contribute to the risk of diseases in the postmenopausal women. Early and regular screening of obese individuals is necessary to prevent any future complications.

Key words: Post-menopausal, Obesity, Sympathetic, Parasympathetic.

*Correspondence to:

Uppalapadu Sudarsana, Tutor, Department of Physiology, FH Medical College, Tundla, UP, India.

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INTRODUCTION

Menopause, a normal aging phenomenon, involves gradual transition of women from reproductive to non-reproductive phase of life. The marked feature of this transition include stoppage of menstrual cycle that signifies the loss of functional ovarian follicles for estradiol production.¹ The median age of menopause is about 50 years.² Perimenopause is another transitional stage prior to menopause and is characterized by irregular menstrual cycle, reduction in estrogen and progesterone level and inconsistent ovulation.³

Menopause transition is characterized by various changes in ovarian functions that occur for several years. The common clinical features presented by women during this phase besides the changes in normal menstrual cycle involve vasomotor symptoms like sweat and hot flushes¹ also regarded as climacteric depression,⁴ suggesting an alteration in cardiovascular reflexes or the local control of blood flow in skin.¹

The autonomic nervous system via sympathetic and the parasympathetic nerve fibers controls most of the visceral functions of the body including that of the uterus which depends on the oestrogen and progesterone levels.³

Aging causes alterations in autonomic functions due to decline in hormonal and physical functions.² Such alterations affect vagal control of cardiac functions causing sympathetic hyperactivity⁵, resulting in both structural as well as functional changes in the cardiac muscles and large arteries leading to hypertension.⁶ This can also cause cardiac arrhythmias that cause left ventricular hypertrophy thereby reducing the compliance of the large arteries.⁷ Sympathetic hyperactivity can also cause sudden death

of cardiac tissues which is suggestive of menopausal women being hypertensive (with increased heart rate) as result of autonomic dysfunction.⁵

Menopause is also accompanied with the decline in physical activity, energy expenditure and altered adipose tissue and fat metabolism causing increased total adiposity and visceral obesity in postmenopausal women. Complications of obesity such as hypertension, insulin resistance, diabetes, hyperandrogenism and hyperlipidemia are common. Increase in body fat can cause marked sympathetic activation or vagal inhibition thus leading to autonomic dysfunction.⁸

Recent attention on postmenopausal health has led us to study autonomic nerve function status in pre and postmenopausal women.⁹ We conducted this study to compare the physiological changes in the autonomic function in both pre and postmenopausal women and assess the effect of obesity on autonomic functions in post-menopausal. Early detection of subclinical autonomic dysfunction can improve the quality of life by proper medication and lifestyle modification.

MATERIALS AND METHODS

This study was conducted in the Department of Physiology, FH Medical College, Tundla UP. 70 normal women volunteers were included in this study. Selection of the subjects was done on the basis of a detailed medical, menstrual history and general physical examination.

Inclusion criteria

Those females who were normotensive, without any gross systemic disease non-smoker and non-alcoholic were included.

Exclusion criteria

Females with diabetes, hypertension and other cardiac problems, renal, hepatic or psychiatric disorders, hysterectomy, using medications on a routine basis were excluded.

The study subjects were divided into two groups. Group I consisted of 30 premenopausal women who had normal menstrual cycles. Group II consisted of 40 menopausal women who had complete cessation of menstruation for a period of one year and more.

Menopausal females were categorized as obese and non-obese based on BMI (Body Mass Index). Out of which 40, 18 females were obese.

Following Autonomic function tests were conducted in the study groups

Tests for parasympathetic functions

- 1. Pulse rate (per minute) by palpatory method.
- 2. Heart rate response in supine and erect positions (HRR)
- 3. Heart rate variability during deep breathing (HRV)
- 4. Valsalva maneuver (VR)
- 5. Heart rate response to postural change (30:15 ratio)
- 6. Expiratory: Inspiratory ratio: (E: I ratio)

Tests for sympathetic functions

- 1. Pulse rate (per minute) by palpatory method.
- 2. Blood pressure recording by auscultatory method
- Orthostatic variation in arterial blood pressure (orthostatic tolerance test (OTT))
- Blood pressure response to sustained isometric handgrip (IHG).
- 5. Cold pressor test

Pulse rate

It can be used for assessing both parasympathetic and sympathetic reactivity because of dual innervation of heart.

Heart rate response in supine and erect positions

The individual was first asked to lie down comfortably and then the heart rate was recorded. After that she was asked to stand up and immediately the heart rate was recorded again. The heart rate was calculated with the help of R-R interval. Heart rate response was taken as a difference between the heart rate in supine and standing positions.

In normal case, the heart rate should increase at least by 10 beats per minute in standing position. If there is no increase in heart rate on standing position it is interpreted as an impairment of autonomic function.

Heart rate variation during deep breathing

The person was asked to take deep inspiration over 5 seconds followed by expiration over next 5 seconds. Six cycles of inspiration and expiration was completed within one minute.

Then the mean of the minimum RR intervals in the six inspiratory cycles and the mean of the maximum RR interval in the six expiratory cycles were calculated. Heart rate during inspiration and expiration were also noted. Then the difference of the heart rate between the maximum in the inspiratory cycle and the minimum in the expiratory cycles was calculated. In normal case, the difference should be \geq 15 beats/min.

Heart rate response to valsalva maneuver

The female was instructed to exhale forcefully through the mouth piece of a modified mercurial sphygmomanometer and to maintain pressure in the manometer up to 40 mmHg for 15 s. Three trials were performed at intervals of 5 minutes. A continuous ECG was recorded 1 min before the maneuver (resting period), during the maneuver (strain period, 15 sec.) and 60 seconds subsequent to the strain period. The Valsalva ratio was calculated as the ratio of the maximum R-R interval after the release of strain to that of the shortest R-R interval during the strain.⁹

In normal case the valsalva ratio should be \geq 1.21. If the ratio is \leq 1.1, then it is considered abnormal autonomic function.

Heart rate response to postural change (30:15 ratio)

The person was asked to be in complete rest. This was achieved by allowing her to lie quietly for 15 min in the supine position. The ECG recording was started. Then she was instructed to stand erect from the supine position as quickly as possible. There was continuous ECG recording for at least 30s. The ratio of the longest RR around 30th beat after standing to the shortest RR interval around 15th beat after standing were calculated for result of 30:15 ratio.

In normal case the 30:15 ratio should be \geq 1.04. If the ratio is \leq 1.00, then it is considered abnormal autonomic function.

Expiratory: Inspiratory ratio: (E: I ratio)

The person was asked to lie down comfortably and take deep breaths slowly in and out, approximately at 6 breaths per minute. The maximum and minimum R-R intervals during each phase of respiration were recorded. The heart rate was calculated. E: I ratio was calculated taking the ratio of longest R-R interval during expiration to the shortest R-R interval during inspiration. The E: I <1.2 is considered abnormal.

Blood pressure measurement

It was done using sphygmomanometer and stethoscope.

Orthostatic tolerance test

First the basal blood pressure was recorded using sphygmomanometer and stethoscope. Then the lady was asked to stand up and the blood pressure was recorded immediately again.

The difference of the systolic blood pressures during supine and standing position was calculated. If the orthostatic tolerance test shows fall in systolic blood pressure (SBP) by:

- 10 mmHg or less: Normal
- 11-29 mm Hg in SBP: Borderline
- 30 mmHg or more: Abnormal

Blood pressure response to sustained isometric handgrip

The lady was allowed to sit and instructed to perform maximum grip of the handgrip dynamometer with her dominant hand and then maximum capacity was noted down. After 5 min she was asked to hold her grip with 30% of the maximum capacity for 5 min. Then the blood pressure was recorded just after release of the grip. The rise in diastolic blood (DBP) pressure was calculated and interpreted. If DBP rises by:

- 16 mmHg or more: Normal
- 11-15 mm: Borderline
- 10 mmHg or less: Abnormal

Cold pressor test

The lady was asked to remain in supine position and immerse the hand in ice cold (4° C) water for one minute. The blood pressure was recorded by auscultatory method and was taken as an index of response. In normal condition, both systolic and diastolic blood pressure should increase at least by 10mm of Hg.

Anthropometric measurements

Body weight: It was measured by a digital weighing scale with an accuracy of \pm 100 g.

Height: The standing height was measured to the nearest 0.5 cm with the use of stadiometer.

BMI (Body Mass Index): BMI was calculated as follows

Those subjects with BMI greater than 25 were categorized as obese and those with BMI less than 25 as non-obese.

Waist-hip ratio: Waist/Hip Ratio (WHR) of these subjects were measured. Waist circumference was measured at the level of the iliac crest and hip circumference at the fullest point around buttocks. WHR was calculated by dividing waist circumference with hip circumference. Person with WHR > 0.9 was considered to be Obese.¹⁵

Table 1: Comparison of parasympathetic functions between premenopausal and post-menopausal women

| Parasympathetic function | Pre-menopausal | Post-menopausal |
|------------------------------|----------------|-----------------|
| Pulse rate (PR) | 77.9±5.6 | 78.6±5.75 |
| Heart rate response (HRR) | 11.8±7.01 | 21.37±12.23* |
| Heart rate variability (HRV) | 27.45±4.3 | 12.5±6.7* |
| Valsalva ratio (VR) | 1.39±0.19 | 1.44±0.16* |
| El ratio | 1.74±0.42 | 1.53±0.1* |
| 30:15 ratio | 1.16±0.35 | 1.14±0.24 |

*Statistically significant (p<0.05)

Table 2: Comparison of sympathetic functions between premenopausal and post-menopausal women

| Pre-menopausal | Post-menopausal |
|----------------|---|
| 77.9±5.6 | 78.6±5.75 |
| 110±4.5 | 122.4±14.8* |
| 70.1±5.2 | 78.2±8.6* |
| 16.88±3.81 | 12.7±4.39* |
| 8.19±4.68 | 31.81±5.8* |
| 12.9±4.71 | 9.03±3.71* |
| 11.53±0.47 | 6.27±3.07* |
| | 77.9±5.6 110±4.5 70.1±5.2 16.88±3.81 8.19±4.68 12.9±4.71 |

*Statistically significant (p<0.05)

| Table 3: Comparison of BMI and WHR between non obese and obese post-menopausal women | | |
|--|------------|------------|
| Parameter | Non obsese | Obese |
| BMI | 19.24±1.8 | 28.33±2.9* |
| WHR | 0.71±0.19 | 0.94±0.07* |
| *Otatiatiaally simulficant (n 40.05) | 0.1120.10 | 0.01±0.01 |

Statistically significant (p<0.05)

Table 4: Comparison of parasympathetic functions between non obese and obese post-menopausal women

| Non obese postmenopausal | Obese postmenopausal |
|--------------------------|---|
| 77.5±8.3 | 78.7±6.6 |
| 19.51±8.72 | 22.97±9.56* |
| 13.68±5.6 | 11.02±3.68* |
| 1.49±0.11 | 1.38±0.07* |
| 1.57±0.05 | 1.41±0.07* |
| 1.14±0.1 | 1.12±0.11 |
| | 77.5±8.3 19.51±8.72 13.68±5.6 1.49±0.11 1.57±0.05 |

*Statistically significant (p<0.05)

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| Sympathetic function | Non obese postmenopausal | Obese postmenopausal |
|--------------------------------|--------------------------|----------------------|
| Pulse rate (PR) | 77.5±8.3 | 78.7±6.6 |
| Systolic blood pressure (SBP) | 122.61±11.6 | 122.93±11.4 |
| Diastolic blood pressure (DBP) | 76.44±6.21 | 80.83±6.84* |
| Isometric hand grip (IHG) | 13.7±4.75 | 11.9±3.29* |
| Orthostatic tolerance (OTT) | 28.22±9.81 | 33.28±7.85* |
| Cold pressor SBP | 9.11±2.86 | 8.69±2.71* |
| Cold pressor DBP | 6.41±3.17 | 6.28±3.14 |

*Statistically significant (p<0.05)

Table 6: Correlation (r) of autonomic functions with BMI and WHR

| Autonomic functions | BMI (r) | WHR (r) |
|--------------------------------|---------|---------|
| Pulse rate (PR) | 0.15 | 0.17 |
| Heart rate response (HRR) | 0.44* | 0.51* |
| Heart rate variability (HRV) | -0.25* | -0.28* |
| Valsalva ratio (VR) | -0.26* | -0.24* |
| El ratio | -0.22* | -0.27* |
| 30:15 ratio | -0.31* | -0.29* |
| Systolic blood pressure (SBP) | 0.33 | 0.39 |
| Diastolic blood pressure (DBP) | 0.23 | 0.31* |
| Isometric hand grip (IHG) | -0.30* | -0.35* |
| Orthostatic tolerance (OTT) | 0.42* | 0.49* |
| Cold pressor SBP | 0.53* | 0.47 |
| Cold pressor DBP | 0.44* | 0.41 |

*Statistically significant (p<0.05)

RESULTS

Parasympathetic functions like HRR and VR were significantly higher whereas HRV and E:I ratio were significantly lower in postmenopausal women as compared to premenopausal women. Sympathetic functions like SBP, DBP, OTT were significantly higher in postmenopausal women as compared to premenopausal women whereas IHG, cold pressor SBP and cold pressor DBP were significantly lower.

When the autonomic function parameters were compared among non-obese and obese post-menopausal women, we found that parasympathetic functions like HRV, VR, EI ratio and sympathetic functions like IHG, cold pressor SBP were significantly lower whereas parasympathetic functions like HRR and sympathetic functions like DBP, OTT were significantly higher in the obese post-menopausal women in comparison to non-obese postmenopausal females (p<0.05).

There were positive correlations of BMI with PR, HRR, SBP, DBP, OTT, cold pressor SBP and cold pressor DBP but significant result could be obtained only for HRR, OTT, cold pressor SBP and cold pressor DBP (p<0.05) . We found negative correlations of BMI with HRV, VR, EI, 30:15and IHG, all of which were statistically significant (p<0.05).

In case of WHR, we found significant positive correlation with HRR, DBP and OTT (p<0.05) and significant negative correlation with HRV, VR, EI, 30:15, and IHG (p<0.05).

DISCUSSION

Menopause is the permanent cessation of menses due to the irreversible loss of a number of ovarian functions including ovulation and oestrogen production. Due to lack of protective effect of estrogen in menopausal women, the risk of cardiovascular diseases gradually increases and the incidence of cardiovascular disease is equal to that in men.³

In this present study we compared autonomic functions (parasympathetic and sympathetic) among pre and postmenopausal women. In case of parasympathetic function tests, we found that HRR and VR were significantly high whereas HRV and E:I ratio were significantly lower in post-menopausal women in comparison to pre-menopausal ones. But we could not find any significant differences in case of pulse rate and 30:15 ratio. Similarly, in case of sympathetic function tests, parameters like SBP, DBP, OTT were significantly higher whereas IHG, cold pressor SBP and cold pressor DBP were significantly low in postmenopausal women. Bhat AN et al, in their study conducted on 24 post-menopausal females observed that sympathetic function parameters like PR, SBO, OTT cold pressor DBP and QTc (corrected QT interval) showed significant variations when the datas obtained in post-menopausal women were compared with normal established ranges whereas variations in DBP, and cold pressor SBP tests were insignificant. They also observed that the parameters reflecting parasympathetic activity i.e. VR, HRR, HRV, E:I ratio and 30:15 ratio also showed significant variations when the results obtained in postmenopausal women were compared with normal established range of responses.¹

Saeki et al studied the difference in autonomic regulation induced by posture change between post-menopausal and young women. They found that cardiac parasympathetic tone may be reduced in older persons in comparison with young women.¹⁰ Du et al have also shown that cardiovascular protection by estrogen is partly mediated through modulation of autonomic nervous system.¹¹

In our study, we also compared autonomic functions among obese and non-obese post-menopausal women. It was found that parasympathetic functions like HRV, VR, EI ratio and sympathetic functions like IHG, cold pressor SBP were significantly lower whereas parasympathetic functions like HRR and sympathetic functions like DBP, OTT were significantly higher in the obese post-menopausal women in comparison to non-obese postmenopausal females but we could not obtain any significant result in cases of PR, 30:15 ratio, SBP, DBP and cold pressor DBP.

Brunetto AF et al observed decreased parasympathetic response in terms of HRV.¹² In study of Valensi P et al. it has been shown that Cardiac parasympathetic dysfunction present in obese subjects could be associated with higher carbohydrate intake and lower fat and protein intake which results in parasympathetic abnormality.¹³ It is also demonstrated that parasympathetic activity increased with weight loss in obese.¹⁴ Grewal S et al in their study found that the mean change in systolic blood pressure before and after CPT was statistically significant (p= 0.006) in obese group as compared to control group. The impaired CPT in obese could possibly be because of hypofunctional sympathetic nervous system. These observations were in accordance to Simone G et al¹⁵, who showed increase in blood pressure during exposure to cold pressor test on loss of around 30% of excess weight following a period of hypocaloric diet. In another study, there was reduced sympathetic responsiveness associated with thermoregulation demonstrated by abnormal heart rate variability on cold exposure.¹⁶

The results of the study of Garg et al elucidated that the valsalva ratio, heart rate response to deep breathing and heart rate response to standing (30:15) in obese subjects were significantly lower as compared to the control group.¹⁷ This indicated the decrease in parasympathetic nerve function and baroreflex sensitivity in obese subjects. Baroreceptors resetting may occur in obese individuals due to atherosclerosis that hardens the carotid sinus walls causing decrease compliance.18 There was also decrease in blood pressure response to isometric handgrip exercise test in the obese people in contrast to the control group. It shows the decreased activity of the sympathetic nervous system¹⁹ or to a lower increase in peripheral resistance to maneuvers activating sympathetic system.²⁰ Baek et al concluded that in normal conditions sympathetic activity increases during isometric handgrip exercise and cold pressor test but decreases in obesity which may be responsible for the maintenance of obese state.21

Valensi et al have demonstrated that glucose induced inhibition of the lipid oxidation rate in obese people is greater in the patients with autonomic dysfunction which could be due to decrease in parasympathetic activity.¹⁷ It has been shown that increased sympathetic activity induced by cold water stress causes norepinephrine release and elevation of blood pressure more in obese subjects. This greater increase in blood pressure might be contributed by more release of endothelins, prostaglandins and angiotensin II.²²

CONCLUSION

The altered sympatho-vagal activity can produce adverse effect on health of post-menopausal females so there is a need to understand the effect of obesity and autonomic function in these women.

As obesity is associated with both sympathetic and parasympathetic nervous system dysfunction, it may result in various cardiovascular complications. If such dysfunctions are diagnosed early by doing various autonomic function tests, it will be of great help in identification of those which are prone to weight gain and at risk of various cardiovascular complications. Dietary modifications, exercise, and yoga may improve autonomic functions in post-menopausal women by reducing body fat and weight.

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