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Original Article

A Comparative Study of Cardiac Autonomic Activity Indices among Reproductive and Menopausal Females of Western Rajasthan By CAN Win

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ABSTRACT
Background and Objectives: Menopause is defined as the cessation of menstrual periods**.**.Hormonal changes after menopause bring alteration in tautonomic functions. So present study was aimed for evaluation of autonomic functions in premenopausal and postmenopausal women . **Material and Methods:**100 healthy women were divided into 2 groups-Control group A (Premenopausal) and Study group B (Postmenopausal).The parasympathetic function tests included the Heart rate response to standing (30:15 RATIO), Heart rate variation during deep breathing(E:I RATIO), Heart rate response to Valsalva Maneuver (VM RATIO) and the sympathetic function tests-Blood pressure response to the Isometric handgrip (DBPΔ) and the Blood pressure response to standing (SBPΔ) .**Results**:There is statistically significant decrease in 30:15 ratio, whereas the results of E:I ratio and Valsalva maneuver test did not show any significant result. The sympathetic function tests significantly increased in postmenopausal women when compared with premenopausal women. **Conclusion:**The parasympathetic activity was reduced and sympathetic activity was increased in postmenopausal women.
Keywords: Menopause, 30:15 ratio, E:I ratio, VM ratio, Blood pressure response to the Isometric handgrip (DBPΔ) and the Blood pressure response to standing (SBPΔ).

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INTRODUCTION

Menopause is a physiological aging phenomenon in women that marks the gradual transition from reproductive to non - reproductive phase of life.[1] Average menopausal age of Indian women is 55 years and is marked by amenorrhea for 12 consecutive months and thereafter[2].The mean age at natural menopause is reported to vary from 45-52.8 years[3].Menopause is multidimensional and influenced by many endogenous and exogenous factors mainly perceived as reproductive hormones deficiency which affects many physiologic and metabolic functions in female body including cardiovascular system.[4]

Loss of ovarian function at menopause leads to non -reproductive state with changes in mood, memory,cognition,behavior, immune function, loco motor system and cardiovascular functions [5]The high incidence of ischemic heart disease in postmenopausal women suggests close association between ovarianhormones levels and cardiovascular system.[6] The presence ofestrogen receptors in heart, vascular smooth muscles and autonomic brainstem centers (nucleustractus solitaries, ventrolateral medulla) suggests regulation of cardiovascular system by ovarian hormones.[7]

Easy accessibility to Medicare and better living conditions has increased life expectancy in recent years. There are over 60 million postmenopausal women above 55 years in India.8 They deserve special attention as many of them often suffer from complications of menopause including autonomic dysfunction.The causes of autonomic dysfunction in postmenopausal women may be multifactorial i.e., dyslipidemia, increased body fat percentage, aging and loss of female sex hormonesThe cardiac vagotonic and sympatholytic effects of estrogen can explain, at least in part, why premenopausal women compared with postmenopausal women have a lower coronary heart disease incidence and mortality rate.[9]Early diagnosis of autonomic dysfunction, medications,

dietary modifications, exercise and change in lifestyle can prevent morbidity and improve health quality of postmenopausal women.

MATERIALS AND METHODS

The present study was carried out in the Department of Physiology in Collaboration with Department of Obstetrics and Gynaecology, Dr. S.N. Medical College on 100 healthy females of western Rajasthan between the age group of 18-65 years using simple random methods asking the subjects about history of menstrual cycle.

Subjects were divided in two group of 50 each, for the ease of assessment and comparison.

GROUP A(18-45 YRS).PRE MENOPAUSAL(n=50)

GROUP B (50-65 YRS) PERI AND POST MENOPAUSAL(n=50)

Subjects with any history of pregnancy, any cardiovascular disease, respiratory disease, diabetes mellitus, systemic hypertension, neurological deficits,hormone replacement therapy, surgical menopause and any other major abdominal surgery were excluded from the study.

Anthropometrical parameters-

1. **Weight** was measured nearest to 0.1 kg by weighing balance(Krup'sWeighing scale)after removal of shoes with light clothing only.

2.Height was measured to nearest 0.5 cm against the wall without shoes using Stadiometer.

3.Resting heart rate- Normal resting heart rates range from 60–100 bpm.Bradycardia is defined as a resting heart rate below 60 bpm. Tachycardia is defined as a resting heart rate above 100 bpm, though persistent rest rates

between 80–100 bpm.[10]

Non- invasive autonomic function tests were performed by CANWin Analysis System

A.The parasympathetic nerve function tests are as follows.

1.Heart Rate variation during deep breathing (Expiration /Inspiration

Ratio)-While recording ECG, the subjects were asked to inhale deeply for 5

seconds followed by exhalation for 5 seconds at a rate of 6 breaths per minute.The ratio between longest R-R interval duringexpiration and shortest R-Rinterval during inspiration (E/I ratio) in each respiratory cycle is calculated forevaluation[11].

Values of E:I Ratio

1. Normal ≥ 1.21
2. Borderline 1.20-1.110
3. Abnormal ≤ 1.10

2..Heart rate response to standing (30 :15 ratio) The subject was instructed to lie down comfortably and ECG wasrecorded to calculate the heart rate .Then the subject was instructed to stand upwithin 3-4 seconds and remain motionless thereafter. The 30:15 is the ratio oflongest R-R interval at beat 30 during inspiration/expiration cycle and theshortest R-R interval at beat 15 after standing. It examines the integrity of theefferent parasympathetic branch[12].

Value of 30:15 ratio:-

a) Normal ≥1.04
b) Borderline 1.03-1.01
c) Abnormal ≤ 1.00

3. Heart rate response to Valsalva maneuver (VM ratio)-The test is used most frequently because it allows evaluation of the entireReflex arc. The subject is asked to blow out or to expire forcefully through amouthpiece attached to the sphygmomanometer to maintain the pressure at about 40 mm of Hg for 15 seconds. The ECG is recorded simultaneously duringthis maneuver and 15 seconds afterwards to see the RR interval changes.The Valsalva ratio = Longest R-R interval after maneuver (after thestrain)/ shortest R-R interval during maneuver (during the strain)[13]

The normal Valsalva ratio is

a) Normal ≥1.21
b) Abnormal ≤1.21.

B. Test of predominantly sympathetic function:-Normal bloodpressure at rest is within the range of 100-140mmHg systolic (top reading) and60-90mmHg diastolic (bottom reading). High blood pressure is said to bepresent if it is persistently at or above 140/90 mmHg[10].

1. Blood - pressure response to standing-The BP of the subject was recorded at lying down and again when the subjectstands up from supine position.In normal subjects systolic BP does not fall bymore than 10 mm Hg and in autonomic dysfunction it falls by >20-30 mm Hg.Orthostatic hypotension was defined as a fall of >20 mm Hg in systolic and /or> 10 mm Hg in diastolic BP from lying to standing position.[14]Values of orthostatic fall in systolic BP:-

a) Normal ≤10 mmHg
b) Borderline 11-29 mmHg
c) Abnormal ≥30 mmHg

2. Blood –pressure response to Sustained Handgrip (SHG)-This test studies the blood pressure response to an isometric handgripexercise. Initially the subject was asked to exert maximal hand grip strength on hand grip dynamometer with dominant hand. First the maximum voluntarycontraction (MVC) (MAXIMAL ISOMETRIC TENSION i.e. Tmax) isdetermined and then the subjects were asked to press the handgrip dynamometerfor at 30% of maximal voluntary effort. The BP was recorded in contralateralarm and rise in diastolic BP was measured .Value of Rise in Diastolic BP after sustained handgrip exercise[Ewing andClarke grading]:-[15]

a) Normal ≥16 mmHg
b) Borderline 11-15 mmHg
c) Abnormal <10 mmHg

Normal, borderline, and abnormal values of Cardiovascular Autonomictests:-[16]

Normal(0score) Borderline(1 score) Abnormal(2 score)

Categorization of subjects for CAN based on different criteria:

1. Ewing's criteria-

NORMAL- All tests normal or one test borderline
EARLY- One of three heart rate tests abnormal ortwo borderline
DEFINITE-Two or more of the heart rate tests abnormal
SEVERE-Two heart rate tests abnormal plus one or both BP tests abnormal or both borderline.

The scoring is added and CAN is classified as per EwingCriteria as follows:-
Classification Category Total Score
No CAN 0-1
Early CAN 2-3
Definite CAN 4-6
Severe CAN Above 6

RESULTS

There is a statistically significant decrease in 30:15 ratio, whereas the results of E:I ratio and Valsalva maneuver test did not show any significant change in postmenopausal women when compared with premenopausal women.The sympathetic function tests significantly increased in postmenopausal women when compared with premenopausal women.

Table A- Comparison of Parasympathetic function tests between Premenopausal and Postmenopausal females groups.

TESTS	GROUP A		GROUP B		P VALUE	RESULT
E:I RATIO	1.33	0.35	1.24	0.22	0.1269	Not Significant
30:15 RATIO	1.12	0.28	1.01	0.22	0.33	Significant
VALSALVA MANUEVERE RATIO	2.36	1.45	1.98	1.64	0.22	Not Significant

Table B- Comparison of Sympathetic function tests between Premenopausal and Postmenopausal females groups

TESTS	GROUP A		GROUP B		P VALUE	RESULTS
Δ SBP mm Hg	6.08	3.51	8.12	7.13	0.072	Not Significant
Δ DBP mm Hg	15.04	5.24	12.0	12.47	0.1152	Not Significant

Table C –Distribution of females in Premenopausal group A(50)

Test Type	Cardiovascular reflex Test	Normal	Borderline	Abnormal
Parasympathetic tests	E:I Ratio	31(62%)	0	19(38%)
	30:15 Ratio	34(68%)	2(4%)	14(28%)
	VM Ratio	49(98%)	0	1(2%)
Sympathetic tests	ΔSBP mm Hg	43(86%)	7(14%)	0
	ΔDBP mm Hg	25(50%)	15(30%)	10(20%)

Table D-Distribution of females in Postmenopausal group B (50)

Test Type	Cardiovascular reflex Test	Normal	Borderline	Abnormal
Parasympathetic tests	E:I Ratio	27(54%)	0	23(46%)
	30:15 Ratio	26(52%)	12(24%)	12(24%)
	VM Ratio	39(78%)	7(14%)	4(8%)
Sympathetic tests	ΔSBP mm Hg	41(82%)	6(12%)	3(6%)
	ΔDBP mm Hg	12(24%)	7(14%)	31(62%)

TableE-Prevalence of Cardiac Autonomic Neuropathy as Per Ewing's Criteria

GROUPS	TOTAL NO.	NORMAL	EARLY	DEFINITE	SEVERE	P VALUE
Group A	50	21 (42%)	16(32%)	13(26%)	0(0%)	0.0029(S)
Group B	50	7(14%)	17(34%)	21(42%)	5(10%)	

DISCUSSION

Evaluation of status of automatic nervous system in pre and postmenopausal females was done with the help of a noninvasive device, Cardiac Autonomic Neuropathy Analysis system, "CAN Win".It analyses both parasympathetic and sympathetic nervous system responses. The measured parameters of autonomic function tests are discussed below:-

A.Parameters for assessment of Parasympathetic activity-

A.Heart rate variation during deep breathing (EXPIRATION /INSPIRATION RATIO)-Table A Mean E:I ratio of group A is 1.33±0.35 and GROUP B is 1.24±0.22 with decline in postmenopausal females group. The heart rate response to deep breathing which is an indicator of parasympathetic function was reduced linearly in postmenopausal females group in our study. Lower E:I ratio values in postmenopausal females was also observed by Naher LAD, et al 2009.[9] No significant changes in E;I ratio were observed in study done by Joshi and Shinde (2015).[17]

B.Heart rate response to standing (30:15 Ratio)-Table A Mean 30:15 ratio of group A is 1.12±0.28 and group B is 1.01± 0.22 with a p value <0.05 which is found to be significant. Our study shows 30:15 ratio decreases in postmenopausal females. Thus heart rate response to orthostatic test which is a sensitive test to assess parasympathetic integrity is decreasing in postmenopausal females.Similar decrease in 30:15 ratio test values was observed by Naher LAD et al 2009[9] and Joshi and Shinde 2015[17].

C.Heart rate response to Valsalva Maneuver Ratio - Table 18 reveals The observed values of VM ratio in group A is 2.36±1.45 and Group B is1.98± 1.64 with p value 0.22 (>0.05) (N.S) VM ratio decreases in postmenopausal females in our study.No significant change in VM ratio in postmenopausal females (Naher LAD et al 2009)[9] and JOSHI and Shinde 2015[17].

Present study results reveal decrease in parasympathetic activity in postmenopausal females which is suggestive of decreased baroreceptor reflex activity and vagal tone, due to decreased estrogen levels in postmenopausal females. Estrogen facilitates the glutamatergic neurotransmission in nucleus tractussolitarius, increases baroreflex sensitivity and vagal tone[18].

B.Parameters for assessment of Sympathetic activity

1.Blood pressure response to standing-Table B shows orthostatic fall in Systolic blood pressure (ΔSBP) in both groups. Group A females present with 6.08±3.51 mm Hg fall in systolic blood pressure while Group B show 8.12±7.13mm Hg. p value<0.05 therefore nonsignificant.Orthostatic Δ SBP was higher in postmenopausal females.

Present results coincide with Naher LAD2009[9] and Joshi –Shinde 2015[17].

2.Blood pressure response to sustained hand grip exercise – Table B. Mean Δ DBP of group A is 15.04±5.24.92 and Group B is 12±12.47 with a nonsignificant p value >0.05. In our study the diastolic blood pressure response to sustained hand grip was significantly lower in postmenopausal females. This is due to lower absolute muscle tension, desensitization of α adrenoreceptors and decreased β adrenergic responsiveness in cardiovascular system[19].

The data reveal a linear increase in abnormal results of cardiovascular reflex tests in postmenopausal females groups (TABLE C and D). This is suggestive of primary stage of cardiac autonomic neuropathy in postmenopausal female. Early diagnosis and management could help prevent morbidity and mortality after menopause in females.

In our study we found significantly increased sympathetic activity and decreased parasympathetic activity in compared to premenopausal women which is similar to the study done by ShikhaG,Nilima S, Om PT, Neerja G in 2011[20] in which they compared cardiac autonomic functions among postmenopausal women with and without hormone replacement therapy, and premenopausal women suggesting the role of estrogen in maintaining the cardiovascular autonomic functions.Similar results were obtained in a study done by Shailaja S, Sandhya T[21] in which they compared cardiac autonomic activity between pre and post-menopausal women using heart rate variability.

Mercuro G et al[22] found a role of endogenous estrogen in the modulation of autonomic nervous system in their study, they observed autonomic changes before and after oophorectomy in premenopausal women which indicates that estrogen has a role in increasing vagal function and reducing sympathetic activity.

Association between various factors and prevalence of CAN - EWING'S tests criteria (Table E) compares prevalence of cardiac autonomic neuropathy in both groups. In premenopausal females group A 42% subjects were found normal, 26% subjects were showing definite autonomic dysfunctions and 32% subjects have shown early autonomic dysfunctions. While in the study group B 14% were found normal, 34% early, 42% definite and 10% with severe autonomic dysfunctions, it show that in postmenopausal females (Group B Study) autonomic dysfunctions were found statistically significant $P<0.05$.

TABLE E is suggestive of increased prevelance of CAN in postmenopausal females.

Limitations of the study:

The sample size is small, greater variations in anthropometric measures of subjects, and it is limited to one geographical area. We have also not measured the estradiol levels, Therefore for more precise results larger sample size with approximately similar anthropometric indices with biochemical test results of females should be evaluated.

Benefits of the study

The present study highlights the undesirable changes that occur in women during menopausal transition. The altered sympatho vagal balance in menopause need special attention for prevention of cardiovascular diseases and other complications in elderly women.

CONCLUSION

The above studies show decline in parasympathetic activity with sympathetic over activity with menopausal transition. The possible explanation could be the decline in level of estrogen from premenopausal to postmenopausal status which favors the shifting of autonomic balance towards the sympathetic dominance. There are several mechanisms through which reproductive hormonal status may influence cardiovascular autonomic reactivity. These include altering receptor sensitivity density or neurotransmitter availability. The role of estrogen on cardiac autonomic modulation action can be explained by its effect on enhancing the cholinergic muscarinic activity in central nervous system and such modulation at central and peripheral levels tends to suppress sympathetic but elevate parasympathetic tone. There is also age related parasympathetic dysfunction which starts after sixth decade.

Hormonal replacement therapy is yet controversial .Hence role of phytoestrogens as a dietary component and role of Yoga in reversing the symaptho –vagal balance in postmenopausal women is the further of scope of the study.

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