

Cardiac Autonomic Neuropathy in Women During Menopausal Transition Period and its Association with Psychological Stress Levels: An Observational Study

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ABSTRACT

Context: Perimenopause is a transitional stage which occurs before menopause in which women experience myriad symptoms like hot flushes, anxiety & depression with increasing, psychological stress levels leading to autonomic dysfunction.

Purpose: Evaluate cardiac autonomic neuropathy (CAN) in women during menopausal transition period and its association with psychological stress levels.

Methodology: Study includes three groups of women, group I: premenopausal in the age group of 25-40 years, group II: perimenopausal women without symptoms and group III: perimenopausal women with symptoms in the age group of 40-50 years of 30 in each (total n=90). CAN was evaluated in terms of presence of resting tachycardia, loss of sinus arrhythmia (DBD) and heart rate response to Valsalva maneuver (VR) by electrocardiogram (ECG). If any two of them found positive, then presence of CAN was confirmed. Psychological stress levels were evaluated using standard women's health questionnaire. Correlation between Psychological stress levels with incidence of CAN was assessed.

Results: There exists a statistically significant positive correlation between DBD and VR with anxiety depressed mood, well being, vasomotor symptoms, somatic symptoms, and memory. (p=0.000**)

Conclusion: This study indicates that CAN have a strong association with psychological stress levels in perimenopausal women.

Keywords: Perimenopausal, Autonomic functions, Valsalva ratio, Sinus arrhythmia

INTRODUCTION

The reproductive period of women, gradually transcends into stage of perimenopause, followed by menopause after couple of years.¹ Perimenopause is a transitional stage which is before menopause which can range from 2 to 10 years. In this stage, menstrual periods are irregular, with 30% decrease in estrogen and

progesterone.¹

Vasomotor symptoms (VMS) such as hot flushes and night sweats are main physical signs that occur in 50-70% of women during menopausal transition period.² In addition, women also experience symptoms like anxiety, mood changes, cognitive deficits and somatic symptoms (SOM).³

The changes in hormonal status during this period, mainly estrogen has potent influence on vital organ systems.² Along with cardiovascular risk, reduction in estrogen level also causes climacteric symptoms like vasomotor, psychological or musculoskeletal disturbances that may contribute to stress among

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women during this period.⁴ Psychological stress itself is an individual risk factor for cardiovascular disease (CVD).⁵ Symptoms of menopausal transition may be attributed to reduction in beneficial effects of estrogen.⁶ Common clinical characteristics of transition are change in women's usually regular menstrual periods and beginning of vasomotor symptoms. These symptoms suggest alteration of either cardiovascular reflexes or local control of blood flow to skin, i.e. alteration of autonomic hemodynamic control.⁷ The high incidence of ischemic heart disease after menopause suggests close association between ovarian hormone levels and cardiovascular system.⁸

Autonomic control of heart plays an important role in cardiac mortality which maintains homeostasis in our body. Alteration in autonomic nerve function may lead to hypertension, cardiac arrhythmia, increased incidence of silent Myocardial infarction or sudden cardiac death.^{9,10} Few studies are conducted to assess the incidence of cardiac autonomic neuropathy in peri menopausal as compared to post-menopausal women. Studies showed that in both peri and post-menopausal women, variations in hot flash frequency and severity were not explained by variations in resting sympathetic activation.¹¹ Study done by Shivwani showed significant increase in sympathetic reactivity in perimenopausal and postmenopausal women- presumably as hormone levels fall with onset of perimenopause. However, parasympathetic functions showed statistically insignificant change.⁷ There are no studies which shows incidence of cardiac autonomic neuropathy in peri menopausal women in association with psychological stress levels, so following study was conducted.

MATERIALS AND METHOD

It is cross sectional study conducted in department of Physiology, SDM medical college and hospital during April-August 2017 after obtaining institutional ethical clearance. The study includes 3 groups. Group I were pre-menopausal women (n=30) of age 25-40 years having regular menstrual cycle once in every 28-30 days in follicular phase (7-14 days). Group II were peri-menopausal women without any symptoms (n=30) of the age 40-50 years. Group III were peri-menopausal women (n=30) of age 40-50 years, with symptoms like Changing periods- length of cycle, hot flushes, night sweats, etc. Sample size was decided based on previous research references. Volunteers were recruited from

staff community and general population after explaining the procedure in detail and obtaining written informed consent.

Exclusion criteria- Pregnant females, with any kind of metabolic disorder like diabetes mellitus, hypertension, irregular menses, any ovarian disorders, amenorrhea for consecutive 12months, any endometrial disorders.

Study design: Subjects were instructed not to have coffee, tea or cola 12 hours before tests. They were asked to come to physiology laboratory at 9 am after having light breakfast. Detailed history was taken on standard proforma regarding history of any peri menopausal symptoms. A written informed consent was taken before conducting study in English and local languages. Subjects were assured that report will be kept confidential and used only for study.

Parameters assessed were cardiac autonomic function test and psychological stress levels. Presence or absence of CAN was determined by performing following 3 different tests.

1. Resting tachycardia
2. Loss of sinus arrhythmia
3. Heart rate response to Valsalva maneuver

If any two tests were positive then presence of CAN was confirmed.

Instrument- ECG instrument with paper speed of 25 mm/sec was used for all tests (BPL, CARDIART 6208 VIEW. BPL LIMITED, BANNERGHATTA ROAD, BANGALORE).

PROCEDURE

1. Resting tachycardia: The subjects were asked to relax in supine position for 30 minutes. Resting heart rate was calculated for evaluation of resting tachycardia and recorded on standard ECG from lead II. Values of >100 beats/minute were considered abnormal.

2. Loss of sinus arrhythmia: Heart rate variation with respiration was observed for loss of sinus arrhythmia. In sitting position, subjects were asked to take 6 deep breaths/minute. A continuous ECG was recorded for six cycles. The maximum and minimum R-R intervals were measured during each breathing cycle and converted

into beats/minute. The results were expressed as mean of difference between maximum and minimum heart rate for six measured cycles. Normal response is difference of ≥ 15 beats/minute, while 10-15 beats and < 10 beats/minute were taken as borderline and definitive CAN respectively.¹²

3. Heart rate response to Valsalva maneuver: In sitting position person was asked to blow into a mouthpiece connected to mercury manometer and holding it at 40 mmHg for 15 seconds, simultaneously monitored by ECG. The ECG continued to be recorded even 15 seconds after release of pressure. The heart rate changes induced by Valsalva maneuver were expressed as ratio of maximal tachycardia during maneuver to maximal bradycardia after maneuver. This ratio was defined as Valsalva ratio and calculated as ratio of longest R-R interval to shortest R-R interval. Normal Valsalva ratio is ≥ 1.2 ; values ≤ 1 were taken as evidence of CAN. Values of 1-1.2 were taken as borderline.¹²

Assessment of menopause-associated symptoms was performed using Women's Health Questionnaire (WHQ).⁶ The WHQ is 23-item self-reported health-related quality of life scale that was designed to assess wide range of physical and emotional symptoms, experienced by middle aged women. There were four response options for each item, ranging from 1-4, where 1 means "yes definitely" and 4 means "not at all." This provides scores on six factors: Anxiety depressed mood, well-being, Somatic symptoms, memory and concentration, vasomotor symptoms, and sleep problems. Raw scores were calculated for each scale. Transformed scores were obtained from raw scores. Scores vary from 0, which indicates "poor health status" to 100 which indicates "good health status."

STATISTICAL ANALYSIS

Statistical analysis was done by using SPSS software version-20. Values were expressed as mean \pm SD. Intergroup and intragroup analysis was done by ANOVA and tukey's post hoc analysis. P values < 0.05 was considered significant & < 0.01 as highly significant. A Pearson's correlation was used to see relationship between psychological stress levels with cardiac autonomic function parameters.

RESULTS

It is cross sectional study done to assess CAN in women during menopausal transition period and its association with psychological stress levels.

Table-1 shows cardiac autonomic function tests values amongst three groups. RHR increases in perimenopausal women with symptoms when compared to premenopausal and perimenopausal women without symptoms but not statistically significant. There is significant reduction in deep breathing difference in perimenopausal women with & without symptoms when compared to premenopausal women ($p=0.00^{**}$). There is statistically significant reduction in Valsalva ratio in all three groups ($p=0.00^{**}$).

Table-2 shows psychological stress levels assessed by six domains of women's health questionnaire. There is significant reduction in scores of anxiety depressed mood, well-being and vasomotor symptoms in perimenopausal women with symptoms when compared to premenopausal and perimenopausal women without symptoms ($p=0.00^{**}$). There is also reduction in scores of somatic symptoms, sleep and memory in perimenopausal women with symptoms when compared to premenopausal and perimenopausal women without symptoms but not statistically significant.

Table-3 shows correlation between RHR with domains to assess psychological stress levels. There is statistically significant negative correlation between RHR with scores of anxiety depressed mood, well being and vasomotor symptoms.

Table-4 shows correlation between DBD with domains to assess psychological stress levels. There is significant positive correlation between DBD with scores of anxiety depressed mood, well being, vasomotor symptoms, somatic symptoms, and memory.

Table-5 shows correlation between VR with domains to assess psychological stress levels. There is significant positive correlation between VR with scores of anxiety depressed mood, well being, vasomotor symptoms, somatic symptoms, and memory.

Table 1: Cardiac autonomic values amongst pre and peri menopausal women.

Cardiac function tests	Group I	Group II	Group III	F value	P value	Post- hoc analysis (p value)
Resting heart rate (beats/min)	73.46±8.33	75.63±7.95	77.90±9.08	2.055	0.134	I Vs II 0.585 I Vs III 0.112 II Vs III 0.556
Deep breathing difference (beats/min)	24.86±5.53	18.43±5.29	16.30±4.05	23.842	0.00**	I Vs II 0.00** I Vs III 0.00** II Vs III 0.230
Valsalva ratio	1.31±.08	1.24±.09	1.13±.09	29.119	0.00**	I Vs II .009** I Vs III 0.00** II Vs III 0.006**

Table 2: Psychological stress levels using women health questionnaire amongst pre and peri menopausal women.

Parameter (transformed scores)	Group I	Group II	Group III	F value	P value	Post hoc analysis p value
Anxiety depressed mood	74.40±3.10	72.63±4.49	54.30±3.83	250.150	.00 **	I Vs II 0.184 I Vs III .00** II Vs III .00**
Well being	72.80±3.71	72.80±5.21	54.46±3.86	180.163	.00**	I Vs II 1.000 I Vs III .000** II Vs III .000**
Somatic symptoms	71.66±2.74	70.00±4.33	69.36±8.15	1.370	.260	I Vs II .480 I Vs III .250 II Vs III .898
Vasomotor symptoms	71.80±3.13	70.46±4.55	54.03±5.16	153.836	.000**	I Vs II 0.467 I Vs III .000** II Vs III .000**
Memory	71.93±3.43	69.66±4.91	70.36±6.42	1.568	.214	I Vs II .200 I Vs III .459 II Vs III .855
Sleep	72.53±3.55	70.63±6.81	70.66±6.97	.988	.377	I Vs II 0.56 I Vs III 0.53 II Vs III 0.44

Group I: pre- menopausal Women, Group II: Peri menopausal women without symptoms,

Group III: Peri menopausal women with symptoms .Values are expressed as mean ± SD. p< 0.05 * is significant. p<0.01** highly significant.

Table 3: Shows correlation of resting heart rate (RHR) with domains assessing psychological stress levels (n=90).

	Anxiety depressed mood	Well being	Somatic symptoms	Vasomotor symptoms	Memory	Sleep
RHR (Beats/min)	r= -.249 p= .018*	r= -.228* p= .031*	r= -.052 p= .629	r= -.240 p= .023*	r= -.008 p= .940	r= -.169 p= .111

r=- (negative correlation): r= + (positive correlation), p < 0.05 is significant, p < 0.01 is highly significant.

Table 4: Shows correlation of deep breathing difference (DBD) with domains assessing psychological stress levels (n=90).

	Anxiety depressed mood	Well being	Somatic symptoms	Vasomotor symptoms	Memory	Sleep
DBD (Beats/min)	r= +0.406 p=0.00**	r= +0.375 p= 0.00**	r=+0 .267 p= .011*	r=+0 .435 p= .00**	r=+0 .328 p= .002**	r=+0 .117 p= .272

r=- (negative correlation): r= + (positive correlation), p < 0.05 is significant, p < 0.01 is highly significant.

Table 5: Shows correlation of valsalva ratio (VR) with domains assessing psychological stress levels (n=90).

	Anxiety depressed mood	Well being	Somatic symptoms	Vasomotor symptoms	Memory	Sleep
VR	r= +0.406 p=0.00**	r= +0.375 p= 0.00**	r=+0 .267 p= .011*	r=+0 .435 p= .00**	r=+0 .328 p= .002**	r=+0 .117 p= .272

r=- (negative correlation): r= + (positive correlation), p < 0.05 is significant, p < 0.01 is highly significant.

DISCUSSION

Results shows deep breathing difference is significantly reduced in perimenopausal women with symptoms when compared to premenopausal women and not significantly reduced when compared to perimenopausal women without symptoms [F (2, 87) =23.842, p=0.000]. Valsalva ratio was significantly reduced in perimenopausal women when compared to pre- and peri-menopausal women without symptoms [F (2, 87) = 29.119, p=0.000]. Results of our study are similar to work done by Shivwani et.al which showed autonomic reactivity in pre, peri and post-menopausal women. There was decrease in Valsalva ratio and tachycardia ratio in peri and postmenopausal women in comparison to premenopausal women; although difference was not statistically significant.⁷ Gibson CJ studied Cardiac autonomic function and hot flashes among perimenopausal and postmenopausal women

which showed strong association between hot flushes and parasympathetic component.¹¹ Perimenopausal women also showed increase in sympathetic activity which was consistent with findings of Kumar et.al with an increase in total body nor-epinephrine spillover. There was decrease in the nor-epinephrine-induced vasoconstriction after estrogen supplementation.¹³

Mercuro et.al also showed that surgical menopause induces a decline in cardiac vagal modulation with a shift towards sympathetic hyperactivity.¹⁴ Du et.al have also shown that cardiovascular protection by estrogen is partly mediated through modulation of autonomic nervous system.¹⁵

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.¹⁶

Our study also shows that all six domains assessing women's health questionnaire are significantly reduced in perimenopausal women with symptoms when compared to premenopausal women which signifies poor health status. Results of our study is consistent with findings of Ashwini and colleagues which showed that symptoms of menopausal transition are attributed to reduction in estrogen level which lead to substantial psychological stress among women during peri menopausal transition period.⁶ Our study also shows positive correlation between deep breathing difference and Valsalva ratio with the psychological stress levels assessed by women's health questionnaire. It demonstrates association between stress levels and autonomic functions in perimenopausal women. The basic cause of symptoms of menopausal transition is complex relationship with estrogen metabolism and autonomic nervous system which is confirmed by Lee et al. Increased sympathetic activity may be a link between reduction in estrogen and psychological stress during menopausal transition period.¹⁷

CONCLUSION

Our study shows that women during menopausal transition period are prone for elevated psychological stress level which has association with cardiac autonomic dysfunction and increases the incidence of cardiac autonomic neuropathy.

Conflict of Interest: None

Source(s) of Funding: Self

Ethical Clearance: Obtained

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