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RESEARCH ARTILCE

Evaluation of cardiovascular autonomic control in chronic pain patients using isometric handgrip and deep breath maneuvers

Atanu Roy, Sanjeev K. Singh

Department of Physiology, Institute of Medical Sciences, Banaras Hindu University, Varanasi, Uttar Pradesh, India

Correspondence to: Sanjeev K. Singh, E-mail: drssks@gmail.com

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ABSTRACT

Background: Chronic pain of musculoskeletal origin can cause severe and prolonged pain which, in turn, can alter the autonomic outflow and thereby cardiovascular system. Various studies have been done on this issue but the same study has not been conducted yet in the population of Eastern Uttar Pradesh, India. **Aims and Objective:** This study was conducted to assess the effects of chronic pain on cardiovascular autonomic control using isometric handgrip test (IHGT) and deep breath test (DBT). **Materials and Methods:** The patients (50 males of the mean age of 38 ± 2.2 years and 28 females of the mean age of 40.5 ± 2.0 years) having the pain of musculoskeletal origin with chronicity of >6 months duration and severity of >3 on visual analog scale were included in the study. The age-sex matched controls (58 males of the mean age of 35 ± 2.2 years and 28 females of the mean age of 39.6 ± 1.2 years) were also selected. The DBT and IHGT were performed, blood pressure (BP) and electrocardiography were recorded, and the heart rate (HR) was calculated. **Results:** During DBT, there is a significant difference in the HR changes in the male cases versus male controls ($P < 0.05$), but expiration: inspiration (E: I) ratio did not show any significant changes among various groups. In IHGT, BP changes in female cases versus female controls and male cases versus female cases were found significantly different ($P < 0.05$) and HR changes were also significantly different in all the three groups ($P < 0.05$). **Conclusions:** The results indicate the parasympatholytic responses in the male and female cases which are further supported by the HR changes in the IHGT. The BP responses indicate the normal sympathetic response in the female cases and subnormal response in the male cases.

KEY WORDS: Isometric Handgrip Test; Deep Breath Test; Pain; Blood Pressure; Heart Rate; Sympathetic; Parasympathetic Reactivity

INTRODUCTION

Chronic pain originating from the musculoskeletal system causes severe and prolonged pain which, in turn, can alter the sympathetic and parasympathetic outflow. Sympathetic hyperactivation has already been shown in fibromyalgia,[1] migraine,[2] chronic neck, and shoulder pain.[3] The sympathetic and parasympathetic systems work together to maintain harmony of the human physiological system but this state can be disrupted by the chronic pain. The autonomic nervous system (ANS) governs the cardiovascular system and this fact has resulted to various studies showing relations between autonomic dysfunction and chronic pain.[4,5] Since any alteration in the ANS brings about the changes in the cardiovascular parameters such as blood pressure (BP) and heart rate (HR), and therefore, isometric handgrip test (IHGT) and deep breath test (DBT) were performed in this study to evaluate the autonomic reactivity.

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Although studies on the effect of chronic pain on autonomic function have been carried out by some other workers elsewhere[4,5] and also on the gender difference,[6-8] the same study has not been conducted yet in the population of Eastern Uttar Pradesh, India, so far the best of our knowledge. Therefore, this study was planned to evaluate the autonomic responses in the male and female cases and their comparison with the normal male and female population of Eastern Uttar Pradesh, India.

MATERIALS AND METHODS

After getting approval from Institute Ethical Committee, this study was conducted to understand the autonomic reactivity in the chronic pain patients and age-sex matched controls using isometric handgrip and deep breathing maneuvers.

Selection of Cases and Controls

All those patients suffering with chronic pain of musculoskeletal origin of severity >3 on visual analog score and duration of >6 months were included in the study with no history of diseases such as diabetes mellitus, hypertension, hyper/hypothyroidsm, and uremia or the use of any medication like diuretics, calcium channel blocker, neuroleptics, antiepileptic, antidepressant and alpha, and beta blockers as exclusion criteria. The age-sex matched healthy persons were selected for the comparisons and defined as control. In the females, the period of performance of the tests was chosen within one week of last menstrual period. 50 male cases and 28 female cases were selected from the pain clinic based on the exclusion and inclusion criteria as mentioned earlier in this paragraph. Non-random (convenient sampling) method was used for the selection of the cases during the period of 1 year. 58 male and 28 female controls were also selected in this study. All the observations were categorized into four groups: Male cases, female cases, male controls, and female controls. All the parameters of male cases were compared with male controls, female cases with female controls and male cases with female cases.

Study Setting

The patients were advised to avoid the drinks and smokes which contain caffeine and nicotine at least 12 h before the recording. They were also told to avoid strenuous activities such as running and jumping at least 2 h before the recordings. Patients were advised to take light meal containing more carbohydrate and less fat and also to take 6-8 h of deep sleep in the previous night. All tests were performed in late morning, after a light breakfast. The temperature of the laboratory was maintained at 25°C ± 2°C with minimum light and noise. The patients were briefed about the various procedures. The height and weight were measured and body mass index was calculated. The patients were allowed to lie down on the bed and were given 10-15 min of rest. With digital BP apparatus (Omron Health Care co. Limited, Japan), the resting BP was measured and electrocardiography (ECG) and respiration were recorded by POLYRITE-D (RMS, Chandigarh, India). Further, HR was computed from the ECG.

DBT

In sitting posture, patient breathes deeply and evenly at 6 breaths per minutes (5 s in, 5 s out) for 3 cycles (30 s). Count "IN-2-3-4-5-OUT-2-3-4-5-as they do. Greatest HR difference is measured during each cycle and average of the 3 differences is considered. Normal: >15 beats/min; Borderline: 11-14 beats/min and Abnormal: <10 beats/min. Furthermore, the average of the maximum RR interval during expiration divided by the average minimum RR interval during inspiration gave the expiration: inspiration (E: I) ratio. Normal range for the E: I ratio is ≥1.21.

IHGT

The dynamometer (Anand Agencies, Pune, India) having a scale in kilograms (0-100) and a marker to show the grip strength were used for isometric exercise test. In this study, 30% of maximum voluntary contraction was used by both cases and controls for 5 min. As per the international standard, the handgrip dynamometer is used in two ways for the test. First, maintaining the handgrip at 50% of the maximum voluntary force generated for up to 1 min, and second, by maintaining the handgrip at 30% of maximum force for 5 min. In this study, 30% of the maximum voluntary force was maintained for 5 min and the systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured at every 1 min, 3 min and 5 min. Normal: >16 mmHg. Borderline: 11-15 mmHg. Abnormal: <10 mm.

Statistical Analysis

Data are presented in the form of mean and standard error of mean. Statistical Analysis is performed using Graph Pad Prism version-6. Unpaired Student's *t*-test and two-way ANNOVA was used wherever required. $P < 0.05$ was considered as significant.

RESULTS

An initial ECG and BP were recorded before the beginning of the maneuver. The increase or decrease in the cardiovascular parameters during the maneuver was considered on the basis of comparisons with the initial findings. Furthermore, the comparisons were made between male cases with male controls, female cases with female controls, and male cases with female cases.

DBT

In this study, the mean HR changes during deep breathing in male cases are 10.1 ± 0.50 bpm versus male controls of 15.4 ± 0.41 bpm. When compared, it was found significantly different ($P < 0.05$ for unpaired t-test). The mean HR changes in female cases are 10.4 ± 0.72 bpm versus female controls of 13.5 ± 1.02 bpm ($P < 0.05$ for unpaired *t*-test). The mean HR changes in male cases are 10.1 ± 0.50 bpm versus female cases of 10.4 ± 0.72 bpm ($P > 0.05$; Figure 1 and Table 1). The international normative HR response to deep breathing is ≥15 bpm, borderline between 11 and 14 bpm and abnormal if it is ≤10 bpm.

The mean E: I ratio of male cases is 1.12 ± 0.02 versus male controls of 1.16 ± 0.02. When compared, it was not found significantly different ($P > 0.05$ for unpaired *t*-test). The mean E: I ratio of female cases is 1.10 ± 0.1 versus female controls of 1.13 ± 0.1 ($P > 0.05$). The mean E:I ratio of male cases is 1.12 ± 0.02 versus female cases of 1.10 ± 0.1 ($P > 0.05$; Figure 1 and Table 1). The international normative E: I ratio of RR intervals is ≥1.21, it is considered abnormal if it is ≤1.21.

IHGT

The SBP recorded at zero time was considered as the initial SBP in the entire four groups. At 1 min after the onset of maneuver, there is an increase in the SBP, DBP, and HR, which is maintained at that level up to 5 min. In the male cases, the handgrip induced SBP changes observed at 1 min (138.0 ± 0.8 mm Hg), 3 min (138.0 ± 1.34 mm Hg) and 5 min (137.0 ± 1.45 mm Hg) were not different than the male controls at 1 min (138.0 ± 1.7 mm Hg), 3 min (139.0 ± 1.35 mm Hg)

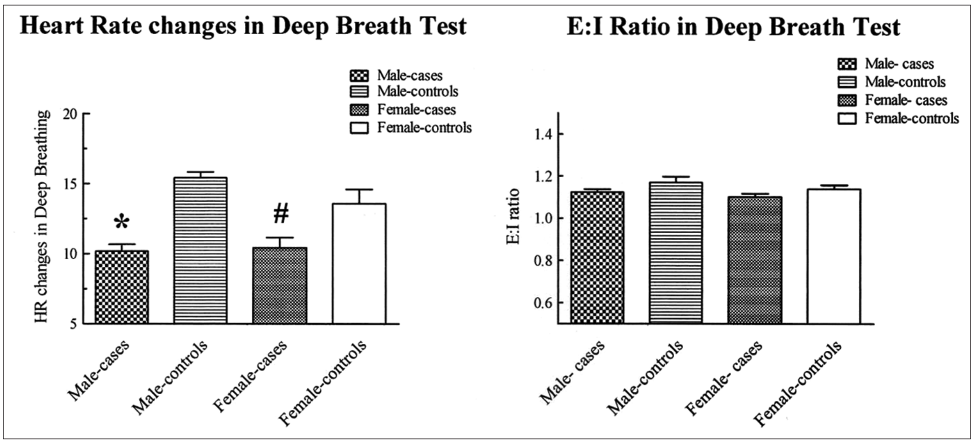

Figure 1: Histograms showing mean ± standard error of mean value of heart rate changes and expiration: inspiration ratio changes during Deep Breathing Test of male cases, female cases, male controls and female controls. *,# $P < 0.05$ (unpaired *t*-test) as compared to male and female controls respectively

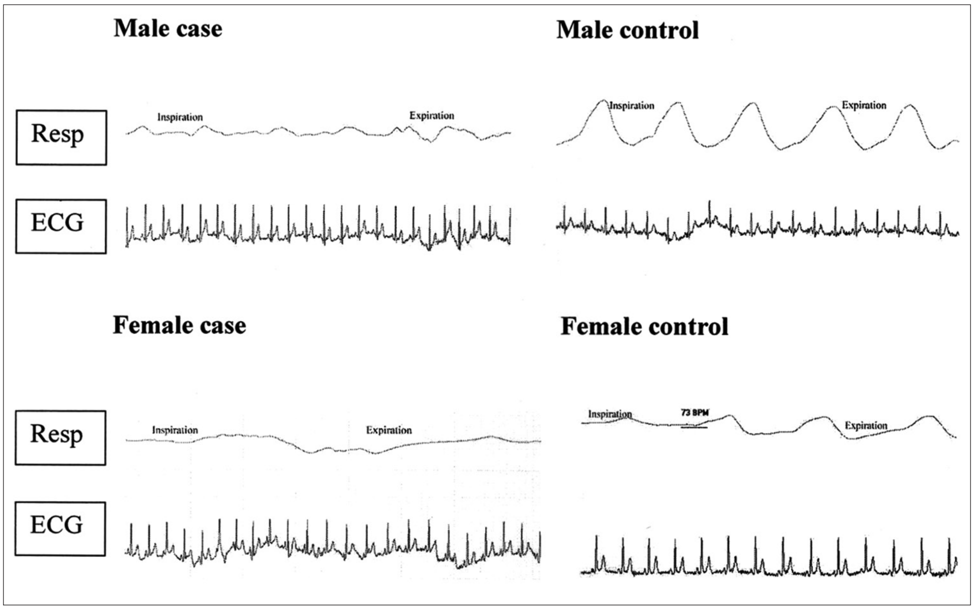

Figure 2: Original tracings showing deep breathing test in male cases, female cases, male controls and female controls. Speed = 15 mm/s, Sensitivity = 500 µv for respectively and 50 µv for electrocardiography

and 5 min (140.0 ± 1.58 mm Hg), respectively (Figures 2 and 3, Table 1). When two-way ANOVA was applied, it was not found significantly different ($P > 0.05$).

The handgrip induced SBP changes observed in the female cases at 1 min (145.8 ± 2.84 mm Hg), 3 min (147.6 ± 2.74 mm Hg) and 5 min (144.0 ± 1.83 mm Hg) were significantly different than the female controls at 1 min (136.3 ± 1.03 mm Hg), 3 min (136.4 ± 0.99 mm Hg) and 5 min (137.3 ± 1.12 mm Hg), respectively. When two-way ANOVA was applied, it was found significantly different ($P < 0.05$; Figures 2 and 3, Table 1).

Table 1: Comparison of parameters in both groups in both gender

Parameters	Male cases (Mean age: 38±2.22 years)				Male controls (Mean age: 35±2.22 years)			
Deep breath test								
ΔHR	10.1±0.50				15.4±0.41			
E:I ratio	1.12±0.02				1.16±0.02			
Handgrip test	**Time in minutes**				**Time in minutes**			
	0	**1**	**3**	**5**	**0**	**1**	**3**	**5**
SBP (in mm Hg)	124±0.78	138±0.8	138±1.34	137±1.45	128±1.47	138±1.7	139±1.35	140±1.58
DBP (in mm Hg)	79.08±1.07	93.44±1.57	92.68±1.29	92.7±1.24	77.43±1.32	91.71±1.37	92.33±1.04	94.47±1.15
HR (in bpm)	80.2±1.78	85.82±1.04	87.64±1.48	87.12±1.12	68.75±1.12	76.06±1.42	77.94±1.47	79.43±1.49
Parameters	**Female cases (Mean age: 40.5±2.00 years)**				**Female controls (Mean age: 39.6±1.19 years)**			
Deep breath test								
ΔHR	10.4±0.72				13.5±1.02			
E:I ratio	1.10±0.10				1.13±0.01			
Handgrip test	**Time in minutes**				**Time in minutes**			
	0	**1**	**3**	**5**	**0**	**1**	**3**	**5**
SBP (in mm Hg)	136.78±2.26	145.85±2.84	147.60±2.74	144±1.83	118.64±1.23	136.28±1.03	136.4±0.99	137.28±1.12
DBP (in mm Hg)	83.10±1.18	102.82±3.54	101.42±2.20	94.96±1.81	76.10±1.19	87.53±1.56	89.92±1.78	87.67±1.35
HR (in bpm)	84.5±1.43	90.64±0.74	94.28±1.99	91.85±1.47	69.28±0.98	84.71±1.13	87.14±1.55	85.64±1.25

HR: Heart rate, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, E:I: Expiration:Inspiration

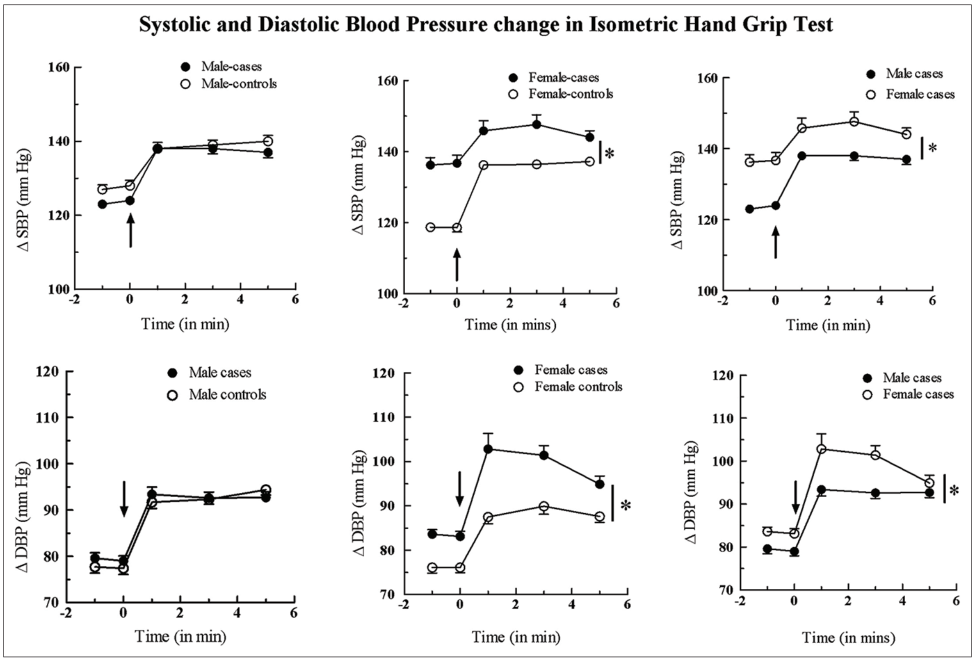

Figure 3: Time-response relationship curve showing mean ± standard error of mean value of systolic blood pressure and diastolic blood pressure of male cases, female cases, male controls and female controls during isometric handgrip test. Arrow indicates the time of beginning of maneuver. *$P < 0.05$ (two way ANOVA)

The handgrip induced SBP changes observed in the male cases at 1 min (138.0 ± 0.8 mm Hg), 3 min (138.0 ± 1.34 mm Hg) and 5 min (137.0 ± 1.45 mm Hg) were significantly different than female cases at 1 min (145.8 ± 2.84 mm Hg), 3 min (147.6 ± 2.74 mm Hg) and 5 min (144.0 ± 1.83 mm Hg), respectively ($P < 0.05$ for two-way ANOVA; Figures 2 and 3, Table 1).

The DBP recorded at zero time was considered as the initial DBP in the entire four groups. In the male cases, the handgrip induced DBP changes observed at 1 min (93.4 ± 1.57 mm Hg), 3 min (92.6 ± 1.29 mm Hg) and 5 min (92.7 ± 1.24 mm Hg) were not different than the male controls at 1 min (91.7 ± 1.37 mm Hg), 3 min (92.3 ± 1.04 mm Hg) and 5 min (94.4 ± 1.15 mm Hg), respectively ($P > 0.05$ for two-way ANOVA; Figures 2 and 3, Table 1).

The handgrip induced DBP changes observed in female cases at 1 min (102.8 ± 3.54 mm Hg), 3 min (101.4 ± 2.20 mm Hg) and 5 min (94.9 ± 1.81 mm Hg) were significantly different than the female controls at 1 min (87.5 ± 1.56 mm Hg), 3 min (89.9 ± 1.78 mm Hg) and 5 min (87.6 ± 1.35 mm Hg), respectively ($P < 0.05$ for two-way ANOVA; Figure 3).

The handgrip induced DBP changes observed in the male cases at 1 min (93.4 ± 1.57 mm Hg), 3 min (92.6 ± 1.29 mm Hg) and 5 min (92.7 ± 1.24 mm Hg) were significantly different than female cases at 1 min (102.8 ± 3.54 mm Hg), 3 min (101.4 ± 2.20 mm Hg) and 5 min (94.9 ± 1.81 mm Hg), respectively ($P < 0.05$ for two-way ANOVA; Figure 3 and Table 1).

The HR recorded at zero time was considered as the initial HR in all the groups. The handgrip induced HR changes observed in the male cases at 1 min (85.8 ± 1.04 bpm), 3 min (87.6 ± 1.48 bpm) and 5 min (87.1 ± 1.12 bpm) were significantly different than the male controls at 1 min (76.0 ± 1.42 bpm), 3 min (77.9 ± 1.47 bpm) and 5 min (79.4 ± 1.49 bpm), respectively ($P < 0.05$ for two-way ANOVA; Figures 2 and 4, Table 1).

The handgrip induced HR changes observed in the female cases at 1 min (90.6 ± 0.74 bpm), 3 min (94.2 ± 1.99 bpm) and 5 min (91.8 ± 1.47 bpm) were found significantly different than the female controls at 1 min (84.7 ± 1.13 bpm), 3 min (87.1 ± 1.55 bpm) and 5 min (85.6 ± 1.25 bpm), respectively ($P < 0.05$ for two-way ANOVA; Figure 4 and Table 1).

The handgrip induced HR changes observed in the male cases at 1 min (85.8 ± 1.04 bpm), 3 min (87.6 ± 1.48 bpm) and 5 min (87.1 ± 1.12 bpm) were found significantly different than female cases at 1 min (90.6 ± 0.74 bpm), 3 min (94.2 ± 1.99 bpm) and 5 min (91.8 ± 1.47 bpm), respectively ($P < 0.05$ for two-way ANOVA; Figure 4 and Table 1).

DISCUSSION

The sympathetic and parasympathetic systems are two dynamic systems of the ANS which balances the cardiovascular and other visceral functions. The ANS, in turn, may be modulated by the exposure of chronic pain. This assumption is based on the fact that blocking the efferent sympathetic supply to the affected region relieves the pain.[9] The arterial and cardiorespiratory barorecptor reflex arcs are involved in cardiac autonomic control that gets activated after stimulation.[10] This forms the basis of assessing ANS by performing provocative maneuvers known as cardiovascular reflex tests like DBT and IHGT.

In the DBT, there is a significant decrease in mean HR changes of male cases and female cases as compared to the male controls and female controls, respectively, indicating decreased parasympathetic reactivity. This is supported by the study elsewhere in which the parasympathetic loss is shown in the rheumatoid arthritis patients.[11] There were no significant differences in the HR changes in the male cases versus female cases indicating less correlation between gender differences which is supported by the study conducted elsewhere.[12] In healthy young individuals breathing at normal rate, the HR varies with the phases of respiration, which accelerates during inspiration and decelerates during expiration, especially if the depth of breathing is increased. This sinus arrhythmia is a normal phenomenon and is primarily due to fluctuations in parasympathetic output

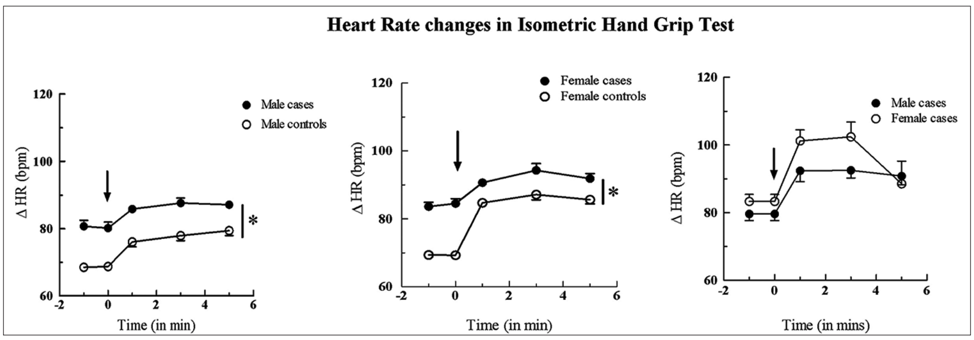

Figure 4: Time-response relationship curve showing mean ± standard mean of error value of heart rate changes of male cases, female cases, male controls and female controls during isometric handgrip test. Arrow indicates the time of beginning of maneuver. *$P < 0.05$ (two-way ANOVA)

to the heart. During inspiration, impulses in the vagi from the stretch receptors in the lung inhibit the cardioinhibitory areas in medulla oblongata. The tonic vagal discharge that keeps the HR slow decreases, therefore the HR rises.[13] Keeping above physiological explanations for the HR, our results indicates reduced parasympathetic reactivity in cases exposed to chronic pain in comparison to their controls, both in males and females. When E: I ratio of male cases versus male controls, female cases versus female controls and male cases versus female cases were compared, no significant differences were found showing less correlation between these groups.

In the studies elsewhere, it is shown that the rise in SBP was more marked in the men after the activities like walking and cycling[14] and women have a dull adrenaline rise in response to postural changes.[15,16] The effects of isometric exercise on the circulatory system are reflexively mediated; the reflex consists of two phases. The initial phase is the result of parasympathetic withdrawal since the effects of this phase on HR can be easily blocked with atropine.[17] The second phase is due to an active stimulation of the sympathetic system because its effects on the heart and peripheral vessels can be abolished with the addition of propranolol and phenoxybenzamine, respectively.[17,18] In this study, IHGT showed significant SBP changes during the maneuver between female cases versus female controls and female cases versus male cases. These findings indicate that sympathetic reactivity in the female cases is more than the female controls and in the female cases more than the male cases. The probable reasons for the decreased sympathetic responses in the male cases may be more sympathetic loss in male cases than the female cases due to exposure of chronic pain. There is no difference in SBP between male cases versus male controls, indicating less association between these groups. The changes in DBP in female cases are significantly higher than the female controls and also higher than the male cases. These changes are consistent with our findings of the SBP changes for the same group, indicating the increased sympathetic reactivity in these groups. The DBP changes in the male cases versus male controls are not different like SBP changes in the same group which indicate that in the male cases sympathetic loss is more than the female cases. This may be the probable reason for the decreased DBP reactivity in the male cases.

The HR changes during the maneuver between male cases versus male controls, female case versus female controls, and male cases versus female cases are significantly different. These results indicate that in male and female cases the parasympathetic reactivity is decreased though, this parasympatholytic effect is seen more in the female cases than the male cases as supported by other workers.[11] The decreased parasympathetic reactivity may be due to the exposure of chronic pain in the patients which, in turn, might be responsible for the alterations in the ANS.

CONCLUSION

The autonomic responses in DBT indicate the parasympatholytic actions in male and female cases which are further supported by the tachycardia in these groups during IHGT. The BP responses are more pronounce in the female cases than the female control and male cases indicating sympatholytic actions in the later groups. Therefore, HR changes may be indicative of parasympathetic loss in female cases and BP changes of sympathetic loss in the male cases.

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