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RESEARCH ARTICLE

Assessment of heart rate variability in the patients suffering with chronic pain of musculoskeletal origin

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ABSTRACT

Background: Prolonged pain of musculoskeletal origin can cause changes in autonomic outflow and thereby cardiovascular system. Various studies have been conducted showing the effect of chronic pain on heart rate variability (HRV), but the same study has not been conducted in the population of Eastern Uttar Pradesh. **Aims and Objectives:** This study was conducted to assess the effects of chronic pain on cardiovascular autonomic control in male cases versus male controls and female cases versus female controls. **Materials and Methods:** The patients were selected from the pain clinic out patient department with chronicity of >6 months duration and severity of >3 on visual analog scale. Age-sex matched controls were also selected. Electrocardiogram was recorded in the resting state and was analyzed for the HRV by using time and frequency domains. **Results:** In male cases, maximum RR interval, minimum RR interval, mean RR interval and in female cases, minimum RR is significantly different than male and female controls, respectively ($P < 0.05$). In frequency domain, low frequency/high frequency (L.F./H.F) ratio in male cases and L.F.m^2 in female cases are different than male and female controls, respectively. **Conclusion:** The observations reveal that there is a decrease in parasympathetic activity and an increase in the sympathetic activity in the cases as compared to their age-sex matched controls leading to the shifting of sympathovagal balance toward the sympathetic side. The pattern of changes is similar, both in male cases versus male controls and female cases versus female controls with little difference in the magnitude.

KEY WORDS: Chronic Pain, Heart Rate Variability, Sympathovagal Balance, Pain and Autonomic Nervous System

INTRODUCTION

Pain is the leading cause of disablement in the society, but the sensitivity for the pain is different in the different individuals. No universal objective assessment scale has been made yet for the measurement of pain as it mainly depends on the emotional responses of the individuals. In a study elsewhere, a correlation between heart rate variability (HRV) and emotional changes has been shown.[1] It is now clear that pain contains prominent affective-motivational component.[2] It is also clear that the sensory and affective components of pain are deeply entangled but have separate neural circuitry.[3-6] The unpleasantness of pain alarms the person to take measures against the diseases and also stimulates the homeostatic machinery for the physiological responses required for the survival of the body.[7]

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Many ongoing researches have shown correlation between chronic pains and cardiovascular changes which are supposed to be mediated by baroreceptors.[8] Changes in the functions of autonomic nervous system (ANS) have been also reported in the conditions such as fibromyalgia, migraine, and chronic neck and shoulder pain.[9-11]

The clinical importance of HRV was noticed in the 1980s when it became clear that HRV is a strong and independent predictor of mortality after the acute myocardial infarction.[12-14] The cardiac automaticity is intrinsic property of various pacemaker tissues; HR and rhythm are mainly under the control of the ANS.[15] The HR is mainly regulated by the vagal efferents in the basal condition. During the challenges, it is modulated by the interplay between vagal and sympathetic activity.

The chronic pain of musculoskeletal origin is very severe and prolonged which is sufficient to alter the basal autonomic tone. It has also been shown elsewhere[16,17] that the autonomic responses to the pain also vary with the variation in the gender.

Although some studies have been done on the association between chronic pain and autonomic changes,[18] the same study has not been done in the population of Eastern Uttar Pradesh, India, so for best of our knowledge is concern. Therefore, this study was conducted to evaluate the changes in the HRV of the male cases versus male controls and female cases versus female controls to understand the effects of chronic pain on the autonomic responses.

MATERIALS AND METHODS

All the experiments were performed in the Autonomic Function Test Lab, Department of Physiology, Institute of Medical Sciences, Banaras Hindu University, Varanasi after obtaining the Ethical Clearance from the Institute Ethical Committee. This study was conducted to compare the HRV in the male cases versus age-sex matched male controls and female cases versus age-sex matched female controls.

Selection of Cases and Controls

The patients suffering with chronic pain of musculoskeletal origin of severity >3 on visual analog scale and duration of >6 months were included in this study. The history of chronic illness such as diabetes mellitus, hypertension, uremia, hyper/hypothyroidsm, and the medication such as calcium channel blocker, antidepressant, neuroleptics, diuretics, antiepileptic, and alpha/beta blockers was considered as exclusion criteria for the selection of patients. The age-sex matched healthy persons were selected for the comparisons of the HRV parameters and defined as control. In the females, the first week of menstrual period was selected for the recording of the tests to avoid the diurnal variations. 50 male cases and 28 female cases were selected from the pain clinic, based on the above-mentioned exclusion and inclusion criteria. The patients were chosen from the pain clinic outpatient department (OPD) during the 1 year of the period who visited the OPD with chief complaint of pain. The same numbers of age-sex matched controls were also selected in this study. All the observations were categorized into 4 groups for the purpose of comparisons of their HRV responses. All the HRV parameters of male cases were compared with male controls and female cases with female controls to compare the effects of chronic pain on autonomic responses.

Study Design

The details regarding the method of recording and laboratory conditions are described by the same author elsewhere.[19] But in short, the patients were briefed about the tests to be performed on them. Then, they were asked to lie down comfortably on the bed and allowed to take rest for 15 min for the stabilization of the ANS. Further, resting blood pressure, respiration rate along with the electrocardiogram (ECG) were recorded. The ECG recording was done in standers limb Lead-II configuration using polyrite-D (RMS, Chandigarh, India). The recording was made for 600 s. A 50 Hz notch filter was used to remove power line noise, and electromagnetic interferences were also minimized. The recording machine was grounded with a proper wire connecting the earth. The signal was processed using RMS polyrite software. The recorded ECG signal was stored on a personal computer and was analyzed later. A careful manual editing was done by visual inspection to mark the peaks. This was done to remove the artifacts as well as insert missing peaks or delete false peaks. Abnormal beats were identified and dealt with adequately, while recordings with a higher number of ectopic beats were discarded from analysis. The analysis of the detected RR waveform was carried out in two domains: Time domain and frequency domain.

In the time domain analysis, RR interval (the minimum, maximum, max/min ratio and mean RR interval), SDNN (standard deviation of the RR interval), RMSSD (the square root of the mean of the sum of the squares of differences between adjacent RR interval), NN50 (The number of interval difference of successive RR intervals >50 m of RR interval), and the pNN 50 (the proportion derived by dividing NN50 by the total number of RR intervals) were used as a parameter.

In the frequency domain analysis, fast Fourier transformation was used for the spectral power density of the different component frequencies in the HR. A hamming window was used, and the power spectrum was subsequently divided into three frequency bands: VLF-0.001 to 0.04 Hz, LF-0.040 to 0.15 Hz and HF-0.15 to 0.4 Hz. The low frequency (L.F.) nu (L.F normalized unit), high frequency (H.F.)nu, L.F.m^2 (L.F absolute unit) H.F.m^2 (H.F absolute unit), and L.H./H.F. ratio were computed from the software.

Statistical Analysis

Pooled data from the recordings are presented in the form of mean and standard error of the mean. Statistical analysis was performed using Graph Pad Prism version-6. Unpaired student's *t*-test and two-way analysis of variance (ANOVA) was used wherever required. $P < 0.05$ was considered as significant.

RESULTS

The HRV parameters were analyzed using time domain and frequency domain methods for the comparisons of autonomic responses in the male cases versus male controls and female cases versus female controls as differential autonomic responses have been shown due to the gender differences.

Time domains

The maximum RR (max RR) interval of male cases is 0.9 ± 0.02 s versus male controls of 1.0 ± 0.02 s, when compared; it was found significantly lesser ($P < 0.05$; Figure 1). Max RR interval of female cases is 0.8 ± 0.03 s versus max RR interval of female controls of 0.85 ± 0.04 s, when compared; it was not significantly lesser ($P > 0.05$; Figure 2).

The minimum RR (min RR) interval of male cases is 0.6 ± 0.02 s versus male controls of 0.75 ± 0.02 s, when compared; it was found significantly lesser ($P < 0.05$; Figure 1). Min RR interval of female cases is 0.6 ± 0.01 s versus female controls of 0.75 ± 0.03 s, when compared; it was found significantly lesser ($P < 0.05$; Figure 2).

The max/min RR ratio of male cases is 1.3 ± 0.04 versus male controls of 1.2 ± 0.03 and female cases is 1.3 ± 0.05 versus female controls of 1.2 ± 0.03. When compared, it was not found significantly greater than the later ($P > 0.05$; Figures 1 and 2).

The mean RR interval of male cases is 0.7 ± 0.02 s versus male controls of 0.9 ± 0.02 s, when compared; it was found significantly lesser ($P < 0.05$; Figure 3). Mean RR interval of female cases is 0.6 ± 0.02 s versus female controls of 0.7 ± 0.02 s, when compared; it was not found significantly lesser ($P > 0.05$; Figure 2).

The mean SDNN of male cases is 51.7 ± 5.28 versus male controls of 45.9 ± 3.72 and of female cases is 36.8 ± 4.02 versus female controls of 30.9 ± 4.41. When compared, it was not found significantly greater ($P > 0.05$; Figures 1 and 2).

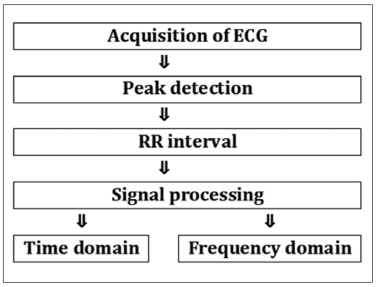

Figure 1: Flow chart showing acquisition of data

The mean RMSSD of male cases is 30.5 ± 2.81 versus male controls of 36.8 ± 4.04 and of female cases is 19.9 ± 2.59 versus female controls of 20.9 ± 3.75. When compared, it was not found significantly lesser ($p > 0.05$; Figures 1 and 2).

The mean NN50 of male cases is 34.8 ± 7.83 count versus male controls of 29.7 ± 6.16 count and of female cases is 14 ± 6.19 count versus female controls of 11.4 ± 5.82 count. When compared, it was not found significantly greater ($P > 0.05$; Figures 1 and 2).

The mean pNN50 of male cases is 16.0 ± 3.01% versus male controls of 19.6 ± 4.51% and of female cases is 6.0 ± 3.01% versus female controls of 6.5 ± 3.30%. When compared, it was not found significantly lesser ($P > 0.05$; Figures 1 and 2).

Frequency Domains

In male cases, the mean L.F normalized unit (L.F.nu), H.F normalized unit (H.F.nu), L.F absolute unit ($L.F.m^2$) and H.F absolute unit ($H.F.m^2$) value is not significantly different than the male controls (Figure 4). However, the L.F./H.F. ratio in the male cases is 6.8 ± 1.5 versus male control of 3.7 ± 0.16) which is significantly greater than the male controls ($P < 0.05$; Figure 4).

In female cases, the mean value of L.F.nu, H.F.nu and H.F absolute unit ($H.F.m^2$) is not significantly different than the female controls but in the female cases, the $L.F.m^2$ value is significantly greater than the female controls ($P < 0.05$; Figure 4). The L.F./H.F. ratio in the female cases is 4.7 ± 0.58 versus female control of 3.8 ± 0.45 which is not significantly greater than the female controls ($P > 0.05$; Figure 5).

DISCUSSION

In the 1970's, some scientists[20] developed a number of simple bedside tests of short-term RR differences to detect autonomic neuropathy in diabetic patients. Later after a decade, another group of scientists[21] introduced power spectral analysis of HR fluctuations to quantitatively evaluate beat-to-beat cardiovascular control. Since then a lot of work has been done in identifying correlations between HRV and chronic pain.[18,22-24] Studies indicate that the involvement of the ANS at both the systemic and local levels is an important element of the pathogenesis of chronic musculoskeletal pain. It is also hypothesized that the treatment of chronic musculoskeletal disorders will improve the ANS balance which in turn will improve the cardiovascular functions.

In our study, we have done both time domain and frequency domain analysis of HRV in the resting state. Although, the task force has advised that the frequency domain parameters are important for a short period of recording and time domain for long period of recording of ECG. As per the task force,

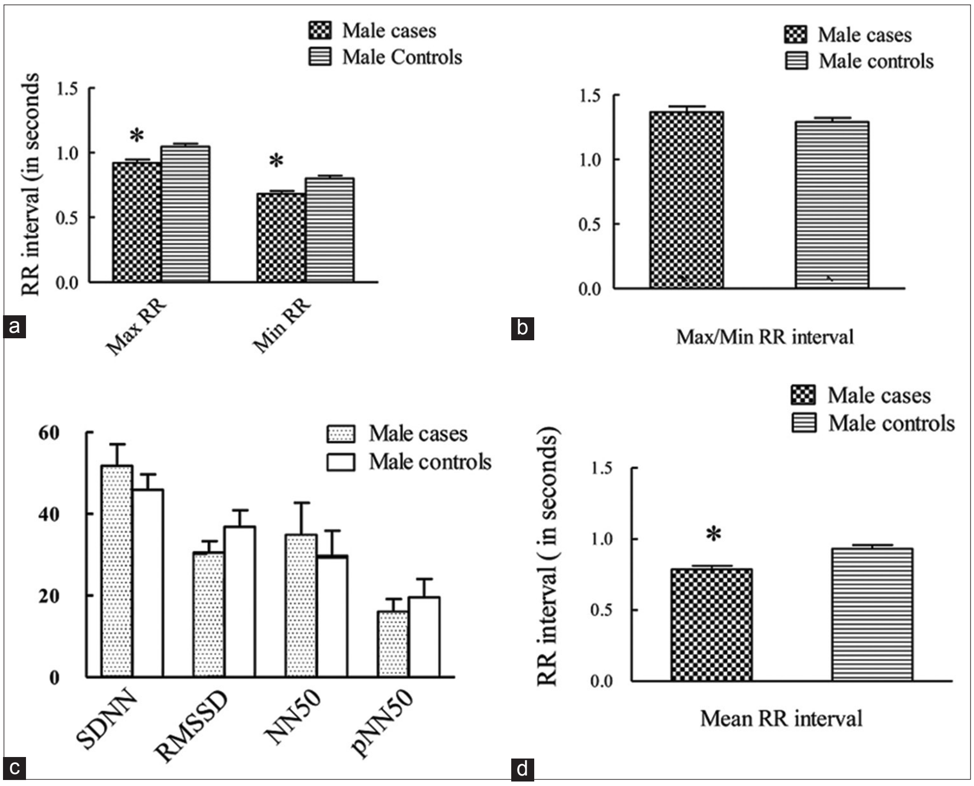

Figure 2: Time domain measures of heart rate variability in male cases and male controls. (a) RR interval maximum and minimum (b) Maximum/Minimum ratio of RR interval (c) SDNN-standard deviation of RRI's, RMSSD - root means of squared successive RRI's, NN50-number of interval difference of successive RR intervals >50 ms of RR interval (d) mean RR interval. An asterisk *indicates *P*<0.05.

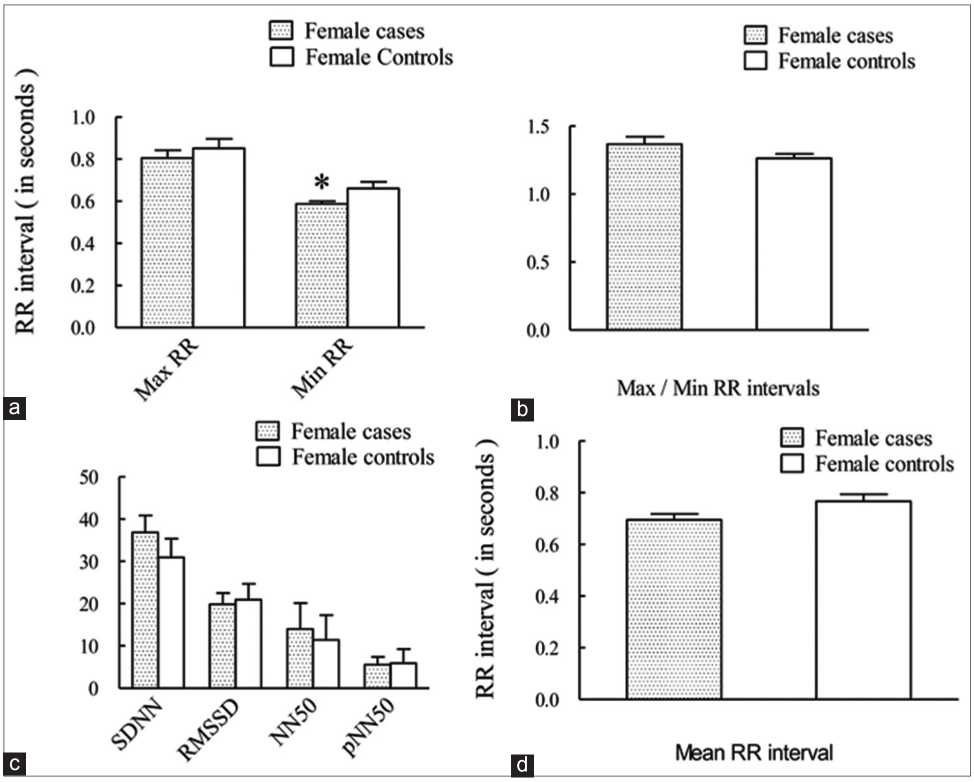

Figure 3: Time domain measures of heart rate variability in female cases and female controls, (a) RR interval maximum and minimum, (b) Maximum/minimum ratio of RR interval, (c) SDNN-standard deviation of RRI's, RMSSD-root means of squared successive RRI's, NN50-number of interval difference of successive RR intervals >50 ms of RR interval (d) mean RR interval. An asterisk *indicates *P*<0.05

the simplest time domain that can be measured is the mean RR interval. It has a reciprocal relationship with HR. Some reporters[25] have also shown their serious concern over the failure to report mean RR intervals in the studies.

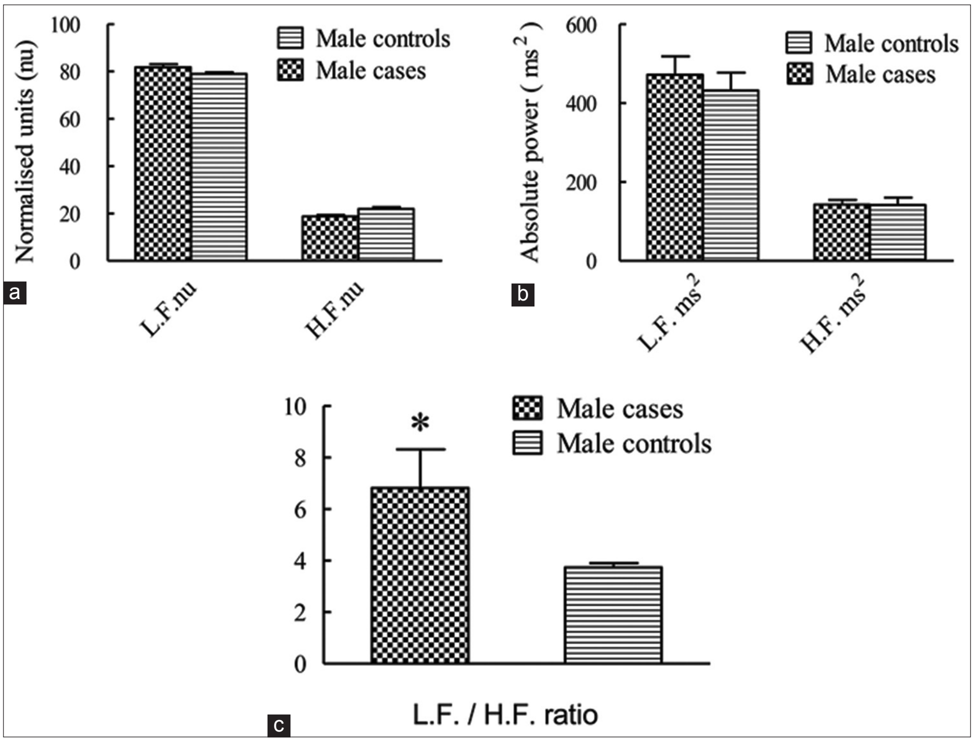

Figure 4: Frequency domain measures of heart rate variability in male cases and male controls (a) - low frequency (L.F.) and high frequency (H.F.) normalized units (b) L.F. and H.F. absolute units m^2 (c) L.F./H.F. ratio. An asterisk *indicates *P*<0.05

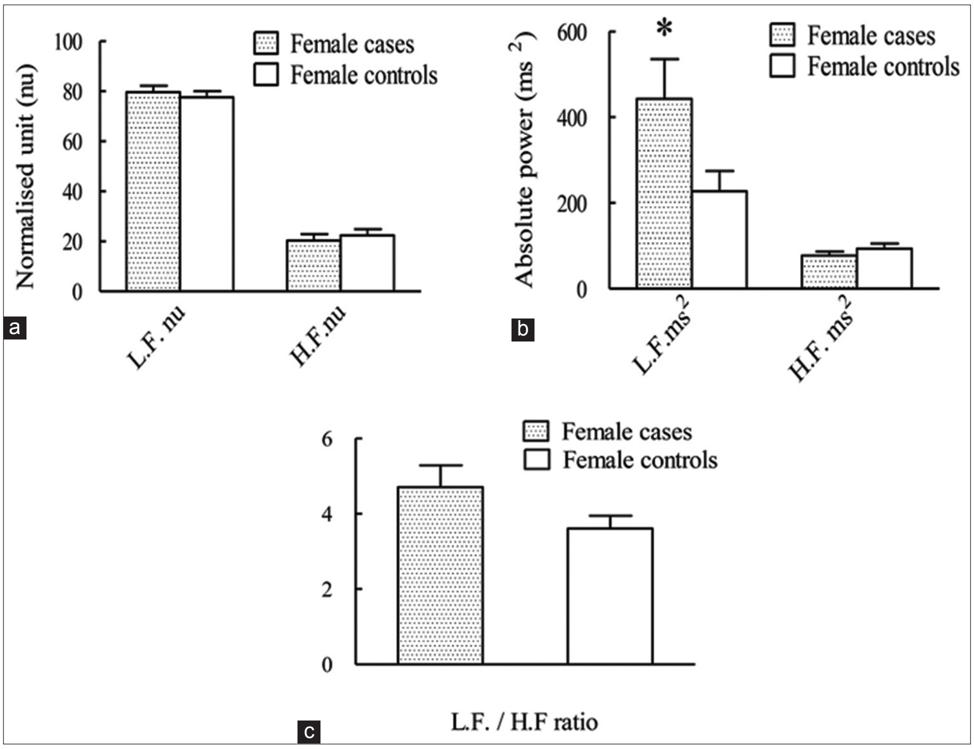

Figure 5: Frequency domain measures of heart rate variability in female cases and female controls, (a) L.F. - low frequency and H.F. - high frequency normalized units (b) L.F. and H.F. absolute units ms^2 (c) L.F./H.F. ratio. An asterisk *indicates *P*<0.05

In this study, max RR and min RR in male cases are significantly lesser than the male controls indicating the increased sympathetic tone in male cases than their controls. Decreased mean RR interval in male cases than the male controls further supports the increased sympathetic activity as decreased mean RR interval indicates the increase in HR. This change in HR indicates that in the cases, there is overactivation of the sympathetic nervous system/withdrawal of parasympathetic nervous system leading to shifting of the sympathovagal balance in the sympathetic side.

SDNN reflects the overall sympathetic and parasympathetic influences on HRV. When SDNN value of male cases was compared with the male controls and female cases with female controls, both the male cases and female cases showed an increase in SDNN depicting an overall increase in HRV in the patients exposed to chronic pain which further indicates that ANS responses to the noxious stimuli are normal.

The most commonly used measures derived from interval differences include RMSSD as this method is preferred to pNN50 and NN50 because it has better statistical properties. Since, RMSSD, NN50, and pNN50 signify parasympathetic activities; therefore, we can infer that in the male cases the changes in the cardiac autonomic tone are parasympatholytic as compared to male controls. The pattern of HRV responses in the female cases versus female controls is almost similar to the male cases versus male controls except the differences in magnitude.

A frequency domain analysis method was selected over a time domain approach because frequency based analysis provides more accurate information of frequency components of HRV and therefore a clearer interpretation of parasympathetic and sympathetic interaction. Measurement of L.F. and H.F. power components is usually made in absolute values of power (ms^2), but L.F. and H.F. may also be measured in normalized units (nu). The representation of L.F.(nu) and H.F. (nu) emphasizes the balanced behavior of the sympathetic and parasympathetic nervous system.

In this study, the absolute power of L.F. is increased in male cases as compared to male controls which are indicative of the sympathetic over activity in the male cases as compared to male controls. Absolute power of H.F. indicates the parasympathetic tone. The absolute power of H.F. is same in male cases as compared to male controls, but there is a slight decrease in the normalized H.F. in male cases as compared to male controls, showing reduced parasympathetic tone.

The L.F./H.F. ratio is indicative of the sympathovagal balance. An increase in this ratio indicates the shifting of sympathovagal balance in the sympathetic side and vice versa. In this study, the L.F./H.F. ratio is increased in the male cases as compared to male controls indicating the shifting of sympathovagal tone toward the sympathetic side. This shifting may be because of decreased parasympathetic tone which is indicated as decrease in absolute power of H.F.

In female cases, the absolute power of L.F. has increased significantly as compared to their controls, but there is no change in the L.F. in normalized units. This observation shows that in female cases there is sympathetic overactivation in comparison to the female controls and thus shifting of the sympathovagal balance toward the sympathetic side. In female cases, the H.F. value is lesser as compared to their controls both in normalized unit and absolute power, though not significantly. The L.F./H.F. ratio has increased in female cases than female controls, though not significantly, indicating the shifting of sympathovagal balance toward the sympathetic side. This may be again mainly because of decreased parasympathetic tone.

CONCLUSION

In conclusion, our observations reveal that there is a decrease in parasympathetic activity and an increase in the sympathetic activity in the cases as compared to their age-sex matched controls leading to the shifting of sympathovagal balance toward the sympathetic side. The pattern of changes is similar, both in male cases versus male controls and female cases versus female controls with little difference in the magnitude indicating the similar effects of exposure of chronic pain on autonomic tone. The reasons for these changes may be the decreased parasympathetic tone more than the sympathetic overactivation.

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