Original Research Article **Allied Science**

International Journal of Pharma and Bio Sciences

ISSN 0975-6299

HEART RATE VARIABILITY IN CHRONIC PAIN PATIENTS: A STUDY ON GENDER DIFFERENCES

SANJEEV K. SINGH[1]*, ATANU ROY[2], AK TIWARI[1], PB SINGH[1]

[1]Department of Physiology, Institute of Medical Sciences, Banaras Hindu University, Varanasi.
[2]Department of Physiology, All India Institute of Medical Sciences, New Delhi.

ABSTRACT

Various studies have been conducted showing the effects of chronic pain on HRV but the same study has not been conducted yet in the Eastern Uttar Pradesh. Present study was conducted to assess the effects of chronic pain on HRV. The patients were chosen from the Pain Clinic with chronicity of > 6 months duration and severity of > 3 on visual analogue scale. The age-sex matched controls were also selected. ECG was recorded in the resting state and was analyzed for the HRV. Max RR interval, Min RR interval, SDNN, RMSSD, pNN50 and mean RR interval in male cases is significantly different than the same parameters of female cases ($p < 0.05$). The frequency domain parameters are not different in male cases and male controls than the female cases and female controls respectively except L.F.ms^2. The observations reveal that the sympathetic tone has either increased or remained normal and the parasympathetic tone has decreased in both, male and female cases indicating the shifting of sympathovagal balance in the sympathetic side. Though the gender related responses are not very consistent, but it can be concluded that the HRV responses are different in males than the female groups.

KEY WORDS: ***Pain, HRV, Hormones, Gender and Autonomic Nervous System***

SANJEEV K. SINGH*

Department of Physiology, Institute of Medical Sciences, Banaras Hindu University, Varanasi.

Received on: 16-02-2017
Revised and Accepted on: 17-03-2017
DOI: http://dx.doi.org/10.22376/ijpbs.2017.8.2.b463-469

INTRODUCTION

The clinical relevance of heart rate variability (HRV) was first registered by a scientist[1] in the year 1965 and was noted that fetal distress was preceded by alterations in inter beat intervals before any appreciable change occurred in the heart rate itself. The clinical relevance of HRV was noticed in the late 1980s when it became clear that HRV is a strong and independent predictor of mortality after the acute myocardial infarction[2-4]. After the availability of new electrocardiographic recorders, HRV has become the potential parameter to provide the information regarding the physiological and pathological conditions of the cardiac muscles activity. The cardiac automaticity is an intrinsic character of pacemaker tissues; heart rate and rhythm are mainly under the control of the autonomic nervous system[5]. The parasympathetic effects on heart rate are mediated via release of acetylcholine by the vagus nerve. Under basal conditions, vagal tone regulates the heart rate and variations in heart rate are mainly dependent on vagal modulation. During the challenges, it is modulated by the interaction between vagal and sympathetic activity constantly. The chronic pain originating from the skeletal system is very severe and prolonged which is sufficient to alter the basal physiological activity of the autonomic nervous system. It is well established that the chronic pain causes alteration in the autonomic outflow. The autonomic alterations and cardiorespiratory changes are suggested to be mediated reflexly by the activation of the peripheral nociceptors[6-7]. The involvement of vanilloid receptor-1 (VR1) has also been shown in this regard[8]. It has also been shown elsewhere[9-10] that the autonomic responses to the pain vary with the gender which is supposed to be mediated by the male and female hormones. Although some studies have been done on the correlation between the chronic pain and autonomic alterations[11] but the same study has not been done yet in the population of Eastern Uttar Pradesh, India. Therefore, this study was conducted to compare the HRV of the male cases versus female cases so that the gender related differences in autonomic responses could be understood. Further, the HRV of male controls was also compared with the female controls to understand the gender related differences in autonomic responses in the population of Eastern Uttar Pradesh, India.

MATERIALS AND METHODS

All the patients were informed about the study and were enlisted after their written consent. Ethical clearance (Ref No. Dean/2014-15/EC/512) was taken before the commencement of the study from the Institute Ethical Committee. This study was conducted to compare the autonomic functions in the male versus female chronic pain patients and also to compare between male and female age-sex matched controls.

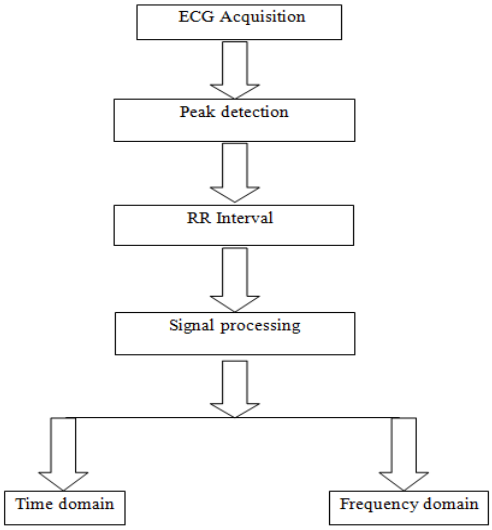
Selection of Cases and Controls

The patients suffering with chronic pain of skeletal origin of severity > 3 on visual analogue score (VAS) and duration of > 6 month were included in this study with no history of chronic illness like diabetes mellitus, hypertension, uremia, hyper/hypothyroidsm etc. Any medication like calcium channel blocker, antidepressant, neuroleptics, diuretics, antiepileptic & alpha and beta blockers was considered for exclusion criteria. The age-sex matched healthy persons were selected for the comparisons of the HRV parameters and defined as control. In the females, first week of menstrual cycle was chosen for the performance of the tests to avoid the endocrinal variations. 50 male cases and 28 female cases were selected from the Pain Clinic, based on the exclusion and inclusion criteria as mentioned above in this paragraph. Non-random (convenient sampling) method was done for the selection of the cases during the period of 1 year. The same numbers of age-sex matched controls were also selected in this study. All the observations were categorized in to four groups: male cases, female cases, male Controls and female controls. All the parameters of male cases were compared with female cases and male controls with female controls to compare the effect of gender difference on the autonomic responses.

Study design

The method of recording is described in details by the same author elsewhere[12]. But in brief, the patient was asked to lie down comfortably and after taking rest for 15 minutes, the ECG was recorded. ECG recording was taken in standers Lead II configuration using POLYRITE-D (RMS, Chandigarh, India). The temperature of the laboratory was maintained at 25 ± 2 ^{0}C, with minimum light and noise. The patients were briefed about the various procedures. The recording was made for 600 seconds. A 50 Hz notch filter was used to remove power line noise while electromagnetic interferences were also minimized, since the laboratory was shielded from electromagnetic influences. The signal was processed using RMS POLYRITE software. The recorded ECG signal was stored on a personal computer and was analyzed later offline. A careful manual editing was then performed by visual inspection to mark the peaks. This was to remove artifacts as well as insert missing peaks or delete false peaks and artifacts. 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.

Flow chart explaining the acquisition of data



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 greater than 50ms of RR interval) and the pNN 50 (the proportion derived by diving NN50 by the total number of RR intervals) were used as a parameter. In the frequency domain analysis, Fast Fourier Transformation (FFT) was used for the spectral power density of the different component frequencies in the heart rate. 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 L.F.nu (low frequency normalized unit), H.F.nu (high frequency normalized unit), L.F.ms^2 (low frequency absolute unit) H.F.ms^2 (high frequency absolute unit) and L.H./H.F. ratio was recorded from the software. Pooled data from the recordings are presented in the form of mean and SEM. Statistical Analysis was done by using Graph Pad Prism version-6. Unpaired student's t-test and two way ANNOVA was used wherever required. P value < 0.05 was considered as significant.

RESULTS

The heart rate variability (HRV) parameters were analyzed using time domain and frequency domain methods for the comparisons of autonomic responses in the male cases versus female cases and male controls versus female controls as differential autonomic responses are proposed due to the gender differences.

HRV analysis of male cases and female cases
Time domain methods

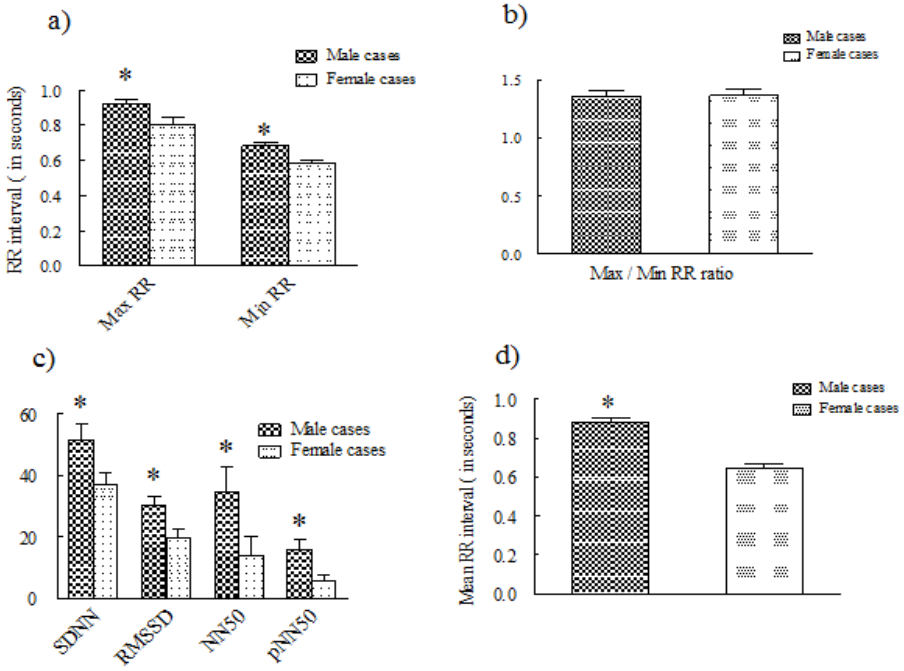


Figure 1

Time domain measures of heart rate variability (HRV) in male cases and female cases, a) RR interval maximum and minimum, b) Maximum / Minimum ratio of RR interval, c) SDNN-standard deviation of RR intervals, RMSSD-root means of squared successive RR intervals, NN50- number of interval difference of successive RR intervals greater than 50 ms of RR interval, d) mean RR interval. An asterisk "*" indicates p < 0.05.

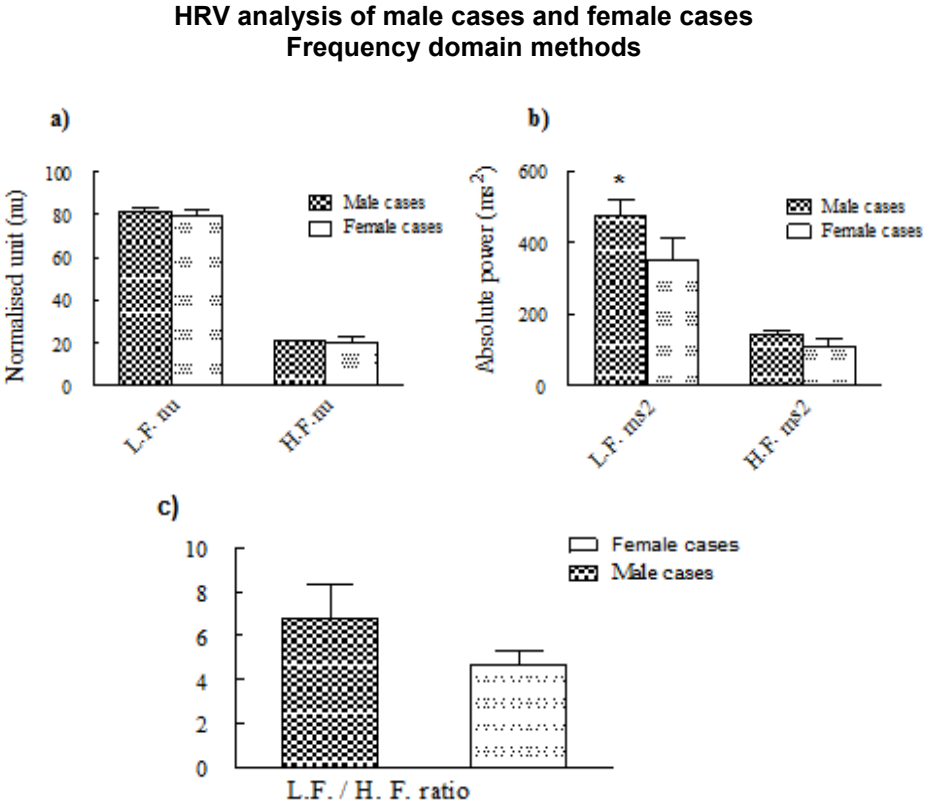


Figure 2

Frequency domain measures of heart rate variability (HRV) in male cases and female cases, a) L.F.nu-Low Frequency normalized unit and H.F.nu-High Frequency normalized unit, b) L.F.ms^2-Low Frequency absolute units and H.F.ms^2-High Frequency absolute unit, c) L.F. / H.F. ratio. An asterisk "*" indicates p < 0.05.

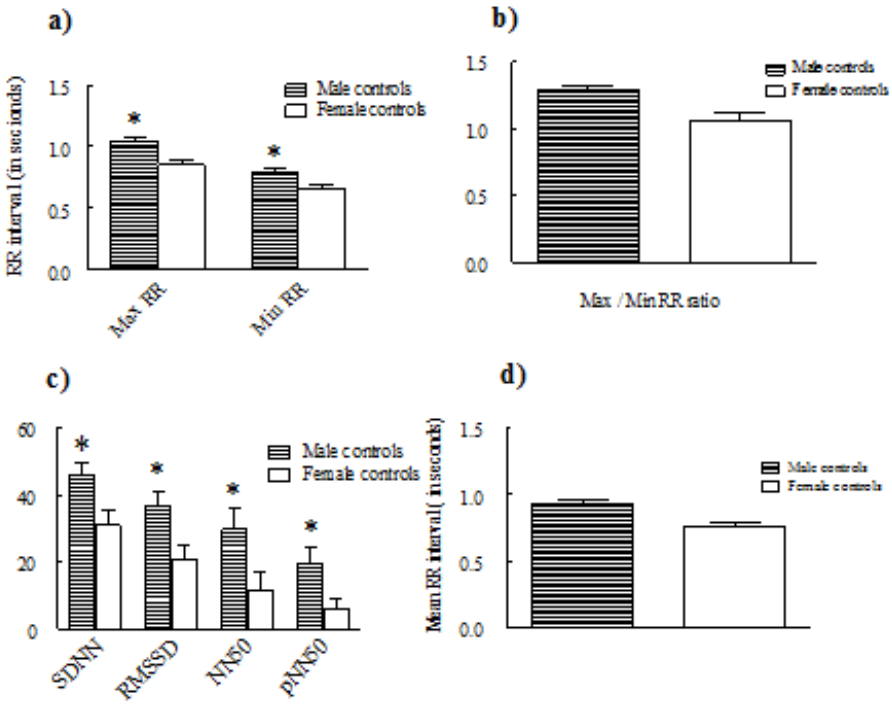


Figure 3

Time domain measures of heart rate variability (HRV) in male controls and female controls, a) RR interval maximum and minimum, b) Maximum / Minimum ratio of RR interval, c) SDNN-standard deviation of RR intervals, RMSSD-root means of squared successive RR intervals, NN50- number of interval difference of successive RR intervals greater than 50 ms of RR interval, d) mean RR interval. An asterisk "*" indicates p < 0.05.

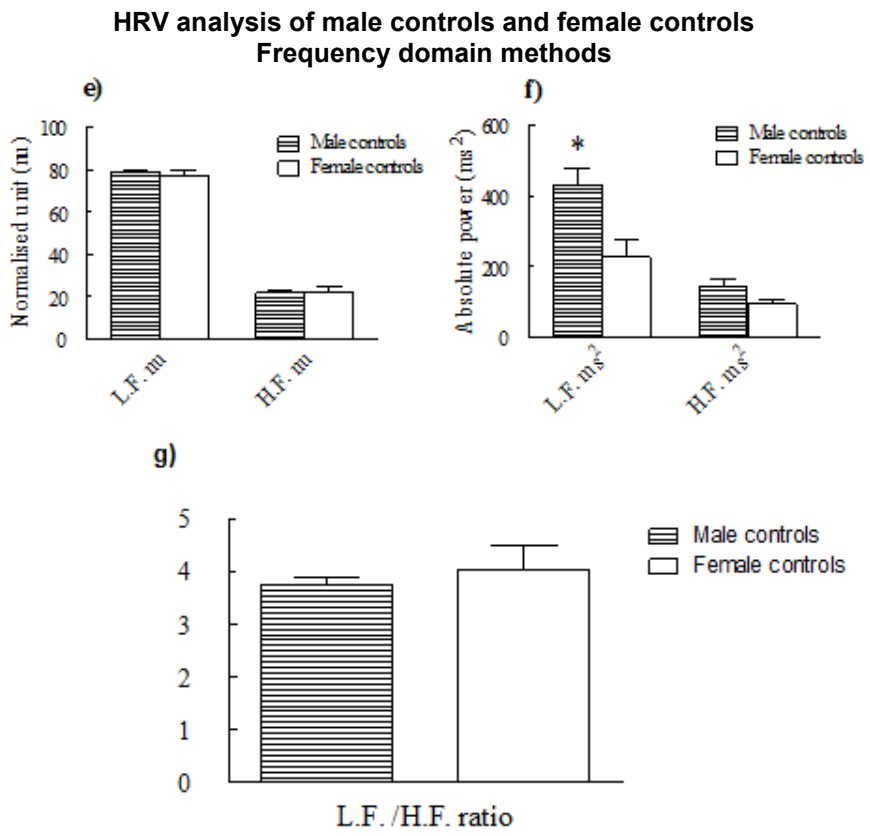


Figure 4

Frequency domain measures of heart rate variability (HRV) in male control and female controls, a) L.F.nu-Low Frequency normalized unit and H.F.nu-High Frequency normalized unit, b) L.F.ms^2-Low Frequency absolute units and H.F.ms^2-High Frequency absolute unit, c) L.F. / H.F. ratio. An asterisk "*" indicates p < 0.05.

Time domains

Maximum RR interval of male cases is 0.9 ± 0.02 s and female cases is 0.8 ± 0.03 s which on comparison was found significantly different than each other (p < 0.05; Fig 1). Maximum RR interval of male controls is 1.0 ± 0.02 s versus female controls of 0.8 ± 0.04 s which was found significantly different than each other (p < 0.05; Fig 3). Minimum RR interval of male cases is 0.6 ± 0.02 s and female cases is 0.5 ± 0.01 s which was found significantly different than each other (p < 0.05 ; Fig 1). Minimum RR interval of male controls is 0.7 ± 0.02 s versus female controls of 0.6 ± 0.03 s which was found significantly different than each other (p < 0.05; Fig 3). Max/min RR ratio of male cases versus female cases and male controls versus female controls is not different than each other (Fig 1 and 3). Mean RR interval of male cases is 0.8 ± 0.02 s and female cases is 0.7 ± 0.02 s which on comparison was found significantly different (p < 0.05; Fig 1). Mean RR interval of male controls is not different than female controls (Fig 3). Mean SDNN of male cases (52 ± 3.21) is different than the female cases (38 ± 3.51; Fig 1) and it is also significantly different in male controls (45.9 ± 3.72 ms) than the female controls (30.9 ± 4.41 ms; p < 0.05, Fig 3). Mean RMSSD of male cases is 30.5 ± 2.81 ms versus female cases is 19.9 ± 2.59 ms which on comparison was found significantly different (p < 0.05; Fig 1). Mean RMSSD of male controls is 36.8 ± 4.04 ms versus female controls of 20.9 ± 3.75 ms which was found significantly different than each other (p < 0.05, Fig 3). Mean NN50 of male cases is 34.8 ± 7.83 count versus female cases is 14 ± 6.19 count which on comparison was found significantly different (Fig 1). Mean NN50 of male controls (30 ± 2.3) is also different than the female controls (6 ± 3.2, Fig 3). Mean pNN50 of male cases is 16.0 ± 3.01 % versus female cases is 5.5 ± 1.85 % which on comparison was found significantly different (p < 0.05; Fig 1). Mean pNN50 of male controls is not different than the female controls (Fig 3).

Frequency Domains

The mean low frequency normalized unit (L.F.nu), High frequency normalized unit (H.F.nu) and high frequency absolute unit (H.F.ms^2) value in male cases is not different than the female cases (Fig 2). But, the L.F.ms^2 in male cases is different than the female cases (Fig 2). The mean L.F.nu and H.F.nu value in male controls is not different than the female controls but the L.F.ms^2 is significantly different in male controls than the female controls (Fig 4). The mean L.F: H.F ratio in male cases is not different than the female cases (Fig 2) and the same is also not different in the male controls than the female controls (Fig 4).

DISCUSSIONS

The autonomic nervous system (ANS) consists of two dynamic systems, sympathetic and parasympathetic systems which balance the cardiovascular and other visceral functions of the body. The basal level of ANS activity may be affected by the exposure of chronic pain. In this study, the heart rate variability (HRV) was assessed and compared in male cases versus female cases and the male controls versus female controls to understand the effect of gender differences on autonomic responses as reported elsewhere[9-10]. Both time domain and frequency domain analysis of HRV was performed in the resting state. Though, the Task

Force of The European Society of Cardiology and The North American Society of Pacing and Electrophysiology has advised that the frequency domain parameters are important for short period of recording and time domain for long period of recording of ECG. As per the task force, the simplest time domain that can be measured is the mean RR interval. In the present study, when male cases were compared with the female cases there was a significant increase in the mean RR interval in male cases, indicating a decreased HR in male cases in comparison to the female cases. Since, both the groups are exposed to chronic pain and the male cases are showing comparative bradycardia and female cases are showing comparative tachycardia which indicates that the compliance to the pain in the male cases is better than the female cases. The male controls has similar mean RR interval than the female controls which indicates that the basal sympathovagal balance is similar in both the group. Standard deviation of the NN interval (SDNN) reflects all the cyclic components responsible for variability in the period of recording and thus is an estimate of overall HRV. The male cases had an increased SDNN as compared to the female cases and male controls showed a significant increase in SDNN when compared with the female controls, depicting probably a gender specific differential response to chronic pain. The role of gender differences in the autonomic nervous system response may be due to the effects of male and female sex hormones which has been reported elsewhere[12]. Such existing hormone levels may also produce differences between pre- and post-menopausal women and amongst pre-menopausal women at different phases of the menstrual cycle[10]. As per the Task force recommendation out of most commonly used interval differences, the RMSSD method is preferred to pNN50 and NN50 because it has better statistical properties. The male cases showed significant increase in RMSSD as compared to female cases and the male controls also showed significant increase when compared with the female controls indicating overall increase in HRV. These findings indicate that there is an increase in sympathetic activity in both the group but more in males than the females. The probable reasons for such changes may be the better compliance to the pain in male cases than the female cases indicating differential responses to the gender[9-10]. Measurement of L.F. and H.F. power components is generally made in absolute values of power (ms^2), which represent the relative value of each power component in proportion to the total power minus the VLF component. In the present study, the absolute power of L.F. is compared between the male and female cases, the male cases showed higher absolute power as compared to the female cases but little or no change in normalized units. These observations indicate the increased autonomic reactivity in male cases than the female cases in response to the exposure of chronic pain. Male cases showed higher L.F./H.F. ratio than the female cases which is again supporting our finding as it is with L.F.ms^2 findings in the male cases versus female cases. Further in a study elsewhere, it has been shown that in the chronic pain male cases there is sympathetic loss and in female cases there is parasympathetic loss[12]. The male controls showed higher absolute power of L.F. as compared to the female controls and no change in normalized units. This observation indicates that in male controls sympathetic activity is more than female control as shown elsewhere[13-17]. The gender-related differences in the ANS reactivity have been noted by several workers previously[9]. For the parasympathetic system, it has been reported that estrogen has a facilitating effect on cardiac vagal function[18]. The opinions on gender-related difference in HRV are still different in the literature[4,19-20].

CONCLUSION

In conclusion, observations reveal that the sympathetic tone has either increased or remained normal and the parasympathetic tone has decreased in the chronic pain patients, both in males and females in comparison to their age-sex matched controls, indicating the shifting of sympathovagal balance in the sympathetic side. Though the gender related responses are not very consistent but it can be concluded that the autonomic responses in the males were greater than the female as found elsewhere.

CONFLICT OF INTEREST

Conflict of interest declared none.

REFERENCES

1. Hon EH, Lee ST. The fetal electrocaerdiogram. 3 Display techniques. Ame j Obstet Gynecol. 1965;91:56-60.
2. Kleiger RE, Miller JP, Bigger JT, Moss AJ, and the Multicenter Post-Infarction Research Group. Decreased heart rate variability and its association with increased mortality after acute myocardial infarction. Am J Cardiol 1987; 59: 256–62.
3. Malik M, Farrell T, Cripps T, Camm AJ. Heart rate variability in relation to prognosis after myocardial infarction: selection of optimal processing techniques. Eur Heart J 1989; 10: 1060–74.
4. Bigger JT, Fleiss JL, Steinman RC, Rolnitzky LM, Kleiger RE, Rottman JN. Frequency domain measures of heartperiod variability and mortality after myocardial infarction. Circulation 1992; 85: 164–71.
5. Jalife J, Michaels DC. Neural control of sinoatrial pacemaker activity. In: Levy MN, Schwartz PJ, eds. Vagal Control of the Heart: Experimental Basis And Clinical Implications. Armonk: Futura 1994:173–205.
6. Donnerer J, Lembeck F. Analysis of the effects of intravenously injected capsaicin in the rat. Naunyn-Schmiedeberg's Arch. Pharmacol 1982; 320: 54-7.
7. Donnerer J, Lembeck F. Capsaicin-induced reflex fall in rat blood pressure is mediated by afferent substance P-containing neurons via a reflex centre in the brainstem. Naunyn-Schmiedeberg's Arch. Pharmacol 1983; 324: 293-5.
8. Smith PJW, McQueen DS. Anandamide induces cardiovascular and respiratory reflexes via

vasosensory nerves in anaesthetized rat. *Br.* J. Pharmacol 2001; 134: 655-63.
9. Gustafson AB, Kalkhoff RK. Influence of sex and obesity on plasma catecholamine response to isometric exercise. J Clin Endocrinol Metab 1982; 55: 703–8.
10. Anthony M. Dart*, Xiao-Jun Du, Bronwyn A. Kingwell: Gender, sex hormones and autonomic nervous control of the cardiovascular system, Cardiovascular Research 2002, 53; 678–87.
11. Azharuddin Fazalbhoy, Ingvars Birznieks and Vaughan G. Macefield; Individual differences in the cardiovascular responses to tonic muscle pain: parallel increases or decreases in muscle sympathetic nerve activity, blood pressure and heart rate. Exp Physiol 2012; 97(10): 1084–92
12. Roy A, Singh SK. Evaluation of cardiovascular autonomic control in chronic pain patients using isometric handgrip and deep breath maneuvers. National Journal of Physiology, Pharmacy and Pharmacology 2016; 6(5): 420-6.
13. Yamasaki Y, Kodama M, Matsuhisa M *et al.,* Diurnal heart rate variability in healthy subjects: effects of aging and sex difference. Am J Physiol 1996; 271: H303–H10.
14. Liao D, Barnes RW, Chambless LE, Simpson RJ, Sorlie P, Heiss G. Age, race, and sex differences in autonomic cardiac function measured by spectral analysis of heart rate variability: The ARIC study. Atherosclerosis Risk in Communities. Am J Cardiol 1995; 76: 906–12.
15. Kuo TB, Lin T, Yang CC, Li CL, Chen CF, Chou P. Effect of aging on gender differences in neural control of heart rate. Am J Physiol 1999; 277: H2233–H9.
16. Gregoire J, Tuck S, Yamamoto Y, Hughson RL. Heart rate variability at rest and exercise: influence of age, gender, and physical training. Can J Appl Physiol 1996; 21: 455–70.
17. Ryan SM, Goldberger AL, Pincus SM, Mietus J, Lipsitz LA.Gender- and age-related differences in heart rate dynamics: are women more complex than men? J Am Coll Cardiol 1994; 24: 1700–7.
18. Du XJ, Dart AM, Riemersma RA. Sex differences in the parasympathetic nerve control of rat heart. Clin. Exp. Pharmacol. Physiol 1994; 21: 485–93.
19. Umetani K, Singer DH, McCraty R, Atkinson M. Twenty four hour time domain heart rate variability and heart rate: relations to age and gender over nine decades. Journal of the American College of Cardiology 1998; 3: 593-601.
20. Merrugat J, Anto JM, Sala J, Masia R. Influence of gender in acute and long term cardiac mortality after a first myocardial infarction. J Clin Epidemiol 1994; 47: 111-8.

Reviewers of this article

Dr Amit Singh

Professor, Dept. of Physiology,
Uttarpradesh University of Medical
Sciences, Saifai ,Etawah ,India - 206130

Prof. Y. Prapurna Chandra Rao

Assistant Proffessor, KLE University,
Belgaum, Karnataka

Prof.Dr.K.Suriaprabha

Asst. Editor , International Journal
of Pharma and Bio sciences.

Prof.P.Muthuprasanna

Managing Editor , International
Journal of Pharma and Bio sciences.

We sincerely thank the above reviewers for peer reviewing the manuscript