Original Article

Access this article online

Quick Response Code:

Website: www.jehp.net

DOI: 10.4103/jehp.jehp_627_19

Depression affects autonomic system of the body? Yes, it does!

Sheena Singla, Shikha Jhamb, Kamal Dev Singh, Avnish Kumar

Abstract:

BACKGROUND: Depression is a disorder of the brain, a state of low mood and aversion to activity that can affect a person's thoughts, behavior, feelings, and sense of well-being and can cause alteration in sympathetic activity of the body, thus affecting heart rate variability (HRV).

AIM: The study was conducted to determine the effects of depression on HRV parameters in clinically known cases of depression.

MATERIALS AND METHODS: A cross-sectional (observational) study was conducted on fifty known patients of depression, aged 18–65 years, and fifty healthy, age-matched, normal controls. HRV test was conducted, and the results were analyzed statistically using Student's "*t*"-test for equal variance, for various parameters.

RESULTS: The study showed that the differences in mean R-R interval(s), mean HR (beats/min), very low frequency (VLF) power (milliseconds squared [ms^2]), and low frequency/high frequency (LF/HF) power (%) (LF/HF ratio) among controls and cases were statistically highly significant, while the differences in LF power (ms^2) in controls and cases were statistically significant. However, the differences in basic anthropometric parameters, STD (standard deviation of the normal to normal)(s), root mean square successive difference (ms), NN50 (count), pNN50 (%), VLF peak (Hz), LF peak (Hz), HF peak (Hz), HF power (ms^2), VLF power (%), LF power (%), HF power (%), LF power (nu), and HF power (nu) were found to be statistically insignificant.

CONCLUSION: Depression leads to changes in autonomic control of the body and changes the autonomic balance in favor of an increased sympathetic tone, which can be detected with fair accuracy with HRV analysis.

Keywords:

Cases, controls, depression, heart rate variability, patients

Introduction

Depression (major depressive disorder or clinical depression) is a common but serious mood disorder. It causes severe symptoms that affect how you feel, think, and handle daily activities, such as sleeping, eating, or working.[1]

Depression is a disorder of the brain. There are a variety of causes, including genetic, biological, environmental, and psychological factors. Depression can happen at any age, but it often begins in teens and young adults. It is much more common in women. Women can also get postpartum depression after the birth of a baby. Some people get seasonal affective disorder in the winter. Depression is one part of bipolar disorder.[2]

Anxiety disorders increase the risk of future cardiovascular disease (CVD) and mortality, even after controlling possible confounding factors such as smoking, lifestyle, and socioeconomic status, irrespective of a history of medical disorders. While impaired vagal function, indicated by reductions in heart rate variability (HRV), may be one mechanism linking anxiety disorders to

Department of Physiology, Government Medical College, Patiala, Punjab, India

Address for correspondence:
Dr. Shikha Jhamb, House No. E-8, Government Medical College, Patiala - 147 001, Punjab, India.
E-mail: dr.shikhajhamb@gmail.com

Received: 19-10-2019
Accepted: 18-03-2020
Published: 31-08-2020

How to cite this article: Singla S, Jhamb S, Singh KD, Kumar A. Depression affects autonomic system of the body? Yes, it does! J Edu Health Promot 2020;9:217.

CVD, prior studies have reported inconsistent findings highlighting the need for meta-analysis.[3]

To be diagnosed with depression, the symptoms must be present for at least 2 weeks.[1]

Symptoms can include:
- Feeling sad or "empty"
- Loss of interest in favorite activities
- Overeating, or not wanting to eat at all
- Not being able to sleep, or sleeping too much
- Feeling very tired
- Feeling hopeless, irritable, anxious, or guilty
- Aches or pains, headaches, cramps, or digestive problems
- Thoughts of death or suicide.[2]

Depression is most common in ages 18 to 25 (10.9%) and in individuals belonging to two or more races (10.5%). Women are twice as likely as men to have had a depressive episode, according to the NIMH and the World Health Organization (WHO). The WHO estimates that more than 300 million people worldwide suffer from depression. It is also the world's leading cause of disability.[4]

Depression is also associated with elevated HR and reduced HRV, which are known risk factors for cardiac morbidity and mortality that may explain the increased risk associated with depression.[5]

Heart rate variability

The human heart beat in a healthy individual is neither absolutely regular nor completely random. It varies based on the interplay between many factors including physical and mental stress, exercise, respiration, thermoregulation, blood pressure regulation, renin–angiotensin system, circadian rhythm, and other unknown complex mechanisms. This subtle fluctuation in sinus rhythm is known as HRV. HRV has proved to be a more sensitive tool for the detection of autonomic balance than mean HR. It is seen as reflective and predictive of general health and overall physiological wellness. HRV is one of the promising markers of autonomic activity. Variations in the HR are dependent on the activities of the sinoatrial (SA) node, which is the natural pacemaker of the heart innervated by the sympathetic and parasympathetic branches of the autonomic nervous system. The degree of balance between sympathetic and vagal nerve activity determines HRV.[6]

Currently, HRV is recognized as an effective and noninvasive tool for evaluating autonomic nervous system regulations of the heart.[7] HRV describes the variation between consecutive heart beats. The rhythm of the heart is controlled by SA node, which is modulated by both sympathetic and parasympathetic branches of the autonomic nervous system. Sympathetic activity tends to increase HR and its response is slow (few seconds). Parasympathetic activity, on the other hand, tends to decrease HR and mediates faster (0.2–0.6 s).[8]

The parasympathetic activity's influence on HR is modulated by acetylcholine released by the vagus nerve on the SA node and the sympathetic influence by the release of epinephrine and norepinephrine.[9]

The continuous modulation of the sympathetic and parasympathetic innervations results in variation in HRs. The most conspicuous periodic component of HRV is the so-called respiratory sinus arrhythmia which is considered to range from 0.15 to 0.4 Hz. In addition to the physiological influence of breathing on HRV, this high-frequency (HF) component is generally believed to be of parasympathetic origin. Another widely studied component of HRV is the low-frequency (LF) component usually ranging from 0.04 to 0.15 Hz including the component referred to as the 10-s rhythm or the Mayer wave. The rhythms within the LF band have been thought to be of both sympathetic and parasympathetic origin, even though some researchers have suggested them to be mainly of sympathetic origin.[8] The very low frequency (VLF) component accounts for all other HR changes including those associated with thermoregulation and hormonal and local factors.[10]

The HRV is evaluated by two ways: time domain analysis and frequency domain analysis.[11]

Frequency domain method, which is also known as power spectral density, provides the basic information on how power as an expression of variance distributes in the function of frequency.[6] VLF, LF, and HF powers are usually measured in absolute values of power (milliseconds squared [ms^2]). LF and HF can be also measured in normalized units (nu) to emphasize the controlled and balanced behavior of the two branches of the autonomic nervous system, as well as baroreflex responsiveness to beat-to-beat variation in arterial blood pressure. Normalization of LF and HF power tends to minimize the effect of the changes in the total power on the values of these two components. Normalized units and absolute values of LF and HF power should both be calculated to provide a better measurement of the degree of autonomic modulation rather than just the level of autonomic tone.[9]

The following parameters are calculated in time domain: mean R-R interval (sec), the standard deviation of intervals between normal beats (SDNN), mean

HR (per minute), the root mean square differences of successive NN intervals (RMSSD), the number of interval differences of successive NN intervals >50 ms (NN50), a measure of the number of adjacent NN intervals which differ by >50 ms (pNN50). On a standard electrocardiogram (ECG), the maximum upward deflection of a normal QRS complex is at the peak of the R-wave, and the duration between two adjacent R-wave peaks is termed as the R-R interval.[12]

According to a research conducted by the Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, in a time-domain analysis, higher values of the SDNN intervals, RMSSD, and percentage of adjacent normal R–R intervals 50 ms (pNN50) indicate stronger parasympathetic dominance. Among the frequency-domain measurement indicators, a HF denotes parasympathetic activity, and a LF is related to the activity of both the sympathetic nervous system and the parasympathetic nervous system.[13]

The term HRV refers, in general, to changes in heart beat interval which is a reciprocal of the HR. The starting point for HRV analysis is the ECG recording from which the HRV time series can be extracted. In the formulation of HRV time series, a fundamental issue is the determination of heart beat period.[8]

A study conducted in 2002 shows that in physically healthy depressed adults, HRV does not differ from healthy controls.[14]

A study conducted in 2008 shows that depression is associated with significantly lowered HRV.[15] The present study was necessitated because of conflicting reports. The aim of the present study was to assess the effect of depression on HRV, by conducting study on clinically known patients of depression in the age group of 18–65 years.

Materials and Methods

A cross-sectional (observational) study was conducted in the department of physiology in the institute during November 2017–November 2018. The participants were divided into two groups: (i) fifty known patients of depression (cases) and (ii) fifty age-matched, normal healthy subjects (controls). The study protocol was approved by the ethical committee of the institute. Written consent was obtained from all the enrolled individuals after explaining them the details of the study in their own language. The participants for the study (cases) were enrolled from patients attending the outdoor clinic of the Psychiatry Department of Government Medical College and Rajindra Hospital, Patiala, whereas the controls were volunteers from among the paramedical and lower staff of the institute.

The subject selection is based on exclusion–inclusion criteria.

Inclusion criteria (Patients were on regular treatment with antidepressants like escitalopram, sertraline).

1. Individuals in the age range of 18–65 years
2. Diagnosed and known cases of depression. Patients were on antidepressants like escitalopram, sertraline, fluoxetine.

Exclusion criteria (Hypertension, renal, endocrine, cardiovascular and respiratory disorders are known to affect autonomic system of the body in many ways; that's why these were chosen as exclusion criteria).

1. Patients with hypertension
2. Patients with renal and endocrine disorders
3. Patients with cardiovascular disorders
4. Patients with respiratory disorders

Medical examination

In every case selected, thorough and detailed history of depression was taken. The participants were diagnosed in accordance with the WHO's depression diagnostic Criteria ICD-10[16] and Hamilton's Rating Scale by the consultant psychiatrist.

Heart rate variability analysis

The HR of each participant was recorded by ECG monitoring, in RR mode (beat to beat), for 5 min at rest, in supine position, using "physiopac hardware" by Medicaid (manufacturers at SAS Nagar, Mohali, Punjab, India); HRV analysis was done as per the procedure given in the manual supplied by RMS Recorders and Medicare Systems (P) Ltd. (Chaunki, Haryana, India). The participant was allowed to relax on a comfortable chair with his/her back toward the recording machine. The following anthropometric parameters were measured according to standardized techniques: height (cm), weight (kg), and body mass index (BMI): BMI was calculated using Quetlet's Index:[17] BMI = weight (kg)/ height^2 (in m); body surface area (BSA): BSA was calculated using Dubois and Dubois formula:[18] BSA in $m^2 = 0.007184 \times \text{weight}^{0.425}$ (kg) $\times$ height $(m)^{0.725}$.

Statistical analysis

The results were compiled in the form of charts and graphs and statistically analyzed by using Student's "*t*"-test. Evaluation of the data was carried out by Microsoft Excel and SPSS/PC+(a statistical program to carry out analysis). "*P*" < 0.05 and 0.01 was considered statistically significant and highly significant, respectively.

Results

The comparison of age (in years), height (in centimeters), and weight (in kg) of controls and cases was done as shown in Table 1. There were no statistically significant differences between the basic data: age, height, and weight of both controls and cases.

The comparison of baseline variables, i.e., BMI (kg/m^2) and BSA (m^2) of controls and cases, was done as shown in Table 2. The differences in BSA and BMI of both controls and cases were found to be statistically insignificant.

The comparison of time domain analysis, i.e., mean RR(s), STD (SDNN)(s), mean HR (beats/min), RMSSD (ms), NN50 (count), and pNN50(%) of controls and cases, was done as shown in Table 3. The differences in mean RR and mean HR of controls and cases were statistically highly significant, with the values of mean RR higher among controls as compared to cases, and the values of mean HR higher among cases as compared to controls. The differences in STD (SDNN), RMSSD (ms), NN50 (count), and pNN50 (%) were found to be statistically insignificant.

The comparison of frequency domain analysis, i.e., VLF peak (Hz), LF peak (Hz), HF peak (Hz), VLF power (ms^2), LF power (ms^2), HF power (ms^2), VLF power (%), LF power (%), HF power (%), LF/HF ratio, LF power (nu), and HF power (nu), of controls and cases was done as shown in Table 4. The differences in VLF (power) (ms^2) and LF/HF (power %) (LF/HF ratio) of controls and cases were statistically highly significant, with values being much higher in cases as compared to controls, while the differences in LF (power) (ms^2) were statistically significant, with the values higher among cases. The differences in VLF (peak) (Hz), LF (peak) (Hz), HF (peak) (Hz), HF (power) (ms^2), VLF power (%), LF power (%), HF power (%), LF (power) (nu), and HF (power) (nu) were statistically insignificant.

Table 1: Comparison of mean and standard deviation of anthropometric parameters in controls and cases

Parameters	Group				*P*	Significance
	Control		Case			
	Mean	SD	Mean	SD		
Age (years)	39.96	14.74	39.58	13.89	0.44	NS
Height (cm)	175.08	5.31	175.08	5.62	0.50	NS
Weight (kg)	70.12	11.45	69.16	8.57	0.31	NS

NS: *P*>0.05, S: *P*<0.05, HS: *P*<0.01. NS=Not significant, HS=Highly significant, SD=Standard deviation, S=Significant

Table 2: Comparison of baseline variables in controls and cases

Parameters	Group				*P*	Significance
	Control		Case			
	Mean	SD	Mean	SD		
BMI (kg/m^2)	22.80	3.03	23.18	2.94	0.26	NS
BSA (m^2)	1.04	0.17	1.38	0.13	0.60	NS

NS: *P*>0.05, S: *P*<0.05, HS: *P*<0.01. BMI=Body mass index, SD=Standard deviation, BSA=Body surface area, NS=Not significant, HS=Highly significant, S=Significant

Discussion

The study was conducted on fifty patients of depression and fifty normal healthy controls to observe the effect of depression on HR, in the age group of 18–65 years. We studied mean RR, STD (SDNN), mean HR, RMSSD, NN50, and pNN50 in time domain analysis and VLF peak, LF peak, HF peak, VLF power, LF power, HF power, VLF power%, LF power%, HF power%, LF/HF ratio, LF power nu, and HF power nu in frequency domain analysis.

The LF component of HRV analysis reflects the sympathetic parameters, whereas the HF component of HRV analysis shows the parasympathetic activity of the body. If the values of LF component increase, it shows that the balance has shifted in favor of sympathetic system, and hence the sympathetic system in the body is overactive.

Higher values of LF/HF ratio also show increased sympathetic activity in the body.

A detailed comparison between our study and those derived from various other well-documented studies was done.

Table 3: Comparison of time domain analysis in controls and cases

Parameters	Group				*P*	Significance
	Control		Case			
	Mean	SD	Mean	SD		
Mean RR(s)	0.87	0.11	0.76	0.09	3.01E-07	HS
(SDNN)(s)	0.05	0.04	0.05	0.03	0.15	NS
Mean HR (beats/min)	70.82	9.90	79.45	7.22	1.53E-06	HS
RMSSD (ms)	38.30	25.80	37.21	26.89	0.41	NS
NN50 (count)	11.43	8.74	12.08	8.77	0.36	NS
pNN50 (%)	8.14	6.47	8.3	6.18	0.45	NS

NS: *P*>0.05, S: *P*<0.05, HS: *P*<0.01. RMSSD=Root mean square successive difference, HR=Heart rate, NS=Not significant, HS=Highly significant, SD=Standard deviation, S=Significant, SDNN=Standard deviation of the normal to normal intervals, RR=Mean interval (in seconds) between 2 consecutive R waves.

Table 4: Comparison of frequency domain analysis in control and cases

Parameters	Group				*P*	Significance
	Control		Case			
	Mean	SD	Mean	SD		
VLF (peak) (Hz)	0.02	0.00	0.02	0.00	0.3	NS
LF (peak) (Hz)	0.09	0.07	0.09	0.12	0.4	NS
HF (peak) (Hz)	0.2	0.21	0.17	0.03	0.45	NS
VLF (power) (ms^2)	5.5	8.22	9.86	9.68	0.008	HS
LF (power) (ms^2)	9.64	14.22	15.64	17.28	0.03	S
HF (power) (ms^2)	4.26	5.84	6.02	9.49	0.13	NS
VLF (power) (%)	24.10	17.56	27.92	14.49	0.11	NS
LF (power) (%)	50.46	15.93	53.23	13.75	0.17	NS
HF (power) (%)	25.45	14.32	19.07	11.77	0.8	NS
LF/HF (power %) (LF/HF ratio)	2.54	1.41	3.36	1.54	0.003	HS
LF (power) (nu)	66.71	14.47	74.70	11.95	0.1	NS
HF (power) (nu)	33.27	14.47	27.31	17.58	0.3	NS

NS: $P>0.05$, S: $P<0.05$, HS: $P<0.01$. LF=Low frequency, HF=High frequency, NS=Not significant, HS=Highly significant, SD=Standard deviation, S=Significant, VLF=Very low frequency

Comparison of anthropometric parameters

Tables 1 and 2 show the comparison of anthropometric parameters of controls and cases. There was no statistically significant difference in the mean age (years), mean height (cm), mean weight (kg), mean BMI (kg/m^2), and mean BSA (m^2) of controls and cases ($P > 0.05$). This may be due to methodological limitations and smaller sample size.

Comparison of time domain analysis

Table 3 shows the comparison of time domain analysis of controls and cases. Our study observed statistically highly significant differences in the mean RR of controls and cases ($P < 0.01$). It showed increase in the mean RR in controls as compared to cases. The values of the mean RR in the present study support the results obtained by Agelink *et al*. (2002),[19] Jonathan *et al*. (2005),[20] Kemp *et al*. (2012),[21] Brunoni *et al*. (2013),[22] Regan *et al*. (2014),[23] Sgoifo *et al*. (2016),[24] Paniccia *et al*. (2017),[25] and Chen *et al*. (2017).[26] The values of the mean RR in the present study are not in agreement with Sayar *et al*. (2002)[14] and Gehi *et al* (2005).[27] These contradictory findings may be due to variation in recording procedure, sample size, manual error, and sensitivity of machine.

No statistically significant differences were observed in the mean STD (SDNN) of controls and cases.

Statistically highly significant differences were observed in the mean HR of controls and cases ($P > 0.05$). Our study showed increase in mean HR of cases as compared to decrease in controls. The values of the mean HR in the present study are in agreement with those of Carney *et al*. (2001),[28] Agelink *et al*. (2002),[19] Jonathan *et al*. (2005),[20] Kemp *et al*. (2012),[21] Brunoni *et al*. (2013),[22] Regan *et al*. (2014),[23] Sgoifo *et al*. (2016),[24] Paniccia *et al*. (2017),[25] and Chen *et al*. (2017).[26] Our study is not in agreement with the findings of Sayar *et al*. (2002)[14] and Gehi *et al*. (2005).[27] These contradictory findings may be due to variation in recording procedure, sample size, manual error, and sensitivity of machine.

No statistically significant differences were found in RMSSD, NN50, and pNN50 of controls and cases ($P > 0.05$).

Comparison of frequency domain analysis

Table 4 shows the comparison of frequency domain analysis parameters in controls and cases. Our study observed no statistically significant differences in mean VLF peak, mean LF peak, and mean HF peak of controls and cases ($P > 0.05$). Our study observed highly statistically significant differences in mean VLF power (ms^2) of controls and cases ($P < 0.01$), with the values higher among cases as compared to controls. The values of the VLF power in the present study are in agreement of the findings of Carney *et al*. (2001),[28] Ha *et al*. (2015),[29] and Chen *et al*. (2017).[18] Statistically significant differences were observed in the mean LF power (ms^2) of controls and cases ($P < 0.05$), with values higher among cases as compared to controls. The values of the LF power in the present study are in agreement with those of Carney *et al*. (2001),[28] Wang *et al*. (2013),[30] and Chen *et al*. (2017).[22] No statistically significant differences were observed in mean HF power (ms^2) of controls and cases. No statistically significant differences were observed in mean HF power %, mean VLF power %, and mean LF power % of controls and cases. The study observed decrease in the mean LF/HF ratio of controls and increase in cases. Statistically highly significant differences were observed in the mean LF/HF ratio of controls and cases ($P < 0.01$). The values of the mean LF/HF ratio in the present study are in agreement with the findings of Carney *et al*. (2001),[28] Wang *et al*. (2013),[30] and Chen *et al*. (2017).[26] The values of the mean LF/HF ratio in the present study are not in agreement with those

of Royster *et al*. (2012).[31] These contradictory findings may be due to variation in recording procedure, sample size, manual error, and sensitivity of machine. LF/HF ratio is considered to mirror the sympathovagal balance or reflect the sympathetic modulations.[32] No statistically significant ($P > 0.05$) differences were observed in the mean LF (nu) and mean HF (nu) of controls and cases.

Our study observed that the values of mean LF power (ms^2) were very high in known cases of depression as compared to controls. In addition, the LF/HF ratio was very high in cases of depression as compared to controls. Both these findings demonstrate that the autonomic nervous system shifts in favor of sympathetic overactivity.

Alterations of autonomic nervous system functioning that promote vagal withdrawal are reflected in the reductions of HRV indices. A high sympathetic and a low cardiovagal activity in patients with major depression (MD) may contribute to the higher cardiac morbidity and mortality of MD patients. Depressed patients showed a higher HR and a significantly lower modulation of cardiovagal activity compared to controls. Sympathetic activity increases in depressed patients, and this enhancement is more obvious which expresses higher complexity of HRV time series. Parasympathetic nervous system of depressed patients is influenced by mental state, and they become dysfunctional under long-term depression.

Keeping in mind the prevalence of depression and its effects on the autonomic nervous system, it is suggested that HRV analysis may also be done as a part of routine screening procedures which are of vital importance in patients with depression.

Conclusion

The results of the present study demonstrate that the depressed patients influence HRV and change the autonomic balance in favor of an increased sympathetic tone. A high sympathetic and/or a low cardiovagal activity in patients with MD may contribute to the higher cardiac morbidity and mortality of MD patients. Parasympathetic nervous system of MD patients is influenced by mental state, and they become dysfunctional under long-term depression. Alterations of autonomic nervous system functioning that promote vagal withdrawal are reflected in the reductions of HRV indices.

Awareness should be created among health professionals involved directly or indirectly in the care of patients of depression and to inform the general public about the association of depression with the effects on HRV and autonomic nervous system. Education and treatment strategies have to be planned accordingly. Special care must be given to patients with depression before a significant change in HRV occurs. In addition, a close follow-up is necessary in patients with depression.

Limitations

- Small sample size of the study
- Methodological limitations
- Sensitivity of the machine
- Possible manual errors.

Acknowledgment

The authors are grateful to all the participants without whose co-ordination and active participation, this work would not have been fruitful. We are also thankful to the clinical labs, for their help and support.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest (None).

References

1. The National Institute of Mental Health: Available from: https://www.nimh.nih.gov/health/topics/depression/index.shtml. [Last accessed on 2018 Feb 25].
2. National Institutes of Health / U.S. National Library of Medicine. Available from: https://medlineplus.gov/depression. [Last accessed on 2018 Jan 11].
3. Chalmers JA, Quintana DS, Abbott MJ, Kemp AH. Anxiety disorders are associated with reduced heart rate variability: A meta-analysis. Front Psychiatry 2014;5:80.
4. Koskie B. Depression: Facts, Statistics and You; 2018. Available from: https://www.healthline.com/health/depression/facts-statistics- infographic#1. [Last accessed on 2019 Jul 25].
5. Carney RM, Freedland KE, Stein PK, Skala JA, Hoffman P, Jaffe AS. Change in heart rate and heart rate variability during treatment for depression in patients with coronary heart disease. Psychosom Med 2000;62:639-47.
6. Sathish B, Bhat R, Damodara M. Autonomic modulation in different phases of menstrual cycle in young and older Indian women. Int J Med Res 2013;1:12-6.
7. Lee CL, Chang WD. The effect of cigarette smoking on aerobic and anaerobic capacity and heart rate variability among female university students. Int J Womens Health 2013;5:667-79.
8. Tarvainen MP, Kubois NJ. HRV Users Guide. Ver. 2.1. Biosignal Analysis and Medical Imaging Group (BSAMIG), Department of Applied Physics, University of Eastern Finland, Kuopio, FINLAND. MATLAB. Copyright 1984-2012 The MathWorks, Inc. MATLAB is a registered trademark of The MathWorks, Inc. 2012. p. 8-12.
9. Gritti I, Defendi S, Mauri C, Banfi G, Duca P, Roi GS. Heart rate variability, standard of measurement, physiological interpretation and clinical use in mountain marathon runners during sleep and after acclimatization at 3480 m. J Behav Brain Sci 2013;3:26-48.
10. Doss SS, Anandhalakshmi S, Rekha K, Akhil AK. Effect of Smoking on heart rate variability in normal healthy volunteers. Asian J Pharm Clin Res 2016;9:230-34.

11. Kaya H, Suner A, Koroglu S, Akcay A, Turkbeyler IH and Koleoglu M. Heart rate variability in familial Mediterranean fever patients. Europ J Rheumatol 2014;1:58-61.
12. Karim N, Hasan JA, Syed SA. Heart rate variability – A review. J Basic Appl Sci 2011;7:71-7.
13. (Authors not listed) Heart rate variability: Standards of measurement, physiological interpretation, and clinical use. Task force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. Eur Heart J 1996;17:354-81.
14. Sayar K, Güleç H, Gökçe M, Ismail AK. Heart rate variability in depressed patients. Bull Clin Psychopharmacol 2002;12:130-33.
15. Licht CM, de Geus EJ, Zitman FG, Hoogendijk WJ, van Dyck R, Penninx BW. Association between major depressive disorder and heart rate variability in the Netherlands study of depression and anxiety (NSEDA). Arch Gen Psychiatry 2008;65:1358-67.
16. Janca A, Hiller W. ICD-10 checklist – A tool for clinicians use of the ICD-10 classification of mental and behavioral disorder. Compr Psychiatry 1996;37:180-7.
17. BMI Classification, Global Database on Body Mass Index. World Health Organization; 2006.
18. Du Bois D, Du Bois EF. A formula to estimate the approximate surface area if height and weight be known. Arch Intern Med. 1916;17:863-71.
19. Agelink MW , Boz C, Ullrich H, Andrich J. Relationship between major depression and heart rate variability. Clinical consequences and implications for antidepressive treatment. Psychiatry Res 2002;113:139-49.
20. Davidson J, Watkins L, Owens M, Krulewicz S, Connor K, Carpenter D, *et al*. Effects of paroxetine and venlafaxine XR on heart rate variability in depression. J Clin Psychopharmacol 2005;25:480-4.
21. Kemp AH, Quintana DS, Felmingham KL, Matthews S, Jelinek HF. Depression, comorbid anxiety disorders, and heart rate variability in physically healthy, unmedicated patients: Implications for cardiovascular risk. PLoS One 2012;7:e30777.
22. Brunoni AR, Kemp AH, Dantas EM, Goulart AC, Nunes MA, Boggio PS, *et al*. Heart rate variability is a trait marker of major depressive disorder: Evidence from the sertraline vs. electric current therapy to treat depression clinical study. Int J Neuropsychopharmacol 2013;16:1937-49.
23. O'Regan C, Kenny RA, Cronin H, Finucane C, Kearney PM. Antidepressants strongly influence the relationship between depression and heart rate variability: Findings from the Irish longitudinal study on ageing (TILDA). Psychol Med 2015;45:623-36.
24. Sgoifo A, Carnevali L, Alfonso Mde L, Amore M. Autonomic dysfunction and heart rate variability in depression. Stress 2015;18:343-52.
25. Paniccia M, Paniccia D, Thomas S, Taha T, Reed N. Clinical and non-clinical depression and anxiety in young people: A scoping review on heart rate variability. Auton Neurosci 2017;208:1-14.
26. Chen X, Yang R, Kuang D, Zhang L, Lv R, Huang X, *et al*. Heart rate variability in patients with major depression disorder during a clinical autonomic test. Psychiatry Res 2017;256:207-11.
27. Gehi A, Mangano D, Pipkin S, Browner W, Whooley M. Depression and heart rate variability in patients with stable coronary heart disease. Arch Gen Psychiatry 2005;62:661-6.
28. Carney RM, Blumenthal JA, Stein PK, Watkins L, Catellier D, Berkman LF, *et al*. Depression, heart rate variability, and acute myocardial infarction. Circulation 2001;104:2024-8.
29. Ha JH, Park S, Yoon D, Kim B. Short-term heart rate variability in older patients with newly diagnosed depression. Psychiatry Res 2015;226:484-8.
30. Wang Y, Zhao X, O'Neil A, Turner A, Liu X, Berk M. Altered cardiac autonomic nervous function in depression. BMC Psychiatry 2013;13:187.
31. Royster EB, Trimble LM, Cotsonis G, Schmotzer B, Manatunga A, Rushing NN, *et al*. Changes in heart rate variability of depressed patients after electroconvulsive therapy. Cardiovasc Psychiatry Neurol 2012;2012:794043.
32. Askelrod S, Gordon D, Ubel FA, Shannon DC, Berger AC, Cohen RJ. Power spectrum analysis of heart rate fluctuation: A quantitative probe of beat-to-beat cardiovascular control. Science 1981;213:220-2.