Original Article

DOI: 10.7860/JCDR/2022/56183.16703

Physiology Section

Correlation of Heart Rate Variability and Inflammatory Markers in Patients with Depression: A Cross-sectional Study

DEEPTI JANGPANGI[1], SUNITA MONDAL[2], RAJIV BANDHU[3], DINESH KATARIA[4], JAYASHREE BHATTACHARJEE[5]

ABSTRACT

Introduction: Depression has been found to be associated with cardiovascular morbidity and mortality. Autonomic dysregulation and inflammation have been implicated as the possible mechanisms. A cross-talk between the autonomic nervous system and inflammatory pathways has been observed in different clinical studies.

Aim: To examine the inter-relationship between Heart Rate Variability (HRV), a measure of autonomic function, and inflammatory biomarkers measured by high sensitivity C-Reactive Protein (hsCRP) and Interleukin-6 (IL-6) in patients with depression, without any co-morbid conditions.

Materials and Methods: This cross-sectional study was conducted in Department of Physiology, in collaboration with the Department of Psychiatry and Biochemistry, Lady Hardinge Medical College, New Delhi, India, from November 2010 to March 2012. Total 30 drug naive cases (without any co-morbid diseases) diagnosed with depression (mild, moderate and severe depression) as per International classification of diseases-10 (ICD-10) guidelines, in the age group of 20-45 years old were included in the study. Heart rate variability measures were recorded and analysed, frequency domain measures Low Frequency (LF), High Frequency (HF) and time domain measures like Standard Deviation of all NN interval (SDNN) and Root Mean Square of Successive differences of NN intervals (RMSSD). The IL-6 and hsCRP levels were also measured and severity of depression by Hamilton Depression Rating Scale (HDRS) was also assessed and correlated. Data was analysed using the Statistical Package for Social Sciences (SPSS) version 16.0. Normality of data was assessed using the Shapiro-Wilk test.

Results: The mean age of the cases was 30.33±6.97 years. There were 14 males and 16 females. There was no significant correlation found between the HRV measures and inflammatory biomarkers (LF vs hsCRP: p-value=0.781, HF vs hsCRP: p-value=0.713, SDNN vs hsCRP: p-value=0.262, RMSSD vs hsCRP: p-value=0.50, LF vs IL-6: p-value=0.477, HF vs IL-6: p-value=0.425, SDNN vs IL-6: p-value=0.137, RMSSD vs IL-6: p-value=0.328). Correlation of HDRS with HRV measures or inflammatory markers was not found to be significant.

Conclusion: Future studies with larger sample size and wide array of inflammatory biomarkers besides IL-6 and hsCRP is warranted. No significant correlation was observed between HRV and inflammatory markers in depression patients.

Keywords: Autonomic nervous system, Inflammation, Major Depressive disorder

INTRODUCTION

Depression has been found to be associated with cardiovascular morbidity and mortality [1]. Autonomic deregulation, and inflammatory processes, associated with depression have been suggested as one amongst the possible mechanisms [2].

Evidences from several prior studies have shown that vagal activity regulates the inflammatory responses [3,4]. Heart Rate Variability (HRV) measures such as High Frequency (HF), Standard Deviation of all R-R interval (SDNN) and Root Mean Square of Successive differences (RMSSD) being mainly modulated by parasympathetic activity were found to be inversely related to levels of inflammatory biomarkers in many study findings [4,5]. A cholinergic anti-inflammatory pathway has been proposed in which it is said that stimulation of vagal efferent, which denotes parasympathetic component of autonomic nervous system, significantly inhibits proinflammatory cytokines levels, thereby reducing systemic inflammation [3].

The mechanism of cholinergic anti-inflammatory pathway involves vagus nerve signals leading to acetylcholine-dependent interaction with the alpha 7 nicotinic acetylcholine receptor subunit (α7nAChR) on monocytes and macrophages, resulting in reduced cytokine production, While the sympathetic system has both pro and anti-inflammatory influences [6]. The HRV has been accepted as a non invasive measure of autonomic nervous system activity. Higher HRV especially the measures which reflect parasympathetic or vagal activity have found to be associated with decreased levels of inflammation, while reduced HRV reflects excessive cardiac sympathetic modulation, inadequate cardiac parasympathetic modulation or both of heart rate with raised inflammation [7,8].

Alteration of the sympathovagal balance could lead to activation of the proinflammatory pathway, resulting in a proinflammatory state [8]. Recently, a meta-analysis showed negative associations between HRV measures and inflammation biomarkers [9]. However, a study reported a positive association between HRV measures and markers of inflammation [8]. Also most of the studies carried out till date to study the correlation between HRV measures and Inflammation have been conducted on patients of depression with co-morbidity or in different clinical scenarios [10,11]. Hence, the present study aimed to explore the relationship between different measures of HRV and IL-6, hsCRP levels in depressive patients without any co-morbid diseases. Additionally, the role and influence of severity of depression, in affecting the relationship between HRV and inflammatory biomarkers was also evaluated.

MATERIALS AND METHODS

This cross-sectional study was conducted in Department of Physiology, in collaboration with the Department of Psychiatry and Biochemistry, Lady Hardinge Medical College, New Delhi, India, from November 2010 to march 2012. The Institute's Ethics Committee approved the study protocol. Written informed consent was obtained from all the patients after informing the objectives of study.

Inclusion criteria: The drug naïve patients of either gender, with a diagnosis of depression by a qualified Psychiatrist as per International classification of diseases-10 (ICD-10) guidelines [12], in the age group of 20-45 years were included in the study.

Exclusion criteria: Patients with any known previous or current systemic diseases, psychiatric illness besides depression, diabetes mellitus, any previous cardiovascular diseases and peripheral neuropathy were excluded from the study. Patients with any known history of substance dependence, using any medications which may affect autonomic functions or inflammatory marker levels, practising yoga were also excluded from the study.

A convenient sample size of 30 drug naïve depression patients as diagnosed by ICD-10 guidelines [12] visiting Department of Psychiatry, Lady Hardinge Medical College were recruited into the study after satisfying inclusion and exclusion criteria.

Procedure

As per the ICD-10 classification of mental and behavioural disorders [12], out of 30 depression patients:

- Mild Depression: n=8
- Moderate depression: n=16
- Severe depression- n=6

In depressive episodes of all three varieties (mild, moderate and severe), the individual usually suffers from depressed mood, loss of interest and reduced energy leading to increased fatigability and diminished activity. Other common symptoms includes, reduced concentration and attention, reduced self-esteem, ideas of guilt, ideas, or acts of self-harm or suicide, disturbed sleep and diminished appetite and unworthiness bleak and pessimistic views of future [12]. All of the basic socio-demographic details were collected by using a semi-structured proforma. Body mass index was also computed as body weight in kilogram (kg) divided by square of standing height in meters [13].

Heart Rate Variability (HRV): A 2 hour fasting was ensured prior to testing and patients were instructed to abstain from caffeine (tea or coffee) or nicotine for at least 24 hours before the recording. The Blood Pressures (BP), was recorded for each subject after 10-15 min of rest. The patients were asked to lie down supine during the recordings, and were awake and relaxed. A 5 minutes segment basal recording of continuous Electrocardiogram (ECG) in standard test conditions was obtained. The HRV was recorded by Autonomic Neuropathy analyzer supplied by Recorders and Medicare System, Chandigarh, India. The data was stored in a computer and analysed using a computer programme developed by RD Recorders and Medicare system, Chandigarh, India to obtain [7]:

- Time domain parameters
  - a) Standard deviation of all R-R intervals (SDNN)
  - b) Root Mean Square of Successive Differences (RMSSD
- Frequency domain parameters
  - a) Low Frequency (LF) in normalized unit
  - b) High Frequency (HF) in normalized unit

The HRV recording and interpretation of data were done as described by the guidelines of Task Force of European Society of Cardiology and the Northern American Society of Pacing Electrophysiology (1996) [7].

Inflammatory biomarkers: A 3 mL of fasting blood was drawn from the same patients and were collected between 9.00 am and 12.00 noon for assessing the baseline levels of IL-6 and hsCRP. Serum samples obtained were immediately stored in aliquots at -70°C until the time of analysis. Inflammatory markers were assayed using Enzyme Linked Immuno-Sorbent Assay (ELISA).

- Serum IL-6 levels were estimated using ELISA kit supplied by Diaclone research (France), sensitivity was less than 2 pg/mL.
- High sensitivity C-reactive Protein (hsCRP) levels were determined by ELISA kit supplied by Calbiotech, Inc., sensitivity of ELISA kit was 0.01 mg/L.

Hamilton Depression Rating Scale (HDRS): This is the most widely used clinician-administered rating scale for depression. The 24-item version of the scale was used, which rated about symptoms of depression. The scale consists of 24 items,

- Rated 0 to 4 for 13 items such as depressed mood, guilt, suicide, work and interests,
- Rated from 0 to 2 for 11 items like insomnia, agitation, general somatic symptoms.

The first 17 items measure the severity of depressive symptoms, while the extra seven items are related to depression, but are not measures of severity [14,15]. Although the HDRS lists 24 items, the total scoring for correlation is obtained from first 17 items

- Eight items were rated from 0 to 4,
- Nine items were rated from 0 to 2

Item 16 was divided into A and B section and each were rated from 0 to 2 and added to provide a cumulative score for the patient. A total score of 0 to 7 was considered to be within normal range, while total scores range from minimum score of 0 to a maximum possible score of 52 [15].

STATISTICAL ANALYSIS

Data was analyzed using the Statistical Package for Social Sciences (SPSS) version 16.0. Normality of data was assessed using the Shapiro-Wilk test. Continuous co-variates were expressed as mean with standard deviation or median with interquartile range. The IL-6 and hsCRP were expressed as Median with Interquartile Range (IQR) due to non normal distributions. Discrete co-variates were expressed as frequencies and percentages. To correlate, Spearman and Pearson correlations were used depending on the distribution of data. The p-value of <0.05 was considered significant in all the tests.

RESULTS

The mean age of the cases was 30.33±6.97 years. The gender distribution among the cases group shows 14 males and 16 females. The distribution of other baseline socio-demographic parameters among cases is shown in [Table/Fig-1].

Variables	Mean (SD)/Median (IQR) or frequency (%)
Age (years)	30.33±6.97
Gender	
Male	14 (46.7)
Female	16 (53.3)
Body mass index (kg/m^2)	22.74±1.75
Heart rate (bpm)	77.63±10.5
Systolic blood pressure (mmHg)	110.50±8.5
Diastolic blood pressure (mmHg)	69.20±7.5
Hamilton depression rating scale score	21.23±4.14
Diagnosis#	
Mild depression	8 (26.7)
Moderate depression	16 (53.3)
Severe depression	6 (20)
Inflammatory biomarker	
IL-6 (pg/mL)	2.6 (1-6.68)
hsCRP (mg/l)	2.2 (1.94-2.34)
Heart rate variability	
LF (nu)	76.13±2.98
HF (nu)	24.09±3.14
SDNN (ms)	58.70±35
RMSSD (ms)	35.40±15.4

[Table/Fig-1]: Baseline demographic and clinical characteristics of depression patients.
SD: Standard deviation; IQR: Interquartile range; IL-6: Interleukin-6; hsCRP: high sensitivity C-reactive protein; LF (nu): Low frequency in normalized unit; HF (nu): High frequency in normalized unit; SDNN: Standard deviation of all R-R intervals; RMSSD: root mean square successive difference; #: ICD-10 Classification of mental and behavioural disorders

Although SDNN and RMSSD, which reflect parasympathetic vagal activity, showed a negative correlation (SDNN vs IL-6: r-value=-0.278, p-value=0.137; RMSSD vs IL-6: r-value=-0.185, p-value=0.328, SDNN vs hsCRP: r-value=-0.211, p-value=0.262; RMSSD vs hsCRP: r-value=-0.128, p-value=0.50) with IL-6 and hsCRP levels, but were not statistically significant. The HF-HRV showed a positive correlation (HF vs IL-6: r-value=0.151, p-value=0.425; HF vs hsCRP: r-value=0.070, p-value=0.713) with inflammatory markers and was not significant [Table/Fig-2].

Variables (N=30)	LF (nu)	HF (nu)	SDNN (ms)	RMSSD (ms)
hsCRP (mg/l)	r=-0.053	r=0.070	r=-0.211	r=-0.128
	p=0.781	p=0.713	p=0.262	p=0.500
IL-6 (pg/mL)	r=-0.135	r=0.151	r=-0.278	r=-0.185
	p=0.477	p=0.425	p=0.137	p=0.328

[Table/Fig-2]: Spearman correlations between heart rate variability and inflammatory markers in patients with depression.
Spearman correlations, *p-value <0.05 was considered as significant

No significant correlation was observed between HDRS scores, which assess the severity of depression with HRV measures, although HDRS scores were negatively correlated with HF (nu), SDNN and RMSSD (HDRS vs HF: r-value=-0.220, p-value=0.243; HDRS vs SDNN: r-value=-0.155, p-value=0.412; HDRS vs RMSSD: r-value=-0.267, p-value=-0.154) signifying reduced parasympathetic activity with increasing HDRS scores. Additionally, HDRS scores and IL-6, hsCRP levels were positively correlated (HDRS vs IL-6: r-value=0.116, p-value=0.540; HDRS vs hsCRP: r-value=0.082, p-value=0.665) reflecting increased inflammatory biomarker levels with increasing HDRS scores, but were not significant [Table/Fig-3].

Variable (N=30)	LF (nu)	HF (nu)	SDNN	RMSSD	hsCRP (mg/L)	IL-6 (pg/mL)
HDRS scores	r=0.195†	r=-0.220†	r=-0.155†	r=-0.267†	r=0.116‡	r=0.082‡
	p=0.303	p=0.243	p=0.412	p=0.154	p=0.540	p=0.665

[Table/Fig-3]: Correlation coefficients between heart rate variability measures, inflammatory markers with HDRS scores in patients with depression.
†Pearson correlations, ‡Spearman correlations, *p-value <0.05 was considered as significant

The results did not find any significant correlation between HRV measures and IL-6, hsCRP with respect to mild, moderate and severe depression, when compared [Table/Fig-4,5]. This shows that severity of depression does not influences or strengthen the correlation between HRV measures and IL-6, hsCRP levels in present study, although it might be attributed to small sample size.

Variables	Interleukin-6 (pg/mL)		
	Mild depression (n=8)	Moderate depression (n=16)	Severe depression (n=6)
LF (nu)	r=-0.070	r=-0.241	r=0.319
	p=0.866	p=0.368	p=0.538
HF (nu)	r=0.071	r=0.299	r=-0.319
	p=0.87	p=0.261	p=0.538
SDNN	r=-0.238	r=-0.272	r=0.348
	p=0.570	p=0.308	p=0.499
RMSSD	r=-0.024	r=0.041	r=0.145
	p=0.955	p=0.879	p=0.784

[Table/Fig-4]: Spearman correlations between heart rate variability measures and IL-6 (pg/mL) levels in patients with mild, moderate and severe depression.
*p-value <0.05 was considered as significant

Variables	hsCRP (mg/L)		
	Mild depression (n=8)	Moderate depression (n=16)	Severe depression (n=6)
LF (nu)	r=-0.144	r=-0.186	r=0.406
	p=0.734	p=0.491	p=0.425
HF (nu)	r=0.143	r=0.196	r=-0.40
	p=0.730	p=0.467	p=0.420
SDNN	r=-0.192	r=-0.150	r=0.667
	p=0.649	p=0.579	p=0.148
RMSSD	r=-0.012	r=0.004	r=0.493
	p=0.978	p=0.987	p=0.321

[Table/Fig-5]: Spearman correlations between heart rate variability measures and hsCRP (mg/L) levels in patients with mild, moderate and severe depression.
*p-value <0.05 was considered as significant

DISCUSSION

The study was done to check the correlation between HRV measures and inflammatory biomarkers in patients with depression. The present study did not find any correlation between HRV measures namely LF (nu), HF (nu), SDNN, RMSSD and hsCRP, IL-6 levels. Recent evidences suggest role of parasympathetic nervous system in regulation of inflammation and experimental studies suggest that inflammatory pathways are under direct control of vagus nerve via cholinergic anti-inflammatory pathway [3,16]. In a meta-analysis study, results showed negative associations between HRV measures and biomarkers of inflammation such as IL-6, C-reactive protein amongst others [9].

The SDNN and power in the high frequency band of HRV (HF-HRV), both reflecting parasympathetic activity, showed the strongest negative correlation with inflammatory markers compared to other time domain and frequency domain measures of HRV. The HF-HRV as another index of cardiac vagal regulation, was also found to be inversely related to inflammatory markers [9]. But in present study HF (nu) which signify parasympathetic influences was not found to be negatively correlated with any of the inflammatory markers. Additionally in the present study, the HRV measures SDNN and RMSSD, which also reflect parasympathetic activity were found to be negatively or inversely correlated to IL-6 and hsCRP levels, in accordance with what prior studies have suggested [4,5], but it was not significant.

Carney MR et al., reported in depressed patients with coronary heart disease, IL-6 levels was negatively correlated with one measure of HRV (total power), and was marginally related to VLF and LF power, while CRP was not significantly related to any measure of HRV [17]. A study done by Alen NV et al., found a robust inverse association of HF-HRV with interleukin-6 (IL-6), C-reactive protein (CRP), similar inverse associations were observed between LF-HRV and IL-6 and CRP [18]. Furthermore, Cooper TM et al., found that HF-HRV and LF-HRV were significantly and inversely related to several inflammatory markers, LF-HRV was found to be inversely associated with CRP and IL-6, while HF-HRV was inversely associated with CRP [19]. However, in present study findings LF-HRV also showed similar negative correlation with IL-6 and hsCRP levels but was not significant, while HF-HRV on contrary showed nonsignificant positive correlation with IL-6 and hsCRP levels.

In a study by Aeschbacher S et al., which was conducted in young and healthy adults showed relationship between SDNN and hsCRP was significant and negatively associated, suggesting interrelationship between inflammatory pathways and the ANS [4]. Frasure-smith N et al., found all HRV measures were negatively and significantly associated with inflammatory markers (IL-6, CRP), and relationship between HRV measures and CRP were stronger in patients with elevated depression symptoms Beck Depression Inventory-II (BDI-II) ≥14 in coronary heart disease patients [20]. Evidences from previous studies are consistent with the cholinergic anti-inflammatory pathway and suggest the parasympathetic modulation of inflammation through the vagus nerve [10,11,21]. However, in present study, no difference in correlation between HRV measures and IL-6, hsCRP levels was observed with increasing severity of depression, although SDNN and RMSSD showed negative correlation with IL-6 and hsCRP levels but were not significantly related.

As there are only few studies done to investigate the relationship between HRV measures and inflammatory markers in depression patients, the present study adds to the growing literature which have investigated the relationship [17,20]. The cholinergic anti-inflammatory pathway could be an important mechanism associated with comorbidity of depression and cardiovascular disease [22,23]. Additionally, the bidirectional relationship between the parasympathetic nervous system and the inflammation could provide a novel insight regarding clinical interventions targeting regulation of both for inflammatory illnesses [24]. Identifying the role of the vagus nerve may aid clinically in the development of new therapies for inflammatory diseases and thus suggest its importance in clinical applications [25].

Limitation(s)

There are some limitations in the present study, one is small sample size which might was not sufficient to detect significant correlation between HRV measures and IL-6, hsCRP levels as suggested by prior studies. The cross-sectional nature of study limits us to draw any inference about the direction and strength of any possible bidirectional relationship exist between HRV and inflammation.

CONCLUSION(S)

Thus, it can be concluded from the study findings, that no correlation was observed in between HRV measures and inflammatory markers (IL-6, hsCRP). There was no significant correlation found between HRV and IL-6, hsCRP, with respect to severity of depression. As there are only few previous studies done in depression patients to study the cross-sectional relationship between autonomic nervous system and inflammatory pathways, and how severity of depression influences the relationship between HRV and inflammation. Therefore, further future research is warranted with a larger sample size and wide array of inflammatory biomarkers besides IL-6, hsCRP could also be included in future studies. The longitudinal studies are required to be done to evaluate the directionality of relationship between HRV and inflammatory markers.

REFERENCES

[1] Rajan S, McKee M, Rangarajan S, Bangdiwala S, Rosengren A, Gupta R, et al. Association of symptoms of depression with cardiovascular disease and mortality in low-, middle-, and high-income Countries. JAMA Psychiatry. 2020;77(10):1052-63.
[2] Tonhajzerova I, Sekaninova N, Bona Olexova L, Visnovcova Z. Novel insight into neuroimmune regulatory mechanisms and biomarkers linking major depression and vascular diseases: The dilemma continues. Int J Mol Sci. 2020;21(7):2317.
[3] Tracey KJ. The inflammatory reflex. Nature. 2002;420(6917):853-59.
[4] Aeschbacher S, Schoen T, Dörig L, Kreuzmann R, Neuhauser C, Schmidt-Trucksass A, et al. Heart rate, heart rate variability and inflammatory biomarkers among young and healthy adults. Ann Med. 2017;49(1):32-41.
[5] Lampert R, Bremner JD, Su S, Miller A, Lee F, Cheema F, et al. Decreased heart rate variability is associated with higher levels of inflammation in middle-aged men. Am Heart J. 2008;156:759 e1-7.
[6] Wang H, Yu M, Ochani M, Amella CA, Tanovic M, Susarla S, et al. Nicotinic acetylcholine receptor alpha7 subunit is an essential regulator of inflammation. Nature. 2003;421(6921):384-88.
[7] Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. Heart rate variability: Standards of measurement, physiological interpretation and clinical use. Circulation. 1996;93:1043-65.
[8] Huston JM, Tracey KJ. The pulse of inflammation: Heart rate variability, the cholinergic anti-inflammatory pathway and implications for therapy. J Intern Med. 2011;269(1):45-53.
[9] Williams DP, Koenig J, Carnevali L, Sgoifo A, Jarczok MN, Sternberg EM, et al. Heart rate variability and inflammation: A meta-analysis of human studies. Brain Behav Immun. 2019; 80:219-26.
[10] Haensel A, Mills PJ, Nelesen RA, Ziegler MG, Dimsdale JE. The relationship between heart rate variability and inflammatory markers in cardiovascular diseases. Psych Neuroendocrinology. 2008;33(10):1305-12.
[11] Wegeberg AL, Okdahl T, Fløyel T, Brock C, Ejskjaer N, Riahi S, et al. Circulating inflammatory markers are inversely associated with heart rate variability measures in type 1 diabetes. Mediators Inflamm. 2020;2020:3590389.
[12] World Health organization. The ICD-10 Classification of Mental and Behavioural Disorders: Clinical Descriptions and Diagnostic Guidelines. Geneva: World Health Organization; 1992.
[13] National Heart, Lung, and Blood Institute. Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults. Bethesda (MD): National Heart, Lung and Blood Institute; 1998.
[14] Guy W. NCDEU assessment manual for psychopharmacology (DHHS Publication No. ADM 91-338) Washington, DC: U.S. Department of Health, Education and Welfare; 1976.
[15] Porter E, Chambless DL, McCarthy KS, DeRubeis RJ, Sharpless BA, Barrett MS, et al. Psychometric properties of the reconstructed Hamilton Depression and Anxiety scales. J Nerv Ment Dis. 2017;205(8):656-64.
[16] Ma Y, Chiriboga DE, Pagoto SL, Rosal MC, Li W, Merriam PA, et al. Association between depression and C-reactive protein. Cardiol Res Pract. 2010;2011:286509.
[17] Carney MR, Freedland KE, Stein PK, Miller GE, Stein Meyer B, Rich MW, et al. Heart rate variability and markers of inflammation and coagulation in depressed patients with coronary heart disease. J Psychosom Res. 2007;62(4):463-67.
[18] Alen NV, Parenteau AM, Sloan RP, Hostinar CE. Heart rate variability and circulating inflammatory markers in midlife. Brain Behav Immun Health. 2021;15:100273.
[19] Cooper TM, McKinley PS, Seeman TE, Choo TH, Lee S, Sloan RP. Heart rate variability predicts levels of inflammatory markers: Evidence for the vagal anti-inflammatory pathway. Brain Behav Immun. 2015;49:94-100.
[20] Frasure smith N, Lesperance F, Irwin MR, Talajic M, Pollock BG. The relationship among heart rate variability, inflammatory markers and depression in coronary heart disease patients. Brain Behav Immune. 2009;23(8):1140-47.
[21] Zila I, Mokra D, Kopincova J, Kolomaznik M, Javorka M, Calkovska A. Vagal-immune interactions involved in cholinergic anti-inflammatory pathway. Physiol Res. 2017;66(2):139-45.
[22] Chen Z, Wu Y, Duan J, Yang L. The cholinergic anti-inflammatory pathway could be an important mechanism underling the comorbidity of depression and cardiovascular disease: A comment to Shao et al. Psychiatry Res. 2020;286:112881.
[23] Pomara N, Bruno D, Plaska CR, Pillai A, Ramos-Cejudo J, Osorio R, et al. Evidence of upregulation of the cholinergic anti-inflammatory pathway in late-life depression. J Affect Disord. 2021;286:275-81.
[24] Hoover DB. Cholinergic modulation of the immune system presents new approaches for treating inflammation. Pharmacol Ther. 2017;179:01-16.
[25] Howland RH. Vagus nerve stimulation. Curr Behav Neurosci Rep. 2014;1(2):64-73.

PARTICULARS OF CONTRIBUTORS:
1. Assistant Professor, Department of Physiology, Dr Baba Saheb Ambedkar Medical College, New Delhi, India.
2. Director Professor and Head, Department of Physiology, Lady Hardinge Medical College and Associated Hospitals, New Delhi, India.
3. Professor, Department of Physiology, Lady Hardinge Medical College and Associated Hospitals, New Delhi, India.
4. Director Professor, Department of Psychiatry, Lady Hardinge Medical College and Associated Hospitals, New Delhi, India.
5. Professor and Head, Department of Biochemistry, Government Institute of Medical Sciences, Greater Noida, Uttar Pradesh, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Dr Deepti Jangpangi,
Flat No. 21, Type-IV Quarter, Dr Baba Saheb Ambedkar Medical College,
Sector-6, Rohini, New Delhi, India.
E-mail: drdeeptijangpangi@gmail.com

PLAGIARISM CHECKING METHODS: [Jain H et al.]
- Plagiarism X-checker: Mar 19, 2022
- Manual Googling: Jun 02, 2022
- iThenticate Software: Jul 22, 2022 (24%)

ETYMOLOGY: Author Origin

AUTHOR DECLARATION:
- Financial or Other Competing Interests: None
- Was Ethics Committee Approval obtained for this study? Yes
- Was informed consent obtained from the subjects involved in the study? Yes
- For any images presented appropriate consent has been obtained from the subjects. NA

Date of Submission: **Mar 07, 2022**
Date of Peer Review: **Apr 29, 2022**
Date of Acceptance: **Jun 02, 2022**
Date of Publishing: **Aug 01, 2022**