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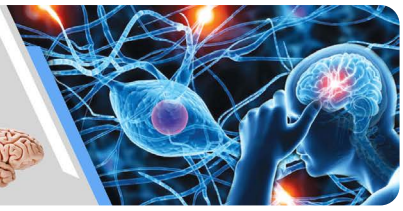
Research Article

JOURNAL OF PSYCHIATRY AND PSYCHIATRIC DISORDERS

ISSN: 2572-519X



Assessment of Anxiety Severity and its Association with Cardiac Autonomic Function Tests and Cardiovascular Risk Factors in Patients with Anxiety Disorder

Kavitha Natarajan[1], Pravati Pal[2], Gopal Krushna Pal[3], Balaji Bharadwaj[4], Nivedita Nanda[5]

Abstract

Background: Anxiety disorders are persistent, excessive, and difficult-to-control anxiety and worry, with a global prevalence of 0.9% to 28.3%. Psychosocial factors, like anxiety, have a significant impact on cardiovascular health, comparable to traditional CV risk factors, and often remain under-recognized.

Aim: This study explores the relationship between anxiety severity and cardiovascular risk factors in anxiety disorder patients.

Methods: This study involved 140 anxiety disorder patients. Anxiety severity was assessed using the hamilton anxiety rating scale. Cardiovascular autonomic functions, like heart rate variability, heart rate response to standing, heart rate response to deep breathing, blood pressure response to isometric handgrip, and baroreflex sensitivity, were measured. Also, Quality of life, metabolic profile and inflammatory markers were assessed across various anxiety severity levels.

Results: Among participants, 21% had mild, 21% had mild to moderate, 29% had moderate to severe, and 29% had very severe anxiety. The heart rate variability indices showed increased sympathetic and decreased parasympathetic activity as the anxiety severity increased. Also, parasympathetic reactivity and baroreflex sensitivity diminished, while sympathetic reactivity increased with greater anxiety. Quality of life scores decreased as anxiety intensified. Biochemically, anxiety severity was associated with increased levels of metabolic, stress and inflammatory markers.

Conclusion: The findings reveal that 60% of anxiety disorder patients have moderate to very severe anxiety, linking anxiety severity to disruptions in cardiovascular function. This underscores the need for treatment strategies addressing both mental and cardiovascular health.

Keywords: Anxiety Disorder; Cardiac Autonomic Function Tests; Heart Rate Variability; Baroreflex Sensitivity, Cardiovascular Risk.

Introduction

Anxiety is a normal response to daily stress and challenges, serving as the brain's warning system. However, it becomes a disorder when persistent, excessive, and irrational feelings disrupt daily functioning. Anxiety disorders are an important mood disorder commonly associated with a higher risk of fatal cardiovascular diseases (CVD), including coronary heart disease, sudden cardiac death and cerebrovascular diseases, with a global prevalence of 0.9% to 28.3% [1, 2].

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Citation: Kavitha Natarajan, Pravati Pal, Gopal Krushna Pal, Balaji Bharadwaj, Nivedita Nanda. Assessment of Anxiety Severity and its Association with Cardiac Autonomic Function Tests and Cardiovascular Risk Factors in Patients with Anxiety Disorder. Journal of Psychaity and Psychaitric Disorders. 8 (2024): 312-325.

Received: December 05, 2024
Accepted: December 17, 2024
Published: December 30, 2024

Kavitha Natarajan, et al., J Psychiatry Psychiatric Disord 2024
DOI:10.26502/jppd.2572-519X0231

Previous studies indicate the impact of psychosocial distress on cardiovascular (CV) morbidity and mortality is nearly as significant as the impact of demographic factors (such as age, sex, and race) and traditional risk markers (including smoking, alcohol use, obesity, diabetes, dyslipidemia, and hypertension) [3,4]. The underappreciation of the role of psychosocial factors in the development and progression of cardiac diseases may partly explain why these diseases remain the leading cause of death in most developed countries. Although several studies investigating the relationship between CVD and negative emotions have focused on depression, a large proportion of patients with confirmed or suspected CVD experience some level of anxiety [5, 6]. Anxiety following a major cardiac event can hinder recovery and is associated with increased morbidity and mortality [7,8].

Anxiety disorders are characterised by autonomic symptoms such as hot flushes, palpitations, perspirations, and tremors, in addition to emotional and cognitive symptoms. The activation of the sympathetic nervous system, indicated by impaired vagal control, reduced heart rate variability, elevated levels of proinflammatory cytokines, and hypercortisolemia resulting from the activation of the hypothalamic–pituitary axis (HPA), is increasingly recognized as a significant link between anxiety and CVD [9-12]. Studies have shown that common mental disorders, such as anxiety disorder, are strongly linked to reduced heart rate variability (HRV) [10]. Diminished vagal control heightens the risk of sympathetically driven cardiovascular ischemia and malignant arrhythmias, contributing to increased mortality rates. This pathophysiological interaction forms a vicious cycle: chronic mental illness disrupts autonomic control of the heart, leading to impaired cardiovascular health, which, in turn, increases susceptibility to stress compromising the quality of life [10].

Cardiovascular autonomic function tests are valuable tools for diagnosing cardiac autonomic neuropathy and as an independent predictor of CV mortality and a marker for progressive autonomic nervous system disorders [11]. Additionally, measuring baroreflex sensitivity provides crucial information for the clinical management and risk stratification of cardiac disease patients [12]. Optimal cardiac health is characterised by increased variability, with lower HRV linked to CVD and mortality. Impaired ANS activity as reduced parasympathetic tone, reflected in decreased HRV and BRS values, is strongly associated with increased risk of CVD in both psychotropic medicated and non-medicated anxiety disorders [10, 13-16]. Despite all these, there are relatively few studies that specifically examine the effects of anxiety severity on CV outcomes. In this study, we have determined the anxiety severity and its association with cardiac autonomic function tests and associated cardiovascular risk factors in patients with anxiety disorder.

Methodology

This study was conducted after receiving approval from the JIPMER Postgraduate Research Monitoring Committee (PGRMC) and Institute Ethics Committee (IEC) for human studies (IEC approval number: JIP/IEC/2019/402), in the Autonomic Function Testing (AFT) Laboratory and Cardiovascular Research Laboratory (CVRL) Laboratory at the Department of Physiology, JIPMER, Puducherry.

Study Participants:

A total of 140 anxiety disorder patients of either sex between the age group 18 and 40 years attending the Psychiatry outpatient department (OPD) in JIPMER participated in the study and were included in the current analysis. Participants were recruited from February 2019 to January 2022. The procedure was explained to these patients in a language comfortable to them, and written informed consent was obtained before the recording of parameters.

Inclusion criteria:

Patients of either sex between the age group 18 and 40 years diagnosed with any anxiety disorders (generalised anxiety disorder, panic disorder, specific phobia, agoraphobia, unspecified anxiety disorder, other specified anxiety disorder, social anxiety disorder, anxiety disorder due to other medical conditions, substance or medication-induced anxiety disorder) based on DSM-5 criteria, who were stable with standard routine treatment for anxiety disorders from psychiatry OPD were included in the study.

Exclusion criteria:

Patients with comorbidities like diabetes, hypertension or cardiac diseases, renal disease, other psychiatric illnesses, autonomic dysfunction and pulmonary disorder were excluded from this study.

Procedure:

After obtaining written and informed consent, participants were advised to attend the Physiology Department's autonomic function test (AFT) laboratory by 07:00 am for fasting blood sample collection. They were asked to return between 9:30 a.m. and 10:00 a.m., after a light breakfast, for autonomic function testing. They were instructed to refrain from vigorous physical activity for 12 hours; to avoid tea, caffeine products, tobacco, and alcohol for 24 hours; and to withhold anticholinergics, antihistaminics, sympathomimetic and parasympathomimetic agents, if any, for 12 hours before the recording. During the recordings, the temperature of the lab was maintained at 25^0C. External noise and disturbances were also avoided to ensure a calm and quiet environment during the recording.

Measures:

Anthropometric Measurement:

Height in centimeters was measured using a wall-

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mounted stadiometer (Easy careTM(NO: 26 SM), and body weight was recorded using an automated weighing machine (Charder Electronics, Taichung, Taiwan 2013). BMI was calculated using Quetelet's index.

Cardiovascular Parameters:

Heart rate (HR), Systolic Blood Pressure (SBP), and Diastolic Blood Pressure (DBP) were recorded after 10 min of rest in the supine position on a couch in the lab (room temperature maintained at 25^0C) using an automated sphygmomanometer– AccuSureTM (Model no: TMB-1490-A). The arm cuff of the automatic sphygmomanometer was 12 cm in width and 44 cm in length, and the cuff tube length was 60 cm. Later, Pulse Pressure (PP), Mean Arterial Pressure (MAP) and Rate Pressure Product (RPP) were calculated.

Short-term Heart Rate Variability (HRV):

The study participants were instructed to void before the recording and were given supine rest in the laboratory for 15 minutes. ECG electrodes were fixed on the subject and connected to the machine for lead II ECG recording for 5 to 10 minutes in a silent room with a room temperature of 25^0C to record HRV using European Task Force guidelines [17]. During the recording, the participants were instructed to reduce body movements to a minimum.

BIOPAC MP 36(MP36E1203002693) was used to record ECG signals during rest. BIOPAC data was transported to Windows-based BIOPAC Student Lab 4.0.0 software. The ECG signals were digitalised and saved for offline analysis on the computer. Artefacts and ectopics, which were filtered with bandpass filters, were deleted. The artefact correction was kept below 5% of total beats. From the 360-second ECG data, the program recognised all R waves and calculated the R-R interval.

HRV analysis:

The R-R intervals for the entire recording were taken and saved in text format. The R-R interval data was analyzed using Kubios version 2.0.(HRV analysis software- Bio-signal Analysis group, Kuopio, Finland). The software was based on Matlab and was compiled into a standalone C program using Mat lab.

For HRV analysis, 360-second data from the R-R tachogram was utilized. The RR tachogram was interpolated at 2 Hz, and the Fast Fourier Transformation (FFT) was computed with the help of the Welch periodogram, which was used for power spectral analysis. Mean RR, RMSSD, SDNN, NN50, and pNN50 were time domain parameters, whereas Total Power (TP ms^2), Low-Frequency power (LF ms^2 & LF nu), High-Frequency power (HF ms^2 & HF nu), and the ratio of low-frequency to high-frequency (LF: HF) were frequency domain parameters.

Heart rate response to standing:

ECG electrodes were connected from the subject to the polygraph for 5 minutes in a silent room with a room temperature of 25^0C after 10 minutes of supine rest. The NIBP cuff was tied around the arm of the participant. The continuous ECG was obtained and monitored using BIOPAC MP-36 throughout the procedure. Resting HR and Blood Pressure (BP) were measured. The participants were then told to stand without assistance in 3 seconds. HR response was continually obtained using the ECG. The data from the BIOPAC MP-36 system was digitalized and analyzed using BIOPAC Student Lab 4.0.0 software, which allowed us to extract the values from the R-R tachogram. The extracted values were plotted on a line graph using Microsoft Excel 2007. Finally, the 30:15 ratio was computed by dividing the largest R-R interval at the 30th beat by the smallest R-R interval at the 15th beat.

Heart Rate response to Deep breathing:

The study participants were asked to sit comfortably under controlled laboratory conditions. ECG electrodes were connected from the subject to the polygraph. The NIBP cuff was tied around the arm of the participant. The continuous ECG was obtained and monitored using BIOPAC MP-36 throughout the procedure. Resting HR and BP were measured. The participants were then instructed to take deep breaths at a level of six each minute (5 seconds for inspiration and expiration for each breath). They were instructed to give maximum effort and not hold their breath between inspiration and expiration. The ECG obtained during the procedure was analyzed using BIOPAC Student Lab 4.0.0 software. Maximum and minimum RR interval with each cycle were recorded and plotted on a line graph using Microsoft Excel 2007, and the average was taken for six cycles. The average value of expiration and inspiration was used to calculate the E: I ratio.

Blood Pressure response to Isometric handgrip:

The study participants were instructed and demonstrated how to use a handgrip dynamometer. The Participants were made to sit comfortably under controlled laboratory conditions. Maximum Voluntary contraction (MVC) was determined 20 minutes before the actual procedure. The participants were requested to hold the dynamometer with their dominant hand with full strength for a few seconds, and the value was recorded. Resting BP and HR were measured. The participants were instructed to hold the dynamometer at 30% of MVC for 3-5 minutes and inform the investigator when they could not maintain the handgrip pressure. BP and HR were measured at the 1-minute interval, just before the release of handgrip pressure, and two minutes after the grip was released, another reading was obtained. ΔDBP was noted as the difference between the maximum DBP during the procedure and the resting DBP.

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DOI:10.26502/jppd.2572-519X0231

Baroreflex Sensitivity:

Baroreflex Sensitivity (BRS) was recorded at rest using a noninvasive, continuous finger arterial blood pressure (BP) monitor Finapres (Finometer Pro, Finapres Medical Systems BV, Amsterdam, The Netherlands). The measurement of finger arterial pressure is developed based on the volume clamp technique of Penaz and the Physiocal criteria of Wesseling [18]. In this technique, the finger arterial pressure is reconstructed to represent brachial arterial pressure using generalized waveform inverse modelling, generalised level correction and individual height correction for the two arteries. The analysis was performed using this reconstructed brachial arterial waveform. The spontaneous oscillations of BP and interbeat intervals were used for time-domain cross-correlation analysis for determining BRS [19]. This technique of cross-correlation was validated against the gold standard technique for measuring BRS, i.e. drug challenge with phenylephrine and nitroprusside [20]. The recording was taken continuously for 10 minutes in a supine posture after 10 minutes of rest in the same position. The BRS values obtained over the time interval were averaged and expressed in ms/mmHg.

Body composition analysis:

The body composition using the bioelectrical impedance technique was analyzed using Bodystat Quad scan 4000 (British-made version 2/02). It estimates electrical impedance by passing electrical current via the body. Reactance and resistance are calculated, which are used to evaluate other parameters using BODYSTAT QUAD SCAN 4000 software. The participants were allowed to relax in a lying posture for 10 minutes. The signal-inducing electrodes were attached on right side metacarpophalangeal and metatarsophalangeal joints. Voltage-sensing electrodes were positioned 5cm proximal to the signal-inducing electrodes on pisiform prominence and between the malleoli of the foot. Anthropometric and physical activity details were fed into the machine. The current of 500 – 800 µA with 50 kHz frequency was applied. From the measured impedance, lean mass and fat mass were derived. The data were extracted using Bodystat R Quadscan for Windows XP (version 4.08 serial no:410436).

Assessment of anxiety severity:

The Hamilton Anxiety Rating Scale (HAM-A) was utilised to assess the participant's anxiety levels [21]. It has 14 items, each represented by a set of psychological and physical symptoms. Each component was rated on a severity scale ranging from 0 (no anxiety) to 4 (severe anxiety), with a total score range of 0–56, with <17 indicating minimal/mild anxiety, 18–24 mild to moderate anxiety, 25–30 moderate to severe anxiety, and > 30 indicating very severe anxiety.

Assessment of quality of life (QoL):

The participant's QoL was assessed using the WHOQoL-BREF questionnaire. It was organized around four dimensions of health: physical, psychological, social, and environmental. It comprises 26 self-administered questions, which were provided in the local language for the convenience of the participants. The first transformation method converted domain scores to a 4-20 scale, which is similar to the WHOQoL-100, while the second transformation method transformed domain scores to a 0-100 scale [22].

Assessment of biochemical markers:

Serum glucose levels (using the glucose oxidase peroxidase method) and lipid profiles were measured immediately with commercially available kits adapted for auto analyzers based on spectrophotometry (Beckman Coulter, Beckman Coulter Inc, Brea, California, USA). Lipid ratios were then calculated from the lipid profile values. Serum cortisol, BDNF, IL-6, insulin, and hs-CRP were analyzed using an Enzyme-Linked Immunosorbent Assay (ELISA) kit and analysed using an ELISA analyzer (Molecular Devices, Spectra Max Plus 384). Cortisol was measured with a Calbiotech, El Cajon, USA, ELISA kit (Category no: CO368S, Detection range: 20–400 ng/ml; Sensitivity: 20 ng/ml), BDNF with Finetest (Fine Biotech), Wuhan, China, ELISA Kit (Category No.:EH0043, Detection range: 31.25–2000 pg/ml; Sensitivity:18.75 pg/ml), IL-6 with Finetest (Fine Biotech), Wuhan, China, ELISA Kit (Category No.:AQ-H0201-B, Detection range: 0.078–5 pg/ml; Sensitivity: 0.046 pg/ml), CRP with Calbiotech El Cajon, USA, ELISA kit (Category No.:CR375C, Detection range: 0.005–0.1 mg/L; Sensitivity: 0.000136 mg/L), and insulin with Calbiotech El Cajon, USA, ELISA kit (Category No.:IN374S, Detection range: 5–300 µIU/L; Sensitivity: 0.11 µIU/L). HOMA-IR was calculated as [Fasting Insulin (µg/ml)]*[Fasting Glucose (mmol/l)]/22.5.

Statistical Analysis of Data:

Categorical variables, such as gender, were represented as frequencies with percentages. Continuous variables were represented as means with standard deviations or medians with ranges, depending on data distribution. The normality of continuous variables was tested using the Kolmogorov-Smirnov (KS) test. Chi-square tests were used to compare the frequencies of categorical variables across groups. Comparisons of continuous variables, including age, anthropometric measures, resting cardiovascular and cardiac autonomic parameters, biochemical markers, and other quantitative variables across different levels of anxiety severity, were carried out using one-way ANOVA or the Kruskal-Wallis test based on data distribution. Karl Pearson's or Spearman's correlation analysis was employed to examine the linear relationships between quantitative variables, anxiety severity, and sympathovagal balance. All statistical analyses were conducted at a 5% significance level, with a p-value < 0.05 considered significant. IBM SPSS (Statistical Package for Social Sciences) version 22.0 (IBM Corp, Armonk, NY) was used for the analysis.

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DOI:10.26502/jppd.2572-519X0231

Results

In this study, we assessed the severity of anxiety disorders in 140 participants using the HAM-A scale. The results revealed that 21% (n=29) had mild anxiety, 21% (n=30) had mild to moderate anxiety, 29% (n=41) experienced moderate to severe anxiety, and 29% (n=40) were classified as having very severe anxiety (Fig 1). The mean age of the participants was 33.17 ± 6.20 years. Among the 140 participants, 86 (61.4%) were male, and 54 (38.6%) were female. Figure 2 shows the gender distribution across anxiety severity levels, with no statistically significant difference in gender across different anxiety levels (p=0.152).

The comparison of anthropometric measurements across different levels of anxiety severity (Table 1) showed no significant differences in height, weight, hip circumference, and BMI. However, there was a significant increase in waist circumference (WC) and waist-to-hip ratio (WHR) (p<0.001). Additionally, when comparing body composition parameters, there was a significant increase in Body Fat Mass Index (BFMI) (p=0.013) and a significant decrease in Free Fat Mass Index (FFMI) (p<0.001) across the different grades of anxiety severity. An increase in body fat percentage and a decrease in lean body mass percentage were observed, although these changes were not statistically significant.

The comparison of basal cardiovascular parameters across the grades of anxiety severity among the study participants as in Table 2 showed a significant increase in heart rate (p<0.001), SBP (p<0.001), DBP (p<0.001), PP(p=0.042), MAP (p<0.001) and RPP (p<0.001).

The comparison of cardiac autonomic function test parameters across varying levels of anxiety severity among the study participants is represented in Table 3. A significant decrease was observed in time-domain HRV indices, including Mean RR (p<0.001), SDNN (p=0.004), RMSSD (p=0.023), NN50 (p=0.001), and pNN50 (p=0.001). In the frequency domain of HRV, there was a significant reduction in Total Power (p<0.001), HF Power (p<0.001), and HF nu (p<0.001), accompanied by a significant increase in LF nu (p<0.001) and the LF/HF ratio (p<0.001) across the grades of anxiety severity. Additionally, in the reactivity tests, a significant decrease was noted in the 30:15 ratio (p<0.001), E: I ratio (p<0.001), with a significant increase in ΔDBP (p<0.001) during the isometric handgrip test. Furthermore, Baroreflex Sensitivity (BRS) also showed a significant decrease (p<0.001) as anxiety severity increased among the participants.

Table 4 compares psychological scores and quality of life across different grades of anxiety disorder among the study participants. The results show a significant increase in HAM-A scores (p<0.001). Additionally, there was a significant decline in various domains of quality of life, including physical health (p<0.001), psychological health (p<0.001), social health (p<0.001), and environmental health (p<0.001), corresponding with increasing anxiety severity.

Table 5 illustrates the comparison of biochemical markers and metabolic profiles across different levels of anxiety severity among patients with anxiety disorders. The analysis revealed a significant increase in Cortisol (p=0.007), IL-6 (p=0.002), CRP (p<0.001) and insulin (p<0.001), along with a significant decrease in BDNF (p<0.001) levels as anxiety severity increased. Additionally, there were significant

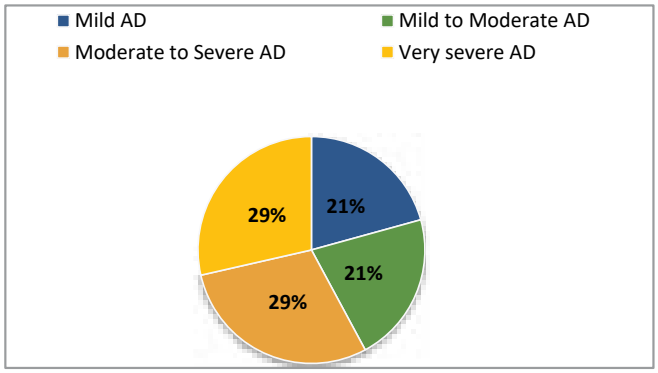

Figure 1: Prevalence of severity of anxiety disorder among the study participants

AD: Anxiety Disorder

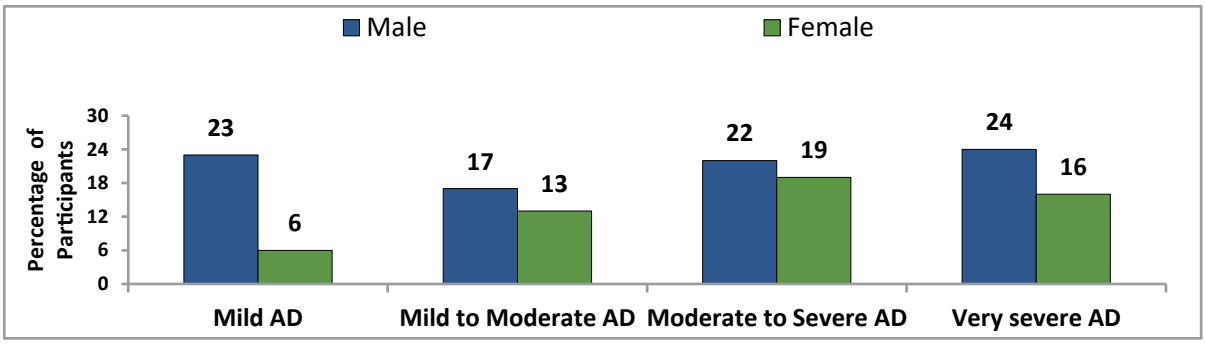

Figure 2: Gender-based distribution of study participants across grades of anxiety disorder (n=140)

AD: Anxiety Disorder

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Table 1: Comparison of Anthropometric and body composition indices across the grades of anxiety disorder among the study participants (n=140).

Parameters	Mild AD (n=29)	Mild to Moderate AD (n=30)	Moderate to Severe AD (n=41)	Very Severe AD (n=40)	p-value
Age#	30.00 (25.00)	32.50 (22.00)	33.00 (21.00)	35.00 (19.00)	0.855
Height (cm)$	168.48 ± 6.06	169.57 ± 6.54	169.55 ± 6.79	169.99 ± 6.51	0.818
Weight (cm)$	67.35 ± 9.54	68.87 ± 6.43	70.16 ± 6.33	71.58 ± 6.14	0.091
WC (cm)$	90.21 ± 10.84	91.53 ± 10.42	93.83 ± 8.98	96.58 ± 8.79^{d}	0.037*
HC (cm)#	97.00 (39.00)	97.50 (34.00)	98.00 (27.00)	99.00 (24.00)	0.942
WHR$	0.93 ± 0.10	0.94 ± 0.07	0.98 ± 0.10	1.01 ± 0.08$^{dd,\ j}$	0.001**
BMI$	23.75 ± 3.34	23.99 ± 2.38	24.46 ± 2.37	24.80 ± 2.10	0.324
Fat %#	29.65 (39.10)	30.47 (37.90)	32.43 (43.20)	34.48 (46.20)	0.487
Lean %#	70.35 (39.10)	69.53 (37.90)	67.57 (43.20)	65.51 (46.20)	0.487
BFMI$	6.51 ± 2.64	7.16 ± 2.12	7.39 ± 2.07	8.43 ± 2.85^{d}	0.013*
FFMI#	19.60 (12.30)	16.85 (9.2)	15.40 (18.20)^{xxx}	13.45 (10.70)$^{ddd,\ jj,}$	<0.001***

$ - The parametric data are presented as Mean ± SD, and its statistical analysis was performed using one way ANOVA test with post hoc Bonferroni test done for intragroup analysis

- The non-parametric data are presented as Median (Range), and its statistical analysis was performed using the Kruskal Wallis test with post hoc Bonferroni test done for intragroup analysis

The p- value <0.05 was statistically considered significant across the groups; ***: p-value <0.001;**: p-value <0.01;*: p-value < 0.05;

within the mild & very severe AD groups ; ddd : p-value <0.001; dd: p-value <0.01; d: p-value < 0.05; within mild to moderate & very severe AD groups jjj : p-value <0.001; jj: p-value <0.01; j: p-value < 0.05; within the mild & moderate to severe AD groups ; xxx : p-value <0.001; xx: p-value <0.01; x: p-value < 0.05

WC: Waist Circumference, HC: Hip Circumference, BMI: Body Mass Index, WHR: Waist Hip Ratio, BFMI: Body Fat Mass Index, FFMI: Free Fat Mass Index

The comparison of basal cardiovascular parameters across the grades of anxiety severity among the study participants as in Table 2 showed a significant increase in heart rate (p<0.001), SBP (p<0.001), DBP (p<0.001), PP(p=0.042), MAP (p<0.001) and RPP (p<0.001).

Table 2: Comparison of cardiovascular parameters across the grades of anxiety disorder

Parameters	Mild AD (n=29)	Mild to Moderate AD (n=30)	Moderate to Severe AD (n=41)	Very Severe AD (n=40)	p-value
SBP (mmHg)$	112.34 ± 10.33	118.37 ± 10.14	122.37 ± 9.45^{xxx}	129.25 ± 7.03^{ddd,jjj,zz}	<0.001***
DBP (mmHg)#	67.00 (35.00)	73.50 (17.00)	77.00 (24.00)^{x}	80.00 (24.00)^{ddd,jj,z}	<0.001***
PP (mmHg)#	42.00 (30.00)	46.50 (34.00)	48.00 (44.00)	50.00 (47.00)^{d}	0.042*
MAP(mmHg)#	81.00 (33.30)	88.00 (23.33)	92.00 (21.60)^{xx}	97.33 (19.60)^{ddd,jjj,zz}	<0.001***
RPP#	73.70 (61.00)	79.46 (70.00)	86.40 (61.00)^{x}	99.32 (57.00)^{ddd,jjj,z}	<0.001***
HR (bpm)#	68.00 (45.00)	68.00 (43.00)	72.00 (40.00)	76.50 (40.00)^{dd,jj}	<0.001***

$ - The parametric data are presented as Mean ± SD, and its statistical analysis was performed using one way ANOVA test with post hoc Bonferroni test done for intragroup analysis

- The non-parametric data are presented as Median (Range), and its statistical analysis was performed using the Kruskal Wallis test with post hoc Bonferroni test done for intragroup analysis

The p- value <0.05 was statistically considered significant across the groups; ***: p-value <0.001;**: p-value <0.01;*: p-value < 0.05;

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HR: Heart Rate, SBP: Systolic Blood Pressure, DBP: Diastolic Blood Pressure, PP: Pulse Pressure, MAP: Mean Arterial Pressure, RPP: Rate Pressure Product

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Table 3: Comparison of cardiovascular autonomic function test parameters across the grades of anxiety disorder among the study participants (n=140)

Parameters	Mild AD (n=29)	Mild to Moderate AD (n=30)	Moderate to Severe AD (n=41)	Very Severe AD (n=40)	p-value
Time domain indices of HRV					
Mean RR (ms)#	882.35 (586.20)	882.35 (465.40)	833.33 (434.10)	784.35 (472.80)^{dd,jj}	<0.001***
SDNN (ms)#	43.40 (79.90)	33.10 (49.30)	32.70 (39.90)^{x}	32.15 (27.40)^{dd}	0.004**
RMSSD (ms)#	39.40 (85.40)	31.65 (81.40)	30.60(49.40)	27.45 (33.60)^{d}	0.023*
NN50 (ms)#	29.00 (41.00)	22.00 (49.00)	19.00 (34.00)	03.00 (20.00)^{dd,zz,jj}	0.001**
pNN50 (ms)#	9.20 (68.70)	7.55 (50.40)	5.60 (28.10)	0.75 (29.30)$^{dd,\ j,\ z}$	0.001**
Frequency domain indices of HRV					
TP (ms^2)$	1376.48 ± 736.28	1127.43 ± 485.93	1024.63 ± 479.28^{xx}	678.28 ± 334.90^{ddd,jjj,z}	<0.001***
LF (ms^2)#	534.00 (1620.00)	418.50 (1023.00)	372.00 (837.00)	255.50 (833.00)^{d}	0.033*
HF(ms^2)#	425.00 (1622.00)	283.50 (865.00)	187.00 (844.00)	93.00 (318.00)^{ddd,jjj,zz}	<0.001***
LF (nu)#	58.37 (72.10)	61.11 (72.60)	66.59 (35.50)	74.00 (19.50)^{ddd,jjj,zz}	<0.001***
HF (nu)#	41.63 (72.10)	38.89 (72.60)	33.41 (35.50)	26.00 (19.50)^{ddd,jjj,zzz}	<0.001***
LF:HF#	1.40 (6.53)	1.58 (6.02)	1.99 (4.95)	2.85 (4.00)^{dd,j}	<0.001***
Autonomic Recativity Tests					
30:15#	1.30 (1.04)	1.16 (0.83)^{cc}	1.13 (0.43)^{xx}	1.09 (0.38)^{ddd}	<0.001***
E:I#	1.32 (0.69)	1.26 (0.48)	1.20 (0.45)^{xxx}	1.14 (0.34)^{ddd,jjj}	<0.001***
ΔDBP$	6.93 ± 3.38	8.73 ± 4.51	10.83 ± 6.13^{x}	12.68 ± 7.07^{ddd,j}	<0.001***
Baroreflex sensitivity					
BRS$	15.93 ± 6.33	13.90 ± 3.62	10.71 ± 3.88^{xxx,q}	7.77 ± 2.80^{ddd,jjj,z}	<0.001***

$ - The parametric data are presented as Mean ± SD, and its statistical analysis was performed using one way ANOVA test with post hoc Bonferroni test done for intragroup analysis

- The non-parametric data are presented as Median (Range), and its statistical analysis was performed using the Kruskal Wallis test with post hoc Bonferroni test done for intragroup analysis

The p- value <0.05 was statistically considered significant across the groups; ***: p-value <0.001;**: p-value <0.01;*: p-value < 0.05;

within the mild & very severe AD groups ; ddd : p-value <0.001; dd: p-value <0.01; d: p-value < 0.05; within mild to moderate & very severe AD groups jjj : p-value <0.001; jj: p-value <0.01; j: p-value < 0.05; within the mild & moderate to severe AD groups ; xxx : p-value <0.001; xx: p-value <0.01; x: p-value < 0.05; within the moderate to severe & very severe AD groups ; zzz : p-value <0.001; zz: p-value <0.01; z: p-value < 0.05; within the mild & mild to moderate AD groups ; ccc : p-value <0.001; cc: p-value <0.01; c: p-value < 0.05; within the mild to moderate & moderate to severe AD groups ; qqq : p-value <0.001; qq: p-value <0.01; q: p-value < 0.05

Mean RR: Mean RR interval, SDNN: Standard deviation of NN intervals; RMSSD: Root mean square of standard deviation; NN50: consecutive NN intervals with difference more than 50ms; pNN50: percentage of NN50 intervals; TP: Total power; LF: Low frequency; HF: High frequency; LF nu: Low frequency in normative units; HF nu: High frequency in normative units; LF: HF ratio: Low frequency: High-frequency ratio; E:I: Expiration: Inspiration; ΔDBP: Diastolic Blood Pressure difference in isometric handgrip test; 30:15: Heart Rate Response to standing from lying to standing BRS: Baroreflex Sensitivity

Table 4: Comparison of psychological scores and quality of life across the grades of anxiety disorder among the study participants (n=140)

Parameters	Mild AD (n=29)	Mild to Moderate AD (n=30)	Moderate to Severe AD (n=41)	Very Severe AD (n=40)	p-value
HAM-A Score#	15.00 (11.00)	22.00 (6.00)^{c}	27.00 (10.00)^{qq,xxx}	41.00 (17.00)^{ddd,jjj,zzz}	<0.001***
Quality of life					
Physical Health#	75.00(38.00)	63.00 (44.00)	50.00 (63.00)^{qqq,xxx}	38.00 (50.00)^{ddd,jjj}	<0.001***
Psychological Health#	69.00 (56.00)	56.00 (50.00)	44.00 (50.00)^{qqq,xxx}	31.00 (50.00)^{ddd,jjj}	<0.001***
Social Health#	75.00(50.00)	62.50 (45.00)^{c}	50.00 (50.00)^{xxx}	44.00 (50.00)^{ddd}	<0.001***
Environmental Health#	76.00 (63.00)	63.00 (44.00)^{c}	56.00 (43.00)^{xxx}	44.00 (56.00)^{ddd,jjj,zzz}	<0.001***

- The non-parametric data are presented as Median (Range), and its statistical analysis was performed using the Kruskal Wallis test with post hoc Bonferroni test done for intragroup analysis

The p- value <0.05 was statistically considered significant across the groups; ***: p-value <0.001;**: p-value <0.01;*: p-value < 0.05;

within the mild & very severe AD groups ; ddd : p-value <0.001; dd: p-value <0.01; d: p-value < 0.05; within mild to moderate & very severe AD groups jjj : p-value <0.001; jj: p-value <0.01; j: p-value < 0.05; within the mild & moderate to severe AD groups ; xxx : p-value <0.001; xx: p-value <0.01; x: p-value < 0.05; within the moderate to severe & very severe AD groups ; zzz : p-value <0.001; zz: p-value <0.01; z: p-value < 0.05; within the mild & mild to moderate AD groups ; ccc : p-value <0.001; cc: p-value <0.01; c: p-value < 0.05; within the mild to moderate & moderate to severe AD groups ; qqq : p-value <0.001; qq: p-value <0.01; q: p-value < 0.05;

HAM-A: Hamilton Anxiety Rating Scale

Citation: Kavitha Natarajan, Pravati Pal, Gopal Krushna Pal, Balaji Bharadwaj, Nivedita Nanda. Assessment of Anxiety Severity and its Association with Cardiac Autonomic Function Tests and Cardiovascular Risk Factors in Patients with Anxiety Disorder. Journal of Psychaity and Psychaitric Disorders. 8 (2024): 312-325.

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DOI:10.26502/jppd.2572-519X0231

Table 5: Comparison of biochemical markers and metabolic profile across the grades of anxiety disorder among the study participants (n=140)

Parameters	Mild AD (n=29)	Mild to Moderate AD (n=30)	Moderate to Severe AD (n=41)	Very Severe AD (n=40)	p-value
Cortisol (ng/mL)#	109.10 (412.14)	129.62 (356.57)	131.34 (343.70)	177.60 (204.16)^{ddd}	0.007**
BDNF (pg/mL)$	2692.97 ± 594.61	2451.46 ± 414.59	2293.14 ± 424.68^{xx}	2113.35 ± 427.30^{ddd,j}	<0.001***
hsCRP (mg/L)#	1.52 (9.31)	1.82 (8.87)	2.71 (8.10)	3.13 (5.87)^{d}	0.02*
hsIL-6 (pg/mL)#	2.04 (6.95)	2.63 (7.65)	4.30 (7.2)	4.78 (8.38)^{ddd,jj}	<0.001***
Insulin (µIU/L)$	8.21 ± 3.04	10.14 ± 3.85	10.94 ± 4.40	13.62 ± 7.02^{ddd,j}	<0.001***
FBS (mg/dL)$	91.14 ± 17.25	93.33 ± 16.1	97.83 ± 12.59	106.78 ± 12.12^{ddd,jj,z}	<0.001***
PPBS (mg/dL)#	115.00 (114.00)	126.00 (86.00)	130.00 (50.00)^{xx}	141.00 (80.00)^{ddd,jj}	<0.001***
HOMA - IR$	1.89 ± 0.85	2.34 ± 0.99	2.60 ± 0.95	3.62 ± 2.07^{ddd,jj,zz}	<0.001***
TC (mg/dL)$	302.41 ± 44.57	316.07 ± 30.66	353.98 ± 29.35^{xxx,qqq}	359.10 ± 26.20^{ddd,jjj}	<0.001***
TG (mg/dL)#	115.00 (104.00)	127.50 (61.00)	151.00 (96.00)^{xxx,qq}	153.00 (70.00)^{ddd,jjj}	<0.001***
HDL (mg/dL)#	42.00 (24.00)	40.00 (23.00)	38.00 (18.00)	34.50 (15.00)^{ddd,jjj,zzz}	<0.001***
LDL (mg/dL)#	108.00 (102.00)	119.50 (75.00)	126.00 (86.00)^{x}	127.50 (76.00)^{dd,j}	<0.001***
TC/HDL$	7.22 ± 1.71	8.00 ± 1.51	9.32 ± 1.27^{xxx,qq}	10.49 ± 1.53^{ddd,jjj,zz}	<0.001***
LDL/HDL$	2.66 ± 0.80	2.86 ± 0.75	3.42 ± 0.75^{q,xx}	3.86 ± 0.86^{ddd,jjj}	<0.001***
TG/HDL$	2.78 ± 0.95	3.28 ± 0.66	3.99 ± 0.79^{xxx,qq}	3.86 ± 0.86^{ddd,jjj,zz}	<0.001***
Atherogenic Coefficient$	6.22 ± 1.71	7.00 ± 1.51	8.32 ± 1.27^{q,xxx,}	9.49 ± 1.53^{ddd,jjj,z}	<0.001***
Atherogenic index$	1.26 ± 0.11	1.32 ± 0.07^{c}	1.38 ± 0.06^{q,xxx}	1.43 ± 0.06^{ddd,jjj,z}	<0.001***

$ - The parametric data are presented as Mean ± SD, and its statistical analysis was performed using one way ANOVA test with post hoc Bonferroni test done for intragroup analysis

- The non-parametric data are presented as Median (Range), and its statistical analysis was performed using the Kruskal Wallis test with post hoc Bonferroni test done for intragroup analysis

The p- value <0.05 was statistically considered significant across the groups; ***: p-value <0.001;**: p-value <0.01;*: p-value < 0.05;

within the mild & very severe AD groups ; ddd : p-value <0.001; dd: p-value <0.01; d: p-value < 0.05; within mild to moderate & very severe AD groups jjj : p-value <0.001; jj: p-value <0.01; j: p-value < 0.05; within the mild & moderate to severe AD groups ; xxx : p-value <0.001; xx: p-value <0.01; x: p-value < 0.05; within the moderate to severe & very severe AD groups ; zzz : p-value <0.001; zz: p-value <0.01; z: p-value < 0.05; within the mild & mild to moderate AD groups ; ccc : p-value <0.001; cc: p-value <0.01; c: p-value < 0.05; within the mild to moderate & moderate to severe AD groups ; qqq : p-value <0.001; qq: p-value <0.01; q: p-value < 0.05;

BDNF: Brain-derived neurotrophic factor; hsIL-6: high sensitive Interleukin - 6; hsCRP: high sensitive C- reactive protein; FBS: Fasting blood glucose; PPBS: Postprandial blood glucose; HOMA-IR: Homeostatic Model Assessment for Insulin Resistance; TC: Total Cholesterol; TG: Triglycerides; LDL: Low-density lipoprotein; HDL: High-density lipoprotein.

elevations in FBS (p<0.001), PPBS (p<0.001), TC (p<0.001), TG (p<0.001), and LDL (p<0.001), coupled with a significant reduction in HDL (p<0.001) levels. The lipid risk ratios (p<0.001) and HOMA-IR (p<0.001) also showed a significant increase across the various grades of anxiety severity.

BDNF: Brain-derived neurotrophic factor; hsIL-6: high sensitive Interleukin - 6; hsCRP: high sensitive C- reactive protein; FBS: Fasting blood glucose; PPBS: Postprandial blood glucose; HOMA-IR: Homeostatic Model Assessment for Insulin Resistance; TC: Total Cholesterol; TG: Triglycerides; LDL: Low-density lipoprotein; HDL: High-density lipoprotein.

Table 6 outlines the association of HAM-A scores and the LF: HF ratio with anthropometric measurements, cardiac autonomic function tests, biochemical markers, and metabolic profiles among the study participants. Among the body composition indices, WHR (p=0.001), BFMI (p=0.003) and FFMI (p<0.001) showed a significant positive correlation with anxiety severity, while BMI showed a non-significant positive correlation. In terms of cardiac autonomic indices, Total Power (p<0.001) and BRS (p<0.001) had a significant negative correlation, whereas the LF: HF ratio (p<0.001) demonstrated a significant positive correlation with anxiety severity. Among the biochemical markers, BDNF (p<0.001) exhibited a significant negative correlation, while insulin (p<0.001), cortisol (p=0.001), IL-6 (p<0.001), and CRP (p=0.004) were significantly positively correlated with HAM-A scores. The metabolic profile parameters, including FBS, PPBS, HOMA -IR and lipid profile components such as TC, TG, LDL, VLDL, atherogenic index, LDL/HDL, TC/HDL, and TG/HDL showed a significant positive correlation (p<0.001) with HAM-A scores, while HDL had a significant negative correlation (p<0.001) with anxiety severity.

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DOI:10.26502/jppd.2572-519X0231

Table 6: Correlation of psychological score (HAM-A) and LF: HF with anthropometric, cardiac autonomic function parameters, Biochemical markers and metabolic profile among anxiety disorder patients.

Parameters	HAM - A score		LF:HF	
	Spearman's coefficient	p value	Spearman's coefficient	p value
HAM-A score	1	1	0.472	<0.001***
WHR	0.267	0.001**	0.15	0.77
BMI	0.113	0.183	0.06	0.479
BFMI	0.246	0.003**	0.165	0.052
FFMI	-0.541	<0.001***	-0.198	0.019*
TP (ms^2)	-0.41	<0.001***	-0.39	<0.001***
LF:HF	0.472	<0.001***	1	1
BRS(ms/mmHg)	-0.564	<0.001***	-0.34	<0.001***
Insulin (µIU/L)	0.293	<0.001***	0.101	0.235
Cortisol (ng/mL)	0.275	0.001**	0.236	0.005**
BDNF (pg/mL)	-0.377	<0.001***	-0.11	0.195
hsCRP (mg/L)	0.24	0.004**	0.093	0.272
hsIL-6 (pg/mL)	0.396	<0.001***	0.238	0.005**
FBS (mg/dL)	0.336	<0.001***	0.226	0.007**
PPBS (mg/dL)	0.43	<0.001***	0.264	0.002**
HOMA-IR	0.348	<0.001***	0.152	0.072
TC (mg/dL)	0.534	<0.001***	0.177	0.036*
TG (mg/dL)	0.54	<0.001***	0.164	0.054
HDL (mg/dL)	-0.466	<0.001***	-0.228	0.007**
LDL (mg/dL)	0.325	<0.001***	0.163	0.054
TC/HDL	0.614	<0.001***	0.279	0.001**
LDL/HDL	0.475	<0.001***	0.256	0.002**
TG/HDL	0.62	<0.001***	0.238	0.005**
Atherogenic Coefficient	0.614	<0.001***	0.279	0.001**
Atherogenic index	0.611	<0.001***	0.242	0.004**

The data were analysed using Spearman's correlation. p <0.05 was considered statistically significant; ***: p-value <0.001;**: p-value <0.01;*: p-value < 0.05;

WHR: Waist Hip Ratio; BMI: Body Mass Index; TP: Total power; LF: HF ratio: Low frequency: High-frequency ratio; BRS: Baroreflex Sensitivity; FBG: Fasting Blood Glucose, PPBS: Post Prandial Blood Glucose; TC: Total Cholesterol, LDL: Low-Density Lipoprotein, TG: Triglycerides, HDL: High-Density Lipoprotein

Additionally, no significant correlation was found between anthropometric measurements and the LF: HF ratio. However, HAM-A scores showed a significant positive correlation with the LF: HF ratio (p<0.001). Among biochemical markers, Cortisol (p=0.005) and IL-6 (p=0.005) had a significant positive correlation with the LF: HF ratio, while BDNF showed a non-significant negative correlation, and CRP showed a non-significant positive correlation. Furthermore, the LF: HF ratio was significantly positively correlated with fasting blood glucose (p=0.004), HbA1c (p=0.003), and lipid profile components including TC (p=0.044), TG (p=0.02), VLDL (p=0.011), TC/HDL (p=0.001), LDL/HDL (p=0.002), TG/HDL (p=0.005), and atherogenic index (p=0.004). There was also a significant negative correlation between the LF: HF ratio and HDL (p=0.007).

Discussion

In this study, we assessed the severity of anxiety disorders in 140 participants using the HAM-A scale. Also, we have analysed the relationship between the anxiety severity and the range of physiological, psychological and biochemical parameters among the study participants.

Prevalence of anxiety symptoms Severity and Gender distribution:

The findings revealed that 21% (n=29) of participants had mild anxiety, 21% (n=30) had mild to moderate anxiety, 29% (n=41) experienced moderate to severe anxiety, and 29% (n=40) suffered from very severe anxiety, highlighting the significant prevalence of higher anxiety levels in the study population. The average age of participants was 33.17 ± 6.20

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DOI:10.26502/jppd.2572-519X0231

years, with a gender distribution of 61.4% males and 38.6% females. Notably, there was no significant gender difference across anxiety severity levels, indicating that both genders are equally affected by varying levels of anxiety. This finding aligns with Steiner et al.'s study on patients with generalized anxiety disorder [23]. These findings emphasize the need to address anxiety disorders across all demographic groups.

Altered Body Composition and Anxiety Severity:

The significant increase in waist circumference (WC) and waist-to-hip ratio (WHR) with increasing anxiety severity suggests a strong link between anxiety and central obesity. This indicates that anxiety may contribute to visceral fat accumulation, a known risk factor for metabolic conditions such as insulin resistance, type 2 diabetes, and cardiovascular disease [24]. A positive correlation between WHR and anxiety severity ($p=0.001$) further supports the connection between central adiposity and anxiety. Interestingly, while body mass index (BMI) showed a non-significant positive correlation with anxiety, fat distribution (measured by WHR) appears to be a more critical factor. This contrasts with a study by Mesharam et al. among medical students, which found no association between WHR, BMI, and anxiety levels [25].

Additionally, the significant increase in Body Fat Mass Index (BFMI) and decrease in Free Fat Mass Index (FFMI) across various anxiety levels highlight the potential influence of anxiety on body composition. This shift is marked by increased fat accumulation and reduced lean muscle mass, which is further supported by the significant positive correlation between BFMI and the HAM-A scores, along with the significant negative correlation between FFMI and HAM-A scores. These findings are consistent with a study by Breanna et al. among college students [26]. Although changes in body fat percentage and lean body mass percentage were not statistically significant, the observed trends suggest an imbalance in body composition as anxiety severity increases. This indicates that anxiety may contribute to or worsen metabolic dysregulation, potentially leading to long-term health consequences.

Cardiovascular Stress in Anxiety Disorder Patients:

The study revealed a significant increase in heart rate, systolic blood pressure (SBP), diastolic blood pressure (DBP), pulse pressure (PP), mean arterial pressure (MAP), and rate-pressure product (RPP) with increasing anxiety severity. These results align with the known link between anxiety and heightened sympathetic nervous system activity, which elevates heart rate and blood pressure, increasing the risk of cardiovascular diseases [27]. The significant rise in SBP, DBP, and MAP suggests that individuals with higher anxiety severity are at increased risk for cardiovascular disease. An increase in RPP, an indicator of myocardial oxygen demand, potentially leads to long-term cardiovascular damage in this population [28].

Cardiac Autonomic Function and Anxiety Severity:

HRV is a well-established marker of autonomic regulation, with lower HRV being associated with a higher risk of cardiovascular morbidity and mortality [29]. HRV was significantly reduced in individuals with severe anxiety, indicating impaired parasympathetic (vagal) activity and heightened sympathetic dominance [30]. The significant decrease in time-domain HRV indices such as Mean RR, SDNN, RMSSD, NN50, and pNN50 suggests diminished autonomic flexibility and an impaired ability to adapt to stressors, which can exacerbate cardiovascular risks [31].

In the frequency domain, the significant reduction in Total Power, HF Power, and HF (nu), along with the significant increase in LF (nu) and the LF/HF ratio, suggests the shift towards sympathetic dominance and reduced parasympathetic activity in individuals with severe anxiety. The LF: HF ratio, an indicator of the balance between sympathetic and parasympathetic activity, with Higher LF:HF ratios reflect greater sympathetic influence, which is associated with increased cardiovascular risk [32].

The significant decreases in the 30:15 ratio, E: I ratio, and ΔDBP during the isometric handgrip test, along with the reduction in BRS, provide additional evidence of the impaired autonomic function associated with severe anxiety. The 30:15 and E: I ratios are measures of autonomic reactivity, with lower values indicating reduced vagal tone and diminished capacity to modulate heart rate in response to postural changes or respiratory cycles [33]. The significant decrease in ΔDBP during the handgrip test, a measure of sympathetic response, suggests blunted autonomic reactivity in individuals with severe anxiety, which could contribute to the increased cardiovascular risk in this population [33]. The significant reduction in BRS with increasing anxiety severity suggests an impaired ability to regulate blood pressure, further increasing cardiovascular risk [33].

In our study, we also found a significant negative correlation between Total Power ($p<0.001$) and BRS ($p<0.001$) with anxiety severity and a significant positive correlation between the LF: HF ratio and anxiety severity ($p<0.001$), suggesting an impaired cardiac autonomic function in individuals with higher anxiety. These findings are consistent with the concept that chronic anxiety leads to chronic reduction in parasympathetic activity, which can lead to long-term decreases in HRV, thereby increasing the risk of CVD [10, 29].

The LF: HF ratio, an indicator of autonomic function, showed significant positive correlations with several metabolic and biochemical markers, including cortisol, IL-6, FBS, insulin and lipid profiles. These findings suggest that sympathetic overactivity in autonomic dysfunction is strongly tied to the metabolic and inflammatory changes seen in anxiety [34]. The significant negative correlation

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DOI:10.26502/jppd.2572-519X0231

between the LF: HF ratio and HDL further suggests that this imbalance contributes to an unfavorable lipid profile, increasing cardiovascular risk [35]. Moreover, the positive correlations between the LF: HF ratio and stress markers like cortisol (p=0.005) and IL-6 (p=0.005) highlight its role in the stress-inflammatory axis [36]. In addition to conventional cardiovascular risk factors, exposure to acute and chronic psychological stress may increase the risk of cardiovascular disease through inflammation mediated by an increased sympathetic output, which results in the release of inflammatory cytokines [37, 38].

Quality of Life in Anxiety Disorder Patients:

The significant decline in various domains of quality of life, including physical, psychological, social, and environmental health, with increasing anxiety severity, underscores the profound impact of anxiety on overall well-being [39]. The significant reduction in the physical health domain suggests that individuals with more severe anxiety experience greater somatic symptoms, such as fatigue, pain, and sleep disturbances, which can further exacerbate their overall health condition. This is in line with studies that have shown that chronic anxiety can lead to physical health problems, including cardiovascular diseases and weakened immune function [40]. Higher anxiety levels were also linked to poorer psychological health, often manifesting as increased stress and depression. Social health is also notably affected, with severe anxiety often leading to social withdrawal, isolation, and difficulties in forming or maintaining relationships [41]. The decline in this domain may reflect the social impairments that accompany anxiety, such as fear of social interactions, avoidance behaviors, and a decrease in social support. The significant decline in environmental health could indicate that individuals with severe anxiety perceive their surroundings as more threatening or less supportive. This may manifest as dissatisfaction with living conditions, safety concerns, or a lack of access to resources that could otherwise mitigate anxiety symptoms [42].

Worsening Biochemical markers and Metabolic Profile with Anxiety Severity:

The study revealed severe anxiety was associated with significant changes in biochemical markers and metabolic profiles. Elevated cortisol levels in participants with severe anxiety point to heightened hypothalamic-pituitary-adrenal axis activation, a hallmark of chronic stress [43]. Chronic elevation of cortisol can disrupt metabolism and contribute to conditions such as type 2 diabetes and cardiovascular disease [44]. The significant rise in inflammatory markers, such as IL-6 (p=0.002) and CRP (p<0.001), suggests that severe anxiety may trigger a systemic inflammatory response, which has been associated with various chronic diseases, including cardiovascular diseases [45]. Significant positive correlations between anxiety severity and markers like cortisol (p=0.001), IL-6 (p<0.001), and CRP (p=0.004) further support the link between anxiety and inflammation potentially leading to long-term health issues such as cardiovascular disease and metabolic syndrome. The significant decrease in BDNF levels was also observed across anxiety severity. Also, the significant negative correlations of BDNF (p<0.001) with HAM-A scores, suggesting that anxiety may impair neuroplasticity, potentially leading to cognitive impairments and metabolic disorders in anxiety disorders [46-48]. BDNF is involved in angiogenesis and promotes the survival of vascular smooth muscle cells, cardiomyocytes, endothelial cells, and atherosclerotic vessels. High BDNF levels play a protective role against CVD and CVD-related mortality, whereas low serum BDFN levels are considered a risk factor for future coronary events [49, 50].

The significant elevations in fasting blood glucose (FBS), postprandial blood glucose (PPBS), insulin, total cholesterol (TC), triglycerides (TG), low-density lipoprotein (LDL), very low-density lipoprotein (VLDL), coupled with the significant reduction in high-density lipoprotein (HDL), reflect a dysregulated metabolic profile in individuals with higher anxiety. The significant rise in lipid risk ratios (p<0.001) and HOMA-IR (p<0.001) across varying levels of anxiety severity further underscores the status of insulin resistance and increased cardiovascular risk in these patients. Elevated ratios of TC/HDL and LDL/HDL are predictive of cardiovascular events [51, 52]. The significant positive correlations between anxiety severity and various components of the metabolic profile including FBS, PPBS, TC, TG, LDL, and VLDL, further emphasize the link between anxiety and metabolic dysregulation. The negative correlation with HDL and the significant rise in lipid risk ratios highlight the cardiovascular risks associated with severe anxiety.

Limitations:

A larger sample size is required to improve the power of the study and substantiate the findings. Additionally, conducting subgroup analyses based on specific types of anxiety disorders could yield more detailed insights.

Conclusion

Our study reveals that 60% of anxiety disorders fall within moderate to severe to very severe categories, indicating a high prevalence of severe anxiety in the population. The findings show significant associations between anxiety (measured by HAM-A scores) and cardiovascular autonomic parameters, with higher anxiety linked to increased blood pressure, heart rate, sympathetic activity, reduced HRV, impaired autonomic reactivity, and decreased baroreflex sensitivity. This underscores the complex relationship between anxiety and physiological functioning. The study highlights how anxiety disorders affect mental, autonomic, metabolic, and inflammatory health, emphasizing the need for comprehensive management strategies for anxiety that address both mental health and physical health risks.

Citation: Kavitha Natarajan, Pravati Pal, Gopal Krushna Pal, Balaji Bharadwaj, Nivedita Nanda. Assessment of Anxiety Severity and its Association with Cardiac Autonomic Function Tests and Cardiovascular Risk Factors in Patients with Anxiety Disorder. Journal of Psychaity and Psychaitric Disorders. 8 (2024): 312-325.

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DOI:10.26502/jppd.2572-519X0231

Implications

Anxiety disorder patients, particularly those with moderate to very severe anxiety, require integrated care that addresses both psychological and cardiovascular health.

Highlights the importance of routine cardiovascular risk assessments in patients with anxiety disorders.

Supports the incorporation of interventions that target autonomic dysfunction, such as biofeedback or mindfulness-based therapies, alongside conventional anxiety treatments.

Promotes the development of integrated mental health and cardiovascular care models within healthcare systems.

Public health initiatives should emphasize the connection between mental and cardiovascular health to encourage early intervention.

Acknowledgement

We acknowledge Jawaharlal Institute of Postgraduate Medical Education and Research, Puducherry, for providing financial assistance in the form of an intramural MD research grant (JIP/ Res/ Intramural/ Sub Com/2020-21/ MD Physiology/ Sl. No.: 5/ Proposal No.: 9 dated 11.09.2020).

Declaration of Competing Interests

The authors declared no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

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