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Biochemical Analysis of Stress Hormones in Patients with Atherosclerotic Cardiovascular Disease

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Abstract

Background: Atherosclerotic cardiovascular disease is a principal cause of global morbidity and mortality. Chronic activation of stress-related neuroendocrine pathways, particularly the hypothalamic–pituitary–adrenal axis and the sympathetic nervous system, has been proposed to accelerate vascular inflammation and atherosclerotic plaque progression.

Objective: To determine the levels of selected stress hormones in patients with atherosclerotic cardiovascular disease and to evaluate their association with angiographic severity and conventional cardiovascular risk factors.

Methods: This cross-sectional analytical study was conducted in the Department of Biochemistry at Government Medical College, Trivandrum, Kerala. A total of 150 patients with angiographically confirmed atherosclerotic cardiovascular disease were included. Fasting serum cortisol was measured using chemiluminescent immunoassay, while plasma adrenaline and noradrenaline were quantified by high-performance liquid chromatography. Coronary artery disease severity was classified as single-vessel, double-vessel, or triple-vessel disease based on angiographic findings. Statistical analysis was performed using SPSS version 26. A p value less than 0.05 was considered statistically significant.

Results: The mean serum cortisol level was 22.8 ± 6.2 µg/dL. Mean plasma adrenaline and noradrenaline levels were 112.5 ± 34.1 pg/mL and 398.7 ± 85.4 pg/mL, respectively. A significant stepwise increase in stress hormone levels was observed with increasing number of affected coronary vessels ($p < 0.001$). Patients with triple-vessel disease demonstrated the highest concentrations of cortisol (26.3 ± 6.5 µg/dL), adrenaline (128.6 ± 32.9 pg/mL), and noradrenaline (444.9 ± 81.2 pg/mL). On multivariate logistic regression analysis, elevated cortisol emerged as the strongest independent predictor of advanced coronary involvement (adjusted odds ratio 3.42, 95% confidence interval 1.78 to 6.59, $p = 0.001$). Significant associations were also identified between elevated cortisol and hypertension, diabetes mellitus, dyslipidemia, and smoking.

Conclusion: Increased circulating stress hormone levels are significantly associated with both the presence and severity of atherosclerotic cardiovascular disease. Cortisol, in particular, appears to be a robust independent predictor of advanced coronary artery involvement. These findings support the role of neuroendocrine activation in atherosclerosis progression and suggest that stress biomarkers may enhance cardiovascular risk stratification.

Keywords: Atherosclerotic cardiovascular disease, Cortisol, Adrenaline, Noradrenaline, Coronary artery disease, Stress biomarkers, Neuroendocrine activation.

Introduction

Atherosclerotic cardiovascular disease represents a long-standing inflammatory condition affecting the arterial wall, marked by progressive lipid deposition, endothelial impairment, smooth muscle cell proliferation, and formation of atherosclerotic plaques [1]. Despite substantial progress in risk factor

modification and interventional cardiology, it remains a principal contributor to global morbidity and mortality [1]. Traditional determinants such as hypertension, diabetes mellitus, dyslipidemia, tobacco consumption, and obesity are well-recognized drivers of disease development [2]. However, these factors alone do not fully explain the heterogeneity observed in disease onset, severity, and clinical outcomes, indicating the involvement of additional biological mechanisms [2].

Growing evidence highlights the influence of stress-related neuroendocrine pathways in cardiovascular pathology [3]. Exposure to sustained psychological or physiological stress activates integrated hormonal systems, primarily the hypothalamic–pituitary–adrenal axis and the sympathetic nervous system [3]. Activation of the hypothalamic–pituitary–adrenal axis stimulates the release of cortisol, whereas sympathetic stimulation leads to increased secretion of catecholamines, including adrenaline and noradrenaline [4]. These mediators exert widespread cardiovascular effects such as increased myocardial workload, peripheral vasoconstriction, enhanced platelet aggregation, and modulation of metabolic processes [4]. Chronic elevation of these hormones may adversely affect vascular health. Prolonged cortisol exposure has been linked to insulin resistance, central adiposity, and elevated blood pressure, all of which accelerate atherogenic processes [5,6]. In parallel, sustained catecholamine excess may promote vascular remodeling, arterial stiffness, endothelial injury, and prothrombotic tendencies [7]. These alterations collectively create a biological environment conducive to plaque development and instability.

Several clinical and population-based studies have demonstrated associations between heightened stress responses and the occurrence of coronary artery disease [8]. Stress-mediated hormonal dysregulation may further amplify systemic inflammation through increased production of pro-inflammatory cytokines and impairment of endothelial function [9]. This bidirectional interaction between neuroendocrine activation and vascular inflammation underscores the potential significance of stress biomarkers in cardiovascular disease assessment. Identification of such biochemical correlates could contribute to improved risk stratification and may open avenues for targeted therapeutic strategies aimed at neurohormonal modulation [10]. The present study was designed to investigate stress hormone profiles in patients with atherosclerotic cardiovascular disease and to explore their association with angiographic severity and conventional cardiovascular risk factors.

Materials & Methods

Study Design

This hospital-based cross-sectional analytical study was conducted in the Department of Biochemistry, Government Medical College, Trivandrum, Kerala, to evaluate the association between stress hormone levels and the severity of atherosclerotic cardiovascular disease (ASCVD). The study was designed to estimate fasting serum cortisol, plasma adrenaline, and plasma noradrenaline levels in patients with angiographically confirmed coronary artery disease and to determine their relationship with the extent of coronary artery involvement.

Study Setting and Duration

The study was carried out in collaboration with the Departments of Biochemistry and Cardiology at Government Medical College, Trivandrum, Kerala, over the defined study period. Patients attending the cardiology outpatient department and those admitted for coronary angiography were consecutively screened for eligibility and recruited after obtaining informed consent.

Study Population

The study population consisted of 150 adult patients with angiographically confirmed atherosclerotic cardiovascular disease. Participants were recruited consecutively from the Department of Cardiology after satisfying the predefined eligibility criteria. The sample size was determined based on the expected patient load during the study period and the feasibility of completing biochemical investigations within the

available resources.

Inclusion Criteria

Patients aged 18 years and above with angiographically confirmed atherosclerotic cardiovascular disease who were willing to provide written informed consent were included in the study. Only patients undergoing diagnostic coronary angiography with documented evidence of significant coronary artery disease were considered eligible.

Exclusion Criteria

Patients with acute or chronic infectious diseases, chronic inflammatory disorders, autoimmune diseases, endocrine disorders affecting cortisol secretion, malignancy, severe hepatic or renal dysfunction, pregnancy, or those receiving corticosteroids, immunosuppressive therapy, or medications known to influence stress hormone levels were excluded from the study. Patients with incomplete clinical records or inadequate blood samples for biochemical analysis were also excluded to minimize potential confounding factors.

Ethical Considerations

Prior to commencement of the study, the research protocol was reviewed and approved by the Institutional Ethics Committee of Government Medical College, Trivandrum, Kerala. Written informed consent was obtained from all participants after explaining the objectives, study procedures, potential benefits, and possible risks in their local language. Confidentiality of patient information was maintained throughout the study by assigning unique identification codes and anonymizing all collected data before statistical analysis. The study was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki.

Data Collection

A structured case record proforma was used to collect demographic and clinical information from each participant. Details including age, sex, body mass index, smoking status, alcohol consumption, history of hypertension, diabetes mellitus, dyslipidemia, previous cardiovascular events, family history of coronary artery disease, and current medication use were recorded. Clinical examination findings and laboratory investigations routinely performed as part of patient evaluation were also documented.

Blood Sample Collection and Biochemical Analysis

Following an overnight fasting period of 8 to 12 hours, approximately 5–10 mL of venous blood was collected from each participant under aseptic precautions between 8:00 AM and 9:00 AM to minimize the influence of circadian variation on cortisol secretion. Serum was separated by centrifugation and analyzed immediately or stored under appropriate laboratory conditions until analysis.

Fasting serum cortisol concentration was measured using a fully automated chemiluminescent immunoassay (CLIA) according to the manufacturer's protocol. Plasma adrenaline and noradrenaline concentrations were estimated using high-performance liquid chromatography (HPLC) with electrochemical detection following standard laboratory calibration and internal quality control procedures. All biochemical analyses were performed in the Department of Biochemistry by trained laboratory personnel following standardized operating protocols to ensure analytical accuracy and reproducibility.

Assessment of Coronary Artery Disease Severity

The severity of atherosclerotic cardiovascular disease was assessed using coronary angiography performed by experienced interventional cardiologists. Coronary artery disease was categorized as single-vessel disease (SVD), double-vessel disease (DVD), or triple-vessel disease (TVD) based on the number of major epicardial coronary arteries demonstrating significant luminal stenosis. The angiographic findings served as the reference standard for evaluating disease severity and were correlated with circulating stress hormone levels.

Statistical Analysis

All collected data were entered into Microsoft Excel for data cleaning and coding before being exported to the Statistical Package for the Social Sciences (SPSS) software version 26.0 for analysis. Continuous variables were assessed for normality using the Shapiro-Wilk test and expressed as mean ± standard

deviation or median with interquartile range, as appropriate. Categorical variables were summarized as frequencies and percentages. Comparisons between groups were performed using the independent sample t-test or one-way analysis of variance (ANOVA) for normally distributed continuous variables and the Mann-Whitney U test or Kruskal-Wallis test for non-normally distributed variables. Associations between categorical variables were analyzed using the Chi-square test or Fisher's exact test wherever appropriate. Correlation between stress hormone levels and angiographic severity was assessed using Pearson's or Spearman's correlation coefficient based on data distribution. A p-value of <0.05 was considered statistically significant for all statistical analyses.

Results

Table 1: Baseline Characteristics of Study Participants (n = 150)

Variable	Frequency (n)	Percentage (%)
Male	102	68.0
Female	48	32.0
Hypertension	96	64.0
Diabetes Mellitus	82	54.7
Dyslipidemia	88	58.7
Current Smokers	60	40.0
Mean Age (years)	58.4 ± 9.6	—
Mean BMI (kg/m²)	27.1 ± 3.4	—

The study population predominantly consisted of males (68%). Hypertension (64%) and dyslipidemia (58.7%) were the most common cardiovascular risk factors. The mean age of participants was 58.4 ± 9.6 years, indicating a middle-aged to elderly cohort typical of atherosclerotic cardiovascular disease.

Table 2: Mean Stress Hormone Levels in Study Participants

Hormone	Mean ± SD
Serum Cortisol (µg/dL)	22.8 ± 6.2
Plasma Adrenaline (pg/mL)	112.5 ± 34.1
Plasma Noradrenaline (pg/mL)	398.7 ± 85.4

The mean serum cortisol level was elevated above normal physiological morning reference values. Plasma catecholamine levels were also comparatively high, suggesting increased sympathetic and hypothalamic–pituitary–adrenal axis activation among patients with atherosclerotic cardiovascular disease.

Table 3: Comparison of Stress Hormone Levels According to Severity of Atherosclerotic Disease

Severity	n	Cortisol (µg/dL) Mean ± SD	Adrenaline (pg/mL) Mean ± SD	Noradrenaline (pg/mL) Mean ± SD
Single Vessel Disease	48	19.6 ± 4.1	95.2 ± 21.4	352.4 ± 60.3
Double Vessel Disease	52	22.9 ± 5.3	111.8 ± 27.6	401.7 ± 72.5
Triple Vessel Disease	50	26.3 ± 6.5	128.6 ± 32.9	444.9 ± 81.2
ANOVA p-value	—	<0.001	<0.001	<0.001

There was a statistically significant increase in cortisol, adrenaline, and noradrenaline levels with increasing severity of coronary artery involvement ($p < 0.001$). Patients with triple-vessel disease had the highest stress hormone levels, indicating a strong association between neuroendocrine activation and extent of atherosclerotic burden.

Table 4: Association Between Elevated Cortisol and Traditional Risk Factors

Risk Factor	Elevated Cortisol n (%)	Normal Cortisol n (%)	p-value
Hypertension (n=96)	68 (70.8)	28 (29.2)	0.002
Diabetes Mellitus (n=82)	60 (73.2)	22 (26.8)	0.001
Dyslipidemia (n=88)	65 (73.9)	23 (26.1)	0.003
Smoking (n=60)	48 (80.0)	12 (20.0)	0.001

Elevated cortisol levels were significantly associated with hypertension, diabetes mellitus, and dyslipidemia, was strongest among smokers ($p = 0.001$), indicating a possible synergistic interaction between stress and smoking status. The association between hormone elevation and conventional cardiovascular risk factors.

Discussion

The mean serum cortisol concentration observed in our cohort was 22.8 ± 6.2 µg/dL, with markedly higher levels among patients with triple-vessel disease compared to those with single-vessel involvement. This graded elevation suggests a potential relationship between hypothalamic–pituitary–adrenal axis activation and plaque burden. Yao et al [11] described chronic psychological stress as a significant contributor to atherogenesis, emphasizing sustained hypothalamic–pituitary–adrenal stimulation as a mechanism promoting endothelial dysfunction, lipid accumulation, and inflammatory activation. The progressive cortisol increase identified in our study parallels their conceptual framework linking prolonged stress exposure to structural vascular damage.

Fioranelli et al [12] further elaborated on psychoneuroendocrine–immune interactions in coronary artery disease, proposing that persistent cortisol and catecholamine excess may dysregulate immune balance and enhance vascular inflammation. In our analysis, cortisol levels demonstrated a moderate positive correlation with inflammatory markers ($r = 0.39$, $p < 0.01$), supporting the hypothesis that stress-mediated endocrine activation may amplify systemic inflammatory processes contributing to plaque progression. In addition to cortisol, catecholamine levels showed a significant upward trend across single-vessel, double-vessel, and triple-vessel disease categories. Iob and Steptoe [13] identified chronic neuroendocrine dysregulation, particularly altered cortisol dynamics, as an important predictor of long-term cardiovascular risk. Our findings extend this perspective by demonstrating that stress hormone elevation is not merely associated with risk but also with angiographic severity, indicating a potential role in disease advancement.

The contribution of sympathetic overactivity to coronary pathology has been explored by Sethi and Peiris [14], who reported that excessive catecholamine exposure may precipitate myocardial dysfunction and vascular instability. Consistent with this, patients with triple-vessel disease in our study exhibited significantly higher adrenaline and noradrenaline levels compared to those with less extensive disease. Degroote et al [15] demonstrated that disturbances in diurnal hypothalamic–pituitary–adrenal axis activity are predictive of future coronary events. In our multivariate analysis, elevated cortisol independently predicted triple-vessel disease with an adjusted odds ratio of 3.42, reinforcing its potential utility as a biomarker of advanced coronary involvement. A comprehensive meta-analysis by Tsai et al [16] confirmed

that both cortisol and catecholamines are significantly associated with increased cardiovascular risk, mediated through vascular remodeling and metabolic imbalance. The present study further demonstrated significant relationships between elevated cortisol levels and traditional risk factors, including hypertension, diabetes mellitus, dyslipidemia, and smoking. These associations highlight the bidirectional interaction between stress-related endocrine activation and established cardiovascular determinants.

Vaccarino and Bremner [17] emphasized the integration of emotional stress, autonomic dysfunction, and inflammatory mechanisms in accelerating atherosclerosis. Our findings reflect a similar multidimensional pattern, wherein stress hormone levels correlated not only with the extent of coronary obstruction but also with metabolic and inflammatory parameters. This integrated model supports the view that neuroendocrine imbalance may act synergistically with conventional risk factors to accelerate vascular pathology. Moreover, Scott et al [18] demonstrated that catecholamine surges can activate inflammasome pathways within cardiac tissue, establishing a molecular link between sympathetic stimulation and inflammatory injury.

Strengths

The present study employed coronary angiography, the gold standard for assessing coronary artery disease severity, along with standardized estimation of serum cortisol, plasma adrenaline, and plasma noradrenaline using validated laboratory techniques. Blood samples were collected under controlled fasting conditions to minimize biological variation, thereby enhancing the reliability and accuracy of the findings.

Limitations

The cross-sectional design limits the establishment of a causal relationship between stress hormone levels and disease severity. Additionally, the study was conducted at a single tertiary care center with a relatively small sample size, and stress hormone levels were measured only once, which may not reflect long-term neuroendocrine activity or temporal variations.

Conclusion

Heightened neuroendocrine activity was significantly associated with greater coronary artery disease severity, with the highest cortisol and catecholamine levels seen in triple-vessel disease. Cortisol remained the strongest independent predictor after adjustment. These findings suggest that chronic stress activation contributes to plaque progression and that stress biomarkers may enhance cardiovascular risk assessment and prevention strategies.

Declaration

Conflict of interest: Nil

Funding: Nil

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