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DISORDERS OF CATECHOLAMINE METABOLISM AND IMMUNE STATUS IN PATIENTS WITH CHRONIC ISCHEMIC HEART DISEASE COMPLICATED BY ATRIAL FIBRILLATION

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Abstract

Background - Atrial fibrillation (AF) is the most common sustained arrhythmia in patients with chronic ischemic heart disease (CIHD). While structural remodeling is well-documented, the exact neurohumoral and inflammatory triggers require further clarification. Objective: To investigate the features of catecholamine metabolism and cellular immune status in patients with CIHD complicated by AF. Methods: A total of 82 patients with CIHD were examined, divided into two groups: Group 1 (n=44) with concomitant AF, and Group 2 (n=38) without AF. The control group consisted of 20 healthy volunteers. Plasma levels of epinephrine and norepinephrine were determined using high-performance liquid chromatography. Immune status was assessed by measuring tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), high-sensitivity C-reactive protein (hs-CRP), and T-lymphocyte subpopulations (CD3+, CD4+, CD8+). Results: Patients with CIHD and AF demonstrated a significant sympathetic overdrive, with norepinephrine levels reaching 485.2 ± 32.4 pg/mL compared to 342.6 ± 28.1 pg/mL in the non-AF group ($p < 0.05$). This was accompanied by profound immune dysregulation. TNF-α and IL-6 concentrations were 1.8 and 2.1 times higher, respectively, in the AF group compared to controls. Furthermore, a decreased CD4+/CD8+ immunoregulatory index was observed in the AF cohort. Conclusion: The presence of atrial fibrillation in CIHD is associated with combined sympathoadrenal hyperactivation and systemic immune-inflammatory response. These pathophysiological shifts likely create a vicious cycle that promotes both electrical and structural myocardial remodeling.

Keywords

chronic ischemic heart disease, atrial fibrillation, catecholamines, immune status, inflammation, cytokines.

НАРУШЕНИЕ МЕТАБОЛИЗМА КАТЕХОЛАМИНОВ И ИММУННОГО СТАТУСА У БОЛЬНЫХ ХРОНИЧЕСКОЙ ИШЕМИЧЕСКОЙ БОЛЕЗНЬЮ СЕРДЦА С ФИБРИЛЛЯЦИЕЙ ПРЕДСЕРДИЙ

Аннотация

Обоснование - Фибрилляция предсердий (ФП) является наиболее частой аритмией у пациентов с хронической ишемической болезнью сердца (ХИБС). Несмотря на изученность структурного ремоделирования, нейрогуморальные и воспалительные триггеры требуют дальнейшего уточнения. Цель исследования: Изучить особенности метаболизма катехоламинов и клеточного иммунного статуса у больных ХИБС, осложненной ФП. Материалы и методы: Обследовано 82 больных ХИБС, разделенных на две группы: 1-я группа (n=44) с сопутствующей ФП, 2-я группа (n=38) без ФП. Контрольную группу составили 20 здоровых добровольцев. Уровень адреналина и норадреналина в плазме крови определяли методом высокоэффективной жидкостной

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хроматографии. Иммунный статус оценивали по уровню фактора некроза опухоли-альфа (ФНО-α), интерлейкина-6 (ИЛ-6), высокочувствительного С-реактивного белка (вч-СРБ) и субпопуляциям Т-лимфоцитов (CD3+, CD4+, CD8+). Результаты: У пациентов с ХИБС и ФП выявлена значительная гиперсимпатикотония: уровень норадреналина достиг 485,2 ± 32,4 пг/мл по сравнению с 342,6 ± 28,1 пг/мл в группе без ФП ($p < 0,05$). Это сопровождалось выраженной иммунной дисрегуляцией. Концентрации ФНО-α и ИЛ-6 были в 1,8 и 2,1 раза выше соответственно в группе ФП по сравнению с контролем. Кроме того, в когорте с ФП наблюдалось снижение иммунорегуляторного индекса CD4+/CD8+. Заключение: Наличие фибрилляции предсердий при ХИБС ассоциируется с сочетанной гиперактивацией симпатоадреналовой системы и системным иммунно-воспалительным ответом. Данные патофизиологические сдвиги, вероятно, формируют порочный круг, способствующий как электрическому, так и структурному ремоделированию миокарда.

Ключевые слова

хроническая ишемическая болезнь сердца, фибрилляция предсердий, катехоламины, иммунный статус, воспаление, цитокины.

INTRODUCTION

Chronic ischemic heart disease (CIHD) continues to be a leading cause of morbidity and mortality worldwide. A frequent and clinically challenging complication of CIHD is atrial fibrillation (AF), which significantly worsens patient prognosis by increasing the risk of heart failure, thromboembolic events, and sudden cardiac death [1]. The pathogenesis of AF in the context of ischemic disease is complex and extends beyond mere myocardial ischemia. Recent literature suggests that the initiation and maintenance of AF are deeply rooted in autonomic nervous system dysfunction and profound alterations in the immune system [2, 3].

The sympathoadrenal system plays a critical role in cardiac electrophysiology. Excessive release of catecholamines—specifically epinephrine and norepinephrine—alters the action potential duration, increases intracellular calcium load, and triggers triggered activity, ultimately creating an arrhythmogenic substrate [4]. While physiological levels of these hormones are essential for cardiac compensation, chronic sympathetic overdrive in CIHD leads to receptor downregulation and myocyte apoptosis [5].

Concurrently, there is a growing body of evidence linking systemic inflammation and immune dysregulation with the pathogenesis of AF [6]. Inflammatory cytokines, particularly interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α), have been shown to directly affect the electrical properties of atrial myocytes and promote the proliferation of cardiac fibroblasts, accelerating structural remodeling [7, 8]. Furthermore, alterations in cellular immunity, specifically shifts in T-lymphocyte subpopulations (CD4+ and CD8+ cells), indicate that autoimmune and chronic inflammatory mechanisms might sustain the fibrillatory processes [9].

Despite individual studies on sympathetic activity and inflammation in cardiovascular pathology, the combined interaction between catecholamine metabolism and cellular immune status in patients suffering from CIHD complicated by AF remains insufficiently explored. Understanding this interplay is vital for developing targeted, pathogenetic therapeutic strategies.

The present study aimed to investigate the specific disorders of catecholamine metabolism and cellular immune status in patients with CIHD complicated by atrial fibrillation, treated at the Department of Faculty Therapy.

MATERIALS AND METHODS

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Study population - The cross-sectional observational study included 82 patients diagnosed with CIHD who were admitted to the cardiology inpatient unit of the clinic of Andijan State Medical Institute. The patient cohort comprised 45 men and 37 women, with an average age of 61.4 ± 6.2 years. Diagnosis verification was based on the European Society of Cardiology (ESC) guidelines, clinical history, ECG, and echocardiographic findings.

Patients were divided into two main clinical groups based on the presence of arrhythmias: Group 1 (n = 44): Patients with CIHD complicated by paroxysmal or persistent atrial fibrillation. Group 2 (n = 38): Patients with CIHD without any history or current evidence of atrial fibrillation (sinus rhythm).

A Control Group (n = 20) comprising healthy volunteers matched for age and gender without any clinical or instrumental signs of cardiovascular disease was also examined to establish baseline normative values.

Exclusion criteria included acute myocardial infarction within the last 6 months, severe valvular heart disease, thyroid dysfunction, acute infectious diseases, active autoimmune disorders, and chronic kidney disease (stage IV-V). All participants provided informed written consent prior to inclusion. The study protocol was approved by the local Ethics Committee.

Laboratory Procedures - Fasting venous blood samples were collected from all participants between 08:00 and 09:00 AM after a 20-minute resting period in a supine position to minimize stress-induced catecholamine fluctuations.

Catecholamine Assessment: Plasma levels of norepinephrine (NE) and epinephrine (E) were determined using high-performance liquid chromatography (HPLC) with electrochemical detection (Agilent Technologies, USA).

Immune Status and Cytokines: Quantitative determination of TNF-α, IL-6, and high-sensitivity C-reactive protein (hs-CRP) was performed using enzyme-linked immunosorbent assay (ELISA) kits (Vector-Best, Russia).

Cellular Immunity: T-lymphocyte subpopulations, specifically total T-cells (CD3+), T-helper cells (CD4+), and cytotoxic T-cells (CD8+), were quantified using flow cytometry (BD FACSCalibur). The immunoregulatory index (IRI) was calculated as the ratio of CD4+ to CD8+ cells.

Statistical Analysis - Data were analyzed using SPSS Statistics version 26.0. Continuous variables were tested for normal distribution using the Shapiro-Wilk test. Normally distributed data were presented as mean ± standard deviation (M ± SD). Group comparisons were performed using the Student's t-test for independent samples. Correlation analysis was conducted using Pearson's correlation coefficient (r). A p-value of < 0.05 was considered statistically significant.

RESULTS

Baseline clinical and demographic characteristics demonstrated no significant differences between the two CIHD groups regarding age, gender distribution, and body mass index, ensuring comparability. However, echocardiographic parameters indicated slightly worse left ventricular ejection fraction and larger left atrial volume in the AF group (Table 1).

Table 1. Clinical and demographic characteristics of the studied groups.

Parameter	Control (n=20)	Group 2 (CIHD without AF, n=38)	Group 1 (CIHD + AF, n=44)
Age (years)	58.2 ± 5.1	60.8 ± 6.4	62.1 ± 5.9
Male / Female (n)	11 / 9	21 / 17	24 / 20
BMI (kg/m²)	24.1 ± 2.2	27.6 ± 3.1*	28.4 ± 3.5*
LVEF (%)	64.5 ± 4.2	56.2 ± 5.1*	52.8 ± 6.3*ƫ

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Left Atrial Volume Index (mL/m²)	22.4 ± 3.1	28.6 ± 4.4*	36.2 ± 5.8*ƫ

*Note: * p < 0.05 compared to Control; ƫ p < 0.05 compared to Group 2.*

Catecholamine metabolism - Analysis of the sympathoadrenal system revealed marked hyperactivation in patients with CIHD, which was most pronounced in patients suffering from atrial fibrillation. As shown in Table 2, plasma norepinephrine levels in Group 1 were 73% higher than in the control group and significantly exceeded the levels observed in Group 2 ($p < 0.05$). Epinephrine levels followed a similar trend, indicating acute and chronic stress responses contributing to the arrhythmogenic milieu.

Table 2. Plasma catecholamine levels in examined patients (M ± SD).

Indicator	**Control (n=20)**	**Group 2 (CIHD without AF)**	**Group 1 (CIHD + AF)**
Norepinephrine (pg/mL)	280.4 ± 22.5	342.6 ± 28.1*	485.2 ± 32.4*ƫ
Epinephrine (pg/mL)	45.2 ± 6.8	68.4 ± 8.2*	94.6 ± 11.5*ƫ

*Note: * p < 0.05 compared to Control; ƫ p < 0.05 compared to Group 2.*

Immune status and cytokine profile - The evaluation of immune parameters demonstrated signs of active systemic inflammation and cellular immunity imbalance in CIHD patients, with maximum alterations noted in the AF cohort. The concentrations of pro-inflammatory cytokines (TNF-α and IL-6) and hs-CRP were dramatically elevated in Group 1 (Table 3).

Flow cytometric analysis of lymphocyte subpopulations showed a reduction in total CD3+ T-cells in both CIHD groups. Notably, in patients with AF, there was a relative decrease in T-helper cells (CD4+) coupled with an increase in cytotoxic T-cells (CD8+). This shift resulted in a depressed immunoregulatory index (CD4+/CD8+ ratio) of 1.28 ± 0.15 in Group 1, suggesting a state of secondary immunodeficiency and chronic autoimmune-like inflammation against myocardial structures.

Table 3. Cytokine profile and cellular immunity parameters (M ± SD).

Parameter	**Control (n=20)**	**Group 2 (CIHD without AF)**	**Group 1 (CIHD + AF)**
hs-CRP (mg/L)	1.8 ± 0.4	4.6 ± 1.2*	8.2 ± 2.1*ƫ
TNF-α (pg/mL)	4.5 ± 0.8	7.9 ± 1.5*	12.4 ± 2.6*ƫ
IL-6 (pg/mL)	3.2 ± 0.6	6.8 ± 1.1*	11.5 ± 1.9*ƫ
CD3+ (%)	68.4 ± 4.2	62.5 ± 5.1*	57.2 ± 4.8*ƫ
CD4+ (%)	44.6 ± 3.5	40.2 ± 3.8	35.4 ± 3.1*ƫ
CD8+ (%)	24.2 ± 2.1	26.5 ± 2.4	28.6 ± 2.5* ƫ
CD4+/CD8+ (IRI)	1.84 ± 0.12	1.51 ± 0.14*	1.28 ± 0.15*ƫ

*Note: * p < 0.05 compared to Control; ƫ p < 0.05 compared to Group 2.*

Correlation analysis in Group 1 revealed a positive, statistically significant relationship between plasma norepinephrine levels and left atrial volume index ($r = 0.54$, $p < 0.01$), as well as between IL-6 and the duration of the AF history ($r = 0.61$, $p < 0.01$).

DISCUSSION

The findings of this study outline a clear pathogenetic triangle in the development of atrial fibrillation among patients with ischemic heart disease: structural heart changes, autonomic nervous system dysregulation (sympathetic overdrive), and immune-inflammatory activation.

Our data regarding catecholamine metabolism align with earlier hypotheses suggesting that chronic ischemia acts as a persistent stressor, leading to a compensatory but ultimately detrimental surge in sympathetic tone [10]. The significantly elevated levels of norepinephrine and epinephrine in the AF group indicate that sympathoadrenal hyperactivation is not just a bystander but a dynamic participant in arrhythmogenesis. High catecholamine concentrations decrease the action potential threshold and shorten the refractory period of atrial myocytes, facilitating the formation of multiple re-entry circuits [11].

Perhaps the most compelling finding of our research is the profound derangement in the immune status of patients with AF. The elevated levels of TNF-α, IL-6, and hs-CRP confirm the presence of low-grade, sterile systemic inflammation. Cytokines like IL-6 can directly modulate calcium handling proteins in the sarcoplasmic reticulum, triggering delayed afterdepolarizations [12]. Furthermore, inflammation promotes the activation of matrix metalloproteinases and fibroblast proliferation, leading to the interstitial fibrosis observed clinically as left atrial enlargement (as seen in our echocardiographic data for Group 1) [13].

The cellular immunity shift, characterized by a dropping CD4+/CD8+ index, points towards a depletion of regulatory immune control and a potential cytotoxic attack on ischemic cardiomyocytes. This implies that AF in CIHD might be sustained by a chronic, low-level autoimmune response to antigens released from damaged cardiac tissue [14, 15].

The positive correlation between norepinephrine levels, inflammatory markers, and atrial dilation suggests a vicious pathophysiological cycle. Sympathetic overactivity promotes inflammation via adrenergic receptors on immune cells, while inflammatory cytokines, in turn, can cross the blood-brain barrier to further stimulate central sympathetic outflow [16]. Breaking this cycle represents a critical target for future pharmacological interventions in the faculty therapy setting.

CONCLUSION

Patients with chronic ischemic heart disease complicated by atrial fibrillation exhibit severe neurohumoral and immune dysregulation. This is characterized by a marked increase in circulating catecholamines (norepinephrine and epinephrine) alongside a robust systemic inflammatory response (elevated IL-6, TNF-α, hs-CRP) and cellular immunosuppression (decreased CD4+/CD8+ ratio).

These alterations highlight that atrial fibrillation is not merely an electrical anomaly isolated to the heart, but a systemic manifestation involving the sympathoadrenal and immune systems. Evaluating these parameters in clinical practice could provide valuable prognostic information and open new avenues for complex, anti-inflammatory, and neuromodulatory therapies in managing AF in ischemic patients.

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