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COMPARATIVE EVALUATION OF CIRCULATING IL-6 AND HSCRP LEVELS IN HEART FAILURE VERSUS STABLE CORONARY ARTERY DISEASE: A CROSS-SECTIONAL STUDY

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ABSTRACT

Background: Inflammatory biomarkers play a crucial role in the pathophysiology of cardiovascular diseases. Interleukin-6 (IL-6) and high-sensitivity C-reactive protein (hsCRP) have emerged as significant predictors of cardiovascular outcomes. However, comparative data regarding these inflammatory markers between heart failure (HF) and stable coronary artery disease (CAD) remain limited.

Methods: This cross-sectional study enrolled 180 participants divided into three groups: heart failure patients (n=60), stable coronary artery disease patients (n=60), and healthy controls (n=60). Serum IL-6 and hsCRP levels were measured using enzyme-linked immunosorbent assay and immunoturbidimetric methods, respectively. Demographic characteristics, clinical parameters, and echocardiographic findings were documented. Statistical analysis was performed using ANOVA, independent t-tests, and Pearson correlation coefficients.

Results: Heart failure patients demonstrated significantly elevated IL-6 levels (18.74 ± 6.82 pg/mL) compared to stable CAD patients (9.56 ± 3.91 pg/mL) and healthy controls (3.21 ± 1.45 pg/mL) ($p<0.001$). Similarly, hsCRP levels were markedly higher in HF patients (8.92 ± 3.67 mg/L) versus stable CAD (4.83 ± 2.14 mg/L) and controls (1.28 ± 0.72 mg/L) ($p<0.001$). A significant negative correlation existed between left ventricular ejection fraction and both IL-6 ($r=-0.68$, $p<0.001$) and hsCRP ($r=-0.54$, $p<0.001$) in heart failure patients.

Conclusion: Circulating IL-6 and hsCRP levels are significantly elevated in heart failure compared to stable coronary artery disease, suggesting a more pronounced inflammatory state in HF. These biomarkers may serve as valuable tools for disease differentiation and risk stratification.

Keywords: Interleukin-6, high-sensitivity C-reactive protein, heart failure, coronary artery disease, inflammation, biomarkers

INTRODUCTION

Cardiovascular diseases remain the leading cause of mortality and morbidity worldwide, accounting for approximately 17.9 million deaths annually **[1]**. Among cardiovascular conditions, heart failure (HF) and coronary artery disease (CAD) represent major clinical entities with significant healthcare burden **[2]**. The pathophysiological mechanisms underlying these conditions are complex and multifactorial, with inflammation emerging as a central mediator in disease progression and adverse outcomes **[3]**.

The inflammatory hypothesis of atherosclerosis has gained substantial evidence over the past two decades **[4]**. Inflammatory processes contribute to endothelial dysfunction, plaque formation, and

plaque instability in coronary artery disease **[5]**. Similarly, heart failure is characterized by chronic low-grade inflammation that promotes myocardial remodeling, fibrosis, and progressive cardiac dysfunction **[6]**. The recognition of inflammation as a therapeutic target has revolutionized cardiovascular medicine, as demonstrated by the landmark CANTOS trial **[7]**.

Interleukin-6 (IL-6) is a pleiotropic cytokine that plays a pivotal role in the inflammatory cascade. It stimulates hepatic synthesis of acute-phase reactants, including C-reactive protein, and promotes activation of endothelial cells and leukocytes **[8]**. Elevated IL-6 levels have been associated with increased cardiovascular risk, disease severity, and mortality in various cardiac conditions **[9]**. High-sensitivity C-reactive protein (hsCRP) serves as a downstream marker of IL-6 activity and has been extensively validated as a predictor of cardiovascular events **[10]**.evious investigations have examined inflammatory biomarkers in heart failure and coronary artery disease separately **[11]**. However, comparative studies directly evaluating the magnitude of inflammatory activation between these two conditions remain scarce. Understanding the differential inflammatory profiles may provide insights into disease-specific mechanisms and guide therapeutic strategies **[12]**. Furthermore, such comparisons may help identify patients who would benefit most from anti-inflammatory interventions.

The research gap exists in the direct comparison of inflammatory biomarker levels between heart failure and stable coronary artery disease populations. Most existing studies have focused on acute coronary syndromes rather than stable disease, limiting the understanding of baseline inflammatory states **[13]**. Additionally, the relationship between inflammatory markers and cardiac functional parameters requires further elucidation.

The aim of this study was to compare circulating IL-6 and hsCRP levels between patients with heart failure and those with stable coronary artery disease, and to evaluate the correlation between these inflammatory biomarkers and echocardiographic parameters of cardiac function.

Materials and Methods

Study Design and Setting

This cross-sectional observational study was conducted at the Department of Cardiology, University Teaching Hospital, between January 2023 and December 2023.

Study Population

A total of 180 participants were enrolled and divided into three groups. Group A comprised 60 patients with established heart failure (NYHA class II-IV) with reduced ejection fraction (HFrEF, LVEF <40%). Group B included 60 patients with angiographically confirmed stable coronary artery disease (≥50% stenosis in at least one major coronary vessel) without heart failure symptoms. Group C consisted of 60 age- and sex-matched healthy controls without any cardiovascular disease.

Inclusion Criteria

For heart failure patients, inclusion criteria were age between 35-75 years, documented heart failure diagnosis for at least 3 months, stable clinical condition for at least 4 weeks, and optimal medical therapy. For stable CAD patients, criteria included angiographic confirmation of coronary stenosis, stable symptoms for at least 2 months, and no hospitalization for acute coronary syndrome within the preceding 6 months.

Exclusion Criteria

Exclusion criteria for all groups included acute infections, chronic inflammatory diseases (rheumatoid arthritis, inflammatory bowel disease), malignancy, chronic kidney disease (eGFR <30 mL/min/1.73m²), hepatic dysfunction, recent surgery or trauma within 4 weeks, use of immunosuppressive medications, and refusal to provide informed consent.

Clinical Assessment

All participants underwent comprehensive clinical evaluation including medical history, physical examination, and documentation of cardiovascular risk factors. Body mass index (BMI) was calculated from height and weight measurements. Blood pressure was recorded as the mean of three readings taken 5 minutes apart in the seated position.

Laboratory Measurements

Venous blood samples were collected after overnight fasting (12 hours). Samples were centrifuged at 3000 rpm for 15 minutes, and serum was stored at -80°C until analysis. Serum IL-6 levels were measured using a commercially available enzyme-linked immunosorbent assay kit (sensitivity: 0.7 pg/mL, intra-assay CV: 4.2%). hsCRP was determined by particle-enhanced immunoturbidimetric assay (sensitivity: 0.1 mg/L). Lipid profile, fasting glucose, glycated hemoglobin, and renal function tests were performed using standard automated analyzers.

Echocardiographic Evaluation

Two-dimensional transthoracic echocardiography was performed by an experienced cardiologist blinded to clinical and laboratory data. Left ventricular ejection fraction (LVEF) was calculated using the modified Simpson's biplane method. Left ventricular end-diastolic diameter (LVEDD), left ventricular end-systolic diameter (LVESD), and left atrial diameter were measured according to American Society of Echocardiography guidelines.

Statistical Analysis

Sample size was calculated based on previous studies estimating a difference of 5 pg/mL in IL-6 levels between groups, with standard deviation of 6 pg/mL, $\alpha=0.05$, and power=80%, yielding a minimum of 54 subjects per group. Data were analyzed using SPSS version 26.0. Continuous variables were expressed as mean ± standard deviation, and categorical variables as frequencies and percentages. Normality was assessed using the Shapiro-Wilk test. One-way ANOVA with post-hoc Tukey test was used for multiple group comparisons. Independent t-tests compared two groups. Pearson correlation coefficient evaluated relationships between continuous variables. Multiple linear regression identified independent predictors. Statistical significance was defined as $p<0.05$.

Results

Baseline Characteristics

The demographic and clinical characteristics of study participants are presented in Table 1. The mean age was comparable across all three groups (p=0.412). Male predominance was observed in heart failure (68.3%) and stable CAD (65.0%) groups. Heart failure patients had significantly higher prevalence of diabetes mellitus (48.3% vs. 38.3% vs. 8.3%, p<0.001) and hypertension (71.7% vs. 63.3% vs. 15.0%, p<0.001). BMI was similar across groups (p=0.287).

Table 1: Baseline Demographic and Clinical Characteristics

Parameter	Heart Failure (n=60)	Stable CAD (n=60)	Controls (n=60)	p-value
Age (years)	58.4 ± 9.7	57.2 ± 10.3	55.8 ± 8.9	0.412
Male, n (%)	41 (68.3)	39 (65.0)	35 (58.3)	0.523
BMI (kg/m²)	27.3 ± 4.1	26.8 ± 3.8	26.2 ± 3.5	0.287
Diabetes mellitus, n (%)	29 (48.3)	23 (38.3)	5 (8.3)	<0.001
Hypertension, n (%)	43 (71.7)	38 (63.3)	9 (15.0)	<0.001
Smoking, n (%)	24 (40.0)	28 (46.7)	14 (23.3)	0.024
Systolic BP (mmHg)	124.6 ± 18.3	132.4 ± 15.7	121.8 ± 12.4	0.002
Diastolic BP (mmHg)	76.2 ± 10.5	82.1 ± 9.8	78.4 ± 8.6	0.008
Heart rate (bpm)	78.5 ± 14.2	68.3 ± 11.6	72.1 ± 9.4	<0.001

Laboratory and Echocardiographic Parameters

Laboratory findings and echocardiographic measurements are summarized in Table 2. Heart failure

patients demonstrated significantly lower LVEF (32.4 ± 6.8%) compared to stable CAD (56.2 ± 7.3%) and controls (62.8 ± 5.1%) (p<0.001). LVEDD was markedly increased in the heart failure group (62.8 ± 7.4 mm vs. 48.3 ± 5.2 mm vs. 46.1 ± 4.8 mm, p<0.001). Fasting glucose and HbA1c were elevated in both cardiovascular disease groups compared to controls.

Table 2: Laboratory and Echocardiographic Parameters

Parameter	Heart Failure (n=60)	Stable CAD (n=60)	Controls (n=60)	p-value
Total cholesterol (mg/dL)	186.4 ± 42.3	198.7 ± 38.6	182.5 ± 35.2	0.057
LDL-C (mg/dL)	112.8 ± 34.7	124.3 ± 32.1	108.6 ± 28.4	0.024
HDL-C (mg/dL)	38.4 ± 9.6	42.1 ± 10.2	52.3 ± 11.8	<0.001
Triglycerides (mg/dL)	168.5 ± 72.4	158.3 ± 64.8	132.6 ± 48.2	0.006
Fasting glucose (mg/dL)	124.6 ± 38.2	118.4 ± 32.6	94.2 ± 12.8	<0.001
HbA1c (%)	6.8 ± 1.4	6.4 ± 1.2	5.4 ± 0.5	<0.001
Creatinine (mg/dL)	1.18 ± 0.32	1.04 ± 0.26	0.92 ± 0.18	<0.001
LVEF (%)	32.4 ± 6.8	56.2 ± 7.3	62.8 ± 5.1	<0.001
LVEDD (mm)	62.8 ± 7.4	48.3 ± 5.2	46.1 ± 4.8	<0.001
LVESD (mm)	48.6 ± 8.2	32.4 ± 4.8	29.8 ± 3.6	<0.001

Inflammatory Biomarker Levels

The comparison of inflammatory biomarkers among study groups is presented in Table 3. IL-6 levels were significantly elevated in heart failure patients (18.74 ± 6.82 pg/mL) compared to stable CAD patients (9.56 ± 3.91 pg/mL) and healthy controls (3.21 ± 1.45 pg/mL) (p<0.001). Post-hoc analysis revealed significant differences between all pairs of groups (HF vs. CAD: p<0.001; HF vs. controls: p<0.001; CAD vs. controls: p<0.001).

Similarly, hsCRP levels showed a stepwise increase from controls (1.28 ± 0.72 mg/L) to stable CAD (4.83 ± 2.14 mg/L) to heart failure (8.92 ± 3.67 mg/L) (p<0.001). All pairwise comparisons were statistically significant.

Table 3: Inflammatory Biomarker Comparison

Biomarker	Heart Failure (n=60)	Stable CAD (n=60)	Controls (n=60)	p-value (ANOVA)
IL-6 (pg/mL)	18.74 ± 6.82	9.56 ± 3.91	3.21 ± 1.45	<0.001
hsCRP (mg/L)	8.92 ± 3.67	4.83 ± 2.14	1.28 ± 0.72	<0.001
IL-6/hsCRP ratio	2.18 ± 0.74	2.04 ± 0.68	2.62 ± 0.92	0.001

Correlation Analysis

In heart failure patients, IL-6 demonstrated significant negative correlation with LVEF ($r=-0.68$, $p<0.001$) and positive correlation with LVEDD ($r=0.54$, $p<0.001$) and NYHA class ($r=0.61$, $p<0.001$). hsCRP showed similar correlations with LVEF ($r=-0.54$, $p<0.001$) and LVEDD ($r=0.48$, $p<0.001$). IL-6 and hsCRP were significantly correlated with each other ($r=0.72$, $p<0.001$).
In stable CAD patients, weaker but significant correlations were observed between IL-6 and the number of diseased vessels ($r=0.38$, $p=0.003$) and between hsCRP and disease severity score ($r=0.34$, $p=0.008$).

Discussion

The present study demonstrates that patients with heart failure exhibit significantly higher levels of circulating IL-6 and hsCRP compared to those with stable coronary artery disease. These findings suggest that the inflammatory burden is substantially greater in heart failure, reflecting the systemic nature of the disease and the ongoing myocardial stress.
Our observation of elevated IL-6 levels in heart failure is consistent with previous reports indicating the central role of this cytokine in cardiac remodeling **[14]**. The failing myocardium produces IL-6 in response to mechanical stress and neurohormonal activation, creating a self-perpetuating cycle of inflammation and dysfunction **[15]**. The magnitude of IL-6 elevation in our heart failure cohort (approximately 6-fold compared to controls) underscores the intensity of inflammatory activation in this condition.
The intermediate elevation of inflammatory markers in stable CAD patients compared to controls and heart failure subjects reflects the chronic low-grade inflammation characteristic of atherosclerosis **[16]**. Unlike heart failure, where inflammation is driven primarily by myocardial factors, inflammation in CAD is largely vascular in origin **[17]**. This distinction may explain the quantitative differences observed between the two disease states.
The significant negative correlation between LVEF and inflammatory biomarkers in heart failure patients merits attention. This relationship has been previously described and suggests that inflammation worsens as cardiac function deteriorates **[18]**. Whether this association is causal or merely associative remains debated. Some investigators have proposed that inflammatory mediators directly impair contractile function through effects on calcium handling and myofilament sensitivity **[19]**.
Our finding that IL-6 correlated more strongly with LVEF than hsCRP ($r=-0.68$ vs. $r=-0.54$) is noteworthy. IL-6 may be a more sensitive indicator of cardiac-specific inflammation, while hsCRP reflects a more generalized inflammatory response **[20]**. This distinction has therapeutic implications, as targeting IL-6 directly may be more effective in heart failure than targeting downstream mediators.
The correlation between inflammatory markers and disease severity in stable CAD patients, albeit weaker than in heart failure, supports the inflammatory hypothesis of atherosclerosis progression **[21]**. Patients with more extensive coronary involvement demonstrated higher IL-6 and hsCRP levels, consistent with greater plaque burden and vascular inflammation.
Several mechanisms may account for the heightened inflammatory state in heart failure. Reduced cardiac output leads to tissue hypoperfusion, activating the innate immune system **[22]**. Gut barrier dysfunction with bacterial translocation contributes to endotoxemia and systemic inflammation **[23]**. Neurohormonal activation, particularly the renin-angiotensin-aldosterone system and sympathetic nervous system, further promotes inflammatory cytokine production **[24]**.
The clinical implications of our findings are multifold. First, inflammatory biomarkers may help differentiate the predominant pathophysiology in patients with overlapping features of heart failure and coronary artery disease. Second, the magnitude of inflammation may guide therapeutic intensity and selection of anti-inflammatory strategies. Third, serial monitoring of these markers may provide prognostic information beyond traditional parameters.
Study limitations include the cross-sectional design, which precludes causal inferences. The single-center setting may limit generalizability. We did not measure other inflammatory cytokines such as TNF-α or IL-1β, which may provide additional mechanistic insights. The inclusion of only HFrEF

patients limits extrapolation to heart failure with preserved ejection fraction.

Conclusion

This study demonstrates that circulating IL-6 and hsCRP levels are significantly elevated in heart failure compared to stable coronary artery disease, with both cardiovascular conditions showing higher inflammatory marker levels than healthy controls. The magnitude of inflammatory activation correlates inversely with left ventricular ejection fraction in heart failure patients, suggesting a relationship between inflammation and disease severity. These findings support the concept of differential inflammatory profiles across cardiovascular disease phenotypes and highlight the potential utility of inflammatory biomarkers for disease characterization and risk stratification. Future prospective studies should evaluate whether targeting inflammation differentially benefits heart failure versus coronary artery disease patients.

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