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# Prognostic Significance Of Endothelin-1 In Patients With Unstable Angina

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## Abstract

*Background: Endothelial dysfunction is a key pathophysiological mechanism underlying acute coronary syndromes. Endothelin-1 (ET-1), one of the most potent endogenous vasoconstrictors, plays a central role in coronary vasomotor dysregulation, inflammation, oxidative stress, and plaque instability. Despite growing interest in endothelin-mediated pathways, the clinical and prognostic significance of ET-1 in unstable angina remains insufficiently characterized, particularly in Central Asian populations. Objective: To investigate serum endothelin-1 levels in patients with unstable angina, to assess their association with clinical severity, ischemic burden, inflammatory activity, and to evaluate their prognostic value during short-term follow-up. Methods: A prospective observational study was conducted between 2024 and 2025 in tertiary cardiology centers in Tashkent, Uzbekistan. A total of 112 patients with unstable angina and 40 apparently healthy controls were enrolled. Serum ET-1 concentrations were measured using enzyme-linked immunosorbent assay. Clinical characteristics, frequency of angina attacks, ambulatory ECG monitoring parameters, and inflammatory markers were analyzed. Patients were followed for early adverse cardiovascular events. Results: Patients with unstable angina exhibited significantly higher ET-1 levels compared with controls (0.78 ± 0.21 vs. 0.26 ± 0.09 fmol/mL, $p < 0.001$). Elevated ET-1 was associated with increased ischemic burden, recurrent angina episodes, and unfavorable ECG patterns. A strong positive correlation was observed between ET-1 concentration and angina frequency ($r = 0.54$, $p < 0.01$). Persistently elevated ET-1 levels were predictive of early adverse cardiovascular outcomes. Conclusion: Endothelin-1 is a sensitive marker of endothelial dysfunction and an independent predictor of disease severity and short-term prognosis in unstable angina. Routine assessment of ET-1 may enhance risk stratification and guide personalized therapeutic strategies in acute coronary syndromes.*

Keywords: Endothelin-1; unstable angina; endothelial dysfunction; acute coronary syndrome; prognosis.



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## 1. Introduction

Cardiovascular diseases (CVDs) remain the leading cause of mortality worldwide, accounting for approximately one-third of all deaths globally. Acute coronary syndromes (ACS), including unstable angina,

non–ST-elevation myocardial infarction, and ST-elevation myocardial infarction, represent the most clinically significant manifestations of ischemic heart disease due to their sudden onset and high risk of fatal complications [1,2]. Unstable angina occupies a critical position within the spectrum of ACS. It is characterized by transient myocardial ischemia without irreversible myocardial necrosis but carries a substantial risk of progression to myocardial infarction and sudden cardiac death. The clinical course of unstable angina is highly heterogeneous, ranging from rapid stabilization to recurrent ischemia and adverse cardiovascular events. Traditionally, the pathogenesis of unstable angina has been attributed to atherosclerotic plaque rupture or erosion, platelet activation, and thrombosis. However, accumulating evidence suggests that endothelial dysfunction plays a central role in initiating and perpetuating ischemic episodes by altering coronary vasomotion, promoting inflammation, and destabilizing atherosclerotic plaques [3,4]. Endothelin-1 is a 21–amino acid peptide predominantly synthesized by vascular endothelial cells. It is recognized as one of the most potent vasoconstrictors in the human cardiovascular system. Beyond its vasomotor effects, ET-1 exerts pro-inflammatory, pro-oxidative, and pro-thrombotic actions, contributing to smooth muscle cell proliferation, endothelial damage, and microvascular dysfunction [5–7]. Elevated circulating levels of ET-1 have been reported in various cardiovascular conditions, including arterial hypertension, chronic heart failure, and stable ischemic heart disease. However, data on the prognostic significance of ET-1 in unstable angina, particularly in real-world clinical settings and specific regional populations, remain limited. Understanding the role of ET-1 may provide valuable insights into disease mechanisms and offer novel opportunities for risk stratification.

### Pathophysiological Role of Endothelin-1 in Unstable Angina

#### Endothelial Dysfunction and Coronary Vasomotion

The vascular endothelium regulates coronary blood flow through a delicate balance between vasodilatory mediators, such as nitric oxide and prostacyclin, and vasoconstrictive factors, including endothelin-1. In unstable angina, this balance is profoundly disrupted, resulting in episodic coronary vasoconstriction and impaired myocardial perfusion. ET-1 exerts its effects via endothelin A (ETA) and endothelin B (ETB) receptors located on vascular smooth muscle cells and endothelial cells. Activation of ETA receptors induces sustained vasoconstriction, while ETB receptor stimulation may exert dual effects depending on receptor localization and functional status [8].

#### Inflammation, Oxidative Stress, and Plaque Instability

Endothelin-1 promotes inflammatory activation by stimulating cytokine release, leukocyte adhesion, and oxidative stress. These mechanisms contribute to endothelial injury and destabilization of atherosclerotic plaques, increasing the likelihood of plaque rupture or erosion—hallmarks of unstable angina [9,10].

#### Microvascular Dysfunction

In addition to epicardial coronary artery effects, ET-1 plays a critical role in coronary microcirculation. Elevated ET-1 levels impair microvascular perfusion, leading to ischemia even in the absence of significant epicardial stenosis. This phenomenon may explain recurrent ischemic episodes in patients with angiographically moderate coronary lesions.

## 2. Methods

### Study Design and Population

This prospective observational study was conducted from January 2024 to January 2025 in cardiology departments of tertiary hospitals in Tashkent, Uzbekistan. A total of 112 consecutive patients diagnosed with unstable angina were enrolled. The cohort included 68 men (60.7%) and 44 women (39.3%), aged 42–76 years (mean age 59.3 ± 8.7 years). Diagnosis was established according to European Society of Cardiology criteria.

The control group consisted of 40 age- and sex-matched apparently healthy individuals without known cardiovascular disease.

### Inclusion and Exclusion Criteria

Inclusion criteria:

- confirmed unstable angina,
- symptom onset within 72 hours,
- informed consent.

Exclusion criteria:

- myocardial infarction,
- NYHA class III–IV heart failure,
- severe renal or hepatic dysfunction,
- active inflammatory or infectious diseases,
- malignancy,
- recent use of endothelin receptor antagonists.

**Clinical and Laboratory Assessment**

All patients underwent detailed clinical evaluation, including assessment of angina frequency, cardiovascular risk factors, and hemodynamic parameters. Ambulatory 24-hour ECG monitoring was performed to assess ischemic burden. Venous blood samples were collected within 48 hours of admission. Serum ET-1 concentrations were measured using enzyme-linked immunosorbent assay. C-reactive protein was determined as a marker of systemic inflammation.

**Follow-Up and Outcomes**

Patients were followed for early adverse cardiovascular events, including recurrent ischemia, rehospitalization, and need for invasive coronary evaluation.

**Statistical Analysis**

Statistical analysis was performed using SPSS version 26.0. Data are presented as mean ± standard deviation. Correlations were assessed using Pearson's coefficient. A p-value $< 0.05$ was considered statistically significant.

## 3. Results

**Baseline Characteristics**

Patients with unstable angina demonstrated a high prevalence of traditional cardiovascular risk factors, including arterial hypertension, dyslipidemia, and smoking. Baseline characteristics were comparable across subgroups. Endothelin-1 Levels: Mean serum ET-1 concentration in patients with unstable angina was 0.78 ± 0.21 fmol/mL, significantly higher than in controls (0.26 ± 0.09 fmol/mL, $p < 0.001$). Marked ET-1 elevation (>0.60 fmol/mL) was observed in 63.4% of patients. These individuals exhibited higher angina frequency, prolonged ischemic episodes, and elevated inflammatory markers. Correlation Analysis: A strong positive correlation was identified between ET-1 levels and angina frequency ($r = 0.54$, $p < 0.01$), as well as total ischemic burden ($r = 0.47$, $p < 0.05$). Correlation between ET-1 and C-reactive protein was moderate ($r = 0.33$, $p < 0.05$). Clinical Outcomes: During short-term follow-up, patients with persistently elevated ET-1 experienced a significantly higher incidence of recurrent ischemia and need for invasive coronary evaluation.

## 4. Discussion

This study demonstrates that endothelin-1 is a key mediator of endothelial dysfunction and ischemic activity in unstable angina. Elevated ET-1 levels reflect both structural and functional vascular abnormalities and are closely associated with disease severity. Unlike nonspecific inflammatory markers, ET-1 provides direct insight into endothelial and microvascular pathology. These findings are consistent with previous experimental and clinical studies highlighting the central role of endothelin signaling in acute coronary syndromes [11–13]. Regional factors, including dietary patterns, metabolic burden, and healthcare access, may modulate endothelial function and amplify endothelin-mediated effects, underscoring the importance of population-specific research.

**Clinical and Preventive Implications**

Assessment of endothelin-1 may enhance early risk stratification in unstable angina, identify high-risk patients, and guide therapeutic decision-making. Integration of endothelial biomarkers into routine practice could support personalized cardiovascular care.

## 5. Conclusion

Endothelin-1 is a sensitive biomarker of endothelial dysfunction and an independent predictor of unfavorable clinical course in unstable angina. Its routine assessment may improve prognostic accuracy and optimize management strategies in patients with acute coronary syndromes.

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