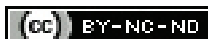


Circulating Endothelin-1 as a Diagnostic Marker in Patients with Acute Myocardial Infarction: A Cross-sectional Study

ANITHA RAJENDIRAN¹, S SUMATHI², S GIRIDHARAN³, V KUZHANDAIVELU⁴

ABSTRACT

Introduction: The most common form of Coronary Heart Disease (CHD) is Acute Myocardial Infarction (AMI). When a coronary artery is blocked, it results in a substantial reduction in blood flow, which causes some of the heart muscle supplied by that artery to become infarcted. The development of Myocardial Infarction (MI) is regulated by a variety of complex processes. Vascular blockage and cardiac ischaemia may be exacerbated by endothelial dysfunction, platelet activation, and inflammation.

Aim: To investigate the potential role of Endothelin-1 (ET-1) in the diagnosis of AMI.

Materials and Methods: This cross-sectional research was carried out at Mahatma Gandhi Medical College and Research Institute in Pondicherry, India over the duration of one year (2023-2024) with a sample size of n=50 for the AMI group and n=30 for the healthy control group. Ethical clearance was obtained prior to the study. Upon admission, a 5 mL sample of peripheral venous blood was collected, centrifuged, and biochemical parameters such as glucose (random), urea, creatinine, and lipid profile were assessed using standard appropriate methods. The

Enzyme-Linked Fluorescence Assay (ELFA) method was used to test troponin I, and the ET-1 immunoassay ELISA kit was utilised to quantify ET-1. Data were recorded and analysed using Statistical Package for Social Science (SPSS) Version 23 software. Categorical variables were analysed using the Chi-square test, whereas non-normally distributed continuous data were assessed with the Mann-Whitney U test. A Receiver Operating Characteristic (ROC) curve was plotted to identify the optimal cut-off value for ET-1 levels in patients with AMI. Bivariate correlation analysis was performed using the Spearman correlation test.

Results: Serum ET-1 levels were significantly higher in AMI subjects compared to the control group (14.02 ± 12.2 pg/mL vs. 3.1 ± 2.8 pg/mL, $p < 0.001$). The ROC curve analysis indicated that the serum ET-1 cut-off level was found to be 6.1 pg/mL. Additionally, serum ET-1 levels showed significant correlations with troponin I levels (correlation coefficient: 0.513, $p = 0.001$).

Conclusion: Elevated serum ET-1 levels at the time of admission were associated with higher troponin-I levels in patients with AMI. Hence, ET-1 can be a promising diagnostic marker for AMI assisting in early detection and prognosis.

Keywords: Acute myocardial infarction, Coronary artery disease, Diagnostic markers, Heart failure

INTRODUCTION

It is commonly recognised that neurohormonal alterations significantly influence the development of an AMI. These alterations are primarily generated to maintain the patient's haemodynamic stability during myocardial injury. One of the primary naturally occurring substances implicated in the aetiology and progression of MI is ET-1. Furthermore, the literature indicates that ET-1 is a significant predictive factor for AMI patients [1]. ET-1 is a 21-amino-acid peptide characterised by two cysteine bonds at its N-terminal end and a hydrophobic tail at the C-terminal end [2]. ET-1 causes significant vasoconstriction, stimulates the production of free radicals, activates platelets, and promotes cellular mitogenesis and proliferation. The onset of cardiovascular dysfunction and disease has been significantly linked to ET-1 [3].

AMI is an acute myocardial injury event caused by a reduction in the oxygenated blood supply provided by the coronary arteries. As a result, ET-1 levels in blood circulation are elevated [4]. Increased levels of ET-1 in the blood are associated with significant complications during hospital stays and left ventricular systolic dysfunction in individuals with ST-Elevation Acute Myocardial Infarction (STEMI) [5]. Elevated ET-1 levels are linked to damage to the coronary microcirculation during the reperfusion technique, as well as a higher risk of significant adverse cardiac events while the patient is in hospital, and within 30 days and a year following discharge from STEMI. Peak ET-1 levels in individuals with non-STEMI, in whom early coronary revascularisation may be postponed, reach their maximum 24 hours after the infarction

begins and may remain elevated for up to 48 hours [5]. Research has shown that circulating ET-1 levels increase significantly during AMI, making it a potential biomarker for diagnosis and prognosis in affected patients [6]. Elevated ET-1 levels have been associated with worse outcomes in AMI, including an increased risk of heart failure and death. Monitoring ET-1 can aid in risk stratification and management of patients post-AMI [4]. Combined analysis of ET-1 and other biomarkers can provide a more comprehensive assessment of AMI.

The role of rising circulating ET-1 levels in AMI during the critical care period remains unclear, as the condition presents a wide range of clinical severity that requires further study. Thus, this study aims to investigate circulating ET-1 as a diagnostic marker for AMI patients in the critical care unit. This manuscript is a part of a larger research project.

MATERIALS AND METHODS

A cross-sectional study was carried out at Mahatma Gandhi Medical College and Research Institute in Pondicherry, India, with a duration of 12 months (August 2023-July 2024). The protocol of the research, MGMCRI/RAC/2021/02/IHEC/27, has been approved by the Institutional Human Ethics Committee (IHEC) at MGMCRI, SBV, Pondicherry, India. A written consent form was obtained from all patient attendants.

Inclusion and Exclusion criteria: The study included subjects who were newly diagnosed with AMI within the age group of 35 to 60 years who were admitted to the critical care unit as cases.

Healthy individuals were included as a control group. Patients with predominant lung and kidney diseases, those who had undergone any major surgery, individuals who were pregnant, and those with anaemia or cancer were excluded.

The subjects of the research were patients diagnosed with AMI. A convenience sample of 50 was taken as the study group, and the healthy control group consisted of 30 individuals. The total number of study subjects was n=80.

Study Procedure

Upon admission, each subject’s demographic and clinical information was recorded during their hospital stay, and a 5 mL peripheral venous blood sample was collected while the subject was in a supine position. The blood samples were then centrifuged, and routine biochemical tests were performed in the hospital’s central laboratory. Troponin I levels were measured using the ELFA technique with the Vitek Immunodiagnostic Assay System (VIDAS) system (Biomérieux). The remaining serum samples were stored at -80°C until they were analysed for ET-1. ET-1 levels were measured and quantified using an immunoassay ELISA kit specific for ET-1. Socio-demographic characteristics such as age, gender, smoking status (smoker or non-smoker), and vital signs such as blood pressure, echocardiogram results, and Killip’s score were collected. ET-1 levels were determined by the ELISA technique using monoclonal antibodies targeting ET-1. The normal reference range is 0.1-3 pg/mL [7].

STATISTICAL ANALYSIS

Data were expressed as mean±SD, and the baseline characteristics were presented as means or medians. Normally distributed continuous data were compared using the Student’s t-test, whereas the Mann-Whitney test was used for continuous data that were not normally distributed. Categorical variables were analysed using the Chi-square test. Additionally, a ROC curve was created to identify the optimal cut-off value for ET-1 in patients with AMI. Bivariate correlation analysis was carried out using the Spearman correlation test. A p-value of 0.05 or less was considered statistically significant, while a p-value of less than 0.001 was considered highly significant. Data were analysed using SPSS version 23 software.

RESULTS

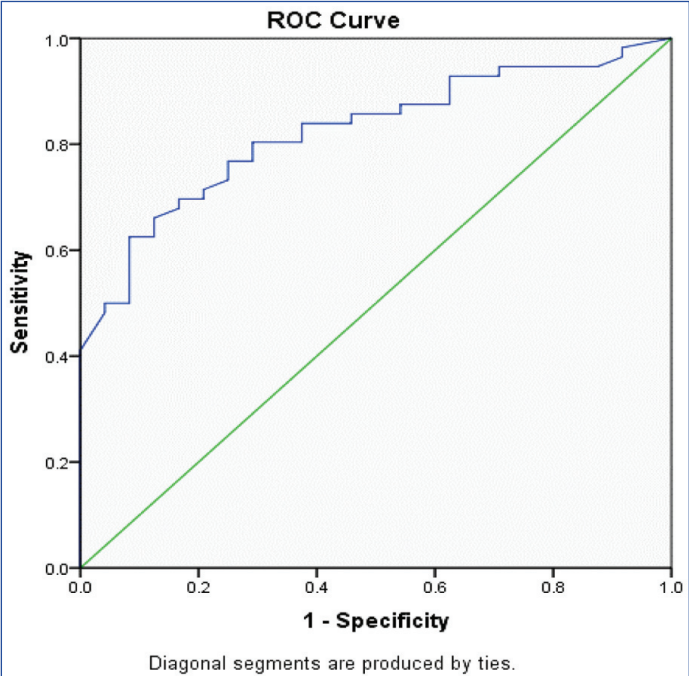
Fifty AMI subjects and thirty individuals in the control group were enrolled in this study. The mean ET-1 level in AMI subjects was 14.02±12.2 pg/mL. AMI patients admitted to critical care showed a significantly higher incidence of smoking and diabetes mellitus, along with lower systolic and diastolic blood pressures. They also had a greater proportion of individuals classified as Killip class ≥II and exhibited elevated levels of urea, creatinine, glucose, troponin I, Triglycerides (TG), High-Density Lipoprotein (HDL), and Very Low-Density Lipoprotein (VLDL) [Table/Fig-1]. Additionally, serum ET-1 levels were significantly elevated in AMI patients compared to the control group (14.02±12.2 pg/mL vs 3.1±2.8 pg/mL, p<0.001).

Demographic characteristics Mean±SD	AMI N=50	Control N=30	p-value
Age (years)	54.36±6.6	52.23±5.9	0.147
Male/female	29/21	10/20	-
Smoking n (%)	26 (52%)	NA	-
Diabetes mellitus, n (%)	36 (72%)	NA	-
Dyslipidemia, n (%)	16 (32%)	NA	-
Hypertension n (%)	39 (78%)	NA	-
Clinics characteristics Mean±SD			
Systolic pressure (mmHg)	157±35.4	120±0.00	<0.001
Diastolic pressure (mmHg)	85.48±13.1	80±0.00	<0.019
Killip class ≥II, n (%)	25 (50%)	-	-

Biochemical parameters Mean±SD			
Glucose (mg/dL)	207.18±90.6	101.90±29.7	<0.001*
Urea (mg/dL)	44.80±35.1	18.07±4.8	<0.001*
Creatinine (mg/dL)	1.7±1.2	0.94±0.13	<0.001*
Total cholesterol (mg/dL)	192.74±42	197.3±34.3	0.413
Tri glycerides (mg/dL)	183±99.3	127.4±53.3	0.017*
HDL (mg/dL)	41.68±12.9	45.13±8.9	0.070
LDL (mg/dL)	115.1±38.8	126.7±27.5	0.147
VLDL (mg/dL)	36.3±20.1	25.5±10.6	0.023*
Troponin I (ng/mL)	9057.43±1576	0.3±0.6	<0.001*
Endothelin-1 (pg/mL)	14.02±12.2	3.1±2.8	<0.001*

[Table/Fig-1]: Presents the demographic profiles of the AMI group and the control group.
HDL: High density lipoprotein; LDL: Low density lipoprotein; VLDL: Very low density lipoprotein;
*Mann-Whitney test

The ROC curve indicated an area under the curve of 0.82. Based on the ROC curve, an ET-1 level of 6.1 pg/mL had a sensitivity of 85% and a specificity of 76% for accurately predicting AMI patients, with a positive predictive value of 56% and a negative predictive value of 24% [Table/Fig-2].



[Table/Fig-2]: Illustrates the ROC curve used to assess the diagnostic accuracy of endothelin-1 (ET-1) (AUC 0.82), cut-off value 6.1 pg/mL (sensitivity 87%, specificity 58%).

Among the continuous variables, serum ET-1 levels showed significant positive correlations with systolic blood pressure (r=0.437, p<0.001), glucose levels (r=0.473, p<0.001), serum urea (r=0.398, p<0.001), serum creatinine (r=0.420, p<0.001), and troponin I levels (r=0.513, p=0.001). However, other variables, such as age and diastolic blood pressure, did not show a significant correlation with serum ET-1 levels [Table/Fig-3].

DISCUSSION

In this study, patients with AMI who required critical care admission were examined. Among the study group, there was a substantial increase in serum ET-1 levels. Specifically, these levels were nearly five times higher in AMI patients compared to the control group, suggesting a significant association between elevated ET-1 and the critical condition of these patients. A cut-off value of 6.1 pg/mL for ET-1 was established as the most effective threshold for differentiating AMI patients from controls. This cut-off is particularly important for risk stratification and monitoring disease severity in AMI cases. However, since ET-1 levels may fluctuate, continuous measurement

Variables	Coefficient correlation	p-value
Age	0.147	0.193
Systole	0.437	<0.001*
Diastole	0.174	0.122
Glucose	0.473	<0.001*
Urea	0.398	<0.001*
Creatinine	0.420	<0.001*
Troponin-I	0.513	<0.001 *
Triglycerides	0.408	<0.001*
VLDL	0.150	0.050*

[Table/Fig-3]: Shows the correlation between Endothelin-1 (ET-1) and other continuous variables.

VLDL: Very low density lipoprotein; Spearman correlation test; *statistically significant

of serum ET-1 over the span of a week is recommended to ensure accuracy and confirm its role in disease progression and patient outcomes. Monitoring over time will allow us to understand the pattern of ET-1 elevation in response to AMI and its potential use as a biomarker for both diagnosis and prognosis in critical care settings.

Hartopo AB et al., showed that ET-1 may serve as a marker of systemic inflammation, which is commonly associated with non-ST Elevation Myocardial Infarction (non-STEMI). In non-STEMI patients who did not undergo coronary revascularisation, ET-1 levels may peak 24 hours after onset, and plasma ET-1 levels were found to be higher in STEMI patients compared to non-STEMI cases. Fitchett DH et al., demonstrated that STEMI is associated with larger infarcts and elevated mortality compared to non-STEMI cases [8]. Similarly, Sainani GS et al., reported a significant rise in plasma ET-1 levels in coronary artery disease, along with the presence of ET-1 immunoreactivity in the smooth muscle cells of the intimal and medial layers of the aorta, which supports the role of ET-1 as a surrogate marker for atherosclerosis [9].

Dąbek J et al., found that early post-hospital cardiac rehabilitation benefits patients after a MI by improving vascular endothelial function. This improvement is linked to a reduction in the transcriptional activity of the ET-1 gene, which plays a role in endothelial health. Lower ET-1 expression may help enhance vascular function, highlighting the importance of early rehabilitation in recovery. Further research could explore its long-term benefits [10].

Kolettis TM et al., suggested that ET-1 contributes to the progression of coronary artery disease and plays a role in ventricular remodelling and fibrosis in the long-term following a MI [11]. Common risk factors for developing coronary artery disease include diabetes and smoking, primarily because they adversely affect endothelial function [12]. In terms of long-term mortality risk, elevated ET-1 levels are associated with increased long-term mortality rates in cardiovascular patients, with higher levels linked to a greater risk of cardiovascular death, influenced by factors such as larger infarct size, higher rates of heart failure, and ongoing ischaemia [13].

Plasma ET-1 concentrations in patients with STEMI were indicative of angiographic no-reflow following successful primary or rescue percutaneous coronary intervention [9]. The elevated release of ET-1 from the endothelium damaged by ischaemia-reperfusion can cause significant and sustained microvascular constriction [3]. Persistent elevations in endothelin levels may indicate ongoing ischaemia caused by incomplete infarction or infarct extension in certain patients. Patients with complicated MI showed a swift rise in plasma immunoreactive ET-1, comparable to the increase observed in patients with uncomplicated infarction. Although ET-1 may primarily function as a marker of disease severity and risk, the

variation in coronary states and plasma ET-1 concentrations implies that it is likely involved in the core mechanisms of atherosclerosis.

Limitation(s)

While ET-1 levels rise in AMI, they are also elevated in other cardiovascular conditions such as hypertension, heart failure, and pulmonary arterial hypertension. This can limit the specificity of ET-1 as a diagnostic marker for AMI alone. Secondly, the total number of controls was less than that of the cases. Although promising, ET-1 is not yet widely adopted as a standard biomarker in clinical practice due to the need for further validation in large, diverse patient populations. The study can be divided into STEMI and non-STEMI groups.

CONCLUSION(S)

Circulating ET-1 shows promise as a diagnostic marker for AMI, particularly for early detection and prognosis. However, further research is necessary to establish its utility in clinical practice and its potential role alongside traditional biomarkers in diagnosing and managing AMI.

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