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Serum levels of inflammatory markers in relation to left ventricular function in cardiac patients

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Abstract:
Background: *After myocardial infarction, inflammation is the important key factor involved in cardiac remodelling. Continuous activation of inflammatory markers like interleukins and tumour necrosis factors will leads to myocardial damage which ultimately results in heart failure. Very few studies have been done so far in relation to various inflammatory markers in relation to left ventricular function in cardiac patients.*
Aim: *To determine serum levels of interleukin-1β, interleukin-2, interleukin-6, interleukin-8, interleukin-10 and tumour necrosis factor-α in relation to left ventricular function in cardiac patients.*
Methods: *We studied 229 cases of CVDs who were enrolled at department of Cardiology and Medicine at a tertiary care hospital, Mumbai. We further categorized above cardiac patients based on left ventricular ejection fraction into two groups i.e. <50% LVEF and >50% LVEF. Serum inflammatory markers were measured with commercially available ELISA kit. Statistical analysis was carried out using SPSS version 16.0 and Microsoft Excel 2007.*
Results: *There was a significant difference between the IL-6 levels (p = 0.003) in cases with LVEF ≤ 50% and those with LVEF > 50%, with the former having higher levels [median (IQR) = 6.5 (14.8) pg/mL] than the latter group [mean (SD) = 4.4 (6.3) pg/mL].*
Conclusion: *Decreased LVEF with increasing severity might be responsible for IL-6 production.*
Keywords:*ELISA, cardiac diseases, LVEF, serum interleukins, serum TNF-α.*

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I. Introduction

An alarm bell is sounded by epidemiologists from all over the world, indicating that the burden of Cardiovascular Disease (CVD) is rising rapidly. It is said, that by 2020 CVD will be the leading cause of death worldwide (1). In India, the prevalence of Heart Failure (HF) has raised mainly due to traditional risk factor like CVD, Rheumatic Heart Disease (RHD), anaemia etc. HF being a predominant disease of the elderly, population risk increases along with the age. Huffman and Prabhakran reported 30 million people who suffered from CHD (Chronic Heart Disease) in 2000, with 3% prevalence in India and the incidence of HF with CHD has increased 0.4% to 2.3% per year(2). Chronic inflammation is the important cause of many diseases. It leads to loss of function in joints, affects blood vessels or acts on entire organs, in cases of heart inflammation, it can be fatal (3). Due to postinfarction cardiac remodelling, long-term prognosis is still hampered by the risk of (HF), in spite of the advancement in invasive and pharmacological treatment of MI. It is thought that sustained activation of inflammatory markers may be linked with enhanced myocardial damage and its dysfunction, and may lead to HF (4). Proinflammatory marker like IL-6 is released from macrophages and T-lymphocyteswhich stimulates release of acute phase reactants like C-reactive protein (CRP)(5).Overexpression of proinflammatory cytokine can produce leftventricular dysfunction, pulmonary edema and cardiomyopathy in human subjects(6).

Accordingly, the aim of the study was to determine the relationship between serum interleukin-1β, interleukin-2, interleukin-6, interleukin-8, interleukin-10 and tumour necrosis factor-α with left ventricular function in cardiac patients.

II. Materials and Methods

We studied 229 cases of CVDs (16 cases of complete heart block, one case of congenital heart disease, 22 cases of heart failure, 169 cases of myocardial infarction, one case of myocarditis and 20 cases of rheumatic heart disease) who were enrolled at department of Cardiology and Medicine at a tertiary care hospital,Mumbai.

Further these cases were classified according to left ventricular ejection fraction (LVEF) i.e. LVEF ≤ 50% and LVEF > 50%. Mean age (in years) for the cases was 54.49±11.71, out of them 161 were male and 68 were female patients. All the cases were diagnosed by cardiologists and final patient selection was done. Diagnostic test included 2D Echo along with electrocardiogram. The inclusion criteria were CVD patients undergoing hospitalization in Cardiology Intensive Care Unit and Medicine ward, who were willing to participate in the study and signed the informed consent. Patients with chronic illnesses such as malignancies, infections, rheumatoid arthritis (where the inflammatory markers are presumed to be raised) were excluded, the study protocol was approved by the institutional ethics committee. Informed consent was taken from all study cases after explaining the purpose of the study.

Venous blood was drawn in a plain tube without anticoagulant and centrifuged for 10 minutes at 2000 rpm at room temperature. Serum was separated in the screw type vials and stored at -40°C (BD Instruments). The serum IL-1β, IL-2, IL-6, IL-8, IL-10 and TNF-α were measured by human Enzyme-Linked Immunosorbent. Assay (ELISA) was performed (kits supplied by Affymetrix, eBiosciences, San Diego, CA, USA) at HinduridaysamratBalasaheb Thackeray Municipal Medical College and Dr. R.N. Cooper General Hospital. Statistical analysis was carried out using the Statistical Package for the Social Sciences (SPSS) version 16.0 and Microsoft Excel 2007.

III. Results

There was a significant difference between the IL-6 levels (p = 0.003) in cases with LVEF ≤ 50% and those with LVEF > 50%, with the former having higher levels [median (IQR) = 6.5 (14.8) pg/mL] than the latter group [mean (IQR) = 4.4 (6.3) pg/mL]. The rest of the inflammatory markers i.e. IL- 1β, IL-2, IL-8, IL-10 and TNF-α did not vary significantly in the two groups. In the group with LVEF ≤ 50%, their median (IQR) values were 0 (2.8) pg/mL, 8.7 (12.2) pg/mL, 102.9 (115.97) pg/mL, 4.6 (9.7) pg/mL and 21.2 (15.3) pg/mL respectively and the group with LVEF > 50% had levels 0 (3.3) pg/mL, 8.5 (8.5) pg/mL, 74.2 (127.1) pg/mL, 5.1 (10.6) pg/mL and 20.8 (11.9) pg/mL respectively (Table 1).

Table 1: Inflammatory Markers and Cardiac function among cases

Inflammatory marker: IL-1		
	Median (Interquartile range)	P value
LVEF ≤ 50% (n= 145)	0 (2.8)	0.141
LVEF > 50% (n= 82)	0 (3.3)	
Inflammatory marker: IL-2		
LVEF ≤ 50% (n= 145)	8.7 (12.2)	0.738
LVEF > 50% (n= 83)	8.5 (8.5)	
Inflammatory marker: IL-6		
LVEF ≤ 50% (n= 146)	6.5 (14.8)	0.003*
LVEF > 50% (n= 83)	4.4 (6.3)	
Inflammatory marker: IL-8		
LVEF ≤ 50% (n= 144)	56.6 (156.6)	0.551
LVEF > 50% (n= 83)	74.2 (127.1)	
Inflammatory marker: IL-10		
LVEF ≤ 50% (n= 146)	4.6 (9.7)	0.357
LVEF > 50% (n= 83)	5.1 (10.6)	
Inflammatory marker: TNF-α		
LVEF ≤ 50% (n= 146)	21.2 (15.3)	0.832
LVEF > 50% (n= 83)	20.8 (11.9)	

*Using Mann-Whitney U test, significant at 0.05 level of significance

IV. Discussion

The relationship between serum cytokines and to left ventricular function in cardiac patients is an area of increasing interest. It is known that certain cytokines play an important role in the pathogenesis of chronic

heart failure and its prognosis(7). Heart failure is the condition with typical symptoms and signs like dyspnea, leg swelling, paroxysmal nocturnal dyspnea, and orthopnea which is the cause of any structural or functional impairment of ventricular filling or ejection of blood. This leads to decrease in oxygen delivering capacity to the metabolizing tissues like kidney, bone marrow and liver (8). Thus, technological developments will likely facilitate the use of multi-marker profiling to individualize treatment of CVD in the future. Therefore, biomarkers can be defined as alterations in the constituents of tissues or body fluids, provide a powerful approach to understanding the spectrum of CVD with applications in at least 5 areas: screening, diagnosis, prognostication, prediction of disease recurrence, and therapeutic monitoring (9). Now a day's atherosclerosis is extensively accepted as a chronic inflammatory disease due to initiators like vascular or extra vascular sources. Various complex network of mediators and signalling pathways are important components of inflammatory reactions. Thus inflammatory markers like interleukins are responsible for communication between white blood cells, chemokines that promote chemotaxis and interferons which have antiviral effects which are further involved in innate and adaptive immunity, playing a noteworthy role in lymphoid tissue oncogenesis, vasculogenesis and tissue repairing (5).There are no reports available on the relationshipbetween serum IL-1β, IL-2, IL-6, IL-8, IL-10 and TNF-α and LV function in CVD patients. Keeping this in the mind, we have aimed to study the role of various serum inflammatory markers in relation to left ventricular function in cardiac patients, as per our knowledgethis is the first study in western parts of Maharashtra, principally in Mumbai city.

The present study shows that the cardiac patients who has LVEF ≤ 50%, there was markedly raised levels of serum IL-6 than the cardiac patients who has LVEF > 50%. Our result correlates with Guillermo Torre-Amione et al (1996) (6), Marco Testa et al (1996)(10), Koller-Strametz J et al (1998) (11), Takayoshi Tsutamoto et al (1998)(12), Mathias Rauchhaus et al (2000)(13). IL-6 plays an important role in ventricular hypertrophy and left ventricular remodelling whereas raised levels may decrease left ventricular hypertrophy through nitric oxide production (with an increase of NOS). It also contributes to abnormalities of endothelium-dependent vasodilatation, vascular resistance, increased vascular permeability or muscle wasting. Vasoconstriction takes place due to increased cAMP levels which increases IL-6 levels through the sympathetic nervous system with alpha receptors(12). Decreased LVEF with increasing severity might be responsible for IL-6 production.

V. Conclusion

Significant correlation between increased serum IL-6 levels and LV systolic as well as diastolic dysfunction suggests possible input of those factors into the postinfarction myocardial damage. The study was carried out with significantly large sample size. Thus, the increase in IL-6 production in the peripheral circulation may contribute to muscle wasting in CVD patients with decreased left ventricular dysfunction suggesting an important role in pathophysiology of clinical severity of cardiac diseases. Implementation of serum IL-6 as a risk factor and an additional marker in the evaluation of cardiovascular disease severity should be encouraged.Supplementary studies are required to validate our data.

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