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Serum Levels of IL-1βIN Patients Presenting with Cardiac Dyspnoe and their Association with NYHA Functional Classification

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Abstract: ***Objectives: A growing body of evidence suggests that inflammation plays the key role in various cardiac diseases. Heart failure (HF) is the leading cause of morbidity and mortality in developed as well as developing countries which is a devasting disease. Despite significant advances in the prevention and treatment of HF, the prognosis is still poor. Serum levels of some cytokines are elevated in patients with chronic heart failure. But very few studies have been done so far in relation to the role of interleukin-1β in cardiac patients whose symptoms ranged from New York Heart Association functional class I to IV. We aimed to determine serum interleukin-1β levels in different cardiac diseases along with NYHA categorisation. Materials and methods: The study population of 229 cases of CVD's who were enrolled at Cardiology and Medicine Department along with 229 age and sex matched healthy controls were included for serum analysis of interleukin-1β. Results: A total of 458 patients were included in the study. Serum interleukin-1β was significantly [median (IQR) 2.5 (5.2) pg/mL] increased inNYHA class IV i. e., in severely symptomatic patients compared to NYHA class II [median (IQR) 0 (3.1) pg/mL]& III [median (IQR) 0 (3.0) pg/mL]. Conclusion: There is a strong correlation between Serum IL-1β and the extent of to NYHA classification in patients with documented CVD. Elevated Serum IL-1β was increased in higher NYHA classes.***

Keywords: Cardiovascular diseases, ELISA, Heart failure, Interleukin-1β, NYHA Classification

1. Introduction

Coronary artery disease (CAD) arises from an atheromatous plaque in the artery (i. e., atherosclerosis-"hardening of the artery") which is a chronic disease with a decrease in arterial lumen diameter which may go ahead to death due to myocardial infarction (MI), cardiovascular events and renal failure. Patients with coronary artery disease (CAD) can perform with stable angina pectoris (SAP), unstable angina pectoris (UAP), or acute myocardial infarction (AMI). Thus, Cardiovascular diseases (CVDs) are the leading cause of mortality and morbidity in India and all over world. Traditional/classical risk factors for MI like family history of premature CAD, diabetes mellitus (DM), cigarette smoking, hypertension, hyperlipidemia, atherosclerosis, obesity, sedentary lifestyle and high-fat/low-fibre diets have been known but the exact pathogenesis of CAD is not fully understood yet (1) . All Along with CAD, Heart failure (HF) is a disorder that has indicated rising morbidity and mortality during the last decades. The pathogenetic processes of HF include deregulation of the neurohormonal system, with disturbance of the balance between sympathetic and parasympathetic tone, and disruption of the renin-angiotensin-aldosterone system along with myocardial hypertrophy. The role of inflammation is also recognised as an important cause in HF (2) . Thus, the inflammatory process can cause myocardial damage, while inflammatory agents contribute to the deteriorating and development of HF. Cytokines recruit cells to the spot of inflammation, stimulate cell division, proliferation, and differentiation along with there is an activation of the immune system, production and release of autoantibodies, pro-inflammatory cytokinesare seen in HF. Increased levels of circulating cytokines associated with severity of HF, measured with the use of New York Heart Association (NYHA) classification and prognosis of disease. Elevated cytokine cause alterations in the heart function because of increase of cardiomyocyte apoptosis, cardiac hypertrophy and matrix metalloproteinase activation (3) .
Very few studies have been done so far in relation to the role ofinterleukin-1β in cardiac patients whose symptoms ranged from New York Heart Association functional class I to IV. To our existing knowledge this is the first study in Western Maharashtra population particularly in Mumbai city. This study was aimed to measure serum IL-1β level in different cardiac diseases along with NYHA categorisation.

2. Materials and Methods

Data collection

This was a case control study carried out at Cardiology and Medicine Department from a tertiary care Hospital, Mumbai, India. In this study 229 cases of CVD's (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). Patients were registered at Cardiology and Medicine Department along with 229 age and sex matched healthy controls. Sample size of 229 cases and 229 controls were attained by consecutive sampling strategy commenced for a period of 10 months. Patients mean age of was 54.49±11.72 years. Patient's history was taken according to NYHA classification. All the cases were diagnosed by cardiologists and final patient selection was done. Diagnostic test included 2D Echo accompanied by 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. Signed the informed consent was taken from the patients. Patients with chronic ill-

nesses 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 subjects, both cases and controls after explaining the purpose of the study. Further cases were classified according to the NYHA classification.

Statistical analysis

All results are presented as median and interquartile range (IQR). Statistical analysis was carried out using the Statistical Package for the Social Sciences (SPSS) version 16.0 and Microsoft Excel 2007. A p-value ≤0.05 was considered statistically significant.

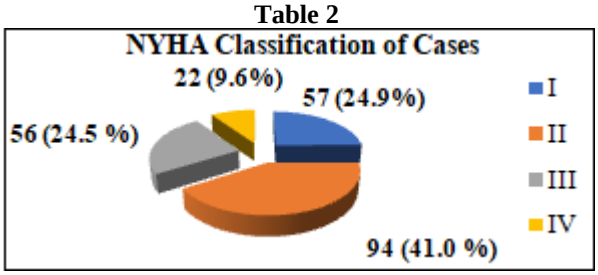
NYHA Classification of Cases:

Table 1

NYHA Class	Frequency	Percent
I	57	24.9
II	94	41.0
III	56	24.5
IV	22	9.6
Total	229	100.0

As per the NYHA Classification, 94 (41.0%) cases belonged to NYHA Class II, 57 (24.9%) cases belonged to Class I, 56 (24.5%) were in Class III and 22 (9.6%) were in Class IV.

Table 2



Interleukin measurement:

Venous blood was drawn in a plain tube without anticoagulant. Samples were 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 was measured by human IL-1β Enzyme-Linked Immunosorbent assay (ELISA) kits (Affymetrix, eBiosciences, San Diego, CA, USA). This ELISA set is precisely engineered for correct and accurate measurement of protein levels from serum samples which recognises the cleaved mature form and uncleaved pro-form of Human IL-1β. Statistical analysis was carried out using SPSS version 16.0 and Microsoft Excel.

3. Results

Median levels of Inflammatory and Cardiac markers for each NYHA Class

Table 3

Marker	NYHA Class	Median	Interquartile range
IL-1β	I	0	2.6
	II	0	3.1
	III	0	3.0
	IV	2.5	5.2

4. Discussion

IL-1β as an Inflammatory Marker among Different NYHA class

The present data demonstrate that, there was a significant difference (p = 0.033) in the level of IL-1β across the NYHA class category of cases.
There is a significant difference between NYHA class II & NYHA class IV (Table 3).

IL-1 is significantly increased in NYHA class IV i. e., in severely symptomatic patients compared to NYHA class II & III.

Our study correlates with Teats M. et al where they found significantly raised IL-1β levels in functional class III & IV (4) .

NYHA classification is a New York Heart Association where the patients are classified either ‘‘mild’’ (NYHA class I or II) or ‘‘severe’’ (NYHA class III or IV) heart failure (5) .

As outlined by the New York Heart Association, the elements of a complete cardiac diagnosis include Etiology, anatomic abnormalities, physiologic disturbances & functional disability. How strenuous is the physical activity required to elicit symptoms? The classification provided by the New York Heart Association has been found to be useful in describing functional disability (6) .

New York Heart Association Functional Classification	
Class I No limitation of physical activity No symptoms with ordinary exertion	**Class III** Marked limitation of physical activity Less than ordinary activity causes symptoms Asymptomatic at rest
Class II Slight limitation of physical activity Ordinary activity causes symptoms	**Class IV** Inability to carry out any physical activity without discomfort Symptoms at rest

Inadequacy of the cardiac output to fulfill the demands of organs and tissues leads to Heart failure (HF) which can further represent the end-stage of several cardiovascular diseases, including ischemic disease, myocardial infarction, or myocarditis, which leads to pathological changes in the myocardium. HF is the leading cause of morbidity and mortality in developed countries. It is also the primary cause of mortality in the elderly worldwide. Shortness of breath, fatigue, and impaired exercise tolerance are the typical clinical representations. Notwithstanding several improvements in the management of HF, it is still an incurable and a progressive disease. Its 5-year mortality has been projected to range between 50% and 70% in the American population (3).

Traditional cardiovascular disease and persistent-pretransitional diseases like rheumatic heart diseases (RHD), anemia has increasing the prevalence of heart failure in India (7).

Several factors have been implicated in HF progress where the pathophysiology and mechanisms of the HF development are difficult. Numerous studies confirmed that HF is not solitary a "pump illness". Progression of HF is a systemic disease, and insistent over activation of different compensatory systems, for example the renin–angiotensin and β-adrenergic system, is one of the most appropriate causes of HF. Still, the use of inhibitory agents blocking those systems did not influence morbidity and mortality satisfactorily, which may propose that we still miss some significant pathways. Numerous trials established that the process of inflammation might be responsible for the initiation and progression of HF (3)

Interleukins are a family of cytokines intricate in immune cells differentiation and activation. These interleukins facilitate the traffic of immune cells to the site of the infection, persuade the increase of the acute phase signaling, activate epithelial cells and mediate the production of secondary cytokines (8).

IL-1β is a pro-inflammatory glycoprotein. It was the first cytokine discovered by Grey and Waksman in 1972 which is a lymphocyte activating factor having a molecular weight of 17 kDa with α and β isoforms. IL-1βis involved in complex reactions of atherosclerosis with initiation of immune cells for plaque formation in arterial walls. Increased levels of serum IL-1β have been reported in some studies of CVD (9).

Cells of healthy individuals does not contain IL-1β. It requires a series of intracellular events before the cytokine can trigger inflammation. Limitednumber of cells, such as blood monocytes, tissue macrophages and dendritic cells produces IL-1β and the rate-limiting step in the production of IL-1β is its transcription (10) . HF is a condition of long-lasting systemic inflammation. In the failing heart, chronic hypoxia and low-grade cell death signals stimulate IL-1 production (11) .

Site of cytokine production

The stimulus and site of production of IL-1β are still poorly understood in patients with congestive heart failure. IL-1β are predominantly produced by activated macrophages, but what triggers such activation is still unclear in congestive heart failure. Probably, the immune system is activated in response to foci of injury, which may develop in the heart or in the periphery, or both (4) . If the raise of circulating cytokine levels resulted principally from an inflammatory response within the heart, one would assume circulating levels of cytokines to be elevated in functional class I patients who have already had a substantial amount of myocardial damage. There can be another reason for the elevation of IL-1 in NYHA class IV. As in the dilated and failing heart with an elevated LV end-diastolic wall stress causes myocardial expression of cytokines, which directly or indirectly influence LV contractile performance and remodelling and raised cytokines are seen (12) . The goal of the present study was not to address the site of activation of IL-1 in congestive heart failure. Evidence for this hypothesis is that patients with symptoms compatible with functional classes I, II and III, whereas circulating levels of IL-1 were consistently elevated only in patients in functional class IV. Therefore, substantial cytokine production, which occurs at a late stage of the syndrome of CVD, suggests that peripheral abnormalities that correlate with symptoms may be an important stimulus for cytokine production. So, this increased IL-1β is the indicator of the generalized inflammatory process which is observed in atherosclerotic diseases and can be considered a good indicator of deterioration.

5. Conclusions

HF is a systemic disease with a multifactorial etiology. High levels of circulating cytokines correlate with the severity of HF, measured with the use of New York Heart Association's classification. In these patients circulating levels of IL-1β can be considered as a sensitive marker of immune activation. It is hoped that this will demonstrate whether counteracting the IL-1β pathway in patients with moderate to severe CVD's in general confers morbidity and mortality benefits. Hence, further studies regarding the assessment of inflammatory pathways in HF in view of identifying new opportunities to expand the quality of life, slow disease progression, and improve the survival need to be carried out.

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