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ELEVATED LEVELS OF INTERLEUKIN - 6 IN CARDIAC FAILURE AND ITS CORRELATION WITH THE SEVERITY OF LEFT VENTRICULAR DYSFUNCTION AND PROGNOSIS OF DISEASE

General Medicine

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ABSTRACT

Background: The recent growth of knowledge in the field of cardiac failure has laid more emphasis on the potential role that proinflammatory cytokines play as mediators of disease progression in the failing human heart. and the cytokine IL-6 significantly elevated in cases of cardiac failure as increase in IL-6 levels were associated with increasing degrees of LV dysfunction measured by the ejection fraction and therefore IL-6 can be used as a predictor of mortality in cardiac failure cases. **Aims & Objectives:** To show that there is elevated IL-6 levels in patients with cardiac failure and to correlate the IL-6 values with the severity of the cardiac failure. **Materials And Methods** : Prospective analytical study of 60 cases and 60 controls, Subjects who presented with signs and symptoms of cardiac failure attending/admitted in the general medicine,OP and study conducted for one year from 1st September 2020 to 30th august 2021 in Alluri sitaramaraju academy of medical sciences, a tertriary care centre in Eluru. **Results** : IL-6 levels were measured in cases at the time of admission and were compared with age and sex matched controls. The mean value of IL-6 in cases was 50.77 pg/ml. The mean value of IL-6 in controls was 1.16 pg/ml. The P-value was <0.001 1 measured by paired t test which is statistically significant at 1%. This concurs with previous studies in which IL-6 levels in cardiac failure compared with controls. **Conclusion:** This study shows that the proinflammatory cytokine IL-6 significantly elevated in cases of cardiac failure.

KEYWORDS

Interleukin-6 , Cardiac Failure, NYHA Grading, LV Dysfunction

INTRODUCTION:

American Heart association (AHA) estimated that there were 23 million people with cardiac failure worldwide, despite improvements in therapy the mortality rate from Heart failure remains high.

Heart failure is a clinical syndrome in which an abnormality of cardiac structure or function is responsible for the inability of the heart to eject or fill with blood at a rate commensurate with the requirements of the metabolizing tissues. Initially HF is viewed as a problem of excessive salt and water retention that was caused by abnormalities of renal blood flow (the "cardiorenal model") Later was hemodynamic measures in which abnormalities of the pumping capacity of the heart and excessive peripheral vasoconstriction were studied, neither of these models explained the "disease progression" but provided the rational basis for the use of diuretics to control the volume status and inotropes and intravenous vasodilators to augment cardiac output, these therapeutic strategies have not prevented HF from progressing

On the basis of these arguments, it has become increasingly apparent that HF can no longer be defined in simple hemodynamic terms.Therefore we focus on the molecular and cellular changes that underlie HF with depressed systolic function, with an emphasis on the role of neurohormonal activation and left ventricular (LV) remodeling as the primary determination for disease progression in HF,as patients transition to symptomatic HF, the sustained activation of neurohormonal and cytokine systems leads to a series of endorgan changes within the myocardium, referred to collectively as "LV remodeling". All nucleated cell types within the myocardium are capable of producing, proinflammatory cytokines in response to a various forms of cardiac injury.

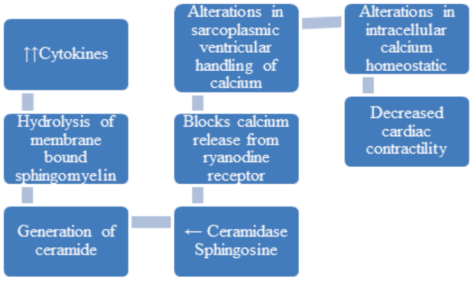

Figure1: The immediate pathway:

Delayed effects were Mediated through inducible NOS 2 expression resulting in Gunaylate cylase mediated alterations in calcium homeostasis & NO- mediated blunting of β - adrenergic stimulated generation of cAMP which decreases contractility.

There is growing evidence that there are critical interactions between inflammatory mediators and the mediators of classic neurohormonal systems. (renin angiotensin aldosterone axis and adrenergic system) It is now becoming increasingly apparent that angiotensin II provokes inflammatory responses in a variety of different tissues and cell and tissue types. Mechanistically AT II activates a redox sensitive transcription factor NF KB that is critical for initiating the coordinated expression of classic components of myocardial inflammatory response. There is growing evidence that many of the conventional therapies for heart failure work at least in part through modulation of proinflammatory cytokines.

Source Of Production Of Proinflammatory Cytokines In Cardiac Failure:

Hypothetical sites for production of proinflammatory cytokines in cardiac failure:

- Immune activation
- Myocardial Bio synthesis
- Hypoperfusion of metabolic tissue
- Endotoxin absorption from the gut
- Neurohormonal activation
- Altered distribution of cytokines.

The myocardium is a potentially important source for production of cytokines in heart failure and cytokines in peripheral circulation may represent spillover of cytokines produced exactly within the myocardium. Inflammatory mediates as therapeutic targets in heart failure. Heart failure remains an unavoidable progressive disease process despite therapy with ACE inhibitors and β blockers.

MATERIALS AND METHODS :

Prospective analytical study of 60 cases and 60 controls, Subjects who presented with signs and symptoms of cardiac failure attending/admitted in the general medicine,OP and study conducted for one year from 1st September 2021 to 30th November 2021 in Alluri sitaramaraju academy of medical sciences, a tertriary care centre in Eluru after taken as cases after informed consent and history and relevant clinical examination was done. Equal number of healthy

subjects with no clinical electrocardiographic and clinical evidence of cardiac failure are also chosen as controls Serum IL-6 levels are measured using ELISA technique.

Inclusion Criteria :
Patients with cardiac failure NYHA Grade II-IV of 2-3 months duration.

Exclusion Criteria:
Acute infections, autoimmune diseases, major organ failure, neoplasms, extensive trauma.

RESULTS:
Total number of subjects included in this study were 120 of these 60 were cases of Cardiac failure and other 60 controls who were healthy with same age and sex

Table 1: Grade Of LV Dysfunction

GRADE	FREQUENCY	PERCENTAGE
Mild	4	11.43
Moderate	7	20.00
Severe	24	68.57

Correlation Of Il-6 With

Table 2: A) Cases (vs) Controls :

IL-6	MEAN	S.D	P-VALUE
CASES	50.77	41.93	<0.001*
CONTROLS	1.16	0.48	

Table 3: B)nyha Grade :

NYHA	MEAN	S.D	P-VALUE
II	29.75	55.98	<0.001*
III	28.18	19.34	
IV	71.29	34.60	

Table 4: C)grade Of Lv Dysfunction:

GRADE	MEAN	S.D	P-VALUE
MILD	13.25	12.50	<0.001*
MODERATE	16.43	2.94	
SEVERE	77.54	40.04	

Table 5: D) Pre And Post Treatment

IL-6	MEAN	S.D	P-VALUE
PRE TREATMENT	50.77	41.93	<0.001*
POST TREATMENT	33.17	29.45	

Table 6: Post Treatment Il-6 And Outcome

OUTCOME	NO.OF.CASES	MEAN	SD	P-VALUE
IMPROVEMENT	54	29.11	36.032	<0.001**
DEATH	6	69.67	61.237	

DISCUSSION:
Total number of subjects included in this study were 120 of these 60 were cases of Cardiac failure of varying degrees of severity and etiologies diagnosed both clinically and through Echocardiography. The other 60 subjects were healthy volunteers who were age and sex matched and were allotted into control group. In this study the mean value of Il-6 in serum was 50.77 pg/ml. The IL-6 level was repeated after 2 weeks in the same group of patients after regular treatment with ACE inhibitors, ß blockers, Nitrates, Aspirin, Digoxin etc.,

IL-6 levels were measured in cases at the time of admission and mean value of IL-6 in cases was 50.77 pg/ml WHEREAS in controls was 1.16 pg/ml. The P-value was <0.001 measured by paired t test which is statistically significant at 1%. This concurs with previous studies in which there was increased IL-6 levels in cardiac failure compared with controls.

The mean IL-6 values for NYHA gr II, III and IV were 29.75, 28.18 and 71.29 pg/ml respectively. The statistical tests used were ANOVA, which is used to compare the mean of more than two groups followed tuckey HSD test, which compares each group with one another.

Thus probability obtained by ANOVA was <0.001 which showed statistical significance. There was no statistical difference between groups II and III whereas there was significant difference between groups II and IV and III and IV. This showS that IL-6 levels in cardiac failure increases with increasing functional class.

The previous studies have shown that IL-6 levels increase with increasing degree of LV systolic dysfunction as evidenced by decreased ejection fraction measured by Echocardiography. In our study the mean IL-6 values in group I, II and III were 13.25, 16.42 and 77.54 respectively. The F probability was 0.0001 which was statistically significant. Among mild and moderate dysfunction there was no significant difference. Between mild and severe dysfunction as well as mod and severe dysfunction there is statistical difference at 5% level which concurs with previous studies.

Comparison Of Il-6 In Patients Before And After Treatment:
The mean IL-6 level of cases at the time of admission was 50.77 pg/ml and mean IL-6 level of cases after 1 month of uninterrupted treatment was 33.17 pg/ml. These values was subjected to t-test for paired samples. The P-value obtained was <0.001 which was significant, Thus regular treatment with drugs that control failure that have impact on the Neurohumoral axis ,These patients also had improvement in their clinical status after treatment as evident by their improved NYHA grade. Thus IL-6 levels can be used to monitor the efficiency of treatment in heart failure cases.

Outcome After 1 Month Of Treatment:
There were no in-hospital deaths. At the end of 1 month there were 6 deaths .Increased mortality was associated with significantly elevated IL-6 values both at the time of admission and after 2 weeks of treatment. Thus elevated IL-6 values at admission and after treatment were independent predictors of mortality due to cardiac failure.

CONCLUSION:
The recent growth of knowledge that has taken place in the field of cardiac failure has laid more emphasis on the potential role that proinflammatory cytokines play as mediators of disease progression in the failing human heart. This study shows that the proinflammatory cytokine IL-6 significantly elevated in cases of cardiac failure. Moreover increasing IL-6 levels were associated with increasing degrees of LV dysfunction measured by the ejection fraction. This points towards a need for more intensive targeting of the inflammatory pathway as well the neurohumoral axis as the degree of LV dysfunction increases.

The mean level of IL-6 in patients treated for 1 month was found to be lower thus indicating that periodical measurement of interleukin- 6 levels could be used to assess the response of the patients to the treatment given. Finally IL-6 can be used as a predictor of mortality in cardiac failure cases. The study in general stresses upon the significant role of the inflammatory pathway in the pathogenesis and progression of cardiac failure. Thus stressing upon the fact that targeting this pathway is the next frontier to be conquered for the sake of ailing patients.

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