The Role of Interleukine-6and Interleukin -1 in failing heart

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Abstract:

Background: Interleukin (IL) 6 has attracted attention with regard to myocardial dysfunction because increased levels adequate correlate with the heart failure. Heart failure is the inability of the heart to supply blood flow and therefore oxygen delivery to peripheral tissues and organs. Under perfusion of organs leads to reduced exercise capacity, fatigue, and shortness of breath. The cytokines like IL-1 may play a significant role in the pathogenesis of several forms of myocardial dysfunction.

Objective: To determine whether the increase level of interleukine-6 and interleukin-1 are important in prognosis of heart failure.

Method: The cytokine profile in patient group with heart failure(n = 80 mean±5.7 ) age (62.3±5.7) years was compared with that of age matched healthy individuals (n = 20, mean±SD) age of (59.7±6.3) years.

Results: The results showed significant increased levels of interleukine-6 (IL-6) and interleukin-1 (IL-1) in patients with heart failure compared with those in the control group.

Conclusion: from this study we can conclude that the pro inflammatory interleukine-6 (IL-6) and interleukin-1 (IL-1) may provoke the condition of heart failure patients.

Introduction:

Heart failure is a major and growing public health problem it appears to result not only from cardiac overload or injury but also from a complex interplay among genetic, neuro hormonal, inflammatory and biochemical changes acting on cardiac myocytes, the cardiac interstitium, or both (Braunwald, 2008).

Heart failure is the inability of the heart to supply adequate blood flow and therefore oxygen delivery to peripheral tissues and organs. Under perfusion of organs leads to reduced exercise capacity, fatigue, and shortness of breath. It can also lead to organ dysfunction in some patients (Klabunde, 2011).
Interleukin (IL)-6 is a cytokine with proinflammatory effects. It seems to have prognostic significance for the development of HF, since it was found that elderly people with elevated IL-6 levels were at increased risk of suffering from HF in the future (Vasan et al., 2003).

Studies have shown that IL-6 is related with the NYHA functional stage of HF and with survival (Kell et al., 2002).

It also seems that in patients with congestive HF the measurement of CT-1 levels has additional prognostic value, either alone or in combination with levels of brain natriuretic peptide (Jougasaki et al., 2003).

A series of studies have documented the pathogenetic role of inflammation in HF and in particular the role of inflammatory cytokines. The so-called “cytokine hypothesis” (Figure 1) asserts that the progression of HF is due, at least in part, to the destructive action of these factors and that many of the pathogenetic sequelae of HF are due to inflammatory cytokines (Evangelos et al., 2011).

Figure 1.

Proinflammatory cytokines act on cardiac and extra-cardiac tissues, thereby participating in the pathogenesis and progression of heart failure.

IL-1α is produced mainly by activated macrophages, as well as neutrophils, epithelial cells, and endothelial cells. In general, Interleukin 1 is responsible for the production of inflammation, as well as the promotion of fever and sepsis (Dinarello, 1997).

A wide variety of other cells only upon stimulation can be induced to transcribe the IL-1α genes and produce the precursor form of IL-1α (Feldmann et al., 2001). Among them are fibroblasts, macrophages, granulocytes, eosinophils, mast cells and basophils, endothelial cells, platelets, monocytes and myeloid cell lines, blood T-lymphocytes and B-lymphocytes, astrocytes, kidney mesangial cells, Langerhans cells, dermal dendritic cells, natural killer cells, large granular lymphocytes, microglia, blood neutrophils, lymph node cells, maternal placental cells and several other cell types (Yin et al., 2001 and Hu et al., 2003).

The cytokines like IL-1 may play a significant role in the pathogenesis of several forms of myocardial dysfunction. The role for IL-1 in this process are:
(1) IL-1 is elevated in several cardiac disease states,
(2) IL-1 is produced by myocardial cells themselves in response to injury,
(3) The alterations in gene expression seen in response IL-1 resembles in many ways the phenotype of the failing heart, and
(4) The co-localization of the IL-1 response with that of several previously described negative transcriptional regulators (making them potential targets for therapeutic manipulation) (Carlin, 2001).
IL-6 is an interleukin that acts as both a pro-inflammatory and anti-inflammatory cytokine. It is secreted by T cells and macrophages to stimulate immune response, e.g. during infection and after trauma, especially burns or other tissue damage leading to inflammation. In terms of host response to a foreign pathogen during infection, IL-6 has been shown, in mice, to be required for resistance against the bacterium, *Streptococcus pneumoniae* (Vander et al., 1997).

**Method:**

The study conducted from December 2010 to May 2011, one hundred subjects include 80 patients (40 male and 40 female) and 20 normal healthy subjects were included at Merjan Teaching Hospital in Babylon Province.

The patients had been referred to the echocardiographic unit from special cardiologist Dr. Amer Saheb Al-Momen in the hospital, they were in different age, the mean age of patients in years was 62.3±5.7 years.

All patients under went medical history and physical examination: age, blood pressure (systolic and diastolic pressure), ECG and pulse rate as well as history of chronic diseases as hypertension, ischemic heart disease, diabetes mellitus and chronic renal failure.

The patients involved in this study were:

- Patients with hypertensive heart failure were admitted in the cardiac care unit and at the medical ward in Marjan teaching hospital.
- Out patients referred from specialist cardiologist for echocardiographic examination at the echo unit in Marjan teaching hospital.

Exclusion criteria:

1. Valvular heart disease like mitral stenosis or regurgitation, or aortic stenosis or regurgitation, etc.
2. Cardiac arrhythmia like atrial fibrillation or sinus tachycardia.
3. Septal defects (ventricular or atrial).

The control group was 20 subject (10 male and 10 female) mean age±SD is 59.7±6.3. all control group are subjected for echocardiographic analysis.

Blood sample was taken from both control and patients groups for interleukine-6 measurement assessment of IL 6 by ELISA Kit (RayBio).

Echocardiography was performed at rest using M-mode images obtained by ultrasound machine (Phillips Invisor/C (2002) Prob frequency S2-4).

**Statistical Analysis**

Results were expressed as mean ± standard deviation (SD) . unpaired *t*-test was employed to the data that were normally distributed, Mann – Whitney U-test was used to compare difference between groups. P value less than 0.05 were considered significant.

**Results**

This study demonstrated that there is a significant increase in interleukin-6 level in patient with heart failure than control (p<0.05) in table -1.

Table (1) show baseline data of patients and control group characteristic age, blood pressure, pulse rate and cytokine profile (Interleukin-6) in control and heart failure patients.

In control group, the mean of interleukin-1-α is (1.2±1.4) pg/ml and those in patients with heart failure was (6.08±9.32) pg/ml. There is significant increase in Interleukin-1-α in patients with heart failure (Table 1).
Table (1): Baseline clinical data of patients with heart failure and control group.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Control n=20</th>
<th>Patients n=80</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (year)</td>
<td>59.7±6.3</td>
<td>62.2±5.6</td>
<td>0.079</td>
</tr>
<tr>
<td>SBP(mmHg)</td>
<td>130.5±8.2</td>
<td>134.1±15.5</td>
<td>0.318</td>
</tr>
<tr>
<td>DBP(mmHg)</td>
<td>80±8.5</td>
<td>82.1±10.3</td>
<td>0.384</td>
</tr>
<tr>
<td>Pulse rate(b/m)</td>
<td>77±2.5</td>
<td>78.6±5.2</td>
<td>0.198</td>
</tr>
<tr>
<td>IL-6 (pg/ml)</td>
<td>7.4±15.3</td>
<td>56.2±101.2</td>
<td>0.001</td>
</tr>
<tr>
<td>IL-1 (pg/ml)</td>
<td>1.2±1.4</td>
<td>6.08±9.32</td>
<td>0.001</td>
</tr>
</tbody>
</table>

(SBP) = Systolic blood pressure  
(DBP) = Diastolic blood pressure  
(IL-6) = Interleukine-6  
(IL-1) = Interleukine-1

The results also show no significant difference between patients with heart failure and control regarding age (years) (p≤0.05) .  
The study indicate that systolic and diastolic blood pressure is not significantly different between patients with heart failure and control (p≤0.05) .  
Regarding pulse rate the shows no significance difference between patients with heart failure and control subjects (p≤0.05).

Discussion

Inflammation is a key component in the myocardial remodeling process that takes place in response to hypertension (Levick et al., 2009 and Kagitani et al., 2004). However, the respective roles of specific cytokines in this process are not well defined. Interleukin (IL) 6 has attracted attention with regard to myocardial dysfunction because increased levels correlate with the severity of heart failure and are strongly prognostic of 1-year mortality (Haugen et al., 2008 and Tsutamoto et al., 1998). There is a growing body of evidence that a similar association exists in hypertensive patients (Bautista et al., 2005 and Chae et al., 2001). Lee et al. (2006) found that induction of IL-6 by angiotensin II contributes to elevations in blood pressure; however, the contribution of IL-6 to myocardial remodeling has not been firmly established. Hirota et al. (1995) demonstrated that concomitant overexpression of both IL-6 and the IL-6 receptor in mice induced concentric hypertrophy typical of that occurring in a hypertensive heart. Although these observations suggest that IL-6 may directly mediate hypertrophic remodeling associated with hypertension (Giselle et al., 2010). No studies have directly investigated the role of IL-6 in mediating cardiac fibrosis or diastolic dysfunction, features that are also characteristic of the hypertensive heart (Sarkar et al., 2004 and Siwik et al., 2000).

Moreover, another study has recently shown that the functional status of HF patients, as assessed by the use of the Kansas City Cardiomyopathy Questionnaire (KCCQ-s), is inversely associated with IL-6 levels (Parissis et al., 2009).

Another study, which included 101 patients with recently diagnosed HF, found that IL-6 was associated with impaired left atrial function and more advanced left ventricular diastolic and systolic dysfunction. Specifically, IL-6 levels were inversely
associated with both left atrial kinetic energy and the systolic wave measured at the level of the mitral annulus using tissue Doppler (Chrysohoou et al., 2009).

Cardiotrophin-1 (CT-1) also belongs to the IL-6 family, being a cytokine that shares a common receptor system with IL-6. This cytokine is associated with a large range of cardiovascular events and its production appears to be stimulated by ventricular dilation (Calabrò et al., 2009 and Pemberton et al., 2005).

In this study there is significant increase interleukin-6 level in patients with heart failure in comparison to control subjects. This results in-agreements with the study of Haugen et al., (2008) and Deswal et al., (2001).

This indicate that inflammation playing an important role in the progression of heart failure (Mann, 2002 and Torre-Amione, 2005). These two researches indicated that there is significance increase interleukin-6 level in heart failure (Stamatis et al., 2002).

In our study there is significant increase interleukin-6 level in patients with heart failure in comparison to control subjects. This results in agreements with research done by (Haugen et al., 2008). This indicate that inflammation playing an important role in the progression of heart failure, particularly in younger patients (Mann et al., 2002 and Torre-Amione et al., 2005). These two researches indicated that there is significance increase interleukin-6 level in heart failure.

Inflammation plays an important role in the development and progression of a variety of cardiovascular conditions, most notably coronary atherosclerosis and congestive heart failure (Willerson et al., 2004). Circulating level of IL-1 are associated with the presence of traditional cardiac risk factors, such as diabetes Mellitus, hypertension, smoking and dyslipidemia. Elevated level of IL-1 result in secretion of chemokines and other cytokine (e.g. IL-6), increase expression of adhesion molecules, activation of endothelial and smooth muscle cell proliferation, macrophage activation and increased vascular permeability. IL-1 and other proinflammatory cytokines have also been implicated in the progression of heart failure, as a result of their negative inotropic effects and deleterious effects on left ventricular remodeling (Mann et al., 2002).

Another important mechanism which IL-1 may enhance atherogenesis and exacerbate left ventricular dysfunction is by contributing to endothelial dysfunction. IL-1 stimulates inducible nitric oxide synthetase, which increases information of reactive oxygen species and reactive nitrogen species (eg. nitrotyrosine), which leads to oxidative and so called nitrosative stress and endothelial dysfunction (William et al., 2008).

Research done by Arnon and Hylton (2001) show increase level of IL-1 in heart failure patients. Persistent immune activation in chronic HF has been found independently of the etiology of HF, possibly representing a final common pathogenic pathway in this disorder. Several studies have reported raised plasma levels of inflammatory cytokines and chemokines in direct relation to deterioration of functional class (i.e. New York Heart Association classification) and cardiac performance (e.g. left ventricular ejection fraction (LVEF)) (Aukrust et al., 1999 and Damas et al., 2000). Moreover, it seems that these inflammatory mediators may give important prognostic information in patients with chronic HF. For example, in a sub-study to Studies on Left Ventricular Dysfunction, patients with plasma levels of TNFαv6.5 pg/mL had a better prognosis than those with higher TNFα levels (Torre-amione et al., 1996). Furthermore, in a large population of HF patients (1200 patients, the cytokine database from the Vesnarinone trial) circulating levels of inflammatory cytokines (i.e. TNFα and IL-6) and cytokine receptors (i.e. soluble TNF receptors
(TNFRs)) were found to be independent predictors of mortality in patients with advanced HF (Lee et al., 2006). These clinical data further support the notion that raised levels of cytokines in HF patients are not only epiphenomena, but may reflect important pathogenic mechanisms in these patients.

The molecules of IL-1 have been referred to as proinflammatory cytokines, insofar as they were traditionally thought to be derived exclusively from the immune system and were therefore considered to be primarily responsible for mediating inflammatory responses in tissues. However, these inflammatory mediators are now known to be expressed by all nucleated cell types residing in the myocardium, including the cardiac myocyte, thus suggesting that these molecules may do more than simply orchestrate inflammatory responses in the heart (Kapadia et al., 1995). The interest in understanding the role of inflammatory mediators in heart failure arises from the observation that many aspects of the syndrome of heart failure can be explained by the known biological effects of proinflammatory cytokines. That is, when expressed at sufficiently high concentrations, such as those that are observed in heart failure, cytokines are sufficient to mimic some aspects of the so-called heart failure phenotype, including (but not limited to) progressive left ventricular (LV) dysfunction, pulmonary edema, LV remodeling, fetal gene expression, and cardiomyopathy (Bozkurt et al., 1998 and Kubota et al., 1997). Thus, the “cytokine hypothesis” for heart failure holds that heart failure progresses, at least in part, as a result of the toxic effects exerted by endogenous cytokine cascades on the heart and the peripheral circulation. It bears emphasis that the cytokine hypothesis does not imply that cytokines cause heart failure, per se, but rather that the overexpression of cytokine cascades contributes to the disease progression of heart failure. Thus, the elaboration of cytokines, much like the elaboration of neurohormones, may represent a biological mechanism that is responsible for worsening heart failure (Seta et al., 1996).

Immune System. In response to injury in the heart muscle cells that occurs when the heart fails, the immune system releases immune factors, as proinflammatory cytokines; activation of the complement system; and production of autoantibodies, intended to protect these areas. Several lines of evidence support a role of immune mechanisms in the pathogenesis of HF. But these proteins can cause inflammation and other damages and are involved in cardiac depression and in the progression of HF. The origin of the immune activation in patients with HF is still unknown. However, two hypotheses have been proposed. One suggests that the wall’s edema leads to bacterial translocation with endotoxin release and immune activation. The second suggests that the heart in HF is the main source of cytokines, tumor necrosis factor-α (TNF-α) and other proinflammatory cytokines (interleukin-1 and -6) (Mancia, 1990).

References
Evangelos Oikonomou1, Dimitris Tousoulis1, Gerasimos Siason1,2, Marina Zaromitidou1, Athanasios G. Papavassiliou2, Christodoulos Stefanadis1. (2011) The Role of Inflammation in Heart Failure: New Therapeutic Approaches. Hellenic J Cardiol; 52: 30-40
Hirota H, Yoshida K, Kishimoto T, Taga T. (1995) Continuous activation of gp130, a signal-transducing receptor component for interleukin 6-related cytokines,


