Correlation Between Interleukins 1 α,6 and Echocardiographic Results in Patients with Heart Failure

Shahlaa Khazal Abed chabuk
Amer Saheb Al-Momen
College Of Medicine, University of Babylon, Hilla, Iraq
Israa F. Alsamaraee
College Of Medicine, University of Baghdad.

الخلاصة :

هنالك فرق في نتائج جهاز صدى القلب بين مرضى عجز القلب ومجموعة الأصحاء، مرض فشل القلب هو عدم قدرة القلب على تزويد الدم وبالتالي تزويد الأوكسجين إلى الأعضاء والأنسجة. السايتوكين رقم (1) يلعب دوراً متميزاً في نشوء عدة أنواع من قصور وظيفة العضلة القلبية، الهدف من الدراسة كان التحري عن العلاقة بين الانترلوكين (1 ، 6) ونتائج جهاز صدى القلب عند مرضى فشل القلب ومقارنة نتائج صدى القلب بين مرضى فشل القلب ومجموعة الأصحاء، ولقد كان عدد مرضى عجز القلب هو (80) ثمانون شخصا و بمعدل عمر 62 سنة ولقد قورنت نتائج المرضى مع نتائج مجموعة السيطرة والبالغ عددهم 20 شخصا وبمعدل عمر 59 سنة .وأجريت الدراسة في وحدة صدى القلب التابع الى مستشفى مرجان التعليمي في محافظة بابل ، ولقد أظهرت النتائج فرقا معنويا في قيم جهاز صدى القلب بين مرضى عجز القلب ومجموعة الأصحاء، وهناك علاقة خطية موجبة وسالبة بين الانترلوكين (1 ، 6) ونتائج جهاز صدى القلب في مرضى فشل القلب.

Abstract:

Background:

Difference in echocardiographic results between normal heart subjects and heart failure patients Heart failure is the inability of the heart to supply blood flow and therefore oxygen delivery to peripheral tissues and organs..The cytokines like IL-1 may play a significant role in the pathogenesis of several forms of myocardial dysfunction. Our aim was to investigate the correlation between Interleukins 1,6 and echocardiographic results in heart failure patients and comparison of the echocardiographic results of heart failure patients with those of normal subjects group.

The cytokine profile and Echocardiographic results in patient with heart failure (n=80) age 62.3±5.7 years was compared with that of age matched healthy individuals (n=20) age of 59.7±6.3 years.

Blood sample was taken from both control and patients groups for interleukine-1 , 6 measurement by ELISA Kit (Ray Bio).

There is significant difference in echocardiographic values between healthy subjects and heart failure patients. A negative and positive linear correlations was found between Interleukin 1, 6 and echocardiographic parameters.

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, 6 in patients with heart failure.

Introduction:

Heart failure is generally defined as the inability of the heart to supply sufficient blood flow to meet the needs of the body. (Jessup, *et al*,2009) Heart failure can cause a number of symptoms including shortness of breath, leg swelling, and exercise intolerance. The condition is diagnosed with echocardiography and blood tests. Treatment commonly consists of lifestyle measures (such as smoking cessation, light exercise including breathing protocols, decreased salt intake and other dietary changes), medications, and sometimes devices or even surgery. Common causes of heart failure include myocardial infarction and other forms of ischemic heart disease, hypertension, valvular heart disease, and cardiomyopathy (McMurray, *et al*, 2005).In developed countries, around 2% of adult people are suffer from heart failure (Dickstein *et al*, 2008).Under perfusion of organs leads to reduced exercise capacity, fatigue, and

shortness of breath. It can also lead to organ dysfunction in some patients. Heart failure is a clinical syndrome caused by disease or other abnormal conditions in the body. Heart failure can be caused by factors originating from the heart (i.e., intrinsic disease or pathology) or from external factors that place excessive demands upon the heart. Intrinsic disease includes conditions such as dilated cardiomyopathy and hypertrophic cardiomyopathy. External factors that can lead to heart failure include long-term, uncontrolled hypertension, increased stroke volume (volume load; arterial-venous shunts), hormonal disorders such as hyperthyroidism, and pregnancy. Left ventricular ejection fraction% (LVEF%) is the amount of blood pumped by left ventricle at each heart beat (Braunwald, *et al*, 1998). Its measurement is equal to the ratio between (end diastolic LV volume – systolic LV volume) and end-diastolic LV volume%, according to the following formula:

$$E.F\% = \frac{diastolic\ LV\ volume - systolic\ LV\ volume}{diastolic\ LV\ volume} \times 100$$

Left ventricular ejection fraction % (LVEF%) is a hemodynamic index indicative for left ventricular function. Its numeric value can be obtained by different methods, such as two-or three dimensional echocardiography. It depend not only on myocardial contractility, but also on preload and after load, as well as, heart rate and left ventricular distensibility (Federico Caccrapuoti, 2010).Echocardiography is non invasive and devoid of ionizing radiation, for special purpose, ultrasound imaging can also be performed semi-invasively via the esophagus or invasively via the vessels (Flaschskanpf, *et al*, 2009).

"M-Mode" echocardiography is a single directional beam of ultrasound that was manually directed toward different reflecting structures and is utilized as part of the standard echocardiographic examination (Solomon,2007).The echocardiographic examination was done using standard views and techniques according to the guide lines of the American Society of echocardiography (Schiller, *et al*, 1989).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) 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) 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 a granular lymphocytes, microglia, neutrophils, lymph node cells, maternal placental cells and several other cell types.(Yin, *et al*, 2001, Hu *et al*, 2003)The cytokines like IL-1 may play a significant role in the pathogenesis of several forms of myocardial dysfunction. Although it seems clear that IL-1 is not acting alone under circumstances of myocardial injury, continued investigations into the cytokine hypothesis will ultimately increase the understanding of how pro-inflammatory molecules influence

myocardial function and how the modulation of such factors may improve the myocardial response to injury. 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)

Material and Method:

Study group**:** The study conducted from November 2010 to June 2011, eighty patients of both gender (40 males and 40 females).Twenty normal healthy subjects (10 males and 10 females) were included .The study done at Marjan Teaching Hospital in Babylon Province. The patients had been referred to the echocardiographic center in the hospital, the mean age of patients in was (62.3±5.7 years), they were subjected to echocardiographic study by the consultant cardiologist.The control group mean age±SD is 59.7±6.3. All control group are subjected to echocardiographic analysis. All patients and healthy subjects underwent full medical history and physical examination including: age, gender, blood pressure (systolic and diastolic), pulse rate and ECG as well as history of chronic disease as hypertension, ischemic heart disease, diabetes mellitus and chronic renal failure. Blood sample was taken from both control and patients groups for interleukine-1 , 6 measurement by ELISA Kit (RayBio).

Echocardiography**:** the echocardiography machine is a digital device .The operator machine of echocardiography is Phillips which provided with transducer for cardiac usage which had capability of cardiac images in the following mod:

1-Tow-Dimensional mod (2D).
2-Motion or M-mode.
3-Doppler, which has different types.

Statistical Analysis:

All analysis were performed by SPSS statistical social sciences package. data were defined as mean ±SD. Echocardiographic and Interleukins results were compared by an unpaired t- test and employed to the data that were normally distributed, Mann – Whitney U-test was used to compare difference between groups. A values of $p< 0.05$ was considered statistically significant.

Results:

1- Echocardiographic results

The study demonstrated that there is a significant difference in percentage of ejection fraction, fractional shortening and stroke volume in patients with heart failure than control group. (Table-1), ($P \leq 0.05$).
The results also show significant increase in IVSTD (mm), IVSTS (mm), LVDIS (mm), LVIDD (mm), PWTS (mm), PWTD (mm), ESV (ml), EDV (ml). (Table-1), ($P \leq 0.05$).Table (1) shows Echocardiographic results in both normal and heart failure patients.

Table (1) : Show Echocardiographic results in control and heart failure groups.

Echocardiographic measurements	Control n=20	Patients n=80	P-value
IVSTD (mm)	10±1.6	15±2.5	Sign*.
IVSTS (mm)	7.7±1.3	12.6±2.5	Sign*.
LVDIS (mm)	37.5±7.2	44.5±10.7	Sign*.
LVIDD (mm)	51.4±6.4	56.9±9.9	Sign*.
PWTS (mm)	7.15±1.04	11±2.7	Sign*.
PWTD (mm)	10.4±1.09	12.9±2.7	Sign*.
FS%	21±2.3	15.5±3.4	Sign*.
ESV (ml)	98.3±53.2	150.3±47.4	Sign*.
EDV (ml)	172.8±51.6	195.7±47.1	Sign*.
. SV (ml)	74.5±9.07	42.3±8.5	Sign*.
. EF%	58.05±5.07	38.03±9.14	Sign*.

1. IVSTD (mm): Interventricular septal diastolic thickness.
2. IVSTS (mm): Interventricular septal systolic thickness.
3. LVDIS (mm): Left ventricular systolic thickness.
4. LVIDD (mm): Left ventricular diastolic thickness.
5. PWTS (mm): Posterior wall systolic thickness.
6. PWTD (mm): Posterior wall diastolic thickness.
7. FS%: Fractional shortening.
8. ESV (ml): End systolic volume.
9. EDV (ml): End diastolic volume.
10. SV (ml): Stroke volume.
11. EF%: Ejection fraction.

* Significance ($P \leq 0.05$).

2-Interleukins:

Table (2) show baseline data of patients and control group characteristic age, blood pressure, pulse rate and cytokine profile (Interleukin-1,6) 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 2).

Table (2): Shows the mean value of interleukin-1-α and interleukin-6 in normal group and heart failure patients.

Parameters	Control n=20	Patients n=80	*P-value
Interleukin-1-α pg/ml	1.2±1.4	6.08±9.32	0.001
Interleukin-6 pg/ml	7.48±15.23	56.2±101.	0.001

*P- Significant ($P \leq 0.05$).

3- Correlation Between Echocardiographic Findings and level of Interleukins in Patients with Heart Failure

The correlation between ejection fraction (EF%) and interleukin-6 (IL-6) as shown in figure (1). There is negative linear correlation ($r = -0.073$, $P = 0.05$).

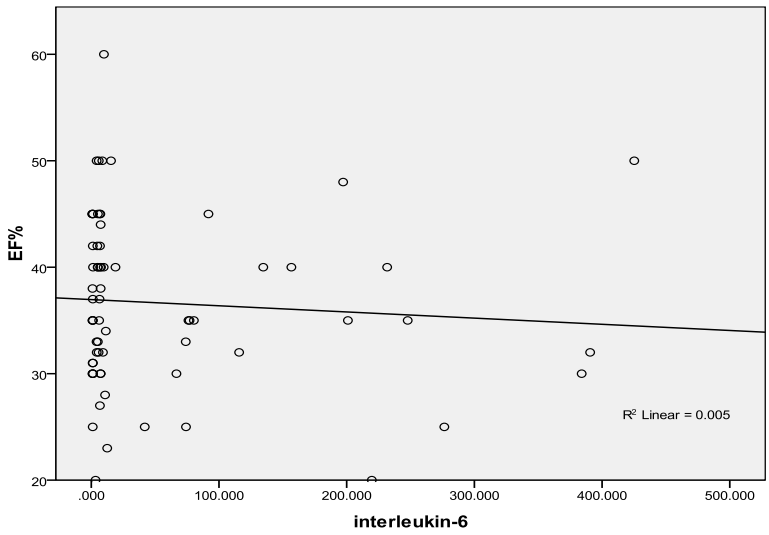

Figure (1): Shows correlation between the ejection fraction (%) and interleukin-6 (pg/ml) in patients group (r =0.073, P = 0.05)this results was significant.

There was positive linear correlation (r = 0.058, P = 0.01) between ejection fraction (EF%) and Interleukin-1 as shown in figure (2).

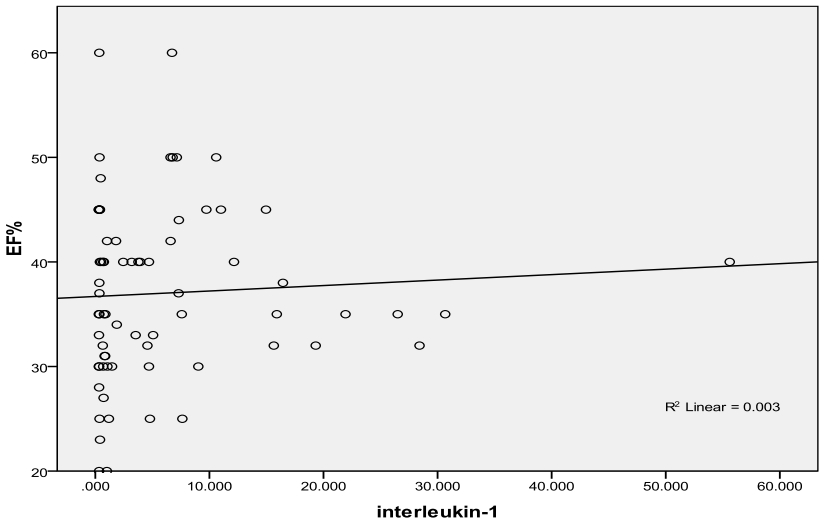

Figure (2): Showed a week correlation between ejection fraction(%) and interleukin-1 (IL-1) (pg/ml) in patients group (r = 0.058, P = 0.01).

Figure (3): showed correlation between stroke volume (SV) and interleukin-6 (IL-6). There was positive linear correlation (r = 0.163, P= 0.05).

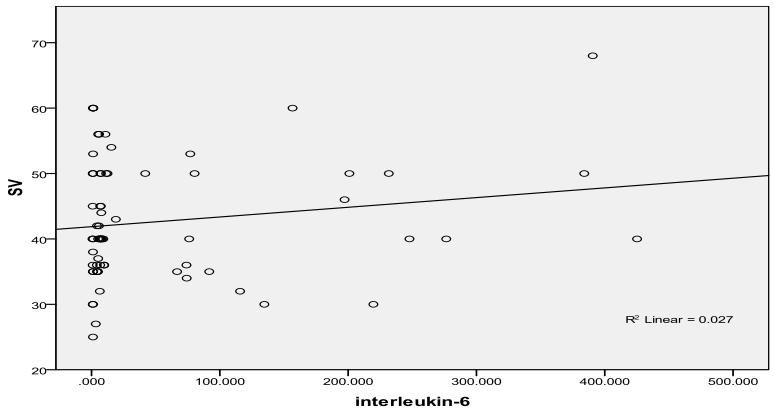

Figure (3) Showed the correlation between (SV) stroke volume (ml) and interleukin-6 (IL-6) (pg/ml) in patients group (r = 0.163, P= 0.05).

There was no correlation between stroke volume (SV) and interleukin-1 (IL-1) (r = 0.026,P = 0.05).

Figure (4) showed the correlation between end diastolic volume (EDV) and Interleukin-6 (IL-6) in which there was positive linear correlation (r = 0.078, P = 0.05).

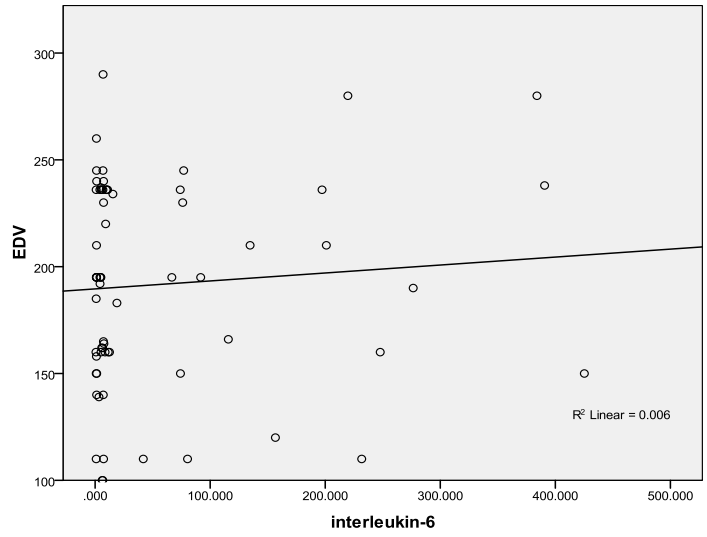

Figure (4) Showed the correlation between (EDV) end diastolic volume (ml) and interleukin-6 (IL-6) (pg/ml) in patients group (r = 0.078, P = 0.05).

There was a negative linear correlation between end diastolic volume (EDV) and interleukin-1(IL-1). Figure (5),(r = 0.189, P = 0.01).

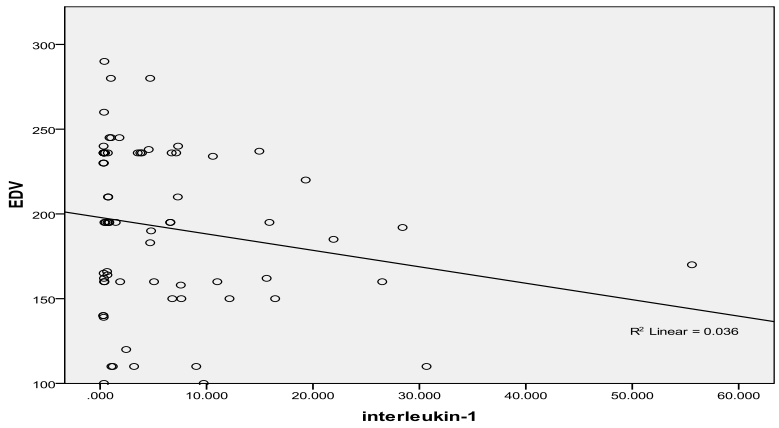

Figure (5) Showed the correlation between (EDV) end diastolic volume (ml) and interleukin-1 (IL-1) (pg/ml) inpatients group(r = 0.189, P = 0.01).

Discussion:

In study done by (Fatih, *et al*, 2008, Bruch, *et al*, 2000) shows that there is significance decrease in percentage of ejection fraction in patients with heart failure in comparison to control subjects and this results are similar to our results in study.EF have significant prognostic importance in patients with heart failure (Florea, *et al*, 2000). An account assessment of left ventricular function is important in the diagnosis and management of several cardiac disease states such as heart failure and post myocardial infarction (Domansku, *et al*, 2006).Serial monitoring of ejection fraction is also useful for the determination of timing of medical or surgical interventions (Watanabe, *et al*,2003).

Fractional Shortening was calculated as the percentage systolic fall in left ventricular dimension with respect to end diastolic (Florea, *et al*, 2000).

Fractional shortening (FS), in percentage, was calculated according to the following formula:

FS = [(LVIDd - LVIDs)/LVIDd] × 100%.

IVSTD and IVSTS: Interventricular septal end diastolic and end systolic thickness. Our study showed increase in IVSTD and IVSTS. This result is similar to results of study done by (Talwar, *et al*,2000).Study done by S. Talwar show increase IVSTD and IVSTS in patients with heart failure in comparison with control group.

PWTD and PWTS: Our study shows significant increase in posterior wall thickness in systole and diastole.(Kitzman, *et al*,2002) Kitzman *et al*., assessed left ventricular function by echocardiography in patients with systolic and diastolic heart failure and in normal controls and the results confirm these morphologic and functional characteristics. LV posterior wall thickness in systole and diastole significantly increase in patient with heart failure which is similar to our results.

Where LVIDD is the LV internal diameter in diastole, and LVIDS is the LV internal diameter in systole (Ahmet, *et al*,2004).

End diastolic and end systolic volume: in our study there is significant increase in end diastolic volume and end systolic volume. This results is supported by study done by(Ahmet, *et al*,2004).

Stroke volume: Our study shows significant decrease in stroke volume in heart failure patients and this result is supported by research done by (Talwar, *et al*,2000).

In our study there is significant increase interleukin-6- level in patients with heart failure in comparison to control subjecs. This results in inagreements with research done by (Espen, *et al*,2008) .This indicate that inflammation playing an important

role in the progression of heart failure, particularly in younger patients (Mann,2002, Torre-Amione, 2005). These two researches indicated that there is significance increase interleukin-6 level in heart failure.

Research done by (Arnon, *et al*,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 (Arnon, *et al*,2001).

The negative linear correlation between the ejection fraction and interleukin-6. were in agreement with(Kell, *et al*,2002, Maeda, *et al*,2000, Torre-Amione, *et al*,1996) and (Takayoshi, *et al*,2001). A study done by(Baitosz, *et al*,2011) found a significant inverse correlation between interleukin-6 concentration and ejection fraction.

There is positive linear correlation between end diastolic volume and interleukin -6 in heart failure patients which goes with results of study done by(Josefina, *et al*,2000) and(Takayoshi, *et al*,2004).

From the results of study there was weak positive linear correlation between percentage of ejection fraction and interlekin-1. Similare finding s reported by(Benjamin, *et al*,2012) which show that IL-1 is a proinflammatory cytokine that become chronically elevated in h.f and exert putative negative inotropic effect.

As noted from there was a positive linear correlation between interleukin -6 and stroke volume. This goes with finding of Testa et. al., (1996) and Van tassell et. al., (2012).

In study done by Van Tassell et. al., (2012) shows strong correlation between interleukin-1 and left ventricular stroke volume, ejection fraction and end diastolic volume were there is reduction in SV, EDV with increase level of IL-1 and this indicate that enhanced inflammation is associated with worsening outcome in heart failure patients and may play a direct role in disease progression.

References

Ahmet I, Kraqczyk M, Heller P: (2004). Beneficial effects of chronic pharmacological manipulation of B-adrenoreceptor subtype signaling in rodent dilated ischemic cardiomyopathy. Circulation, 110(9):1083-1090).

Arnon Blum and Hylton Miller (2001). Pathophysiological role of cytokines in conjestive heart failure. Annua. Review of Medicine. Vol. 52:15-27.

Bartosz Hudzik, Janusz Szkodzinski, Wojciech Romanowski, Aleksander Danikiewicz, Krzysztof Wilczek, Andrzej Lekston, Lech Polonski, Barbara Zubelewicz-Szkodzinska, (2011). Serum interleukin-6 concentration reflects the extent of asymptomatic left ventricular dysfunction and predicts progression to heartfailure in patients with stable coronary artery disease, Cytokine, Volume 54, Issue 3, June, Pages 266–271.

Benjamin W. Van Tassell, Ross A. Arena, Stefano Toldo, Eleonora Mezzaroma, Tania Azam, Ignacio M. Seropian, Keyur Shah, Justin Canada, Norbert F. Voelkel, Charles A. Dinarello, Antonio Abbate, (2012). Enhanced Interleukin-1 Activity Contributes to Exercise Intolerance in Patients with Systolic Heart Failure, , PLoS ONE 7(3): e33438.

Braunwald E. Normal and abnormal myocardial function. In: Fauci AS, Braunwald E, Isselbacher KJ, Eds. (1998). Harrison's Principles of Internal Medicine, New York: NY-McGraw-Hill; pp. 1278-86)

Bruch C., A. Schmermunal, D. Marin, M. Katz, T. Bartel, J. Schaar and R. Erbel. (2000). Tei-index in patients with mild-to-moderate congestive heart failure. European Heart Journal 21,1888-1895).

Carlin S. Long. (2001). The Role of Interleukin-1 in the Failing Heart. Heart Failure Reviews; Volume 6, Number 2, 81-94,

Chrysohoou C, Pitsavos C, Barbetseas J, et al. (2009). Chronic systemic inflammation accompanies impaired ventricular diastolic function, detected by Doppler imaging, in patients with newly diagnosed systolic heart failure (Hellenic Heart Failure Study). Heart Vessels.; 24: 22-26.

Dickstein K, Cohen-Solal A, Fillippatos G, et al., (2008). ESC Guidelines for diagnosis and treatment of acute and chronic heart failure.: The Taskforce for the diagnosis and treatment).

Dinarello CA (June 1997). "Induction of interleukin-1 and interleukin-1 receptor antagonist". Semin. Oncol. 24 (3 Suppl 9): S9–81–S9–93. PMID 9208877.

Domanski MJ, Nanda N. (2006). Echocardiographic determination of left ventricular function. J Am Soc Echocardiogr; 19:941-2).

Espen Haugen, Lihing Gan, Azra Isic, Tomas, Skommerak and Michael Fu. (2008). Increase Interleukin-6 but not tumour necrosis factor alpha predicts mortality with population of elderly heart failure patients. Exp. Clin. Cardiol. Spring; 13(1):19-24.

Fatih Bayrak , Gokhan Kahveci, Muzaffer Fegertekin and Buland Multu. (2008). Echographic predictors of sever heart failure symptoms in hypertrophic cardiomyopathy patients with sinus rhythm. Trials Journal, 9:11.

Federico Caccrapuoti. (2010). Are Clinical Heart Failure and ejection Fraction always connected? -Open Heart Failure Journal, ,3,1-8

Feldmann M, Saklatvala J (2001). "Proinflammatory cytokines". In Durum SK, Oppenheim JJ, Feldmann M. Cytokine reference: a compendium of cytokines and other mediators of host defense. Boston: Academic Press. pp. 291–306. ISBN 0-12-252673-2.

Flaschskanpf, F.A; Voigt, J. and Daniel, W.G. (2009). The ESC book of cardiovascular medicine, 2ne edition, chapter 4)

Florea VG, , MY, Henein, SD, Anker, DP, Francis, JS, Chambers, P, Ponikoski and AJS, Coats. (2000). Prognostic value of changes over time in exercise capacity and echocardiographic measurements in patient with chronic heart failure. . European Heart Journal 21, 146-153).

Hu B, Wang S, Zhang Y, Feghali CA, Dingman JR, Wright TM (August 2003). "A nuclear target for interleukin-1alpha: interaction with the growth suppressor necdin modulates proliferation and collagen expression". Proc. Natl. Acad. Sci. U.S.A. 100 (17): 10008–13.

Jessup. M, et al. (2009). Focused Update: ACCF/AHA Guidelines for the Diagnosis and Management of Heart Failure in Adults. Circulation. Apr 14;119(14):1977-2016

Josefina Orús, Eulalia Roig, Felix Perez, Carlespare, Manel Azqueta, Xavier Filella, Magda Heras, Gines Sanz. (2000). Prognostic value of serum cytpkines in patients with cohesive heart failure. The Journal of Heart and Lung transplantation, Vol. 19, Issue 5, , p. 419-425.

Kell R, Haunstetter A, Dengler TJ, Zugck C, Kübler W, Haass M. (2002). Do cytokines enable risk stratification to be improved in NYHA functional class III patients? Comparison with other potential predictors of prognosis. Eur Heart J.; 23: 70-78.

Kitzman DW., Little WC, Bruker PH, etal. (2002). Pathophysiological characterization of isolated diastolic heart failure in comparison systolic heart failure. JAMA;288:2144-50.

Maeda K., Tsutamoto T., Wada A., et al., (2000). High levels of plasma brain natriuretic peptide and interleukin-6 after optimized treatment for heart failure are independent risk factors for morbidity and mortality in patients with congestive heart failure. J Am Coll Cardiol;36:1587-1593.

Mann Dl. (2002). Inflammatory mediators and the failing heart: past, present, and foreseeable future Circ. Res.; 91:988-998)

McMurray JJ, Pfeffer MA. (2005). "Heart failure". Lancet 365 (9474): 1877–89..

Schiller NB, Shah PM, Crawford M et al., (1989). Recommendations for quantification of the left ventricle by two dimensional echocardiography. J. Am. Soc. Echo.; 2:358-67).

Solomon, S.D. (2007). Essential Echocardiography: a practical handbook with DVD. Humane Press, Totowa,NJ.

Takayoshi Tsutamoto, Atsuyuki Wada, Keiko Maeda, Naoko Mabuchi, Masaru Hayashi, Takashi Tsutsui, Masato Ohnishi, Masanori Fujii, Takehiro Matsumoto, Takashi Yamamoto, Xinwen Wang, Shigeru Asai, Tetsuo Tsuji, Hitoshi Tanaka, Yoshihiko Saito, Koichiro Kuwahara, Kazuwa Nakao, and Masahiko Kinoshita, (2001). Relationship between plasma level of cardiotrophin-1 and left ventricular mass index in patients with dilated cardiomyopathy, J Am Coll Cardiol,; 38:1485-1490.

Takayoshi Tsutamoto, Atsuyuki Wada, Masato Ohnishi, Takashi Tsutsui, Chitose Ishii, Keijin Ohno, Masanori Fujii, Takehiro Matsumoto, Takashi Yamamoto, Tomoyuki Takayama, Tomohiro Dohke and Minoru Horie, (2004). Transcardiac increase in tumor necrosis factor-α and left ventricular end-diastolic volume in patients with dilated cardiomyopathy. Eur J Heart Fail 6 (2): 173-180.

Talwar S., I.B. Squire, P.F. Downie, R.J. O'brien, J.E. Davies and L.NG. (2000). Elevated circulating cardiotrophin-1 in heart failure: relationship with parameters of left ventricular systolic dysfunction. Clinical Science 999(83-88)).

Testa M., M Yeh, P Lee, R Fanelli, F Loperfido, JW Berman, and TH LeJemtel, (1996). Circulating levels of cytokines and their endogenous modulators in patients with mild to severe congestive heart failure due to coronary artery disease or hypertension, J Am Coll Cardiol,; 28:964-971.

Torre-Amione G. (2005). Immune activation in chronic heart failure. Am. J. Cardiol.; 95:13C-8C)

Torre-Amione G., Kapadia S., Benedict C., Oral H., Young J.B., Mann D.L. (1996). Proinflammatory cytokine levels in patients with depressed left ventricular ejection fraction: a report from the studies of left ventricular dysfunction (SOLVD). J Am Coll Cardiol;27:1201-1206.

Vasan RS, Sullivan LM, Roubenoff R, et al. (2003). Inflammatory markers and risk of heart failure in elderly subjects without prior myocardial infarction: the Framingham Heart Study. Circulation.; 107: 1486-1491.

Watanabe M, Murakami M, Furukawa H, et al., (2003). Is measurement of plasma brain natriuretic peptide levels a useful test to detect for surgical timing of valve disease? Int J Cardiol; 96:21-4).

Yin H, Morioka H, Towle CA, Vidal M, Watanabe T, Weissbach L (August 2001). "Evidence that HAX-1 is an interleukin-1 alpha N-terminal binding protein". Cytokine 15 (3): 122–37.