THE NEW ARMENIAN MEDICAL JOURNAL
Vol.9 (2015), No 4, p.102-105

ROLE OF ENDOTHELIN-1 IN LEFT VENTRICULAR REMODELING PROCESS

Sisakyan H.S., Sahakyan L.G.*

Department of General and Invasive Cardiology, Yerevan State Medical University Hospital No 1, Yerevan, Armenia

Received 08/22/2015; accepted for printing 08/22/2015

Abstract

Endothelin-1 level was shown to be elevated in blood samples of patients with heart failure, to predict outcome and play a negative role for cardiac remodeling. The aim of the study was the determination of interrelation between endothelin-1 activation and left ventricular structural remodeling parameters which are involved in the progression of heart failure.

The first study group was consisted of 80 patients with compensated chronic heart failure II to IV class by New York Heart Association classification and with ejection fraction <45%. All patients underwent routine echocardiography and measurement of plasma endothelin-1 level which was determined using the immunoferment analysis. Twenty one healthy individuals were included from the hospital staff in the second group. Left ventricular end-diastolic diameter was measured from left parasternal view. Correlation between humoral biomarker's indices and echocardiographic parameters was studied by linear regression and Pearson correlation analyses.

Endothelin-1 level was significantly higher in blood plasma of patients with chronic heart failure than in healthy individuals. As a result of the study a negative but statistically significant correlation was noticed between plasma endothelin-1 level and left ventricular end-diastolic diameter in the group of patients with heart failure which indicates the pathogenetic role of endothelin-1 in the development of left ventricular remodeling process. Endothelin-1 is overactivated in patients with chronic heart failure.

Despite the existence of numerous studies, the data regarding endothelin-1 effects are controversial, that's why further clinical studies are necessary for the determination of endothelin-1 activation role in the progression of chronic heart failure and anti-endothelial treatment effectiveness in present pathology.

Keywords: *heart failure, endothelin-1, echocardiography, left ventricular remodeling.*

Introduction

It is known that the level of various neuroendocrine and humoral markers is elevated and correlate with the severity of heart failure [*Rockman H et al., 2002*]. Among them, the role of endothelin-1 (ET-1) has been extensively studied [*Barton M, Yanagisawa M., 2008*]. Endothelin-1 is a peptide mostly secreted by vascular endothelial cells, the predominant isoform expressed in vasculature by endothelin-converting enzyme and the most known potent vasoconstrictor nowadays [*Agapitov A, Haynes W, 2002*]. Though ET-1 is generally synthesized in endothelial cells, ET-1 synthesis is also produced in heart, kidney, central nervous system and posterior pituitary [*Gray G, 1995*]. ET-1 synthesis is increased by vasoactive hormones, growth factors, hypoxia, shear stress, free radicals, endotoxins. ET-1 synthesis is inhibited by endothelium-derived NO, nitrovasodilators, natriuretic peptides, heparin and prostaglandins [*Gray G, 1995*]. Increase of endothelin-1 level was shown to be elevated in blood samples of heart failure patients, to predict outcome and play a negative role for cardiac remodeling [*McMurray J et al., 1992*]. Several experimental studies on animal models have revealed that endothelin is detected in healthy and failing myocardia and its activity both by immunohistochemistry and radioimmunoassay is not changed in congestive heart failure [*Yamauchi-Kohno R et al.,*

Address for Correspondence:
Clinic of General and Invasive Cardiology
60 Abovyan Street, Heratsi No 1 Hospital Complex, Yerevan, Armenia
Tel.: (+374 10) 56-57-68, (+374 55) 17-03-86
Email: cardioclinic@ysmu.com

1999]. Furthermore, the elevation of endothelin in blood plasma is typical in severe congestive heart failure and not in asymptomatic or mild congestive heart failure [*Krum H et al., 2001*]. In addition, the degree of plasma elevation of ET correlates with the magnitude of alterations in cardiac hemodynamics and functional class [*Wei C et al., 1994*]. The possible role of endothelin in congestive heart failure and studies of anti-endothelin therapies were reviewed in several preclinical studies. Unfortunately, while the pathophysiology of congestive heart failure strongly implicates endothelin in the progression of disease, the endothelin inhibition as a new therapeutic strategy didn't give any results in clinical trials. However clinical data regarding ET-1 overexpression and left ventricular remodeling are lacking and the results of some studies are controversial. The aim of the study was the determination of interrelation between endothelin-1 activation and left ventricular structural remodeling parameters which are involved in the progression of heart failure because endothelin-1 is activated in patients with heart failure.

MATERIALS AND METHODS

The first group was consisted of eighty patients with compensated heart failure II to IV class by New York Heart Association classification who were receiving both outpatient and inpatient treatment at the department of general and invasive cardiology, Yerevan State Medical University hospital No 1, among whom 26 (33%) were women (mean age 67±10 years). The patients were on conventional therapy for heart failure according to the international guidelines. All patients underwent routine echocardiography and measurement of plasma endothelin-1 level. Patients with ejection fraction <45% were included in the study. Endothelin-1 level was determined using the immunoenzyme analysis (ELISA) with a microplate reader Stat Fax-3200 ("Vector Best" reagent set, Russia). ET-1 level was determined using the immunoenzyme analysis (ELISA) by means of set of reagents "BioChemMack" (Russia) with a microplate reader Stat Fax-3200.

The second group was consisted of twenty one healthy individuals who were included from the hospital staff, among whom 7 (33%) were women with mean age of 59±12. Clinical examination and echocardiography were normal for all control subjects. The study was conducted in accordance with the World-wide Medical Association Declaration of Helsinki. The research protocol was approved by Yerevan State Medical University research ethics committee.

Echocardiography: Transthoracic echocardiography was performed using a HP 1000 model (HP Corporation, USA). Left ventricular end-diastolic diameter was measured from left parasternal view. Left ventricular ejection fraction was calculated by Simpson's rule. All the measurements were performed according to the American Society of Echocardiography guidelines for echocardiography [*Lang R et al., 2005*].

Statistics: Data are presented as mean ± standard deviation. Linear regression and Pearson correlation analyses were performed to examine the echocardiographic correlates of biomarker levels. Correlation was significant at the 0.05 level. Comparisons of continuous variables were performed using either Student's t test or the Mann–Whitney test, as appropriate. SPSS version 20 was used for statistical analysis.

RESULTS AND DISCUSSION

While comparing the data of study group and healthy individuals a significant difference was noticed in echocardiographic parameters and plasma ET-1 levels.

Echocardiographic and laboratory characteristics of patients with heart failure and healthy individuals are demonstrated in Table.

There was a negative but statistically significant correlation between plasma ET-1 level and left ventricular end-diastolic diameter (R=-0.295, p=0.008) in group of patients with chronic heart failure as a result of the study.

As figure shows, higher levels of ET-1 are asso-

TABLE.

Echocardiographic and biochemical findings in patients with heart failure and in healthy individuals

Indices	Groups		p
	Patients	Healthy individuals	
Ejection fraction, %	33.4±7.9	56±2.8	<0.001
Left ventricular end-diastolic diameter, *cm*	5.3±0.7	4.0±0.3	<0.001
Endothelin-1, *pg/ml*	22.1±8.7	7.19±5.3	<0.001

ciated with smaller left ventricular end diastolic diameters.The study demonstrated negative correlation between plasma ET-1 level and left ventricular end-diastolic diameter parameters which indicates the pathogenetic role of ET-1 in the development of left ventricular remodeling process. Heart failure patients had significantly higher plasma ET-1 levels in a comparison with healthy individuals.

Although numerous clinical studies suggest elevated plasma levels of ET-1 in patients with heart failure, the mechanisms of ET-1 activation still remain incompletely investigated. Several studies recorded the interrelation between ET-1 elevation and congestive heart failure functional class [*Hiroe M et al., 1991; Wei C et al., 1994*].

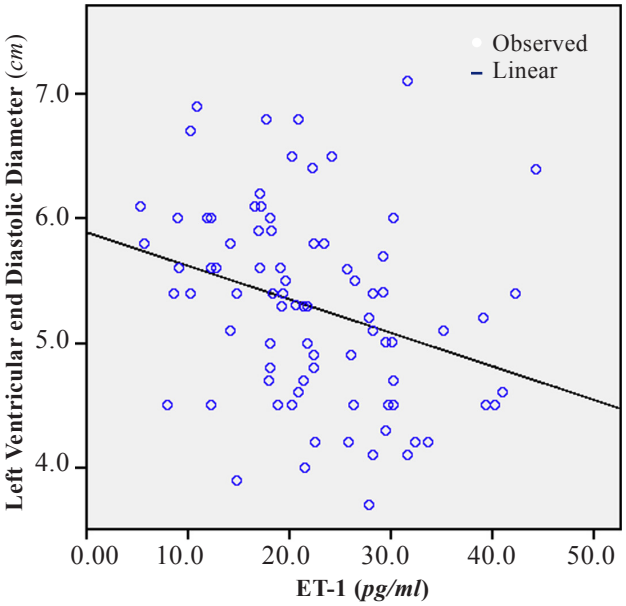

FIGURE. *Correlation between left ventricular end-diastolic diameters and ET-1 level according to echocardiography data.*

The study conducted by T. von Lueder and coauthors, demonstrates that a complex cardiopulmonary interaction revealed by pulmonary congestion causes increased pulmonary production and secretion of ET-1 due to enhanced pulmonary endothelin converting enzyme-1 activities. Pulmonary secretion of ET-1 during evolving congestive heart failure is an important contributor to elevated plasma ET-1 levels in the systemic circulation [*von Lueder T et al., 2004*]. It should be noted that patients with heart failure II to IV by New York Heart Association class were included in study, moreover, the clinical status of patients with heart failure II by New York Heart Association functional classification often does not comply with congestive lung condition. A wide selection of patients according to the severity of circulatory failure and predominance of patients with congestive heart failure II-III class could be the possible reason of weak negative correlation between ET-1 elevation and left ventricular end-diastolic diameter parameters. ET-1 biosynthesis mainly occurs in the epithelial cells of bronchi and alveoli, therefore the degree of pulmonary tissue involvement and activation of proinflammatory markers determine the degree of ET-1 elevation and left ventricular remodeling in heart failure.

As mentioned above, ET-1 synthesis is elevated during the transition from left ventricular hypertrophy to congestive heart failure [*Iwanaga Y et al., 1998*]. The study demonstrated that this process is due to ET-1 myocardial synthesis. The study indicates that accelerated myocardial synthesis of ET-1 contributes directly to left ventricular contractile dysfunction which may be a possible impact of ET-1 activation on the transition to failure. The activation was not parallel to the progression of left ventricular hypertrophy but rather to the deterioration of left ventricular systolic function. Furthermore, ET-1 concentration in heart not in plasma is related to left ventricular systolic dysfunction. Thereby, based on this data, it can be assumed that myocardial synthesis of ET-1 directly regulates left ventricular function.

Despite the existence of numerous studies, the data regarding ET-1 effects and anti-endothelial treatment effectiveness are controversial. Therefore more extensive research is required for further evaluation of ET-1 role in the progression of heart failure.

CONCLUSION

According to the discussed study data endothelin-1 is overactivated in patients with congestive heart failure and its level in blood plasma negatively correlate with left ventricular end diastolic diameter. Further clinical studies are necessary to determine the pathophysiological role of ET-1 activation in the progression of heart failure and the effectiveness of anti-endothelin therapy in such

THE NEW ARMENIAN MEDICAL JOURNAL, Vol.9 (2015), No 4, p. 102-105

REFERENCES

1. *Agapitov A, Haynes W*. Role of endothelin in cardiovascular disease. J Renin Angiotensin Aldosterone Syst. 2002; 3(1): 1-15.
2. *Barton M, Yanagisawa M*. Endothelin: 20 years from discovery to therapy. Can J Physiol Pharmacol. 2008; 86(8): 485–498.
3. *Gray GA*. Generation of endothelin. In: Gray GA, Webb DJ (eds.). Molecular Biology and Pharmacology of the Endothelins. Austin: RG Landes. 1995. 13-32.
4. *Hiroe M, Hirata Y, Fujita N., et al*. Plasma endothelin-1 levels in idiopathic dilated cardiomyopathy. Am Heart J. 1991; 68: 1114 –1115.
5. *Iwanaga Y, Kihara Y, Hasegawa K., et al*. Cardiac endothelin-1 plays a critical role in the functional deterioration of left ventricles during the transition from compensatory hypertrophy to congestive heart failure in salt-sensitive hypertensive rats. Circulation. Nov 10, 1998; 98(19): 2065-2073.
6. *Krum H, Denver R, Tzanidis A, Martin P*. Diagnostic and therapeutic potential of the endothelin system in patients with chronic heart failure. Heart Fail Rev. Dec, 2001; 6(4): 341-352.
7. *Lang RM, Bierig M, Devereux RB., et al*. Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. J Am Soc Echocardiogr. Dec, 2005; 18(12): 1440-1463.
8. *McMurray JJ, Ray SG, Abdullah I., et al*. Plasma endothelin in chronic heart failure. Circulation. 1992; 85(4): 1374–1379.
9. *Rockman HA, Koch WJ, Lefkowitz RJ*. Seven-transmembrane-spanning receptors and heart function. Nature. 2002; 415(6868): 206–212.
10. *von Lueder TG, Kjekshus H, Edvardsen T., et al*. Mechanisms of elevated plasma endothelin-1 in CHF: congestion increases pulmonary synthesis and secretion of endothelin-1. Cardiovasc Res. Jul 1, 2004; 63(1): 41-50.
11. *Wei CM, Lerman A, Rodeheffer RJ., et al*. Endothelin in human congestive heart failure. Circulation. 1994; 89: 1580–1586.
12. *Yamauchi-Kohno R, Miyauchi T, Hoshino T., et al*. Role of endothelin in deterioration of heart failure due to cardiomyopathy in hamsters: Increase in endothelin-1 production in the heart and beneficial effect of endothelin-A receptor antagonist on survival and cardiac function. Circulation. Apr 27, 1999; 99(16): 2171-2176.