

The role of endothelial dysfunction in the development of postinfarction heart failure

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ABSTRACT

Heart failure has remained completely unresolved problem yet. Coronary artery disease (CAD) has been considered as the most common cause of heart failure. Endothelial dysfunction has been regarded as an important factor involved in the development of cardiovascular diseases, and plasma endothelin-1 levels as their prognostic and severity marker. The purpose of the present study was elucidation of the role of endothelial dysfunction in the development of postinfarction heart failure. A total of 63 patients with heart failure of I-IV (NYHA) functional classes were observed. Each of these groups was divided into two subgroups. First subgroup included patients who had myocardial infarction not later than 6 weeks. Second subgroup was represented by patients with non-ischemic heart failure caused by acquired and congenital valvular heart diseases, dilated cardiomyopathy. Endothelial dysfunction occurs at the early stages (I-II) postinfarction heart failure. Plasma levels of ET-1 was significantly increased in postinfarction sub-group ($75,58 \pm 5,99$ pg/ml) compared to control group ($52,60 \pm 3,87$ pg/ml) and non-ischemic sub-group ($58,13 \pm 2,5$ pg/ml) ($p < 0,01$). Positive correlation was found between ET-1 plasma levels and severity of heart failure that did not depend on the genesis of cardiac insufficiency.

KEYWORDS: *endothelial dysfunction, heart failure, endothelin-1*

Heart failure has remained completely unresolved problem yet. According to current statistics, approximately 1-4% of population suffers from heart failure worldwide [1]. Despite the elaboration of rather effective methods of treatment, lethality rates reaches 10-15%. Thus, the more studies are needed to elucidate pathogenetical factors leading to the development of heart failure. During the last decade, besides well-known neurohumoral theory, hypothesis regarding possible role of inflammatory cytokines (TNF- α ; IL-1; IL-6) in the development of heart failure has become more and more attractive. The latter implies cytokines hyperactivation, negative inotropic effect on myocardium, development of cardiomyocytes apoptosis, remodelling of heart muscle and development of endothelial dysfunction leading to further progression of heart failure [5].

In 1980 Furchgott and Zavadzki hypothesized ability of arteries to regulate their own tonus without influence of ventral (neurohumoral) factors. Their proposed the particular role of endothelial cells they defined as "cardiovascular endocrine organ" [2]. Further studies confirmed that endothelium is not only mechanical barrier between vascular wall and blood, on contrary it might be considered as an active organ involved in the development of virtually all cardiovascular diseases (atherosclerosis, arterial hypertension, coronary artery disease, heart failure, etc) [8]. Endothelium is involved in the regulation of vascular tonus through secretion of biologically active vasoconstrictor and vasodilator factors), enhances cellular proliferation, controls blood coagulation properties.

Endothelial cells "humoral response" is triggered by the following factors: changes in intravascular blood flow, platelet-derived mediators (serotonin, ADP and thrombin) and circulating neurohormones (catecholamines, vasopressin, acetylcholin, bradykinin, hystamin). The common response to the aforementioned stimuli has been vasodilation due to release of endothelial relaxing factors, namely production of nitric oxide (NO). Besides NO, vasodilation is mediated via secretion of prostacyclines and endothelium-dependent hyperpolarizing factor that leads not only to vascular dilation, but to preservation of vascular wall integrity as well, prevention of thrombus formation and vascular cells proliferation [7].

Long-term influence of various pathological processes (hypoxia, intoxication, hemodynamical overload) causes exhaustion of endothelium relaxing ability and stimulation of vasoconstrictor response expressed as endothelial dysfunction. Usually endothelium responds to above mentioned stimuli with vasoconstriction and cellular proliferation.

Endothelial dysfunction has been considered as an important factor involved in the development of cardiovascular diseases, and plasma endothelin-1 levels as their prognostic and severity marker [3].

Coronary artery disease (CAD) has been considered as the most common cause of heart failure. According to SOLVD survey, in case of heart failure due to postmyocardial infarction the incidence of hospitalization increases two-fold and mortality – 4 times [9]. Endothelin 1 and its receptors were discovered in coronary arteries endothelium as well as in myocardium [6]. Endothelial damage (due to influence of chemical, microbial or physical factors) facilitates progression of atherosclerosis. Cytokines are actively involved in this process that in turn stimulates proliferation of vascular cells. Notably, at this stage endothelial cells produce vasodilators, prostacyclines, kinins, nitric oxide and hyperpolarizing factor. Along with prostacyclins they interfere progression and development of atherosclerosis and thrombogenesis. This process in turn activates vasoconstrictor peptides – angiotensin II, and endothelin 1. These factors activate thrombogenesis and therefore contribute to the development of CAD [4].

The purpose of the present study was elucidation of the role of endothelial dysfunction in the development of postinfarction heart failure.

MATERIALS AND METHODS

A total of 63 patients (24 females and 36 males, with mean age 68 ± 13 years) with heart failure of I-IV NYHA functional classes were observed. Patients were divided into 2 groups. Group I was composed of 32 patients without or minimal clinical signs (NYHA I-II). Thirty one patients with clinical signs of congestive heart failure (NYHA III-IV) represented group II. Correspondingly each of these groups was divided into two subgroups. First subgroup included patients who had myocardial infarction

not later than 6 weeks. Second subgroup was represented by patients with non-ischemic heart failure caused by acquired and congenital valvular heart diseases, dilated cardiomyopathy. According to subgroups patients were distributed as follows: group I included 22 patient from first subgroup and 10 patients from second subgroup. Group II was composed of 19 patients from the first subgroup and 12 patients from second subgroup. Patients with diabetes mellitus, arterial hypertension and acute inflammatory were not included in the study. 18 healthy subjects were included in the control group.

ET-1 plasma levels were determined by radioimmunoassay (IBL- Imuno-Biological Lab. Germany).

RESULTS

According to echocardiographi studies, in Group I (Tab.1) end-systolic volume (ESV) was 45±12 ml; end-diastolic volume (EDV) was 145±12 ml, ejection fraction (EF) 50±6%. ET-1 plasma levels in postinfarction heart failure (1 subgroup) was 75,58±5,99 pg/ml and significantly exceeded controls (52,60±3,87, p<0,001). ET-1 concentration was significantly lower in non-ischemic heart failure compared to postinfarction group (58,13±2,5 pg/ml, p<0,001).

In group II ESV was 62±13 ml. EDV 152±23 ml, EF - 42±10%. In postinfarction group (1 subgroup) plasma level of ET-1 was 82,01±7,89 pg/ml, while in group with non-ischemic heart failure (2 subgroup) ET-1 concentration 91,67±8,07 pg/ml (p<0,05).

Plasma levels of ET-1 significantly correlate with severity of heart failure (r=-0,46, p<0,05).

	NYHA	n	ET-1 (subgroup 1) pg/ml	ET-1 (subgroup 2) pg/ml
Group I	I-II	32	75,58±5,99 *	58,13±2,5
Group II	III-IV	31	82,01±7,89**	91,67±8,07*
Control group	-	18	52,60±3,87	

Note: *- p<0,05; ** - p<0,01

Tab.1 Plasma levels of ET1 in patients with heart failure.

Concentrations of ET-1 in postinfarction group significantly exceeded those of control group starting from early stages (NYHA I-II) (p<0,0001), while in severe heart failure (NYHA III-IV) no significant difference was found between I and II groups (Fig.1).

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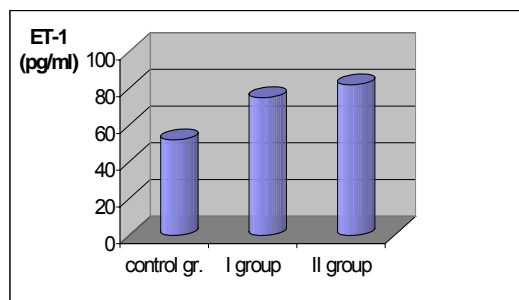


Fig.1 Plasma levels of ET-1 in patients with heart failure due to myocardial infarction.

Plasma levels of ET-1 in I group was significantly increased in postinfarction sub-group compared to non-ischemic sub-group (p<0,01) (Fig.2) and did not change in group II (Fig.3).

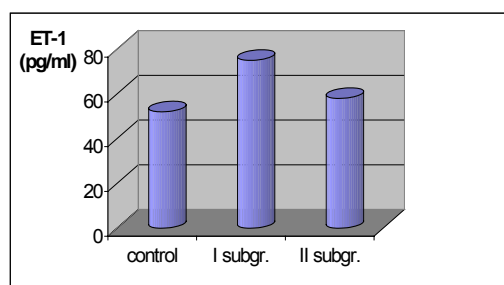


Fig.2 Plasma levels of ET-1 in patients with heart failure (NYHA I-II).

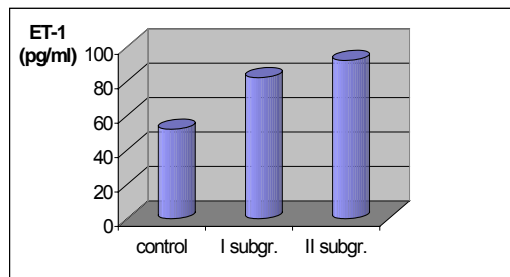


Fig.3 Plasma levels of ET-1 in patients with heart failure (NYHA III-IV).

CONCLUSIONS

1. Positive correlation was found between ET-1 plasma levels and severity of heart failure that did not depend on the genesis of cardiac insufficiency.
2. Endothelial dysfunction occurs at the early stages (I-II) postinfarction heart failure in contrast to non-ischemic heart failure. No significant changes in Et-1 plasma levels were detected in severe heart failure due topostinfarction and nonOischemic conditions.

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Роль эндотелиальной дисфункции в развитии сердечной недостаточности после перенесенного инфаркта миокарда

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Р Е З Ю М Е

Целью исследования являлось выяснение роли эндотелиальной дисфункции в патогенезе сердечной недостаточности после перенесенного инфаркта миокарда. Наблюдение проводилось за 63 пациентами с хронической сердечной недостаточностью I-IV степени (NYHA). Больные, в свою очередь, подразделялись на 2 подгруппы по этиологическому фактору (ишемическая и неишемическая форма СН). Во всех случаях определялась концентрация Эндотелина-1 в плазме. В результате выявилось, что эндотелиальная дисфункция при сердечной недостаточности соответствует тяжести заболевания независимо от этиологического фактора. При сердечной недостаточности ишемического генеза наблюдалось значительное повышение концентрации ЭТ-1 уже на I-II степени заболевания по сравнению с контрольной группой и подгруппой СН неишемического генеза.

Ключевые слова: эндотелиальная дисфункция, сердечная недостаточность, эндотелин-1

□ **International committee of medical journal editors. Uniform requirements for manuscripts submitted to biomedical journals.** *Ann Intern Med* 1997;126:36-47.

CDI, clinical dermatology illustrated [monograph on CD-ROM]. Reeves JRT, Maibach H. CMEA Multimedia Group, producers. 2nd ed. Version 2.0. San Diego: CMEA; 1995.

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