DAHİLİ BİLİMLER / *MEDICAL SCIENCES*
Araştırma Makalesi / Research Article

Assessment Of Neurohumoral Regulation And Oxidative Stress Indices In Patients With Postinfarction Cardiosclerosis

Postinfarktüs Kardiyosklerozlu Hastalarda Oksidatif Stres Parametreleri ve Nörohumoral Regülasyonun Değerlendirilmesi

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Purpose: The purpose of this study was to assess the indices of natriuretic peptide and oxidative stress in patients with CHF.

Methods: In 52 patients, men (age: 38-60) with postinfarction cardiosclerosis, complicated by chronic heart failure, we determined levels of NP – NT-pro BNP, malondialdehyde – like activity (MDA), enzymes – catalase and superoxide dismutase (SOD), NO metabolites ($NO_2 - NO_3$), NADPH-diaphorase (eNOS), Nitrate reductase (iNOS) and Peroxinitrate ($ONOO^-$) in blood plasma of all patients and performed six-minute walk test.

Results: Baseline NT-pro BNP was elevated by 2,4 and 3,4 times, MDA level by 2,5 and 3,5 times, formation of $ONOO^-$ by 2 and 3,1 times, SOD index by 35 and 44,7% in NYHA II – III Classes, respectively, compared to the control group. eNOS was decreased by 24,6 and 42,6%, NO metabolites by 28,6 and 45,4%, catalase level by 37 and 46,3% in NYHA II – III Classes, respectively, compared to the control group.

Conclusion: The analysis of NT-pro BNP level has demonstrated its correlation with the NYHA Classes and the severity of oxidative stress. Along with different NYHA Classes, we noted increasing level of natriuretic peptide and enhancing oxidative stress processes, characterized by elevated MDA indices and decreased antioxidant enzymes and NO metabolites.

Key Words : ***CHF, Oxidative stress, NT-pro BNP, 6-minute walk test.***

Amaç: Kronik kalp yetmezlikli hastalarda oksidatif stres ve natriüretik peptid seviyelerini değerlendirmeyi amaçladık

Metodlar: Kalp yetmezliği ile komplike olmuş postinfarktüs kardiosklerozlu 52 erkek hastada(yaş:38-60), NP-NT-pro BNP, malondialdehid-benzeri aktivite (MDA), enzimler-katalaz ve superoksit dismutaz (SOD), NO metabolitleri (NO2-NO3), NADPH-diaforaz(eNOS), nitrat redtiktaz(INOS) ve peroksinitrat (ONOO) ın kan plazma seviyeleri ölçüldü ve 6 dakika yürüme testi uygulandı.

Sonuçlar: Kontrol grubu ile kıyaslandığmda NYHA sınıf 2-3 hastalarda sırasıyla bazal NT-proBNP seviyelerinin 2,4 ve 3,4 kat, MDA seviyelerinin 2,5 ve 3,5 kat, ONOO formunun 2 ve 3,1 kat, SOD indeksinin %35 ve %44,7 oranında arttığı saptandı. NYHA sınıf 2-3 de kontrol grubu ile kıyasla sırasıyla eNOS %24,6 ve %42,6, NO metabolitleri %28,6 ve %45,4, katalaz seviyesi %37 ve %46,3 arttığı görüldü.

Tartışma: NT-proBNP seviyelerinin NYHA sınıfı ve oksidatif stresin ciddiyeti ile ilişkili olduğu gösterilmiştir. Farklı NYHA sımflarına bağlı olarak natriüretik peptid seviyesinin ve oksidatif stres ürünlerinin ki bvınlar artmış MDA ürünleri ve azalmış antioksidan enzimler ve NO metabolitleri olup, bunların artmış olduğunu saptadık.

Anahtar Sözcükler: ***KKY, Oksidatif stres, NT-pro BNP, 6 dk yürüme testi***

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Myocardial infarction (MI) is one of the main causes of chronic heart failure (CHF). With respect to CHF pathophysiology, it was determined that neurohumoral adaptation is the major factor leading to cardiac dysfunction starting from the changes in the heart structure up to the development of postinfarction remodeling. Increasing activity of sympathoadrenal system promotes the mobilization of the renin -angiotensin - aldosterone system (RAAS), neurohormones and mediators including cytokines, endothelin, a system of natriuretic peptide (NP) (1,2). At present, determining levels

of NP in the blood has a great prognostic value as a marker of increased morbidity, mortality, and by determining elevated level of N-terminus of brain type natriuretic peptide prohormone (NT-pro BNP), the patients with left ventricular dysfunction can be identified before emerging clinical and instrumental signs of CHF (3,4). Several studies have revealed that left ventricle remodeling and the development of heart failure can be advanced by the mitochondrial damage of the cardiac myocytes, accompanied by the formation of oxygen free radicals (5,6). During chronic hypoxia in CHF, free radical accumulation in the cells is autocatalytic due to separation of oxidative phosphorylation and oxigenase activation. Its coexistence with the antioxidant system (AOS) depletion promote the development of a state in the body, called oxidative stress (7,8). Elevated lipid peroxidation (LPO) products and the rate of consumption or the degree of the loss of antioxidant resources may serve as oxidative stress indices.

Methods

We examined 52 patients with postinfarction cardiosclerosis, complicated by chronic heart failure - men aged 38-60 years at the Tashkent Medical Academy, I Clinic, Cardiology Department. Following written informed consent, patients having myocardial infarction with Q wave within 2 months – 3 years were randomly selected and assigned to two groups according to the New York Heart Association (NYHA) Classes of CHF, analyzing six-minute walk test (6′WT) (9). The study did not include patients with diabetes mellitus, cardiac arrhythmias, and chronic obstructive pulmonary disease. All the patients were divided into two groups: first - 27 CHF patients with NYHA Class II CHF, second - 25 patients with Class III CHF. Control group consisted of 18 healthy volunteers. The study was approved by the local Ethics Committee.

Determination of NP – NT-pro BNP level in blood plasma of all patients was carried out by enzyme-linked immunosorbent assay (ELISA) using Biomedica reagents (Austria). Lipid peroxidation marker – malondialdehyde-like activity (MDA) was determined, and the status of antioxidant enzyme system was judged by the activity of the enzymes - catalase and superoxide dismutase (SOD). The level of nitric oxide (NO) was determined by the amount of nitrate and nitrite (NO2 and NO3) metabolites, nitrate reductase activity – cytokine inducible nitric oxide synthase (iNOS) and NADPH-diaphorase – endothelial type nitric oxide synthase (eNOS) activity. The level of peroxynitrite (ONOO⁻) was determined by the oxidation of hydroxylamine (NH₂O⁻), forming peroxynitrite.

Statistical processing of research results was performed on a personal computer type IBM PC/AT using a spreadsheet package EXCEL 7,0 Windows-95. Parameters were described in the form of: arithmetic mean ± standard deviation (M ± SD).

Results

Performing 6′WT in examined patients has discovered a reduced tolerance to physical load, regardless of NYHA Classes of CHF. It was 1,9 times less in the patients with Class II CHF compared to the control group, while with Class III - 2,5 times.

The study of initial NT-pro BNP level

Table 1: Initial indices of NT-pro BNP in patients with NYHA Classes II and III CHF.

Index	Control n=18	The first group (FC II) n=27	The second group (FC III) n=25
NT- pro BNP fmol/ml	252,3±12,1	610,4±15,3 **	876,7 ±12,5**

** P <0,001, compared to the control group

Table 2: Baseline indices of LPO, AOS and NO systems in patients with NYHA Classes II and III

Index	Control n=18	The first group (Class II) n=27	The second group (Class III) n=25
MDA, nmol/ml	1,93±0,106	4,4±0,236 **	6,72±0,553**
SOD, UU/ml	3,22±0,212	2,08±0,135 *	1,78±0,16*
Catalase, mcmol/l	15,93±1,121	10,07±0,697*	8,65±0,804**
NO metabolites (NO2-NO3), mcmol/l	10,26±0.985	7,33±0,7*	5,6±0,634**
NADPH-diaphorase (eNOS), mcmol/min/l	13,05±1,287	9,83±0,956*	7,49±0,865**
Nitrate reductase (iNOS), mcmol/min/l	0,62±0,09	3,7±0,407**	4,52±0,664**
Peroxinitrite (ONOO-), mcmol/l	0,17±0,046	0,35±0,094*	0,53±0,149*

* P<0,05

** P<0,001, compared to the control group

in examined patients showed that the patients with NYHA Class II of CHF had this level 2,4 times higher compared to healthy volunteers, and it was 3,4 times higher in patients with Class III (Table 1).

NT-pro BNP level had a direct correlation (r = 0.47, P <0.05) with the NYHA Classes of CHF.

The analysis of NT-pro BNP level has demonstrated its correlation with the NYHA Classes of CHF and the severity of oxidative stress.

Study of oxidative stress indices in patients with CHF revealed elevating MDA level in patients with Class II by 2,5 times, Class III by 3,5 times, respectively, compared to the control group (tab.2).

MDA – malondialdehyde-like activity (lipid peroxidation marker)

SOD – superoxide dismutase

eNOS – endothelial type nitric oxide synthase

iNOS – cytokine inducible nitric oxide synthase

The LPO intensity is conditioned by reduced expression of NO-synthase, as

evidenced by the decrease in eNOS by 24,6% in patients with Class II CHF and by 42,6% in patients with Class III CHF, accompanied by the decrease in NO metabolite (NO_2-NO_3) by 28,6 and 45,4% in respective II and III Classes, due to vascular remodeling, characterized by endothelial dysfunction, predominance of vessel vasoconstrictor responses and the consequent reduction in NO production (10). Increased oxidative stress processes are also characterized by intensive formation of $ONOO^-$: in Class II CHF patients, the index was 2 times and in Class III CHF 3,1 times higher compared to the control group. High concentrations of $ONOO^-$ further the delay of many enzyme systems, including the antioxidant enzyme system - SOD and catalase (11). SOD index in patients with Class II CHF was elevated by 35%, Class III by 44,7%, respectively, compared to the control group. Depressed catalase level by 37 and 46.3% in patients with Class II and III CHF, respectively, compared to the control group, is indicative of AOC activity, which is associated with participation of SOD and catalase to suppress O_2^- over-excretion, which is

used in tissues for NO reactions and formation of $ONOO^-$ (12).

Thus, patients in NYHA Class III compared to Class II, had increased level of natriuretic peptide and enhancing oxidative stress processes, characterized by elevated MDA indices and decreased antioxidant enzymes and NO metabolites.

Conclusions

1. In patients with chronic heart failure, the level of NT-pro BNP has a direct correlation with NYHA Classes: along with lessening the tolerance to physical load marked an elevation of NT-pro BNP level by 2,4 times in patients with NYHA Class II and 3,4 times with Class III CHF compared to healthy volunteers.

2. Enhancing oxidative stress processes in patients with chronic heart failure is conditioned by reduced expression of NO-synthase, as indicated by depressed eNOS, accompanied by a decrease in NO metabolite (NO_2-NO_3) to 28,6 and 45,4%, in II and III NYHA Classes, respectively.

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