The use of hypoxene in the treatment of patients with chronic heart failure

El uso del hipoxeno en el tratamiento de pacientes con insuficiencia cardíaca crónica

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Abstract

This study aimed to compare the effect of treatment with hypoxene and standard medical treatment for the oxidative stress (catalase (CAT), lipid peroxidation (LPO), inhibition of superoxide dismutase (SOD), diene conjugates (DC) and malondialdehyde (MDA) at the admission and at the end of treatment in hospital, after 6 months, 1 year in patients with CFH. This prospective study included 158 patients with CHS who were treated at the State Budgetary Institutions "Clinical Hospital № 1 of Grozny" and "Clinical Hospital № 5 of Grozny" in 2017. All the patients divided into two groups. Group A treat hypoxen and standard medical therapy, and Group B – non-treat hypoxene and standard medical therapy, as a control group. The patients of group A were then given 750 mg/d hypoxene for 4 weeks. Blood samples were collected from the patients on admission and at the end of the study, after 6 months, 1 year. Mean age of group A patients were 49±6.3 years while in control group it was 51±9.4 years. There were 48 males in group A patients and 43 males in control subjects. The levels of LPO were found to be significantly increased in group A patients compared to control (P< 0.05). The catalase, MDA, DC and SOD levels were significantly decreased (P< 0.05) in group A patients compared to controls. During the treatment of patients of the studied groups showed a significant decline in lipid peroxidation.

Keywords: oxidative stress, hypoxene, chronic heart failure, lipid peroxidation.

Resumen

Este estudio tuvo como objetivo comparar el efecto del tratamiento con hipoxeno y el tratamiento médico estándar para el estrés oxidativo (catalasa (CAT), peroxidación de lípidos (LPO), ingestión de superóxido dismutasa (SOD), conjugados de dieno (DC) y malondialdehído (MDA) en la admisión y al final del tratamiento en el hospital, después de 6 meses, 1 año en pacientes con HFC. Este estudio prospectivo incluyó 158 pacientes con CHS que fueron tratados en el "Hospital Clínico Estatal № 1 de Grozny" de las Instituciones Presupuestarias del Estado y Hospital clínico № 5 de Grozny "en 2017. Todos los pacientes se dividieron en dos grupos. El grupo A trata el hipoxeno y la terapia médica estándar, y el Grupo B - hipoxeno sin tratamiento y la terapia médica estándar, como grupo de control. Los pacientes del grupo A luego se administraron 750 mg / d de hipoxia durante 4 semanas. Se recogieron muestras de sangre de los pacientes al ingreso y al final del estudio, después de 6 meses, 1 año. La edad media de los pacientes del grupo A fue de 49 ± 6,3 años mientras estaba en el control agruparlo, wa s 51 ± 9.4 años. Había 48 hombres en los pacientes del grupo A y 43 hombres en los sujetos control. Se encontró que los niveles de LPO aumentaron significativamente en los pacientes del grupo A en comparación con el control (P <0,05). Los niveles de catalasa, MDA, DC y SOD disminuyeron significativamente (P <0.05) en los pacientes del grupo A en comparación con los controles. Durante el tratamiento de pacientes de los grupos estudiados se observó una disminución significativa en la peroxidación lipídica.

Palabras clave: estrés oxidativo, hipoxeno, insuficiencia cardíaca crónica, peroxidación lipídica.

Introduction: Heart failure (HF) is a progressive syndrome, characterized by exercise intolerance, dyspnea, fatigue, and decrease in quality of life resulting from the inability of the heart to maintain a cardiac output sufficient to meet tissue demands [1, 2]. It is a relatively common clinical condition, and is the final stage of several forms of cardiovascular disease [3]. The deteriorated heart function, per se, is able to modulate the inflammatory response and the production of reactive oxygen species (ROS). In heart failure, tissue hypoxia caused either by low cardiac output or by sympathetic vasoconstriction may also trigger an increase in the production of free radicals [4]). Inflammation can also induce oxidative stress. The main goal of the treatment of acute congestive heart failure (CHF) is to provide symptomatic relief.

Traditional therapies for acute heart failure syndromes (AHFS), such as oxygen, loop diuretics, nitrates, and morphine remain the cornerstone of early management today[5-9]. Despite earlier initiation of evidence-based chronic HF therapies during hospitalization, post-discharge re-hospitalization and mortality event rates remain high [10-12]. Such high post-discharge event rates represent a societal burden given the number of patients who present with AHFS and the resultant cost.

In the USA, over one million hospitalizations occur each year for HF, an increase of over 175% in the last 25 years[10, 13]. These hospitalizations account for the bulk of the 39 billion USD spent each year for HF care [7, 8]. Similar rates of hospitalization occur in the countries represented by the European Society of Cardiology (ESC), although with geographical variations in the length of stay, re-hospitalization rates, and in-hospital mortality [5, 6, 14]. Thus, oxidative stress and inflammation are involved in a self-perpetuating cycle.

Given the above observations, we aimed to evaluate oxidative stress markers in patients with CHF before and after treatment hypoxene. In addition, we investigated the association between changes in these markers and the New York Heart Association classification (NYHA) in CHF patients.

Materials and methods

Research design

This prospective study included 158 patients with CHS who were treated at the State Budgetary Institutions "Clinical Hospital № 1 of Grozny" and "Clinical Hospital № 5 of Grozny" (mean age 46.23±17.81 years) in 2017. Diagnosis was based on clinical, radiological, endoscopy and histological findings. All the patients divided into two groups. Group A treat hypoxen and standard medical therapy, and Group B – non-treat hypoxene and standard medical therapy, as a control group. Baseline heart function tests were performed in each patient. The patients of group A were then given 750 mg/d hypoxene for 4 weeks. Patients were hospitalized and the treatment was continued until the symptoms and signs of volume overload disappear. Blood samples were collected from the patients on admission and at the end of the study, after 6 months, 1 year.

Patients with acute CHF were undergo evaluation (were evaluated) for potential precipitating factors, including myocardial ischemia, arrhythmias (commonly atrial fibrillation), underlying valvular disease, exacerbation of hypertension, anemia, thyroid disorders, and drug interactions. Other concomitant conditions, such as pneumonia and pulmonary embolism, may also be contributing factors.

We have considered medical records at the beginning and at the end of inpatient treatment including CHF, characteristics of CHF lesions, smear status, activity of indices such as catalase (CAT), lipid peroxidation (LPO), inhibition of superoxide dismutase (SOD), diene conjugates (DC) and malondialdehyde (MDA).

Oxidative stress indices such as SOD, CAT, LPO, MDA and DC levels were determined in patients at admission and end of the treatments in hospital.

Superoxide dismutase activity (SOD) was assayed according to the method of Kono [6], where in the reduction of nitrobluetetrazolium chloride (NBT) was inhibited by the superoxide dismutase and measured at 560 nm spectrophotometrically. Results were expressed as percentage inhibition of reduction of NBT [6, 15].

Catalase activity was assessed by the method of Luck [5], where the breakdown of H_2O_2 was measured. The assay mixture consisted of 3 ml of H_2O_2 phosphate buffer (0.0125 M H_2O_2) and 0.05 ml of supernatant serum of patients (10%) and the change in the absorbance were measured at 240 nm. The enzyme activity was calculated using the millimolar extension coefficient of H_2O_2 (0.07). The results were expressed as micromoles of H_2O_2 decomposed per minute per milligram of protein [16].

The quantitative measurement of lipid peroxidation was done by the method of Wills [17]. The amount of malondialdehyde (MDA) formed was measured by reaction with thiobarbituric acid at 532 nm. The results were expressed as nanomloes of MDA per mg protein, using the molar extension coefficient of chromophore (1.56×105 M-1 cm-1).

The concentration of diene conjugates (DC), which characterizes rate of lipid peroxidation process in studied patients, was measured spectrophotometrically by intensive light absorption at 220 nm by conjugated lipid hydroperoxide structures [18].

Before their inclusion in the study, eligible participants were informed about the study protocol and consent was obtained. Written informed consent was obtained from all subjects. The study was approved by the Institutional Review Board and followed the principles of good clinical practice.

Statistical analysis

Nominal data were compared using Pearson's chi-square test between independent groups and results were presented as frequency and percentage (%). Kolmogorov-Smirnov. Test was used in the normality test of the numerical variables. Independent samples t-test was used in order to evaluate the presence of a difference between the treatment methods in terms of the initial values of these variables. Afterwards independent samples t-Test was used to compare the two groups about these percent change as treatment effect. Results were considered statistically significant if P-value was found less than 0.05. Statistical analyses were carried out using the Statistical Package for Social Science for Windows (SPSS) version 18.0 (SPSS Inc, Chicago, IL, USA).

Results and Discussion

A total of 158 adults participated in the study. The baseline demographic and clinical characteristics are shown in Table 1. Heart failure was the dominant chronic disease in both groups.

Table 1. Baseline characteristics of consecutive patients with CHF

Variable	Group A (n=86)		Group B (n=72)		Value
Gender:	n	%	n	%	
Male	48	55.8	43	59.7	p>0.05
Female	38	44.2	29	40.3	
Age, years	49±6.3		51±9.4		p>0.05
NYHA class					
I	32	37.2	26	36.2	
II	30	34.9	24	33.2	p>0.05
III	24	27.9	22	30.6	

The study showed, in the hypoxene-treated group, a significant reduction in hospital admissions and HYHA functional class (Table 2).

Table 2. Effect on oxidative stress parameters NYHA class

	NYHA I		NYHA II		NYHA III	
	Group B (n=26)	Group A (n=32)	Group B (n=24)	Group A (n=30)	Group B (n=22)	Group B (n=24
at addmision						
CAT,µmol/mg	0.34±0.06	0.34±0.03*	0.24±0.03	0.22±0.02*	0.17±0.02	0.16±0.03*
LPO,nmol/mg	4.18±0.20	4.15±0.20*	3.41±0.11	3.42±0.12*	2.84±0.12	2.87±0.11*
SOD, UI/mg	1.19±0.18	1.19±0.17*	0.99±0.10	0.98±0.12*	0.80±0.11	0.82±0.10*
DC, nmol/mg	2.13±0.16	2.17±0.16*	3.33±0.12	16.5±2.9*	4.30±0.19	4.32±0.17*
MDA,nmol/mg	12.8±2.4	12.6±2.4*	3.29±0.19	16.6±2.8*	18.6±2.7	18.8±2.6*
After treatmant						
CAT, µmol/mg	0.33±0.04	1.82±0.09*	1.21±0.16	0.35±0.06*	0.22±0.05	0.31±0.06*
LPO, nmol/mg	4.62±0.18	8.9±2.1*	3.96±0.21	4.89±0.12*	3.07±0.21	3.46±0.2*
SOD, UI/mg	1.21±0.16	0.33±0.04*	1.05±0.18	1.21±0.16*	0.93±0.18	1.07±0.10*
DC, nmol/mg	1.82±0.09	1.74±0.06*	0.24±0.03	0.35±0.01*	3.04±0.18	2.18±0.05*
MDA,nmol/mg	8.9±2.1	8.7±2.3*	3.41±0.11	4.89±0.12*	15.8±2.3	10.7±2.1*

CAT: catalase, LPO: lipid peroxidation, SOD: ingibition of superoxide dismutase, DC: diene conjugates, MDA: malondialdehyde. Each value represents mean ± SEM. * Treatment group compared to control group (p<0.05)

Figure 1. Levels of lipid peroxidation (LPO), catalase (CAT), inhibition of superoxide dismutase (SOD), diene conjugates (DC) and malondialdehyde (MDA) in patients with NYHA II group A and group B (control) after 6 months. Note: Each value represents mean ± SEM. * Treatment group compared to control group (p<0.05)

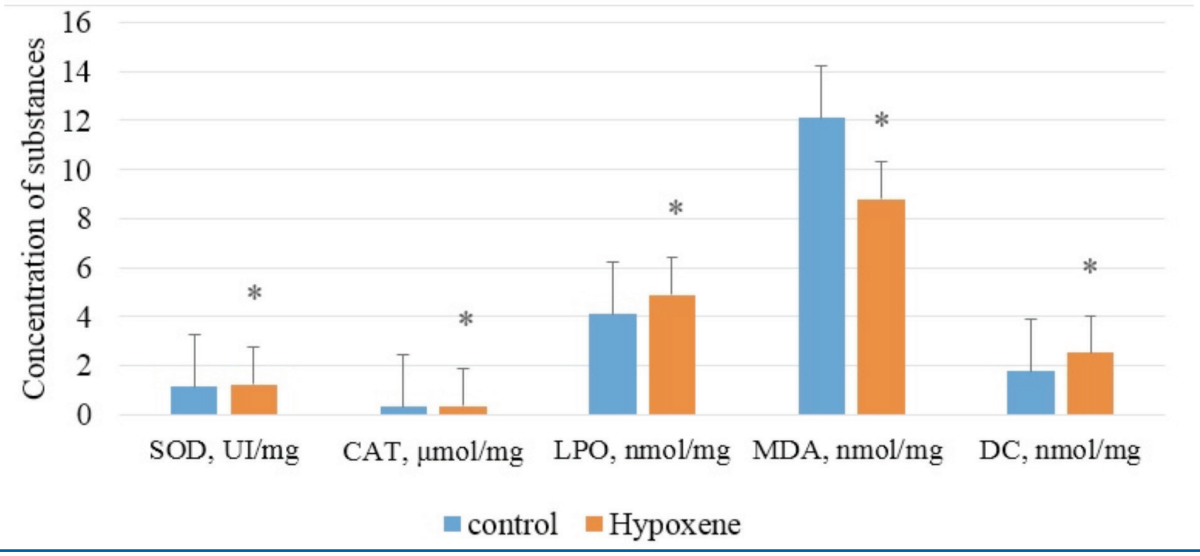
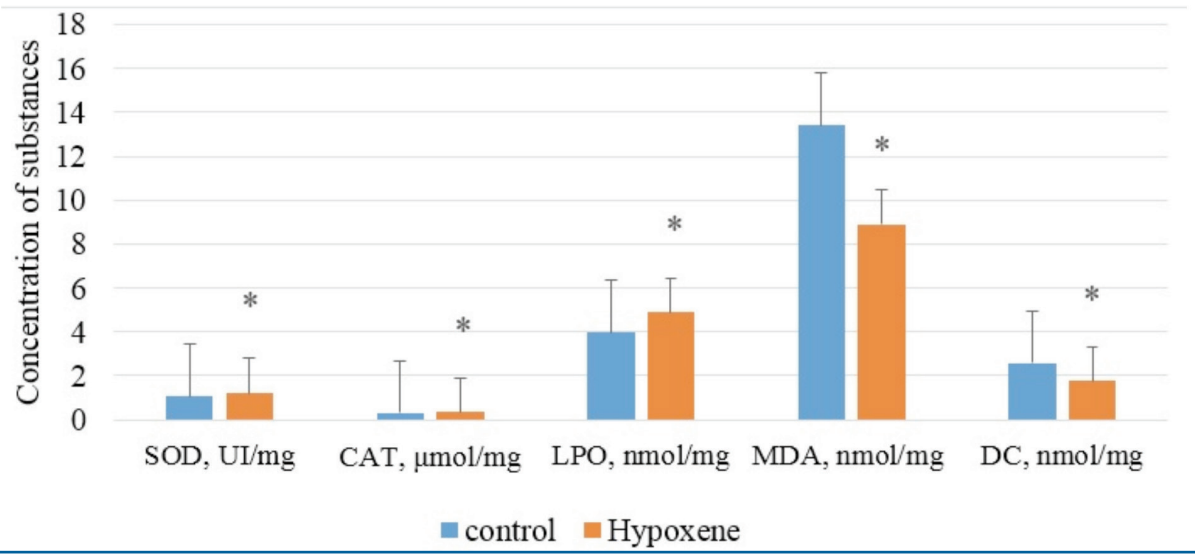


Figure 2. Levels of lipid peroxidation (LPO), catalase (CAT), ingibition of superoxide dismutase (SOD), diene conjugates (DC) and malondialdehyde (MDA) in patients with NYHA II group A and group B (control) after 1 year. Note: Each value represents mean ± SEM. * Treatment group compared to control group (p<0.05). Each value represents mean ± SEM.



Thus, the results of the study of clinical and functional parameters and the state of the oxidative stress in patients with CHF NYHA class II in dynamics (within 6 and 12 months) indicate that the use of hypoxene in complex therapy: i) has a positive effect on long-term outcomes of the disease: reduces the frequency of exacerbations by 1.6 times and the duration of their treatment by 2, 3 days; ii) was a positive effect on the symptoms of the disease and lung ventilation parameters; iii) was a beneficial effect on the initially impaired processes of free radical oxidation, which is manifested in the weakening of the activity of the DC and MDA, activation of SOD, CAT and LPO.

To our knowledge, this is the first study comparing the effects of hypoxene and complex therapy on oxidative stress markers in patients with heart failure. The study aims to gather initial physiological measurements from patients with heart failure that mark the initiation of the oxidative stress. To accomplish this, the study addresses two types of treatment, standard drug therapy and hypoxene therapy, and their effect on the patient status.

Another aim of the study, considering the adverse cardiac effects of oxidative stress, was to determine the appropriate method in maintenance therapy in these patients. One of the important diseases that affect oxidative stress is heart failure. Hill et al. designed a study to investigate the antioxidant enzyme activities and oxidative stress on the myocardium of rats with myocardial infarction. In this study, they showed that SOD, CAT and GSH-Px activities decreased progressively in 16 weeks. The authors suggested that heart failure following myocardial infarction may be associated with an antioxidant deficit as well as increased myocardial oxidative stress [19, 20]. Radovanovic et al. designed a study to explore the oxidative stress markers in chronic heart failure. The researchers investigated the relation of plasma MDA, GSH-Px, SOD and other oxidative stress markers to severity and prognosis in patients with chronic heart failure secondary to ischemic cardiomyopathy. They indicated that because only MDA was associated with death, its levels might be a useful parameter to monitor chronic heart failure patients and plan their management [13, 17]. Correlatively, Keith et al. found significant correlation between the class of heart failure and MDA and GSH-Px. They suggested progressive increase in free radical injury and encroachment on antioxidant reserves with the evolution of heart failure[11, 18]. In our study, we did not observe significant changes in concentrations of the oxidative stress markers despite the effective fluid removal in both groups. The reason for these differences is that all of the patients had heart failure and healthy subjects were not included in our study. Thus acute fluid removal may not affect the oxidative stress markers in a short-term period in patients with chronic heart failure. It is also speculated that the increase in oxidative stress markers could be associated with other factors in these patients. Therefore, neither MDA nor the other markers may be a predictor of prognosis in patients with chronic heart failure in a short-term period.

Once the patient is stabilized, definitive medical therapy for heart failure should be commenced. Usually an ACE inhibitor (or an angiotensin-II receptor antagonist, if ACE inhibitors are not tolerated) is started first, followed by the addition of beta-blockers. The dose of ACE inhibitors and beta-blockers should be increased to the maximum tolerated dose depending upon BP and heart rate. Patients who have persistent signs of fluid overload will need ongoing diuretics. Patients with ongoing symptoms, despite this therapy, should be treated as having chronic CHF. In patients with reduced left ventricular ejection fraction (LVEF), an aldosterone receptor antagonist should be prescribed [13, 21].

For patients with normal or preserved ejection fraction (diastolic heart failure), good control of blood pressure, arrhythmias, and underlying ischemia is essential. No treatment has been convincingly shown to reduce mortality in this subset of patients. A meta-analysis of 6 prospective randomized controlled trials, evaluating the use of a number of renin-angiotensin inhibitors (e.g., perindopril, enalapril, ramipril, valsartan, candesartan, and irbesartan) was done on patients with heart failure and preserved ejection fraction. It found that treatment with renin-angiotensin inhibitors leads to an improvement in 6-minute walk distance and quality of life, and reduction in worsening heart failure events. However, it did not reduce total or cardiovascular mortality [10, 19].

Hepoxene significantly reduces the risk of composite end point of mortality or hospitalization in ambulatory chronic heart failure patients with NYHA class 2 or 3 symptoms, LVEF <25%, or cardiothoracic ratio of >55%, and should be considered in these patients [22]. In patients with heart failure who are in sinus rhythm, use of hypoxene has no effect on mortality but is associated with a lower rate of hospitalization and clinical deterioration [23].

Conclusions

Thus, the inclusion of hypoxene in complex therapy in patients with CHF leads to more positive changes in the system of oxidative antioxidants than in patients who received only standard medical therapy. At the same time, more significant changes in the qualitative and quantitative characteristics of indicators of oxidative stress occur in patients with CHF moderate severity compared with patients with HYHA class I –III.

Conflict of Interests: The authors declare that there is no conflict of interests regarding the publication of this paper.

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