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Effect of L-arginine on blood pressure profile and bronchial patency in patients with hypertension burdened by pulmonary hypertension of bronchopulmonary origin

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Abstract
The article deals with the problem of peripheral hemodynamics correction in the systemic and pulmonary circulation, circadian profiles of blood pressure and respiratory ventilation in patients with stage 2 hypertension, burdened by obstructive pulmonary disease, with the use of L-arginine – exogenous source of nitric oxide.
Material and methods of investigation: This study investigated 100 patients with stage 2 hypertension (2^{nd}- and 3^{rd}-degree) including 80 patients with hypertension, burdened by stage 2 pulmonary hypertension of bronchopulmonary origin, and 20 patients with essential hypertension of the identical stage and degree at the age of 56.5±4.12.
Results: It has been observed that chronic obstructive disease burdens the course of hypertension by peripheral hemodynamics deterioration and systolic pressure increase in the pulmonary circulation leading to heart remodeling. A number of positive effects of L-arginine on the course of the cardiovascular and respiratory systems comorbide pathology have been established.
Conclusions: L-arginine, used in combination therapy in patients with hypertension accompanied by chronic obstructive disease, induces antihypertensive therapy potentiation, bronchial patency improvement, and circadian profiles of blood pressure resetting.

Keywords: hypertension, chronic obstructive pulmonary disease, pulmonary hypertension, L-arginine.

1. Introduction
Attention is being increasingly focused on the problem of comorbidity of diseases of the cardiovascular and respiratory systems because the cardiovascular pathology, principally arterial hypertension (AH), constitute a great part in the structure of adult population morbidity (from 33% to 80% depending upon age) with high incidence of complications and disability [10] as is the case with chronic obstructive pulmonary disease (COPD) being one of the leading causes of morbidity and mortality nowadays [11, 12].
Arterial hypertension associated with COPD is diagnosed in a wide range – between 6.8% and 76.3% patient averaging 34.3% [3-6].
Association of AH with COPD significantly complicates timely diagnosis and treatment of both pathologies being an immediate problem of the clinical practice. The reason for this is close functional relationship between systems of blood circulation and respiration, burdened interference of these pathologies with the systemic and cardiac hemodynamics followed by the development of pulmonary hypertension and hypertrophy of both heart sides [7]. Pulmonary hypertension (PH) causes the left ventricle to increase in size (hypertrophy and/or dilatation) and eventually leads to the right-sided heart failure (Cor Pulmonale) [8, 9, 12]. Pulmonary hypertension is also aggravated by the development of the left ventricle diastolic dysfunction in AH [12].
Recently features of intercellular interaction in the development of chronic endobronchial inflammation, a leading factor in COPD progression, and endothelial dysfunction, a factor of the vascular injury leading to a persistent high blood pressure (BP), have been studied intensively[1, 5].
Besides the fact that endothelial dysfunction (ED) is involved in development of the systemic and pulmonary circulation hypertension it also contributes to its progressing. On the other hand, endothelium morphology and function change in both systemic and pulmonary circulation. Hypertension causes oxidal stress in vessel walls resulting in the reduced endothelium-dependent vasodilatation (EDVD) [2, 6, 9]. Because endothelial dysfunction, especially reduction of NO production, is an important factor in the development and progression of the systemic and pulmonary circulation hypertension, its presence as well

as degree must be considered in patients with diseases of the respiratory and cardio-vascular systems when choosing optimum treatment [1, 7].

2. Materials and Methods

This study investigated 100 patients with stage 2 hypertension (2nd- and 3rd-degree), 80 patients of which had arterial hypertension burdened by stage 2 pulmonary hypertension of bronchopulmonary origin with COPD in remission. Comparison group included 20 patients with essential hypertension of the identical stage and degree. The average patients' age was 56.5±4.12 years. Hypertension lasted 6.2±1.78 years, COPD–10.4±2.93 years. All patients received background antihypertensive therapy according to the international guidelines "2013 Guidelines for the management of arterial hypertension of European Society of Hypertension (ESH) and European Society of Cardiology (ESC)" [2013], Order of the Ministry of Public Health of Ukraine No 348 dated 24.05.2012 "Concerning approval and implementation of medical-and-technical documents on standardization of medical care in arterial hypertension" and COPD according to the Unified clinical protocol of the primary, secondary (specialized) and tertiary health care and health rehabilitation approved by Order of the Ministry of Public Health of Ukraine No 555 dated 27.06.2013 "Concerning approval and implementation of medical-and-technical documents on standardization of medical care in chronic obstructive pulmonary disease" and international congress "Global Strategy for the Diagnosis, Management and Prevention of Chronic Obstructive Pulmonary Disease" (2013).

According to the treatment 80 patients with AH and COPD were divided into 2 groups being statistically homogenous as to the age, sex, AH and PH duration. Group 1, control group (CG), included 40 patients receiving background treatment only: angiotensin-converting-enzyme inhibitors (ACEi) – perindopril in a dose of 10 mg a day, calcium channel blockers – amlodipine in a dose of 5 mg a day, diuretics – indapamide 2.5 mg/day, beta-adrenoblockers – nebivolol 5 mg/day, as well as acetylsalicylic acid (ASA) in a dose of 75 mg a day, and short-acting bronchodilator – Atrovent 1-2 inhalations on-demand according to the abovementioned protocols.

Group 2, treatment group (TG), included 40 patients receiving, in addition to the background treatment, intravenous infusions of 4.2% solution L-arginine hydrochloride (100 ml) No 5 followed by its oral dosage form (1 measuring spoon 5 times a day) taking for 3 months. Examination was performed before, 2 weeks and 3 months after the treatment. Indicators of circadian AP fluctuation were detected on the basis of the 24-hour monitoring of blood pressure using ABPM-04, "Meditech" (Hungary). Research protocol included AP measurement every 15 minutes during the day time and every 30 minutes at night. Using the computer programme, parameters characterizing circadian BP variability were calculated. Based on the diurnal index (DI) values we isolated types of diurnal curves for SBP and DBP on an individual basis. Normal level of nocturnal BP reduction characterizes DI 10-20% – "Dipper" group, insufficient level of nocturnal BP reduction – DI 0-10% – "Non-dipper" group, excessive nocturnal BP reduction with DI > 20% – "Over-dipper" group, and the stable increase of nocturnal BP is indicated by DI < 0% – "Night-peaker". Value of the systolic pressure in the pulmonary artery was detected by maximum speed of the transtricuspidal regurgitation and magnitude of the transtricuspidal pressure gradient during echo-CG by doppler "Logic-500" (Kranzhuhler) by the formula SPPA = ΔP + pressure in the right atrium (mm Hg), where ΔP = 4 VT × 2, where VT – maximum speed of transtricuspidal regurgitation in ms^{-1}.

Pulmonary function test was estimated by means of spirography using apparatus "MasterScreenPneumo", "Jaeger-VIASYS" (Germany USA). For analysis we used indices of the forced expiration volume in the first second (FEV_1), forced lung vital capacity (FLVC), as well as their ratio (FEV_1/FLVC) – Tiffeneau index.

We made computer statistical processing of the obtained data using a license program "Statistica 6.0 for Windows". Statistically significant differences were estimated at significance level $p<0.05$. Statistical significance of mean values was estimated using the Student's t-test.

3. Results and Discussion

The course of AH, burdened by COPD, is characterized be a greater severity – prevailing headaches (in 44% of patients vs. 30% in the comparison group), dizziness (in 32% of patients vs. 15%, respectively), susceptibility to vertigo (in 16% of patients vs. 10%), palpitation (in 32 % of patients vs. 20%, respectively). Because COPD was in remission the complaints corresponded to the respiratory failure severity.

BP value before treatment in patients under investigation corresponded to 2nd-3rd degree AH according to the classification of the disease (WHO), but in patients with the concomitant COPD levels of systolic (SBP) and diastolic blood pressure (DBP) were higher. Average 24-hour systolic BP was 19.7% higher then in the comparison group ($p < 0.05$), average daily – 21.9% higher ($p < 0.001$), average nocturnal, when paroxysm of apnea and increase of blood pressure in the pulmonary circulation are most likely to occur, – 38.5% higher than in the treatment group ($p < 0.001$). Diastolic BP was higher in patients with COPD in the comparison group: average 24-hour – 12.5% higher, average daily – 13.4% higher, and average nocturnal – 17.1% higher (total < 0.05)

The value of systolic pressure in the pulmonary circulation in patients with AH without bronchial obstruction corresponded to the reference range – 27±13 mm Hg, but in patients with AH burdened by COPD, 1st degree pulmonary hypertension according to the classification of M. M. Amosov (1971) – 48±3.2 mm Hg., that is 78% higher then the level of the comparison group ($p< 0.001$). As stated above all patients' complaints depended upon the disease severity – BP value and degree of the respiratory failure (bronchial obstruction). It was evidenced by the dyspnea, cyanosis and forced expiration volume in the first second constituting, according to the spirogram findings in patients with comorbidity, 48±1.1% vs. indices in patients without COPD – 70±2.8% ($p< 0.01$). Thus, the peripheral hemodynamics and bronchial patency significantly worsen in patients with AH associated with COPD that lead to an increase of the systolic pressure in the pulmonary circulation causing all pathogenetic conditions for the development of AH complications and heart remodeling. Taking the abovementioned into account L-arginine, being an exogenous nitric oxide donator and universal vasodilator, was introduced in the medicinal treatment. The performed treatment suggested that condition of the patients receiving L-arginine differs significantly from that of the control group patients. Therefore, after two weeks of treatment average daily SBP (Table 1) decreased by 10.7% ($p< 0.05$) in patients with AH without COPD, in patients with AH associated with COPD, being administered the background therapy,

hypertension was resistant and the tendency to BP decrease was observed, and in patients treated with L-arginine AH decreased by 33% ($p< 0.01$). These changes persisted for 3 months of treatment

Table 1: Dynamics of SBP and DBP in patients with hypertension and hypertension burdened with pulmonary hypertension and COPD before treatment, 2 weeks and 3 months after the treatment with L-arginine

BP Value	Patients with hypertension (n = 20)			Patients with hypertension and COPD					
				Control group (n = 40)			Treatment group (n = 40)		
	Before treatment	2 weeks after treatment	3 months after treatment	Before treatment	2 weeks after treatment	3 months after treatment	Before treatment	2 weeks after treatment	3 months after treatment
SBP a.	147±2.5	142±6.2	140±5.3	176±9.3**	166±3.6	158±8.3	176±6.1**	140±5.1*,Δ	132±4.1*,Δ
SBPd a.	155±5.4	140±4.8*	137±9.1*	183±7.4**	170±8.1	168±2.8*	189±6.2**	142±3.8*,Δ	135±4,1*,Δ
SBP n.	117±6.7	119±4.3	117±6,5	163±6.1**	154±3.4	149±3.9*	162±5.4**	138±4.1*,Δ	130±4.1*,Δ
DBP a.	88±4.1	82±4.3	83±3,2	99±4.8**	92±3.8	90±6.2	98±3.7**	82±3.2*,Δ	80±3.7*
DBPd a.	97±3.5	86±3.3*	82±5,1*	110±5.2**	96±4.5*	94±5.1*	106±4.1**	88±6.1*	81±4.5*,Δ
DBP n.	76±4.2	75±4,6	74±4.3	89±4.9**	88±4.7	88±4.2	88±1.3**	80±3.3*	80±1.3*,Δ

Note: Statistical significance of value: * – in groups before and after the treatment ** – in treatment group and comparison group Δ – in homologous groups between CG and TG

Analogous changes were observed in DBP after three weeks of treatment: average 24-hour DBP decreased by 32.1% in TG patients ($p < 0.01$), at the same time CG patients demonstrated only a tendency to its decrease in the course of the background treatment, and in patients without COPD the background treatment significantly decreased average daily DBP by 18% ($p< 0.01$).

Identical significant changes of the peripheral hemodynamics influenced by L-arginine were observed in the pulmonary circulation blood pressure having decreased upon completion of the treatment to 31±1.8 mm Hg ($p< 0.01$), and types of BP circadian profiles also changed (Fig.1). If among patients suffering from AH without burdened diseases profile "Dipper" before treatment was in 60% of patients, "Non-dipper" – in 30%, and "Over-dipper" – in 10%, then among patients with AH burdened by COPD profile "Non-dipper" was in 60% of patients, "Night-peaker" – in 15%, "Dipper" – 10%, and "Over-dipper" – only in 5%. Three months after the treatment by L-arginine 24-hour BP profiles have greatly changed demonstrating that 45% of the treatment group patients had profile "Dipper", 40% – "Non-dipper", 10% – "Night-peaker", and 5% – "Over-dipper".

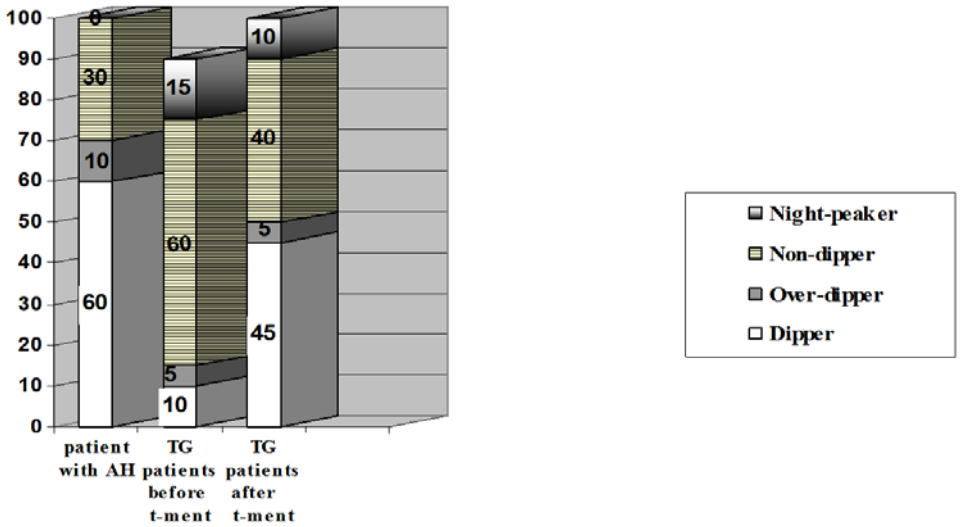

Fig 1: Types of circadian blood pressure profiles in patients with AH and AH with PH of bronchopulmonary origin before treatment and 3 months after treatment with L-arginine

Consequently, the long-term broncho-obstructive syndrome and pulmonary hypertension with hypoxia, hypercapnia is a stress mechanism for the cardio-vascular system and causes BP increase and change of the 24-hour profile in some patients to "Non-dipper" and "Night-peaker". It contributes to the development of complications and increased cardiovascular disease mortality.

This indicates, on the other hand, the activation of the neurohumoral system [11]. Such a condition is accompanied by an increased headache, feeling unwell, and susceptibility to vertigo, and BP resistant to treatment (Table 1). Significantly lower BP value in the systemic and pulmonary circulation, redistribution of the circadian profiles types increasing the number of patients with the type "Dipper" and decreasing the number (Fig. 1) of patients with pathological types "Non-dipper" and "Night-peaker" show the additive antihypertensive action of L-arginine. Reduction of BP in the pulmonary circulation influenced by the treatment facilitated the improved ventilation and gas exchange as evidenced by the vital pulmonary capacity improvement and, in particular, by increase of Tiffeneau index approaching (66±2.3%, $p< 0.001$) 3 months after the treatment initiation.

While determining the degree of the correlation dependence between the value of Tiffeneau index and average daily SBP

we ascertained a negative significant correlation of moderate density (r = -0.70; $p< 0.05$). The positive relationship was found out between the systolic pressure in the pulmonary circulation and daily average DBP (r = 0.67; $p < 0.05$).

4. Conclusions

1. Broncho-obstructive syndrome in patients with AH is a confounding comorbidity that contributes to a persistent increase in BP, changes BP to "Night-peaker" and "Non-dipper", leads to the development of refractivity in the treatment with antihypertensive drugs.
2. L-arginine used in the combination therapy of patients with arterial and pulmonary hypertension of broncho-pulmonary origin potentiates hypotensive action of hemodynamic drugs.
3. L-arginine administered for 3 months in the combination treatment of patients with AH associated with COPD normalizes BP circadian profile (reduces the number of patients with profile "Night-peaker" and "Non-dipper"), decreases the severity of pulmonary hypertension, and has positive effect on the values of bronchial patency.

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