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Effect of L-Arginine on pathogenetic mechanisms of hypertension formation in both the pulmonary and systemic circulations of patients with arterial hypertension and co-existent pulmonary hypertension of bronchopulmonary origin

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Abstract
The aim of the research was to determine the relationship between the activity of serum immunoinflammatory and neuro humoral factors as well as blood pressure in both the pulmonary and systemic circulations of patients with arterial hypertension and chronic obstructive pulmonary disease and the possibility of their optimization using L-arginine.

Materials and Methods: The study included 140 patients with stage II second-degree/third-degree arterial hypertension; among them, there were 82 patients with arterial hypertension and co-existent first-degree/second-degree pulmonary hypertension of bronchopulmonary origin in chronic obstructive pulmonary disease remission phase. The comparison group included 58 patients with arterial hypertension of a similar stage and degree. The average age of patients in the main group was 58.5±5.12 years; the average age of patients in the comparison group was 59.5±3.22 years. The duration of arterial hypertension in the main group was 6.2±1.78 years; the duration of chronic obstructive pulmonary disease was 10.4±2.93. According to treatment, 82 patients with arterial hypertension and chronic obstructive pulmonary disease were divided into two homogeneous groups according to age, sex, duration of arterial hypertension and chronic obstructive pulmonary disease. Group I included 40 patients undergoing basic therapy only. Group II included 42 patients, who, in addition to basic therapy, received intravenous infusion of 4.2% L-arginine hydrochloride solution No 5 (Tivortin, manufactured by Yuria-Pharm, Ukraine) at a dose of 100 ml and continued taking the medicine using oral dosage form (1 tablespoon 5 times a day) for three months.

Results and Discussion: The activity of proinflammatory factors was significant in both patients with arterial hypertension and co-existent chronic obstructive pulmonary disease and those with essential hypertension. In patients with comorbidity, the concentration of interleukin-6 was 8.2 times higher as compared to healthy individuals and 1.4 times higher ($p<0.001$) as compared to patients with arterial hypertension. The activity of tumor necrosis factor-alpha increased as well. In patients of the main group, serum atrial natriuretic peptide concentration was 66% higher as compared to those with isolated arterial hypertension ($p<0.05$) and 6 times higher than that in healthy individuals ($p<0.001$). Serum endothelin-1 concentration was 1.3 and 3.9 higher, respectively ($p<0.001$). After the two-week course of treatment with L-arginine, the clinical condition of patients of the main group improved significantly - apparently due to a reduction in blood pressure in both the pulmonary and systemic circulations. Serum concentration of interleukin-6 and tumor necrosis factor-alpha decreased by 32% and 38%, respectively, undergoing significant changes similar to vasoactive substances – atrial natriuretic peptide and endothelin-1, 3 months after treatment ($p<0.05$).

Conclusions: L-arginine, which was used in combination treatment of patients with arterial hypertension and co-existent chronic obstructive pulmonary disease, affected pathogenetic mechanisms of both diseases and improved their clinical course.

Keywords: Arterial Hypertension, Chronic Obstructive Pulmonary Disease, Pulmonary Hypertension, L-Arginine, Cytokine System

1. Introduction

In recent years, two opposing views on the pathogenesis of structural and functional changes in the co-occurrence of pulmonary hypertension (PH) secondary to chronic obstructive pulmonary disease (COPD) and arterial hypertension (AH) have been actively discussed in the literature.

The peculiarities of cardiorespiratory comorbidity formation are determined by the fact that in two-thirds of patients, COPD occurs secondary to pre-existing AH [11, 12].

In other cases, AH manifests itself on the background of COPD only and, therefore, is regarded as symptomatic hypertension [2, 6, 7]. In such a case, an increase in blood pressure (BP) on the background of COPD exacerbation as well as BP reduction and even its normalization in the remission phase or after eliminating bronchial obstruction and active inflammation are observed [1, 3].

The coexistence of AH and COPD is pathogenetically interrelated [5, 7, 8]. The persistence of nonspecific inflammation, elevated levels of fibrinogen, atrial and brain natriuretic peptides, troponin T, oxidative stress which are typical for both AH and COPD and result in the development of endothelial dysfunction contribute to the formation of mutual pathogenetic mechanisms which aggravate and accelerate the clinical course of AH and COPD [4, 9, 10].

2. The Aim of the Research

The aim of the research was to determine the relationship between the activity of serum immunoinflammatory and neurohumoral factors as well as BP in both the pulmonary and systemic circulations of patients with AH and COPD and the possibility of their optimization using L-arginine.

2.1. Materials and Methods

The study included 140 patients with stage II second-degree/third-degree AH; among them, there were 82 patients with AH and co-existent first-degree/second-degree PH of bronchopulmonary origin in COPD remission phase- main group (MG). The comparison group (CG) included 58 patients with AH of a similar stage and degree. The average age of patients in the main group was 58.5±5.12 years; the average age of patients in the comparison group was 59.5±3.22 years. The duration of AH in patients of the main group was 6.2±1.78 years; the duration of COPD in patients of the main group was 10.4±2.93.

All patients underwent basic therapy for AH according to 2013 Clinical Practice Guidelines for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and the European Society of Cardiology (ESC), the Order of Ministry of Health of Ukraine of May 24, 2012 No 384 “On Approval and Implementation of Medical and Technical Documents on Standardization of Medical Care in Arterial Hypertension” and treatment of COPD according to “Unified Clinical Protocol of Primary, Secondary (Specialized) and Tertiary (Highly Specialized) Medical Care and Medical Rehabilitation” approved by the Order of Ministry of Health of Ukraine of June 27, 2013 No 555 “On Approval and Implementation of Medical and Technical Documents on Standardization of Medical Care in Chronic Obstructive Pulmonary Disease” and the guidelines of the International Congress “Global Strategy for the Diagnosis, Management and Prevention of Chronic Obstructive Pulmonary Disease” (updated 2013).

According to treatment, 82 patients with AH and COPD were divided into two homogeneous groups according to age, sex, AH and COPD duration. Group I included 40 patients undergoing basic therapy only: angiotensin-converting enzyme inhibitor Perindopril at a dose of 8 mg a day (Gedeon Richter, Poland); calcium channel blocker Amlodipine at a dose of 5 mg a day (KRKK, Slovenia); diuretic Trifas Cor at a dose of 5 mg a day (Berlin-Chemie, Germany); beta-blocker Nebivolol Sandoz at a dose of 5 mg a day (Sandoz, Switzerland); acetylsalicylic acid Aspirin Cardio at a dose of 100 mg a gay (Bayer AG, Spain/Germany); short-acting bronchial spasmolytic Atrovent Aerosol at a dose of 10 ml (200 doses) (Boehringer Ingelheim, Germany) - 1-2 inhalations if necessary, according to the above-mentioned protocols. Group II included 42 patients, who, in addition to basic therapy, received intravenous infusion of 4.2% L-arginine hydrochloride solution No 5 (Tivortin, manufactured by Yuria-Pharm, Ukraine) at a dose of 100 ml and continued taking the medicine using oral dosage form (1 tablespoon 5 times a day) for three months. The indicators of studied patients were compared with those in 20 apparently healthy individuals. The examination was performed before, 14 days and 3 months after treatment.

Exclusion criteria included patients with ischemic heart disease and atrioventricular block, congenital and acquired valvular heart disease, NYHA functional class III and IV cardiac failure, acute and chronic renal and hepatic failure, acute cerebrovascular disease, diabetes mellitus or impaired carbohydrate tolerance, COPD exacerbation and bronchial asthma, uncompensated pulmonary heart disease, severe comorbidity being able to alter the pharmacokinetics and pharmacodynamics of drugs used in the study, arginine intolerance or the absence of written informed consent for participation in the research study.

The range of pulmonary artery systolic pressure (PASP) was determined by the peak velocity of transtricuspid regurgitation and the value of systolic transtricuspid pressure gradient when performing ECHO-CG using Logic-500 Doppler (Kranzbuhler) by the formula PASP = ΔP + right atrial pressure (mm Hg), where ΔP = 4 VT × 2, (VP - peak velocity of transtricuspid regurgitation measured in m/s $^{-1}$)

The activity of serum immunoinflammatory and neurohumoral factors was determined in all the patients before and after the course of therapy: the concentration of interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α) was determined applying the enzyme-linked immunosorbent assay with use of the reagent kit Vector-Best (Russia); serum concentration of atrial natriuretic peptide (ANP) and vasoactive endothelin-1 (ET-1) was determined using the reagent kit Biomedica (Austria).

Echocardiography was performed using Logic 500 PRO Ultrasound Machine (Kranzbuhler). Left ventricular (LV) end-systolic dimension (ESD) and end-systolic volume (ESV) as well as LV end-diastolic dimension (EDD) and end-diastolic volume (EDV), the diameter of the right ventricle (RV) were analyzed. To study diastolic function, the indicators of early (E) and late (A) LV filling velocity and the E/A ratio as well as the deceleration time of early diastolic filling (DecT) and isovolumic relaxation time (IVRT) were analyzed. LV diastolic dysfunction was determined as an inverse E/A ratio (E/A<1), the prolongation of DecT and/or IVRT.

The obtained results were processed using the statistical software package STATISTICA 6. To compare two independent groups, the Student’s t-test was used. The Pearson correlation coefficient (r) was used to determine the strength of relationships between quantitative variables.

3. Results and Discussion

Despite the fact that the study included patients with COPD in the remission phase, the clinical course of AH was significantly severer according to clinical data, the indicators of systolic blood pressure (SBP) and diastolic blood pressure (DBP), as well as structural and functional changes in the left and right ventricles. In the main group, the number of patients

with COPD and pain in the frontal and parietal lobes, as well as the neck of the head exceeded that in the comparison group by 16%, the number of patients with COPD and shortness of breath exceeded that in the comparison group by 82%, the number of patients with COPD and heartbeat sensation exceeded that in the comparison group by 57%. The indicators of average daily BP (SBP and DBP) were higher as well – by 20% and 12%, respectively ($p<0.05$).

The indicator of SBP in the pulmonary circulation of patients with AH without bronchial obstruction (the comparison group) corresponded to normal values, while in patients with AH and co-existent COPD, it corresponded to first-degree PH according to the classification proposed by Amosov MM (1971) - 48±3.2 mm Hg exceeding that in the comparison group by 92% ($p<0.001$) (Table 2).

AH altered the structure of both ventricles, especially in patients with comorbidity: LV ESV increased by 1.4 times, LV EDV increased by 1.1 times, left atrial EDV increased by 7.4% and right ventricular (RV) EDV increased by 93% (all the indicators $p<0.05$). In patients of this group, there was observed a decrease in the indicators of the peak early (E) filling velocity and increase in the late (A) filling velocity. Since the E/A ratio was not significantly different between groups, it was more reasonable to pay attention to the prolongation of the deceleration time of early diastolic LV filling (DecT) ($p<0.05$) by 5.9% as well as isovolumic relaxation time (IVRT) by 7.8% ($p<0.05$) in patients of the main group as compared to those of the control group that indicated the development of type I diastolic dysfunction (Table 2).

Cytokine system being involved in the inflammatory process manifested itself more pronounced in patients with comorbidity despite the absence of COPD exacerbation phase (Table 1).

Table 1: Effect of L-arginine on cytokine system and factors of neurohumoral regulation in patients with AH, co-existent PH and COPD

Indicator	Healthy individuals	Patients with AH(CG)			Patients with AH and co-existent COPD (MG)					
					Group I			group II		
		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
IL-6, pg/ml	2.1±0.3	12.3±1.1	11.8±0.9	10.3±0.3*	17.3±1.9	16.2±1.9	16.3±1.1	16.9±1.1 **	14.8±1.3*,˚	10.2±1.2*,˚
TNF, pg/ml	3.1±0.2	6.5±0.9	6.4±0.7	6.4±0.3	11.8±1.1	10.9±1.3	7.1±1.1*	12.1±1.2 **	9.8±1.1*,˚	6.1±0.9*,˚
ANM nmol/ml	1.46±0.2	5.3±0.8	5.1±0.7	5.4±0.3	8.8±0.3	8.9±0.2	9.1±0.9	8.2±0.9 **	7.5±0.3*,˚	6.7±0.2*,˚
ET-1 fmol/ml	0.26±0.05	2.9±0.03	2.4±0.02	2.3±0.02	3.8±0.03	3.7±0.02	3.6±0.01	3.6±0.03 **	3.6±0.02	3.3±0.01*,˚

Notes: statistical significance of the indicators:
* - in both groups before and after treatment;
** - in the main group and patients with AH;
˚ - in the corresponding groups between the control group and the main group

In patients with AH, serum concentration of IL-6 was 5.9 times higher as compared to healthy individuals ($p<0.05$), while in patients with comorbidity, it was 8.2 times higher as compared to healthy individuals and 1.4 times higher than that in patients with AH ($p<0.001$). There was observed similar increase in the activity of TNF-α.

ANP is responsible for the regulation of vascular tone and the state of the atria indicating pronounced changes in vascular filling of patients with AH, co-existent COPD and PH. In patients of the main group, serum ANP concentration was 66% higher as compared to patients with isolated AH ($p<0.05$) and 6 times higher than that in healthy individuals ($p<0.001$). Serum concentration of vasoactive ET-1 was higher as well – by 1.3 and 3.9 times, respectively ($p<0.001$). The Pearson correlation analysis revealed a direct correlation between serum level of ET-1 and the level of PASP (r=+0.41; $p<0.05$). Considering the aforementioned data, it can be stated that changes in neurohumoral regulation of vascular tone and the functional state of the atria as well as the inflammatory component which worsens the clinical course of hypertensive disease, increases BP in both the pulmonary and systemic circulations, contributes to the progression of structural and functional changes in the cardiovascular system are the basis for pathogenetic changes, clinical condition of patients with AH and PH.

Correction of AH according to basic therapy with the inclusion of a universal vasodilator as well as an exogenous nitric oxide donor –L- arginine after long-term therapy (for 3 months) significantly changed the patients' clinical condition: the severity and duration of headache as well as the number of patients complaining of it reduced; shortness of breath and heartbeat sensation occurred during periods of increased physical exertion in a smaller number of patients. The number of patients with AH and co-existent PH suffering from headache reduced by 42% 2 weeks after therapy and by 65% 3 months after therapy; the number of patients with AH and co-existent PH suffering from shortness of breath reduced by 25% and 54%, respectively, and the number of patients with heartbeat sensation reduced by 30% and 72%, respectively. It was obviously associated with the reduction in BP in both the pulmonary and systemic circulations: average daily SBP reduced by 26% and 33% ($p<0.05$) 2 weeks and 3 months after therapy, respectively. In patients, who did not receive L-arginine, changes were statistically insignificant: average daily DBP reduced by 19.5% and 22.5%, respectively ($p<0.05$). There were observed similar changes in average daily BP.

Despite significantly reduced BP in the systemic circulation, average BP in the pulmonary artery of patients with AH and co-existent COPD reduced by 54% 3 weeks after treatment with L-arginine ($p<0.001$) (Table 2).

Table 2: Structural and functional indices of the heart in patients with AH and co-existent COPD before and 3 months after treatment

Indicators	Healthy individuals, n=20	Patients with AH, n=58(CG)		Patients with AH and co-existent COPD n=82 (MG)			
				n=40 (group I)		n=42 (group II)	
		before treatment	after treatment	before treatment	after treatment	before treatment	after treatment
	1	2	3	4	5	6	7
LV ESV, ml	45.9±2.01	50.6±2.71 p_{2-1}>0.05	49.2±1.8 p_{3-1}>0.05 p_{3-2}>0.05	73.3±3.6 p_{4-1}<0.001 p_{4-2}<0.001	70.2±2.1 p_{5-3}<0.001 p_{5-4}<0.001	74.1±2.6 p_{6-1}<0.001 p_{6-2}<0.01	68.2±1.8 p_{7-6}>0.05 p_{7-5} >0.05
LV EDV, ml	120±5.2	135±3.4 p_{2-1}<0.05	134±3.7 p_{3-1}<0.05 p_{3-2}>0.05	145±3.1 p_{4-1}<0.01 p_{4-2}<0.05	142±2.8 p_{5-3}<0.05 p_{5-4}<0.001	144±3.2 p_{6-1}<0.001 p_{6-2}<0.05	143±3.5 p_{7-6}>0.05 p_{7-5} >0.05
LV ESD, ml	35.9±2.54	37.6±2.1 p_{2-1}>0.05	36.9±2.2 p_{3-1}>0.05 p_{3-2}>0.05	44.3±2.89 p_{4-1}<0.05 p_{4-2}>0.05	40.3±2.11 p_{5-3}>0.05 p_{5-4}>0.05	43.9±2.59 p_{6-1}<0.001 p_{6-2}<0.05	38.9±2.33 p_{7-6}>0.05 p_{7-5} >0.05
LA, mm	37.42±1.31	40.5±2.22 p_{2-1}>0.05	40.1±2.13 p_{3-1}>0.05 p_{3-2}>0.05	43.5±2.13 p_{4-1}<0.05 p_{4-2}<0.05	43.4±1.8 p_{5-3}<0.05 p_{5-4}<0.05	42.7±2.73 p_{6-1}<0.05 p_{6-2}>0.05	40.9±2.13 p_{7-6}>0.05 p_{7-5} >0.05
RV, mm	26.13±1.12	27.2±1.24 p_{2-1}>0.05	26.3±1.4 p_{3-1}>0.05 p_{3-2}>0.05	52.5±2.22 p_{4-1}<0.001 p_{4-2}<0.001	50.7±2.51 p_{5-3}<0.001 p_{5-4}<0.001	53.2±1.42 p_{6-1}<0.001 p_{6-2}<0.001	49.8±1.32 p_{7-6}<0.05 p_{7-5} >0.05
LV E/A	1.2±0.22	0.91±0.03 p_{2-1}<0.01	0.93±0.02 p_{3-1}>0.05 p_{3-2}>0.05	0.95±0.04 p_{4-1}>0.05 p_{4-2}>0.05	0.96±0.01 p_{5-4}>0.05 p_{5-3}>0.05	0.94±0.03 p_{6-1}>0.05 p_{6-2}>0.05	0.94±0.01 p_{7-6}>0.05 p_{7-5}>0.05
LV IVRT, ms	81.0±2.9	89.9±4.4 p_{2-1}<0.05	87.8±3.2 p_{3-2}>0.05 p_{3-1}>0.05	97.5±5.1 p_{4-1}<0.001 p_{4-2}<0.001	94.5±6.2 p_{5-3}<0.05 p_{5-4}>0.05	98.1±4.2 p_{6-1}<0.001 p_{6-2}<0.05	94.8±5.8 p_{7-6}>0.05 p_{7-5}>0.05
LV DecT, ms	173.5±2.3	205±10.2 p_{2-1}<0.001	201±9.8 p_{3-2}>0.05 p_{3-1}<0.001	217±10.4 p_{4-1}<0.001 p_{4-2}<0.05	215±8.9 p_{5-3}>0.05 p_{5-4}>0.05	216±10.8 p_{6-1}<0.001 p_{6-2}<0.05	214±9.3 p_{7-6}>0.05 p_{7-5}>0.05
Mean PA pressure, mmHg	21±0.9	25±1.3 p_{2-1}<0.05	25±0.8 p_{3-2}>0.05 p_{3-1}<0.01	48±2.6 p_{4-1}<0.001 p_{4-2}<0.001	45±2.1 p_{5-3}<0.001 p_{5-4}>0.05	48±3.2 p_{6-1}<0.001 p_{6-2}<0.001	31±1.8, p_{7-6}<0.05 p_{7-5}<0.05

Notes:

p_{2-1}, p_{4-1} p_{6-1}, - statistically significant difference between groups of patients and healthy persons before treatment;

p_{4-2} p_{6-2}, - statistically significant difference between groups of patients before treatment;

p_{5-3}, p_{7-5} - statistically significant difference between groups of patients after treatment;

p_{3-2}, p_{5-4} p_{7-6} - statistically significant difference between groups of patients before and after treatment.

Table 1 indicates whether such changes were related to the effect of vascular tone on neurohumoral activators and proinflammatory factors. 2 weeks after treatment, serum concentration of IL-6 and TNF-α reduced by 32% and 38%, respectively, undergoing significant changes similar to vasoactive substances – ANP and ET-1, 3 months after treatment (p<0.05).

Thus, treatment with the inclusion of arginine as a universal vasodilator as well as an exogenous nitric oxide donor had a positive effect on the clinical course of AH with co-existent COPD as well as pathogenetic factors forming AH in both the pulmonary and systemic circulations.

4. Conclusions

1. AH with co-existent COPD, even in the remission phase, had severer clinical course accompanied by pronounced structural and functional changes in all the compartments of the heart and the development of diastolic dysfunction.
2. Cytokine markers (IL-6, TNF) and neurohumoral factors (ANP, ET-1) play a key role in the pathogenesis of hypertension in both the pulmonary and systemic circulations.
3. The long-term usage of arginine positively affects pathogenetic mechanisms of the development of AH and co-existent COPD thereby improving the clinical course of both diseases.

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