ANGIOTENSIN CONVERTING ENZYME INHIBITORS AND PULMONARY HYPERTENSION

C. Martiniuc¹, A. Braniste², T. Braniste³
1. IMSP Institute of Phthisiopneumology “Chiril Draganiuc”, Chisinau
   University of Medicine and Pharmacy, “Grigore T. Popa” - Iasi
2. Faculty of Medicine
   State Medical and Pharmaceutical University “Nicolae Testemitanu”, Chisinau
3. Faculty of Medicine

ANGIOTENSIN CONVERTING ENZYME INHIBITORS AND PULMONARY HYPERTENSION (Abstract): **Aim:** To evaluate the efficacy of angiotensin converting enzyme inhibitors Enalapril, Fosonopril and Moexipril on mean and systolic pulmonary artery pressure. **Material and methods:** The study included 111 patients with chronic obstructive bronchopneumopathies associated with arterial hypertension and mild to moderate heart failure (NYHA I-II class). The patients were examined at baseline and after 60 days of treatment. The central hemodynamic parameters and mean and systolic pulmonary artery pressure were studied by Doppler echocardiography (Phillips HD11XE). The pulmonary artery was viewed by left parasternal approach – cross section of the aorta. The following were measured: pulmonary artery flow acceleration and deceleration time (pafAT/ pafDT), right ventricular izovolumetric relaxation time (IVRT), mean and peak pulmonary blood flow velocities, right ventricular/pulmonary artery systolic pressure (RV/ PASP). The mean pulmonary artery pressure (MPAP) was estimated based on pulmonary flow acceleration time and right ventricular ejection time. **Results:** Following the treatment with angiotensin converting enzyme inhibitors a positive dynamics of SF pattern close to the normal one – a domelike contour with the maximum almost in the middle of diastole was noticed. **Conclusions:** The quantitative estimation revealed the considerable reduction in pulmonary artery systolic pressure (PASP) (from 46.3 ± 3.3 mmHg at baseline to 32.1 ± 2.6 mmHg after treatment, p < 0.01) and MPAP – from 26.7 ± 3.2 mmHg at baseline to 23.2 ± 2.6 mmHg after treatment, p <0.01. **Keywords:** ANGIOTENSIN CONVERTING ENZYME INHIBITORS, CHRONIC OBSTRUCTIVE BRONCHOPNEUMOPATHY, PULMONARY HYPERTENSION, HEART FAILURE.

The cause of the disease has not been proven so far, but vasoconstriction represents an important pathogenic link of PH (1, 2, 3, 4).

Rennin-angiotensin-aldosterone system (RAAS) is important in maintaining vascular tone. The main role of RAAS dysfunction in systemic arterial hypertension (SAH) is well accepted, whereas in pulmonary hypertension it is less obvious.

MPAP > 60 mmHg revealed an increase in serum renin activity (SRA), aldosterone (AS), vasopressin (VP), converting enzyme activity, and AII concentration. Evaluating RAAS related to SRA, it was observed: RAAS increase in patients with PPH is an
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adjunct to the increase in SRA, AII, AS and VP levels. Future research of the role of RAAS in the appearance and progress of PH could determine the strategy and a standardized treatment for PH in patients with obstructive lung disease (5, 6, 10, 11). The role of ACEIs in preventing pulmonary hypertension was demonstrated (e.g. use of Captopril and Cilazapril in hypoxic pulmonary hypertension led to hypertrophic changes in tunica media of pulmonary veins (12, 13, 14). The vasodilating effect of ACEIs might be less important than the humoral activity. Here, smaller doses of ACEIs may cause the blockade of RAAS and activate bradykinin to form L-arginine/nitric oxide, and, it would not lead to systemic hypotension, thus being beneficial in patients with PH. Patients with PH presented a significant activation of RAAS which correlates with pulmonary artery pressure and severity of heart failure. The use of ACEIs in the treatment of patients with PH needs to be re-evaluated.

This study was aimed at assessing the efficacy of ACEIs Enalapril, Fosinopril and Moexipril on mean and systolic pulmonary artery pressure in patients with chronic obstructive bronchopneumopathy (COBP) in association with arterial hypertension (AHT) and mild to moderate heart failure (HF) NYHA I-II class.

MATERIAL AND METHODS

Group I: 61 patients (40 men and 21 women), aged between 18 and 65 years (mean age 46.1 ± 1.3 years) with moderate COBP (Tiffeneau index < 70%; 50% ≤ VEMS < 80%) associated with AHT and mild to moderate heart failure (NYHA I-II class). The patients were assessed at baseline and after 8 weeks of treatment with Enalapril (Ednyt, Geden Richter, Hungary), 10-40 mg once daily (mean dose 21.0 ± 4.3 mg). Group II: 26 patients (12 men and 14 women, mean age 56 ± 0.9 years) with similar forms of COBP, treated with Fosinopril (Monopril, Bristol Myers Squibb, UK), 5-10 mg once daily (mean dose 7.3 ± 0.5 mg). Group III: 24 patients (8 men and 16 women, aged 54.4 ± 6 years) treated with Moexipril (Moex, Schwarz Pharma, Germany) 7.5 mg once daily – initially and after 60 days of treatment.

The central hemodynamic parameters and mean and systolic pulmonary artery pressure were studied by Doppler echocardiography (Phillips HD11XE), according to the traditional Teccholtz method (2, 3, 4). The pulmonary artery was viewed by left parasternal approach – cross section of the aorta. The sample volume was situated at the level of pulmonary artery distal the pulmonary valve or in the cone ejection of the right ventricle close to the pulmonary valve (thus highlighting the turbulent post valvular flow sample). The following were determined: pulmonary artery flow acceleration and deceleration time (pafAT/pafDT), right ventricular izovolumetric relaxation time (IVRT), mean and peak pulmonary blood flow velocities, right ventricular/pulmonary artery systolic pressure (RV/PASP). To determine quantitative ratios we used Bernoulli’s modified formula (3): P = 4V^2, where P – pressure gradient, V – flow velocity, m/ sec.

The pulmonary artery systolic pressure in PA (SPPA) was calculated upon the formula derived from L. Burstin’s nomogram (7, 8, 9):

PAP = TIR + HR – 107.5

where TIR – RV izovolumetric relaxation time, m/ sec, HR-heart rate, beat/ min.

MPAP was estimated based on pulmonary flow acceleration time in the ejection
tract of the right ventricle (9): \( \text{Log} 10 (\text{mPAP}) = 2.8 \ \text{AT/RVET} + 2.4 \), where \( \text{AT} \) – pulmonary flow acceleration time (m/sec), \( \text{RVET} \) – right ventricle ejection time (m/sec).

**RESULTS AND DISCUSSION**

After the immediate test with Enalapril (5 mg) the hypertensive action of the preparation began within 1.5-2 hours, the maximum effect – over 4-6 hours, and duration of the action – 24-26 hours. After two months of Enalapril treatment, a significant decrease in SBP by 11.4% and DBP by 9.5% was noticed, \( p<0.05 \) (tab. I).

All patients had normal indices of left ventricular myocardial mass (< 120 g/ m²), right ventricular telediastolic diameter (2.64 ± 0.25 cm), and right ventricular anterior wall thickness (5.77 ± 0.22 mm). The baseline qualitative estimation of SF at the pulmonary valve orifice and right ventricular outflow tract showed the predominance of typical forms of pulmonary hypertension (two waved, triangular or mixed). After treatment with Enalapril, the dynamics of the systolic flow pattern close to normal – domelike contour with the maximum almost in the middle of diastole was noticed. The quantitative assessment revealed the considerable reduction in PASP level (from 46.3 ± 3.3 mmHg at baseline to 32.1 ± 2.6 mmHg after treatment, \( p<0.01 \)) and mPPA (from 26.7 ± 3.2 mmHg at baseline to 23.2 ± 2.6 mmHg after treatment, \( p<0.01 \) (tab. II).

<table>
<thead>
<tr>
<th>Ratios</th>
<th>SBP, mmHg</th>
<th>DBP, mmHg</th>
<th>HR, beat/ min</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline</strong></td>
<td>172.5 ± 5.9</td>
<td>108.2 ± 3.9</td>
<td>75.1 ± 1.5</td>
</tr>
<tr>
<td><strong>After treatment</strong></td>
<td>137.5 ± 5.1**</td>
<td>87.2 ± 2.4**</td>
<td>71.5 ± 1.5</td>
</tr>
</tbody>
</table>

\*p<0.05; **p<0.001

<table>
<thead>
<tr>
<th>Ratios</th>
<th>PASP mmHg</th>
<th>TAPF, m/ sec</th>
<th>TIR, msec</th>
<th>TPR, dyn·cm·sec⁻¹</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline</strong></td>
<td>46.3 ± 3.3</td>
<td>96.7 ± 2.5</td>
<td>78.6 ± 1.7</td>
<td>386.5 ± 22.7</td>
</tr>
<tr>
<td><strong>After treatment</strong></td>
<td>32.1 ± 2.6**</td>
<td>126.1 ± 3.0**</td>
<td>61.4 ± 2.9*</td>
<td>230.4 ±12.0*</td>
</tr>
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</table>

In parallel, a significant reduction in total pulmonary resistance (TPR) and total vascular resistance (TVR): 386.5 ± 22.7 vs. 230.4 ± 12.0 dyn·sec·cm⁻⁵, \( p<0.05 \) and 3200.4 ± 54.0 vs. 1850.5 ± 75.9 dyn·sec·cm⁻⁵, \( p<0.05 \) were noticed. HR values were actually the same during the research (from 75.1 ± 1.5 beat/ min at baseline to 71.5 ± 1.5 beat/ min after treatment, \( p>0.05 \)). Data analysis revealed a tendency towards the shortening of systolic acceleration time SAT) (< 100 msec) in the presence of pulmonary hypertension (SPPA > 32 mmHg) that can be used as a predictive criterion in the early stages of obstructive pulmonary disease. After treatment with Moexipril there was a statistically significant
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reduction in SBP and DBP (by 12.9% and 10.2%, respectively) associated with a decrease in SPPA (42.1 ± 1.1 mmHg vs. 28.2 ± 0.8 mmHg, p<0.01), MPPA (from 28.0 ± 4.5 mmHg at baseline to 23.4 ± 2.1 mmHg after treatment, p<0.05), and TPR (424.5 ± 25.0 vs. 226.6 ± 15.5 dyn·sec·cm⁻⁵, p<0.05) were also found (tab. III, IV).

**TABLE III**

<table>
<thead>
<tr>
<th>Ratios</th>
<th>PASP, mmHg</th>
<th>TASF, msec</th>
<th>FRI, msec</th>
<th>TVR, dyn·cm·sec⁻⁵</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>42.1 ± 1.1</td>
<td>104.4 ± 7.5</td>
<td>51.5 ± 2.2</td>
<td>2900 ± 33.2</td>
</tr>
<tr>
<td>After treatment</td>
<td>28.2 ± 0.8*</td>
<td>138.1 ± 10.0*</td>
<td>47.7 ± 1.7</td>
<td>1750 ± 57.4*</td>
</tr>
</tbody>
</table>

**TABLE IV**

<table>
<thead>
<tr>
<th>Ratios</th>
<th>SBP, mmHg</th>
<th>DBP, mmHg</th>
<th>HR, beat/ min</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>160.9 ± 8.2</td>
<td>98.0 ± 3.4</td>
<td>98.2 ± 4.4</td>
</tr>
<tr>
<td>After treatment</td>
<td>140.1 ± 3.0*</td>
<td>88.1 ± 2.7*</td>
<td>86.1 ± 3.3*</td>
</tr>
</tbody>
</table>

The patients treated with Fosinopril presented a significant reduction in TAS by 14.1%, TAD by 12.4% (p<0.01), and cardiac frequency by 10.1% (p<0.01). Also noticed was a significant decrease of SPPA from 35.3 ± 3.07 mmHg to 23.1 ± 2.64 (p < 0.01), APPA (from 28.0 ± 4.5 mmHg at baseline to 23.4 ± 2.1 mmHg after treatment, p<0.05), and TPR (424.5 ± 25.0 vs. 226.6 ± 15.5 dyn·sec·cm⁻⁵, p<0.05). There was an inversely proportional correlation between TAPF and SPPA (tab. V).

**TABLE V**

<table>
<thead>
<tr>
<th>Ratios</th>
<th>PASP mmHg</th>
<th>TAPF msec</th>
<th>TPR dyn·cm·sec⁻⁵</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>38.3 ± 3.1</td>
<td>112.4 ± 7.3</td>
<td>424.4 ± 16.6</td>
</tr>
<tr>
<td>After treatment</td>
<td>27.1 ± 2.6**</td>
<td>142.1 ± 6.5**</td>
<td>226.6 ± 15.5</td>
</tr>
</tbody>
</table>

* p < 0.05; ** p < 0.01

Thus, Fosinopril proved to be efficient in reducing SPPA and MPPA in patients with chronic obstructive bronchopneumopathies in association with AHT and moderate heart failure.

**CONCLUSIONS**

Angiotensin converting enzyme inhibitors reduce significantly after two months of treatment the systolic and mean pulmonary artery pressure and mean arterial pressure in patients with chronic obstructive broncho-
pneumopathies associated with AHT and mild to moderate heart failure. The qualitative and quantitative estimation of the systolic flow pattern at the orifice of pulmonary valve and across the right ventricular outflow tract allows the early diagnosis of pulmonary hypertension in patients with COBP. Right ventricular hypertrophy is a late and unnecessary sign of central and pulmonary hemodynamic disturbance in patients with chronic obstructive bronchopneumopathies and arterial hypertension; the key to establishing and creating the changes in the pulmonary hemodynamics is obviously the stable increase of systolic and mean pressure in the pulmonary artery.

REFERENCES