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ORIGINAL PAPER

Importance of the Adrenergic Nerve System in the Response of Gases in the Arterial Blood Following the Provoked Bronchospasm

Hilmi Islami[1], Arta Veseli[2], Emir Behluli[3], Naim Morina[4]
Department of Pharmacology, Faculty of Medicine. University of Prishtina. Clinical Centre, Prishtina. Kosova[1]
Department of Pharmacy, Faculty of Medicine. University of Prishtina. Clinical Centre, Prishtina. Kosova[2,3,4]
Department of Pediatric, Faculty of Medicine, University of Prishtina, Clinical Centre, Prishtina, Kosova[3]

Introduction: this work, partial pressure of the respiratory gases in the capillary blood (pH, PaO2, PaCO2) was studied, following the protective action of the beta2-adrenergic stimulator-Hexoprenaline and alpha2-adrenergic blocker-Tolazoline in the bronchoconstriction caused by a beta-blocker-Propranolol. **Material and methods:** in patients with increased bronchial reactibility. pH, oxygen partial pressure (PaO2), dioxide carbon partial pressure (PaCO2) in the arterial blood, with the assistance of the analyzer IL, following some minutes of sample taking were defined in all patients. As a standard to verify the accuracy of the measurement, ampoule solutions of pH, PaO2 and PaCO2 were utilized (Acidobasel, Berlin). **Results and discussion:** Following the inhalation of the beta-blocker-Propranolol (20 mg/ml–aerosol), there was an evident decrease ($p<0.05$) of pO2 and a non-significant increase ($p>0.1$) of pCO2. Beta2-adrenergcic stimulator–Hexoprenaline (2 inh x 0.2 mg), shows an protective effect in the decrease of pO2 ($p<0.05$) following the bronchoconstriction being provoked by Propranolol. Alpha2-adrenergic blocker-Tolazoline (20 mg/ml-aerosol), has not shown a protective action in the bronchoconstriction caused with propranolol, therefore significant decrease ($p<0.05$) of pO2 and a non-significant increase ($p>0.1$) of pCO2 appeared. This shows that stimulation of beta2-adrenergic receptor has protective action in changes of the respiratory gases. Meantime, blocker of the alpha2-adrenergic receptor (Tolazoline) has not shown a protective action in changes of the respiratory gases. Key words: Propranolol, Hexopranaline, Tolazoline.

Corresponding author: prof Hilmi Islami, MD PhD. Institute of Clinical Pharmacology and Toxicology Faculty of Medicine. Prishtina University. Mob. Phone: 00377 45 437 415. Fax. 00 381 38 551 001
E-mail address: islamihilmi@hotmail.com

1. INTRODUCTION

Monitoring of the gases in the arterial blood in patients with manifested respiratory insufficiency is of a great importance for assigning and following-up of the therapy with oxygen.

Controlling mechanisms, which assures the regularity and intensity of the breathing cycles, act in the closed circuit as per the principle of the reciprocal action. In this system, basic elements are respiratory neurons where impulses are created and which can be found in the efferent routes in the respiratory muscles (1). Joint action of these neurons in muscle manifests with the increase of the sternum area and with the sufficient decrease of intrapleural pressure in order to prevail the:

Lung elasticity depends on the functional ability of the lung parenchyma, respectively from the elastic fibers and surface matter "surfactant" which covers the terminal alveoli and bronchiole. Surfactant, besides opposing to the excessive distending of the lung parenchyma, also enables alveoli to remain opened even during the low pressure and enables the existence of the alveoli with different sizes against same pressure (2). Lack of this matter turns the lung to be unstable which helps the alveolar collapse.

Reduced surface activity was confirmed in the lungs of passed away kids due to disease of the hyaline membrane, in patient being subject to high percentages of oxygen, following the open heart surgery, in cases of severe hypoxia, aci-

demia, pulmonary embolism, overflow, aspiration or shock. In such cases, hypoperfusion state may develop, with the lack of the surfactant as a consequence which manifest with lung instability and a tendency towards creation of the atelectatic focuses (3).

Manifestation of spontaneous bronchoconstriction as a consequence of the bronchial hyper-reactivity represents one of the main mechanisms in cases of patients with bronchial asthma (4).

Bronchial hyper-reactivity in patients with asthma is considered to be as a consequence of the autonomous system disorder, which manifest with the reduced function of the beta-adrenergic system and an increase in the cholinergic and alpha-adrenergic reply towards different stimulators (5).

Although some other nerve structures and some other modulator substances, which are not yet clearly defined, by indicating the complexity of this pathologic process are considered as responsible for these bronchial hyper-reactivity (6, 7).

A number of clinical researches have reported regarding the role of the alpha-adrenergic receptor in the tonus of the smooth musculatures although despite some of the results, role of the adrenergic system is not defined clearly within adjustment of the tonus of the airways smooth musculature (8, 9, and 10).

Research of the airways reactivity was mainly based on the measurement of the airflow resistance in airways (11, 12). Nonetheless, rate of the bronchoconstriction besides the impact on the increase of the airflow resistance in airways is also monitored with the changes in the relation of ventilation/perfusion, which manifests with a change in PO_2 and PCO_2 (13, 14).

Therefore, relation of ventilation/perfusion is an important indicator in interpreting of the rate of the bronchoconstriction, respectively in interpreting of the role of adrenergic system in the tonus of the airways smooth musculature in patients with bronchial asthma (15).

Therefore, aim of this work is to determine the role of the adrenergic system through changes in the relation of ventilation/perfusion, respectively of PO_2 and PCO_2 values following the action Propranolol and Tolazoline and Hexoprenaline in patients with bronchial asthma.

2. MATERIAL AND METHODS

Program of researching of the persons with pulmonary chronic obstructive diseases includes data as follows:

- Questionnaire for respiratory symptoms,
- Medical visits of diseased,
- Functional research of lungs,
- X-ray screening of lungs,
- ECG,
- Laboratory researches, including defining of the acid – basic state and gases in the capillary blood (pH, paO_2, $paCO_2$)
- Skin tests related to inhaled allergens,
- Usage of substances and drugs,
- Bronchoconstrictor provoking with Propranolol, (as aerosol) prior and after administration of the Hexoprenaline and Tolazoline.

Results were processed with a computer statistic program GraphPad InStat III with t-test of comparison of two working groups.

Researched has included some persons with pulmonary chronic obstructive diseases. pH, oxygen partial pressure (PaO_2), dioxide carbon partial pressure ($PaCO_2$) in the arterial blood, with the assistance of the analyzer IL, following some minutes of sample taking were defined in all patients. As a standard to verify the accuracy of the measurement, ampoule solutions of pH, PaO_2 and $PaCO_2$ were utilized (Acidobasel, Berlin).

Following taking of the samples, ear roll hyperemia was caused by the massage with the help of devices for hyperization (butyl nicotinate capsaicin). Preparation, as a cream, is placed in the smooth part of the ear roll with the help of a special plate, and after 10-15 min. cream placed in the ear roll is removed, and afterwards boring is done with the micro lancet in the middle third of the marginal part in a depth of 2-3 mm. Afterwards, two capillary pipes are filled with the heparinized blood with spontaneous pressure without pressing it. Time of sample taking is estimated two minutes, and then reading was immediately done with the machine – analyzer IL.

3. RESULTS

Work has included (n=23) patients with bronchial asthma and bronchial hyper-reactibility. Aim of this work is to define as follows: reply of pH, PaO_2, and $PaCO_2$, in capillary blood following the bronchoconstriction caused with beta-blocker-Propranolol (20 mg/ml-aerosol). Stimulation of $beta_2$-adrenergic receptor with Hexoprenaline (2 inh. x 0.2 mg) shows protective effect in decrease of the pO_2 ($p < 0.05$) following the bronchoconstriction

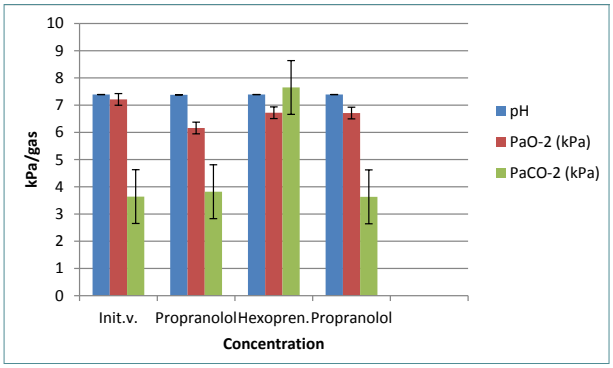

Figure 1. Presenting of pH, partial pressure of PaO2, and PaCO2 in patients with increased bronchial reactibility following the protective action of Hexoprenaline (2 inh. x 0.2 mg) in the bronchoconstriction caused with Propranolol (20 mg/ml–aerosol); (n=16; X ± SEM).

Researched	Years	Body length	Body weight	Index Brok
Female (9)	32.4±2.9	160.3±1.3	64.8±4.5	107.7±7.9
Male (14)	38.6±4.4	173.2±2.4	77.0±5.5	104.6±5.1

Table 1. Main parameters of the pulmonary function of patients with increased bronchial reactibility.

pH	PaO_2 (kPa)	$PaCO_2$ (kPa)
X ± SEM	X SEM	X SEM
7.37 0.03	8.38 0.12	5.11 0.06

Table 2. Presenting of pH, partial pressure of respiratory gases of PaO2, PaCO2 in capillary blood in patients with increased bronchial reactibility. PaO2 – Partial pressure of the oxygen in arterial blood, PaCO2- Partial pressure of the dioxide carbon in arterial blood

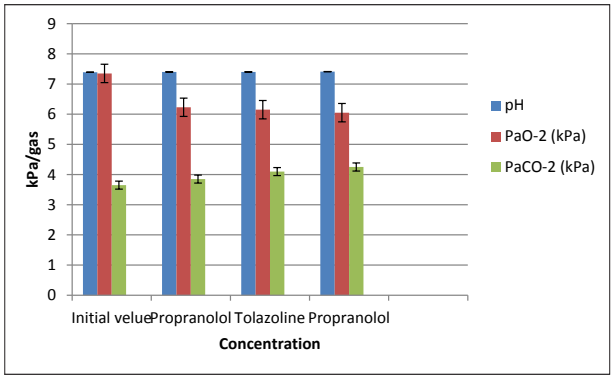

Figure 2. Presenting of pH, partial pressure of PaO2, and PaCO2 in arterial blood of patients with increased bronchial reactibility following the protective action of Tolazoline (20 mg/ml–aerosol) in the bronchoconstriction caused with Propranolol (20 mg/ml–aerosol); (n=7; X ± SEM).

provoked with Propranolol (fig.1). **Alpha$_2$-adrenergic blocker**–Tolazoline **(20 mg/ml-aerosol),** has not shown protective action in the bronchoconstriction caused with propranolol, therefore significant decrease ($p < 0.05$) of pO_2 and a non significant increase ($p > 0.1$) of pCO_2 appeared (fig.2).

In below tables, basic features of the patient and gases in the arterial blood are presented.

Hexoprenaline has protective effect in decrease of the pO_2 ($p<0.05$), in the bronchoconstriction provoked with Propranolol.

From the gained results, it can be seen that Tolazoline has no important protective effect in decrease of the pO_2 ($p < 0.1$), in the bronchoconstriction provoked with Propranolol.

4. DISCUSSION

By analyzing gases in the arterial blood, gas exchange within the lungs can be assessed. With simultaneous determination of gases in the arterial blood and in the expired air in silent condition or physical load and during the O_2 intake as well, explanation regarding disorder of the physiologic response can be concluded at the rate of 100% as a disorder which manifests with respiratory insufficiency (16).

Disorder of the gases in the arterial blood, **hypoxemia**, may appear also during the normal alveolar airing and when features of the alveolar membrane are normal, if the perfusion of respiratory units is damaged. Parts of the pulmonary areas where alveoli airing are maintained, but the blood perfusion is limited or in extreme cases when there is no perfusion at all (areas well ventilated-poorly finalized) contributes to the increase of the physiologically dead area. Defining of the "useless, lost ventilation", especially during the load, may be important in defining of the obstructive changes in the pulmonary vessel net (17).

High values of $PaCO_2$ prove the alveolar hypoventilation which is always followed with a decrease of PaO_2. Alveoli-arterial difference higher than 10 mmHg is most often a sign of noncompliance in between distribution, ventilation and perfusion of the lungs. Unusual changes in between the pressure of the alveolar oxygen and arterial oxygen with relatively normal values of functional-laboratory tests may be of a special importance because this can prove regarding disease of the breathing peripheral routes. Since changes in the gas exchange may impact in the arterial pH with renal compensatory measures, as a consequence, metabolic disorders activate the respiratory compensatory mechanisms, and determination of the acid-basic balance is an important component in assessing of the pulmonary functional changes. Since that the possibility to be equipped with the device for defining of the pH and $PaCO_2$ in blood is facilitated, defining of gases and of pH in arterial blood should be as a part of the protocol for diseased examination with pulmonary diseases or with metabolic disorders, same as defining of the hemoglobin, erythrocyte and leukocyte is (18).

Gas defining during the physical engagement is surely one of the most important tests of respiratory function. Since that biggest part of the patients in physical engagement manifest their disability, measurement of the partial arterial pressure of the oxygen, carbonic gas and of pH, and also ventilation, oxygen consumption, relation dead area/ respiratory air and the gradient A-a, during the engagement, may indicate a damage and in cases when all other parameters of the pulmonary function are normal. Therefore, gas exchange needs to be defined during the physical engagement in all patients complaining to dyspnea (19).

Results of this research indicate that patients with bronchial asthma following the application of histamine have an evident decrease of pO_2 and a non significant increase of pCO_2, assumed to be caused as a consequence of the change in ventilation/perfusion relation. This conclusion matches with results of the author Burke et al, which have presented decrease in estimated 20% of FEV_1 which has resulted with a decrease of pO_2 in patients with mild asthma after the application of aerosol of histamine (20).

Significant decrease of the pO_2 values supposedly derives directly from the bronchoconstriction which, as a consequence, has the disorder of the ventilation/perfusion equilibrium, and in this case we had no opening of the vascular pulmonary shunts which could have impacted the pO_2 values. Although adjustment of the ventilation/perfusion equilibrium in patient with bronchial asthma is quiet complex and remains to be clarified in its entirety (21,22,23).

Authors Poppius and Stenius in their research have ascertained an decrease of pO_2 following the inhaling of the histamine only in a period of 90 seconds of bronchoconstriction, and this condition was improved following the inhaling of the isoproterenol which has enabled the elimination of the bronchoconstriction (24).

Furthermore, we have ascertained that Hexoprenaline administered prior and after the application of the Propranolol had a stabilizing effect in the ventilation/perfusion equilibrium by not allowing the action of the histamine in disorder of this equilibrium.

From this, we have ascertained the role of the stimulators of the beta$_2$-adrenergic receptor in the permeability of airways, respectively in the process of gas exchange in the lungs.

In the group of patients, during the inhaling of the blockers of alpha-adrenergic receptor (Tolazoline) there is no protective action in the process of gas exchange caused by inhaling of the propranolol.

Although, author Ballester with et al. have ascertained a non significant decrease of pO_2 in patients with induced bronchoconstriction with methacholine following the administration of nifedipine with vasodilator effect in vascular pulmonary vessels (25).

Researches from different authors refers that process of gas exchange in patient with asthma is disordered also after the inhaling of methacholine, different allergens and different inflammatory mediators (26,27,28,29).

Results of our research indicate that adrenergic system–stimulators of beta-adrenergic receptor have important place in the permeability of the tracheobronchial system, respectively in the process of gas exchange in lungs and in the ventilation/perfusion equilibrium, whilst this function cannot be attributed to the blocker of the alpha-adrenergic receptor-Tolazoline. Therefore, role of the adrenergic system remains to be further investigated and also the impact of other possible factors in ventilation/perfusion equilibrium that has a direct impact to partial pressure of the pO_2 and pCO_2.

5. CONCLUSION

Based on gained results, it can be concluded as follows:

Following the inhalation of the Propranolol (20 mg/ml–aerosol), there was an evident decrease ($p < 0.05$) of pO_2 and a non significant increase ($p > 0.1$) of pCO_2. Stimulators of $beta_2$-adrenergic receptor (hexoprenaline), shows protective action in changes of respiratory gases caused by inhaling of the propranolol.

Following the inhalation of the Propranolol (20 mg/ml–aerosol), there was an evident decrease ($p < 0.05$) of pO_2 and a non significant increase ($p > 0.1$) of pCO_2. Inhaling of the Tolazoline (20 mg/ml–aerosol) as a blocker of $alpha_1$-adrenergic receptor, has not caused a protective action in the bronchoconstriction caused by propranolol, and therefore appeared a significant decrease ($p < 0.05$) of pO_2 and a non significant increase ($p > 0.1$) of pCO_2.

This suggests that stimulators of $beta_2$-adrenergic receptor plays an important role in maintaining of the partial pressure of pO_2 in the permeability of the tracheobronchial system and by this reduces the appearance of allergic processes, bronchospasm and appearance of the asthmatic attacks. In despite the blockers of the $alpha_2$-adrenergic receptor which do not manifest protective affect in the airways permeability.

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