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## ORIGINAL PAPER

# Response of the Adrenergic System After Provoked Bronchoconstriction in Patients with Bronchial Asthma

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### ABSTRACT

**Objective:** In this paper, effect of the Tolazoline as antagonist of the alpha<sub>2</sub>-adrenergic receptors in patients with bronchial asthma and chronic obstructive bronchitis was studied, and also the effect of stimulation with Hexoprenaline of beta<sub>2</sub>-adrenergic receptor after bronchi-constriction caused with Propranolol, and Acetylcholine. **Methods:** Lung function parameters are determined with Body plethysmography. In patients with bronchial asthma and chronic obstructive bronchitis was registered resistance (Raw), was determined the amount of intrathoracic gas volume (ITGV), and specific resistance was calculated as well (SRaw). Aerosolization was done with standard aerosolizing machine–Asema. **Results:** The study included a total of 21 patients. Two hours after the inhalation of Propranolol, in experimental group, it was applied the blocker of alpha<sub>2</sub>-adrenergic receptors (Tolazoline 20 mg / ml with inhalator ways), which did not cause changes in bronchomotor tonus of tracheobronchial system ( $p > 1.0$ ). Meanwhile, at the same patient, stimulation of beta<sub>2</sub>-adrenergic receptor with Hexoprenaline (2 inh x 0.2 mg) is associated with a significant decrease of the specific resistance of airways (SRaw,  $p < 0.01$ ). Control group results show that after bronchi-constriction caused by Propranolol–aerosol (20 mg / ml) in patients with bronchial asthma and chronic obstructive bronchitis, an increase of specific resistance in airways was caused (SRaw,  $p < 0.01$ ), which confirms the presence of hyper-reactive bronco-constrictor effects intermediated by vagal ways. Two hours after Propranolol, inhaled Hexoprenaline has blocked the action of Propranolol, but not entirely. Furthermore, two hours after acetylcholine-aerosol (1 mg / ml) was applied, inhaled Ipratropium (2 inh x 1 mg) has fully blocked the action of chemical bronchoconstrictor mediators, causing a decline of specific resistance in the airways (SRaw;  $p < 0.01$ ). **Conclusion:** This suggests that primary mechanism, which would cause reaction in patients with increased bronchial reactivity, is prevalence of the cholinergic system over adrenergic one, and not the relationship in between alpha<sub>2</sub>- and beta<sub>2</sub>-adrenergic receptors. **Key words:** Airways, Tolazoline, Propranolol, Hexoprenaline, Ipratropium, and Acetylcholine.

## 1. INTRODUCTION

Importance of the autonomous nerve system, in the airways bronchomotor tonus, is intensively researched last years. Especial care is exercised to adrenergic impacts. Importance of adrenergic action in the regulating of the bronchomotor tonus is not quite known. They might affect through the beta or alpha – adrenergic receptors in the airways smooth musculature and to modify their permeability (1).

Bronchial irritability of the asthmatics airways is also caused by an autonomous disbalance, which derives from the decreased beta-adrenergic function, which results with cholinergic and alpha-adrenergic reaction to different stimulators (2). Many researchers emphasize that within the group of the selected asthmatic patients, in which there was no effects of other drugs, administration of alpha-adrenergic antagonist leads towards improvement of the airways function (3). Alpha-adrenergic antagonists (e.g. indoramine)

cause bronchidilation due to blockage of alpha-adrenergic receptors and they can be useful therapeutics for a certain population of asthmatics (4). Remains unclear whether these results are caused by the blockage of stimulation of mastocyte's alpha-adrenergic receptor, or airways smooth musculature (5).

Tonus of the airways smooth musculature is under influence of some other different **neurotransmitters**, hormones, drugs and mediators that manifest their action through the connection with the specific receptors surface in the airways smooth musculature cells. All these factors related to the airways smooth musculature tonus manifest their action through excitatory effect (agonist) and inhibitor (antagonist) during the connection to respective receptors localized in the cells of airways musculature (6).

“**In vivo**” researches in the experimental animals and in the isolated segments of the bronchi in humans have proved the presence of a small number of alpha-

adrenergic receptors. Also, in these researches was proved that number of these receptors in pulmonary diseases has increased by suggesting the role of these receptors in the mechanism of bronchial asthma (7). Up to date, some pathophysiologic aspects, diagnosis, and therapeutic treatment and prophylaxis of bronchial asthma have remained unclear (8).

In order to evaluate the importance of the alpha-adrenergic system in the regulation of the bronchomotor tonus of patients with obstruction of airways, Tolazoline (blockers of  $\alpha_2$ -adrenergic receptors) effect in this regulation following the preliminary provocation with Propranolol and Acetylcholine was researched in this work.

## 2. EXAMINATIONS AND METHODS

This study project was approved by the Ethical Committee of Medical Faculty in Prishtina.

Examinations are done in 21 diseased people from bronchial asthma and obstructive chronic bronchitis. Patients were selected based on anamnestic data, clinical researches and functional researches of the respiratory system. Basic features and those of the pulmonary function of researches are provided in the tables 1 and 2.

Table 1. Basic feature of the researched people.

n	Age (y)	Length (m)	Mass (kg)
21	44,12 ± 1.30	166.9 ± 0.1	70,98 ± 1.6

Table 2. Pulmonary function features in the researched people.

n	VC (%)	FEV <sub>1</sub> (%)	Raw (kPa L/s)	ITGV (L)
21	64.9 ± 2.2	50.9 ± 2.4	0.64 ± 0.03	5.38 ± 0.17

VC = vital capacity (%), FEV<sub>1</sub> = forced expiratory volume within 1 second, Raw = resistance of the air flow in lung (kilopascal liter in a second), ITGV = intrathoracic volume of gases (liters).

Researched people were informed regarding the aim of examination. At least 48 hours prior beginning of the research, examined has not administered any drugs and substances that would have impacted results of this examination.

Lung function was performed in the silence condition. This determination is constituted from the measurement of the slowed vital capacity (VC), forced expiratory volume within 1 second (FEV<sub>1</sub>) by the pneumotest of the Godardt Company, and afterwards by the determination of the resistance of the air flow in lung (Raw) and intrathoracic volume of gases (ITGV) by the body plethysmography. From the gained Raw and ITGV values, specific resistance SRaw was calculated:

$$SRaw = Raw \times ITGV$$

Diseased of the first group (experimental group—composed of 7 patients) following the determination of respective parameters of the lung function were given Propranolol – aerosol by inhalation in a dose of (20 mg/min).

Two minutes after inhaling of the Propranolol,

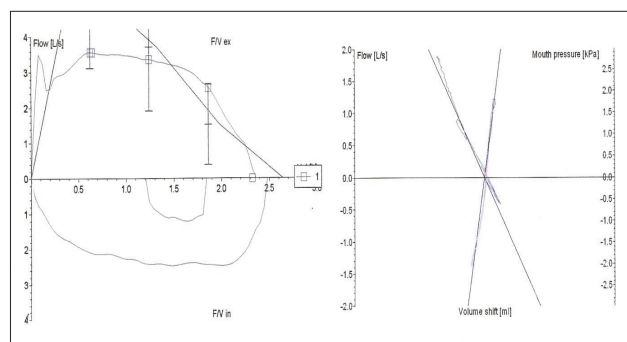


Figure 1. Measurements with body plethysmography. a. Measurement of parameters of the gases volume in the chest (ITGV); registration of flux-volume curve (inspiratory flux and expiratory flux—L/min); b. Resistance of the airways (Raw—L/sec.) expressed in kPa.

through the inhalator Asema with a possibility of aerosolization of 0.5 ml in a minute), Raw and ITGV were measured and MEPV curve was registered. Two hours after measurements, they were repeated and Tolazoline (20 mg— aerosol) were given as aerosol and after 5 minutes same parameters were measured. Following this, propranolol, were inhaled again and same parameters of the airways permeability were defined. At the end, patients were given Hexoprenalin-aerosol (2 inhalations) and above mentioned parameters were measured.

Diseased of the second group (control group—composed of 14 patients) after the defining of the respective parameters of the lung function were given Propranolol – aerosol by inhalation in a dose of (20 mg/min) or Acetylcholine-aerosol (1 mg/ml) to other group.

Two minutes after inhalation of Propranolol and Acetylcholine (through the inhalator Asema with a possibility of aerosolization of 0.5 ml in a minute), Raw and ITGV were measured and MEPV (Maximal Expiratory Flow Volume) was registered too.

Two hours after measurements, they were repeated and then were given a two inhaling of Hexoprenaline and after 5 minutes same parameters were measured. Following this, Propranolol and Acetylcholine were inhaled again and same parameters of the airways permeability were defined. In the end, patients were given Hexoprenaline or Ipratropium-aerosol and above mentioned parameters were measured.

Results were processed in the computer statistical program GraphPad InStat III with the t-test and comparison of two working groups.

## 3. RESULTS

Results of this research, in diseased with bronchial asthma and with chronic obstructive bronchitis, shows that blockage of  $\alpha_2$  adrenergic receptor with Tolazoline (20 mg with inhalator ways) does not change in a significant manner ( $p > 0.1$ ) the bronchomotor tonus of the tracheobronchial system, in comparison to Hexoprenaline ( $\beta_2$  adrenergic agonist) and Ipratropium bromide (anticholinergic), which are very effective in the removal of the increased bron-

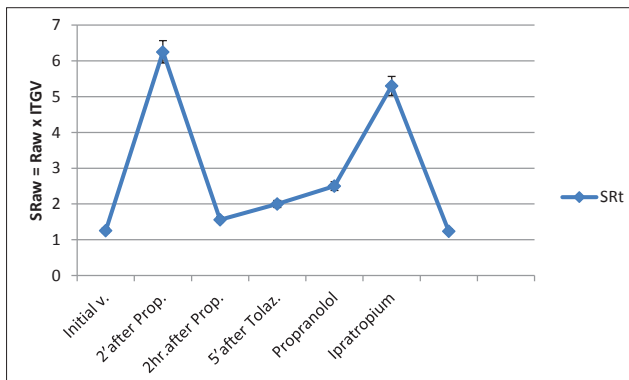


Figure 2. Protective action of Tolazoline – aerosol (20 mg/ml) in the bronchoconstriction caused by Propranolol – aerosol (20 mg/ml). ( $X \pm SEM$ ).

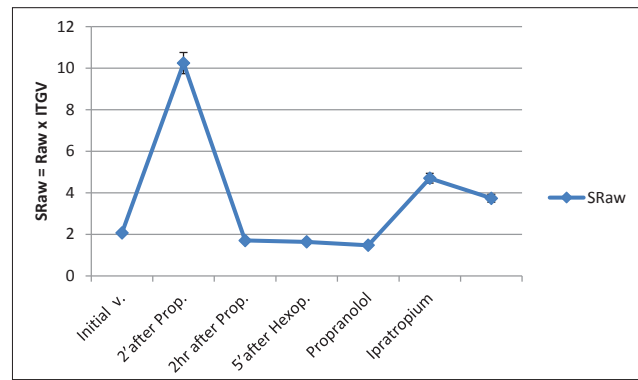


Figure 3. Protective action of Hexoprenaline (2 inh. x 0.2 mg) in the bronchoconstriction caused by Propranolol – aerosol (20 mg/ml). ( $X \pm SEM$ ).

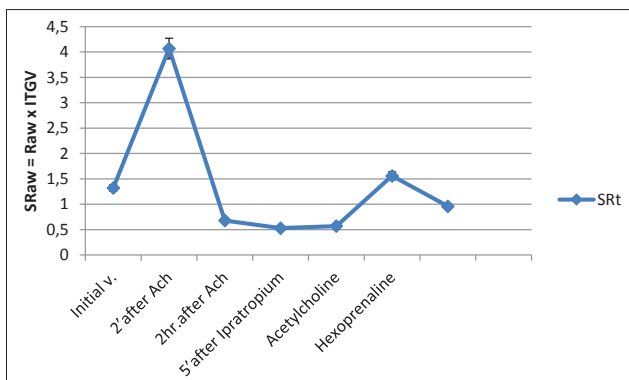


Figure 4. Protective action of Ipratropium (2 inh. x 0.25 mg) in the bronchoconstriction caused by Acetylcholine – aerosol (1 mg/ml). ( $X \pm SEM$ ).

chomotor tonus, by causing decrease of the resistance (Raw), respectively specific resistance (SRaw), after provocation with Propranolol and Acetylcholine. Gained data with this research shows a statistical significance ( $p < 0.01$ ). See fig. 2, 3 and 4.

#### 4. DISCUSSION

Gained results shows that after the bronchoconstriction caused with Propranolol – aerosol (20 mg/ml) in patients from bronchial asthma and chronic obstructive bronchitis, has caused increase of the airways resistance ( $p < 0.01$ ), which proves the presence of hyper-reactive bronco-constrictor effects intermediated by vagal ways. Two hours after Propranolol, inhaled Hexoprenaline has blocked the action of Propranolol, but not entirely. Two hours after Acetylcholine-aerosol (1 mg/ml), inhaled Ipratropium bromid has fully blocked the action of chemical bronchconstrictor mediators ( $p < 0.01$ ). Whilst, two hours after the administration of Propranolol and Acetylcholine, applying of the  $\alpha_2$  adrenergic receptor blockers (Tolazoline 20 mg/ml, with inhalator ways), does not change the bronchomotor tonus of the tracheobronchial tree ( $p > 0.1$ ). Meanwhile, at the same patient, stimulation of  $\beta_2$  adrenergic receptor with Hexoprenaline (2 inh. x 0.2 mg) is associated with a significant decrease of the resistance of the airways ( $p < 0.01$ ).

Even though Szentivany's theory (2) considers that

adrenergic receptor activity is reduced, our results indicate that adrenergic receptor activity is increased to counteract the constriction impacts of cholinergic system. In addition, this research was conducted to examine whether respiratory smooth musculature constriction is mediated by the two subtypes of alpha-adrenergic receptor ( $\alpha_1$  and  $\alpha_2$ ). Therefore, there are no previous reports by which to prove two subtypes of alpha-adrenergic receptor in respiratory smooth musculature and also reports on effects of Clonidine in receptors of smooth musculature (9). Earlier researches have not demonstrated receptors  $\alpha_2$  adrenergic in the epithelial respiratory surface (10). Lately, experiments conducted in vivo shows that clonidine intermediates an inhibitor control over the activity of vagal excitation (11). Inhibitor effect of clonidine in bronchoconstriction, can be induced with direct bronchidilation, or through inhibition of the vagal reflex, or with inhibition of the histamine release, inhibition caused with antigen (10).

Role of the phentolamine in the airways tonus should not be eliminated in whole due to the fact that author Giussani with et al. has reported that systemic administration of phentolamine causes increase of incidence, scale and amplitude of respiratory movements of the ewe's fetus in utero during hypoxia. This proves interconnection of phentolamine in the central respiratory mechanisms, also (12).

Thomson with et al. and Barnes with et al. find no reply on prazosin which is very powerful selective antagonist of  $\alpha_1$  adrenergic receptor (13, 14).

In the favour of the facts for non-significant role of phentolamine in airways are conclusions of the author Mue with et al, which presents that phentolamine dose not cause myorelaxant effect after inducing the bronchoconstriction from the inhalator therapy with methacholine and histamine in the experiment with apes. Isoprenaline has manifested direct myorelaxant effect after inducing the bronchoconstriction with aerosol therapy with methacholine and histamine. Meanwhile, atropine has manifested a partial bronchidilator effect only after inhaling of methacholine but not after the inhalator therapy with histamine (15).

Thomson with et al. has verified that in the group of asthmatics, inhaled phenylephrine (agonist of alpha adrenergic receptors) does not cause significant effect in the resistance of airways (13). In the regulation of airways calibre, dominant role has cholinergic nerve system. In patients with asthma, it is supposed that a hyper-reactivity of the cholinergic system manifest due to the fact that anticholinergic drugs can cause emphasized bronchodilator effect in these patients whilst this effect does not manifest in healthy people. Although, hyperactivity mechanisms of this system are not yet known entirely (16, 17, 18).

In a group of researched patients, we could not have demonstrated any significant effect of the alpha<sub>2</sub> adrenergic receptor antagonist in the resistance of airways. This suggests that activity of receptors alpha<sub>2</sub> adrenergic in the smooth bronchial musculature is not a primary mechanism which would cause reaction in patients with increased bronchial reactivity.

## 5. CONCLUSION

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

- Blockage of alpha<sub>2</sub> adrenergic receptors with Tolazoline aerosol (20 mg/ml) does not lead towards bronchodilation ( $p > 0.1$ ), which proves the opinion that relation in between alpha<sub>2</sub> and beta<sub>2</sub> adrenergic receptors, is not a primary mechanism in causing of bronchial reactivity.
- Gained results shows that following the bronchoconstriction caused by Propranolol – aerosol (20 mg/ml) at patients from bronchial asthma and chronic obstructive bronchitis, an increase in the airways resistance was caused ( $p < 0.01$ ), which proves the presence of hyper-reactive bronchoconstrictor effects intermediated with vagal ways. Two hours after Propranolol, inhaled Hexoprenaline has blocked the action of Propranolol, but not entirely. Regarding this, it can be concluded that in the patients with bronchial asthma abnormal cholinergic bronchoconstrictor effects are main disorders in the changed bronchomotorics of airways.
- Bronchoconstrictor action of Acetylcholine-aerosol (1 mg/ml), inhaled Ipratropium bromid has blocked in a significant manner ( $p < 0.01$ ).
- Administration of anticholinergic substances (Ipratropium) provides good affects same as under the influence of beta<sub>2</sub>-adrenergic agonist, which tells about bronchoconstrictor effect of cholinergic system in patients with bronchial asthma and with chronic obstructive bronchitis.
- Consequently these data show that activity of receptors beta<sub>2</sub>-adrenergic is increased to counteract the cholinergic constriction impulses in patients with bronchial asthma. Whilst, the alpha adrenergic receptors' activity is insignificant in this mechanism.
- We hereby declare: that the manuscript is original

and the work has not been published elsewhere. The authors have no conflicts of interest that are directly relevant to the content of this article.

CONFLICT OF INTEREST: NONE DECLARED

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