

Action of the Oxedrine and Tolazoline in Alpha-Adrenergic Receptor at Patients with Increased Bronchial Reactibility

Hilmi Islami^{1*}, Mehmedali Azemi², Emir Behluli³, Feim Haliti⁴, Arta Dauti⁴, Shpend Dragusha⁴ and Bedri Abdullahu⁴

¹Department of Pharmacology, Faculty of Medicine, University of Prishtina, Clinical Centre, Prishtina, Kosova

²Department of Pediatric, Faculty of Medicine, University of Prishtina, Clinical Centre, Prishtina, Kosova

³Department of Pediatric, Faculty of Medicine, University of Prishtina, Clinical Centre, Prishtina, Kosova

⁴Department of Pharmacy, Faculty of Medicine, University of Prishtina, Clinical Centre, Prishtina, Kosova

Abstract

Objective: In this work, effect of Oxedrine stimulation in alpha₁ adrenergic receptor and the effect of Tolazoline as a blocker of alpha₂ adrenergic receptor in patients with increased bronchial reactivity of respiratory ways were studied.

Methods: Parameters of the lung function were determined by Body plethysmography. Raw and ITGV were registered and SRaw was calculated as well. Aerosolization is done with standard aerosolizing machine - Asema. Patients, in order to make a detailed study, were divided in two groups: middle reactor and severe reactor.

Results: Results obtained from this research, show that stimulation of alpha₁ adrenergic receptor with Oxedrine tartrate (120 mg-aerosol) caused an increase of the airways specific resistance after 60 minutes, but it has not undergone a significant change ($p > 0.1$) in comparison to the inhalation of hexoprenaline (and Ipratropium bromide (2 inh x 0.25 mg) ($p < 0.01$). Blockage of the alpha₂-adrenergic receptor with Tolazoline hydrochloride (20 mg - aerosol) as well has not changed the airways permeability in a significant manner ($p > 0.1$)

Conclusion: This suggests that the activity of alpha₁ and alpha₂ adrenergic receptors in the smooth musculature are not a primary mechanism that cause bronchial reaction, in comparison to agonists of beta₂ adrenergic receptor and cholinergic antagonists which emphasize their significant action in the reduction of specific resistance of airways.

Keywords: Oxedrine; Tolazoline; Hexoprenaline; Ipratropium

Introduction

Airways smooth musculature tonus is under the influence of different neurotransmitters, hormones, drugs, and mediators which manifest their action by connecting to the surface of a specific receptor in airways smooth musculature cells. All these factors, related to the tonus of airways musculature, manifest their action by an excitatory effect (agonist) and inhibitory effect (antagonist) during binding to the respective receptor localized in airways musculature cells [1]. In the mechanism of bronchial hyper-reactibility, important role has also the modulator substances released following the inflammatory processes and other substances following the degranulation process of mastocyte [2].

In adjusting of the airways caliber, cholinergic nerve system plays the predominant role. Supposedly, in asthmatic patients it is manifested with a hyperactivity of the cholinergic system due to the fact that anticholinergic drugs may cause severe bronchodilator effect in these patients whilst this effect does not manifest in healthy persons. Although, mechanism of this hyperactivity of this system is not yet entirely known [3,4].

In patients with increased bronchial reactivity, the importance of alpha-adrenergic system is not fully clarified [5]. Many researchers accentuate that in the group of selected asthmatic patient, without effects of other medicaments, administration of alpha-adrenergic antagonist leads towards the improvement of airways function [6]. Alpha-adrenergic antagonist (e.g. indoramin) causes bronchodilation, due to the blocking of alpha-adrenergic receptors, and can be useful therapeutics for a certain asthmatic population [7]. It remains unclear whether these results are caused by the blockage of stimulation of alpha-adrenergic receptors of mastocytes or airways smooth muscles [8]. Some researchers have verified that in the group of asthmatics

inhaled phenylephrine, as an agonist of alpha-adrenergic receptor, does not cause a significant effect in the airways resistance. Despite this response, this suggests an even more detailed study of this receptor in adjusting of the bronchomotor tonus [9].

Activation of action of some of the above mentioned factors can be initiated also by the outside environment factors such are physical activity or exposure to the cold air. Actually, it is supposed that during the exposure to the cold air, bronchoconstriction can be initiated through the increase of the alpha adrenergic receptors' activity. Therefore, this fact has enhanced the role of alpha adrenergic receptors in the mechanism of asthma.

Researches in experimental animals and in isolated segments of human bronchi have proved the presence of a small number of alpha-adrenergic receptors. These researches have also proved that the presence of this receptor in pulmonary diseases is increased by suggesting the role of this receptor in the patho-physiologic mechanism of bronchial asthma [10]. Up to date, some aspects of patho-physiology, diagnoses, treatment, and prophylaxis in asthma have remained yet unexplained [11].

***Corresponding author:** Hilmi Islami, MD PhD, Institute of Clinical Pharmacology and Toxicology, Faculty of Medicine, Prishtina University, Clinical Centre, Mother Theresa Str., 10000, Prishtina, Kosova; E-mail address: islamihilmi@hotmail.com

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In order to evaluate the importance of the alpha-adrenergic system in the regulation of the bronchomotor tonus in patients with middle and severe bronchial reactivity, effects of the Oxedrine (stimulator of alpha₁-adrenergic receptor) and Tolazoline (blocker of alpha₂-adrenergic receptor) in this adjustment were researched, in comparison to the effects of the beta₂-adrenergic receptor (Hexoprenaline) and anticholinergic substances (Ipratropium bromide).

Material and Methods

This study project was approved by the Ethic Committee of the Medical Faculty in Prishtina. Selection of patients for this study was done based on the data from anamnesis, clinical-laboratory ascertainment, and functional pulmonary examinations. Study involved overall 21 patients. At least 48 hours prior research of bronchial reactivity response, patients has not administered any of the bronchodilatory substances. Examined were informed regarding manner of the functional pulmonary examinations. Patients were suffering from asthma, with or without being followed by bronchitis. Average of the disease lasting was 11 ± 6 years (from 4-20 years). Average of their age was 44 ± 7 years (from 29 - 45 years), whereas average of relative weight was 70 ± 7% (from 65 - 72%). The aim of the examination was explained to each of the patients in advance. Pulmonary function was defined at the rest, which was composed of measurement of vital capacity (VC), forced expiratory volume (FEV₁), resistance in the airways (Raw) and intrathoracic gas volume (ITGV).

In addition to the measurement of these parameters of the pulmonary ventilator function, Maximum Expiratory Flow-Volume Curve (MEF) was also defined. Curve (MEF) was registered in a seating position with same breathing action as the forced vital capacity. Person breathed with mouth (closed nose), through a muzzle of the pneumotachograph.

Airflow was measured with the help of the pneumotachograph, whereas the volume through a volume-integrator. MEF curve was registered in the X-Y writer (Hewlett-Packard).

Flow was registered in the ordinate, and the volume in abscissa. Several parameters were calculated, whereas Maximum Expiratory Flow was taken for analyses after it has expired 25, 50 and 75% of VC (MEF₂₅, MEF₅₀, and MEF₇₅ - l/s).

These parameters were analyzed since they are situated in the part of the curve which primarily depends on mechanic features of the lungs and not from the expiratory force and also because of being more sensitive than FEV₁ in measurement of bronchial reactivity. Prior to the provoking of bronchoconstriction, at least two reproducible MEF curves, blood pressure, and pulse were measured as well.

General resistance of the airflow in the airways (Raw) and the volume of the intrathoracic gas (ITGV) were researched in patients. The patient was placed in the cabin of the plethysmograph that was closed in a hermetic manner, and was connected to the pneumotachograph through an oral mask in order to breathe the air. During the inspirium, with an expansion of the sternum, air in the cabin compresses; whereas, it decompresses in the lung, namely it comes to the decrease of the intrathoracic pressure with the proportional increase of the pressure in the cabin. During the expirium, the opposite situation appears: increase of intraalveolar pressure and proper decrease of the pressure

in the cabin. In the end of the rest expirium, when there is no flow, equation of pressure in alveoli and bronchi with pressure in the mouth happens very fast. Due to this, measurement of the pressure in the mouth provides accurate information for the alveolar pressure. The difference of the pressure in the mouth and at the cabin is checked by two sensitive manometers.

Overall quantity of the volume of the intrathoracic gas (ITGV) was measured with the plethysmography method, including closed gas that do not ventilate. If the residual functional capacity is taken from the ITGV, obtained by the plethysmography method, we will gain information regarding quantity of closed gas due to a severe obstruction, cystic lungs or pneumothorax. In healthy persons with a normal pulmonary function, volume of the intrathoracic gas is equal with the residual functional capacity. From the beta and alpha angles, with the help of tables, values of the airways resistance and volume of the intrathoracic gas are calculated. From gained values, specific rezistance was calculated (SRaw = Raw × ITGV). Raw and the SRaw were taken for analyses. Research of the bronchial response to different substances was done with the measurement of Raw and the SRaw as very sensitive indicators, compared to the parameters calculated from the MEF curve, and therefore they are very important in the research of the bronchoconstriction and bronchodilation. Realized values of MEF₂₅, MEF₅₀, show that calculated parameters from the curve flow-volume during the volumes in small parts of the lung are more sensitive than classic indicators of the measured obstruction with the spirometric examinations (FEV₁, 100 × FEV₁/FVK). Comparison of direct variables obtained from Raw, and SRaw and indirect indicators of the airways obstruction (FEV₁, 100 × FEV₁/FVK, RME₂₅, and RME₅₀) is very important in patients with bronchial asthma and lung obstructive diseases. Basic features and those of the pulmonary function of researched are provided in Table 1.

First group of patients, in order to make a detailed study, was divided in: middle reactor and severe reactor. Following the measurement of respective parameters of lung function, patients were administered Oxedrine tartrate as aerosol (120 mg/3 ml/5 min) through inhalator Asema with a possibility of aerosolization of 0.5 ml per minute. Immediately after the inhalation, Raw and ITGV, arterial pressure, and pulse were measured and measurements were repeated after 15, 30 and 60 minutes following the inhalation.

Same patients, after defining of the lung function parameters, administered Hexoprenaline (2 inh. x 0.2 mg), or Ipratropium bromide (2 inh. x 0.25 mg), and afterwards Raw and ITGV, arterial pressure, and pulse were measured and repeated after 15, 30 dhe 60 min.

Second group of patients, in order to make a detailed study, was also divided in: middle reactor and severe reactor. Following the defining of respective parameters of lung function, patients were administered Tolazoline hydrochloride as aerosol (20 mg/3 ml/5 min) through inhalator Asema with a possibility of aerosolization of 0.5 ml per minute. Immediately after the inhalation, Raw and ITGV, arterial pressure, and pulse were measured and measurements were repeated after 15, 30 and 60 minutes.

Afterwards, following the measurement of lung function parameters, patients were administered Hexoprenaline (2 inh. x 0.2 mg), or Ipratropium (2 inh. x 0.25 mg), then Raw and ITGV, arterial

n	Age(v)	Height (cm)	Mass (kg)	VC (%)	FEV1 (%)	Raw (kPa L/s)	ITGV (L)
21	44.12 ± 1.30	179.19 ± 1.17	70.81 ± 0.78	101.21 ± 3.2	106.35 ± 3.46	0.11 ± 0.01	4.08 ± 0.14

Table 1: Basic characteristics and pulmonary function in examined.

pressure, and pulse were measured and similarly were repeated after 15, 30 and 60 minutes.

In order to observe changes in the airways permeability after inhaling of aerosol of Oxedrine, Tolazoline, and Hexoprenaline or Ipratropium, index of changes in percentage was calculated, namely Raw, ITGV and SRaw (%P) values were calculated as follows:

$$\text{Ind. of decrease} = \frac{\text{Initial values} - \text{minimal value after the inhaling of certain substance}}{\text{Initial values}} \times 100$$

Hypothesis that changes in the adrenergic system is not important and not related to the development of bronchial asthma or other obstructive diseases which are not related to the allergic manifestation were utilized.

Obtained results were grouped and analyzed. Statistic processing of data included the defining of the average values (X), standard deviation (SD), standard mistake (SEM), and testing of the significance of changes in between groups of Patients treated with Propranolol, Tolazoline and control with Hexoprenaline.

Obtained results were tested by a test (t-test) in order to ascertain significant changes in between examined groups. Data were processed with a computer statistic software InStat-3 and Statistica for Windows.

Results

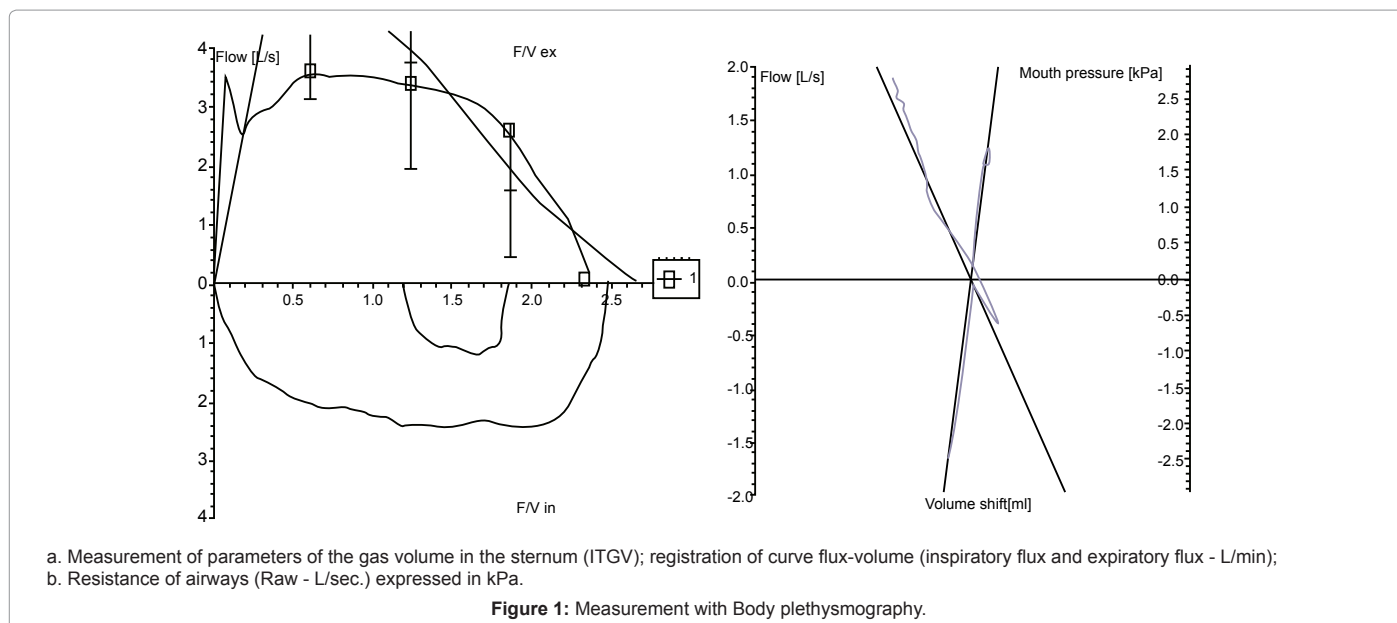
Results of this research, in patients with bronchial reactivity (middle reactor and severe reactor), show that stimulation of alpha₁ - adrenergic receptor with Oxedrine tartrate (120 mg-aerosol) causes an increase of airways specific resistance after 60 minutes and their blockage with Tolazoline hydrochloride (20 mg-aerosol) does not change significantly (p > 0.1) the bronchomotor tonus of the tracheobronchial system, in comparison to Hexoprenaline (beta₂-adrenergic agonist) and Ipratropium bromide (anticholinergic), which are very effective in the removal of increased bronchomotor tonus, by causing significant decrease of the resistance (Raw), respectively of specific resistance (SRaw) (p < 0.01). See Figure 2, 3, 4 and 5. Changes

in arterial pressure and pulse are not significant.

Discussion

Importance of adrenergic action in the regulation of bronchomotor tonus is not quiet known. They can act through beta or alpha - adrenergic receptor in the smooth musculature of airways and modify their permeability [12].

Results of this research, in patients with bronchial reactivity (middle and severe reactor), shows that stimulation of alpha₁ - adrenergic receptor with Oxedrine tartrate (120 mg-aerosol) and their blockage with Tolazoline hydrochloride (20 mg-aerosol) does not change significantly (p > 0.1) the bronchomotor tonus of the tracheobronchial system, in comparison to Hexoprenaline (beta₂-adrenergic agonist) and Ipratropium bromide (anticholinergic), which are very effective in removal of increased bronchomotor tonus, by causing significant decrease of the resistance (Raw), respectively of specific resistance (SRaw) (p < 0.01). This research was done also to examine whether the constriction of smooth respiratory musculature is caused by two sub-types of alpha adrenergic receptors (alpha₁ and alpha₂ adrenergic). Regarding this, there are neither earlier reports by which to prove two sub-types of alpha adrenergic receptors in the airways musculature nor reports over effects of clonidine in the receptors of smooth musculature [13]. Earlier researches have not demonstrated any of the alpha₂ adrenergic receptor in the respiratory epithelial surface. Lately, experiments *in vivo* show that clonidine intermediates an inhibitor control over the vagal excitation activity [14,15]. Inhibitory effect of the clonidine in bronchoconstriction might be induced with straight bronchodilation, or through inhibition of the vagal reflex, or with the inhibition of the release of histamine as an inhibition caused by an antigen [16]. In the group of the researched patients with middle and severe bronchial reactivity, we couldn't demonstrate any significant effect of stimulators and of blockers in alpha₁ and alpha₂-adrenergic receptor in the airways resistance. This suggests that the activity of alpha₁ and alpha₂-adrenergic receptor in the smooth bronchial musculature and in the epithelial part of airways is not a primary mechanism which to cause response in patients with middle and severe bronchial reactivity.



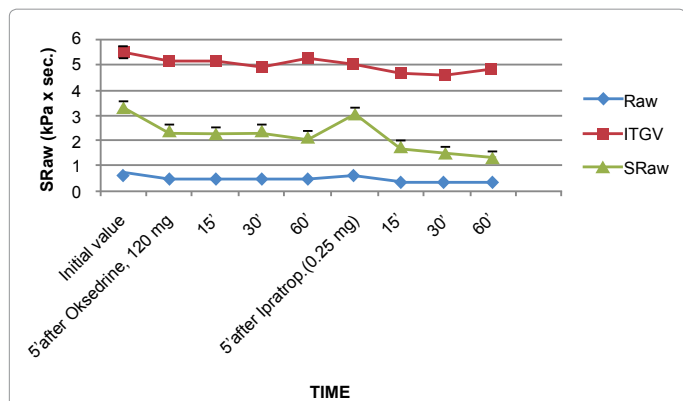


Figure 2: Action of Oxedrine tartrate and Ipratropium in SRaw in persons with middle reactivity ($X \pm SEM$).

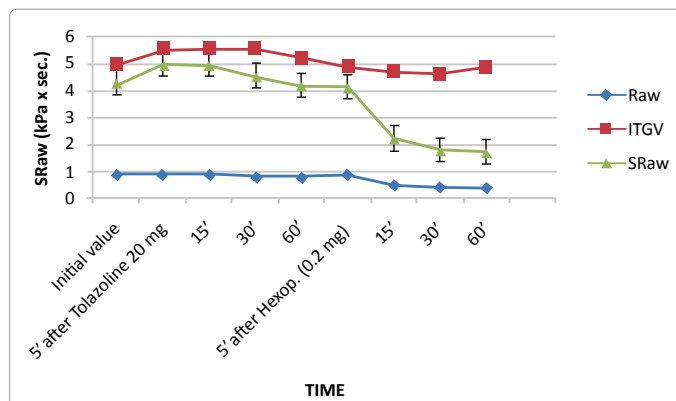


Figure 5: Action of Tolazoline and Hexoprenaline in SRaw in persons with severe reactivity ($X \pm SEM$).

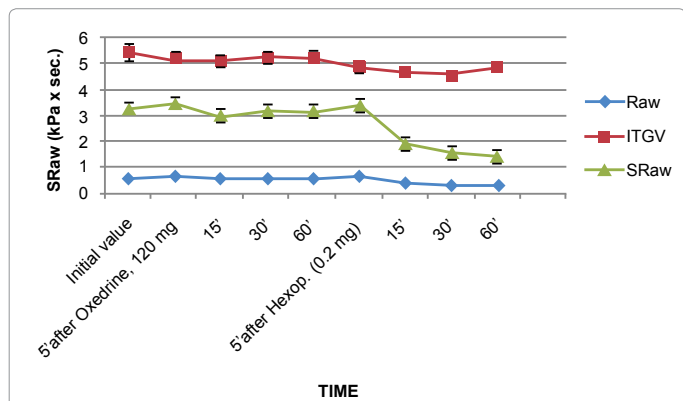


Figure 3: Action of Oxedrine tartrate and Hexoprenaline in SRaw in persons with severe reactivity ($X \pm SEM$).

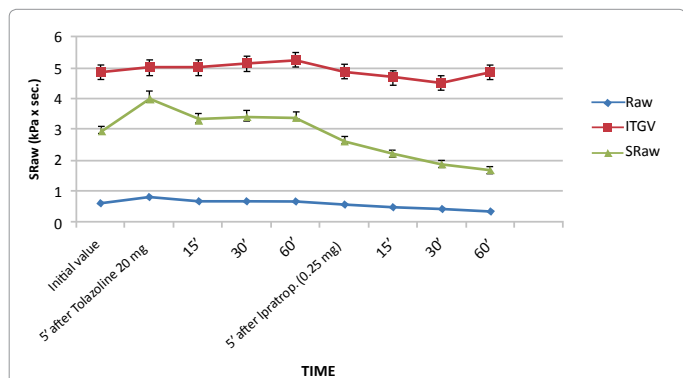


Figure 4: Action of Tolazoline hydrochloride and Hexoprenaline in SRaw in persons with middle reactivity ($X \pm SEM$).

Bronchial tree of a healthy person have equilibrium of the alpha-adrenergic and beta₂-adrenergic system activity in the favor of domination of beta₂-receptor activity. Due to this fact, it is assumed that in case of hypoactivity of the beta₂-adrenergic system dominates alpha-adrenergic system, thus it was supposed that this mechanism plays the main role in the bronchoconstriction in patients with bronchial asthma [17].

According to Szentivan, increased bronchial irritability of airways in asthmatics is caused by the autonomous disbalance, which derives from the decreased beta-adrenergic function, and which results with

an increase of cholinergic and alpha-adrenergic response towards different stimulators [18].

Despite the theory of Szentivany, which considers that the adrenergic system activity is decreased, our results show that the activity of the beta₂-adrenergic receptor is increased in order to contra pose cholinergic constrictor impulses in patients with increased bronchial reactivity. Meanwhile, the activity of alpha-adrenergic receptor is not important in this mechanism.

Research on effect of the phentolamine in patients with bronchial asthma has not registered any changes of lung functional tests parameters (FEV₁, GAV/WL; V₂₅ and V ERV₂) by ascertaining that the increased activity of alpha-adrenergic receptor is not the central mechanism in causing of the asthma disease and by emphasizing the dominant role of beta₂ receptor agonists [19]. Nonetheless, this author presents that asthmatic patients included in the research have manifested heterogenic response to phentolamine by categorizing these patients with positive reaction, patients with negative reaction and patients without reaction to phentolamine. This author assumes that this different reaction to phentolamine is as a result of the different relation of the activity of beta adrenergic receptor, alpha adrenergic and cholinergic receptor at the bronchial tree [19]. Blockage of alpha-adrenergic receptor through the application of phentolamine has no significant impact to the reaction of the airways smooth musculature to histamine. Although, in some of patients with asthma are registered improvements of lung functional tests (FEV₁) but without any significant impact [20]. Role of the phentolamine in the airways tonus should not be totally eliminated because systemic administration of phentolamine causes the increase of the incidence, rate and amplitude of respiratory movements of sheep fetus in utero during hypoxia. This proves regarding relation of phentolamine in the central mechanisms of breathing, also [21]. Phentolamine dose not cause the myorelaxant effect following the induction of bronchoconstriction from the inhalatory therapy with metakolin and histamine in the experiment with apes. Isoprenaline has manifested direct myorelaxant effect following the induction of bronchoconstriction with aerosol therapy with metakolin and histamine. Meantime, atropine has manifested the partial bronchodilator effect only after inhalation of metakolin yet not after the inhalatory therapy with histamine [22].

Results of this research, and of other authors also, indicate related to the pharmacologic relevance of beta₂ agonists (Hexoprenaline) and anti-cholinergic substances (Ipratropium) in improvement of lung

functional test values in patients with asthma and chronic obstructive diseases [22].

All of these results suggest that role of Oxedrine and Tolazoline depends directly on the presence and structural extension of alpha adrenergic receptor, respectively from two sub-types of these receptors. Therefore, further researches of the configuration and sub-types of these receptors would help out in a clearer defining of the role of these receptors in the pathophysiologic mechanism of asthma and pulmonary obstructive diseases.

Conclusion

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

- Inhalation of Oxedrine (120 mg-aerosol), stimulator of α_1 -adrenergic receptor applied to the patients with middle and severe bronchial reactivity does not change the increase of the specific resistance (SRaw) of airways ($p > 0.1$).
- Application of Tolazoline (20 mg-aerosol), as blocker of α_2 -adrenergic receptor applied to the patients with middle and severe bronchial reactivity also does not change the decrease of the specific resistance (SRaw) of airways ($p > 0.1$).
- Application of Hexoprenaline through inhalation to the patients with middle and severe bronchial reactivity causes significant decrease of specific resistance (SRaw) of airways ($p < 0.01$).
- Ipratropium as antagonist of the cholinergic system applied as aerosol in patients with middle and severe bronchial reactivity also causes significant decrease of specific resistance (SRaw) of airways ($p < 0.01$).
- This suggests that the application of agonists and antagonists in patients with middle and severe bronchial reactivity does not change the activity of α_1 and α_2 adrenergic receptor in the smooth bronchial musculature and it is not a primary mechanism which causes reaction in patients with middle and severe bronchial reactivity. There is a possibility that subtypes of α_1 and α_2 adrenergic receptors persist, yet in insufficient size to react significantly with agonist and antagonist alpha-adrenergic substances.

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