

ORIGINAL PAPER

Importance of Alpha-adrenergic Receptor Subtypes in Regulating of Airways Tonus at Patients with Bronchial Asthma

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E-mail: islamihilmi@hotmail.com**ABSTRACT**

Background: In this work, effect of Tamsulosin hydrochloride as antagonist of α_{1A} and α_{1B} - adrenergic receptor and effect of Salbutamol as agonist of β_2 - adrenergic receptor in patients with bronchial asthma and increased bronchial reactivity was studied. **Methods:** Parameters of the lung function are determined by Body plethysmography. Raw and ITGV were registered and specific resistance (SRaw) was also calculated. Tamsulosin was administered in per os way as a preparation in the form of the capsules with a brand name of "Prolosin", producer: Niche Generics Limited, Hitchin, Herts. **Results:** Results gained from this research show that blockage of α_{1A} and α_{1B} - adrenergic receptor with Tamsulosin hydrochloride (0.4 mg and 0.8 mg in per os way) has not changed significantly ($p > 0.1$) the bronchomotor tonus of tracheobronchial tree in comparison to the inhalation of Salbutamol as agonist of β_2 - adrenergic receptor (2 inh. x 0.2 mg), ($p < 0.05$). Arterial blood pressure showed no significant decrease following the administration of the dose of 0.8 mg Tamsulosin. **Conclusion:** This suggests that the activity of α_{1A} and α_{1B} - adrenergic receptor in the smooth musculature is not a primary mechanism which causes reaction in patients with increased bronchial reactivity, in comparison to agonists of β_2 - adrenergic receptor which emphasizes their significant action in the reduction of specific resistance of airways.

Key words: Tamsulosin hydrochloride, Salbutamol.

1. INTRODUCTION

Effect of autonomic nervous system in the bronchomotor tonus of the airways was researched intensively last years. Particular care is paid to the adrenergic and cholinergic effects. Importance of adrenergic action in the regulation of bronchomotor tonus is not quite known. They can effect through α , or β_2 - adrenergic receptor in the smooth musculature of airways and to modify their permeability (1).

Increased bronchial irritability of airways in asthmatics is caused also by the autonomic dis-balance, which derives from the decreased β_2 -adrenergic function, which results in increase of cholinergic and alpha-adrenergic response to different stimulators (2). Many researchers emphasize that in the group of selected asthmatic patients, without effects from other medicaments, administration of alpha-adrenergic antagonist leads towards improvement of the airways function (3, 4). Alpha-adrenergic antagonist (e.g. indoramin) causes the bronchodilation due to the blocking of alpha-adrenergic receptor and can be useful therapeutics for a certain asthmatic population (5). Remains unclear whether these results are caused

by the blockage of stimulation of alpha-adrenergic receptor of mastocytes, or airways smooth muscles (6).

Lately, experiments performed in vivo show that clonidine intermediates an inhibitory control over the existing activity of vagal excitation (7, 8). However, these results are not verified by other researchers. Some authors have verified that in the group of asthmatics, agonist of α_1 -adrenergic receptor, inhaled phenylephrine does not affect in the airways resistance (9).

Airways smooth musculature tonus is under the effect of different neurotransmitters, hormones, drugs, and mediators which do manifest their action by connecting to the surface of the specific receptor in airways smooth musculature cells. All these factors, related to the tonus of airways musculature, manifest their action by excitatory effect (agonist) and inhibitory effect (antagonist) during the connection to respective receptor localized in airways musculature cells (10).

Researches "in vivo" in experimental animals and in isolated segments of human bronchi has proved the presence of a small number of alpha-adrenergic

receptor. These researches have also proved that number of these receptors in pulmonary diseases is increased by suggesting the role of these receptors in the patho-physiologic mechanism of bronchial asthma (11). Up to date, some aspects of mechanism, diagnoses, treatment and prophylaxis in asthma have remained yet unclear (12).

In the mechanism of lung obstructive diseases and of bronchial asthma, important role has also modulator substances being released following the inflammatory processes and other substances following the degranulation process of mastocyte (7).

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 cold air. Actually, it is supposed that during the exposure to cold air, bronchoconstriction can be initiated through the increase of the alpha adrenergic receptor activity. Therefore, this fact has placed in the focus the role of alpha adrenergic receptor in the mechanism of asthma (13).

Ileen et al. consider that α_1 adrenergic receptors in the smooth bronchial musculature may be stimulated only with a direct action of catecholamine in circulation, and only in physiologic doses because of very weeded-out sympathetic innervations found on bronchial tree (14).

Work aims the assessment of the importance of alpha-adrenergic system in the regulation of bronchomotor tonus in patients with bronchial asthma and bronchial increased reactivity. Effect of the Tamsulosin hydrochloride as the **alpha_{1A} and alpha_{1B}-adrenergic** receptor antagonist in patients with increased bronchial reactivity in comparison to the effect of beta₂ adrenergic agonists (Salbutamol) was studied in this work.

2. MATERIAL AND METHODS

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

Examinations were done on 31 patients with bronchial asthma and increased bronchial reactivity.

Selection of patients for this study was done based on the data from anamnesis, clinical-laboratory ascertainments, and functional examinations of respiratory system. Study involved 31 patients. At least 48 hours prior research of bronchial reactivity response, patients has not administered any of the bronchodilator 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 45 ± 7 years (from 29 – 45 years), whereas average of relative weight was $71 \pm 7\%$ (from 66 – 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 in the first second (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 were defined, and 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 intra alveolar 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 individuals 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 x ITGV). Raw

n	Age(v)	Height (cm)	Mass (kg)	VC (%)	FEV ₁ (%)	Raw (kPa L/s)	ITGV (L)
31	45.11 ± 1,20	178.18 ± 1.13	71.91 ± 0.67	103.33±3.3	104.44±2.46	0.12±0.05	4.08±0.13

Table 1. Basic characteristics and pulmonary function in examined.

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 MEF_{25v}, MEF_{50v} 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 (FEV_{1v}, 100 x FEV_{1v}/FVK). Comparison of direct variables obtained from Raw, and SRaw and indirect indicators of the airways obstruction (FEV_{1v}, 100 x FEV_{1v}/FVK, RME_{25v}, and RME_{50v}) is very important in patients with bronchial asthma and lung obstructive diseases.

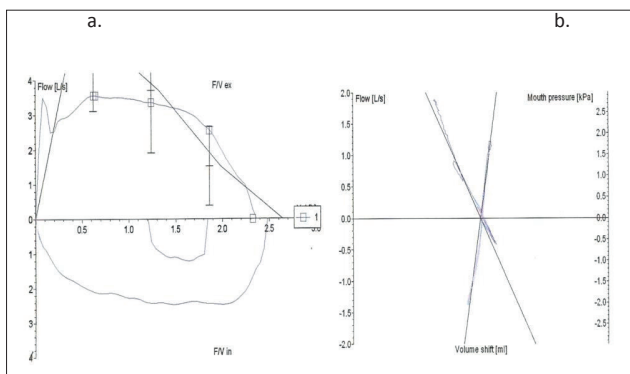


Figure 1. Measurement with Bodyplethysmography: a. Measurement of parameters of the gas volume in the sternum (ITGV); registration of curve flux-volume (inspiratory flux and expiratory flux–L/min); b. Resistance of airways (Raw–L/sec.) expressed in kPa.

Basic features and those of the pulmonary function of researched are provided in Table 1.

Researched were informed regarding the aim of examination. At least 48 hours prior research commencement, examined patients has not administered any of the drugs or substances which to affect the results of the examination. Lung function was determined in the silence condition. This determination is composed of the measurement of the slowed vital capacity (VC), forced expiratory volume (FEV₁) with Godardt Company pneumo test, and afterwards by metering of the resistance of the air flow in lung (Raw) and intrathoracic volume of gases (ITGV) with the body plethysmography. From the gained Raw and ITGV results, specific resistance (SRaw) was calculated.

$$SRaw = Raw \times ITGV$$

In patients with bronchial asthma and increased bronchial reactivity (n=31) following the measurement of initial values, Tamsulosin hydrochloride was applied (**alpha_{1A}** and **alpha_{1B}**-adrenergic antagonist) with per os way (0.4 mg and 0.8 mg), and after 60 and

120 minutes, Raw and ITGV were measured, and afterwards salbutamol as aerosol was applied in the end (beta₂-adrenergic agonist) in a dose of (2 inh. x 0,2 mg), Raw and ITGV values were measured again and SRaw was calculated.

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

Acquired results were grouped and analysed. Statistic data processing included definition of the average values (X), standard deviation (SD), standard mistake (SEM), and testing of significance of changes in between groups of patient treated with Tamsulosin.

Acquired results were tested with a test (t-test) by which significant changes can be ascertained in between examined groups. Records were processed by using the computer statistic software GraphPad In-Stat III.

3. RESULTS

Results of this research, in patients with bronchial asthma, show that blockage of alpha_{1A} and alpha_{1B}-adrenergic receptor with Tamsulosin hydrochloride (0.4 mg and 0.8 mg with per os way) does not change sig-

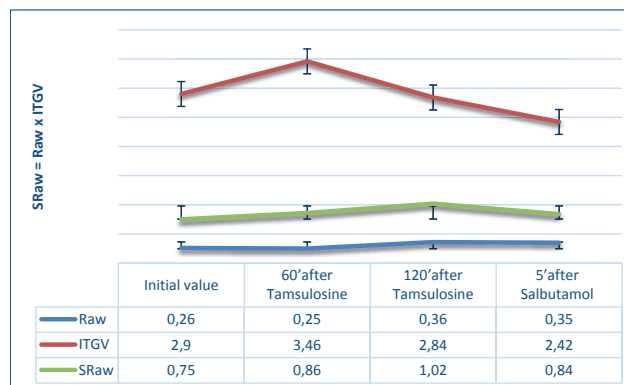


Figure 2. Action of Tamsulosin hydrochloride (0.4 mg – per os), and Salbutamol. (2 inh. x 0.2 mg); in ITGV (n = 9; X ± SEM).

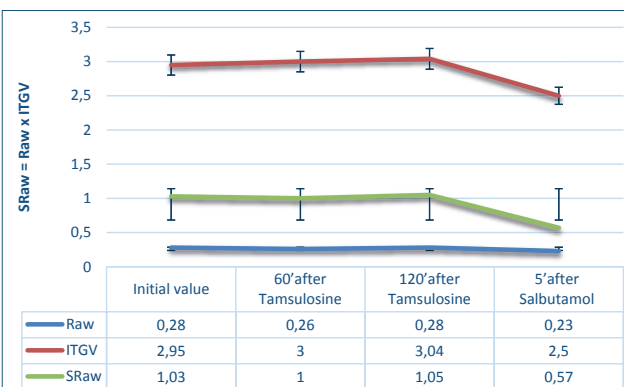


Figure 3. Action of Tamsulosin hydrochloride (0.8 mg – per os), and Salbutamol. (2 inh. x 0.2 mg); in Raw (n = 22; X ± SEM).

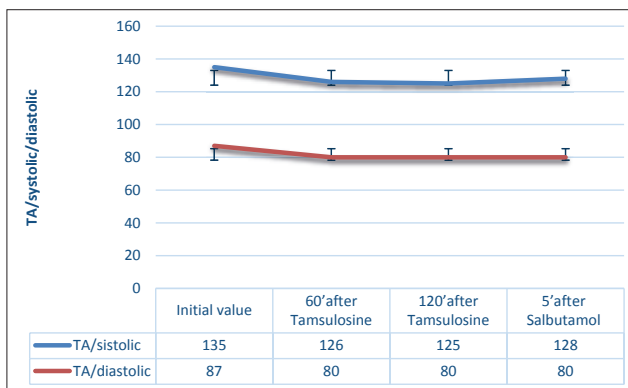


Figure 4. Action of Tamsulosin hydrochloride (0.8 mg – per os) and Salbutamol in arterial pressure (systolic/diastolic AP); ($n = 22$; $X \pm SEM$).

nificantly ($p > 0.1$) the bronchomotor tonus of the tracheobronchial system, in comparison to Salbutamol (β_2 -adrenergic agonist) which is very effective in removal of the increased bronchomotor tonus, by causing significant decrease of the resistance (R_{aw}), respectively of specific resistance (SR_{aw}) ($p < 0.05$). See fig. 2 and 3.

Tamsulosin, as blocker of **alpha_{1A} and alpha_{1B}-adrenergic** receptor, in doses of 0.8 mg lowers the arterial systolic and diastolic pressure (AP) but not in a significant manner ($p > 0.1$). See fig. 4.

4. DISCUSSION

Role of autonomic nerve system in regulating of the airways tonus are not quite known. A huge number of studies dealing with research of regulating of the airways function and their mechanism indicate the considerable role of relaxing effects of the β_2 adrenergic receptor and constrictor actions of alpha adrenergic receptor and interaction of neurohumoral factors in this regulation. Existing of these receptors and their role in healthy and ill people from bronchial asthma and increased bronchial reactivity is yet discussable.

A fact is that Tamsulosin caused no reaction of α_{1A} and α_{1B} adrenergic receptors in the permeability of airways with reversible changes of the lung function. Despite our results, some other researchers found α_1 -adrenergic response in airways of patients with bronchial asthma and increased bronchial reactivity.

Results of this work show that blockage of α_{1A} and α_{1B} adrenergic receptor with Tamsulosin hydrochloride (0.4 mg and 0.8 mg per os) does not change the bronchomotor tonus in patients with increased bronchial hyper-reactibility ($p > 0.1$). Meantime, agonists of β_2 -adrenergic receptor (salbutamol) are very effective in removal of increased bronchomotor tonus ($p < 0.05$). Our earlier results also shows that administration of phentolamine (10 mg, inhalatory and intravenous ways) has not manifested any change in the airways bronchomotor tonus ($p > 0.1$) (15).

Role of phentolamine in the airways tonus should

not be totally eliminated due to the fact that some authors have concluded that systemic administration of phentolamine causes the increase of the incidence, rate and amplitude of respiratory movements of sheep's fetus in utero during hypoxia. This proves regarding relation of phentolamine in the central mechanisms of breathing, also (16).

In favor of the facts related to the non-significant role of phentolamine in airways are also conclusions of some of the authors which speaks about α_1 blockers not causing the myorelaxant effect following the induction of bronchoconstriction from the inhalatory therapy with methacholine and histamine in the experiment with apes. Isoprenaline has manifested direct myorelaxant effect following the induction of bronchoconstriction with aerosol therapy with methacholine and histamine. Meantime, atropine has manifested the partial bronchodilator effect only after inhalation of methacholine yet not after the inhalatory therapy with histamine (17).

Nonetheless, some authors have concluded 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 (18).

A question appears whether constriction of smooth respiratory musculature is caused by two sub-types of alpha adrenergic receptors (α_{1A} and α_{1B})? 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 (19). Previous researches have not demonstrated any of the α_2 adrenergic receptor in the respiratory epithelial surface (19). 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 (20).

Results of some researchers indicate regarding the pharmacologic relevance of β_2 agonists (hexoprenaline) and anti-cholinergic substances (ipratropium bromid) in improvement of lung functional test values in patients with bronchial asthma and increased bronchial reactivity. These results are in full coherence with the results of author Mue et al. (17).

Results suggest that action of Tamsulosin hydrochloride depends directly on the presence and structural extension of alpha adrenergic receptor, respectively two sub-types of these receptors, α_{1A} and α_{1B} -adrenergic receptor. Therefore, further researches of the configuration and sub-types of these receptors would assist in clearer defining of the role of these receptors in the mechanism of bronchial

asthma and patients with increased bronchial reactivity.

5. CONCLUSION

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

- Application of Tamsulosin hydrochloride-blocker of receptor (α_{1A} and α_{1B} -adrenergic) applied with per os way in doses of (0.4 mg and 0.8 mg) in patients with bronchial asthma and increased bronchial reactivity, does not cause significant decrease of specific resistance (SRaw) of airways ($p > 0.1$).
- Salbutamol as an agonist of the β_2 -adrenergic receptor applied inhalatory in patients with increased bronchial hyper-reactibility causes a significant decrease of specific resistance (SRaw) of airways ($p < 0.05$).
- Tamsulosina has caused decrease of systolic and diastolic arterial pressure but not in a significant ($p > 0.1$).
- This suggests that the activity of α_{1A} and α_{1B} adrenergic receptor in the smooth bronchial musculature is not a primary mechanism which will cause reaction in patients with increased bronchial reactivity. There is a possibility that sub-types of α_{1A} and α_{1B} adrenergic receptors persist, yet in insufficient way to react significantly with antagonist alpha-adrenergic substances.

CONFLICT OF INTEREST: NONE DECLARED.

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