Airways hyperresponsiveness to different inhaled combination therapies in adolescent asthmatics

Daniel Machado[1], MD
Celso Pereira[1,2], MD, PhD
Beatriz Tavares[1], MD
Graça Loureiro[1], MD
António Segorbe-Luís[1], MD, PhD

1. Coimbra University Hospitals, Immunoallergy Department, Coimbra, Portugal
2. Immunoallergy Department, Diagnosis Center, Covilhã, Portugal

Running-head: Exercise and asthma therapy in adolescents.

Key-words: Exercise challenge test. Exercise induced hyperresponsiveness. Lung function. Asthma control. Inhaled combination therapy.

Correspondence address:
Daniel Machado
Apartado 9057
3001-301 Coimbra
Portugal
Phone: +351309902002
Fax: +351309902002
Mobile phone: +351936257428
danielmachadooliveira@gmail.com

Airways hyperresponsiveness to different inhaled combination therapies in adolescent asthmatics.

Background: Inhaled combined therapy improves the pulmonary function in asthmatic patients. The effect on the airway hyperresponsiveness (AHR) and the efficacy of different pharmacological schedules is not well clarified on adolescent asthmatics.

Objective: Evaluate the responses to different combined inhaled therapies in adolescent asthmatics and study its impact on exercise induced AHR.

Methods: Basal lung function tests (LFT) were performed in 30 adolescents (13 to 16 years old; 19 female) with allergic asthma. They were submitted to exercise challenge test (EC) followed by bronchodilator test (BD). During 4 weeks, 15 adolescents were submitted to inhaled fluticasone/salmeterol (group A) and other 15 to inhaled budesonide/formoterol (group B). After this period, they underwent another functional evaluation as previous.

Results: Before treatment, pulmonary function was similar in both groups. After 4 weeks of treatment, these groups showed an improvement of the basal LFT ($p=0.001$ for FEV1 in both), decrease on bronchoconstriction induced by exercise (NS for both) and less recovery on BD response ($p=0.001$ and 0.002, for FEV1 respectively groups A and B). Group B showed a better performance, with higher improvement of basal FEF 25/75 ($p=0.001$), reduced bronchoconstriction response to EC ($p=0.008$ for FEV1) and fewer response to

BD test ($p<0.0001$ for FEV1 and 0.024 for FEF 25/75) No adverse events were observed.

Conclusion: After 4 weeks of inhaled combined therapy, these patients improved their pulmonary function and bronchomotricity. Those under budesonide/formoterol showed the highest improvement. These medications are a safe measure in controlling the asthma in these patients.

Introduction

The airway hyperresponsiveness (AHR) is a key feature from asthma, found in nearly all patients with this condition[1]. The intensity of AHR can greatly vary among patients with asthma and, also, there is a vast variability within the same person[1]. In order to understand the mechanisms of AHR, it is possible to consider 2 components that contribute to this response: persistent and variable[2]. The persistent component is related with structural changes in the airway[3,4] whereas the variable component is connected with airway inflammation associated with allergen and occupational exposure, respiratory infections and treatment[3,5]. It is possible to establish an association between AHR and the severity and activity of asthma, especially when the variable component of AHR is analyzed[3].

There are several factors that can exacerbate the AHR, such as viral infections, allergenic and occupational exposition, as well as exercise[2]. These factors are usually classified in those who act “directly” on specific receptors on the bronchial smooth muscle (direct stimuli) and stimulus that induce “indirectly” airway narrowing, causing the endogenous release of mediators of bronchoconstrition (indirect stimuli)[2]. The direct stimuli include agents like methacholine and histamine, which have a clinical and diagnostic utility[2,3] , while the indirect stimuli include exercise and other physical stimuli and some chemicals, like mannitol[3,6].

Exercise is an important exacerbation factor of asthma, especially in children[7,8]. The institution of adequate therapeutic measures can promote an

effective control of the exercise-induced symptoms[9] and, being so, the tolerance to exercise can reflect the efficacy of asthma therapies and the disease control[10,11].

The most important goal of asthma treatment is to achieve the disease control[12]. Children who have an uncontrolled asthma are usually under inhaled corticosteroids (ICS) in low-dose, so a step-up therapy should be implemented in these patients in order to achieve asthma control, such as the ICS step-up, association with a long-acting β2-agonist inhaled (LABA) or association with a leukotriene-receptor antagonist[12,13]. Some studies have proved the efficacy and safety of these therapeutics in this specific group of patients[13-16].

This study was aimed to assess the clinical and functional responses to two different combined inhaled therapies available in the market, studying their impact on exercise-induced AHR.

Methods

Patients

We selected 30 adolescent patients, aged 13 to 16 years old, with asthma. The inclusion criteria were moderate persistent[17], controlled asthma[12], positive skin prick tests to at least one aeroallergen and a previous lung function test (LFT) with positive bronchodilator test (BD).

All parents or guardians of the children gave informed consent, as well as the patients. This study was approved by the Institutional Review Board of the institution.

Study protocol

All patients underwent a clinical observation and pletismographic test (MasterLab Jaeger) to determine the basal LFT. Forced expiratory volume in one second (FEV1), forced vital capacity (FVC), mean forced expiratory flow between 25% and 75% of FVC (FEF 25/75), residual volume (RV) and airway resistance (RAW) were evaluated. They were submitted to standardized treadmill exercise challenge test (EC) followed by bronchodilator test (BD). The procedures and the interpretation of the results were according as defined by ATS/ERS Task Force criteria[11,18-20]. The protocol used was:

1. Baseline determinations of dynamic volumes, static volumes and airways resistance, as the best of two measures.
2. Treadmill exercise test (Exer), while breathing ambient air (20ºC) with a nose clip, in order to ensure mouth breathing, and monitoring of the cardiac frequency. In order to achieve approximately 80% of the maximum predicted heart rate (220 - age in years) after a 1 minute warm-up at a lower work rate, the patients performed a near maximal constant load exercise for 6 minutes in a treadmill. At least two acceptable FEV1 values were obtained at 1 and 5 minutes after cessation of exercise and the lowest FEV1 value was selected to calculate the fall from baseline by the following equation: % fall in FEV1 = (pre-exercise FEV1 - lowest FEV1 post-exercise) / pre-exercise FEV1 x 100%. The exercise test was considered positive when there was a fall in FEV1 ≥15%.

3. Bronchodilator test (BD), with the administration of an inhaled short acting b2 agonist (100 µg of albuterol) in a spacer, with the re-assessment of the lung function 15 minutes later. A positive bronchodilator response was considered when there was an increase in FEV1 and/or FVC ≥12% of control[18].

Patients then went to a randomized period of 4 weeks: 15 adolescents submitted to inhaled fluticasone/salmeterol (group A) and the other 15 adolescents to inhale budesonide/formoterol (group B). All the doses were adjusted according to clinical, lung function, age and weight. After this period, all the patients underwent another functional evaluation, using the same protocol described above.

Primary outcome and safety evaluation

The primary outcome was the differential response to the 2 different inhalatory therapies, assessed by the bronchomotricity on EC and BD.

The safety was evaluated by the incidence of side effects, adverse events and discontinuation because of adverse events.

Statistical analysis

It was performed frequencies distribution, median and range according to the groups mentioned above.

The Mann-Whitney test was used to establish the differences with statistical significance of each respiratory factor between the two study groups. The Wilcoxon Signed Ranks test was applied in order to study the impact of physical exercise and bronchial dilation, as well as the impact of the treatment on each LFT parameter in each group. The statistical analysis was performed using SPSS 18.0® program (2007 SPSS Inc, Chicago, Ill, USA); $p<0.05$ was considered as the statistical relevance standard.

Results

Table 1 shows the demographic data and lung function test results according to the groups involved as well as the comparison between these groups. Figure 1 represents the results of the different lung function evaluations, before and after the treatment and according the 2 studied groups.

No patients presented asthma exacerbations during the 4 weeks period.

Before the treatment, basal LFT were similar in both groups. After the EC group A decreased FEV1 ($p=0.004$) but group B improved this LFT parameter, although without statistical significance. Both groups improved the FEF 25/75

on EC (p=0.020 for both). The BD performance was similar in the 2 groups, improving FEV1 (p=0.001 for both).

After 4 weeks of treatment, there was an improvement of basal FEV1 (p=0.001 for both groups), FVC (p=0.033 and 0.177, groups A and B respectively), PEF (p=0.001 for both) and FEF 25/75 (p=0.001 for both groups), with a decrease of RV (p=0.001 and 0.002, respectively groups A and B) and RAW (p=0.001 for both groups). The bronchial response induced by exercise was reduced with a less reduction on FEV1 (NS), a smaller increase of RAW (p=0.012) and a higher improvement of FEF 25/75 (p=0.049); it was found a less recovery on FEV1 with the BD test (p<0.0001). However, group B showed a better performance, with higher improvement for basal FEF 25/75 (p=0.001), reduced bronchial response to EC (p=0.008 for FEV1) and a fewer response to the BD test (p<0.0001 for FEV1 and 0.024 for FEF 25/75).

Both medications were well tolerated in this study. No side effects were observed with these therapeutic measures and none of the patients has discontinued the treatment because of adverse events.

Discussion

In this study we have evaluated different inhaled combination therapies in adolescent asthmatics. All patients improved their lung function and bronchomotricity after 4 weeks of treatment, but those under inhaled budesonide/formoterol had a better response.

We choose to study different combined inhaled therapies because this route of administration is the cornerstone of asthma treatment for children of all ages[12]. In addition, the combination of a different class of medication can be required in order to achieve the disease control[13]. Recently, the association of an inhaled LABA with an inhaled corticosteroid have been proved to be safe to use in children[13-16]. In this study we did not found any adverse event associated with these therapeutic measures.

The method that we used to evaluate the AHR was using the exercise as the provocative stimulus and then assessing the response to a bronchodilator. It is recognized that direct stimuli like methacholine are more sensitive in the diagnosis of AHR than indirect stimuli like exercise, but the last ones have a higher specificity and may reflect more directly the ongoing airway inflammation[11,21]. Furthermore, in children, exercise is one of the main factors of asthma exacerbation[7] and tolerance to exercise can represent a good response to the therapeutics implemented, therefore to the control of the disease[10].

Both groups studied were similar at the beginning, with similar distribution of gender, medium age and disease evolution time. The basal LFT before treatment did not have significant differences between the 2 groups.

The two therapeutic measures applied in this study were effective leading to an improvement of the several basal lung function parameters evaluated, a less exercise induced AHR and a less recovery on the BD test. Diverse studies had proved that the combination of a LABA with a ICS lead to more beneficial effects on lung function than increasing the dose of ICS, with increments of FEV1 and FEF 25/75[14,16,22,23]. Although the period of the study was somehow short, we observed significant improvements in the lung function. In a study

conducted by de Blic et al., they found significant enhancements of the MEF50 after 4 weeks of treatment with salmeterol/fluticasone[14]. Similarly to our study, Fogel et al. had also obtained significant improvement of the exercise induced AHR after 4 weeks of inhaled salmeterol/fluticasone[15]. This early enhancements may be dependent on the combination of the LABA leading to an anticipation of the therapeutic effects[14]. The reduction on the reversibility with the BD test observed in our study was also established by the groups mentioned before[14,15]. Although the chronic use of a LABA was associated with a loss of effectiveness of inhaled short-acting β2-agonist as acute bronchodilator[15,24] and with the development of tolerance and increased risk of exacerbations during time[25], we think that this decrease in reversibility is due to a pre-bronchodilator effect, rather than to a tolerance mechanism. Besides this, none of the patients had exacerbations during the study period. Even so, the long term effects of these therapies need to be assessed in future studies.

The protective effect of inhaled corticosteroids on exercise-induced asthma is considered time-dependent and is one of the clinical features which control is achieved later[26]. Despite the slight divergence related to EC observed before treatment in the 2 groups, there were not significant differences, in spite of a basal minor decrease in Group A, but the further behaviour all over the study was similar in both groups.

Additionally to these data, the association budesonide/formoterol was most likely to provide the best response in this adolescent patient group, however some patients presented a better response with the association fluticasone/salmeterol. Other groups had compared the efficacy of the different combined inhaled therapy plans in children. In a study conducted by Bousquet

et al. the therapeutic plan with budesonide/formoterol maintenance and reliever reduced the incidence of severe asthma exacerbations and hospitalisation/ER treatment with similar daily symptom control compared with sustained high-dose salmeterol/fluticasone plus SABA; also in this study they did not found any differences in measures of the lung function between the treatments[27]. On the other hand a previous study from Vogelmeier et al. found a statistically significant difference in post-terbutaline FEV1 in favour of patients in the budesonide/formoterol group, in addition to a less use of reliever therapy[28]. However none of these studies had focused the influence of these therapies in the exercise induced AHR. We have demonstrated that both therapeutic plans decrease the bronchoconstriction induced by exercise, with a less recovery on BD, render to an airway hyperresponsiveness modulation; these facts were more evident in those under inhaled budesonide/formoterol.

Similarly to results reported by other studies, both medications were safe and well tolerated by the patients[13-16,27,28].

Conclusion

In summary, in this group of adolescent asthmatics both inhaled therapeutic plans improved the lung function and the bronchial reactivity on the EC and BD tests; however, patients submitted to budesonide/formoterol had the best performance.

Declaration of Interest

All the authors disclose any financial, consulting, and personal relationships with other people or organizations that could influence (bias) the author's work.

None of the authors has any financial or commercial association that may pose a conflict of interest. This study was carried out without funding.

References

1. Busse WW. The relationship of airway hyperresponsiveness and airway inflammation: Airway hyperresponsiveness in asthma: its measurement and clinical significance. Chest 2010; 138 (Suppl): 4S-10S.
2. O'Byrne PM, Gauvreau GM, Brannan JD. Provoked models of asthma: what have we learnt? Clin Exp Allergy 2009; 39: 181-92.
3. Cockcroft DW, Davis BE. Mechanisms of airway hyperresponsiveness. J Allergy Clin Immunol 2006; 118: 551-9.
4. Homer RJ, Elias JA. Airway remodeling in asthma: therapeutic implications of mechanisms. Physiology 2005; 20: 28-35.
5. Covar RA. Bronchoprovocation testing in asthma. Immunol Allergy Clin North Am 2007; 27: 633-49; vi-vii.
6. Van Schoor J, Pauwels R, Joos G. Indirect bronchial hyper-responsiveness: the coming of age of a specific group of bronchial challenges. Clin Exp Allergy 2005; 35: 250-61.

7. Anderson SD, Daviskas E. The mechanism of exercise-induced asthma is. J Allergy Clin Immunol 2000; 106: 453-9.
8. Randolph C. Exercise-induced asthma: update on pathophysiology, clinical diagnosis, and treatment. Curr Probl Pediatr 1997; 27: 53-77.
9. Tilles SA. Exercise-induced respiratory symptoms: an epidemic among adolescents. Ann Allergy Asthma Immunol 2010; 104: 361-7.
10. Anderson SD. Indirect challenge tests: Airway hyperresponsiveness in asthma: its measurement and clinical significance. Chest 2010; 138 (Suppl): 25S-30S.
11. Joos GF, O'Connor B, Anderson SD, et al. Indirect airway challenges. Eur Respir J 2003; 21: 1050-68.
12. Global Strategy for Asthma Management and Prevention [Internet]. Global Initiative for Asthma (GINA); [updated 2009; cited 2011 Mar 25]. Available from: http://www.ginasthma.org/Guidelineitem.asp??l1=2&l2=1&intId=1561.
13. Lemanske RF Jr, Mauger DT, Sorkness CA, et al. N Engl J Med 2010; 362: 975-85.
14. de Blic J, Ogorodova L, Klink R, et al. Salmeterol/fluticasone propionate vs. double dose fluticasone propionate on lung function and asthma control in children. Pediatr Allergy Immunol 2009; 20: 763-71.
15. Fogel RB, Rosario N, Aristizabal G, et al. Effect of montelukast or salmeterol added to inhaled fluticasone on exercise-induced bronchoconstriction in children. Ann Allergy Asthma Immunol 2010; 104: 511-7.

16. Berger WE, Leflein JG, Geller DE, ey al. The safety and clinical benefit of budesonide/formoterol pressurized metered-dose inhaler versus budesonide alone in children. Allergy Asthma Proc 2010; 31: 26-39.
17. Global Strategy for Asthma Management and Prevention [Internet]. Global Initiative for Asthma (GINA); [updated 2008; cited 2009 Mar 08]. Available from: http://www.ginasthma.org/Guidelineitem.asp??l1=2&l2=1&intId=1561.
18. Pellegrino R, Viegi G, Brusasco V, et. al. Interpretative strategies for lung function tests. Eur Respir J 2005; 26: 948-68.
19. Roca J, Whipp BJ, Agustí AGN, et al. ERS Task Force on Standardization of Clinical Exercise Testing. Clinical exercise testing with reference to lung diseases: indications, standardization and interpretation strategies. Eur Respir J 1997; 10: 2662-89.
20. Crapo RO, Casaburi R, Coates AL, et al. Guidelines for methacholine and exercise challenge testing-1999. Official Statement of the American Thoracic Society. Am J Respir Crit Care Med 2000; 161: 309-29.
21. Machado D, Tavares B, Loureiro G, et al. Body mass index and airway hyper-responsiveness in individuals without respiratory disease. Eur Ann Allergy Clin Immunol 2008; 40: 130-7.
22. Pohunek P, Kuna P, Jorup C, et al. Budesonide/formoterol improves lung function compared with budesonidealone in children with asthma. Pediatr Allergy Immunol 2006; 17: 458-65.
23. Tal A, Simon G, Vermeulen JH et al. Budesonide/formoterol in a single inhaler versus inhaled corticosteroids alone in the treatment of asthma. Pediatr Pulmonol 2002; 34: 342-50.

24. Storms W, Chervinsky P, Ghannam AF, et al. A comparison of the effects of oral montelukast and inhaled salmeterol on response to rescue bronchodilation after challenge. Respir Med 2004; 98: 1051-62.
25. Bisgaard H, Szefler S. Long-acting b2-agonists and paediatric asthma. Lancet 2006; 367: 286-8.
26. Pedersen S, Hansen OR. Budesonide treatment of moderate and severe asthma in children: a dose-response study. J Allergy Clin Immunol 1995; 95: 29-33.
27. Bousquet J, Boulet LP, Peters MJ, et al. Budesonide/formoterol for maintenance and relief in uncontrolled asthma vs. high-dose salmeterol/fluticasone. Respir Med 2007; 101: 2437-46.
28. Vogelmeier C, D'Urzo A, Pauwels R, et al. Budesonide/formoterol maintenance and reliever therapy: an effective asthma treatment option? Eur Respir J 2005; 26: 819-28.

Table

		Group A	Group B	Total	p
Female / Male		9 / 6	10 / 5	19 / 11	
Medium age		14±3 years	14±3 years	14±3 years	NS
Disease evolution time		7±8 years	6±11 years	7±11 years	NS
Basal LFT Before	FEV1	87.20±12.9	88.20±16.9	88.15±16.9	NS
	FVC	94.50±12.7	94.30±21.2	94.40±21.2	NS
	PEF	82.60±17.2	82.10±22.1	82.35±24.2	NS
	FEF 25/75	72.70±30.5	74.20±36.1	72.70±36.1	NS
	RV	121.30±35.0	131.00±53.0	124.75±53.0	NS
	RAW	162.80±72.0	158.00±82.0	160.40±83.0	NS
EC test Before	FEV1	83.30±9.7	90.10±31.0	86.10±31.0	0.005
	FVC	94.60±9.1	92.90±20.3	94.20±20.3	NS
	PEF	79.20±10.7	87.30±29.0	80.80±29.0	0.003
	FEF 25/75	77.50±20.1	82.40±36.4	78.95±36.4	NS
	RV	109.50±90.0	109.50±78.0	109.50±98.0	NS
	RAW	113.00±100.1	121.00±135.9	119.15±135.9	NS
BD test Before	FEV1	118.20±14.3	111.40±44.7	115.85±44.7	0.04
	FVC	101.20±13.5	100.90±19.9	101.20±19.9	NS
	PEF	110.70±14.0	109.20±33.0	109.70±33.0	0.046
	FEF 25/75	136.20±30.6	126.80±57.0	133.95±57.0	NS
	RV	88.40±29.0	99.50±48.0	91.45±48.0	0.034
	RAW	91.20±51.2	89.60±78.8	90.70±78.8	NS
Basal LFT After	FEV1	92.10±10.6	93.80±15.1	92.45±17.5	NS
	FVC	99.70±11.2	100.20±18.7	100.15±18.7	NS
	PEF	90.20±10.0	90.00±16.5	90.05±17.5	NS
	FEF 25/75	82.40±20.4	89.00±14.5	87.35±22.9	0.002
	RV	104.10±33.0	104.00±38.0	104.05±43.0	NS
	RAW	124.00±77.0	122.00±62.0	122.50±89.0	NS
EC test After	FEV1	88.30±10.3	96.50±21.0	91.85±26.2	<0.0001
	FVC	97.20±10.0	101.70±19.8	99.30±19.8	NS
	PEF	85.60±13.1	94.50±23.8	89.10±28.9	<0.0001
	FEF 25/75	90.20±36.4	111.20±47.7	105.25±55.4	0.002
	RV	102.30±42.0	102.40±47.0	102.30±58.0	NS
	RAW	110.60±38.0	99.50±50.0	107.30±57.0	NS
BD test After	FEV1	108.20±21.1	102.30±20.9	104.05±23.0	NS
	FVC	99.50±10.0	100.70±14.7	99.90±16.7	NS
	PEF	100.10±20.3	99.70±23.0	99.90±23.4	NS
	FEF 25/75	106.20±45.6	107.00±32.7	106.60±47.0	NS
	RV	96.20±19.0	101.00±39.0	98.25±39.0	NS
	RAW	95.90±41.0	92.30±87.0	93.65±87.0	NS

Table 1 – Demographic and lung function data, before and after 4 weeks of treatment.

The results of the lung function are % of the predicted and indicated as median±range.

The p value corresponds to the comparison between groups A and B.

LFT – lung function test. EC – exercise challenge test. BD – bronchodilator test. FEV1 – forced expiratory volume in 1 second. FVC – forced vital capacity. FEF

25/75 – mean forced expiratory flow between 25% and 75% of FVC. RV – residual volume. RAW – airway resistance. NS – Not significant ($p>0.05$).

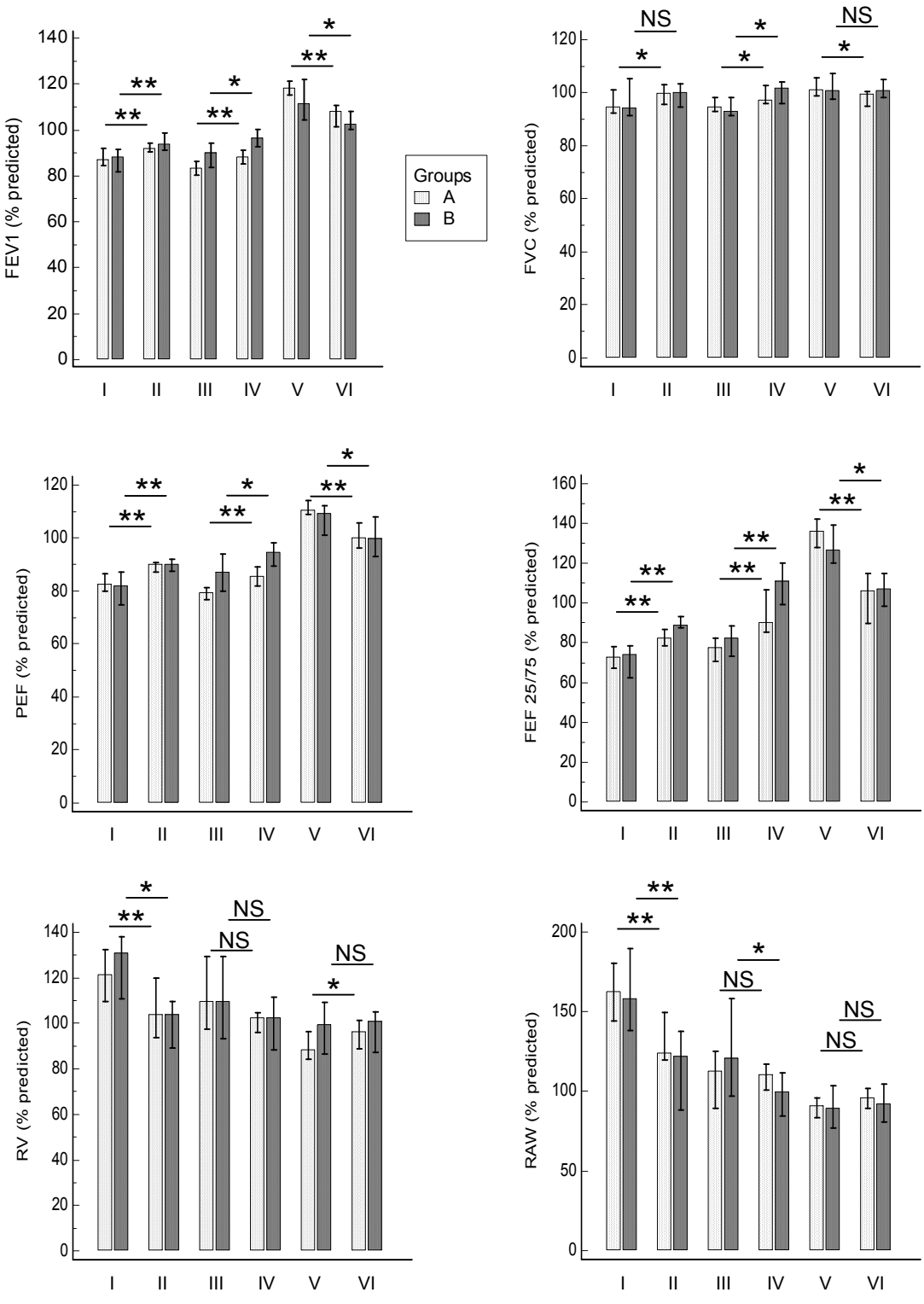
Figure

Figure 1 – Lung function results on the several evaluations performed (basal, EC and BD), before and after the treatment. Results are medians (error bars: 95% confidence interval for median).

∗ - p≤0.05. ∗∗ - p≤0.001. NS – not significant (p>0.05).

I – basal results before treatment. II – basal results after treatment. III – EC results before treatment. IV – EC results after treatment. V – BD results before treatment. VI – BD results after treatment.

FEV1 – forced expiratory volume in 1 second. FVC – forced vital capacity. FEF 25/75 – mean forced expiratory flow between 25% and 75% of FVC. RV – residual volume. RAW – airway resistance.


FEV1 (% predicted)
FVC (% predicted)
PEF (% predicted)
FEF 25/75 (% predicted)
RV (% predicted)
RAW (% predicted)
Groups
A
B
I
II
III
IV
V
VI
NS
*
**