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RESEARCH ARTICLE

Parameters of dynamic spirometry before and after administration of salbutamol in COPD patients

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Introduction: The aim of this research was to examine the existence of broncho-obstruction of the airways in patients suffering from chronic obstructive pulmonary disease, as well as changes in resistance values in this part of the bronchial tree after inhalation of salbutamol.
Methods: This study was designed as a prospective, interventional clinical trial that included a sample of 147 patients suffering from COPD. Patients were stratified into four groups of thirty patients each based on the severity of airflow limitation (based on the post-bronchodilator FEV1 value), according to the GOLD grade. The test was conducted at the University Clinical Center Sarajevo, Clinic for Lung Diseases and Tuberculosis "Podhrastovi"
Results: The results of our research showed that the average values of FEV1 compared to the predicted values of this parameter in subjects in the GOLD 4 group before the administration of salbutamol were statistically significantly lower than the average values of FEV1 in other subjects of the GOLD group. After the administration of salbutamol, a statistically significant increase in the value of FEV1 was registered in all tested groups. When the response to salbutamol was compared among the GOLD groups, it was assessed that the difference in the percentage increase in predicted FEV1 values after the administration of salbutamol among the tested groups was not statistically significant.
Conclusion: Bronchodilation with salbutamol and additional ipratropium had a significant effect on both mentioned parameters, especially in the COPD group, which speak in favor of the presence of increased peripheral resistance in all groups of patients. A statistically significant bronchodilator response was obtained in GOLD 1 and GOLD 2 groups, i.e. in groups of patients with milder forms of the disease.

Keywords: COPD, salbutamol, patients, GOLD, FEV

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Introduction

Chronic obstructive pulmonary disease (COPD) is a common, preventable and treatable disease, with a worldwide prevalence of 10.1% in people aged 40 years or older [1,2]. In 2019, COPD was the third leading cause of deaths globally, contributing to 3.23 million deaths, with most deaths (80%) occurring in low- and middle-income countries [3,4]

The prevention and control of chronic obstructive pulmonary disease (COPD) was established as a global priority by the UN General Assembly at a high-level meeting in 2011 [5]. COPD causes a substantial and growing burden of morbidity and mortality worldwide and perpetuate poverty, with people disproportionately affected throughout their life course in low-income and middle-income countries (LMICs) [6-8] Access to effective treatment is central management, reflected in targets set out in WHO's Global Action Plan for the prevention and control of COPD and in the UN's 2030 Agenda for Sustainable Development [9]. WHO's Global Action Plan includes a voluntary target of 80% availability of the essential medicines required to treat major symptoms, which means presence of the medicines in 80% of both public and private facilities. Sustainable Development Goal target 3.8 calls for universal health coverage by 2030, with access to safe, effective, quality, and affordable essential medicines for all.

The goal of COPD treatment is to reduce symptoms, prevent disease progression, prevent exacerbations and improve quality of life. The treatment of this disease is complex and includes pharmacological treatment.

Non-pharmacological treatment includes smoking cessation, physical activity and vaccination against influenza and pneumococcus for all GOLD stages, while pulmonary rehabilitation is recommended for stage B-D patients in addition to the above measures. Pharmacological therapy is based on the use of short- and long-acting bronchodilators, inhaled corticosteroids and combination therapy (inhaled corticosteroids and bronchodilators).

Bronchodilators are the basis of symptomatic COPD therapy today. Three basic classes of bronchodilators are used: short-acting and long-acting ß2-adrenergic agonists (salbutamol, salmeterol), anticholinergics (ipratropium, tiotropium), xanthines (theophylline, aminophylline). ß2-adrenergic agonists are recommended in the GOLD guidelines, and these drugs lead to improvement of lung function, reduction of disease symptoms and protection against exertion-induced dyspnea [10]. GOLD 2023 provided further updates, including the discouragement of LABA + ICS as a COPD treatment regimen. Instead, patients on LAMA or LABA monotherapy with persistent exacerbations should now be escalated directly to triple therapy (LABA + LAMA + ICS) if blood eosinophil count is ≥300 cells/μL, or to LABA + LAMA if blood eosinophil count is ≤300 cells/μL [9]. In line with the 2019 GOLD rec-

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ommendations, patients already receiving LAMA + LABA are considered for an escalation to triple therapy (LAMA + LABA + ICS) if the blood eosinophil count is ≥100 cells/μL. For patients already receiving ICS + LABA, GOLD 2023 recommends an escalation to triple therapy if there are further exacerbations. A switch to LAMA + LABA is considered if the patient has major symptoms without exacerbations [11].

Long-acting bronchodilators are the mainstay of maintenance therapy for patients with chronic obstructive pulmonary disease (COPD). However, treatment guidelines provide different recommendations on when to initiate long-acting muscarinic antagonist (LAMA)/long-acting β2-agonist (LABA) dual therapy rather than LAMA or LABA monotherapy. The Global Initiative for Chronic Obstructive Lung Disease (GOLD) strategy report typically recommends a stepwise approach with escalation to LAMA/LABA dual therapy for patients who have persistent dyspnoea or exacerbations on LAMA or LABA monotherapy, although LAMA/LABA dual therapy can also be considered as an initial maintenance therapy option for patients with severe symptoms [10]. In contrast, the American Thoracic Society (ATS) and the UK National Institute for Health and Care Excellence (NICE) guidelines recommend initiating treatment with LAMA/LABA dual therapy for all patients with dyspnoea [12-14]. GOLD 2024 also discusses the potential environmental impact of different inhalers and recommend to use, whenever possible, green inhalers. On the other hand, GOLD 2023 made a practical recommendation to consider initial treatment with triple therapy in E patients with more than 300 Eos/mL [15].

The aim of this research was to examine the existence of bronchial obstruction in patients suffering from chronic obstructive pulmonary disease, as well as the change in the resistance value in this part of the bronchial tree after inhalation of salbutamol.

Methods

This study was designed as a prospective, interventional clinical trial that included a sample of 147 patients with COPD. Patients were stratified into four groups of thirty patients each based on the severity of airflow limitation (based on the post-bronchodilator FEV1 value), according to GOLD grades.

The test was conducted at the University Clinical Center Sarajevo, Clinic for Lung Diseases and Tuberculosis "Podhrastovi". All respiratory functional explorations were performed during daytime between 09-10 a.m. All patients underwent spirometry with measurement of airway resistance using the IOS method before and 15 minutes after inhalation of 200 micrograms of salbutamol. On the day of the examination, the patients did not take the morning dose of regular chronic bronchodilator therapy.

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Inclusion criteria

Patients with a diagnosis of COPD (regardless of the degree of obstruction) who are treated on an outpatient basis or in a hospital due to exacerbation of COPD symptoms.

Exclusion criteria

Patients suffering from other obstructive and non-obstructive lung diseases, patients with cardiac diseases and consequent repercussions at the level of the small airways, and patients with COPD who have diseases of other organ systems.

All patients included in the study underwent spirometry with measurement of airway resistance using the IOS method.

Jaeger Master Screen IOS, manufactured by CareFusion, was used for spirometry and pulse oscillometry. The apparatus was calibrated every day using a pump with a capacity of 3 l for volume calibration and a reference resistance (0.2 kPa/l/s) for pressure calibration.

The values of the following parameters were of interest: forced expiratory volume in the first second (FEV1), forced vital capacity (FVC), vital capacity (VC), resistance at 5Hz (R5), resistance at 20 Hz (R20), reactance at 5 Hz (X5) and peripheral resistance (R5-R20) before and after the bronchodilation test.

Ethical approval

The study approval was obtained from the Ethics Committee of the University Clinical Center Sarajevo, Sarajevo, Bosnia and Herzegovina

Statistical analysis

The results were processed using the computer program SPSS (SPSS-Statistical Package for Social Sciences) version 16.0. To test the significance of the difference in the deviation from the normal distribution, the Kolmogorov-Smirnov test and the Shapiro-Wilk test were used. For variables that followed a normal distribution, the data were presented as mean value (X) and standard deviation (SD), or as median and interquartile range for variables that did not follow a normal distribution. ANOVA test was used to test the significance of the difference in variables between groups of patients with different degrees of COPD, after which a posthoc test (Tuckey test) was applied to test the significance of the difference in variables between two individual groups of patients with different degrees of COPD. To test the significance of the difference in variables measured in two time intervals, the student t-test for dependent samples was applied. The student t-test for independent samples was also used, and parametric tests were applied to

examine the difference in variables. A value of p<0.05 was taken as statistically significant.

Results

In the GOLD 4 group, men were represented by 67.7%, in GOLD 3 by 59.5%, GOLD 2 by 45.2% and GOLD 1 by 48.4%, but no significant difference in gender representation was observed among the observed groups (X2=4.4; NS) (Table 1).

The average values of registered FEV1 (expressed in liters) in subjects in the GOLD 4 group before the administration of salbutamol were 0.77±0.6 L and were statistically significantly lower compared to the average values of FEV1 in subjects in GOLD 3 (1, 0±0.3 L; p=0.025), GOLD 2 (1.4±0.3 L; p<0.001), GOLD 1 (2.1±0.6 L, p<0.001) (Figure 1).

The average values of FEV1 expressed in liters in subjects in the GOLD 4 group after administration of salbutamol were 0.85±0.24 L and were statistically significantly lower compared to the average values of FEV1 in subjects in GOLD 3 (1.16±0 .4 L; p=0.028), GOLD 2 (1.57±0.42 L; p<0.001) and GOLD 1 group (2.45±0.7 L, p<0.001) (Figure 2).

The median increase in registered FEV1 values expressed as a percentage after the administration of salbutamol in the GOLD 4 group was 13.5 (2.0-22.8)%, in the GOLD 3 group 9.6 (2.2-19.5) % , in GOLD 2 group 10.3 (2.6-23.2) % and in GOLD 1 group 16.1 (10.5-22.7) %, but the difference in the increase in registered FEV1 values after the administration of salbutamol among the tested groups was not statistically significant (Figure 3).

In subjects in the GOLD 4 group, a drop in FEV1/FVC values was observed after the administration of salbutamol compared to the basal values by 1.9% (42.3±8.7 vs. 41.5±9.1%), however, the the decline is not statistically significant (Figure 4).

Table 1. Distribution of respondents by gender within GOLD groups

			Group				
			GOLD1	GOLD2	GOLD3	GOLD4	p-value
Gender	Male	N	15	19	25	21	
		%	48.4%	45.2%	59.5%	67.7%	X^2=4.4 NS
	Female	N	16	23	17	10	
		%	51.6%	54.8%	40.5%	32.3%	

Data are presented as absolute and percentage values. Parameters of dynamic spirometry at baseline, before the administration of salbutamol.

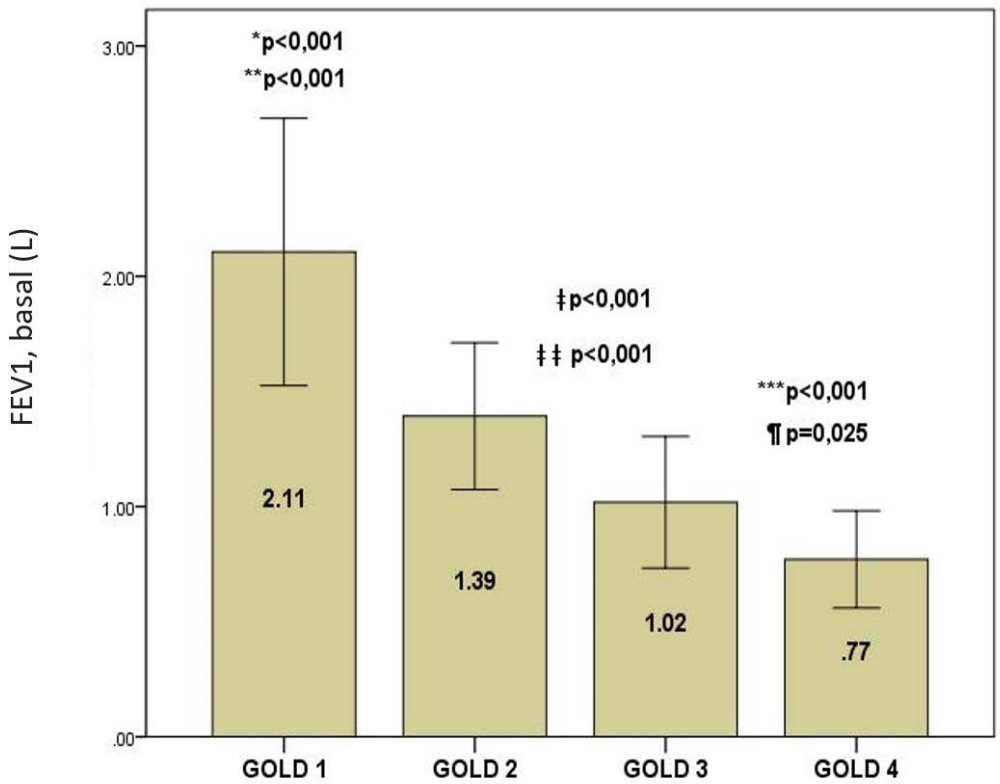

Fig. 1. Registered values of FEV1 expressed in liters in subjects classified according to GOLD criteria, basally before the administration of salbutamol. * significance of the difference between respondents in GOLD 1 compared to GOLD 2 group; ** significance of the difference between subjects in GOLD 1 compared to GOLD 3 group; *** significance of the difference between subjects in GOLD 1 compared to GOLD 4 group; ‡ significance of the difference between subjects in GOLD 2 compared to GOLD 3 group; ‡ ‡ significance of the difference between subjects in GOLD 2 compared to GOLD 4 group; ¶ significance of the difference between subjects in GOLD 3 compared to GOLD 4 group; Data are presented as mean value‡SD. Parameters of dynamic spirometry after administration of salbutamol.

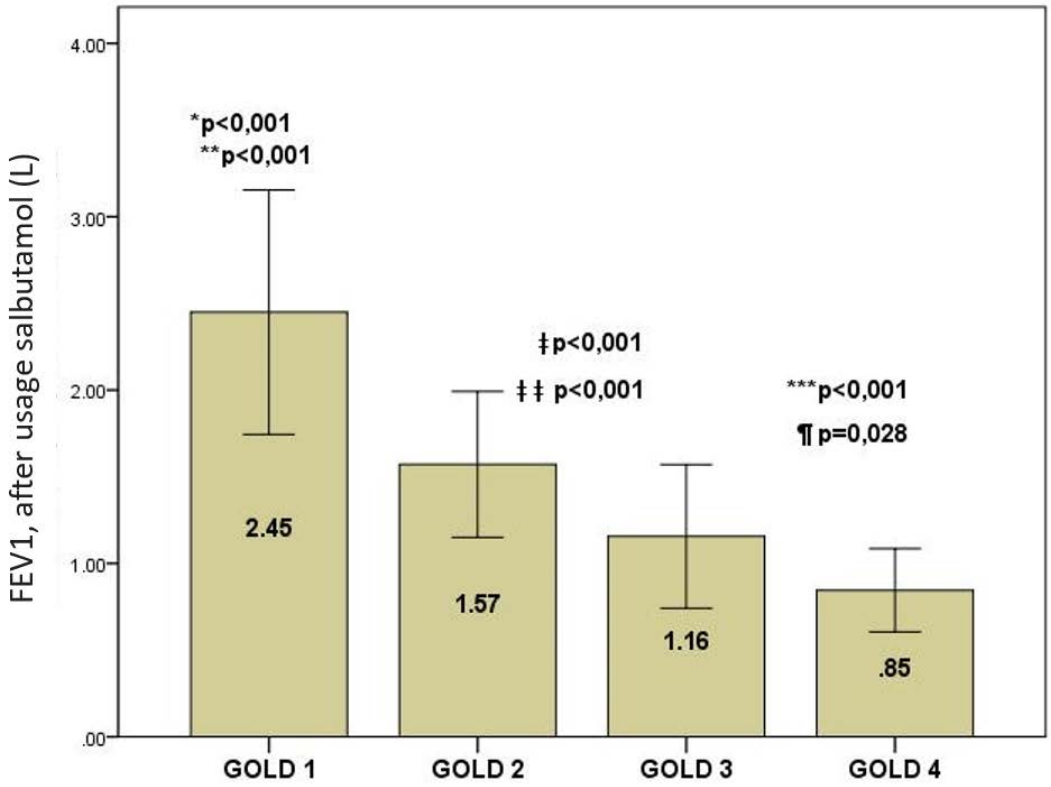

Fig. 2. Registered FEV1 values expressed in liters in subjects classified according to GOLD criteria, after administration of salbutamol. * significance of the difference between respondents in GOLD 1 compared to GOLD 2 group; ** significance of the difference between subjects in GOLD 1 compared to GOLD 3 group; *** significance of the difference between subjects in GOLD 1 compared to GOLD 4 group; ‡ significance of the difference between subjects in GOLD 2 compared to GOLD 3 group; ‡ ‡ significance of the difference between subjects in GOLD 2 compared to GOLD 4 group; ¶ significance of the difference between subjects in GOLD 3 compared to GOLD 4 group. Data are presented as mean value‡SD.

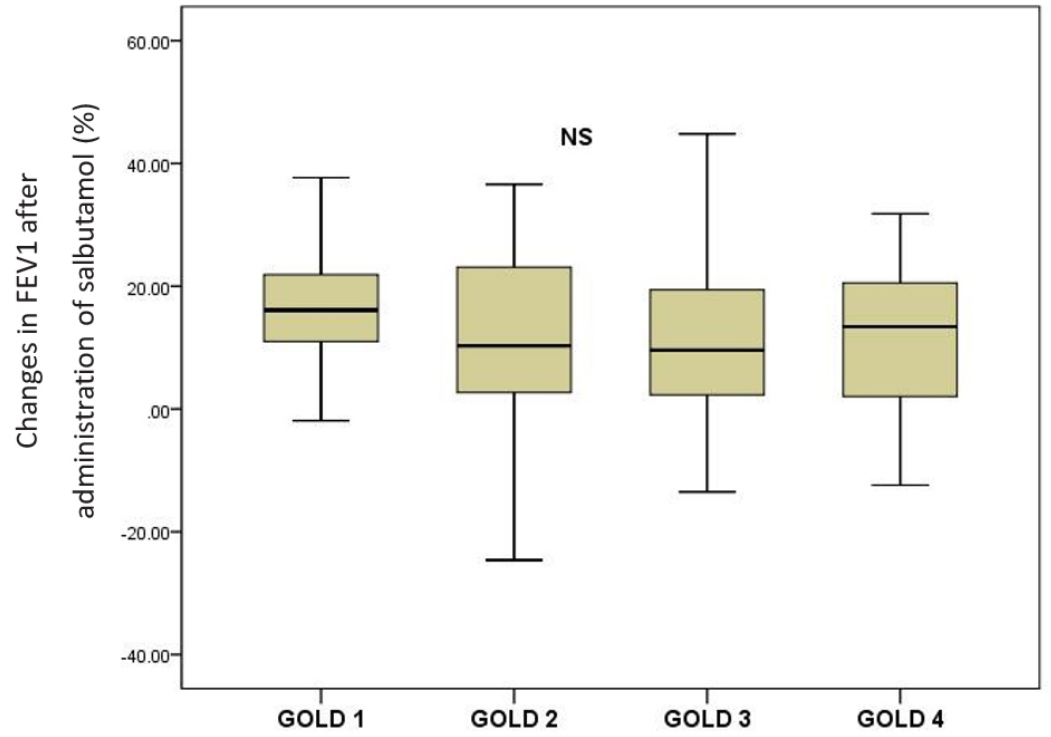

Fig. 3. Increase in registered FEV1 values in subjects classified according to GOLD criteria after administration of salbutamol. * significance of the difference between respondents in GOLD 1 compared to GOLD 2 group; ** significance of the difference between subjects in GOLD 1 compared to GOLD 3 group; *** significance of the difference between subjects in GOLD 1 compared to GOLD 4 group; ‡ significance of the difference between subjects in GOLD 2 compared to GOLD 3 group; ‡ ‡ significance of the difference between subjects in GOLD 2 compared to GOLD 4 group; ¶ significance of the difference between subjects in GOLD 3 compared to GOLD 4 group. Data are presented as median and interquartile range.

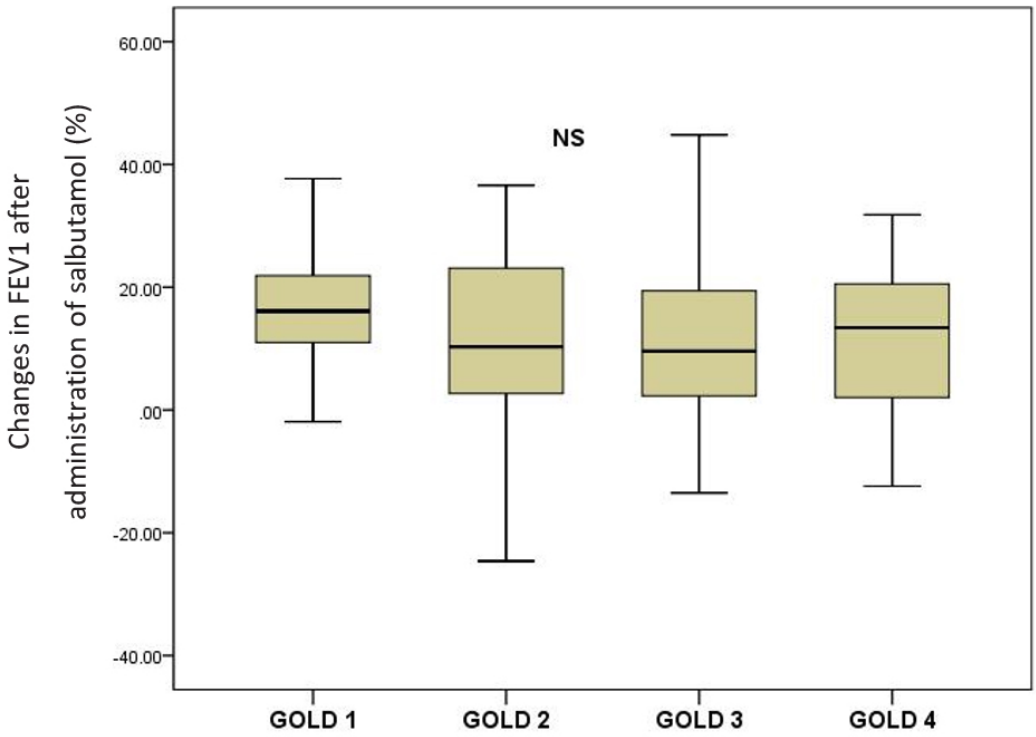

Fig. 3. Increase in registered FEV1 values in subjects classified according to GOLD criteria after administration of salbutamol. * significance of the difference between respondents in GOLD 1 compared to GOLD 2 group; ** significance of the difference between subjects in GOLD 1 compared to GOLD 3 group; *** significance of the difference between subjects in GOLD 1 compared to GOLD 4 group; ‡ significance of the difference between subjects in GOLD 2 compared to GOLD 3 group; ‡ ‡ significance of the difference between subjects in GOLD 2 compared to GOLD 4 group; ¶ significance of the difference between subjects in GOLD 3 compared to GOLD 4 group. Data are presented as median and interquartile range.

In the GOLD 1, GOLD 2 and GOLD 3 group of subjects, an increase in the FEV1/FVC value was observed after the administration of salbutamol, compared to the basal values by 7.5%, 3.8% and 1.6%, but the said increase was statistically significant only in the GOLD 1 group (p<0.001) (Figure 4).

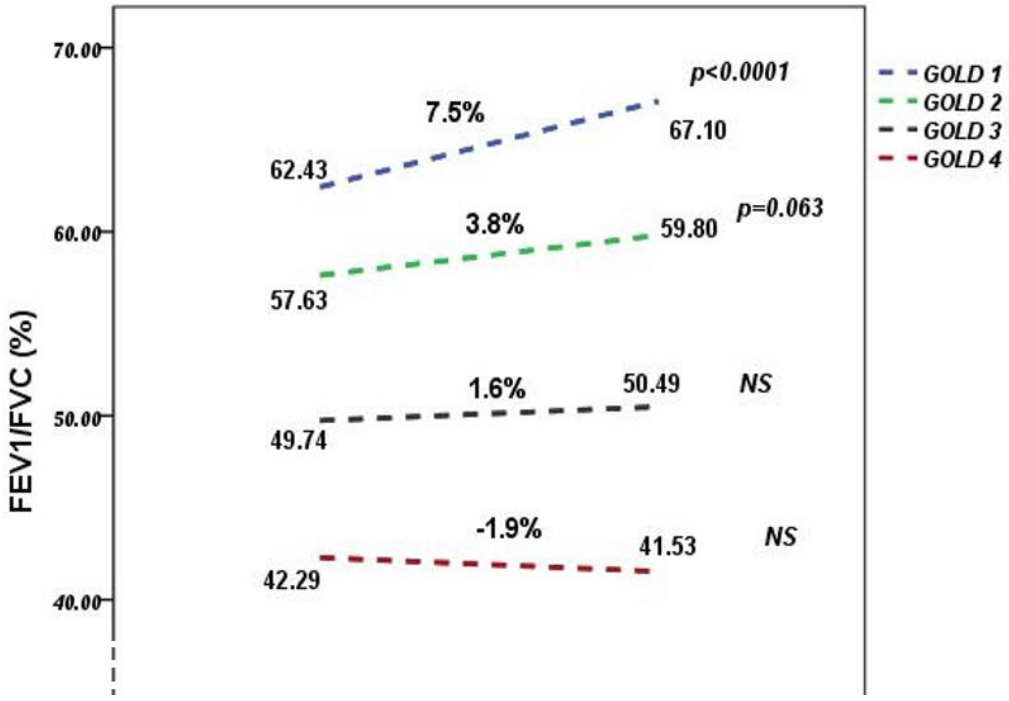

Fig. 4. Changes in the basal values of the FEV1/FVC ratio in relation to those after the administration of salbutamol in subjects classified according to GOLD groups. Data are presented as an average value and percentage changes in the average value. Airway resistance before and after salbutamol administration.

The median value of airway resistance measured at 5 Hz (R5) in the GOLD 4 group before the administration of salbutamol was 0.7 (0.6-0.98) kPa/L/s and was not statistically significantly different from the median value R5 before therapy in the GOLD 3, GOLD 2 and GOLD 1 groups (Table 2). Also, after the administration of salbutamol, no statistically significant difference was found in the R5 values among the tested groups (Table 2).

The median value of R5 after the administration of salbutamol compared to the median R5 before the administration of salbutamol in the GOLD 4 group dropped by 5.5% and in the GOLD 3 group by 6.1%, but the difference was not statistically significant (Figure 5). In the GOLD 1 group, the median value of R5 after the administration of salbutamol compared to the median R5 before the administration of salbutamol decreased by 22.2%, which was a statistically significant decrease (p=0.015) (Figure 5). In the GOLD 2 group, the median R5 value after the administration of salbutamol compared to the median R5 before the administration of salbutamol decreased by 21.9%, which was a statistically significant decrease (p=0.003) (Figure 5).

No statistically significant difference was observed in predicted R5 values before salbutamol administration between GOLD 4 (208.8 (157.5-275.5)%), GOLD 3 (185.8 (152.9-228.7)%) , GOLD 2 (172.7 (130.2-221.3)%) and GOLD 1 groups (181.3 (124.5-218.3)%) (Figure 6).

The change in predicted R5 values after salbutamol administration was significantly higher in GOLD 1 (-17.7 (-36.2- -5.6)%) and in GOLD2 group (-21.3 (-39.0- -0.53)%) compared to GOLD 3 (-6.8 (-21.9- -8.3)%; p<0.05) and compared to GOLD 4 group (-6.7 (-17.5- - 25.2)%; p<0.05) (Figure 7). However, no significant difference was observed in changes in predicted R5 values after the administration of salbutamol between the GOLD 1 and GOLD 2 groups, nor between the GOLD 3 and GOLD 4 groups (Figure 7).

The median value of airway resistance measured at 20 Hz (R20) in the GOLD 4 group before the administration of salbutamol was 0.33(0.25-0.4) kPa/L/s and was not statistically significantly different from the median value of R20 before therapy in the GOLD 3, GOLD 2 and GOLD 1 groups (Table 3). Also, after the administration of salbutamol, no significant difference in R20 values was found between the tested groups (Table 3).

Table 2. Airway resistances measured at 5 Hz (R5) in subjects classified according to GOLD groups basally before and after salbutamol administration

	GOLD				
	1	2	3	4	P
R5 basal (kPa/L/s)	0.63 (0.46-0.79)	0.64 (0.44-0.8)	0.66 (0.5-0.8)	0. 7 (0.6-0.98)	NS
R5 after salbutamol-a (kPa/L/s)	0.5 (0.36-0.57)	0.5 (0.37-0.6)	0.62 (0.5-0.76)	0.63 (0.54-0.82)	NS

Data are presented as median and interquartile range.

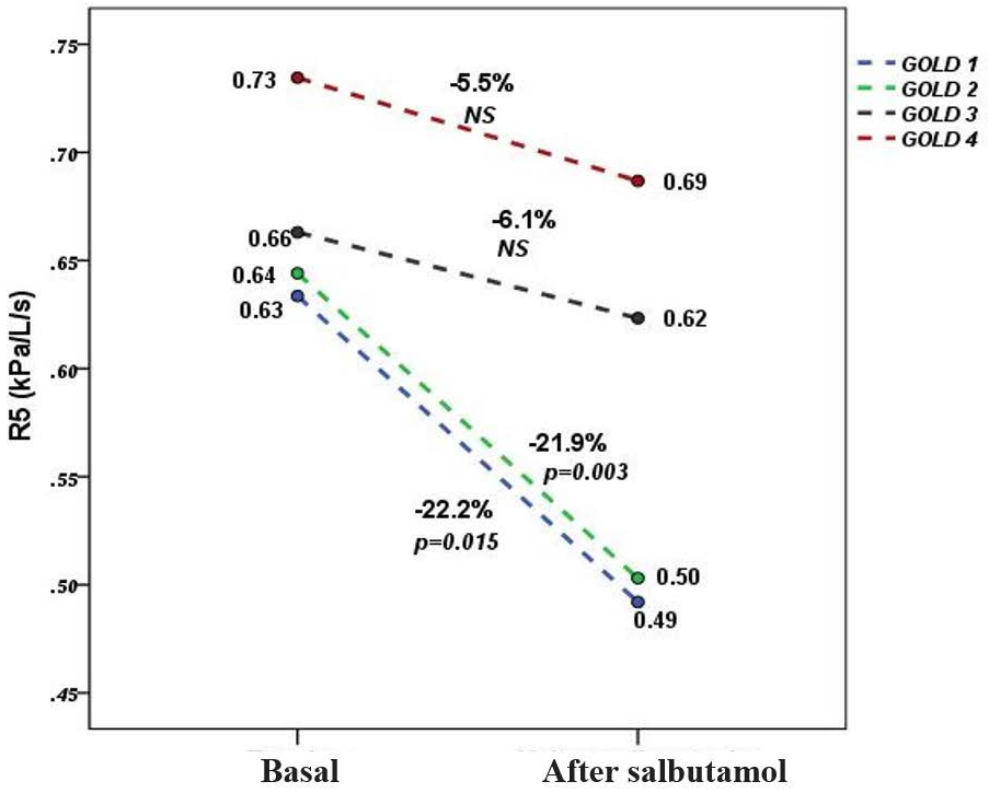

Fig. 5. Changes in airway resistance values measured at 5 Hz (R5) in subjects classified according to GOLD groups basally before and after salbutamol administration. Data are presented as an average value and percentage changes in the average value.

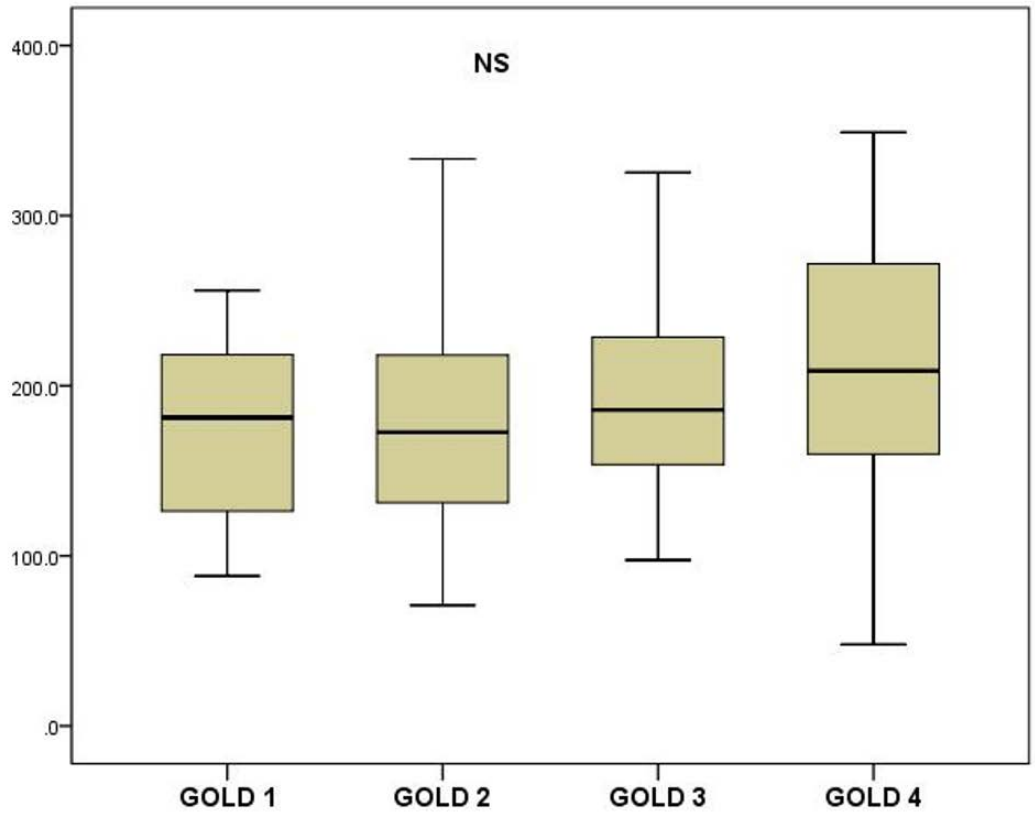

Fig. 6. Deviation from the predicted values of resistance in the airways measured at 5 Hz (R5) in subjects classified according to GOLD groups basally before the administration of salbutamol. NS-no statistically significant difference between groups. Data are presented as median and interquartile range.

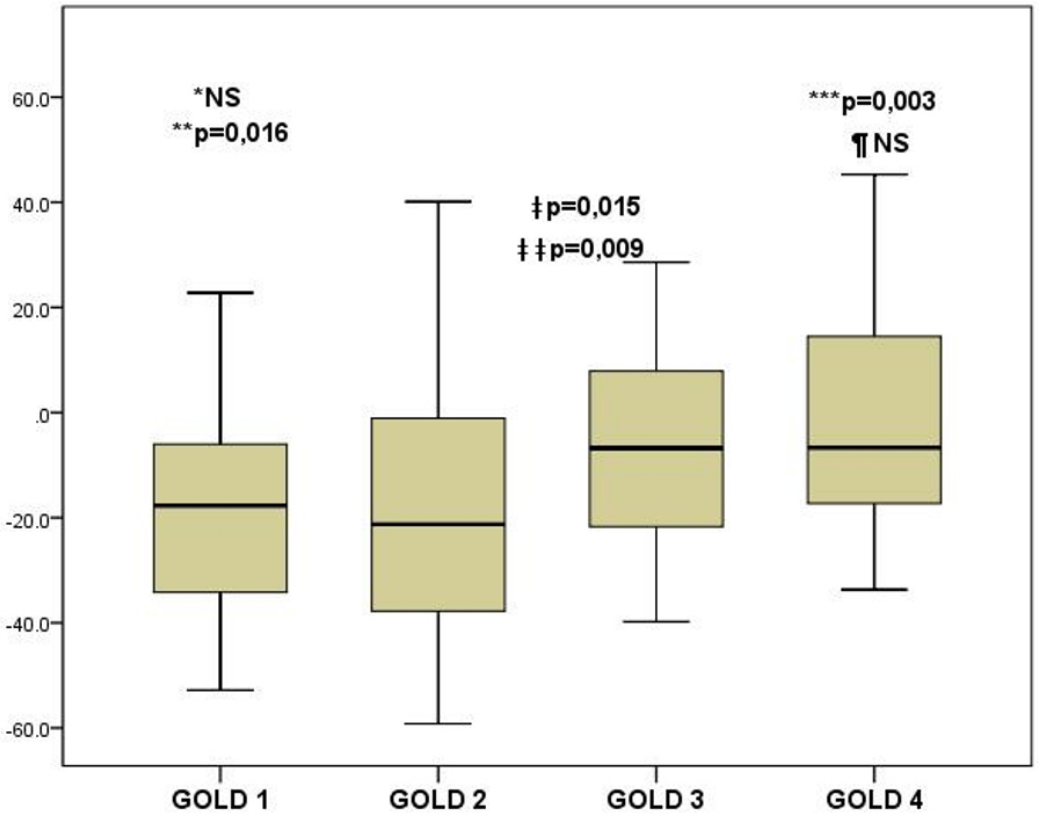

Fig. 7. Percentage change in airway resistance measured at 5 Hz (R5) in subjects classified according to GOLD groups after administration of salbutamol. * significance of the difference between respondents in GOLD 1 compared to GOLD 2 group; ** significance of the difference between subjects in GOLD 1 compared to GOLD 3 group; *** significance of the difference between subjects in GOLD 1 compared to GOLD 4 group; ‡ significance of the difference between subjects in GOLD 2 compared to GOLD 3 group; ‡ ‡ significance of the difference between subjects in GOLD 2 compared to GOLD 4 group; ¶ significance of the difference between subjects in GOLD 3 compared to GOLD 4 group. Data are presented as median and interquartile range.

Table 3. Airway resistance measured at 20 Hz (R20) in subjects classified according to GOLD groups basally before and after administration of salbutamol

	GOLD				
	1	2	3	4	P
R20 basal (kPa/L/s)	0.38 (0.3-0.49)	0.38 (0.26-0.43)	0.32 (0.28-0.37)	0. 33 (0.25-0.4)	NS
R20 after salbutamol (kPa/L/s)	0.35 (0.27-0.4)	0.32 (0.27-0.39)	0.33 (0.27-0.38)	0.33 (0.28-0.38)	NS

Data are presented as median and interquartile range

The median value of R20 after the administration of salbutamol compared to the median R20 before the administration of salbutamol in the GOLD 4 group decreased by 2.9%, in the GOLD 2 group by 8.1% and in the GOLD 1 group by 12.2%, but the difference before and after the administration of salbutamol is not statistically significant (Figure 8). In the GOLD 3 group, the median value of R20 after the administration of salbutamol compared to the median R20 before the administration of salbutamol increased by 3.1%, but the increase was not statistically significant (Figure 8).

The change in percentage values of R20 after the administration of salbutamol was significantly higher in the GOLD 1 (-10.9 (-20.7- 2.5)%) and in the GOLD2 group (-9.4 (-19.3- 2.2)%)) compared to GOLD 3 (-0.6 (-13.3 - -18.3)%; p<0.05) and compared to GOLD 4 group (2.0 (-12.8- 39.9) %; p<0.05) (Figure 9).

The median value of the reactance measured at 5 Hz (X5) in the GOLD 3 group before the administration of salbutamol was statistically significantly higher compared to the median reactance in GOLD 2 (-0.29 (-0.39- -0.2); p <0.001) and GOLD 1 group (-0.23 (-0.4- -0.12); p<0.001) (Table 4). The median value of the reactance measured at 5 Hz (X5) in the GOLD 4 group after the administration of salbutamol was -0.5 (-0.6- -0.3) kPa/L/s and was statistically significantly higher compared to the median reactances in GOLD 2 (-0.2 (-0.3- -0.1); p<0.001) and GOLD 1 group (-0.2 (-0.25- -0.1); p<0.001) (Table 4). The median value of the reactance measured at 5 Hz (X5) in the GOLD 3 group after the administration of salbutamol was also statistically significantly higher compared to the median reactance in the GOLD 2 and GOLD 1 groups (p<0.001) (Table 4). However, no significant difference was observed in the median reactance measured at 5 Hz (X5) between GOLD 4 and GOLD 3 groups before or after salbutamol therapy.

The median predicted reactance value at 5 Hz (X5%) before salbutamol administration was statistically sig-

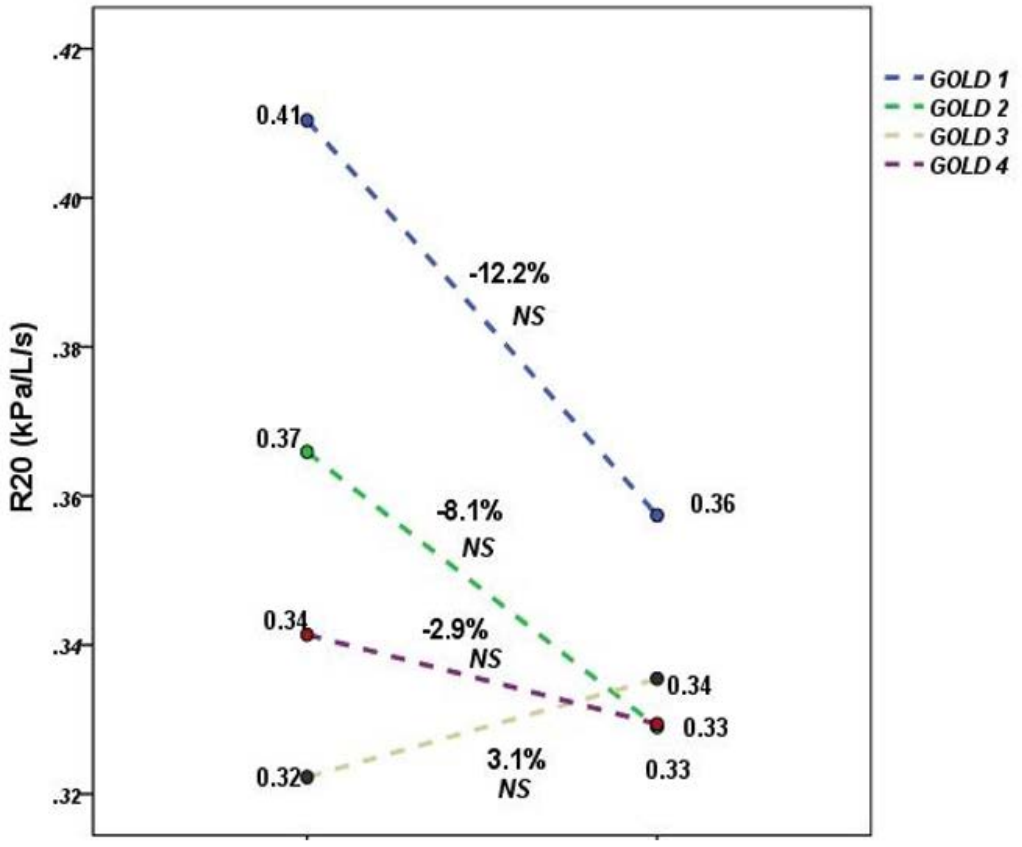

Fig. 8. Changes in the percentage values of resistance in the airways measured at 20 Hz (R20) in subjects classified according to GOLD groups basally before and after the administration of salbutamol. Data are presented as average value and percentage changes of average values.

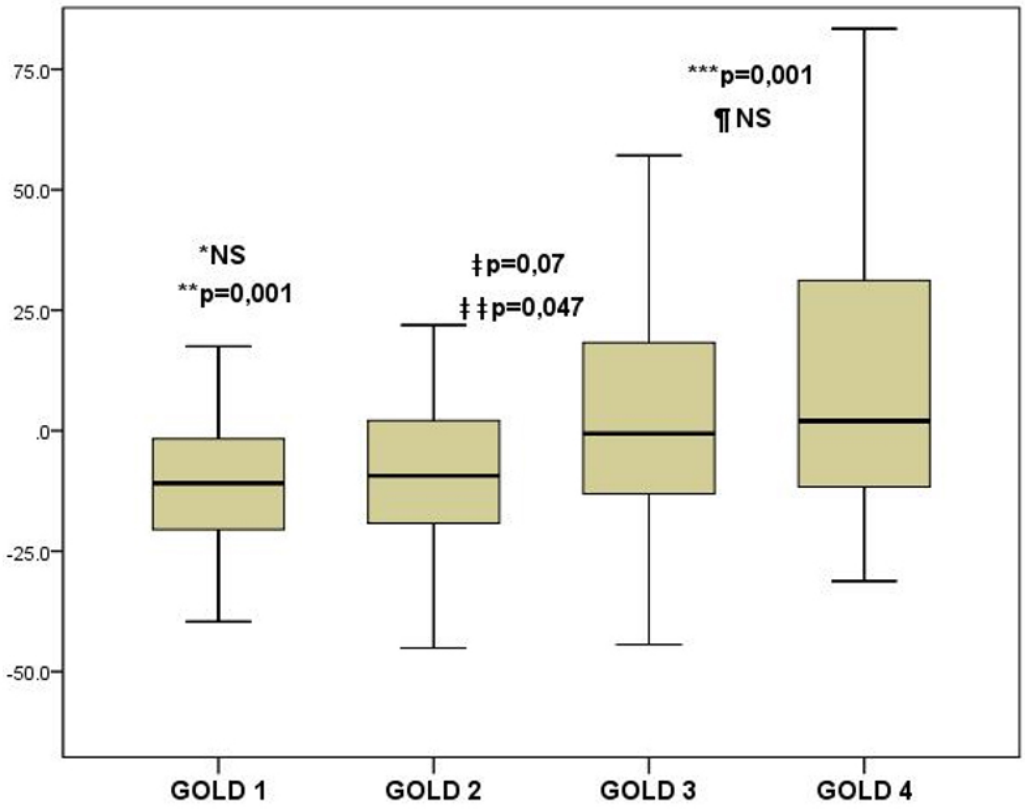

Fig. 9. Percentage changes in airway resistance measured at 20 Hz (R5) in subjects classified according to GOLD groups after administration of salbutamol. * the significance of the difference between subjects in GOLD 1 compared to GOLD 2 group; ** significance of the difference between subjects in the GOLD 1 group compared to the GOLD 3 group; *** significance of the difference between subjects in the GOLD 1 group compared to the GOLD 4 group; ‡ significance of the difference between subjects in the GOLD 2 group compared to the GOLD 3 group; ‡ ‡ significance of the difference between subjects in the GOLD 2 group compared to the GOLD 4 group; ¶ significance of the difference between respondents in the GOLD 3 group compared to the GOLD 4 group. Data are presented as median and interquartile range.

Table 4. Reactance measured at 5 Hz (X5) in subjects classified according to GOLD groups basally before and after administration of salbutamol

	GOLD				
	1	2	3	4	P
X5 basal (kPa/L/s)	-0.23 (-0.4- -0.12)	-0.29 (-0.39- -0.2)	-0.4 (-0.55- -0.25)	-0.4 (-0.6- -0.34)	<0.001
X5 after salbutamol (kPa/L/s)	-0.2 (-0.25- -0.1)	-0.2 (-0.3- -0.1)	-0.37 (-0.5- -0.2)	-0.5 (-0.6- -0.3)	<0.001

Data are presented as median and interquartile range

nificantly higher in the GOLD 4 group (1589.0 (763.2-3370.6) %) compared to GOLD 1 (388.5 (128.3-858.0) %; p<0.001) and compared to the GOLD 2 group (605.4 (323.4 -1122.0)%; p=0.001) (Figure 10). However, no statistically significant difference was observed in the basal values of X5% between the GOLD 4 and GOLD 3 groups, nor between the GOLD 1 and GOLD 2 groups of subjects (Figure 10).

The median change in the predicted reactance value at 5 Hz (X5%) after the administration of salbutamol was statistically significantly lower in the GOLD 4 group (-7.2 (-26.2 – 32.8) %) compared to GOLD 1 (- 25.2 (-45.0- -5.8)%; p=0.04) and compared to the GOLD 2 group (-36.5 (-56.4 - -12.0) %; p=0.006)(Chart 17). However, no statistically significant difference was observed in the change of X5 after the administration of salbutamol between the GOLD 4 and GOLD 3 groups, nor between the GOLD 1 and GOLD 2 groups of subjects (Figure 11).

Discussions

The aim of this research was to examine the existence of bronchial obstruction in patients suffering from chronic obstructive pulmonary disease, as well as the change in the resistance value in this part of the bronchial tree after inhalation of salbutamol.

The results of our research showed that the average values of FEV1 compared to the predicted values of this parameter in subjects in the GOLD 4 group before the administration of salbutamol were statistically significantly lower than the average values of FEV1 in subjects in the other GOLD groups. After the administration of salbutamol, a statistically significant increase in the value of FEV1 was registered in all tested groups. When the response to salbutamol was compared among the GOLD groups, it was observed that the difference in the percentage increase in predicted FEV1 values after the administration of salbutamol among the tested groups was not statistically significant.

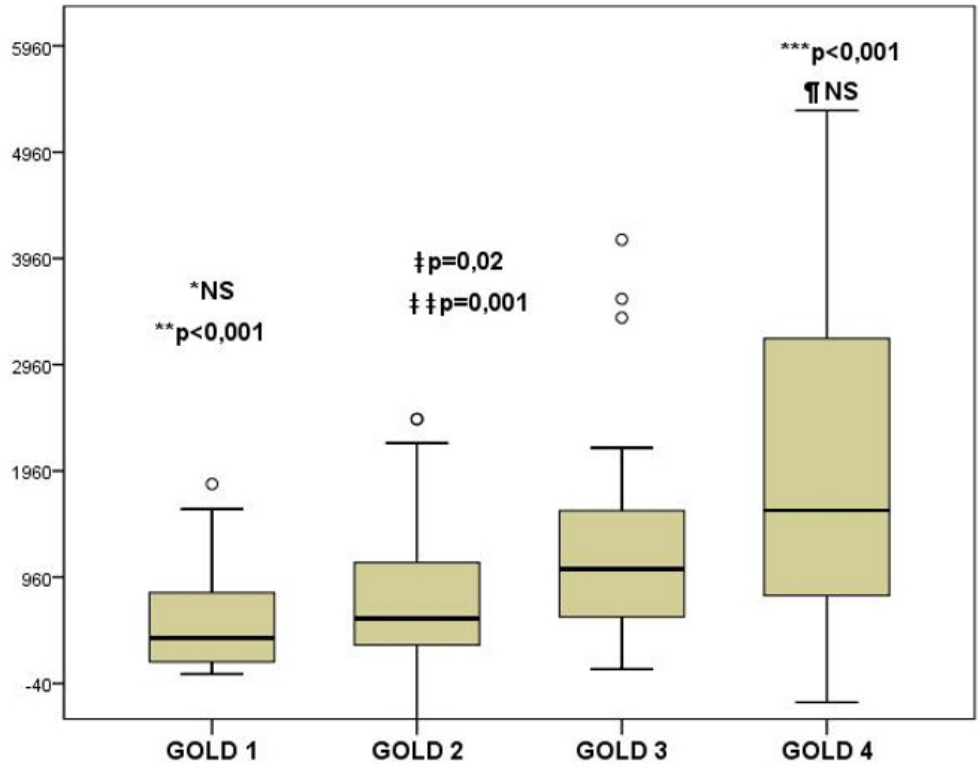

Fig. 10. Values of reactance measured at 5 Hz (X5) in subjects classified according to GOLD groups basally during salbutamol administration. * significance of the difference between respondents in GOLD 1 compared to GOLD 2 group; ** significance of the difference between subjects in GOLD 1 compared to GOLD 3 group; *** significance of the difference between subjects in GOLD 1 compared to GOLD 4 group; ‡ significance of the difference between subjects in GOLD 2 compared to GOLD 3 group; ‡ ‡ significance of the difference between subjects in GOLD 2 compared to GOLD 4 group; ¶ significance of the difference between subjects in GOLD 3 compared to GOLD 4 group. Data are presented as median and interquartile range.

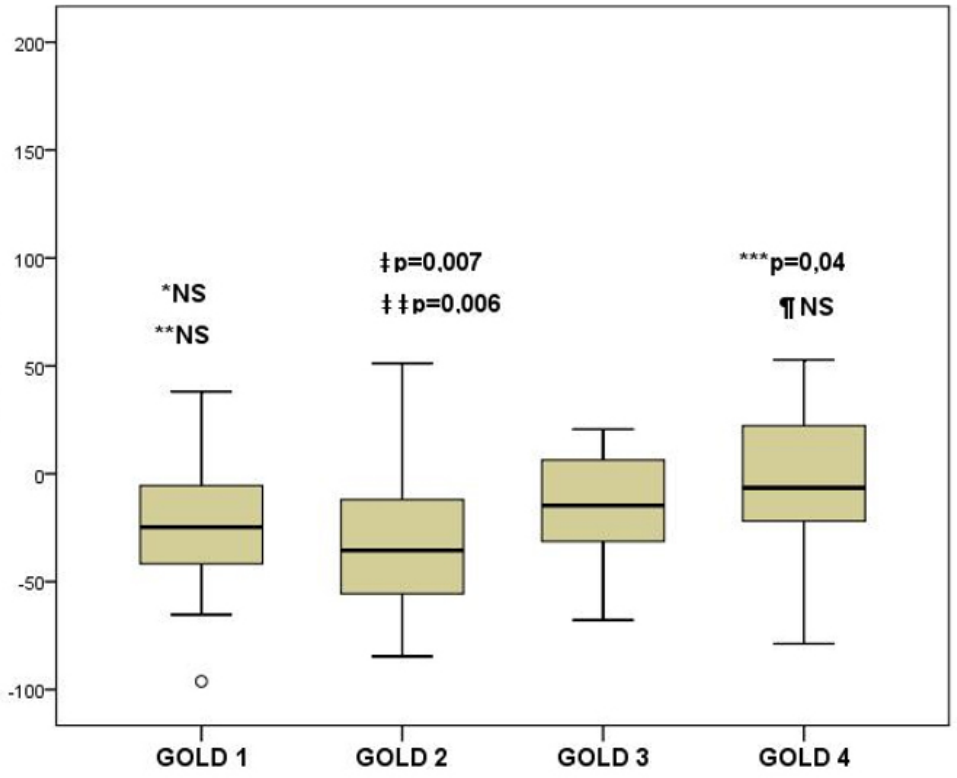

Fig. 11. Percentage change in predicted reactance values measured at 5 Hz (X5) after administration of salbutamol in subjects classified according to GOLD groups. * significance of the difference between respondents in GOLD 1 compared to GOLD 2 group; ** significance of the difference between subjects in GOLD 1 compared to GOLD 3 group; *** significance of the difference between subjects in GOLD 1 compared to GOLD 4 group; ‡ significance of the difference between subjects in GOLD 2 compared to GOLD 3 group; ‡ ‡ significance of the difference between subjects in GOLD 2 compared to GOLD 4 group; ¶ significance of the difference between subjects in GOLD 3 compared to GOLD 4 group. Data are presented as median and interquartile range.

Although there is no standardized definition of a positive bronchodilator response in COPD, the available definitions are based on the absolute or percentage improvement of FEV1, FVC or both parameters together in relation to the achieved pre-bronchodilator values [16,17].

According to the ATS/ERS guidelines, the range of minimal clinically important changes in FEV1 compared to the pre-bronchodilator value (MCID-minimal clinically important difference) is 100-140 mL, i.e. a percentage improvement of 5% - 10% also compared to the pre-bronchodilator value [16]. The obtained results are in accordance with these guidelines because a positive bronchodilator response was noted in all four GOLD groups.

Mahler et al [18] investigated the acute response to a bronchodilator in their randomized, double-blind, 12-week study involving 411 patients with COPD. This study assessed the efficacy of salmeterol 42 micrograms twice daily compared with ipratropium 35 micrograms four times daily and placebo. The results of this study showed a positive bronchodilator response in 65% of patients according to ATS guidelines.

A study by Schermer et al [19] involving 2210 patients divided into four groups using the GOLD spirometric classification examined the bronchodilator response to 400 micrograms of salbutamol. According to the stages of the disease, ΔFEV1 decreased as the stage of the disease was more severe, while the value of ΔFVC increased from GOLD 1 to GOLD 4 stages.

In another study, the results of Calverley et al [20] pointed to the fact that the bronchodilator response in patients with moderate and severe COPD is variable. The study was conducted on a sample of 660 patients. During the first visit after the spirometry, the patients were prescribed 400 micrograms of salbutamol and the test was repeated after 30 minutes. After that, all patients received 80 micrograms of ipratropium and a new spirometry was performed after a break of 30 minutes. At the second visit (after 4 weeks), the order of administration of bronchodilators was changed. At the third visit, again after four weeks, the patients were immediately given a dose of 80 micrograms of ipratropium 30 minutes after the first spirometry after salbutamol and after 30 minutes a second spirometry was performed. Patients were then randomized into two groups: patients in the first group continued to use 500 micrograms of fluticasone twice a day, and patients in the second group received a placebo. In the following period, spirometric tests were performed for both groups of patients every three months for a total of 3 years. What was observed in this research is that already after the first visit, a significant increase in FEV1 and FVC was recorded. Additional bronchodilation with ipratropium led to a further improvement in the values of both parameters. The pre-bronchodilator FEV1 value expressed in absolute values had no influence on the change in FEV1 expressed in absolute values or percentages. Additional bronchodilation with either salbutamol or ipatropium led to an improvement in median FEV1 and thus shifted patients who had a negative bronchodilator response to one of these bronchodilators into the category of those with a positive bronchodilator response.

In all patients included in this study, the post-bronchodilator value of the FEV1/FVC parameter was less than 0.7. Analyzing the average values of FEV1/FVC in this study, it was observed that this parameter after administration of salbutamol was statistically significantly lower in patients from the GOLD 4 group compared to the values of this parameter in the other GOLD groups. A statistically significant increase in FEV1/FVC values was also registered in GOLD 1 group patients.

The decrease in the FEV1/FVC value in the GOLD 4 group could be explained by the increase in the FVC value, which was found in the aforementioned Calverley study. The increase in FVC is associated with the degree of hyperinflation of the lung parenchyma, and the loss of the elastic properties of the lungs. These pathological changes also reduce the diameter of the airways, and lower the flow of air through them.

An increase in the total resistance of the respiratory system (R5) was observed in all patients before inhalation of salbutamol. The mean values of R5 obtained in this study and compared among patient groups stratified according to the GOLD guidelines before the prescription of bronchodilators did not differ significantly. No significant difference in R5 values was observed between groups even after these patients received 200 micrograms of salbutamol [21].

In the GOLD 1 and GOLD 2 groups, there was a statistically significant decrease in the value of R5 to the prescribed bronchodilator, while in the GOLD 3 and GOLD 4 groups there was no statistically significant change in this value.

Swensson et al [21] studied the effect of salbutamol and ipratropium on obstructive disorder in patients with COPD using the impulse oscillometry method. The results of this study showed that patients with COPD included in this research had significantly increased prebronchodilator values R5, R20 and R5-R20 compared to healthy smokers.

Our results are in accordance with their results, where bronchodilation with salbutamol and additional ipratropium had a significant effect on both parameters, especially in the COPD group, which speak in favor of the presence of increased peripheral resistance in all patient groups. A statistically significant bronchodilator response was obtained in GOLD 1 and GOLD 2 groups, i.e. in groups of patients with milder forms of the disease.

In this study, it was observed that resistances in the airways measured at frequencies of 20 Hz were not increased by bronchodilators, nor did the administration of salbutalmol lead to a statistically significant change in their value. Also, after the administration of salbutamol, no significant difference in R20 values was found between the tested groups.

Analyzing the results of resistance measurement using the IOS method at 20 Hz in this study, the conclusion is that the results of this study are in accordance with the results of the study by Kanda et al [22], which showed an increase in the resistance of R5 and R5-20, but not R20, in patients with COPD. while R20 values were statistically significantly higher in asthmatics compared to the other two groups of patients.

In the last 15 years, several studies have been published that evaluated the possibilities of pulse oscillometry for diagnosing obstructive pulmonary diseases. The mean value of the reactance measured at 5 Hz (X5) in the GOLD 4 group after the administration of salbutamol was statistically significantly higher compared to the mean value of the reactance in the GOLD 2 and GOLD 1 groups. However, no significant difference was observed in the mean value of reactance measured at 5 Hz (X5) between GOLD 4 and GOLD 3 groups before or after salbutamol therapy.

Although the results of this study indicate an improvement in FEV1 in all patients included in this research after inhalation of salbutamol, it was shown that this drug has no effect on the change in reactance values and it is assumed that lung compliance is also reduced in GOLD 3 and GOLD 4 group patients.

Also in the previously mentioned study by Kanda et al [20], in addition to a significant increase in R5, a significantly more negative X5 was observed in patients with COPD compared to healthy controls, especially in patients with a more severe stage of the disease. The observed changes were significantly correlated with the severity of the disease. The mean value of X5 measured during expiration in normal breathing became significantly more negative than in inspiration in patients with GOLD 3 and GOLD 4 stages, while in asthmatics and healthy smokers there was no difference in X5 in the two breathing phases.

These results suggested that with the help of IOS, changes in the mechanical properties of the airways that cannot be detected by spirometry alone can be detected. Also, large changes in X5 values between expiration and inspiration could be explained by airway collapse during expiration in severe stages of chronic obstructive pulmonary disease. Numerically expressed reactance always has a negative sign, and more negative values of this parameter indicate reduced lung compliance. The overall lung compliance in patients suffering from COPD is reduced probably due to broncho-obstruction, although in the presence of emphysema the compliance increases due to the destruction of the lung parenchyma.

Observed changes in reactance parameters in this study in patients with more severe stages of COPD speak in favor of reduced compliance. For a clearer idea of the pathophysiological basis of these observations, it would be advisable to perform plethysmography and HRCT of the lungs.

Conclusion

The results of our research showed that the average values of FEV1 compared to the predicted values of this parameter in subjects in the GOLD 4 group before the administration of salbutamol were statistically significantly lower than the average values of FEV1 in subjects in the other GOLD groups. After the administration of salbutamol, a statistically significant increase in the value of FEV1 was registered in all tested groups. When the response to salbutamol was compared among the GOLD groups, it was observed that the difference in the percentage increase in predicted FEV1 values after the administration of salbutamol among the tested groups was not statistically significant. The evidence of increased small airways resistance was found in all GOLD groups except GOLD 1. Patients in GOLD 4 group had significantly higher small airways resistance as compared to patients in GOLD 1 and GOLD 2 groups. Salbutamol inhalation produced a significant decrease of small airways resistance in this part of bronchial tree. The largest number of patients with small airways obstruction was found in GOLD 4 group-16,1%, followed by GOLD 3 group-7,1% while GOLD 2 group contained 4,8% of these patients. Salbutamol produced marked decrease of small airways resistance in all patient groups except GOLD 4 group. This finding suggests that in these patients, an irreversible parenchymal destruction has already occurred.

This research has also shown that salbutamol indirectly improved permanent bronchoopstruction parameter (FEV1/FVC) by decreasing small airways resistance. We also observed a statistically significant negative correlation between small airways resistance change and FEV1 after salbutamol inhalation in all patients.

Authors' contribution

MR (Conceptualization; Data curation; Project administration; Writing – review & editing; Funding acquisition; Resources; Writing – original draft; Supervision; Validation; Visualization)

MD (Formal Analysis; Funding acquisition; Investigation; Methodology; Project administration; Resources; Writing – review & editing; Software; Supervision; Validation)

Conflict of interest

None to declare.

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