Acute Effect of Long-Acting Bronchodilators on Thoracic Gas Compression in Patients with COPD

KOAH'lı Hastalarda Uzun Etkili Bronkodilatörlerin Torasik Gaz Kompresyonuna Akut Etkileri

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ABSTRACT

Objective: Thoracic gas compression (TGC) has a negative effect on expiratory flow. In patients with chronic obstructive pulmonary disease (COPD), TGC is high. Bronchodilators may affect thoracic gas compression by reducing airway resistance and improve maximal expiratory flow. The aim of this study was to investigate the effects of long-acting bronchodilators (formoterol 12 µg and tiotropium 18 µg) on thoracic gas compression, forced expiratory volumes measured at the mouth and in a plethysmograph in patients with COPD.

Material and Method: Bronchodilator response to formoterol and tiotropium was assessed in 40 COPD patients using maximum expiratory flow-volume curve values measured at the mouth (m) and plethysmograph (p). Volume of compression (V Comp= ΔV lung - ΔV mouth) was obtained.

Results: The repeated measurements were performed at baseline, 30., 60. and 120. minutes. Formoterol and tiotropium had significant bronchodilator effects, and formoterol produced a higher increase in FEV_1 m ($p<0,001$) compared to tiotropium. Thoracic gas compression volumes did not change significantly after either long-acting bronchodilator administration in patients with COPD. With regard to thoracic gas compression volume at 25, 50 and 75 % of VC (Vcomp25, Vcomp50, Vcomp75, no relevant difference was found between the two drugs. The thoracic gas compression volumes did not differ between stage II–III and stage IV COPD patients.

Conclusion: The results of this study suggest that thoracic gas compression volume did not change significantly after administration of long-acting bronchodilators, even if both study drugs elicited significant bronchodilation in spirometric measurements, and the disease severity did not influence the effect of the long acting bronchodilator agents on thoracic gas compression volumes.

(Tur Toraks Der 2009;11:122-9)

Key words: Thoracic gas compression, formoterol, tiotropium, COPD, plethysmography

Received: 16. 02. 2009 *Accepted: 23. 02. 2009*

ÖZET

Amaç: Torasik gaz kompresyonunun (TGK) ekspiratuar akım üzerine olumsuz etkisi vardır. Kronik obstrüktif akciğer hastalığı (KOAH) olan hastalarda TGK yüksektir. Bronkodilatörler hava yolu direncini azaltarak ve maksimal ekspiratuar akımı iyileştirerek torasik gaz kompresyonunu etkileyebilir. Bu çalışmanın amacı uzun etkili bronkodilatörlerin (formoterol 12 µg ve tiotropium 18 µg) KOAH'lı hastalarda torasik gaz kompresyonu, ağızda ve pletismografta ölçülen zorlu ekspiratuar volümlerine etkilerini araştırmaktı.

Gereç ve Yöntem: KOAH'lı 40 hastada, ağızdan (m) ve pletismograftan (p) ölçülen maksimum ekspiratuar akım-volüm eğrilerini kullanarak formoterol ve tiotropiuma bronkodilatör yanıt değerlendirildi. Kompresyon volümü (V Comp= ΔV akciğer - ΔV ağız) elde edildi.

Bulgular: Bazal, 30., 60. ve 120. dakikalarda tekrarlanan ölçümler yapıldı. Formoterol ve tiotropiumun belirgin bronkodilatör etkisi oldu ve formoterol tiotropiumla karşılaştırıldığında FEV_1 m'de daha fazla ($p<0.001$) artış oluşturdu. Torasik gaz kompresyon volümleri KOAH'lı hastalarda her iki uzun etkili bronkodilatörden sonra anlamlı olarak değişmedi. Vital kapasitenin %25, 50 ve 75'inde (Vcomp25, Vcomp50, Vcomp75) torasik gaz kompresyon volümlerinde iki ilaç arasında belirgin farklılık bulunmadı. Torasik gaz kompresyon volümleri evre II–III ve IV KOAH'lı hastalar arasında farklılık göstermedi.

Sonuç: Bu çalışmanın sonuçları her iki çalışma ilacının spirometrik ölçümlerde anlamlı bronkodilatör etki göstermekle birlikte torasik gaz kompresyon volümlerinin uzun etkili bronkodilatör verilmesinden sonar belirgin olarak değişmediğini ve hastalık şiddetinin uzun etkili bronkodilatör ilaçların torasik gaz kompresyon volümlerine olan etkisini değiştirmediğini düşündürmektedir.

(Tur Toraks Der 2009;11:122-9)

Anahtar sözcükler: Torasik gaz kompresyon, formoterol, tiotropium, KOAH, pletismografi

Geliş Tarihi: 16. 02. 2009 *Kabul Tarihi: 23. 02. 2009*

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INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is characterised by airflow limitation that is usually progressive and not fully reversible. Expiratory flow limitation is the hallmark physiological change of COPD [1,2]. During a forced expiration, lung volume decreases because of the volume of gas expired from the mouth, and also due to compression of alveolar gas by the positive intrathoracic pressure. The change in lung volume exceeds the volume displacement from the mouth, and this is due to compression of thoracic gas [3,4]. The volume of compressed gas will depend on alveolar pressure and absolute lung volume, which, in turn, depends on the interaction of respiratory muscle strength and force-velocity relationship, effort, hyperinflation and airway resistance [5]. It has been shown that maximum expiratory flow-volume curve (MEFVC) values measured by plethysmograph remain higher than values measured at the mouth. This is because forced vital capacity measured in a plethysmograph (FVCp) includes both expired volume and volume of thoracic gas compression (Vcomp), whereas the FVC derives from gas expired from the mouth (FVCm) alone. This difference is increased in patients with airway obstruction due to increased lung volume and airway resistance. It is also related to the degree of airflow limitation [3-8]. In normal subjects, Vcomp is small, but it should be taken into consideration in patients with airflow obstruction, as bronchodilator therapies may affect Vcomp in this circumstance, and the reduction in thoracic gas compression volume may create a reduction of the negative effect of this phenomenon on forced expiratory flow. This issue has been addressed in only a few studies evaluating the postbronchodilator effect of short-acting agents. Desmond et al. reported that there were increases and decreases in Vcomp values after salbutamol for both asthmatic children and cystic fibrosis patients, but a significant postbronchodilator decrease in compression has been shown only in those with asthma [9]. Walamies et al. found that in healthy and asthmatic children, Vcomp profiles were not changed significantly in either group following the administration of rimiterol [10]. Sharafkhaneh et al. reported very recently that the thoracic gas compression index was significantly larger in patients with COPD, and it diminished after 180 µg of albuterol inhalation compared to baseline [11].

Inhaled bronchodilator therapy is central in the treatment of COPD, according to the recently published international guidelines for the diagnosis and treatment of COPD. If symptoms persist, regular treatment with mono or combined therapy of long-acting bronchodilators is recommended [1,2]. Presently, two types of inhaled long-acting bronchodilators are available: the long-acting ß2-agonists (LABAs) formoterol and salmeterol, and the long-acting anticholinergic tiotropium. The most important consequence of bronchodilator therapy is considered to be through the relaxation of airway smooth muscle and an improvement in lung emptying [12,13]. Body plethysmographs can register gas compression volume during the flow-volume manoeuvre with no extra effort by the user, and the investigation of the possible changes in gas compression after administration of a bronchodilator may be valuable in assessing the effect of bronchodilators. The purpose of the present study was to evaluate the effects of long-acting bronchodilators (formoterol 12 µg and tiotropium 18 µg) on thoracic gas compression, forced expiratory volumes measured at the mouth and in a plethysmograph in patients with COPD.

PATIENTS and METHODS

Patients

Patients were required to have a clinical diagnosis of COPD according to the GOLD criteria [2]. They were recruited after obtaining their informed consent according to the Helsinki II Declaration before any study procedure was undertaken. Patients were outpatients regularly followed-up in an university hospital, aged ≥ 40 years, and current or former smokers with a ≥ 10 pack-years smoking history. Patients with any of the following were excluded; history of asthma, atopy, allergic rhinitis or an elevated blood eosinophil count, clinically significant disease other than COPD, recent history of myocardial infarction, heart failure, cardiac arrythmia requiring drug treatment, requirement for oxygen therapy. Patients with respiratory tract infections or COPD exacerbation in the 6 weeks before screening were also excluded.

Study Design

Eligible patients were recruited consecutively. The long-acting bronchodilators were withdrawn one week before, and short-acting bronchodilators 8 h prior to the study. Use of systemic corticosteroids, methylxanthines, and oral long-acting ß2-agonists were not permitted during the study period, and salbutamol was used as rescue medication. Each patient received a single dose of 12 µg formoterol dry capsule delivered via a single breath-actuated inhaler (Aerolizer®) on the first test day, and lung function measurements were performed. The washout period was 72 h between the test days. During this washout period, patients were allowed only salbutamol usage as rescue medication. On the second test day, the same measurements were obtained from the same patient after administration of a single dose 18 µg of tiotropium bromide dry powder capsule delivered via the HandiHaler®.

Measurements

Pulmonary function testing (PFT) of each subject was determined by a pressure / volume (flow) plethysmog-

raph (Autobox 6200, SensorMedics). Study drugs were administered at the same time each test day (between 7:00 AM and 9:00 AM). On the first test day, after a 30-min rest, baseline measurements just prior to the administration of single dose of 12 µg formoterol via the Aerolizer® were recorded. At least three adequate forced expiratory maneuvers were performed and the best forced expiratory maneuvers were determined according to ATS criteria [14]. Predicted normal values were based on the tables for standardized lung function tests of the European Coal and Steel Community [15]. Forced vital capacity (FVC), forced expiratory volume in 1s (FEV_1), forced expiratory flow between 25 and 75% of vital capacity (FEF_{25-75}), $FEF_{25, 50, 75}$ and MEFVC were obtained by the patient seated in the plethysmograph with the door closed. In this way, both mouth flow/mouth volume and mouth flow/lung volume values were plotted. For each MEFVC, plethysmograph measures MEFVC measured in the plethysmograph (MEFVCp) and MEFVC measured at the mouth (MEFVCm) were obtained simultaneously. Results obtained from this measurement are expressed as following; mouth flow/mouth volume parameters were recorded as FVC m, FEV_1 m, FEV/FVC m, FEF_{25-75} m, FEF_{25} m, FEF_{50} m, FEF_{75} m, PEF m and mouth flow/lung volume parameters were recorded as FVC p, FEV1 p, FEV/FVC p, FEF_{25-75} p, FEF_{25} p, FEF_{50} p, FEF_{75} p, PEF p. SensorMedics Autobox 6200 measures compressed gas volume (Vcomp) in three levels of expired vital capacity (VC) : 25 % of VC (Vcomp25), 50% of VC (Vcomp50), and 75% of VC (Vcomp75). Thoracic gas compression volumes were calculated as the difference between lung volume change and integrated mouth volume (Vcomp = ΔV lung - ΔV mouth). Postinhalational measurements were performed at 30,60 and 120 min. After the 72 h washout period, on the second test day, the same measurements were obtained after a 30-min rest, just prior to the administration of a single dose 18 µg of tiotropium via the HandiHaler®. Postinhalational measurements were performed at 30,60 and 120 min. Changes in perception of dyspnea were assessed with the standard visual analogue scale (VAS) method as well as with the modified Borg scale [16,17]. The VAS scale is a 100 mm long horizontal line labeled "very much worse" at the left end, "very much better" at the right end, and "no change" in the middle. The Borg scale is a 0 to 10 rated scale used to evaluate their dyspnea. Patients were instructed to rate only breathlessness by these scales. They marked the level of breathlessness before the administration of the long-acting bronchodilator, and also 30, 60 and 120 min. after the inhalation of the drug.

Statistical analysis

All statistical measurements were made using SPSS Package for the Social Sciences, Version 11.5 for Windows; SPSS Inc., Chicago, IL. Demographic and baseline lung function data are presented as mean ± standard deviation or number (percentage). We used Student's t test to compare the plethysmographic and spirometric measurements. The analysis of consecutive measurements at baseline, 30., 60., 120. minutes were performed by repeated measurements of ANOVA. The comparison between the two study drugs for their effect on expiratory flows and on thoracic gas compression volumes were made by repeated measurements of two way ANOVA. A p value of less than 0.05 was considered significant.

Table 1. Baseline demographics and characteristics of patients

Parameters	n (%)	Mean ± SD
Number of patients	40	
Age (years)		63.98±9.18
BMI (kg/m2)		24.67±3.59
Smoking (pack-years)		31.62±13.02
Current smokers	9 (22.5%)	
Previous smokers	31(77.5%)	
Lung function		
FEV_1 L		1.25 ± 0.50
FVC % pred		63.05±16.59
FEV_1 % pred		42.63±15.88
FEF 25-75 % pred		19.37±19.16
COPD severity #		
Stage II	11 (27.5%)	
Stage III	19 (47.5%)	
Stage IV	10 (25%)	

BMI: Body mass index
SD : Standard deviation
: According to Global Initiative for Chronic Lung Obstructive Lung Disease (GOLD) criteria (2)

RESULTS

A total of 44 patients were recruited in the study. Two of the patients prematurely discontinued the study after the first test day. Two other patients experienced an acute exacerbation during the study period, and they were withdrawn prior to the first test day. Overall, 40 patients completed the study. The baseline demographics and characteristics of the 40 patients are presented in Table 1.

Lung Functions

Formoterol achieved a significant bronchodilator response after inhalation in repeated measurements for FVC m, FEV_1 m, FEV_1/FVC % m, PEF m, FEF_{25-75} m, FEF_{25}m, FEF_{50} m, FEF_{75}m,. In plethysmographic measurements; FVC p, FEV_1 p, PEF p increased after inhalation of formoterol, and FEV_1/FVC % p values increased significantly after formoterol. When we compared the spirometric and plethysmographic measurements, all expiratory flow rates, except PEFR and FVC, were higher by plethysmographic measurement and the difference was statistically

Table 2. Results of pulmonary function tests after the administration of single dose of 12 µg formoterol

	Baseline Mean ± SD	30 Min. Mean ± SD	60 Min. Mean ± SD	120 Min. Mean ± SD	P value
FVC p (L)	2.41±0.82	2.76±0.80	2.84±0.79	2.70±0.68	**< 0.001**
FEV_1 p (L)	1.80±0.62	1.94±0.65	1.98±0.64	1.87±0.59	**0.001**
FEV_1/FVC $\%_p$	75.47±13.74	69.92±11.51	69.63±11.39	68.68±11.58	**< 0.001**
PEF p (L/sec)	3.76±1.54	4.24±1.54	4.27±1.37	4.24±1.44	**< 0.001**
FEF_{25-75} p (L/sec)	2.39±4.38	1.75±2.06	1.84±1.97	1.68±2.15	0.12
FEF_{25} p (L/sec)	3.32±1.57	3.54±1.92	3.41±1.76	3.46±1.75	0.63
FEF_{50} p (L/sec)	1.57±0.96	1.56±0.92	1.70±1.01	1.58±0.99	0.29
FEF_{75} p (L/sec)	0.73±0.55	0.70±0.31	0.71±0.48	073±071	0.57
FVC m (L)	2.39±0.79	2.77±0.79	2.84±0.79	2.72±0.70	**< 0.001**
FEV_1 m (L)	1.27±0.59	1.49±0.65	1.53±0.61	1.49±0.56	**< 0.001**
FEV_1/FVC %	51.72±9.06	52.68±9.75	52.98±9.05	53.72±9.05	**0.01**
PEF m (L/sec)	3.72±1.37	4.23±1.55	4.27±1.37	4.23±1.43	**0.002**
FEF_{25-75} m (L/sec)	0.63±0.39	0.77±0.47	0.79±0.51	0.78±0.44	**< 0.001**
FEF_{25} m (L/sec)	1.63±1.29	2.08±1.68	2.10±1.50	2.07±4.13	**< 0.001**
FEF_{50} m (L/sec)	0.73±0.46	0.90±0.63	0.92±0.67	0.91±0.53	**< 0.001**
FEF_{75} m (L/sec)	0.31±0.15	0.36±0.17	0.38±0.20	0.37±0.17	**< 0.001**

significant (p< 0.001). This difference was maintained at the same level of significance during the test period. The results of pulmonary function tests after the administration of a single dose of 12 µg formoterol are presented in Table 2 with mean values of each parameters at consecutive measurements.

The baseline spirometric values of the first test day with formoterol and the second test day with tiotropium were comparable, confirming the adequacy of the washout. The results of pulmonary function tests after the administration of tiotropium are presented in Table 3 with mean values of each parameter at consecutive measurements.

Tiotropium produced a significant increase in FVC m, FEV_1 m, and in PEF m values. In FEF_{25-75} m, FEF_{25} m, FEF_{50} m, FEF_{75} m measurements, there were no significant changes during the test period. After inhalation of tiotropium, plethysmographic measurements revealed that FVC p, PEF p increased significantly, while FEV_1 p, FEF_{25-75} p, FEF_{25} p, FEF_{50} p, FEF_{75} p values were not changed in consecutive measurements. FEV_1/FVC % p values increased significantly after tiotropium. In the comparison of the spirometric and plethysmographic measurements, all expiratory flow rates, except PEFR and FVC, were higher by plethysmographic measurement and the difference was statistically significant (p< 0.001). The statistical significance was unchanged from the baseline throughout the repeated measurements, and this finding was similar to the results of formoterol.

When we compared two drugs by repeated measurements after inhalation of their single dose, formoterol produced a higher increase in FEV_1 m compared to tiotropium (p<0,001), as well as FEF_{25} m (p<0,001), FEF_{50} m (p<0,05), FEF_{75} m (p<0,05) values which were also signi-

Table 3. Results of pulmonary functions tests after the administration of single dose 18 µg of tiotropium

	Baseline Mean ± SD	30 Min. Mean ± SD	60 Min. Mean ± SD	120 Min. Mean ± SD	P value
FVC p (L)	2.40±0.71	2.56±0.68	2.66±0.79	2.61±0.70	**0.01**
FEV_1 p (L)	1.79±0.63	1.77±0.55	1.86±0.55	1.83±0.54	0.31
PEF p (L/sec)	3.60±1.19	3.72±1.28	3.90±1.23	3.87±1.20	0.002
FEV_1/FVC $\%_p$	74.43±13.74	70.13±13.40	70.65±12.23	70.45±11.75	**0.02**
FEF_{25-75} p (L/sec)	2.08±2.00	1.73±1.78	1.73±2.63	1.66±2.20	**0.12**
FEF_{25} p (L/sec)	3.11±1.40	3.08±1.52	3.25±1.38	3.29±1.37	0.16
FEF_{50} p (L/sec)	1.54±0.90	1.39±0.72	1.54±0.88	1.52±0.89	0.35
FEF_{75} p (L/sec)	0.68±0.36	0.70±069	0.61±0.32	0.62±0.34	0.65
FVC m (L)	2.40±0.71	2.56±0.69	2.66±0.79	2.61±0.70	**< 0.001**
FEV_1 m (L)	1.26±0.51	1.33±0.49	1.36±0.53	1.38±051	0.001
FEV_1/FVC % m	51.83±8.87	51.25±10.01	50.58±9.15	51.85±8.88	0.32
PEF m (L/sec)	3.56±1.127	3.74±1.26	3.90±1.23	3.88±1.20	**0.001**
FEF_{25-75} m (L/sec)	0.66±0.32	0.70±0.44	0.66±0.34	0.69±0.34	0.61
FEF_{25} m (L/sec)	1.61±1.16	1.65±1.19	1.66±1.08	1.69±1.07	0.83
FEF_{50} m (L/sec)	0.75±0.53	0.79±0.49	0.76±0.49	0.81±0.48	0.48
FEF_{75} m (L/sec)	0.33±0.13	0.33±0.13	0.32±0.13	0.35±0.14	0.53

Table 4. Thoracic gas compression volume measurements after formoterol and tiotropium inhalation

	Baseline Mean ± SD	30 Min. Mean ± SD	60 Min. Mean ± SD	120 Min. Mean ± SD	P value
Formoterol					
Vcomp25 (L)	0.55±0.32	0.53±0.40	0.54±0.37	0.47±0.29	0.24
Vcomp50 (L)	0.50±0.29	0.45±0.31	0.46±0.30	0.40±0.27	0.06
Vcomp75 (L)	0.41±0.20	0.34±0.21	0.36±0.22	0.32±0.22	0.04
Tiotropium					
Vcomp25 (L)	0.57±0.39	0.56±0.37	0.58±0.35	0.53±0.36	0.50
Vcomp50 (L)	0.54±0.38	0.50±0.34	0.51±0.28	0.45±0.29	0.18
Vcomp75 (L)	0.37±0.21	0.34±0.21	0.39±0.19	0.36±0.19	0.21

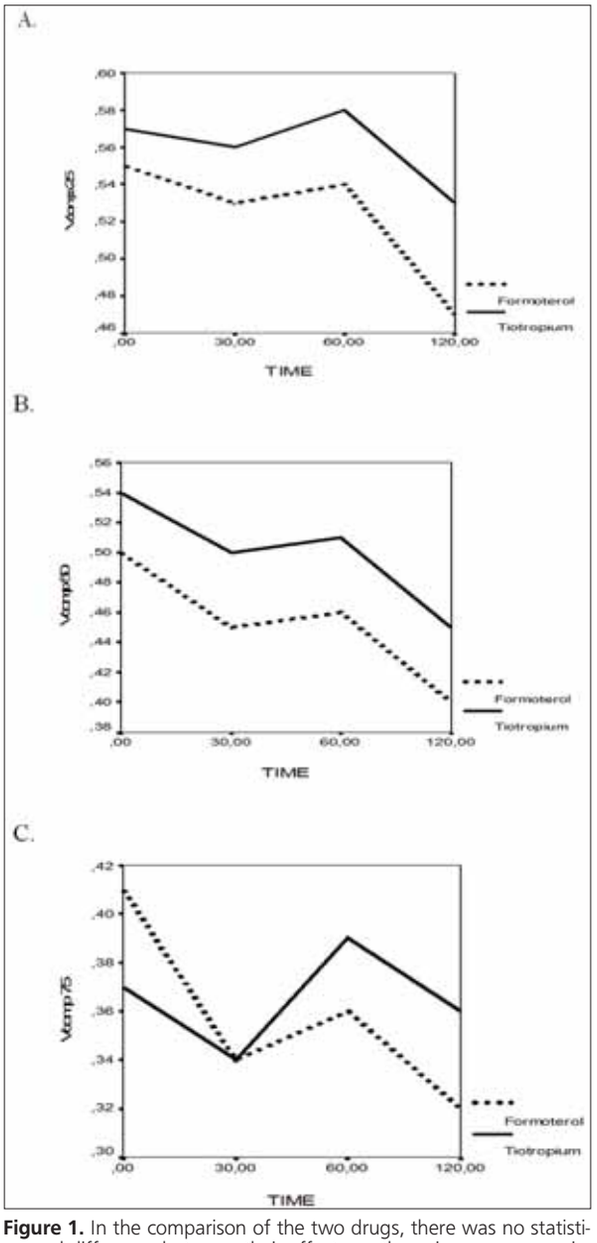

Figure 1. In the comparison of the two drugs, there was no statistical difference between their effects on thoracic gas compression volume at 25, 50 and 75 % of VC

A. Vcomp25 changes during the study period after inhalation of tiotropium (straight line) and after inhalation of formoterol (dashed line)

B. Vcomp50 changes during the study period after inhalation of tiotropium and formoterol

C. Vcomp75 changes during the study period after inhalation of tiotropium and formoterol

ficantly increased after inhalation of formoterol compared to tiotropium. There were no comparable differences for any of the plethysmographic values (FVC p, FEV_1p, FEF_{25-75} p, FEF_{25}p, FEF_{50} p, FEF_{75} p) between the two study drugs.

Thoracic gas compression volumes

Formoterol produced a significant decrease in Vcomp 75 by repeated measurements of ANOVA (Table 4). Tiotropium did not produce a significant decrease in thoracic gas compression volume by repeated measurements after inhalation. The mean values on consecutive measurements for the two study drugs are presented in Table 4. When we compared the two drugs, there was no statistical difference between their effects on thoracic gas compression volume at 25, 50 and 75 % of VC (Vcomp25, Vcomp50, Vcomp75). Since thoracic gas compression is related to the degree of airflow limitation, in addition to the entire group evaluation, we performed a subgroup analysis to assess whether, in the 10 subjects at stage IV, the effect of the two bronchodilators is different from that which occurs in the less severe patients (stage II and III). Thoracic gas compression volumes during the test period did not differ between groups either for formoterol or tiotropium (Figure 1).

Dyspnea

Tiotropium induced a significant dyspnea improvement according to the VAS and Borg scores. Formoterol also provided a significant decrease in dyspnea scores, and the two drugs were equally efficient in terms of dyspnea relief. No significant correlation was found between gas compression volumes and dyspnea scores in consecutive measurements after inhalation of the study drugs.

DISCUSSION

It has been noted previously that alveolar gas is compressed from atmospheric pressure to a higher pressure during a forced expiration. The body plethysmograph measures the volume decrease of the chest, which exceeds the volume of gas exhaled during flow , the difference being the compression of the alveolar gas (7). In

patients with obstructive lung diseases, this difference may be appreciable because of the increased lung volume, airway resistance, and also there may be a correlation between the severity of airflow limitation and the amount of the thoracic gas compression volume measured at different levels of a forced expiration maneuver [4,7,8]. If this effect is mainly increased by the high airway resistance and hyperinflation, it would be expected that the diminishing effect of a bronchodilator agent on thoracic gas compression volume in patients with COPD could be detected. For this reason, we examined the effects of formoterol and tiotropium on thoracic gas compression volumes in patients with stable COPD. According to the previous reports on the efficacy profile of both study drugs [18-23], thoracic gas compression volumes, forced expiratory volumes measured at the mouth and in a plethysmograph in patients with COPD were assessed in serial measurements within a two hour study period.

The results of this study suggest that thoracic gas compression volume was not diminished after the long-acting bronchodilator drug administration. Although Vcomp 75 decreased after formoterol, this effect was not detectable for Vcomp25 and 50 and it was not considered a significant finding in terms of thoracic gas compression profile changes. When we compared the two study drugs, there was no statistical difference between their effects on thoracic gas compression volume at 25, 50 and 75% of VC (Vcomp25, Vcomp50, Vcomp75) by repeated measurements. Furthermore, the lack of correlation between thoracic gas compression volume changes and dyspnea scores might raise the question about the clinical impact of thoracic gas compression in COPD. At this point, we investigated whether the severity of the disease might be another possible determinant for thoracic gas compression volume changes in patients with COPD. Nevertheless, the change in thoracic gas compression profile did not differ between 10 subjects at stage IV and 30 subjects at stage II and III within a 2-hour study period for both drugs.

In the present study, formoterol elicited an effective sustained bronchodilation during the test period, and dyspnea scores of the patients were improved significantly. In spirometric measurements, tiotropium also induced a significant bronchodilator effect within the study period, which was apparent from 30. min. of its administration. According to the results of our study, formoterol elicited a significantly higher increase than tiotropium in mean FVC, FEV_1, FEF_{25-75}, FEF_{25}, FEF_{50} and FEF_{75} values within a 2-h study period in spirometric measurements. The comparison of the spirometric and plethysmographic measurements revealed a significant difference in all expiratory flow rates within 2h of testing after the inhalation of formoterol and tiotropium. This difference was constant during the test period for the two drugs. FEV_1/FVC % p values increased significantly after formoterol and tiotropium administration. Both FEV_1 and FVC increased with the use of tiotropium and formoterol, but it appeared that the decrease in FEV_1/FVC % p was due to a larger increase in FVC compared with FEV_1.

It was shown that optimal bronchodilatory responses after tiotropium are achieved in a pharmacodynamic steady state over the first 48h [21]. Cazzola et al. reported that formoterol showed a significantly faster onset of action and a trend for a greater maximum bronchodilation than tiotropium, and they also pointed out that the mean FEV_1 at 24 h was higher than the predosing value following tiotropium compared to formoterol [24]. In a recent study, van Noord et al. demonstrated that, following the initial dose of tiotropium or formoterol, tiotropium and formoterol had a comparable bronchodilating effect until 8 h after dosing. From 8 to 12 h, postdose tiotropium provided a significantly greater improvement in FEV_1 compared to formoterol, and it was also shown that tiotropium bromide needs repeated administrations to reach full activity [25]. Richter et al. published that, in patients with moderate to severe COPD, formoterol had a significantly faster onset of action and greater bronchodilation effect compared with tiotropium within the first 2 h of inhalation and comparable bronchodilation after 12 h [26]. These results indicate that formoterol and tiotropium have different profiles regarding their bronchodilator effect, with a faster onset of action for formoterol, longer duration of action and need for repeated doses in order to obtain full activity for tiotropium.

The volume of compressed gas is related to alveolar pressure and absolute lung volume, and is consequently increased due to hyperinflation and high airway resistance in patients with obstructive airway diseases [3-8]. The recent data available about the effects of long-acting bronchodilators on resting lung volumes elicited that formoterol had a rapid increase in inspiratory capacity (IC), reaching a peak value after 30 min [27]. O'Donnell et al reported an immediate reduction of FRC (functional residual capacity) after the first dose of tiotropium, and Santus et al. recently documented that tiotropium was able to modify IC and TGV even after 2h of the administration at rest, and this effect was found to be more effective when compared with single inhaler budesonide / formoterol. These results suggested that the drug had the capacity of influencing expiratory flow rapidly [28,29]. The current study did not address resting lung volumes after the inhalation of the two drugs. To date, thoracic gas compression has been addressed only in a few studies evaluating the postbronchodilator effect of short-acting bronchodilators. Their results revealed both increases and decreases of thoracic gas compression volume

in patients with airway obstruction, and it was also found that the bronchodilator response had an individual variation [9-11]. Our study was aimed to evaluate the gas compression profile during the flow-volume manoeuvre by body plethysmograph with one manoeuver, and long-acting bronchodilators did not produce a significant change in TGC. According to the results of this study, thoracic gas compression volumes are not influenced by the calibre of the airways, and this was concordant with the findings of Walamies [10]. At this point, this finding should be carefully interpreted without lung volume measurements, and the effect of lung volume changes in COPD patients on thoracic gas compression profiles after the administration of long-acting bronchodilators will give additional information for drawing more definite conclusions.

In conclusion, the results of this pilot study suggest that thoracic gas compression volume was not changed significantly after the administration of long-acting bronchodilators, even if both study drugs elicited significant bronchodilation in spirometric measurements. In addition, thoracic gas compression volumes did not correlate with improvement in symptoms, and its clinical impact in COPD seems to be negligible. However, it will be more definitive to investigate the effect of the repeated administrations of long-acting anticholinergic and LABA's because of their different bronchodilator profiles, as well as the impact of resting lung volumes on the changes of thoracic gas compression volumes, with further studies.

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