Volume Response to a Bronchodilator in Patients with COPD

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Abstract

The chronic obstructive pulmonary disease (COPD) is characterized by persistent airflow limitation. It is a frequent, known and treatable disease. The diagnosis requires tobacco smoking personal history or expositional history and evidence of an obstructive pattern at the spirometry measured before and after bronchodilators.

The degree of reversibility of airflow differs between patients, and does not predict the response to bronchodilator therapy. It can be seen in terms of forced vital capacity or forced expiratory flow, depending on the severity of the disease.

This paper presents the differences in bronchodilator response in terms of measurements of the flow and the volume in patients diagnosed with COPD at different stages of GOLD. The bronchodilator response and its relationship to the severity of the disease were analized.

Key words: COPD, spirometry, vital capacity, forced expiratory volume

Introduction

According to ATS/ERS task force, bronchodilator response is measured using the percent change from baseline and absolute changes in FEV1 and/or FVC[1]. Twelve percent and 200 mL increase in FEV1 or FVC compared to baseline value are suggestive of a significant response to bronchodilator[1, 2]. However, some patients with severe chronic obstructive pulmonary disease (COPD), forced vital capacity (FVC) remarkably increases in response to bronchodilator administration whereas FEV1 remains substantially unchanged[3-5]. This isolated volume response is generally interpreted as sign of bronchodilatation[6]. Thereductionof hyperinflation[7] and/or the presence of severe emphysema[8] have been proposed as underlying mechanisms of this volume response.

If severe emphysema and lung inflation alters airway caliber, due either to loss of lung elastic recoil or to space competition, airway calibre should be independent of airways smooth muscle tone at high lung volume, explaining at least in part the lack of sensitivity to bronchodilatation as assessed by changes in FEV1[8]. It would mean that the isolated volume response should be more prevalent in more severe disease. The objective of our study was to assess the differences between flow and volume responses after bronchodilator reversibility testing in patients over different clinical COPD stages (GOLD stage I to GOLD stage IV) in order to test if the association between flow and volume responses becomes weaker as the disease becomes more severe

Material and methods

We retrospectively reviewed the pulmonary function of 594 consecutive patients with chronic obstructive pulmonary disease who attended our laboratory between January 2013 and June 2014. Patients were included only if the referral diagnostic of the pulmonologist in charge was COPD and were 40 years of age or older and the spirometry confirmed a post-bronchodilator FEV1/FVC ratio < 0.70. When two or more tests of the same patient were included in the database, the most recent test for each individual patient was selected. All patients who reported to be lifelong non-smokers were excluded. Any patients with a diagnosis of bronchial asthma, bronchiectasis or any other respiratory disease were excluded.

All spirometric measurements were made using identical spirometers, pneumotrac 6800 vitalo-

graph with pneumotachograph of Fleisch and software Spirotracacoording to standardisation of spirometry ATS/ERS[9].

Forced expiratory manoeuvres were performed in a standardised fashion and the best FEV1 and FVC recordings within 50 ml of each other were accepted. All studies were performed by the same 3 technicians that met proficiency requirements in the use of the equipment and demonstrated the ability to perform technically acceptable pulmonary function tests according to ATS criteria. Patients were asked to omit short-acting inhaled bronchodilators for at least 8 hours, and long-acting beta-agonists for at least 12 hours. Bronchodilator responsiveness was assessed by performing spirometry before and 15 minutes after the patient had received salbutamol, 400 μg, inhaled using a spacer in 4 separate doses). Bronchodilator response is expressed as an absolute change in millilitres and as a percentage of the baseline value.

FEV1 responsiveness was assessed using published criteria: >12% and >200 mL improvement[10, 11] and also an increase in FVC of at least 200 mL and 12% from baseline values, we used these criteria in our study[10].

Patients were stratified according to the severity of obstruction into one of the four GOLD stages: mild (stage I: FEV1 > 80% of predicted); moderate (stage II: FEV1 50-80% of predicted); severe (stage III: FEV1 30-50% of predicted); and very severe COPD (stage IV: FEV1 o 30% of predicted)[12]. Information regarding the presence of chronic respiratoryfailure was not available, therefore the criterion FEV1 < 50% of predictedplus chronic respiratory failure to classify a patient in GOLD stage IV was not applied.

Statistical analysis:

Data are presented as mean plus standard deviation for whole group data. Comparisons were made using analysis of variance (ANOVA) for multiple groups. Bonferroni test showed: A significant difference for all the included variables in the Group of volume responders compared to flow responders and non responders. However the group of non-responders was not different from the flow responders. Differences in subject characteristics between GOLD stage subgroups were analysed by analysis of variance (ANOVA). Differences in flow and volume responses between GOLD stages and interaction between flow response, volume response, and GOLD stage were statistically tested using a linear regression model with deltaFVC as the dependent variable. Statistical analysis was performed using SPSS version 13.0 and significance set at a level of 95% (p < 0.05).

Results

After applying our selection requirements, 594 patients fulfilled the entry criteria and had available complete data of bronchodilator assessments. The overall proportions of males in this sample was 66, 5% (n = 395). The age range in the sample was 40–93 years. Baseline lung function of the whole population isshown in Table 1. Neither mean age (p =0,464) nor mean BMI (p= 0,308) were different amongst the patients with different GOLD stages. Most of patients were classified as GOLD II (Table 2).

Seventy nine (13, 3%) subjects were isolated volume responders (only FVC response to Bd), 30 (5, 1%) were isolated flow responders (only FEV1 response after Bd), 118 (19, 9%) were flow and volume responders and 367 (61%) were non-responders. The characteristics of the 4 groups are shown in Table 3. Volume responders had a lower FEV1 (% predicted), lower FVC (% predicted), and a lower FEV1/FVC ratio. There was no relationship between the absolute change in FEV1

TABLA 1

	Mean	SD
Age	64.3	9.1
BMI	29.1	13.7
FVC (L)	2.88	0.9
FVC (% of pred)	81.2	19.5
FEV1 (L)	1.63	0.67
FEV1 (% Of pred)	60.2	20.3
FEV1/FVC ratio	0.55	0.10

TABLE 2

GOLD stage	n	%
I	149	25.1
II	304	51.2
III	120	20.2
IV	21	3.5
Total	594	100

and the baseline FEV1 value (r = 0,003, p = 0,945) but the change in FVC post-bronchodilator was significantly related to the decrease in baseline FEV1 values (r = 0, 24; p = < 0,001).

Table 4 shows the responses on flow and volume after the administration of bronchodilators in the different GOLD stages. The mean values for the change in FEV1 (DFEV1) and in FVC (DFVC) were 0, 15 ± 0, 13 L and 0, 21 ± 0, 26 Lrespectively. The magnitude of DFEV1 decreased as the GOLD stage became more severe and the DFVC increased in the more severe GOLD stages.

There was a positive correlation between DFEV1 and DFVC within the GOLD stages I to III (GOLD I: r = 0, 71, p = < 0,001; GOLD II r = 0, 64, p = < 0,001, GOLD III: r = 0,689, p = < 0,001) but not in GOLD stage IV (r = 0, 33, p = 0,135) (Fig 1).

Discussion

Our study demonstrated that a considerable amount of COPD patients show some sort of response to bronchodilators and that the more severe the airway obstruction the higher the probability of showing only volume response to bronchodilators.

Bronchial responsiveness is usually assessed by the change in the FEV1 after the administration of a bronchodilator. Other measures of lung function, such as lung volumes, are not routinely assessed before and after the administration of a bronchodilator agent in most pulmonary laboratories. The proportion of patients classified as "responders" will entirely depend on the definition of responsiveness. For instance, in the cohort studied by Tashkin et al, 65.6% met the criterion of a o15% increase in FEV1; 53.9% met the criterion of an increase in FEV1 of both o12% and o200 mL (73% of patients showed an increase of o12%, and55% of o200 mL); and 38.6% were characterised asreversible based on a o10% absolute improvement inpercentage predicted FEV1[13]. By using the currently ATS/ERS criteria, the magnitude of bronchodilator responsiveness was greater than expected with more than 40% of patients showing some type of responsiveness. Until recently, COPD had been characterised as a disease with largely irreversible airflow obstruction. Although it is now widely accepted that COPD is characterised by partially reversible airflow obstruction, the magnitude of acute responsiveness to bronchodilator drugs for COPD has not been rigorously analysed[13]. In fact, the distinction from chronic

TABLE 3

Group	Isolated volumen responders (mean ± SD)	Isolated flow responders (mean ± SD)	Flow and volume responders (mean ± SD)	No responders (mean ± SD)	P
Age	66.6 ± 9.3	61.6 ± 8.8	63.8 ± 8.4	64.1 ± 9.1	< 0.001
CVF (L)	2.22 ± 0.62	3.26 ± 0.76	2.57 ± 0.73	3.10 ± 0.9	< 0.001
CVF (% predicho)	67.78 ± 17.7	85.4 ± 13.1	72.5 ± 17.6	86.4 ± 18.7	< 0.001
VEF1 (L)	1.11 ± 0.45	1.82 ± 0.4	1.37 ± 0.468	1.81 ± 0.69	< 0.001
FEV1 (% pred)	45.4 ± 19.2	62.4 ± 14.1	50.6 ± 16.2	66.2 ± 19.5	< 0.001
FEV1/FVC ratio	0.49 ± 0.11	0.55 ± 0.07	0.52 ± 0.09	0.57 ± .10	< 0.001

TABLE 4

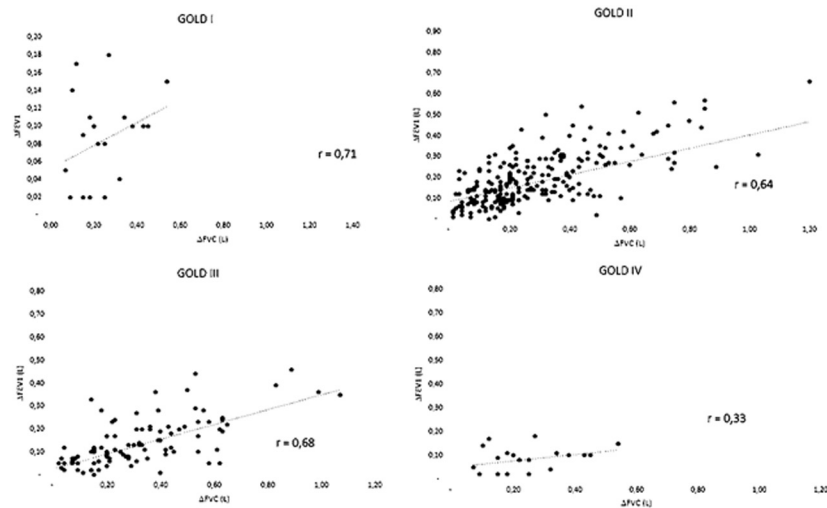|	GOLD I	GOLD II	GOLD III	GOLD IV	p
ΔFEV1 abs (L)	0.15 ± 0.13	0.15 ± 0.14	0.11 ± 0.11	0.08 ± 0.06	< 0.001
ΔFEV % baseline	7.0 ± 8.3	10.4 ± 10.5	13.5 ± 13.7	15.1 ± 11.5	< 0.001
ΔFVC abs (L)	0.17 ± 0.23	0.21 ± 0.28	0.27 ± 0.24	0.26 ± 014	< 0.001
ΔFVC % baseline	5.2 ± 8.0	9.2 ± 28.1	13.4 ± 13.3	16.0 ± 1.9	< 0.001

Figure 1

asthma with limited reversibility remains difficult, and many physicians still use in their daily practice the spirometric response to a bronchodilator drug to aid the diagnosis and, in some cases, to make recommendations about treatment decisions. In spite of the fact that some previous studies have found no clear distinction spirometrically between asthma and COPD in milder disease[14-16].These criteria have been still applied in the selection of patients for inclusion in treatment trials whose results are still in use[17, 18].

There was a heterogeneous response in our population with 79 (13, 3%) subjects showing isolated volume response, slightly more patients (n = 118, 19.9%) exhibiting changes in both volume and flow and only 5.1% improving FEV1 with a little change in FVC. This latter group had better initial spirometry. This distribution shows a slightly lower prevalence of responders than the series of Walker &Calverley in266 COPD patients who attended theirpulmonarylaboratory in Liverpool. Those differences may be explained because of a different definition of responsiveness, as the subjects in their study were classified as volume responders if FVC increased > 330 ml post-bronchodilator and FEV1 by < 160 ml[19]. In accordance to our findings, their patients who were in the volume responder group had a significantly lower baseline FEV1. They also demonstrated that this group exhibited a greater reduction in inspiratory capacity and an increased residual volume compared to the unresponsive and flow responsive patients alone. In our

patients in the volume responder group, the FEV1/ FVC ratio tended to worsen after the bronchodilator, probably due to the disproportionate increase in volume relative to flow.

The change in FEV1, expressed as an absolute value was uninfluenced by the pre-bronchodilator FEV1 when measured in absolute units. However, when the data were expressed as a percentage change from baseline there was a clear influence of the pre-bronchodilator FEV1; the more severe the baseline obstruction, the higher the increase of FEV1 as a percent of the baseline value. This has also been shown in the Calverley' study in patients recruited from the outpatient clinics of 18 UK hospital centres[20]. It may simply reflect the fact, demonstrated in previous studies, that the response of FEV1 measured as a percent of the baseline value has the worst likelihood ratio to differentiate between responders and not responders because it over scores bronchodilator response in patients with low FEV1[21, 22].

Bronchodilator responsiveness according to GOLD stage in our study showed that the magnitude of FEV1 response decreased progressively with increasing disease severity, whereas the magnitude of the volume response increased as the GOLD stage was higher. Similar findings we described by Taskin et al that showed that the percentage of COPD patients exhibiting a flow response decreased progressively with the increase of GOLD stage[13]. At the same time, the association between flow and volume responses changes as COPD beco-

mes more severe, shown by the significant correlation between the increase of FEV1 and FVC in milder COPD stages that is lost in the most severe COPD patients. In a similar way, Schermer et al have demonstrated that the GOLD stage produces a 'shift' in the association between flow and volume response producing that from GOLD stage I to GOLD stage III the slope of the regression line became gradually steeper, which indicated that a particular FEV1 response was accompanied by a higher FVC response as the GOLD stage was more severe[23].That decrease of the flow response and increase of the volume response as the airway obstruction is more severe may be explained by the fact that the FEV1 is determined by the airflow at high to medium lung volumes, whereas FVC is mainly determined by airway narrowing and flow limitation at low lung volumes[23].It could mean that a post bronchodilator change in FVC without a concomitant change of FEV1 were determined by the fact that the airway smooth muscle tone—the site of action of all inhaled bronchodilators—is a major determinant of airway calibre at low, but not at high lung volumes[8]. On the other hand, Newtonet al[23]reported significant increases in FVC following the administration of salbutamol in severely and moderately hyperinflated COPD patients, as the same time that the inspiratory capacity improved and the functional residual capacity and residual volume decreased, despite significant improvements in FEV1 in only a minority of patients.

Cerveri et al, had shown in an elegant study in 10 patients, that there was an inverse relationship between salbutamol-induced increments in FEV1 and various indexes of emphysema, in spite of conspicuous increments of FVC. They showed that the airway caliber increased with lung volume in all FVC-FEV1responders but decreased or remained unchanged in most FVC responders[8]. They measured the small-airway caliber by high-resolution computed tomography at functional residual capacity and total lung capacity in five chronic obstructive pulmonary disease patients with an isolated increase of FVC (FVC responders) and five with an increase of both FVC and FEV1(FVC-FEV1 responders) after inhalation of salbutamol. In FVC-FEV1 responders, the airway diameter increased with the cube root of increase in lung volume but was unchanged or even decreased in four of five FVC responders. They concluded that

isolated volume response to bronchodilators is a characteristic of severe emphysema involving more than 40% of lung parenchyma.

A limitation of our study comes from the design that was based on the retrospectively reported standardised data collected in an unselected group of patients with a clinical and physiological diagnosis of COPD. One of the theoretical limitations of the studies performed byusing lung function data obtained for routine diagnostic purposes in primary care, is the lower proportion of mild COPD patients. However, more than a quarter of our patients were classified as GOLD stage I, we used the old GOLD classification because in the pulmonary laboratory all the clinical data was not available in order to classify the patients beyond the FEV1.

We used only salbutamol (as it is the standard practice in our laboratory) rather than a combination of salbutamol and ipratropium, which may have added some additional effects at both low and high dose combinations[25]. However, the additive effect of combining drugs is considered quite modest and should not have a significant impact on the results.

We only included patients diagnosed as COPD by a certified pulmonologist, however, even when they had data regarding respiratory symptoms, (self-reported) bronchial hyper responsiveness and allergies, it is known that none of these characteristics is specific for asthma[25]and we cannot exclude that COPD and asthma could have co-existed within the same patient in some of our subjects. This may have influenced the rate of bronchial responsiveness. The exclusion of patients without a smoking history decreases but not completely excludes the possibility of some overlap categories amongst our patients[27]. An additional limitation in our study was that we did not include (because the small proportion of patients in whom it was available) lung volume and DLCO measurement to certify the presence of hyperinflation and or parameters suggestive of emphysema.

This dissociated response in volume and flow, may explain a frequent clinical finding: that patients with COPD –even if nonresponders in terms of FEV1– may benefit from bronchodilators. It could be the result of being able to breathe at a lower lung volume due to reduced airtrapping, although they are still flow limited[28]. The clinical significance of these changes in in accordance with

the observation that improvements in exercise endurance and dyspnoea during exercise following bronchodilator therapy, correlate better with increases in inspiratory capacity than with increases in FEV1[29].

In summary, we have identified a significant number of COPD patients who exhibited an increase only in forced vital capacity after the administration of salbutamol. We have also shown in a primary care COPD population, that patients with milder GOLD severity differ from the more severe in terms of flow (FEV1) and volume (FVC) responses after bronchodilators. Future studies should identify the reproducibility and most accurate cut-off values of these volume-based definitions that appear to be useful in defining the effect of bronchodilators in symptomatic COPD patients.

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