Original Article

Determining the optimal time to assess the reversibility of airway obstruction

Jamel El Ghoul, Maher Abouda¹, Meriem Triki¹, Abdessalem Ghourabi, Ridha Charfi¹

Department of Pulmonary Disease and Critical Care medicine, Hbib Bourguiba Hospital, Medenine, ¹Department of Pulmonary, Internal Security Forces Hospital, La Marsa, Tunisia

ABSTRACT

Context: The optimal time to interpret bronchodilator reversibility remains controversial. This time may affect a positive diagnosis and manage asthma and chronic obstructive pulmonary disease (COPD). **Aims:** We sought to document the time when maximum respiratory function is reached after inhalation of salbutamol and to define the optimal time of bronchodilator response to assess the reversibility or non reversibility of airway obstruction. **Subjects and Methods:** This prospective analytical study was spread over 8 months and included 58 patients with asthma or COPD with airway obstruction. Spirometry was performed before and at 5, 10, 15, 20, and 30 min after salbutamol inhalation (200 mcg) administered through pressurized metered-dose inhalers and large volume spacer. **Results:** After salbutamol inhalation, the mean individual peak bronchodilation occurred at 20 min for the forced vital capacity and at 30 min for the forced expiratory volume in 1 s. The percentage of reversible patients in our sample was guideline dependent. It increased from 53% to 67.2% when using the American Thoracic Society/European Respiratory Society definition compared to using the Global Initiative for Chronic Obstructive Lung Disease. The maximum number of reversible patients was significantly different at 20 min compared to 5 and 10 min. **Conclusions:** Interpreting bronchodilator reversibility after 20 min was the ideal time to judge the reversibility or nonreversibility in obstructive ventilatory disorders in adults.

KEY WORDS: Airway obstruction, asthma, bronchodilator response, chronic obstructive pulmonary disease, respiratory function tests

Address for correspondence: Dr. Jamel El Ghoul, Department of Pulmonary Disease and Critical Care Medicine, Hbib Bourguiba Hospital, Erriadh City, Medenine - 4100, Tunisia. E-mail: j.elghoul@hotmail.fr

INTRODUCTION

Identifying airway obstruction using spirometry is common in pneumology practice. Spirometric reversibility testing classifies the airway obstruction as reversible or irreversible and thereby guides therapeutic choices for most patients.

Bronchodilator reversibility depends on airway resistance variability after bronchodilator treatment, which causes variation in expiratory volumes. The definition of reversibility by learned societies has evolved over time, particularly regarding the expired volume and its increase.

A commonly used recommendation in clinical practice is the recommendation proposed by the American Thoracic Society (ATS) and the European Respiratory Society (ERS). The ATS/ERS guidelines define reversibility as an increase from baseline values by at least 12% and 200 mL in forced vital capacity (FVC) or in the forced expiratory volume in 1 s (FEV1).[1]

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The time of interpreting bronchodilator reversibility, which is the interval between the administration of a bronchodilator and postbronchodilator spirometry, remains controversial. To our knowledge, no clear consensus exists regarding the ideal time to interpret the bronchodilator response (BDR). Current ATS/ERS spirometry guidelines recommend that, when testing the response to salbutamol, an interval of 10–15 min should pass to allow the drug to take effect.[2] By contrast, the American Association of Respiratory Care guidelines suggest a minimum waiting time of 15 min before retesting lung function.[3] This lack of consensus in international guidelines reflects the uncertainty surrounding the assessment of the BDR within clinical respiratory laboratories.

Thus, the objective of this work was to define the optimal BDR time to assess the reversibility or nonreversibility of airway obstruction.

SUBJECTS AND METHODS

Study design and patients
This was a prospective analytical study, which was spread over 8 months, to determine the best time to interpret bronchodilator reversibility. The study was conducted at the Pulmonary Department of La Marsa Internal Security Forces Hospital (Tunisia).

All patients who presented with asthma or chronic obstructive pulmonary disease (COPD) or who had chronic symptoms lasting >3 months that were consistent with asthma or COPD were included and underwent an initial spirometry. Only patients aged 18–75 years who had airway obstruction, as defined by an FEV1/FVC ratio <0.7 and FEV1 <80%, were accepted in the study. The exclusion criteria were as follows: the presence of an acute exacerbation of asthma or COPD; the presence of certain lung diseases which may be responsible for airway obstruction such as bronchiectasis, bronchiolitis, sarcoidosis, or cystic fibrosis; cardiovascular diseases such as a recent myocardial infarction (<3 months), acute heart failure, and unstable blood pressure; an uncooperative patient; abnormal chest X-ray imaging results; systemic corticosteroid use; and recent infection.

Spirometry measurements
Spirometry was conducted using an electronic spirometer (Vmax AGAIN; Viasys Healthcare, Yorba Linda, CA, USA) and using the official ATS/ERS statement on pulmonary function testing in adults. These guidelines include the recommended reproducibility and acceptability to rule out abnormal or unacceptable curves.[1,2,4] Patients were asked to omit using short-acting beta-agonists for at least 8 h, long-acting beta-agonists for at least 12 h, and oral theophylline or long-acting bronchodilators (indacaterol and tiotropium) for at least 24 h.

Spirometry was performed with the patient seated while wearing a nose clip. After bronchodilator inhalation, three acceptable and repeatable forced expiratory maneuvers were performed at baseline and at each time point (as detailed below). The best test at each stage was reported per international standards.[4]

The bronchodilator was the short-acting β_2-mimetic salbutamol (Aérol; Pharmabolix), which was administered through pressurized metered-dose inhalers (pMDIs) in combination with a large volume spacer (Volumatic; GlaxoSmithKline, United Kingdom). The patients inhaled two puffs of salbutamol in 1-min intervals for a total dose of 200 mcg. Spirometry was performed after 5, 10, 15, 20, and 30 min.

Statistics and data analysis
Data were analyzed using the IBM SPSS 20 (IBM, Armonk, NY, USA). The Student's *t*-test on paired series was used to compare the results of spirometry before and after bronchodilation. McNemar's test was used to compare reversibility between different time points. Statistical significance was accepted at the 0.05 level.

Ethical consideration
This study had no direct benefit to patients. Written informed consent was obtained once, after explaining to the patients the study goals, its interests, its progress and the manoeuver to be performed. The study was conducted after obtaining the approval of the hospital ethics committee.

RESULTS

One hundred and fifty-four consecutive patients evaluated in the respiratory department and for whom pulmonary function testing was indicated were recruited to participate in the study. After verifying whether they met the inclusion criteria or the exclusion criteria, 69 patients were selected. Eleven patients missed a postbronchodilator spirometry assessment, as follows: two patients missed the 5-min postbronchodilator assessment; four patients, the 10-min postbronchodilator assessment; and five patients, the 15-min postbronchodilator assessment. Only 58 patients underwent the protocol comprehensively. The overall proportion of men was 65.5% (*n* = 38). Thirty-two patients were current smokers, and three patients were former smokers.

Table 1: Baseline lung function and characteristics of the whole population

	Mean±SD
Age (years)	54±15
BMI	28±3.6
FEV_1 (L)	2±0.8
FEV_1 (percentage of predicted)	62±15
FVC (L)	3.22±1.14
FVC (percentage of predicted)	82.4±18
FEV_1/FVC ratio	61±7.5

SD: Standard deviation, BMI: Body mass index, FVC: Forced vital capacity, FEV_1: Forced expiratory volume in 1 s

The baseline lung function and characteristics of the whole population are shown in Table 1. The distribution of our patients was as follows: 28 patients had asthma and were classified with moderate persistent asthma (46%), severe persistent asthma (43%), or mild persistent asthma (11%); 14 patients had moderate COPD (64.2%) or severe COPD (35.8%) and were stratified by the severity of obstruction into one of the four Global Initiative for Chronic Obstructive Lung Disease (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 (Stage IV: FEV1 <30% of predicted);[3] 16 unlabeled patients were undergoing a consultation for the first time.

Spirometry results after bronchodilation

The increase in FEV1 and FVC from their baseline values was variable, depending on the measurement period [Table 2]. After the inhalation of salbutamol, the mean individual peak bronchodilation (i.e., the maximum increase in FVC or FEV1 from the baseline values) occurred at 20 and 30 min for FVC and FEV1, respectively [Figure 1].

The absolute increase in the postbronchodilator FEV1, compared to the initial FEV1, was significant at different measurement times. The mean absolute change in the postbronchodilator FEV1 (i.e., ΔFEV1) was not statistically significant between the 5th min and the following time points. However, the ΔFEV1 was statistically significant between the 10th min and the following time points [Table 3]. Furthermore, the mean absolute change in the postbronchodilator FVC from the baseline value (i.e., ΔFVC) was statistically significant for different

time relative to the initial FVC. However, as with FEV1, the FVC was decreased but not significantly, at 10 min postbronchodilation [Table 4].

The GOLD defines acute bronchodilator reversibility as a FEV1 improvement from the predose value by 12% and >200 mL. Based on this definition, this study had 31 (53%) reversible patients with the maximum value occurring at 20 min and the minimum value occurring at 10 min.

Based on the guidelines of the ATS/ERS, which defines reversibility as an increase in the FEV1 or the FVC by >12% from the initial value in association with an absolute increase of >200 mL, this study had 39 (67.2%) reversible patients with the maximum value occurring at 20 min ($n = 33$) [Figure 2]. This number of reversible patients was significantly greater at 20 min than at 5 ($P = 0.012$) and 10 min ($P = 0.039$).

Analysis of subgroups

The mean changes in FEV1 and FVC from the baseline value in the reversible and nonreversible patient groups at different measurement times are shown in Tables 5, 6 and Figure 1.

Results of the reversible patient group (n = 39), based on American Thoracic Society/European Respiratory Society criteria

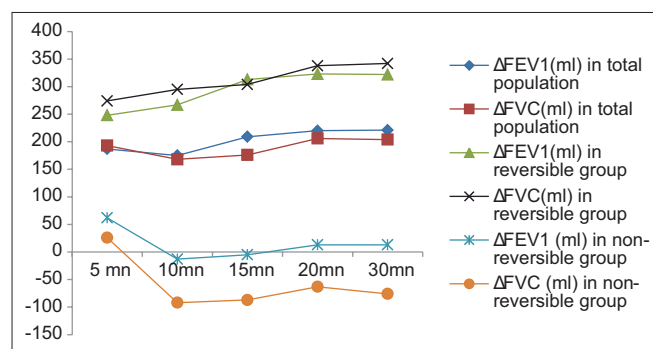The mean absolute increase in the FEV1 and the FVC from

Figure 1: The mean absolute change in forced expiratory volume in 1 s (Δ forced expiratory volume in 1 s) and forced vital capacity (Δ forced vital capacity) at different measurement times in the total population and in both groups (reversible and nonreversible)
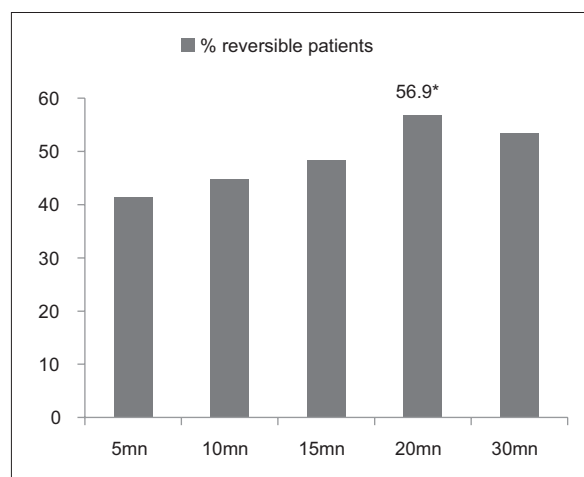

Figure 2: Proportion of reversible patients according to the American Thoracic Society/European Respiratory Society guidelines

Table 2: Forced expiratory volume in 1 s and forced vital capacity after bronchodilation and their mean absolute change from baseline at different measurement period

	Initial	5 mn	10 mn	15 mn	20 mn	30 mn
FEV₁ (L)	2.001±0.83	2.191±0.83	2.180±0.83	2.214±0.84	2.226±0.84	2.227±0.85
ΔFEV₁ (mL)		187±0.17	175±0.25	209±0.23	220±0.23	221±0.23
FVC (L)	3.22±1.12	3.419±1.12	3.393±1.08	3.401±1.11	3.432±1.12	3.430±1.14
ΔFVC (mL)		193±0.23	168±0.34	176±0.32	206±0.33	204±0.35

ΔFEV₁: Mean absolute change in the postbronchodilator FEV₁ from baseline value, ΔFVC: Mean absolute change in the postbronchodilator FVC from baseline value, FVC: Forced vital capacity, FEV₁: Forced expiratory volume in 1 s

Table 3: Comparison of the mean absolute change in the postbronchodilator forced expiratory volume in 1 s (mean absolute change in the postbronchodilator forced expiratory volume in 1 s from baseline value) at different measurement times in the total population

	ΔFEV_1 (mL)	*P*
Initial FEV_1 versus FEV_1		
5 mn	187±0.17	<0.001*
10 mn	175±0.25	<0.001*
15 mn	209±0.23	<0.001*
20 mn	220±0.23	<0.001*
30 mn	222±0.23	<0.001*
FEV_1 5 mn versus FEV_1		
10 mn	−11.9±0.2	0.66
15 mn	21.9±0.16	0.32
20 mn	33.6±0.16	0.11
30 mn	34.1±0.16	0.17
FEV_1 10 mn versus FEV_1		
15 mn	33.7±0.1	0.015*
20 mn	45.5±0.13	0.013*
30 mn	46±0.15	0.025*
FEV_1 15 mn versus FEV_1		
20 mn	11.7±0.12	0.47
30 mn	12.2±0.13	0.5
FEV_1 20 mn versus FEV_1		
30 mn	0.5±0.1	0.5

*Significant difference ($P<0.05$). ΔFEV_1: Mean absolute change in the postbronchodilator FEV_1 from baseline value, FEV_1: Forced expiratory volume in 1 s

Table 4: Comparison of the mean absolute change in the postbronchodilator forced vital capacity (mean absolute change in the postbronchodilator forced vital capacity from baseline value) at different measurement times in the total population

	ΔFVC (mL)	*P*
Initial FVC versus FVC		
5 mn	193±0.23	<0.001*
10 mn	168±0.34	<0.001*
15 mn	176±0.32	<0.001*
20 mn	206±0.33	<0.001*
30 mn	204±0.35	<0.001*
FVC 5 mn versus FVC		
10 mn	−25.5±0.27	0.47
15 mn	−17.9±0.26	0.61
20 mn	13.2±0.23	0.66
30 mn	11.2±0.27	0.75
FVC 10 mn versus FVC		
15 mn	7.9±0.13	0.66
20 mn	38.7±0.18	0.12
30 mn	36.7±0.19	0.15
FVC 15 mn versus FVC		
20 mn	30.8±0.2	0.24
30 mn	28.7±0.2	0.28
FVC 20 mn versus FVC		
30 mn	2.07±0.14	0.91

*Significant difference ($P<0.05$). ΔFVC: Mean absolute change in the postbronchodilator FVC from baseline value, FVC: Forced vital capacity

the baseline value was progressive and increased over time and reached its maximum at 20 min for FEV1 and at 30 min for FVC. The mean ΔFEV1 in this group was significant from the 15th min and the following time points, compared to the 5th and 10th min. However, the difference was not significant between the 5th and 10th min. The mean ΔFVC,

unlike ΔFEV1, was not significant between the 10th and the following time frames. However, the variation was significant between the 5th and 20th min.

Results of the nonreversible patient group (n = 19), based on American Thoracic Society/European Respiratory Society criteria

The mean ΔFEV1 and ΔFVC were irregular as a function of the measurement time. An increase in the FEV1 occurred only at 5 min. This increase was only significant, compared to the initial FEV1. At 10 min, the FEV1 decreased insignificantly. The average variation in the FVC was insignificant at the different measurement times. An increase was observed only at 5 min. Beyond this time frame, the FVC decreased from the baseline.

DISCUSSION

The main results of this study are the following:
1. The maximum response occurred after 20 and 30 min for FVC and FEV1, respectively
2. A simultaneous and nonsignificant fall in FEV1 and FVC was observed at 10 min, particularly in the group of nonreversible patients. This decline disappeared when considering the subpopulation of reversible patients
3. The percentage of reversible patients in our sample was guideline dependent. It increased from 53% to 67.2% when using the ATS/ERS definition compared to using the GOLD
4. The maximum number of reversible patients was significantly different at 20 min compared to 5 and 10 min.

Asthma and COPD are dominant pathologies of airway obstruction. The clinical distinction between these two entities is generally easy. However, when an obstructive syndrome is present, the distinction between asthma and COPD is confusing in many patients. In this situation, bronchodilator reversibility testing is a major distinguishing criterion. The method used to assess reversibility may be crucial because the degree of response may be affected by many factors such as the dose and type of bronchodilator, the method of administration, and the time elapsed between drug administration and repeat spirometry to assess BDR.

Time to maximal bronchodilator response

Some research indicates that short-acting β_2-mimetic bronchodilators exert their effect very quickly, usually as early as 1 min, and the effect persists for 3–6 h.[5] However, the time required for the maximum BDR is ill-defined and remains variable, depending on the study protocol. Studies quantifying the time course of salbutamol in adult asthmatic patients using nebulizers, dry powder inhalers, or pMDIs suggest that the maximum increase in FEV1 following salbutamol administration occurs between 45 and 60 min with approximately 80% of the maximal response occurring within the first 10 min.[5-11] Matera *et al.*

Table 5: Comparison of the mean absolute change in the postbronchodilator forced expiratory volume in 1 s (mean absolute change in the postbronchodilator forced expiratory volume in 1 s from baseline value) at different measurement times in both groups (reversible and nonreversible)

	ΔFEV1 in reversible group (mL)	*P*	ΔFEV1 in nonreversible group (mL)	*P*
Initial FEV$_1$ versus FEV$_1$				
5 mn	248±0.16	<0.001*	62.1±0.11	0.024*
10 mn	267±0.16	<0.001*	−13.1±0.29	0.84
15 mn	313±0.16	<0.001*	−5.2±0.22	0.92
20 mn	323±0.18	<0.001*	13.1±0.16	0.73
30 mn	322±0.18	<0.001*	13.6±0.17	0.73
FEV$_1$ 5 mn versus FEV$_1$				
10 mn	18.9±0.13	0.39	−75.2±0.29	0.28
15 mn	65.3±0.12	0.002*	−67.3±0.2	0.17
20 mn	74.9±0.14	0.004*	−48.9±0.15	0.18
30 mn	74.3±0.18	0.015*	−48.4±0.17	0.24
FEV$_1$ 10 mn versus FEV$_1$				
15 mn	46.4±0.09	0.004*	7.8±0.12	0.78
20 mn	55.8±0.09	0.001*	26.3±0.19	0.57
30 mn	55.3±0.13	0.012*	26.8±0.19	0.54
FEV$_1$ 15mn versus FEV$_1$				
20 mn	9.5±0.12	0.67	18.4±0.12	0.53
30 mn	8.9±0.14	0.69	18.9±0.13	0.55
FEV$_1$ 20 mn versus FEV$_1$				
30 mn	0.5±0.11	0.97	0.5±0.07	0.97

*Significant difference ($P<0.05$). ΔFEV$_1$: Mean absolute change in the postbronchodilator FEV$_1$ from baseline value, FEV$_1$: Forced expiratory volume in 1 s

Table 6: Comparison of the mean absolute change in the postbronchodilator forced vital capacity (mean absolute change in the postbronchodilator forced vital capacity from baseline value) at different measurement times in both groups (reversible and nonreversible)

	ΔFVC in reversible group (mL)	*P*	ΔFVC in nonreversible group (mL)	*P*
Initial FVC versus FVC				
5 mn	274±0.22	<0.001*	26±0.14	0.43
10 mn	295±0.23	<0.001*	−92±0.38	0.31
15 mn	304±0.21	<0.001*	−87±0.34	0.28
20 mn	338±0.27	<0.001*	−63±0.29	0.36
30 mn	342±0.29	<0.001*	−76±0.29	0.26
FVC 5mn versus FVC				
10 mn	20.2±0.16	0.44	−119±0.4	0.21
15 mn	29.7±0.17	0.30	−114±0.36	0.18
20 mn	63.8±0.19	0.045*	−90.1±0.28	0.17
30 mn	67.1±0.25	0.1	−103±0.29	0.14
FVC 10 mn versus FVC				
15 mn	9.4±0.14	0.68	4.74±0.11	0.86
20 mn	43.5±0.15	0.095	28.9±0.23	0.60
30 mn	46.9±0.19	0.13	15.7±0.2	0.74
FVC 15 mn versus FVC				
20 mn	34.1±0.20	0.30	24.2±0.2	0.60
30 mn	37.4±0.22	0.31	11.05±0.14	0.73
FVC 20 mn versus FVC				
30 mn	3.33±0.16	0.89	−13.16±0.11	0.63

*Significant difference ($P<0.05$). ΔFVC: Mean absolute change in the postbronchodilator FVC from baseline value, FVC: Forced vital capacity

and Lötvall *et al*.[12,13] reported that the peak FEV1 response occurred at 30 and 15 min, respectively, after administering salbutamol with a spacer. In 2000, based on a postal survey, which requested details of methods used to assess and interpret bronchodilator reversibility, Borg *et al*.[14] reported wide variations in the waiting times that ranged 4–20 min with a median waiting time of 10 min. These results were consistent with a survey on BDR testing that was conducted in Australia and New Zealand in 2003.[15]

The BDR in children also varies, based on some research.[16,17] In a study involving asthmatic children, Stavreska *et al*.[18] concluded that a minimum interval of 20 min is required before retesting spirometry to document the maximal BDR. In our study, the maximum response occurred after 20 and 30 min for FVC and FEV1, respectively. In the subgroup study, the maximum increase in FEV1 and FVC occurred at 20 and 30 min, respectively, in the reversible group. The maximum BDR occurred at 5 min in the nonreversible group. In the literature, the BDR varies significantly in nonreversible patients, particularly in patients with COPD. Some patients have increases in FEV1 and in FVC, some patients have changes in FEV1 or FVC alone, and minority of the patients do not have changes in either.[19] Our results were in agreement with

studies showing partial improvement in volume and pulmonary discharge after bronchodilator administration but without achieving the threshold of reversibility. First, changes in the end-expiratory lung volume after the administration of a short-acting bronchodilator reflect changes in the residual volume and improvement in the FVC, irrespective of the GOLD grade.[20] On the other hand, increases in FEV1 primarily occur because of lung volume recruitment: the FEV1/FVC ratio is unaltered or may decrease postbronchodilator administration. Moreover, bronchodilators are associated with reduced airway resistance and elastic loading of the inspiratory muscles, which can improve FEV1.[21,22]

The length of time before repeating spirometry to assess reversibility varies considerably in adults and children. It is, therefore, imperative that guidelines for standardizing the time period between bronchodilator inhalation and the retesting of lung function are based on studies using similar delivery devices and methods (e.g., drug choice and dose, delivery method) to assist in the development of evidence-based guidelines for performing and interpreting the BDR.

Paradoxical response to the bronchodilator
A paradoxical response to salbutamol particularly occurred in the nonreversible patients. After an initial increase

in response at 5 min, we noted a simultaneous fall in the FEV1 and FVC at 10 min, compared to the baseline value [Figure 1].

Paradoxical response after bronchodilator administration has been described in several studies and case reports.[23,24] Nicklas[25] reported paradoxical bronchospasm in response to salbutamol in 126 individuals during a 14-year period (1974–1988) in the United States; Mirsadraee *et al.*[26] described a paradoxical response in 3% of patients with asthma; and Bhatt *et al.*[27] reported a paradoxical response to albuterol (salbutamol) in 4.54% of patients, and the paradoxical response frequency was similar in patients with COPD and smokers without airflow obstruction.

A subclinical paradoxical response may be considerably more common than symptomatic bronchospasm,[27,28] as evidenced in our study in which all patients had an asymptomatic fall in FEV1 and FVC. The mechanisms underlying paradoxical response remain unknown, and several mechanisms have been proposed such as an immunoglobulin E-mediated reaction to excipients in the pMDI (e.g., soybean lecithin),[29] irritation secondary to propellants or preservatives, airflow turbulence due to inappropriate inhaler technique, and solution osmolality or pH. Preservatives such as benzalkonium chloride and ethylenediaminetetraacetic acid cause dose-related acute decreases in lung function.[30-34] Some investigators have suggested that a fall in FEV1 or FVC postbronchodilator administration is common and likely related to spontaneous variability in repeated measurements.[35-37] Burns and Gibson[38] theorized that deep inhalation in the presence of obstruction might cause large swings in intrathoracic pressure, resulting in airway edema and worsening airway smooth muscle shortening. Hodder *et al.*[39] suggest that an asymptomatic drop in FEV1 may not reflect administration-induced paradoxical bronchoconstriction alone but may in the part result from repeated spirometry maneuvers. In our opinion, this hypothesis could explain the decline of the FVC that occurred beyond the 5th min, especially in the nonreversible group. Therefore, the paradoxical phenomenon did not occur in the reversible patients. This finding could be explained by the dominance of the bronchodilatory effect of the drug over its bronchoconstrictor effect. Thus, further studies in this direction are needed to better specify the pathophysiological mechanisms of the bronchodilator.

Bronchodilator reversibility testing

Testing airway reversibility is an important diagnostic tool when investigating patients with obstructive airway diseases. However, there is no clear consensus concerning which definition of acute bronchodilator reversibility should be universally adopted because several factors may influence the determination of bronchodilator reversibility. The two most commonly used definitions are the GOLD 2006 criteria[40] and the ATS/ERS 2005 criteria.[1] The GOLD definition only opts for variation in the FEV1, whereas the

ATS/ERS Task Force recommends including FVC when assessing bronchodilator responsiveness.

In our study, at 5 min after bronchodilation, the FVC was more reactive in absolute terms, compared to the FEV1 (193 mL vs. 187 mL). Beyond 5 min, the FEV1 was more responsive [Table 2]. In reversible patients, the FVC was more reactive in absolute value over the different time periods, except for the 15-min time point [Figure 1]. As a result, the percentage of reversible patients in our sample was guideline dependent: 53% for the GOLD criteria and 67.2% for the ATS/ERS criteria. In another study involving COPD patients, Ben Saad *et al.* demonstrated that the proportion of "responders" depended entirely on the definition of responsiveness and was 31% and 52%, based on the GOLD and ATS/ERS criteria, respectively.[41] In a cohort study by Tashkin *et al.*, the magnitude of bronchodilator responsiveness when using the current ATS/ERS criteria was greater than expected: >40% of patients showed some type of responsiveness.[28] In fact, the interpretation of reversibility, based on the unique variations in FEV1, underestimates the true effects of the bronchodilator and the rate of patients responding to the bronchodilator reversibility testing. Thus, the addition of FVC improves sensitivity and optimizes the assessment of bronchodilator responsiveness as the improvement of the effects of dynamic hyperinflation is better evaluated using the FVC. Including the FVC response increases the number of positive responses in patients with airway obstruction of >50% and is particularly relevant in elderly patients with severe airway obstruction.[35] For this reason, we opted to use the ATS/ERS definition for the subgroup study. By applying this definition, we found that 67.2% of patients responded to the bronchodilator reversibility test in our sample and the maximum response was at 20 min.

Limitation of the study

This study has some limitations. First, this work only includes 58 patients to modify a well-established reversibility regimen after bronchodilators at 20 min. Second, limiting the measurement time to 30 min after bronchodilatation may be insufficient to determine accurately the time to maximal BDR. Waiting longer before retesting FEV1 after the test dose will probably result in the detection of a greater change in FEV1 in some patients and hence increase the number of patients regarded as having a reversible response. An additional limitation in our study was that the maximum BDR was calculated according to absolute change in FEV1 and FVC from baseline. Recent studies suggest that the most appropriate expression of the BDR is using the change in FEV1 or FVC as percentage of the predicted value or as *Z*-scores.[40] However, the aim of the current study was not to examine the most clinically appropriate way of expressing a BDR. As long as there is no standardization between bronchodilator inhalation and retesting of lung function within clinical respiratory laboratories, it is unlikely that consensus will be reached on the most appropriate way to express the BDR.

CONCLUSIONS

The ATS/ERS definition for BDR is more sensitive for assessing bronchodilator reversibility. By adopting this definition, more than one-half of our population (67.2%) could be considered "reversible," with the maximum response occurring at 20 min and a minimum response at 5 min. The bronchodilator reversibility rate and the maximum BDR (expressed as the maximum increase in FEV1 + FVC over the baseline values) were better at 20 min than at 15 or 30 min. In daily practice and for practical reasons, assessing the BDR does not exceed 10 min. Thus, we suggest repeating a spirometry after 20 min in patients who have not achieved the threshold of reversibility after 5 or 10 min. Further large-scale studies in this direction are needed to modify the current clinical practice.

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Conflicts of interest
There are no conflicts of interest.

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