Peer reviewed article

Bronchodilator response in residual volume in irreversible airway obstruction

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Summary

Background: Although airway obstruction, as defined by improvement of forced expiratory volume in one second (FEV_1) and/or forced vital capacity (FVC), is irreversible in patients with COPD, they clearly seem to benefit from treatment with inhaled bronchodilators.

Aims: To assess the response pattern of residual volume (RV) compared to FEV_1 after bronchodilation in patients with reversible and irreversible airway obstruction.

Methods: Changes in static lung volumes were compared with improvement in dynamic lung volumes in 396 consecutive patients undergoing reversibility testing with repeat bodyplethysmography. Reversibility was defined as improvement of FEV_1 >200 ml and >12% after inhalation of fenoterol hydrobromide.

Results: Irreversibility was found in 297 out of 396 patients with airway obstruction.

Except for total lung capacity (TLC), all parameters (residual volume [RV], vital capacity [VC], forced inspiratory vital capacity [IVC], forced vital capacity [FVC], forced expiratory volume in one second [FEV_1] and the FEV_1/VC ratio) showed statistically significant changes after bronchodilation in 396 patients.

The multiple linear regression model adjusted for age, sex and BMI showed a non-linear relationship between ΔFEV_1 or ΔVC compared to ΔRV after bronchodilation. If the increase in ΔFEV_1 is lower than 0.1 L, ΔRV remains constant. However, if the increase in ΔFEV_1 is more than 0.1 L, ΔRV decreases too. The same is found at an increase in VC of 0.3 L.

Conclusion: In summary, in patients with irreversible airway obstruction ΔRV cannot be predicted by ΔFEV_1 or ΔVC after bronchodilation. Therefore, spirometric assessment should be complemented by bodyplethysmography.

Key words: bodyplethysmography; COPD; FEV_1; hyperinflation; lung function; reversibility

Introduction

On the basis of current guidelines [1], chronic obstructive pulmonary disease (COPD) is defined as a post-bronchodilation ratio of FEV_1/FVC <0.7. Possible asthma can be differentiated on the strength of reversible airway obstruction, which is defined as post-bronchodilator improvement of FEV_1 and/or FVC >200 mL and >12% [2]. Measurement of FEV_1 is not only important for detection of airway obstruction; it further allows the severity of airway obstruction to be determined. However, changes in FEV_1 often do not correlate with improvements in symptoms, exercise capacity and quality of life in patients with COPD [3]. Additionally, post-bronchodilator changes in FEV_1 have no predictive value for disease progression in COPD [4].

An autopsy study has shown that airway calibre increases with augmented lung volumes [5]. However, in patients with emphysema, the calibre of small airway changes does not correspond to changes in lung volumes [5]. Hyperinflation as a consequence of persistent airway obstruction causes increased breathing work and dyspnoea in patients with COPD [6]. Although airway obstruction is irreversible in patients with COPD, they clearly seem to benefit from treatment with inhaled bronchodilators. Bronchodilators have been shown not only to improve symptoms but also to increase exercise capacity in COPD, without producing significant changes in FEV_1 [7–9].

We postulated that inhaled bronchodilators might decrease static lung volumes following administration of bronchodilators in patients with irreversible airway obstruction. In this study we assessed the response pattern of RV compared to FEV_1 after bronchodilation in patients with obstructive lung disease.

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Patients and methods

The study population comprised 396 consecutive patients with airway obstruction (FEV_1/FVC <70%; 267 men and 129 women; age 20–92 years) undergoing reversibility testing with two subsequent bodyplethysmographies at the pulmonary function laboratory of Basel University Hospital over a 24-month period. Patients were asked to abstain from taking short-acting bronchodilators for at least 12 hours and long-acting bronchodilators for at least 24 hours prior to lung function testing. Bodyplethysmography was performed in the sitting position before and 15 minutes after inhalation of 200 µg fenoterol hydrobromide on a Masterlab Pro bodyplethysmography and with LAB Software Ver.4.3 from Erich Jäger GmbH, Germany. The predicted normal values were derived from the European Community for Coal and Steel Study [10].

For the analysis patients were stratified to either a reversible or an irreversible obstructive group. Reversibility was defined by improvement of FEV1 >200 ml and >12% after inhalation of fenoterol hydrobromide [11].

Absolute improvements in static and dynamic lung volumes, such as total lung capacity (TLC), residual volume (RV), vital capacity (VC), forced inspiratory vital capacity (IVC) and forced vital capacity (FVC) were compared to the absolute changes of forced expiratory volume in one second (FEV_1) after bronchodilation.

Data are expressed as mean unless otherwise stated. For subgroup comparisons lung function parameters were standardised as % of predicted normal values. Statistical analysis of pre- and postbronchodilator comparisons was performed using paired t-test (SPSS 11.0 and 12.0; Excel 2002). A p value of <0.05 was taken to be of statistical significance. Relationships were determined using the Pearson correlation for normally distributed variables.

A nonlinear regression model with restricted five knot cubic splines was performed.

Independent parameters are ΔFEV1 ($dFEV_1$) and ΔVC (dVC), the dependent parameter is ΔRV (dRV). Change (Δ or d) is defined as post- minus prebronchodilation. To adjust for a possible age, body mass index (BMI) and gender effect, these parameters were included as linear factors in the regression model (using R version 2.5).

Results

396 consecutive patients, 267 men and 129 women, were included. The mean age was 62.5 (SD 0.7) years with a range of 20–92 years. The mean age of patients with irreversible airway obstruction was 63.7 (SD 0.8) years and significantly higher compared to patients with reversible airway obstruction (58.8 (SD 1.6) years; p = 0.0014). The mean body mass index of all patients was 26.0 kg/m² (SD 0.27) (table 1).

Out of the total of 396 patients 99 (25%) showed reversible airway obstruction (ΔFEV_1 improvement of 0.39L [SD 0.23]) (table 2) and 297/396 patients (75%) irreversible airway obstruction (ΔFEV_1 improvement of 0.09 L [SD 0.09]) (table 3).

Except for TLC, all parameters such as RV, VC, IVC, FVC, FEV_1 and the FEV_1/VC ratio showed statistically significant changes after bronchodilation in the whole study group (table 2 and 3). The mean %RV decrease and %FEV_1 increase were 8.4% (SD 15.3) and 25.4% (SD 14.0) respectively (table 2) in the group of patients with reversible airway obstruction and 0.5% (SD16.5) and 5.9% (SD6.8) respectively in the group of patients with irreversible airway obstruction (table 3).

By performing a multiple linear regression model adjusted for age, sex and BMI, we found a non-linear relationship between ΔFEV_1 or ΔVC compared to ΔRV after bronchodilation. There is a highly significant contribution of the spline to the regression model (p <0.001), indicating a non-linear relationship between ΔFEV_1 and ΔRV as shown in figure 1. Below a ΔFEV_1 value of about 0.1 L ΔRV remains constant, whereas above a ΔFEV_1 value of 0.1 L ΔRV decreases.

ΔRV is also dependent in a nonlinear manner on ΔVC (p <0.001). ΔRV decreases until a ΔVC value of 0.3L as shown in figure 2. Differences between ΔRV from the 25th to the 75th quantile of ΔFEV_1 or ΔVC are estimated from the regression model and summarised in table 4.

Table 1

Sex, age, height and body mass index (BMI) in patients with reversible and irreversible airway obstruction.

	All patients	Reversible obstruction	Irreversible obstruction
Number	396	99	297
M / F	267 / 129	73 / 26	194 / 103
Age years	62.5 (SD 0.7)	58.8 (SD 1.6)	63.7 (SD 0.8)
Height (cm)	169 (SD 1.0)	170 (SD 1.0)	168 (SD 1.0)
BMI (kg/m²)	26.0 (SD 0.3)	26.6 (SD 0.6)	25.8 (SD 0.3)

Data are presented as mean SD; Reversible obstruction: >12% and 200ml FEV_1 improvement after bronchodilation; Irreversible obstruction: <12% and /or <200 ml FEV_1 and or FVC improvement after bronchodilation; M / F: male/female; BMI: body mass index

Table 2

Static and dynamic lung volumes pre- and postbronchodilation in 99 patients with *reversible* airway obstruction.

	Pre bd		Post bd		Δ pre-post		p-value
	Litre	Pred	Litre	Pred	Litre	% change	
TLC	6.46 (SD 1.36)	104% (SD 19)	6.40 (SD 1.38)	103% (SD 19)	–0.06 (SD 0.52)	–0.8% (SD 7.8)	0.245
RV	3.34 (SD 1.18)	151% (SD 48)	3.01 (SD 1.03)	137% (SD 44)	–0.33 (SD 0.55)	–8.4% (SD 15.3)	<0.001
VC	3.12 (SD 3.12)	81% (SD 19)	3.39 (SD 0.96)	88% (SD 19)	+0.27 (SD 0.32)	+9.8% (SD 11.8)	<0.001
IVC	2.96 (SD 0.94)	77% (SD 18.)	3.37 (SD 0.94)	88% (SD 18)	+0.41 (SD 0.27)	+16.0% (SD 12.3)	<0.001
FEV_1	1.64 (SD 0.62)	56% (SD 18)	2.04 (SD 0.74)	69% (SD 21)	+0.39 (SD 0.23)	+25.4% (SD14.0)	<0.001
FEV_1/VC	52% (SD 10.6)		59% (SD 12.00)		+7% (SD 5.61)		<0.001
FVC	2.63 (SD 0.85)	71% (SD 18)	3.03 (SD 0.90)	82% (SD 19)	+0.40 (SD 0.27)	+16.5% (SD 11.8)	<0.001

Pre: values prior to bronchodilation; Post: values after bronchodilation; Δ pre-post: difference of the value before and after bronchodilation of the respective parameter; %change: %change after bronchodilation based on pre-bronchodilation values; Pred: Percentage of predicted lung volumes; TLC: Total lung capacity; RV: Residual volume; VC: Vital capacity; IVC: Forced inspiratory vital capacity; FEV_1: Forced expiratory volume in 1 sec.; FEV_1/VC: Tiffeneau quotient, quotient of forced expiratory volume in 1 sec to vital capacity; FVC: Forced vital capacity

Table 3

Static and dynamic lung volumes pre- and postbronchodilation in 297 patients with *irreversible* airway obstruction.

	Pre		Post		Δ pre-post		p-value
	Litre	Pred	Litre	Pred	Litre	% change	
TLC	6.05 (SD1.42)	101% (SD 18.8)	6.08 (SD 1.38)	102% (SD 17.4)	+0.03 (SD 0.46)	+1.0% (SD 7.9)	0.251
RV	3.17 (SD 1.13)	142% (SD 48.5)	3.09 (SD 1.02)	138% (SD 43.6)	–0.08 (SD 0.45)	–0.5% (SD 16.5)	0.004
VC	3.07 (SD 3.28)	81% (SD 18.8)	3.19 (SD 3.51)	84% (SD 18.7)	+0.12 (SD 0.31)	+4.3% (SD 8.4)	<0.001
IVC	2.83 (SD 0.94)	80% (SD 18.7)	2.94 (SD 0.95)	83% (SD 18.4)	+0.11 (SD 0.22)	+4.7% (SD 9.2)	<0.001
FEV_1	1.60 (SD 0.69)	59% (SD 20.0)	1.69 (SD 0.72)	62% (SD 20.7)	+0.09 (SD 0.09)	+5.9% (SD 6.8)	<0.001
FEV^1/VC	54.1% (SD 12.0)		55.2% (SD 12.8)	+1.2% (SD 4.0)		<0.001	
FVC	2.49 (SD 0.88)	73% (SD 18.7)	2.61 (SD 0.89)	76% (SD 18.4)	+0.12 (SD 0.20)	+5.8% (SD 9.8)	<0.001

Pre: values prior to bronchodilation; Post: values after bronchodilation; Δ pre-post: difference of the value before and after bronchodilation of the respective parameter; %change: % difference of the value before and after bronchodilation of the respective parameter referring to the greater value prebronchodilation; Pred: percentage of predicted lung volumes; TLC: Total lung capacity; RV: Residual volume; VC: Vital capacity; IVC: Forced inspiratory vital capacity; FEV_1: Forced expiratory volume in 1 sec.; FEV_1/VC: Tiffeneau quotient, quotient of forced expiratory volume in 1 sec to vital capacity; FVC: Forced vital capacity

Table 4

Differences between ΔRV from the 25th to the 75th quantile of ΔFEV_1 or ΔVC.

	25th-75th quantile	ΔRV	95% CI
ΔFEV_1	0.05–0.22	–0.15	–0.14, 0.03
ΔVC	0.0–0.26	–0.26	–0.37, –0.16

Δ: difference of the value before and after bronchodilation of the respective parameter; RV: Residual volume; VC: Vital capacity; FEV_1: Forced expiratory volume in 1 second; CI: confidence interval

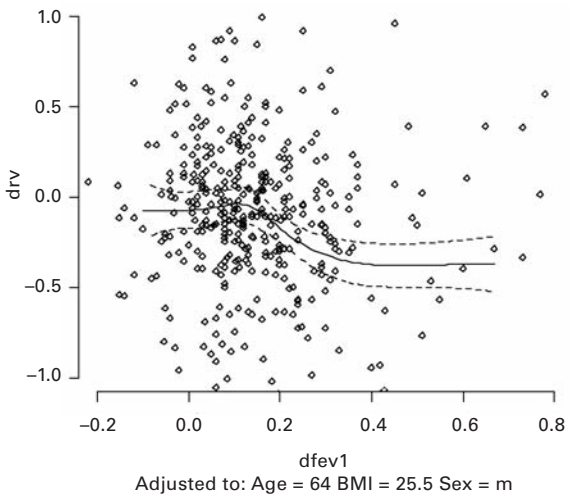

Figure 1

Adjusted multiple linear regression model showing a non-linear relationship between ΔFEV_1 compared to ΔRV after bronchodilation.
d: difference in the value of the respective parameter before and after bronchodilation; RV: Residual volume in litre, FEV_1: Forced expiratory volume in 1 second in litres.

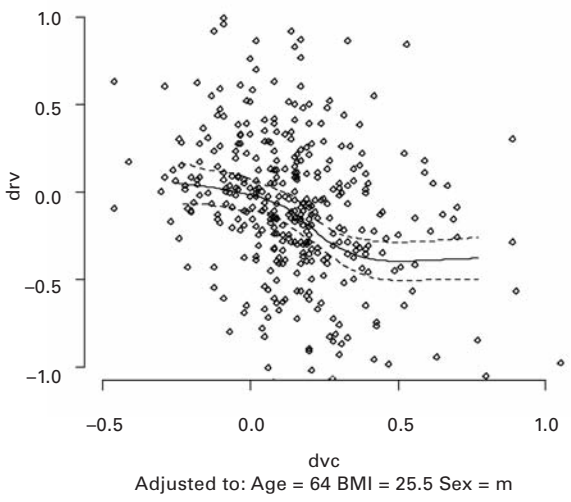

Figure 2

Adjusted multiple linear regression model showing a non-linear relationship between ΔVC compared to ΔRV after bronchodilation.
d: difference in the value of the respective parameter before and after bronchodilation; RV: Residual volume in litres, VC: Vital capacity in litres

Discussion

Thus far postbronchodilator reversibility based on improvement in FEV_1 has been defined arbitrarily [13]. Although measurement of FEV_1 is of major diagnostic value in distinguishing between asthma and COPD, short-term post-bronchodilator improvement of FEV_1 is of no value as a predictor of disease progression [4] or long-term bronchodilator response in COPD. However, there is evidence that patients with irreversible airway obstruction benefit from inhaling bronchodilators [14, 15]. A significant decrease in lung hyperinflation without improvement in FEV_1 has been demonstrated after administration of low-dose salbutamol in selected patients with emphysema [12]. Data on exercise tolerance in patients treated with bronchodilators also support the notion that volume response may be an important feature in patients showing no significant improvement in FEV_1 after bronchodilation [14].

In the current study, we investigated volume response in almost 300 unselected consecutive patients with irreversible airway obstruction undergoing repeat bodyplethysmography after bronchodilation. All lung function parameters except TLC showed statistically significant changes after bronchodilation. The highest change was observed for RV. These findings are supported by O'Donnell et al. [12] who described a similar decrease in RV and minimal changes in TLC in a group of highly selected patients with COPD. In our multiple regression model we found a non-linear relationship between ΔFEV_1 or ΔVC compared to ΔRV after bronchodilation with a constant ΔRV in ΔFEV_1 values below 0.1 L and a decreasing ΔRV in ΔFEV_1 values above 0.1 L. Our study therefore shows that in irreversible airway obstruction changes in RV cannot be predicted by changes in FEV_1. These changes need to be studied systematically as they may potentially explain the symptomatic or quality-of-life benefit of bronchodilators in patients with irreversible airway obstruction.

Spirometric assessment of airway obstruction in patients with irreversible airway obstruction may be inadequate. Our findings argue in support of repeated measurements of static volumes with bodyplethysmography for functional assessment of COPD. This could potentially provide more precise lung function based outcome parameters for studies testing new therapies for COPD. We postulate that only a single lung function parameter may not be sufficient to study clinically important effects in assessment of drug response in combination with concomitant relief of symptoms and improvement of general health status [12, 16–20].

To sum up, in patients with irreversible airway obstruction changes in RV after bronchodilation cannot be predicted by changes in FEV_1 or VC. Spirometric assessment should therefore be complemented by bodyplethysmography.

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References

1 Rabe KF HS, Anzueto A, Barnes PJ, Buist SA, Calverley P, Fukuchi Y, et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary. Am J Respir Crit Care Med. 2007;176(6):532–55.
2 Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, et al.; ATS/ERS Task Force. Standardisation of spirometry. Eur Respir J. 2005;26(2):319–38.
3 O'Donnell DE. Assessment of bronchodilator efficacy in symptomatic COPD: is spirometry useful? Chest. 2000;117(2 Suppl):42S–7S.
4 Calverley PM, Burge PS, Spencer S, Anderson JA, Jones PW. Bronchodilator reversibility testing in chronic obstructive pulmonary disease. Thorax. 2003;58(8):659–64.
5 Wilson AG, Massarella GR, Pride NB. Elastic properties of airways in human lungs post mortem. Am Rev Respir Dis. 1974; 110(6):716–29.
6 Newton MF, O'Donnell DE, Forkert L. Response of lung volumes to inhaled salbutamol in a large population of patients with severe hyperinflation. Chest. 2002;121(4):1042–50.
7 Ikeda A, Nishimura K, Koyama H, Tsukino M, Mishima M, Izumi T. Dose response study of ipratropium bromide aerosol on maximum exercise performance in stable patients with chronic obstructive pulmonary disease. Thorax. 1996;51(1): 48–53.
8 Guyatt GH, Townsend M, Pugsley SO, Keller JL, Short HD, Taylor DW, et al. Bronchodilators in chronic air-flow limitation. Effects on airway function, exercise capacity, and quality of life. Am Rev Respir Dis. 1987;135(5):1069–74.
9 Boni E, Corda L, Franchini D, Chiroli P, Damiani GP, Pini L, et al. Volume effect and exertional dyspnoea after bronchodilator in patients with COPD with and without expiratory flow limitation at rest. Thorax. 2002;57(6):528–32.
10 Quanjer PH, Tammeling GJ, Cotes JE, Pedersen OF, Peslin R, Yernault JC. Lung volumes and forced ventilatory flows. Work Group on Standardization of Respiratory Function Tests. European Community for Coal and Steel. Official position of the European Respiratory Society. Rev Mal Respir. 1994;11 (Suppl 3):5–40.
11 Standardization of Spirometry, 1994 Update. American Thoracic Society. Am J Respir Crit Care Med. 1995;152(3):1107-36.
12 O'Donnell DE, Forkert L, Webb KA. Evaluation of bronchodilator responses in patients with "irreversible" emphysema. Eur Respir J. 2001;18(6):914–20.
13 Siafakas NM, Vermeire P, Pride NB, Paoletti P, Gibson J, Howard P, et al. Optimal assessment and management of chronic obstructive pulmonary disease (COPD). The European Respiratory Society Task Force. Eur Respir J. 1995; 8(8):1398–420.

14 O'Donnell DE, Fluge T, Gerken F, Hamilton A, Webb K, Aguilaniu B, et al. Effects of tiotropium on lung hyperinflation, dyspnoea and exercise tolerance in COPD. Eur Respir J. 2004;23(6):832–40.
15 Santus P, Centanni S, Verga M, Di Marco F, Matera MG, Cazzola M. Comparison of the acute effect of tiotropium versus a combination therapy with single inhaler budesonide/formoterol on the degree of resting pulmonary hyperinflation. Respir Med 2006;100(7):1277–81.
16 Belman MJ, Botnick WC, Shin JW. Inhaled bronchodilators reduce dynamic hyperinflation during exercise in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 1996;153(3):967–75.
17 O'Donnell DE, Lam M, Webb KA. Measurement of symptoms, lung hyperinflation, and endurance during exercise in chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 1998;158(5 Pt 1):1557–65.
18 O'Donnell DE, Lam M, Webb KA. Spirometric correlates of improvement in exercise performance after anticholinergic therapy in chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 1999;160(2):542–9.
19 Tantucci C, Duguet A, Similowski T, Zelter M, Derenne JP, Milic-Emili J. Effect of salbutamol on dynamic hyperinflation in chronic obstructive pulmonary disease patients. Eur Respir J. 1998;12(4):799–804.
20 Ramirez-Venegas A, Ward J, Lentine T, Mahler DA. Salmeterol reduces dyspnea and improves lung function in patients with COPD. Chest. 1997;112(2):336–40.

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