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ORIGINAL RESEARCH

Bronchodilator response of advanced lung function parameters depending on COPD severity

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Background: COPD is defined as partly irreversible airflow obstruction. The response pattern of bronchodilators has not been followed in advanced lung function parameters.

Purpose: The aim of this study was to investigate bronchodilator response pattern in advanced lung function parameters in a continuous fashion along forced expiratory volume in 1 second (FEV_1) percent predicted (%p) in COPD patients and controls.

Patients and methods: Eighty-one smokers/ex-smokers (41 controls and 40 COPD) performed spirometry, body plethysmography, impulse oscillometry and single-breath helium dilution carbon monoxide diffusion at baseline, after salbutamol inhalation and then after an additional inhalation of ipratropium.

Results: Most pulmonary function parameters showed a linear increase in response to decreased FEV_1%p. The subjects were divided into groups of FEV_1%p <65 and >65, and the findings from continuous analysis were verified. The exceptions to this linear response were inspiratory capacity (IC), forced vital capacity (FVC), FEV_1/FVC and expiratory resistance (R_{ex}), which showed a segmented response relationship to FEV_1%p. IC and FVC, with break points (BP) of 57 and 58 FEV_1%p respectively, showed no response above, but an incresed slope below the BP. In addition, in patients with FEV_1%p <65 and >65, response of FEV_1%p did not correlate to response of volume parameters.

Conclusion: Response of several advanced lung function parameters differs depending on patients' baseline FEV_1%p, and specifically response of volume parameters is most pronounced in COPD patients with FEV_1%p <65. Volume and resistance responses do not follow the flow response measured with FEV_1 and may thus be used as a complement to FEV_1 reversibility to identify flow, volume and resistance responders.

Keywords: COPD, IOS, body plethysmography, bronchodilation, lung function, reversibility

Introduction

COPD is one of the world's leading causes of death and is defined to have a progressive, partly irreversible airflow limitation due to a chronic inflammation in the airways. It is heterogenic in nature with varying degrees of emphysema and chronic bronchitis. COPD is diagnosed in patients using anamnesis and spirometry, but it is known that flow–volume spirometry mainly measures alterations in the central airways. Recently, it has been observed that destruction in the peripheral airways is present prior to changes observed by spirometry,[1] and methods to measure the peripheral airway changes are necessary. We have previously shown that baseline impulse oscillometry (IOS) parameters seem to be more affected in moderate-to-severe COPD patients, while volume and diffusion parameters are more affected in severe and very severe COPD patients. In addition, we showed that the lung function parameters are widely spread in Global Initiative for chronic Obstructive Lung Disease (GOLD) stage 2.[2] Post hoc

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investigations of this study identified break points (BPs) in the linear relationship between forced expiratory volume in 1 second (FEV_1) percent predicted (%p) and advanced lung function parameters, identifying a change in the lung function pattern when FEV_1%p drops below 65.[3] However, how these patterns change due to bronchodilators is not known. The topic of whether the bronchodilator response in FEV_1 is limited in COPD patients has been discussed,[4] and studies have explored the reversibility of FEV_1, forced vital capacity (FVC) and FEV_1/FVC based on disease stage (based on GOLD stages).[5,6] Other studies suggest that the reversibility of FEV_1 is not a useful tool in COPD and that there might be many other relevant parameters when evaluating the response.[4] In some studies, other advanced lung function parameters are used to evaluate the response,[7–13] but there is no information about the clinically significant response and the parameters that are most effective to use. The use of volume parameters for assessing bronchodilator response in patients with hyperinflation has shown that bronchodilation decreases hyperinflation.[14] The response of parameters of forced oscillometry (FOT) after salbutamol has recently been described in different GOLD stages. These data showed a significant response in milder stage of COPD compared to controls with a tendency of lower response in more advanced stage.[15] However, the bronchodilator response of parameters measured by the closely related IOS method and volume parameters measured by body plethysmography in correlation to other parameters has not been investigated in relation to COPD disease severity based on FEV_1%p.

We aimed to investigate the response of advanced lung function parameters, beyond FEV_1, to short-acting bronchodilators in a continuous fashion over a broad range of FEV_1%p. Hence, we identified the relevant parameters that are most important when assessing bronchodilator response and at which disease severity patients benefit most from the treatment.

Patients and methods

Study participants

A total of 81 volunteers (smokers and ex-smokers) were included in the study (Table 1) and were classified as controls (fixed ratio FEV_1/FVC >0.7; n=41) or COPD patients (FEV_1/FVC <0.7; n=40). After the continuous analysis, subjects were also divided into FEV_1%p <65 and >65 (independent of FEV_1/FVC) to assess subjects at different disease stages. This division was based on our previous study that indicates that the disease patterns change around FEV_1%p of 65%p.[3] All study participants refrained from their inhaled bronchodilators 8 hours (short-acting β2 agonist [SABA] or short-acting muscarinic antagonist [SAMA]) and 48 hours (long-acting β2 agonist [LABA] or long-acting muscarinic antagonist [LAMA]), respectively, before the visit. All participants had ≥10 pack-years and had no previous diagnoses of asthma or any other pulmonary disease (except COPD) or any lower respiratory infection/exacerbation within the last 3 weeks.

Study design

Study participants performed IOS (MasterScreen, Erich Jaeger GmbH, Würzburg, Germany) giving information about total airway resistance (R5), central airway resistance (R20), peripheral airway resistance (R5–R20), reactance at 5 Hz (X5), reactance area (AX) and resonance frequency (F_{res}).[16] Body plethysmography with spirometry (MasterScreen Body, Erich Jaeger GmbH)[17] provided information about flow and volume parameters, FEV_1, FVC, FEV_1/FVC, functional residual capacity (FRC), residual volume (RV), inspiratory capacity (IC) and total lung capacity (TLC), and resistance, including inspiratory resistance (R_{in}) and expiratory resistance (R_{ex}). Single-breath helium dilution carbon monoxide diffusion (MasterScreen Diffusion, Erich Jaeger GmbH)[18–20] was performed to obtain diffusion capacity of the lung for carbon monoxide ($D_{L,CO}$), alveolar volume (VA), $D_{L,CO}$/VA, RV, FRC and TLC. These measurements were performed at baseline, 10 minutes after inhalation of SABA (400 µg salbutamol; Buventol®, Easyhaler®) and then again 40 minutes after inhalation of additional SAMA (80 µg ipratropium; Atrovent®, Handihaler®) (Figure 1). Lung function measurements were performed according to manufacturer's instructions and European Respiratory Society/American Thorax Society recommendations.[19,21,22] The reference values used were established by Crapo et al[23] (spirometry), Quanjer et al[24] (body plethysmography and single breath) and Vogel[25] (IOS). Study participants also filled the Clinical COPD Questionnaire.

This study was approved by the Regional Ethical Review Board in Lund (431/2008) and followed the guidelines set in the Declaration of Helsinki, and all study participants signed the informed consent.

Statistics

To detect BPs, a regression model allowing segmented relationships was performed as previously described.[3] Shortly, this method estimates a new model having a segmented relationship from an existing linear regression (LR) model.[3] Ordinary LR and a nonparametric fit by the loess (local regression) line are also used for visual purpose.[26–28]

Figure 2A and B shows the FVC%p at baseline and after inhalation of SABA and additional SAMA, respectively, in

Table 1 Patient characteristics, daily medication and baseline lung function

	All	Group 1 (FEV_1% <65)	Group 2 (FEV_1% >65)
Demographics			
N	81	27	54
Age (range), years	67 (65–68)	65 (61–67)	67 (66–69)**
Current/former smoker, n	19/62	4/23	15/39
Pack-years (range)	30 (23–40)	38 (28–50)	27 (21–37)**
Sex, females/males	39/42	13/14	26/28
COPD, n	40	27	13
BMI (range), kg/m^2	26 (24–29)	25 (23–29)	27 (24–29)
ICS, n	22	17	5
SABA, n	13	11	2
LAMA, n	24	18	6
LABA, n	21	17	4
CCQ score (range)	6 (2–14)	14 (8–21)	4 (2–7)***
Body plethysmography			
FEV_1 (range), L	2.1 (1.6–2.9)	1.1 (1.0–1.8)	2.6 (2.1–3.2)***
FEV_1 (range), %p	82 (50–94)	42 (33–50)	91 (80–98)***
FVC (range), L	3.4 (2.7–4.2)	2.8 (2.2–3.2)	3.8 (3.0–4.3)***
FVC (range), %p	90 (78–101)	74 (63–82)	97 (88–104)***
FEV_1/FVC (range)	0.67 (0.51–0.74)	0.44 (0.37–0.51)	0.73 (0.67–0.76)***
RV (range), %p	122 (105–152)	171 (141–190)	117 (96–126)***
TLC (range), %p	109 (100–116)	115 (107–129)	108 (100–113)**
Impulse oscillometry			
R5 (range), %p	105 (83–127)	150 (124–199)	94 (75–108)***
R20 (range), %p	88 (71–107)	100 (84–145)	83 (67–94)***
R5–R20 (range), %p	183 (100–342)	400 (284–681)	133 (83–233)***
X5 (range), %p	306 (178–566)	587 (966–314)	226 (144–366)***
Helium diffusion carbon monoxide diffusion			
D_{LCO} (range), %p	67 (51–77)	46 (34–53)	71 (65–80)***
VA (range), %p	87 (80–96)	79 (71–87)	90 (86–97)***
D_{LCO}/VA (range), %p	77 (61–91)	59 (51–66)	82 (72–93)***

Notes: **$P<0.01$ and ***$P<0.001$, compared to Group 1.

Abbreviations: FEV_1%p, forced expiratory volume in 1 second percent predicted; BMI, body mass index; SABA, short-acting β2 agonist; LAMA, long-acting muscarinic antagonist; LABA, long-acting β2 agonist; CCQ, Clinical COPD Questionnaire; FVC, forced vital capacity; RV, residual volume; TLC, total lung capacity; VA, alveolar volume; ICS, inhaled corticosteroids.

relation to post-bronchodilator FEV_1%p. The light gray line shows the smooth loess; the straight line the LR; and the broken line, where half the line is dotted, is the segmented linear regression (SLR). The dot in Figure 2B shows where the BP is with 95% confidence interval. BP is given as

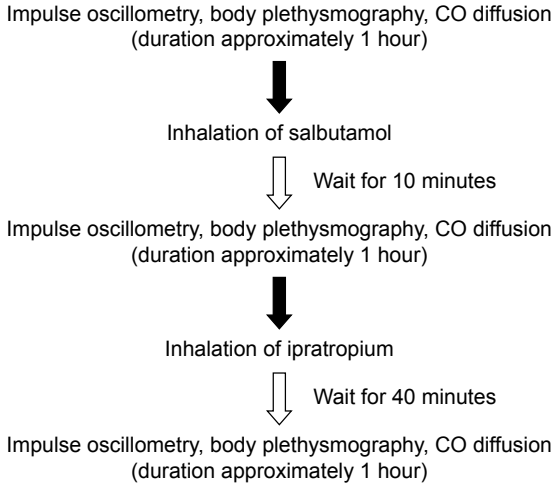


Figure 1 Flowchart of the study design.

FEV_1%p. The estimated LR (Figure 2A) or SLR (if significant over LR; Figure 2B) of each graph is then plotted into one graph to visualize the lung function before and after SABA+SAMA (Figure 2C), which shows a shift of the curves. This method is also applied in graphs in Figure 3A–D. LR and SLR were also investigated in the absolute response in Figure 4A–D.

All responses shown in Tables 2–4 and S1 are displayed as absolute response (Δ)[29] and with parameters expressed as %p when possible.

Normally distributed (FEV_1, FVC, FVC%p and IC%p) paired data were analyzed using analysis of variance with Bonferroni's multiple comparison test, and uneven distributed paired data were analyzed using Friedman test with Dunn's multiple comparison test. Normally distributed unpaired data were analyzed using Unpaired students *t*-test, and uneven distributed unpaired data were analyzed using Mann–Whitney *U* test. Data are presented as median with interquartile range. A *P*-value <0.05 was considered significant. Statistical calculations were performed in R or GraphPad Prism (version 5).

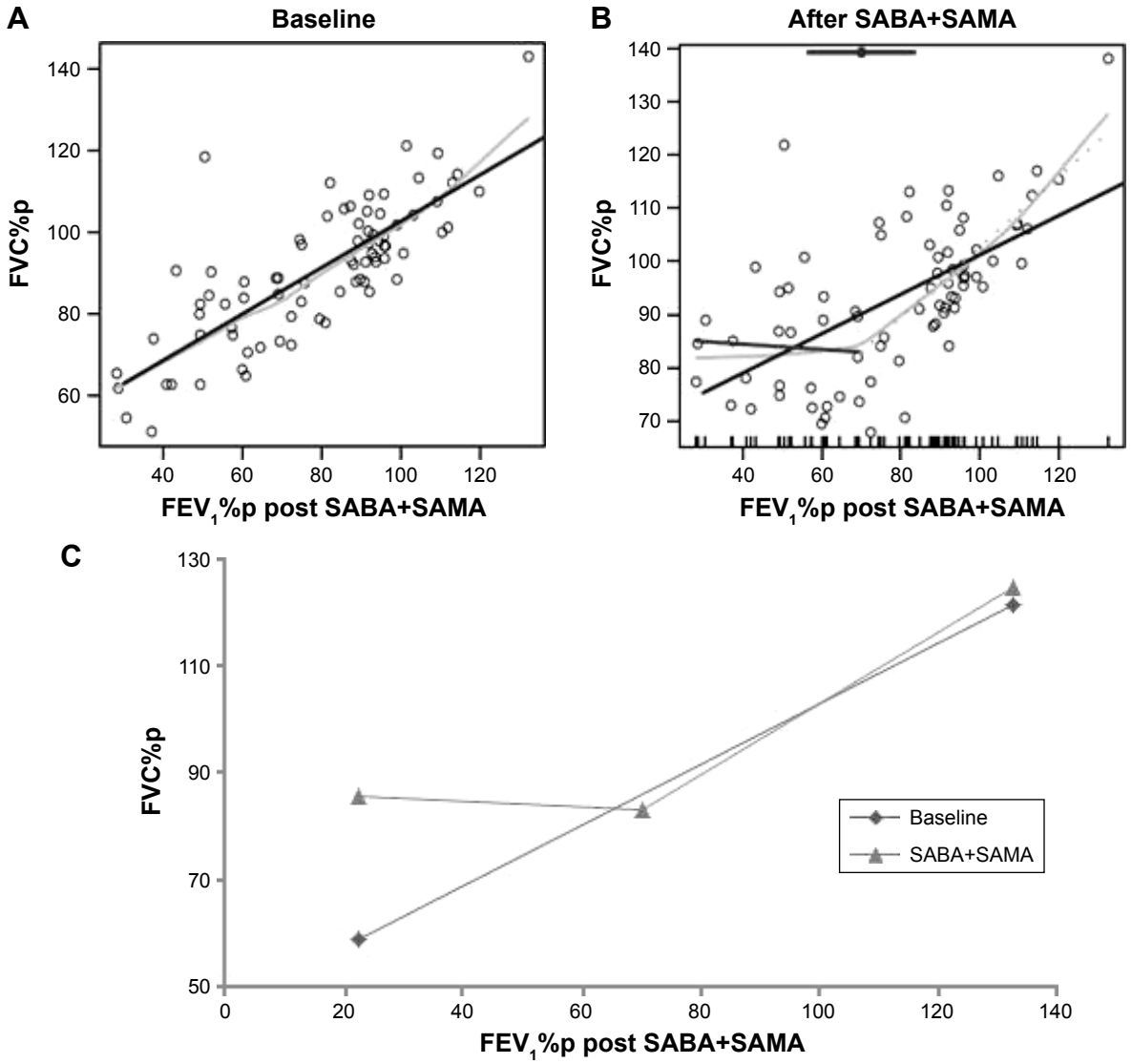


Figure 2 FVC%p at (**A**) baseline and (**B**) after inhalation of SABA and additional SAMA in COPD patients and controls.
Notes: The solid line to left and the hatched line to right of the BP are the segmented linear fits that join at the BP, estimated in the top of the figure (circles with the associated 95% confidence intervals). An ordinary LR line (hatched gray) and the reference and a nonparametric fit by the loess (local regression) method (gray line) are also displayed. Dots show the values of each subject. (**C**) The first two (**A** and **B**) linear/segmented linear curves plotted into one graph to illustrate bronchodilator response.
Abbreviations: FVC, forced vital capacity; %p, percent predicted; SABA, short-acting β2 agonist; SAMA, short-acting muscarinic antagonist; BP, break point; LR, linear regression.

Results

Continuous analysis of lung function at baseline and after inhalation of SABA with additional SAMA

Most of the parameters that show linearity or segmented linearity at baseline maintain this pattern even after inhalation of SABA with additional SAMA, except FVC%p (Figure 2), FEV_1/FVC (Figure 3A), IC%p (Figure 3B) and R_{ex} (Figure 3C).

FVC%p and IC%p change from favoring linear relationship at baseline to segmented relationship after inhalation of SABA+SAMA, while R_{ex} changes from being segmented at baseline to linear after inhalation of SABA+SAMA. FEV_1/FVC shows BPs at both tests, but the BP is much lower after inhalation of SABA+SAMA.

Continuous analysis of absolute response to SABA with additional SAMA

The bronchodilator response to SABA+SAMA was analyzed for LR and SLR, and the following parameters showed a significant SLR (BP within parenthesis; Figure 4; Table 2), ie, the same parameters change their pattern as described earlier (Figure 3): ΔFVC%p (58%; Figure 4A), ΔFEV_1/FVC (52%; Figure 4B), ΔIC% (57%; Figure 4C) and ΔR_{ex} (44%; Figure 4D).

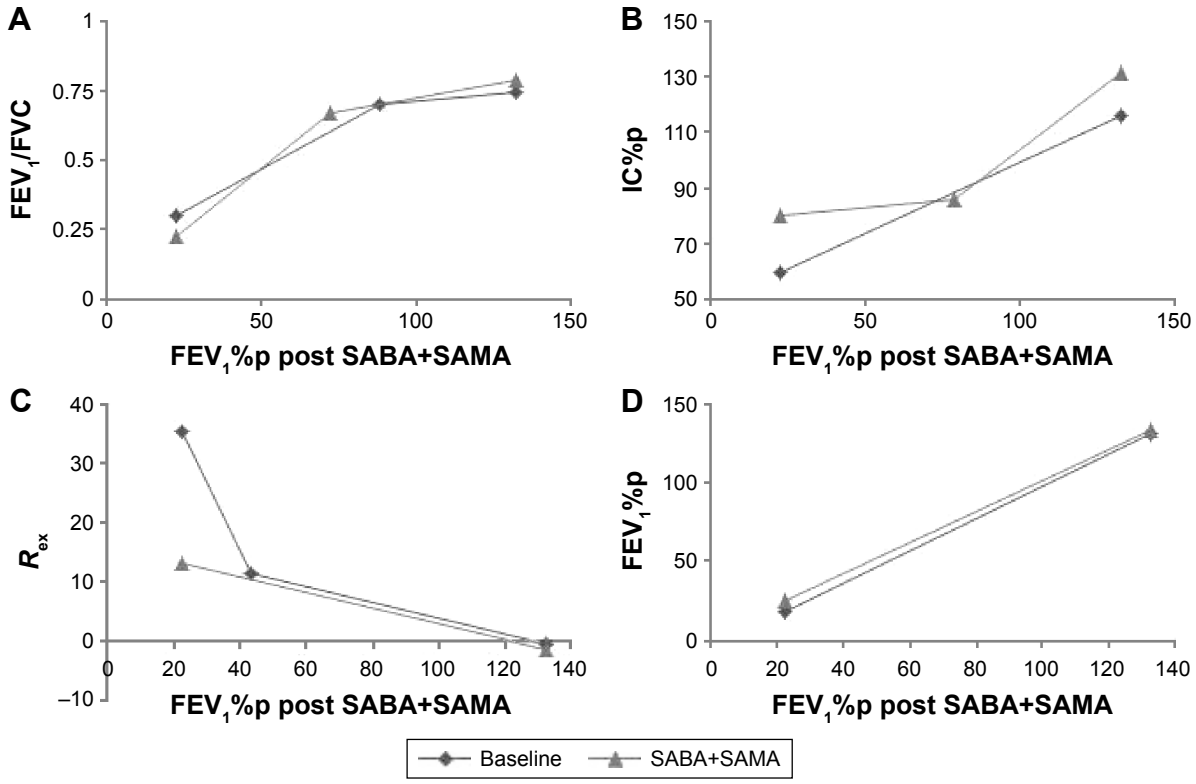


Figure 3 Lungfunction, before and after bronchodilators.
Notes: (**A**) FEV_1/FVC, (**B**) IC%p, (**C**) R_{ex} and (**D**) FEV_1%p at baseline and after inhalation of SABA and additional SAMA in COPD patients and controls. Graphs show linear regression lines or segmented regression lines (if segmentation was significant).
Abbreviations: FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; IC, inspiratory capacity; %p, percent predicted; SABA, short-acting β2 agonist; SAMA, short-acting muscarinic antagonist.

All the four parameters showed a significant slope at the left side of the BP (= at low FEV_1%p), while the slope to the right (= at high FEV_1%p) was not significant (Table 2).

The following parameters showed a significant LR slope when the response was linearly increasing to a decrease in FEV_1%p (Table 2): ΔRV%p, ΔFRC%p, ΔR_{in}, ΔRtot%p, $\Delta D_{L,CO}$%p, ΔR5%p, ΔR5–R20%p and ΔAX.

The remaining parameters showed no significant LR slope or SLR (Table 2), but ΔFEV_1%p, ΔX5%p and $\Delta D_{L,CO}$/VA%p showed significant intercepts, indicating a similar response over the severity range. ΔTLC%p, ΔR20%p and ΔVA%p showed no significant slope or intercept, indicating an insignificant response over the severity range.

Response to SABA with additional SAMA in subjects with FEV_1%p <65 or >65

In our previous study,[3] several parameters had BPs around FEV_1 65%p. A related pattern is shown in this study, investigating the continuous relationship between the bronchodilator response and FEV_1%p. To investigate the potential difference in the bronchodilator response (compared to baseline) of the different lung function parameters, the subjects were therefore further divided into groups of FEV_1%p <65 and >65 (Tables 1 and 3).

Some of the lung volume parameters showed a significant bronchodilator response only in patients with FEV_1%p <65 (Table 3): RV%p and FVC%p.

Other lung function parameters showed a significant bronchodilator response in both the groups (FEV_1%p <65 and >65) (Table 3): FEV_1%p, FRC%p, IC%p, FEV_1, R5%p, R5–R20%p, X5%p, AX, F_{res}, R_{in}, R_{ex} and Rtot%p.

All the above parameters showed a significantly higher bronchodilator response for the group below FEV_1%p <65, except: FEV_1, IC%p, R20%p and F_{res}.

The remaining parameters showed no response to the bronchodilator (or very little; data not shown): TLC%p, $D_{L,CO}$%p, VA%p and $D_{L,CO}$/VA%p.

Correlation between response in flow, volume, resistance and reactance parameters to SABA with additional SAMA

The correlations between ΔFEV_1%p (flow), ΔFVC%p (flow volume), ΔRV%p (volume), ΔRtot%p (resistance),

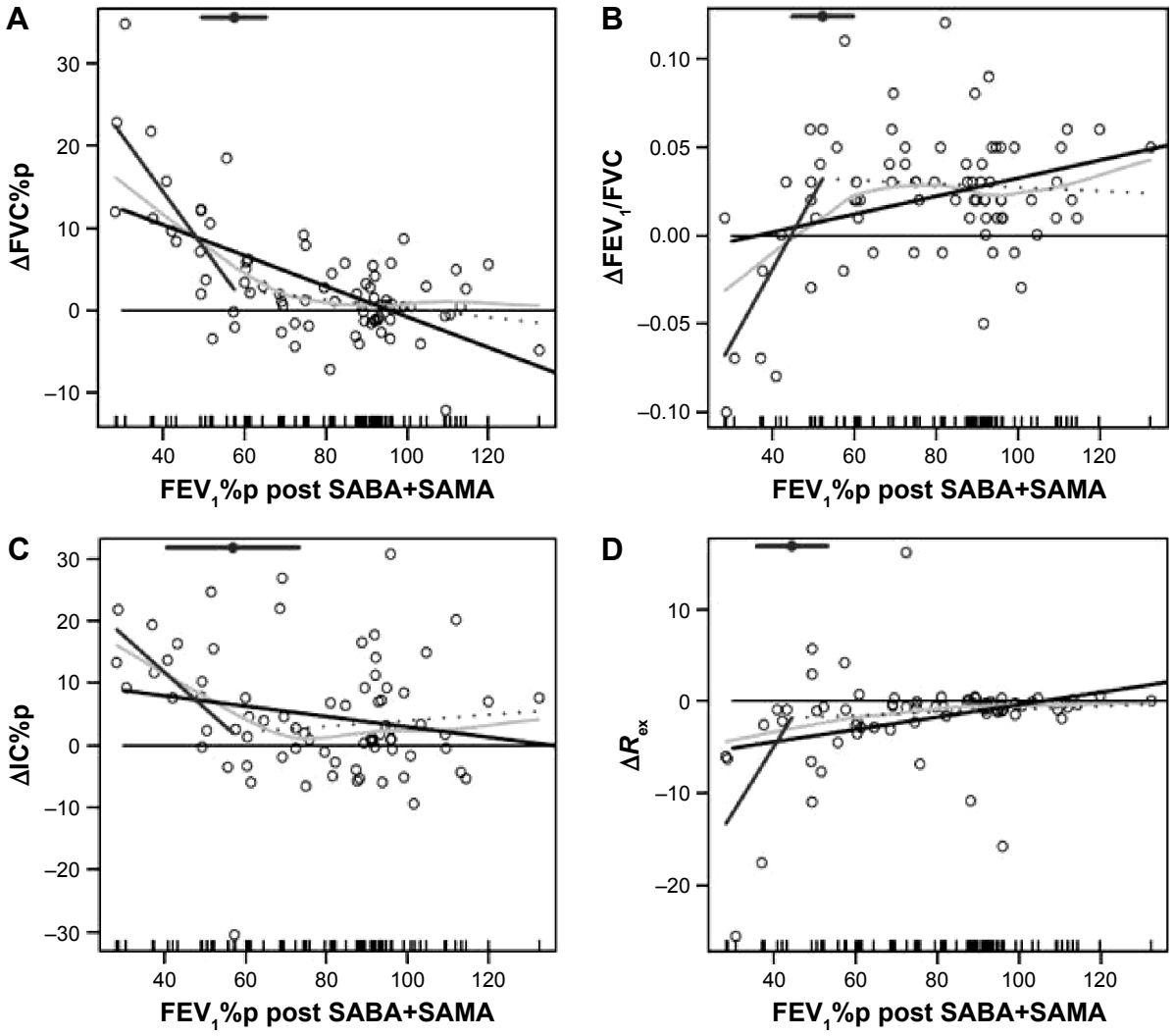


Figure 4 Bronchodilator response.
Notes: (**A**) ΔFVC%, (**B**) $\Delta FEV_1/FVC$, (**C**) ΔIC%p and (**D**) ΔR_{ex} in COPD patients and controls. The solid line to the left and the hatched line to the right of the BP are the segmented linear fits that join at the BP, estimated in the top of the figure (circles with the associated 95% confidence intervals). An ordinary LR line (hatched gray) and the reference and a nonparametric fit by the loess (local regression) method (gray line) are also displayed. Dots show the values of each subject.
Abbreviations: FVC, forced vital capacity; FEV_1, forced expiratory volume in 1 second; IC, inspiratory capacity; %p, percent predicted; BP, break point; LR, linear regression, SABA, short-acting β2 agonist (salbutamol); SAMA, short-acting muscarinic antagonist (ipratropium).

R5–R20%p (peripheral resistance) and ΔAX (reactance) were investigated to define the relationship within the response of different lung function parameters. In subjects with FEV_1%p <65, ΔFEV_1%p correlated only with ΔFVC%p, while ΔFVC%p, ΔRV%p, ΔRtot%p and ΔAX correlated with most of each other (Table 4). In contrast, in subjects with FEV_1%p >65, ΔFEV_1%p correlated with ΔFVC%p, ΔR5–R20%p and ΔAX, while no correlations were found among ΔFVC%p, ΔRV%p, ΔRtot%p and ΔAX (Table 4).

Response in volume, resistance and reactance correlated with each other but not with FEV_1%p. To visualize the relationships and the individual responses, ΔRV%p was plotted against ΔFEV_1%p (Figure 5). Some patients were both flow and volume responders, while some were either flow or volume responders, but no clear grouping could be demonstrated. Flow responders were defined as having a response in FEV_1%p above the median response in this cohort, while volume responders were defined as having a response in RV%p above the median response in this cohort. With this definition, 18 subjects (11 controls and 7 COPD) were classified as neither flow nor volume responders (nonresponders in Figure 5).

Analysis of response to only SABA

All patients were also tested for the response to only SABA. A similar pattern was seen for the "continuous analysis of lung function at baseline and after inhalation of SABA" and for the "continuous analysis of absolute response to SABA"

Table 2 LR and SLR for lung function response to SABA and additional SAMA

Parameters	LR or SLR[a] (BP)[b]	*P*-value for BP	Slope (left/right)[c]	*P*-value for slope (left/right)[d]	Intercept[e]	*P*-value for intercept[f]
ΔFVC%p	SLR (58)	<**0.001**	–0.68/–0.05	<**0.001**/0.150	41.69	<**0.001**
ΔFEV_1/FVC	SLR (52)	<**0.001**	0.00/0.00	<**0.001**/0.670	–0.19	<**0.001**
ΔIC%p	SLR (57)	**0.044**	–0.58/0.05	**0.036**/0.516	35.22	**0.004**
ΔR_{ex}	SLR (44)	**0.004**	0.72/0.02	**0.001**/0.533	–33.59	**0.001**
ΔR_{in}	LR	ns	0.02	<**0.001**	–2.10	<**0.001**
ΔRtot%p	LR	ns	1.05	<**0.001**	–116.26	<**0.001**
ΔAX	LR	ns	0.01	<**0.001**	–1.23	<**0.001**
ΔRV%p	LR	ns	0.37	**0.001**	–37.47	<**0.001**
ΔR5–R20%p	LR	ns	1.41	**0.004**	–169.50	<**0.001**
ΔFRC%p	LR	ns	0.14	**0.026**	–16.67	**0.001**
$\Delta D_{L,CO}$%p	LR	ns	–0.06	**0.029**	4.92	**0.040**
ΔR5%p	LR	ns	0.20	**0.046**	–31.91	<**0.001**
ΔFEV_1%p	LR	ns	–0.03	0.144	7.04	<**0.001**
ΔX5%p	LR	ns	5.20	0.056	600.25	**0.008**
$\Delta D_{L,CO}$/VA%p	LR	ns	–0.06	0.061	5.58	**0.029**
ΔR20%p	LR	ns	0.02	0.746	–11.33	0.062
ΔTLC%p	LR	ns	0.03	0.384	–3.37	0.243
ΔVA%p	LR	ns	–0.03	0.096	1.71	0.306

Notes: Bold numbers indicate significance ($P<0.05$). Δ indicates absolute response. [a]Parameter is labeled SLR if there is a significant SLR (defined from *P*-value in the next column: "*P*-value for BP"), otherwise it is labeled LR. [b]The subsequent BP from the SLR is shown in parentheses. [c]Slope (left/right) is the slope of the linear regression line or the slope of the two regression lines if there is a significant segmented linear regression (then the slopes of the regression lines [left and right] of the BP are shown within parentheses). [d]*P*-value for slope (left/right) indicates if the slope is significant (ie, if there is a slope that is different from a horizontal line). [e]Intercept indicates where the regression line crosses the *Y*-axis. [f]*P*-value for intercept indicates a significant response (ie, the response lines are significantly different from a horizontal line at $y=0$).
Abbreviations: LR, linear regression; SLR, segmented linear regression; SABA, short-acting β2 agonist (salbutamol); SAMA, short-acting muscarinic antagonist (ipratropium); BP, break point; FVC, forced vital capacity; FEV_1, forced expiratory volume in 1 second; %p, percent predicted; IC, inspiratory capacity; AX, reactance area; RV, residual volume; FRC, functional residual capacity; VA, alveolar volume; TLC, total lung capacity.

Table 3 Absolute response of lung function parameters after SABA with additional SAMA

Parameters	Group 1 (FEV_1% <65)	Group 2 (FEV_1% >65)	Significance[a]
Body plethysmography			
ΔFEV_1 (L)	**0.21 (0.10 to 0.25)**	**0.10 (0.04 to 0.19)**	ns
ΔFEV_1%p	**6.0 (3.1 to 8.9)**	**3.3 (1.5 to 6.5)**	*
ΔFVC (L)	**0.35 (0.10 to 0.52)**	0.01 (–0.07 to 0.12)	***
ΔFVC%p	**9.6 (3.3 to 15.6)**	0.5 (–1.5 to 2.8)	***
ΔFEV_1/FVC	0.01 (–0.02 to 0.03)	**0.03 (0.01 to 0.05)**	*
ΔRV (L)	**–0.46 (–0.82 to –0.06)**	–0.04 (–0.26 to 0.14)	***
ΔRV%p	**–20.9 (–39.7 to –2.2)**	–2.2 (–12.0 to 5.9)	**
ΔFRC%p	**–11.9 (–16.6 to –3.9)**	**–4.2 (–11.2 to 2.2)**	**
ΔIC%p	**7.8 (2.4 to 13.7)**	**1.4 (–2.1 to 7.2)**	ns
ΔR_{ex} (kPa·s/L)	**–2.29 (–6.14 to –0.76)**	**–0.60 (–1.03 to –0.16)**	**
ΔR_{in} (kPa·s/L)	**–1.23 (–2.30 to –0.51)**	**–0.45 (–0.63 to –0.14)**	***
ΔRtot%p	**–55.5 (–95.6 to –21.3)**	**–15.2 (–26.8 to –4.5)**	***
Impulse oscillometry			
ΔR5%p	**–27.1 (–45.9 to –11.7)**	**–13.9 (–20.8 to –4.5)**	**
ΔR20%p	**–11.9 (–22.2 to –1.3)**	**–9.0 (–17.5 to –2.5)**	ns
ΔR5–R20%p	**–117.0 (–250.0 to –25.0)**	**–33.0 (–75.0 to 0.0)**	**
ΔF_{res} (Hz)	**–1.84 (–3.51 to –0.47)**	**–1.54 (–4.12 to –0.03)**	ns
ΔX5%p	**–102.9 (–226.2 to –21.7)**	**–47.6 (–94.9 to –22.1)**	*
ΔAX (kPa/L)	**–0.54 (–1.39 to –0.11)**	**–0.08 (–0.37 to –0.01)**	**
Single-breath helium dilution carbon monoxide diffusion			
$\Delta D_{L,CO}$%p	2.0 (–2.5 to 3.5)	0.0 (–4.0 to 3.0)	ns

Notes: Data show median response (and IQR) within each group. Bold numbers indicate significant bronchodilator response compared to baseline. [a]Significant difference between Group 1 and Group 2 in response (*$P<0.05$, **$P<0.01$ and ***$P<0.001$). ns, no significant difference. Δ indicates absolute response.
Abbreviations: SABA, short-acting β2 agonist (salbutamol); SAMA, short-acting muscarinic antagonist (ipratropium); FEV_1, forced expiratory volume in 1 second; %p, percent predicted; FVC, forced vital capacity; RV, residual volume; FRC, functional residual capacity; IC, inspiratory capacity; AX, reactance area; IQR, interquartile range.

Table 4 Correlation between absolute response in lung function parameters (in Δ values) after inhalation of SABA+SAMA

	ΔFEV$_1$%p	ΔFVC%p	ΔRtot%p	ΔRV%p	ΔR5–R20%p
Group 1 (FEV$_1$% <65)					
ΔFVC%p	**0.44***				
ΔRtot%p	–0.34	**–0.71*****			
ΔRV%p	–0.29	**–0.61*****	–0.06		
ΔR5–R20%p	–0.14	–0.18	0.29	**0.44***	
ΔAX	–0.32	**–0.41***	**0.46***	**0.40***	**0.87*****
Group 2 (FEV$_1$% >65)					
ΔFVC%p	**0.56*****				
ΔRtot%p	–0.09	–0.21			
ΔRV%p	–0.13	–0.27	0.22		
ΔR5–R20%p	**–0.36****	–0.11	–0.12	0.17	
ΔAX	**–0.36****	–0.23	0.04	0.14	**0.80*****

Notes: Δ indicates the absolute response in each parameter after inhaling SABA+SAMA. *P<0.05, **P<0.01, and ***P<0.001 show significance of the correlation (significant correlations are bolded for clarification). Numbers presented as correlation coefficients.
Abbreviations: SABA, short-acting β2 agonist; SAMA, short-acting muscarinic antagonist; FEV$_1$, forced expiratory volume in 1 second; %p, percent predicted; FVC, forced vital capacity; RV, residual volume; AX, reactance area.

(Table S1) as for the double bronchodilators. Although FEV$_1$/FVC did not show any response, $D_{L,CO}$%p and R5%p did not have a significant slope, while R20%p did have. For "response to SABA in subjects with FEV$_1$%p <65 or >65", there seemed to be less effect of only SABA on several parameters compared to SABA+SAMA (Table S2). When looking at the "correlations between flow/volume/resistance/reactance response to SABA", a similar pattern was observed for SABA+SAMA with few correlations to ΔFEV$_1$ in the FEV$_1$%p <65 group, but to all except volume in the FEV$_1$%p >65 group (Table S3).

Discussion

In this study, we found that several volume and resistance parameters (measured by body plethysmography and IOS) differ from the response pattern seen in FEV$_1$%p. We found that parameters reflecting volume response were more prominent in patients with more severe stage of COPD, while resistance parameters were more significant in less advanced stage. Most of the resistance and reactance parameters from IOS and body plethysmography responded to SABA, while the volume parameters were affected only mainly in patients with FEV$_1$%p <65 or in patients who needed not only SABA but also the addition of SAMA to gain a significant effect.

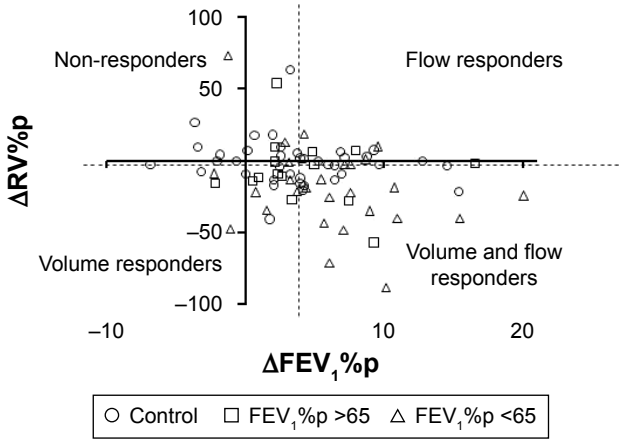


Figure 5 Relationship between ΔFEV$_1$%p and ΔRV%p.
Notes: To visualize the flow versus volume response in each patient. Dotted lines are median of ΔFEV$_1$%p and ΔRV%p.
Abbreviations: FEV$_1$, forced expiratory volume in 1 second; %p, percent predicted; RV, residual volume.

The overall clinical aim in COPD should be to improve function in the small peripheral airways both by improving flow and by decreasing the degree of alveolar hypoventilation (flow responders) as well as decreasing air trapping and hyperinflation (volume responders). The degree of air trapping relates to the degree of dyspnea and the functional aspects, including BODE index as a composite score.[30] In order to evaluate the effect of bronchodilators, it is thus important to go beyond the information provided by FEV$_1$, mainly reflecting flow resistance in the central airways.[4] These results indicate that the use of FEV$_1$%p as a tool to investigate the effect of bronchodilators is not representative of the changes occurring in the respiratory system. Also, the bronchodilator response of many parameters, such as RV and Rtot, tends to be greater in patients with more severe disease (lower FEV$_1$%p) and not correlating to the FEV$_1$%p response. The addition of SAMA to SABA seems to be most effective in more severe patients whose volume parameters are affected, although data show that the combination of therapies can be beneficial to patients already in an early stage.

Regarding the response of IOS parameters, most of the parameters showed a better response with more severe disease, as previously stated. This is almost in accordance with the

findings of da Costa et al[15] regarding bronchodilator response using FOT, since we had more patients with milder disease.

Response to SABA was 1.4%–4% (40–120 mL), which is very low compared to the clinically relevant response.[31] Additional inhalation of SAMA increased the response, especially in patients with FEV_1%p <65, to 6% (210 mL). The continuous analysis did not detect higher response in more severe patients (nonsignificant slope), but the intercept was significant and thereby in accordance with the response analysis. Calverley et al[4] questioned the clinical relevance of reversibility tests in COPD, which is in line with our SABA data, showing the importance of not only using double bronchodilators for optimal bronchodilation but also addition of other parameters measuring volume, resistance and reactance.

Only patients with lower FEV_1%p (FEV_1%p <65) showed a significant response in RV%p and FVC%p, and this improvement also differed significantly compared to subjects with FEV_1%p >65. ΔFVC%p showed a significant SLR with BP at FEV_1%p at 57, with no improvement in patients over this BP. This suggests that these improvements are a trait only in patients with more severe COPD and that there is no use in measuring at least FVC%p response over FEV_1%p at 57. ΔRV%p showed a highly significant LR, crossing the *X*-axis around FEV_1%p at 100%, implying that the response is very low in high FEV_1%p but gradually increases as the disease progresses.

All parameters (except for F_{res}) that were significantly reversible in both groups to SABA and SABA+SAMA showed a significantly higher improvement in patients with more severe COPD. These data imply that the main effects of bronchodilators on lung function parameters other than FEV_1%p are in the more severe group.

When the correlations and relationship of the difference in bronchodilator response were investigated, we observed a bronchodilator effect in the volume, resistance and reactance, beyond what can be measured with ΔFEV_1%p. Data suggest that it might be beneficial to use RV%p in addition to FEV_1%p when evaluating response to bronchodilators, since this parameter did not correlate with FEV_1%p but with those of the peripheral airways (R5–R20%p, AX) in patients with FEV_1%p <65. This also implies that there might be an importance in measuring the response but that more parameters should be evaluated to provide a fair picture of the response pattern. To visualize if a patient is a flow or a volume responder, the ratio of $\Delta RV\%p/\Delta FEV_1\%p$ may be used, since there seems to be patients being only flow responders, only volume responders, or both flow and volume responders. However, this method should be further verified to define a stable limit, dividing nonresponders from responders. Here, we used the median in the population. Another approach could be using zero response or a set limit (eg, what is clinical relevant). Further characterization of these patient subgroups in a clinical context would be of interest. This could also be applied to identify resistance and reactance parameters by using $\Delta AX/\Delta FEV_1$%p and ΔRtot%p (or ΔR5–R20%p)/ΔFEV_1%p, respectively.

Many lung function parameters did significantly improve, and many improvements were significantly better in the FEV_1%p <65 group than in the subjects with FEV_1%p >65, and this is supported by the fact that many parameters showed LR and SLR in the same direction. This also implies that the changes, even those in the peripheral airways, are only partially irreversible and that patients below the BP could benefit from bronchodilators even if they are not reversible in FEV_1%p.

A limitation of this study is not only the number of patients but also the distribution of disease severity. Due to difficulties in performing all maneuvers repeatedly or difficulties refraining from medications, the population is a bit skewed toward the milder/moderate disease.

By identifying the parameters that show an effect in response to bronchodilators, it is possible to obtain a deeper understanding about what happens in the airways when bronchodilators are inhaled. By studying these parameters, it would be possible to measure the effectiveness of bronchodilators in different phenotypes/severities of COPD patients. A future perspective is to elucidate if these data hold true in a longitudinal study with long-acting bronchodilators to connect the effects in lung function parameters to those of clinical symptoms and dyspnea.

Conclusion

Some lung function parameters are significantly reversible along FEV_1%p, while resistance and volume parameters show different response patterns along the FEV response curve. Measuring the response to resistance may be more informative in milder stages, while volume response parameters are more important in patients with lower FEV_1%p. Thus, knowing that the bronchodilator effect in volume and resistance does not follow the FEV_1%p response, those parameters should therefore be considered when characterizing patients according to bronchodilator response. This approach can help us in gaining insight into individualizing the diagnosis and therapy of COPD.

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Disclosure

The authors report no conflicts of interest in this work.

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Supplementary materials

Table S1 Continuous analysis of SABA

Parameters	LR or SLR (BP%)	*P*-value for BP	Slope (left/right)	*P*-value for slope (left/right of BP)	Intercept	*P*-value for intercept
ΔFVC%p	SLR (86)	**0.028**	−0.21/0.06	<**0.001**/0.206	17	<**0.001**
ΔFEV_1/FVC	LR	ns	0	0.091	−0.015	0.277
ΔIC%p	SLR (61)	**0.033**	−595/0.07	0.10/0.451	36	**0.001**
ΔR_{ex}	SLR (47)	<**0.001**	0.53/0.008	**0.012**/0.691	−26	**0.001**
ΔR_{in}	LR	ns	0.02	<**0.001**	−2.0	<**0.001**
ΔRtot%p	LR	ns	0.94	<**0.001**	−99	<**0.001**
ΔAX	LR	ns	0.01	**0.003**	−0.87	<**0.001**
ΔRV%p	LR	ns	0.29	**0.001**	−28	<**0.001**
ΔR5–R20%p	LR	ns	1.01	**0.036**	−116	**0.004**
ΔFRC%p	LR	ns	0.12	**0.027**	−13	**0.003**
ΔD_{LCO}%p	LR	ns	−0.04	0.093	4.2	**0.033**
ΔR5%p	LR	ns	0.12	0.184	−21	**0.006**
ΔFEV_1%p	LR	ns	−0.03	0.128	4.8	**0.004**
ΔX5%p	LR	ns	4.86	0.076	−534	**0.018**
ΔD_{LCO}/VA%p	LR	ns	−0.04	0.123	5.4	**0.018**
ΔR20%p	LR	ns	1.01	**0.036**	−116	**0.004**
ΔTLC%p	LR	ns	0.02	0.457	−2.2	0.362
ΔVA%p	LR	ns	−0.02	0.164	1.1	0.326

Notes: Bold numbers indicate significance ($P<0.05$). Δ indicates absolute response.
Abbreviations: SABA, short-acting β2 agonist (salbutamol); LR, linear regression; SLR, segmented linear regression; BP, break point; FVC, forced vital capacity; %p, percent predicted; FEV_1, forced expiratory volume in 1 second; IC, inspiratory capacity; AX, reactance area; RV, residual volume; FRC, functional residual capacity; D_{LCO}, diffusion capacity of the lung for carbon monoxide; TLC, total lung capacity; VA, alveolar volume; ns, no significant difference.

Table S2 Response to SABA

Parameters	Group 1 (FEV_1% <65)	Group 2 (FEV_1% >65)	Significance
Body plethysmography			
ΔFEV_1, L	**0.12 (0.03 to 0.21)**	**0.04 (−0.05 to 0.13)**	**
ΔFEV_1%p	**4.0 (1.1 to 5.9)**	1.4 (−1.5 to 4.4)	*
ΔFVC, L	**0.28 (0.11 to 0.36)**	0.01 (−0.08 to 0.07)	***
ΔFVC%p	**6.8 (2.7 to 10.0)**	−0.1 (−2.1 to 1.8)	***
ΔFEV_1/FVC	0.01 (−0.02 to 0.03)	0.01 (−0.01 to 0.03)	ns
ΔRV, L	**−0.44 (−0.74 to −0.16)**	−0.02 (−0.19 to 0.11)	***
ΔRV%p	**−17.8 (−31.5 to −6.4)**	−1.1 (−9.0 to 4.3)	***
ΔFRC%p	**−8.5 (−16.4 to −3.1)**	−2.3 (−7.3 to 2.2)	***
ΔIC%p	**6.8 (0.5 to 11.7)**	−0.7 (−3.8 to 7.3)	ns
ΔR_{ex}, kPa·s/L	**−1.86 (−3.51 to −0.70)**	**−0.37 (−0.97 to 0.13)**	**
ΔR_{in}, kPa·s/L	**−1.13 (−1.86 to −0.32)**	**−0.31 (−0.63 to −0.01)**	***
ΔRtot%p	**−38.8 (−76.4 to −14.9)**	**−12.1 (−24.0 to 0.3)**	***
Impulse oscillometry			
ΔR5%p	**−17.9 (−43.9 to −3.8)**	**−8.7 (−19.9 to −0.4)**	*
ΔR20%p	−10.5 (−19.1 to 2.3)	**−6.7 (−13.7 to −0.5)**	**ns**
ΔR5–R20%p	−67.0 (−156.3 to 35.5)	−21.0 (−54.3 to 0.00)	ns
ΔF_{res}, Hz	**−1.57 (−3.07 to −0.35)**	**−0.99 (−3.73 to 0.08)**	**ns**
ΔX5%p	**−88.8 (−209.3 to −24.9)**	**−28.9 (−62.2 to −6.8)**	**
ΔAX, kPa/L	**−0.43 (−0.98 to −0.05)**	**−0.07 (−0.28 to −0.02)**	**
Single-breath helium dilution carbon monoxide diffusion			
ΔD_{LCO}%p	**3.0 (1.0 to 3.8)**	1.0 (−1.0 to 3.0)	*

Notes: Bold numbers indicate significant bronchodilator response. Significant difference (*$P<0.05$, **$P<0.01$ and ***$P<0.001$) between Group 1 and Group 2. ns, no significant difference. Δ indicates absolute response.
Abbreviations: SABA, short-acting β2 agonist (salbutamol); FEV_1, forced expiratory volume in 1 second; %p, percent predicted; FVC, forced vital capacity; RV, residual volume; FRC, functional residual capacity; IC, inspiratory capacity; AX, reactance area; D_{LCO}, diffusion capacity of the lung for carbon monoxide.

Table S3 Correlation of lung Δ function parameters after inhalation of SABA

	ΔFEV$_1$%p	**ΔFVC%p**	**ΔRtot%p**	**ΔRV%p**	**ΔR5–R20%p**	**ΔAX**
Correlations of Δ lung function parameters in FEV$_1$%p <65						
Group 1 (FEV$_1$% <65)						
ΔFVC%p	0.25					
ΔRtot%p	−0.23	−**0.64*****				
ΔRV%p	0.02	−**0.46***	**0.45***			
ΔR5–R20%p	−0.39	−0.21	0.19	−0.03		
ΔAX	−**0.65*****	−**0.49***	0.36	0.03	**0.79*****	
Correlations of Δ lung function parameters in FEV$_1$%p >65						
Group 2 (FEV$_1$% >65)						
ΔFVC%p	**0.40****					
ΔRtot%p	−**0.28***	−0.26				
ΔRV%p	0.08	−0.22	−0.10			
ΔR5–R20%p	−**0.27***	−0.07	0.25	0.01		
ΔAX	−**0.42*****	−0.15	**0.42****	−0.04	**0.66*****	

Notes: Δ indicates the change in each parameter after inhaling salbutamol. Significant difference (*P<0.05, **P<0.01 and ***P<0.001) of the correlation. Bold numbers indicate significance. Numbers presented as correlation coefficients.

Abbreviations: SABA, short-acting β2 agonist (salbutamol); FEV$_1$, forced expiratory volume in 1 second; %p, percent predicted; FVC, forced vital capacity; RV, residual volume; AX, reactance area.

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