Assessment of acute bronchodilator effects from specific airway resistance changes in stable COPD patients

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Abstract

Background: In COPD patients, reversibility is currently evaluated from the changes of forced expiratory volume at 1s (ΔFEV_1) and forced vital capacity (ΔFVC). By lowering peripheral airway smooth muscle tone, bronchodilators should decrease dynamic hyperinflation, gas trapping, and possibly dyspnea at rest. Hence, we hypothesize that specific airway resistance changes (ΔsR_{AW}) should better characterize the acute response to bronchodilators.

Methods: On two days, 60 COPD patients underwent dyspnea evaluation (VAS score) and pulmonary function testing at baseline and one hour after placebo or 300 μg indacaterol administration.

Results: Spirographic and ΔsR_{AW}-based criteria identified as responders 24 and 45 patients, respectively. ΔsR_{AW} correlated with changes of intrathoracic gas volume ($\Delta ITGV$) ($r=0.61$; $p<0.001$), residual volume (ΔRV) ($r=0.60$; $p<0.001$), ΔFVC ($r=0.44$; $p=0.001$), and ΔVAS ($r=0.73$; $p<0.001$), while ΔFEV_1 correlated only with ΔFVC ($r=0.34$; $p=0.008$). Significant differences in terms of $\Delta ITGV$ ($p=0.002$), ΔRV ($p=0.023$), and ΔVAS ($p<0.001$) occurred only if patients were stratified according to ΔsR_{AW}.

Conclusions: In assessing the acute functional effect of bronchodilators, ΔsR_{AW}-based criterion is preferable to FEV_1-FVC-based criteria, being more closely related to bronchodilator-induced improvements of lung mechanics and dyspnea at rest.

Key Words: Adrenergic beta-Agonists; Dyspnea; Plethysmography; Respiratory Function Tests; Reversibility; Short-term variability

1. Introduction

Studies concerned with the evaluation of the efficacy of bronchodilator therapy in patients with chronic obstructive pulmonary disease (COPD) have used the forced expired volume in one second (FEV_1) as the end point measure. A significant increase of the group mean value of FEV_1 is taken as an indicator of the bronchodilating properties, and its amount used to assess the effectiveness of the drug. Furthermore, FEV_1 is commonly used as a tool for the evaluation and classification of COPD severity (Global Initiative for Obstructive Lung Disease (GOLD), 2013).

On the other hand, ATS/ERS guidelines (Pellegrino et al., 2005) recommend that changes in FEV_1 should also be used to evaluate the acute response to bronchodilators of single COPD patients, i.e. to assess reversibility, although it has been recognized that this variable reflects intrapulmonary airway resistance poorly (Pride, 1971; Skinner and Palmer, 1974). Furthermore, FEV_1 measurements are obtained with a maneuver which by itself can affect the airway caliber, besides being often poorly performed. Indeed, after bronchodilator administration flow increases less if forced expirations start from total lung capacity rather than near the end of a normal inspiration, and this leads to an underestimation of FEV_1, flow at any given absolute lung volume, and forced vital capacity (FVC) (Barnes et al., 1981; Berry et al., 1985; Pellegrino et al., 1998), the other variable the changes of which concur in assessing reversibility according to ATS/ERS criteria (Pellegrino et al., 2005). Although some investigations have reported a substantial increase of reversibility based on FVC changes, at least in very severe COPD patients (Newton et al., 2002; Taskin et al., 2008), other studies have suggested that this additional criterion has a minor impact, because FEV_1 and FVC are strongly related (Sourk and Nugent, 1983; Schermer et al., 2007; Deesomchok et al., 2010). Finally, a further limitation of ATS/ERS reversibility criteria is represented by the dependency of the acute changes of FEV_1 and FVC on the severity of the disease: in fact, the percentage of severe COPD patients who meet these criteria can be very small (Newton et al., 2002; Deesomchok et al., 2010). While the need for the evaluation of novel procedures for acute bronchodilator reversibility testing has been stressed in the most recent review

article on reversibility in COPD (Hanania et al., 2011), no alternatives to current criteria seem to have been taken into consideration, although there are indications that plethysmography and/or impulse oscillometry might better reflect bronchodilation in COPD patients (Borrill et al., 2004).

In COPD patients, bronchodilators should significantly improve lung function and relieve respiratory symptoms to the extent that they decrease airway resistance during tidal breathing, thus preventing or reducing dynamic hyperinflation and increasing inspiratory capacity (IC) (Barnes et al., 1981; Berry et al., 1985; Pellegrino et al., 1998). Because in these patients the disease affects more the small than the large airways, another favorable effect of reducing bronchomotor tone could be the decrease of airway closing pressure, leading to a fall in the residual volume (RV) and increase in the vital capacity (VC). Surprisingly, few studies in COPD patients have evaluated the effects of acute bronchodilation on specific total airway resistance (sR_{AW}), a variable that accurately reflects peripheral airway resistance (Bassiri et al., 1997; Borrill et al., 2004; Mahut et al., 2012), although its relative changes were found systematically greater than those of FEV_1 and FVC (Ramsdell and Tisi, 1979; Smith et al., 1992; Taube et al., 2000; Borrill et al., 2004; Deesomchok et al., 2010). Furthermore, sR_{AW} changes with bronchodilator administration have never been related to those of the variables commonly used to evaluate the improvement of lung function.

This investigation was undertaken to assess whether changes of sR_{AW} during quiet breathing occur beyond their short term variability in response to acute bronchodilation even in COPD patients who do not meet the current criteria for reversibility (Pellegrino et al., 2005), and to determine whether sR_{AW} changes adequately predict those of commonly used pulmonary function parameters. In addition, we have investigated the relationships between the changes in dyspnea scores at rest and those of sR_{AW}, static and dynamic lung volumes.

2. Materials and methods

2.1 Patient population

Sixty consecutive COPD patients were recruited from a Lung Rehabilitation and Academic Medical Center. Inclusion criteria were: >50 years of age; FEV_1/FVC <0.7 and FEV_1 <80% of predicted value; current or former smokers with a smoking history of more than 20 pack years; stable conditions at time of inclusion and absence of respiratory tract infections or exacerbations for at least 2 months; no change of inhalation therapy for at least 4 weeks. Exclusion criteria were: known unstable or moderate-severe heart disease (recent ischemic heart disease, hyperkinetic arrhythmia); history of asthma or other active pulmonary disease; neuromuscular or disabling cognitive problems; drug abuse; change in medications for COPD within the four weeks prior to the screening visit. Nine patients were receiving oxygen therapy. At the time of the study, ten patients were being treated with a long acting either β-adrenergic or muscarinic-antagonist bronchodilator, fifty with an association of the two kinds of drug. No patient had received any drug during the 48 hours preceding the measurements. Patient characteristics are reported in Table 1.

The study was approved by the local Ethics Committee (Fondazione Salvatore Maugeri–654 CEC), and each patient gave written, informed consent. The trial has been registered at www.clinicaltrials.gov (NCT01377051).

2.2 Experimental procedure

A cross-over, randomized, controlled versus placebo, double-blind study was carried out. On two occasions, separated by 3-4 days, each patient underwent dyspnea evaluation, pulmonary function testing, and arterial blood gas analysis while breathing room air in the sitting position. Assessments were performed under basal conditions and one hour after the inhalation of indacaterol (Novartis Farma, Italy) or placebo, when the bronchodilator effect is maximal in terms of ΔFEV_1 (Vogelmeier et al, 2010; Rossi et al., 2012). Indacaterol (300 μg) and placebo in the form of dry powder were given via Breezhaler (Novartis Farma), the sequence of administration being randomized. Dyspnea was assessed using the visual analog scale (VAS) according to ATS

indications (American Thoracic Society, 1999). Ratings were expressed as percentage of the scale length; a change ≥15% was considered as clinically relevant (Ries, 2005; 2006). Reliability of dyspnea ratings was satisfactory, as indicated by the correlation between baseline VAS scores of the two test days (r=0.88). Static and dynamic lung volumes and sRAW were assessed by means of a constant-volume body plethysmograph (Master Screen Body, Erich Jaeger GmbH, Würzburg, Germany) according to current recommendations (Wanger et al., 2005). Intra-thoracic gas volume, taken as close as possible to the end-expiratory lung volume, and sRaw were obtained from the same sequence of measurements. Arterial blood gasses values were measured with GEM Premier 3000 (Instrumentation Laboratory, Lexington, MA, USA). All measurements were collected at the same time under basal conditions and after indacaterol or placebo administration.

2.3 Statistics

Data, presented as mean and SD, were analyzed using SPSS 19.0 (SPSS Inc., Chicago, USA). Normal distribution of data was assessed by means of the Kolmogorov-Smirnow test. The 95% confidence interval of both percent and absolute changes of pulmonary function variables after placebo was obtained as SD times the *t* value for 59 degree of freedom, and used to assess the short term variability of that variable (Sourk and Nugent, 1983). Predicted normal values were from Quanier (1983). Comparisons were performed with a two-way mixed between-within groups ANOVA; when significant differences were found, values of each variable were compared using paired or unpaired Student *t*-test with Bonferroni correction. GOLD stage distribution was analyzed by means of χ^2 test. Relationships between variables were assessed by means of linear regression analysis. Statistical significance was taken at $p \leq 0.05$.

3. Results

The effects of indacaterol or placebo on pulmonary function and dyspnea at rest are shown in Table 2, together with measures of short term variability. No difference in any variable occurred at baseline between the two test days, nor did placebo cause significant changes. In contrast, indacaterol caused significant changes in all variables both relative to baseline and placebo, except FEV_1/FVC, total lung capacity (TLC) and expiratory reserve volume (ERV) which never changed, and shall be, therefore, ignored subsequently. At baseline, tidal volume, breathing frequency, inspiratory-to-expiratory duration, and mean expiratory flow averaged 0.63±0.2 L, 17.2±3.9 min^{-1}, 0.65±0.21, and 0.33±0.13 $L \cdot s^{-1}$, and were unaffected by indacaterol or placebo administration. On both test days, 15 patients did not perceive dyspnea at rest, nor did indacaterol or placebo modify their perception, whereas in 18 patients the decrease of VAS score with indacaterol was ≥ 15%, i.e. clinically relevant (Ries, 2005; 2006).

At baseline, lung volumes were significantly correlated to both FEV_1 and sR_{AW}, whether expressed in absolute or relative terms (Fig. 1), independent of the presence of reversibility as defined by the ATS/ERS criteria (Pellegrino et al. 2005).

Table 3 reports the effects of indacaterol in patients stratified according to the ATS/ERS criteria for reversibility, i.e. an increase of FEV_1 and/or FVC ≥ 12% of control and ≥ 200 mL (Pellegrino et al., 2005). At baseline, there was no significant difference in any variable between the two groups of patients, including physical characteristics, Medical Research Council (MRC) score, and GOLD stage distribution. Indacaterol administration caused significant changes of all the variables, except TLC and FEV_1/FVC in both groups and FVC in non-reversible patients. Indacaterol induced changes, with the exception of FEV_1 and FVC, were not significantly different between reversible and non-reversible patients, except for FEV_1 and FVC which were greater in the former group.

Table 4 shows the effects of indacaterol in patients stratified according to the presence of reversibility based on sRAW short term variability. At baseline, no significant differences occurred between the two groups of patients. In reversible patients, all variables changed significantly with indacaterol administration, whereas in non-reversible patients this was the case only for FEV1. Both the absolute and relative changes of all variables were significantly larger in reversible patients, except those of FEV1 and FVC which did not differ between groups.

At baseline, the FEV1 *vs* sRAW relationship was markedly curvilinear, as previously shown (Deesomchock et al., 2010), with no distinction between reversible and non-reversible patients identified by ATS/ERS criteria, independent of whether data were expressed in absolute or relative terms (Fig. 2). Compared to the other relationships, the FEV1-sRAW relationship exhibited the highest correlation coefficient (Fig. 1). In contrast, no significant relationship occurred between FEV1 and sRAW changes, both in reversible and non-reversible patients. This dissociation was reflected in the relationships between the bronchodilator induced changes in lung volumes and FEV1 or sRAW, whether expressed in absolute (Fig. 3) or relative terms (Fig. 4): sRAW changes correlated with those of all variables, whereas FEV1 changes correlated only with those of FVC. Because sRAW includes ITGV, the relationship between ITGV and RAW changes was also examined: the slope was significant both when changes were expressed in absolute terms (0.50 ± 0.14 $L^2 \cdot kPa^{-1} \cdot s^{-1}$; $r=0.37$; $p=0.004$) and relative to baseline values (0.123 ± 0.038; $r=0.38$; $p=0.003$).

In the 45 patients who perceived dyspnea at rest, indacaterol administration decreased the VAS score by ~45%. The changes of VAS score were independent of those of FEV1, but correlated with those of sRAW (Fig. 3 and 4), besides VC, RV, FVC, IC, and ITGV changes ($r=0.59$, 0.52, 0.49, 0.48, and 0.45, respectively; $p<0.001$). Stepwise linear regression analysis showed, however, that VAS changes were significantly correlated with those of sRAW only.

Pulse rate, arterial blood gasses, pH, Na^+ and K^+ concentration were not appreciably affected by indacaterol or placebo administration.

4. Discussion

Indacaterol caused acute bronchodilation, reduced lung hyperinflation, and alleviated dyspnea perception at rest (Table 2). The changes in static and dynamic lung volumes were consistent with those observed with indacaterol in previous studies (Rennard et al., 2008; Beier et al., 2009; Rossi et al., 2012), as well as with salbutamol in very large samples of COPD patients (Newton et al., 2002; Deesomchock et al., 2010). In fact, both the severity of the disease evaluated by MRC score or GOLD stage, and lung function parameters at baseline were similar among these studies. Furthermore, the relative changes of sR_{AW} were markedly greater than those of FEV_1 or lung volumes (Table 2), in line with previous observations (Ramsdell and Tisi, 1979; Taube et al., 2000; Borrill et al., 2004; Deesomchok et al., 2010). These similarities suggest that the present results are representative of the response to bronchodilators.

At baseline, static and dynamic lung volumes correlated significantly with FEV_1 (Fig. 1), in line with observations on over 2000 patients (Deesomchok et al., 2010), as well as with sR_{AW}. This could be expected because the loss of lung elastic recoil, the other main mechanical alteration of COPD, should affect airway caliber, closing volume, dynamic compression, and in combination with changes of bronchomotor tone sR_{AW} and FEV_1. Furthermore, the correlation between the latter variables and TLC, ITGV, and RV suggests that obstructive and emphysematous components proceeded in a roughly parallel fashion. Both FEV_1 and sR_{AW} are, therefore, good predictors of the functional worsening of the disease: in fact, the relationship between these two variables, especially if expressed as percent predicted, showed the highest correlation coefficients (Fig. 2).

Despite the practical relevance of the improvements of lung volume parameters produced by bronchodilators, the use of FEV_1 is still recommended as the primary efficacy end-point in assessing the response to COPD medications, whereas volume-based measures are not (Guidance for Industry, 2007). Although both FEV_1 and sR_{AW} changed substantially with indacaterol (Table

2), and the FEV_1 *vs* sR_{AW} relationships obtained before and after bronchodilation did not differ significantly, no relation was found between the changes of these variables produced by bronchodilator administration (Fig. 2), supporting the notion that FEV_1 is a poor evaluator of intrapulmonary airway resistance (Pride, 1971; Pellegrino et al., 1998). Furthermore, the changes of FEV_1 did not correlate with those of lung volume variables, except FVC (Fig. 3 and 4), thus indicating that the increase of FEV_1 is mainly due to that of FVC, as previously suggested (Sourk and Nugent, 1983; Deesomchok et al., 2010). In contrast, the relationships between the changes of sR_{AW} and those of VC, IC, ITGV, and RV were highly significant (Fig. 3 and 4). Indeed, while no change in TLC can be anticipated because of bronchodilation, the fall of airway resistance in the resting tidal volume range, monitored by sR_{AW} changes, is expected to cause a fall of ITGV with a consequent increase of IC. The dynamic nature of lung hyperinflation during quiet breathing is also shown by the fact that the fall of ITGV with bronchodilation occurred without changes in the breathing pattern, particularly mean expiratory flow. Furthermore, sR_{AW} appears to monitor adequately the bronchomotor tone of peripheral airways, because only the fall of the latter can provide for lung unit recruitment with the consequent reduction of RV and increase of VC and FVC. Moreover, the lowered bronchomotor tone could have decreased the shear forces exerted on airway walls (Nucci et al., 2003), limiting epithelial damage (D'Angelo et al., 2004; 2008) and secretions with thinning of the mucous layer (Widdicombe et al.,1994), promoting better airway clearance, thus reducing the effective closing pressure of peripheral airways and allowing for a more complete lung deflation. Dynamic factors do not play a major role in the fall of RV with bronchodilation: although VC and FVC changes were well correlated ($r=0.65$), the latter were, however, significantly smaller (Table 2; $p=0.012$). This should limit the use of FVC changes in assessing bronchodilator efficacy.

The percentage of patients who demonstrate ATS/ERS defined reversibility (40%; Table 3) was similar to that found on very large populations (Newton et al., 2002; Deesomchock et al., 2010), whereas a much higher percentage (75%; Table 4) exhibited a decrease of sR_{AW} greater than

its short term variability, as computed from placebo testing (Table 2). Because the short term variability of FEV_1 and FVC (Table 2) was close to the threshold values for reversibility established for COPD patients (Pellegrino et al., 2005), it seems conceivable that the short term variability of sR_{AW} observed in the present patients, and used as the threshold value for reversibility, represents that of the COPD population. Interestingly, the stratification based on sR_{AW} derived reversibility allowed separation of patients with or without significant lung volume responses, whereas no distinction occurred between reversible and non reversible patients identified by ATS/ERS criterion. However, neither criterion allowed inference of reversibility from pre-bronchodilator values of any variable (Table 3 and 4).

The choice of sR_{AW} as an estimator of airway resistance during quiet breathing was mainly due to the widespread availability of adequate instrumentation in lung function laboratories. Furthermore, its assessment requires little or no cooperation from the patients, especially with certain types of plethysmographs. An alternative could be represented by impulse oscillometry, which, however, does not control for concomitant lung volume changes, seems to be less sensitive in detecting bronchodilation (Borrill et al., 2004), and has a more limited use as compared to plethysmography.

Under baseline conditions, dyspnea was felt by 75% of the present COPD patients, and in 62% of them it was clinically relevant (VAS≥15%). About 70% of the patients exhibited partial relief from dyspnea with bronchodilator administration, and in 40% the relief was of clinical relevance. At baseline, the strongest correlation of the VAS score was with sR_{AW} and FEV_1 (Fig. 1), independent of the presence of reversibility as defined by ATS/ERS criteria (Pellegrino et al., 2005), whereas with bronchodilation, the strongest correlation of ΔVAS was with ΔsR_{AW} only (Fig. 3). Indeed, stepwise regression analysis with VAS or ΔVAS as independent variable indicated that among all parameters, sR_{AW} or ΔsR_{AW} was the only significant predictor of the level of dyspnea at rest or its change with bronchodilation. Only few studies have assessed the acute effects of bronchodilators on dyspnea at rest (Wolkove et al., 1989; Noseda et al., 1993; Taube et al., 2000; Di

Marco et al., 2003). Comparisons are cumbersome because of differences in rating procedures, statistical analyses, ongoing therapeutic treatments, and severity of the disease; however, common to all studies is the range of incidence (55-70%) of patients who perceive a significant improvement of dyspnea at rest, as well as the indication that the concomitant changes of FEV_1 are poor or unfit indicators of dyspnea relief.

5. Conclusions

The present results support the notion that the effects of bronchodilators should be evaluated from the changes of airway resistance in the resting tidal volume range rather than FEV_1 and/or FVC, especially in connection with the dependent improvement of dyspnea. In contrast, both FEV_1 and sR_{AW} are equally good evaluators of the severity of bronchoconstriction at baseline. It is also shown that the decrease of RV and ITGV is mainly due to changes in the mechanical properties of the peripheral airways leading to decreased resistance and closing pressure. Finally, the ability to lower dyspnea at rest appears mainly related to the concomitant reduction of airway resistance rather than lung deflation.

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Table 1

Anthropometric and baseline lung function data.

M/F	48/12	
age, yr	72±7	
height, cm	167±9	
weight, kg	73±15	
MRC score	2.9±1.2	
VAS score %	15±14	
Post-bronchodilator		
FEV_1, L	1.24±0.49	(47±17)
FEV_1/FVC, %	46±12	(62±16)
Pre-bronchodilator		
FEV_1, L	1.14±0.47	(43±17)
FVC, L	2.57±0.85	(78±19)
FEV_1/FVC, %	45±11	(60±15)
VC, L	3.01±0.93	(89±19)
IC, L	2.18±0.77	(81±23)
ERV, L	0.83±0.45	(93±47)
sR_{AW}, kPa·s	4.01±2.23	(352±192)
TLC, L	6.85±1.39	(113±19)
ITGV, L	4.82±1.27	(144±34)
RV, L	3.87±1.20	(158±52)

Values are mean±SD from 60 COPD patients; data in parentheses are % of predicted values (Quanjer, 1983).

Abbreviations: M, male; F, female; MRC, Medical Research Council dyspnea scale; VAS, visual analog scale; FEV_1, forced expiratory vital capacity in one second; FVC, forced vital capacity; VC, slow expiratory vital capacity; IC, inspiratory capacity; ERV, expiratory reserve volume; sR_{AW}, total specific airway resistance; TLC, total lung capacity; ITGV, intrathoracic gas volume; RV, residual volume.

Table 2

Acute effects of indacaterol or placebo administration.

	indacaterol	p-value	placebo	p-value	p-value*	CI
ΔFEV1, L	0.10±0.11	<0.001	0.01±0.09	n.s.	<0.001	0.19
% baseline	9.4±11.2	<0.001	0.7±5.8	n.s.	<0.001	13
% predicted	3.5±3.9	<0.001	0.0±2.4	n.s.	<0.001	5
ΔFVC L	0.14±0.27	<0.001	-0.02±0.12	n.s.	<0.001	0.24
% baseline	6.0±10.7	<0.001	-2.1±5.7	n.s.	<0.001	11
% predicted	4.0±7.6	<0.001	-0.7±3.6	n.s.	<0.001	7
ΔFEV1/FVC %	1.5±5.2	n.s.	1.2±3.2	n.s.	n.s.	
ΔVC, L	0.21±0.23	<0.001	-0.02±0.11	n.s.	<0.001	0.21
% baseline	8.0±8.8	<0.001	-0.5±4.9	n.s.	<0.001	10
% predicted	6.3±6.7	<0.001	-0.5±4.2	n.s.	<0.001	8
ΔIC, L	0.20±0.25	<0.001	0.00±0.11	n.s.	<0.001	0.22
% baseline	11.0±14.2	<0.001	-0.3±5.7	n.s.	<0.001	12
% predicted	7.5±9.4	<0.001	-0.1±4.6	n.s.	<0.001	9
ΔERV, L	0.02±0.20	n.s.	-0.02±0.11	n.s.	n.s.	0.22
ΔsRAW, kPa·s	-1.03±1.19	<0.001	-0.02±0.12	n.s.	<0.001	0.24
% baseline	-20±21	<0.001	-0.7±3.9	n.s.	<0.001	8
% predicted	-89±102	<0.001	-2.0±10.7	n.s.	<0.001	21
ΔTLC, L	0.00±0.17	n.s.	0.00±0.11	n.s.	n.s.	0.22
ΔITGV, L	-0.29±0.37	<0.001	0.00±0.09	n.s.	<0.001	0.19
% baseline	-5.8±7.6	<0.001	-0.1±2.1	n.s.	<0.001	4
% predicted	-8.4±10.4	<0.001	0.0±2.8	n.s.	<0.001	6
ΔRV, L	-0.22±0.26	<0.001	0.02±0.10	n.s.	<0.001	.19
% baseline	-5.6±7.5	<0.001	0.2±3.1	n.s.	<0.001	6
% predicted	-8.6±10.3	<0.001	0.6±4.6	n.s.	<0.001	9
ΔVAS score, %	-7±8	<0.001	-2±7	n.s.	<0.001	13
% baseline	-44±27	<0.001	-11±25	n.s.	<0.001	51

Values are mean±SD from 60 COPD patients, except for ΔVAS, % baseline which refers to the 45 patients who felt dyspnea at rest.

Abbreviations: Δ, post- minus pre-intervention values; CI, placebo derived 95% confidence interval; see Table 1 for explanation of other abbreviations.

*indacaterol *vs* placebo.

Table 3

Acute effects of indacaterol administration in COPD patients stratified according to ATS/ERS criteria for reversibility.

	Reversible			Non-reversible			
	baseline	Δ	p-value	baseline	Δ	p-value	p-value*
M/F	21/3			27/9			
age, yr	70±7			74±7			
height, cm	169±9			165±9			
MRC	3.0±1.3			2.9±1.2			
GOLD II/III/IV	9/10/5			14/17/5			
FEV_1, L	1.04±0.39	0.18±0.09	<0.001	1.21±0.51	0.04±0.07	0.023	<0.001
% baseline		19±10	<0.001		3.2±6.9	n.s.	<0.001
FVC, L	2.56±0.80	0.32±0.29	<0.001	2.57±0.89	0.02±0.17	n.s.	<0.001
% baseline		13±12	<0.001		1.1±5.8	n.s.	0.001
FEV_1/FVC, %	41±9	2.1±7.1	n.s	47±12	1.1±3.4	n.s.	n.s.
VC, L	3.10±0.91	0.29±0.24	<0.001	2.95±0.95	0.15±0.20	<0.001	n.s.
% baseline		10±9	<0.001		6.3±8.0	<0.001	n.s.
IC, L	2.19±0.65	0.27±0.23	<0.001	2.17±0.84	0.15±0.26	0.018	n.s.
% baseline		15±15	<0.001		8.7±13.8	0.005	n.s.
sR_{AW}, kPa·s	4.59±2.28	-1.32±1.42	0.002	3.75±2.01	-0.83±0.98	<0.001	n.s.
% baseline		-25±22	<0.001		-17±19	<0.001	n.s.
TLC, L	7.38±1.22	-0.02±0.19	n.s	6.50±1.40	0.02±0.16	n.s.	n.s.
ITGV, L	5.30±1.24	-0.41±0.30	<0.001	4.49±1.20	-0.23±0.39	0.015	n.s.
% baseline		-7.7±6.1	<0.001		-4.9±8.2	0.009	n.s.
RV, L	4.28±1.20	-0.33±0.27	<0.001	3.60±1.13	-0.14±0.22	0.005	n.s.
% baseline		-7.9±7.4	<0.001		-4.1±7.4	0.018	n.s.
VAS score %	18±13	-10±9	<0.001	13±14	-5±7	<0.001	n.s.

Values are mean±SD from 60 COPD patients.

Abbreviations: GOLD, Global Initiative for Obstructive Lung Disease; see Tables 1 and 2 for explanation of other abbreviations.

*Reversible *vs* Non-reversible Δ values.

Table 4

Acute effects of indacaterol administration in COPD patients stratified according to the presence of reversibility based on sR_{AW} placebo derived confidence interval.

	Reversible			Non-reversible			
	baseline	Δ	p-value	baseline	Δ	p-value	p-value[a]
M/F	35/10			13/2			
age, yr	73±7			70±8			
height, cm	167±9			165±10			
MRC	3.0±1.1			2.7±1.3			
GOLD II/III/IV	12/24/9			9/5/1			
FEV_1, L	1.02±0.36	0.10±0.11	<0.001	1.51±0.55	0.08±0.08	0.030	n.s.
% baseline		10±12	<0.001		6.8±9.5	0.023	n.s.
FVC, L	2.43±0.76	0.18±0.27	<0.001	2.97±0.99	0.00±0.22	n.s.	n.s.
% baseline		7.5±11.3	<0.001		1.5±7.1	n.s.	n.s.
FEV_1/FVC, %	43±11	1.2±5.5	n.s	51±11	2.6±4.1	n.s.	n.s.
VC, L	2.85±0.84	0.27±0.21	<0.001	3.49±1.05	0.02±0.15	n.s.	<0.001
% baseline		10±9	<0.001		1.2±4.3	n.s.	<0.001
IC, L	2.05±0.64	0.26±0.23	<0.001	2.55±0.99	0.01±0.23	n.s.	0.015
% baseline		14±15	<0.001		2.0±8.4	n.s.	0.002
sR_{AW}, kPa·s	4.41±2.04	-1.34±0.96	<0.001	3.11±2.13	-0.17±1.33	n.s.	<0.001
% baseline		-28±15	<0.001		0±16	n.s.	<0.001
TLC, L	6.92±1.43	0.02±0.16	n.s	6.65±1.30	-0.05±0.19	n.s.	n.s.
ITGV, L	5.02±1.32	-0.40±0.34	<0.001	4.19±0.88	-0.02±0.28	n.s.	0.002
% baseline		-7.9±6.9	<0.001		-0.5±6.4	n.s.	0.007
RV, L	4.07±1.19	-0.27±0.26	<0.001	3.27±1.03	-0.07±0.19	n.s.	0.023
% baseline		-6.5±7.2	<0.001		-3.0±8.0	n.s.	0.043
VAS score %	16±13	-9±8	<0.001	10±14	-1±4	n.s.	<0.001

Values are mean±SD from 60 COPD patients. [a]Reversible *vs* Non-reversible Δ values. See Table 3 for explanation of abbreviations.

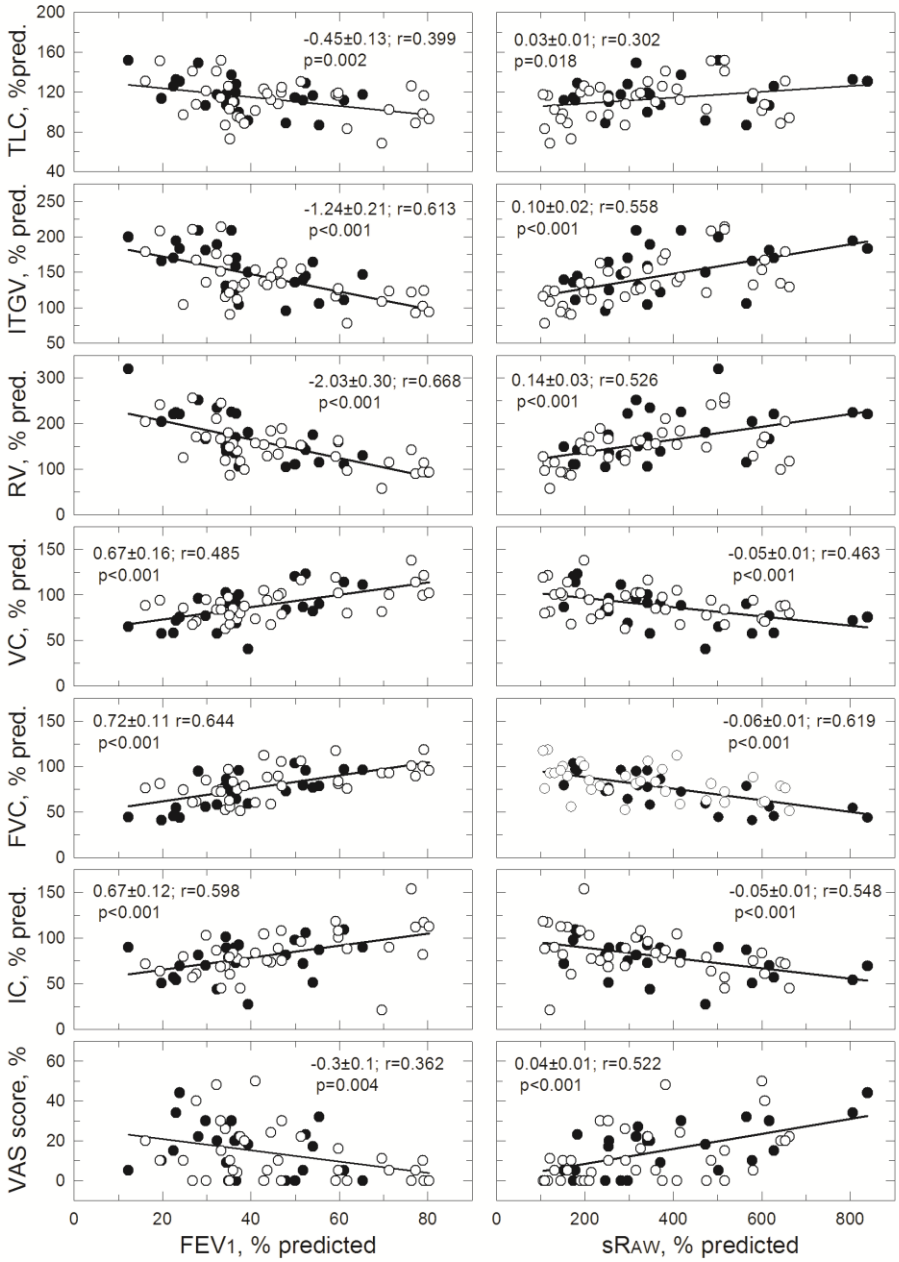
LEGENDS

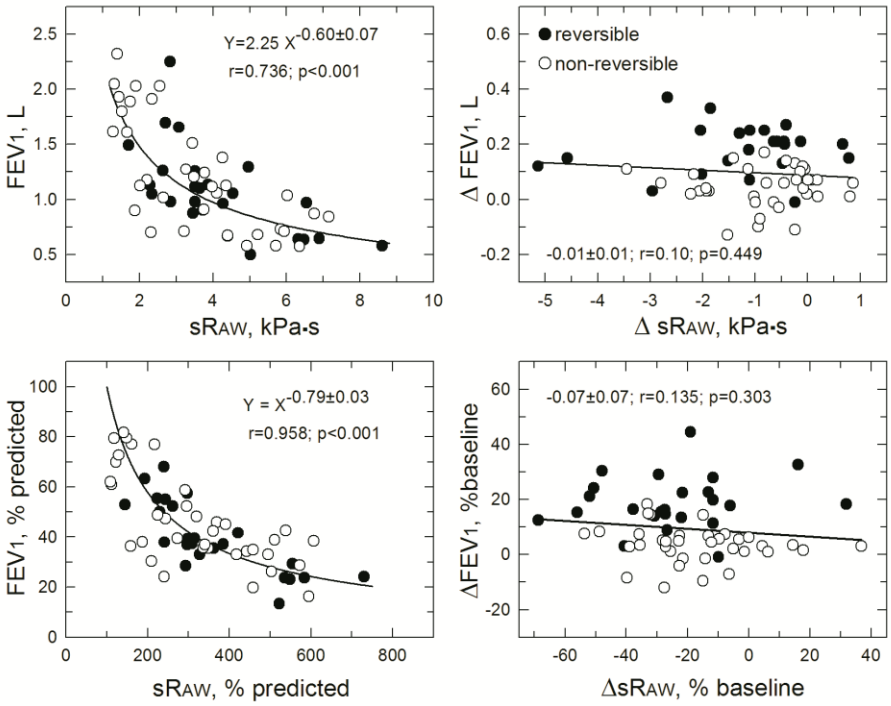
Fig. 1. The relationships between FEV_1 or sR_{AW} and lung volumes and dyspnea score at baseline. Slope (±SE), correlation coefficient, and p-value are shown in the inserts. Closed and open symbols indicate reversible (n=24) and non-reversible COPD patients (n=36), identified according to ATS/ERS criteria (Pellegrino et al., 2005).

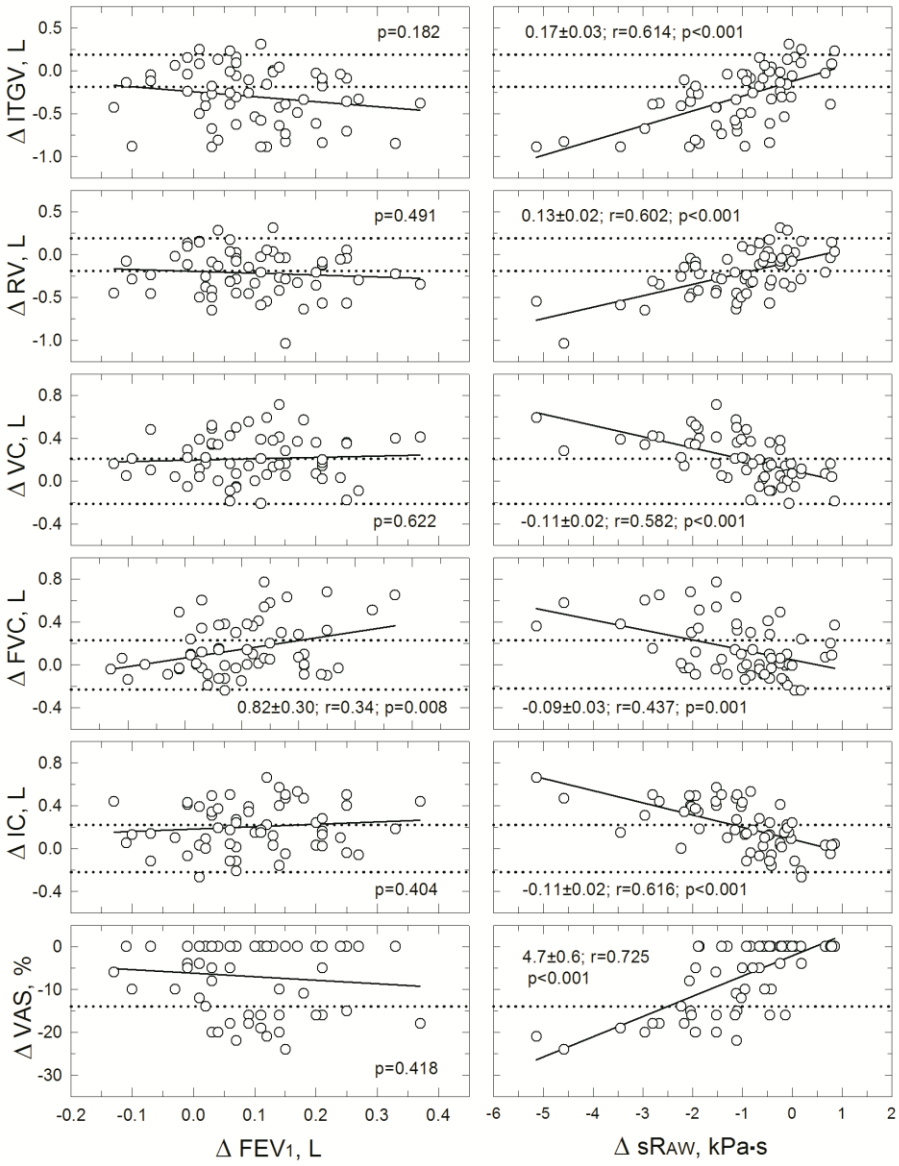
Fig. 2. The relationship between FEV_1 and sR_{AW} at baseline (left panels), and between FEV_1 and sR_{AW} changes due to indacaterol administration (right panels) obtained in 60 COPD patients, identified as reversible (closed symbols) or non-reversible (open symbols) according to ATS/ERS criteria (Pellegrino et al., 2005). Equation or slope (±SE), correlation coefficient, and p-value are shown in the inserts.

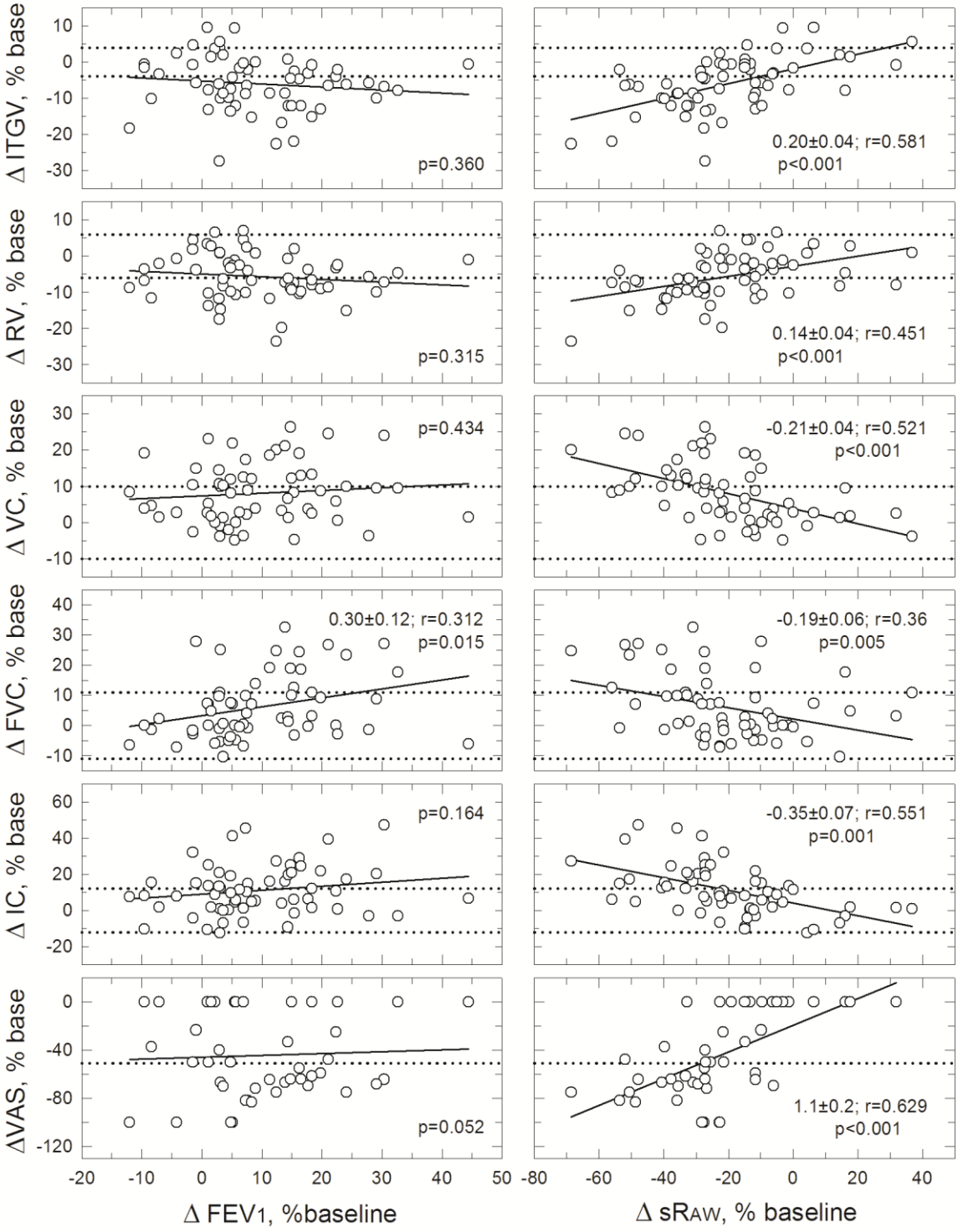
Fig. 3. The relationships between changes of FEV_1 or sR_{AW} and those of lung volumes and dyspnea score due to indacaterol administration obtained in 60 COPD patients. Slope (±SE), correlation coefficient, and p-value are shown in the inserts, only p-values being reported for non significant relations. Dotted lines represent the confidence limits of the variability with placebo administration.

Fig. 4. The relationships between the relative changes of FEV_1 or sR_{AW} and those of lung volumes and dyspnea score due to indacaterol administration obtained in 60 COPD patients, except for the ΔVAS relations which refer to the 45 patients who felt dyspnea at baseline. Slope (±SE), correlation coefficient, and p-value are shown in the inserts, only p-values being reported for non significant relations. Dotted lines represent the confidence limits of the variability with placebo administration.


TLC, %pred.
-0.45±0.13; r=0.399
p=0.002
0.03±0.01; r=0.302
p=0.018
ITGV, % pred.
-1.24±0.21; r=0.613
p<0.001
0.10±0.02; r=0.558
p<0.001
RV, % pred.
-2.03±0.30; r=0.668
p<0.001
0.14±0.03; r=0.526
p<0.001
VC, % pred.
0.67±0.16; r=0.485
p<0.001
-0.05±0.01; r=0.463
p<0.001
FVC, % pred.
0.72±0.11 r=0.644
p<0.001
-0.06±0.01; r=0.619
p<0.001
IC, % pred.
0.67±0.12; r=0.598
p<0.001
-0.05±0.01; r=0.548
p<0.001
VAS score, %
-0.3±0.1; r=0.362
p=0.004
0.04±0.01; r=0.522
p<0.001
FEV1, % predicted
sRAW, % predicted


Y=2.25 X-0.60±0.07
r=0.736; p<0.001
FEV1, L
sRAW, kPa•s
reversible
non-reversible
-0.01±0.01; r=0.10; p=0.449
Δ FEV1, L
Δ sRAW, kPa•s
Y = X-0.79±0.03
r=0.958; p<0.001
FEV1, % predicted
sRAW, % predicted
-0.07±0.07; r=0.135; p=0.303
ΔFEV1, %baseline
ΔsRAW, % baseline


Δ ITGV, L
p=0.182
0.17±0.03; r=0.614; p<0.001
Δ RV, L
p=0.491
0.13±0.02; r=0.602; p<0.001
Δ VC, L
p=0.622
-0.11±0.02; r=0.582; p<0.001
Δ FVC, L
0.82±0.30; r=0.34; p=0.008
-0.09±0.03; r=0.437; p=0.001
Δ IC, L
p=0.404
-0.11±0.02; r=0.616; p<0.001
Δ VAS, %
p=0.418
4.7±0.6; r=0.725
p<0.001
Δ FEV1, L
Δ sRAW, kPa·s


Δ ITGV, % base
p=0.360
0.20±0.04; r=0.581
p<0.001
Δ RV, % base
p=0.315
0.14±0.04; r=0.451
p<0.001
Δ VC, % base
p=0.434
-0.21±0.04; r=0.521
p<0.001
Δ FVC, % base
0.30±0.12; r=0.312
p=0.015
-0.19±0.06; r=0.36
p=0.005
Δ IC, % base
p=0.164
-0.35±0.07; r=0.551
p=0.001
ΔVAS, % base
p=0.052
1.1±0.2; r=0.629
p<0.001
Δ FEV1, %baseline
Δ sRAW, % baseline