Airway distensibility and volume recruitment with lung inflation in COPD

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Baldi S, Dellacà R, Govoni L, Torchio R, Aliverti A, Pompilio P, Corda L, Tantucci C, Gulotta C, Brusasco V, Pellegrino R. Airway distensibility and volume recruitment with lung inflation in COPD. J Appl Physiol 109: 1019–1026, 2010. First published July 22, 2010; doi:10.1152/japplphysiol.00147.2010.—The effects of full lung inflation on respiratory conductance (Grs) and reactance (Xrs) were measured in 15 subjects with moderate to severe chronic obstructive pulmonary disease (COPD) and 11 matched healthy control subjects. Airway distensibility was estimated from the ratio of the difference of Grs between functional residual capacity and total lung capacity to the relevant changes in lung volume (ΔGrs/ΔVL) or transpulmonary pressure (ΔGrs/ΔPtp). Similar analysis was applied to Xrs to estimate volume recruitment (ΔXrs/ΔVL) or transpulmonary pressure changes (ΔXrs/ΔPtp). The extent of emphysema in COPD subjects was estimated from the percentage of low attenuation area (LAA) at high-resolution computed tomography.

In COPD patients with intrinsic airway narrowing, airway conductance is expected to increase with Ptp less than in normal subjects, presumably because of irreversible airway remodeling, increased airway smooth muscle tone, and loss of parallel airways (35). In the case of emphysema without intrinsic airway narrowing (panlobular emphysema), airway conductance is expected to increase with lung inflation less than in normal subjects but in proportion to Ptp. A modern way to identify the extent of emphysema is by high-resolution computed tomography (HRCT), a technique that has been standardized (30) but is limited by radiation exposure and cannot identify the dynamic mechanisms of airflow obstruction.

In COPD patients with smoking history, centrilobular emphysema is variably associated with chronic bronchitis. Thus airway distensibility may be reduced even in the presence of sizable emphysema, as a result of the coexisting intrinsic airway narrowing, and the mechanisms of reduced airway conductance cannot be distinguished by simply plotting airway conductance against Ptp. We reasoned that if airway smooth muscle tone is the major contributor of intrinsic airway narrowing its removal by a bronchodilator should restore airway distensibility irrespective of the amount of emphysema. This should not be the case in the presence of irreversible airway wall stiffening, loss of parallel airways, or paradoxical decrease in airway caliber with lung inflation due to emphysema (5).

With these assumptions, we hypothesized that the effect of a bronchodilator intervention on the relationship between airway caliber and Ptp may differ in smokers with COPD depending on the extent of emphysema, thus providing additional information for patient phenotyping. To test this hypothesis, we used the noninvasive intrabreath forced oscillation technique, which at a frequency below resonant frequency allows instantaneous measurements at any lung volume of respiratory conductance (Grs), an index deemed to depend on both airway caliber and number of parallel ventilated units, and reactance (Xrs), an index theoretically reflective of the elastic properties of lung periphery (33). In this way we attempted to distinguish the effects of lung inflation on airway caliber, lung volume, and peripheral airways recruitment before and after bronchodilation.

METHODS

Subjects. Fifteen subjects with a clinical diagnosis of COPD and airflow obstruction confirmed by a forced expiratory volume in 1 s (FEV1)/forced vital capacity (FVC) below the lower limit of normality (32, 36) participated in the study (Table 1). Fourteen of these were former smokers (60 ± 21 pack·yr), one was a current smoker, and none had a monary pressure (Ptp) at different lung volumes (6, 25, 35). In COPD patients with intrinsic airway narrowing, airway conductance is expected to increase with Ptp less than in normal subjects, presumably because of irreversible airway remodeling, increased airway smooth muscle tone, and loss of parallel airways (35). In the case of emphysema without intrinsic airway narrowing (panlobular emphysema), airway conductance is expected to increase with lung inflation less than in normal subjects but in proportion to Ptp. A modern way to identify the extent of emphysema is by high-resolution computed tomography (HRCT), a technique that has been standardized (30) but is limited by radiation exposure and cannot identify the dynamic mechanisms of airflow obstruction.

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EXCESSIVE AIRFLOW LIMITATION and reduction of airway conductance are characteristic features of chronic obstructive pulmonary disease (COPD). These abnormalities reflect a decrease of airway caliber, which can be due to airway wall remodeling (the so-called “intrinsic” airway narrowing), loss of lung elastic recoil, or both (25, 35). It has been proposed that these two conditions can be differentiated by an index of airway distensibility, i.e., the relationship of airway conductance to transpulmonary pressure; chronic bronchitis; emphysema

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Table 1. Subjects’ main anthropometric and baseline lung function data

<table>
<thead>
<tr>
<th>COPD</th>
<th>Healthy</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men/women</td>
<td>12/3</td>
<td>8/3</td>
</tr>
<tr>
<td>Age, yr</td>
<td>67 (55–79)</td>
<td>61 (42–80)</td>
</tr>
<tr>
<td>Height, cm</td>
<td>165 (161–169)</td>
<td>169 (164–174)</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>26 (24–28)</td>
<td>27 (24–30)</td>
</tr>
<tr>
<td>FEV₁, % of predicted</td>
<td>45 (33–57)</td>
<td>106 (98–114)</td>
</tr>
<tr>
<td>FEV₁/FVC, %</td>
<td>39 (32–46)</td>
<td>78 (74–82)</td>
</tr>
<tr>
<td>FRC, % of predicted</td>
<td>147 (129–165)</td>
<td>98 (84–112)</td>
</tr>
<tr>
<td>RV, % of predicted</td>
<td>161 (156–186)</td>
<td>97 (88–106)</td>
</tr>
<tr>
<td>TLC, % of predicted</td>
<td>112 (105–119)</td>
<td>98 (92–104)</td>
</tr>
<tr>
<td>DLCO, % of predicted</td>
<td>48 (34–62)</td>
<td>88 (80–96)</td>
</tr>
<tr>
<td>PtpTLC, % predicted</td>
<td>69 (51–87)</td>
<td>NA</td>
</tr>
<tr>
<td>LAA, %</td>
<td>26 (22–30)</td>
<td>NA</td>
</tr>
<tr>
<td>D</td>
<td>1.71 (1.53–1.89)</td>
<td>NA</td>
</tr>
</tbody>
</table>

Data are means (95% confidence interval) except for age [means (range)]. Differences between groups were tested with unpaired t-test except for sex (χ² Fisher’s exact test). BMI, body mass index; FEV₁, forced expiratory volume in 1 s; VC, vital capacity; FRC, functional residual capacity; RV, residual volume; TLC, total lung capacity; DLCO, single-breath lung diffusion capacity; PtpTLC, transpulmonary pressure at TLC; LAA, whole lung area with attenuation values lower than −960 HU; D, slope in the log-log domain of the cumulative frequency distribution of LAA cluster size. NA, not available.

The COPD subjects attended the laboratory in the morning of two separate days. On the first day, lung volumes, lung diffusion capacity for carbon monoxide (DLCO), maximal flow-volume curves, respiratory impedance, and lung mechanics were measured at baseline and 20 min after 400 μg of albuterol by metered-dose inhaler with spacer. On the second day, a HRCT of the lung was obtained. Healthy subjects attended the laboratory only once for lung function measurements.

Lung function. Inspired and expired volumes were obtained by numerical integration of mouth flow measured by a mass flowmeter (SensorMedics, Yorba Linda, CA). FEV₁ and forced (FVC) and slow (VC) vital capacities were measured according to Miller et al. (28).

Absolute lung volume (VL) was measured according to American Thoracic Society (ATS)/European Respiratory Society (ERS) recommendations (39), with subjects sitting in a body plethysmograph (Masterlab, Jaeger, Würzburg, Germany) and panting at the end of tidal expiration against a closed shutter at a frequency slightly above 1 Hz with their cheeks supported by hands. Total lung capacity (TLC) was obtained as the sum of thoracic gas volume and the linked inspiratory capacity. Functional residual capacity (FRC) was obtained from thoracic gas volume corrected for any difference between the volume at which the shutter was closed and the average end-expiratory volume of the four preceding regular tidal breaths. Residual volume was the difference between TLC and VC. Predicted values for spirometry and lung volumes were from Quanjer et al. (36).

Single-breath lung diffusing capacity (DLCO) was measured by a Baires System (Biomedin, Padua, Italy) using a gas mixture containing 0.3% CO₂, 10% He, 23.5% O₂ and balance N₂, according to ATS/ERS recommendations (27). Reference values were from Cotes (10).

Quasi-static pressure-volume curves were measured in nine patients during intermittent and brief interruptions of flow during a relaxed expiration from TLC. Esophageal pressure was measured in the lower third of the esophagus by a 10-cm-long balloon filled with 1 ml of air, while mouth pressure was measured by a catheter inside the mouthpiece. Ptp was the difference between esophageal and mouth pressures gauged by two identical piezoelectric pressure transducers (Microswitch, ±200 cmH₂O). Placement of the balloon was considered correct if Ptp remained stable during gentle inspiratory and expiratory efforts against a partially occluded airway. Volume and Ptp values were measured at the points of zero flow. Ptp values taken at FRC and TLC were used to estimate the dependence of Grs and Xrs on lung elastic recoil. Predicted values are from Colebatch et al. (7).

The intrabreath impedance of the respiratory system was measured by imposing a sinusoidal pressure oscillation of 2 cmH₂O at 8 Hz at the mouth, while the cheeks were firmly supported by the operator. The forcing signal was generated by a personal computer connected to an A/D-D/A board (DAQ-CARD 1200, National Instruments, Austin, TX) and sent to a power amplifier (Proline EQ552, Eurosound, Milan, Italy) connected to a 25-cm-diameter loudspeaker (model HS250, Ciare, Ancona, Italy) mounted on a rigid box of ~3.0-liter internal volume. The loudspeaker was connected to the mouthpiece through a short connecting tube (22-cm length, 19-mm ID). A low-resistance, high-inertance tube (35-mm ID and 1.5-m length) connecting the pressure generator to atmosphere allowed the subject to breathe. The additional dead space of the tube was reduced by a 15 l/min bias flow applied between pressure generator and pneumotachograph. Pressure at airway opening was measured by a piezoelectric pressure transducer (model SCX01, SenSym, Milpitas, CA) connected to the mouthpiece. Flow was measured by a screen-type pneumotachograph (model 4700A; Hans Rudolph, Kansas City, MO) connected to a Celesco pressure transducer (model LCVR, 0–2 cmH₂O; Celesco Instruments, Canoga Park, CA). This allowed simultaneous measurement of lung volume. All signals were sampled at 200 Hz by the same A/D-D/A board used to generate the forcing signal. The frequency response of the system was tested by a high-impedance calibrator (4) and was flat up to 30 Hz. Intra-breath respiratory impedance was derived from the pressure and flow signals with an algorithm based on cross-correlation (12, 18, 20, 22, 34) and partitioned into respiratory resistance (Rs) and Xrs. Measurements were taken at least in duplicate during 2 min of tidal breathing at FRC and at the end of a 5-s inspiratory maneuver to TLC. The ratio of the difference between the mean values of Grs (1/Rs) at FRC and TLC to the simultaneous changes in Vi. as % TLC predicted (ΔGrs/ΔVt) or to the difference in quasi-static Ptp between the two Vt. (ΔGrs/ΔPtp) was used to estimate airway distensibility. The reported values are the average of the two sets of maneuvers. The same calculations were replicated to estimate the effects of lung inflation on volume recruitment (ΔXrs/ΔVt. and ΔXrs/ΔPtp).

Imaging. Lung HRCT was obtained with a multidetector row spiral CT scanner (Asteion; Toshiba Medical) in all COPD patients. The scans were obtained with four detector rows, 2-mm section thickness, and table speed of 12–16 mm per 0.5- to 0.75-s scanner rotation (i.e., pitch 6–8). Scanning was performed from apex to base at 1-cm intervals at 120 kV and 200–250 mA-s, with a 512 × 512 matrix. The data were retrospectively reconstructed by appropriate algorithm to obtain 2-mm-thickness sections at 5-mm intervals. Three slices representative of upper, middle, and lower lung were analyzed. The upper section was obtained 1 cm above the superior margin of the aortic arch, the middle section 1 cm below the carina, and the lower section 3 cm above the top of the diaphragm. All scan images were processed off-line with a semiautomated image-processing program, which extracts boundaries of the lungs, calculates lung cross-sectional areas and histograms of attenuation values (CT numbers) of individual highlighted sections, and summarizes data to obtain the frequency distribution of attenuation values for both lungs. From the frequency distribution of CT numbers, the percentage of the whole lung area with attenuation values lower than −960 HU [low attenuation area (LAA)]% were derived. LAA% was taken as an index of the extent of emphysema (23, 37). As the cumulative frequency distributions and size of LAA are expected to vary linearly on a log-log plot (29), the exponent (D) of the cumulative distribution (log) function vs. cluster (log) sizes was taken as an index of the size distribution of LAA.
clusters (29). High and low values of D suggest the presence of small and large cluster sizes, respectively.

Statistical analysis. Data are expressed as means ± SD. Relationships between variables were tested by linear regression analysis. A two-way analysis of variance (ANOVA) with Tukey honestly significant difference (HSD) post hoc comparisons was used to assess the significance of differences between categories of subjects before and after albuterol. χ² Fisher’s exact test was used for categorical data. P < 0.05 was considered statistically significant.

RESULTS

The main anthropometric and functional characteristics of the COPD patients and control subjects are reported in Table 1. In COPD subjects, airflow obstruction ranged from mild to very severe [FEV₁ 13–80% predicted (pred)] and was associated with a variable degree of lung hyperinflation (TLC 85–131% pred and FRC 91–209% pred). According to Global Initiative for Chronic Obstructive Lung Disease (GOLD) severity classification (31a), one patient was in stage I, five in stage II, six in stage III, and three in stage IV. Ptp at TLC (PtpTLC) varied from 39 to 107% pred, and DLCO from 20 to 93% pred. At FRC, Grs was significantly lower and Xrs more negative than in healthy subjects and unrelated to LAA (r = 0.27, P = 0.404 and r = −0.53, P < 0.075, respectively), thus reflecting greater airflow obstruction and reduced amount of ventilated lung independent of the COPD phenotype. The values of D and LAA were widely variable among subjects and significantly and negatively correlated with each other (r = −0.6182; P = 0.0015) (Fig. 1), without significant differences between upper and lower lung regions (P = 0.094 for LAA and P = 0.1249 for D). These findings attest to a variable presence of diffuse emphysema in COPD.

The control subjects matched with the COPD patients for age, sex, height, and body mass index (BMI). None of them was a smoker. Lung function was normal in all subjects.

Prebronchodilator effects of lung inflation. In control subjects, ∆Grs/∆Vl was significantly different from zero (P < 0.001), thus confirming airway distensibility with lung inflation. In contrast, ∆Xrs/∆Vl was not significantly different from zero (P = 0.4607).

In COPD subjects, ∆Grs/∆Vl and ∆Xrs/∆Vl were significantly less than in healthy subjects (Table 2), suggesting that

![Fig. 1. Relationship between the exponent of the log-log plot of the cumulative distribution function vs. cluster sizes (D) and % of low attenuation area (LAA) in the chronic obstructive pulmonary disease (COPD) group. Patients are identified by numbers that are replicated in Figs. 3 and 4 to facilitate comparison of the data.](image-url)
both airway distensibility and volume recruitment with lung inflation were reduced in the former. \( \Delta \text{Grs/} \Delta \text{Vt}, \Delta \text{Grs/} \Delta \text{Ptp}, \Delta \text{Xrs/} \Delta \text{Vt}, \) and \( \Delta \text{Xrs/} \Delta \text{Ptp} \) of individual subjects before bronchodilator are shown in Fig. 2 (continuous lines).

With respect to LAA, no correlations were found for \( \Delta \text{Grs/} \Delta \text{Ptp} \) (top, Fig. 3, top), \( \Delta \text{Grs/} \Delta \text{Vt} \) (Fig. 3, top), \( \Delta \text{Xrs/} \Delta \text{Ptp} \) (Fig. 3, bottom), \( \Delta \text{Xrs/} \Delta \text{Vt} \) (Fig. 3, bottom), and \( \Delta \text{Gr/} \Delta \text{Vt} \) (bottom, Fig. 4). These changes were statistically significant (Table 2). The increments of either parameters were no longer correlated with each other (top, Fig. 3, top, \( r = -0.2879, P = 0.4880 \)), suggesting that airway distensibility and volume recruitment were affected differently by the presence of airway smooth muscle tone. No significant correlations with D were observed.

After albuterol, mean FEV\(_1\) was not significantly increased whereas FVC achieved significantly higher values that were, however, marginal and well below the threshold of natural variability (Table 2). The increments of either parameters were not correlated with LAA (FEV\(_1\): \( r = -0.3000, P = 0.2980; \) FVC: \( r = -0.1679, P = 0.5660 \)). Mean Grs was not significantly increased at FRC or at TLC, and neither change was inversely correlated with LAA (top, Fig. 3, bottom, \( r = -0.4710, P = 0.1220 \) at FRC and \( r = -0.5069, P = 0.0930 \) at TLC). Mean Xrs became significantly less negative at both lung volumes (Table 2), and this was independent of LAA (bottom, Fig. 4, \( \Delta \text{Xrs}_{\text{FRC}}: r = 0.1949, P = 0.5430; \) \( \Delta \text{Xrs}_{\text{TLC}}: r = 0.1208, P = 0.7090 \)).

**DISCUSSION**

The main results of the present study are the following: 1) the effects of lung inflation on Grs and Xrs were attenuated in smokers with COPD compared with healthy subjects, independent of the presence or extent of emphysema, suggesting reduced airway distensibility and volume recruitment; and 2) after bronchodilator, airway distensibility increased more in subjects with less emphysema, while lung volume recruitment improved independently of the presence or extent of emphysema.

**Comments on methodology.** Forced expiratory flows corrected for thoracic gas compression have been used in the past to construct the relationship between airway caliber and Ptp, but they are variably dependent on volume history and do not allow direct estimation of airway caliber at TLC (25). Measurements of pulmonary conductance by esophageal balloon

![Fig. 2. Respiratory system conductance (Grs, top) and reactance (Xrs, bottom) plotted against lung volume as % of predicted total lung capacity (TLC, left) and absolute transpulmonary pressure (Ptp, right) in individual subjects before (continuous lines) and after (dashed lines) albuterol. Thick and thin lines identify COPD and control subjects, respectively.](http://jap.physiology.org/content/109/10/A1023.full.png)
are difficult to obtain over a sufficient number of tidal breaths at high lung volume, and values at TLC still need to be extrapolated from those obtained below it. The measurement of pulmonary conductance with the interrupted technique during a slow expiration from maximum inflation appears to be simpler (6), but even with this technique lung mechanics at TLC have to be extrapolated from values at lower lung volume. In any case, the measurement of Ptp requires the positioning of an esophageal balloon, for which reason the technique is of limited application in clinical practice or large trials. The forced oscillation technique used in the present study has the advantage of allowing rapid measurements of lung mechanics and simultaneous changes in lung volume (3, 19), thus providing direct impedance values even at TLC. Ptp was measured on separate maneuvers and matched with the corresponding impedance measurements at FRC and TLC. We do not think, however, that this limited the validity of our results because ΔGr at baseline was the same during Ptp and impedance measurements and the results of ΔGr/ΔPtp and ΔXr/ΔPtp were a reflection of ΔGr/ΔVl and ΔXr/ΔVl.

The frequency of 8 Hz was chosen because respiratory system impedance at this frequency is mostly determined by airway rather than lung tissue or chest wall properties (22). As the contribution of the latter further decreases at high lung volume, presumably because the increased tissue stiffness prevents the transmission of forcing signal to chest wall (1), the difference in Grs between TLC and FRC can be assumed as a valid index of airway distensibility (19).

Another advantage of the forced oscillation technique is that it provides measurements of Xrs. In a simple model of parallel alveolar units, Xrs at 8 Hz is the sum of the reactance of all single units reached by the input signal, thus reflecting the amount of ventilated lung. With a full lung inflation, ventilated lung volume in our COPD patients increased and Xrs became less negative, presumably reflecting peripheral airway and alveolar unit recruitment. Several studies lend support to this interpretation. In piglets with induced acute lung injury, Xrs at 8 Hz decreased proportionally to the decrease in nonaerated lung tissue after a large lung inflation (11), thus suggesting reopening of collapsed alveoli and/or subtended closed or near-closure airways. In asthmatic patients and in animal models of airflow obstruction, Xrs near resonance frequency decreased after a full inflation, suggesting opening of peripheral airways and ensuing increased alveolar volume (13, 21, 26). Our finding that in healthy subjects lung inflation was not associated with significant changes in Xrs is not in contrast with this hypothesis, because at maximal lung inflation stiffening of the respiratory system under these conditions possibly overcame the effects of lung volume recruitment on Xrs. Therefore, for the purpose of this study we assumed that the decrement in Xrs with lung inflation in our subjects reflected recruitment/reopening of peripheral airways.

A limitation of this study is that all our healthy subjects refused to have the esophageal balloon positioned and the comparison between COPD and control subjects was therefore based on ΔGr/ΔVl instead of ΔGr/ΔPtp. Although a reduced ΔGr/ΔVl does not allow us to distinguish between “intrinsic” airway narrowing and loss of elastic recoil (25, 35), it can be...
taken as a sign of reduced airway distensibility that is not fully related to reductions in lung recoil (3).

**Interpretation of results.** Studies on lung structure and function in COPD have documented the presence of several mechanisms that can impair airway-to-parenchyma interdependence, thus reducing the bronchodilator effect of lung inflation. They include loss of alveolar attachments (8), increased airway wall thickness and stiffness, and excess of mucus (15, 16). The finding of a reduced ∆Grs/∆Ptp or ∆Grs/∆Vl and LAA suggests that the reduced airway distensibility in our COPD subjects was independent of the prevailing disease phenotype, which may appear at variance with the prediction of a normal ∆Grs/∆Ptp in emphysema (35). A likely explanation for this finding is that airway distensibility is reduced because of the concomitant presence of “intrinsic” airway narrowing in smokers with a sizable amount of emphysema. To support this hypothesis, we studied three nonsmokers with α₁-antitrypsin deficiency and homogeneously distributed emphysema (Table 3). ∆Grs/∆Vl before and after albuterol is shown in Fig. 5 for individual subjects. In two subjects, ∆Grs/∆Vl was similar to control subjects and both ∆Grs/∆Ptp and ∆Grs/∆Vl were greater than in our smokers with COPD. In one subject, both slopes were negative, possibly because of paradoxical airway narrowing at maximum lung inflation (5). Therefore, a decrease in ∆Grs/∆Ptp and ∆Grs/∆Vl in COPD compared with healthy control subjects is not specific of paradoxical airway narrowing at maximum lung inflation (5). The lack of correlation between ∆Grs/∆Ptp or ∆Grs/∆Vl and LAA suggests that the reduced airway distensibility in our COPD subjects was independent of the prevailing disease phenotype, which may appear at variance with the prediction of a normal ∆Grs/∆Ptp in emphysema (35). A likely explanation for this finding is that airway distensibility is reduced because of the concomitant presence of “intrinsic” airway narrowing in smokers with a sizable amount of emphysema. To support this hypothesis, we studied three nonsmokers with α₁-antitrypsin deficiency and homogeneously distributed emphysema (Table 3). ∆Grs/∆Vl before and after albuterol is shown in Fig. 5 for individual subjects. In two subjects, ∆Grs/∆Vl was similar to control subjects and both ∆Grs/∆Ptp and ∆Grs/∆Vl were greater than in our smokers with COPD. In one subject, both slopes were negative, possibly because of paradoxical airway narrowing at maximum lung inflation (5). Therefore, a decrease in ∆Grs/∆Ptp and ∆Grs/∆Vl in COPD compared with healthy control subjects is not specific of paradoxical airway narrowing but may also be due to the coexistence of emphysema.

After bronchodilator, ∆Grs/∆Ptp and ∆Grs/∆Vl increased more in those subjects with a lower extent of emphysema, thus suggesting that airway smooth muscle tone made a major contribution to airway stiffening in these subjects with presumably predominant “intrinsic” airway narrowing. This hypothesis would find support in the increased airway smooth muscle mass reported in the small airways of COPD subjects with moderate to severe airflow obstruction (2, 15, 16, 40), the increase in the thickness of bronchiolar smooth muscle in smokers and patients with pulmonary emphysema (9), and the increased capacity to generate force in isolated human peripheral airways from COPD patients (31). In three subjects, there was a paradoxical decrease of ∆Grs/∆Ptp after bronchodilator, which may suggest a relative decrease in airway caliber at TLC, presumably as a result of exaggerated longitudinal airway traction or space competition between hyperinflated lung and small airways (5). Therefore, the changes in either direction of ∆Grs/∆Ptp and ∆Grs/∆Vl after albuterol justify the lack of significant results for the group as a whole and highlight the complexity of mechanisms decreasing flow in individual COPD patients.

In contrast to ∆Grs/∆Vl, ∆Xrs/∆Vl in COPD was higher than in control subjects, and both ∆Xrs/∆Vl and ∆Xrs/∆Ptp were independent of LAA. To the extent that Xrs reflects the fraction of lung volume participating in breathing (11, 33), these findings suggest that ventilation is quite heterogeneous in either chronic bronchitis or emphysema but improves under the effect of deep breathing. Unlike ∆Grs/∆Vl and ∆Grs/∆Ptp, however, both ∆Xrs/∆Vl and ∆Xrs/∆Ptp decreased after bronchodilator because of a reduction in XrsFRC, thus indicating that the cause of heterogeneity of ventilation was presumably located within the peripheral airways. With exposure of the airways to a bronchodilator agent and physical stretching, more lung was available to ventilation, thus explaining the significant decrease in ∆Xrs/∆Vl and ∆Xrs/∆Ptp. However, their relationships with LAA remained insignificant, suggesting that volume recruitment improved also in patients with higher emphysema extent. The lack of relationship between Xrs and HRCT data is not a novelty of the present study. Similar findings have been observed in asthmatic subjects during induced bronchoconstriction (24). Presumably, the parameters of CT attenuation in obstructive diseases reflect changes in parenchymal morphology, mechanics, and interdependence in addition to heterogeneous airway narrowing. Analysis of XrsTLC in individual COPD patients brings some additional information. Both before and after albuterol, XrsTLC was still significantly more negative than in the healthy control subjects, thus suggesting that some lung areas remained little or not ventilated at maximal inflation despite exposure to the bronchodilator agent and the mechanical stretching. This presumably reflects the real irreversible component of the disease resulting from severe airflow obstruction with airway closure and coexistence of emphysema. That this may be so is corroborated, though not proven, by the fact that the two patients with the most negative XrsTLC also had the lowest values of FEV₁ (17% and 13% pred), a high extent of emphysema (44% and 31%), and the lowest inspiratory capacity. The low TLC in one of these patients, however, is not in contrast with this interpretation, given the numerous mechanisms that may affect TLC independently of the obstructive condition.

No relationships were observed as for ∆Grs/∆Ptp or ∆Xrs/∆Ptp before and after salbutamol and D, an index of cluster size of terminal air spaces. Even though D is related to LAA

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**Table 3. Main data of three patients with emphysema and α₁-antitrypsin deficiency**

<table>
<thead>
<tr>
<th>Patient</th>
<th>FEV₁, % of predicted</th>
<th>TLC, % of predicted</th>
<th>LAA, %</th>
<th>D units</th>
<th>PtpTLC, cmH₂O</th>
<th>Cstat, l-cmH₂O⁻¹-s⁻¹</th>
<th>GrsFRC, l-cmH₂O⁻¹-s⁻¹</th>
<th>GrsTLC, l-cmH₂O⁻¹-s⁻¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>59</td>
<td>130</td>
<td>36</td>
<td>1.81</td>
<td>5.3</td>
<td>0.5</td>
<td>0.20</td>
<td>0.70</td>
</tr>
<tr>
<td>2</td>
<td>33</td>
<td>135</td>
<td>31</td>
<td>1.78</td>
<td>5.3</td>
<td>0.8</td>
<td>0.19</td>
<td>0.45</td>
</tr>
<tr>
<td>3</td>
<td>55</td>
<td>135</td>
<td>38</td>
<td>1.14</td>
<td>8</td>
<td>0.9</td>
<td>0.42</td>
<td>0.24</td>
</tr>
</tbody>
</table>

Cstat, static lung compliance. Other abbreviations as in Tables 1 and 2.

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**Fig. 5. Ratio of ∆Grs between TLC and FRC to the relevant ∆Vl before and after albuterol (gray and black columns, respectively) in the 3 patients with α₁-antitrypsin deficiency emphysema.**
and reflects the progression of the disease in terms of terminal air space enlargement, the relationship was relatively flat. A similar trend appears in Fig. 3 of Reference 29, although the relationship appears more a linear than ours, with a predominant increase in D at low LAA values. These data suggest that the impact of the cluster size of the lesions on ΔGrs/ΔPtp or ΔXrs/ΔPtp is of limited interest when the disease is advanced, whereas what constrains the response of airways to lung inflation is the increase in amount of emphysema.

Altogether, the findings of the present study suggest that significant “intrinsic” airway narrowing may be present in smokers with COPD, even with a sizable extent of emphysema. With the above assumptions that an increase in Grs with lung volume or Ptp mainly reflects an increase in size of the overall airways and in Xrs an increase in the number of recruited peripheral units, one could interpret our results as suggesting that airway smooth muscle contributes to airway stiffness in the bronchitic phenotype and to peripheral heterogeneity of ventilation in emphysema. In a way, these data reopen the question on what causes the reduction of flow in COPD and the role of airway smooth muscle tone. Previous studies have been inconclusive in this respect, presumably because of the multitude, complexity, and time dependence of the mechanisms limiting flow in COPD. However, the remarkable Grs response to albuterol observed in the patients with less emphysema and less decrease of FEV1 or FEV1/FVC would suggest a nonnegligible role of airway smooth muscle at least in the early stages of the disease. This is not in contrast with the lack of relationship reported between the FEV1 as percentage of predicted and airway smooth muscle mass in cartilaginous airways (38) or the large contribution of the small airways to total lung resistance (17). It can be hypothesized that the airway smooth muscle plays an important role in the natural history of the disease before irreversible mechanisms, such as peripheral airway fibrosis and loss of lung elastic recoil, become predominant. The low values of ΔGrs/ΔV1 or ΔGrs/ΔPtp after albuterol remain more difficult to interpret. In the past, this has been taken as an index of irreversible intrinsic airway narrowing (25, 35). The present data cannot exclude that this may also be due to the presence of emphysema, possibly contributing to mechanically collapse the airways at TLC (5). Be that as it may, these findings point to the need of functional phenotyping of COPD to direct the best bronchodilator therapy in individual patients and facilitate the interpretation of epidemiologic and clinical studies.

It is apparent from the results of the present study that only ΔGrs/ΔV1 or ΔGrs/ΔPtp allowed assessment of the role of airway smooth muscle in COPD as a function of LAA. Changes in FEV1 with albuterol were very small and well below the expected natural variability, and changes in Grs did not reach statistical significance. More importantly, neither FEV1 nor Grs changes at FRC correlated with LAA%. We believe that ΔGrs/ΔV1 and ΔGrs/ΔPtp were capable of better documenting the bronchodilator response in subjects with prevalent chronic bronchitis because they reflect the additive effects of albuterol and mechanical stretching on airway smooth muscle tone. In view of the importance of maintaining adequate lung function not only within the range of resting tidal breathing but also at increased lung volumes, e.g., for exercise hyperpnea, these parameters offer a more comprehensive evaluation of bronchodilator response in obstructive lung diseases.

In conclusion, airway distensibility and volume recruitment are impaired in COPD with chronic bronchitis, with or without emphysema. However, both of these improve after a bronchodilator intervention in subjects with prevalent chronic bronchitis, whereas only the latter ameliorates in patients with predominant emphysema. We suggest that examination of the volume dependence of Grs and Xrs at baseline and after a bronchodilator agent may be an adjunct tool for COPD phenotyping.

DISCLOSURES
No conflicts of interest, financial or otherwise, are declared by the author(s).

REFERENCES