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 pressure (Pavia), Italy (e-mail: simonetta.baldi@fsm.it).

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Airway distensibility and volume recruitment were affected differently 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, or 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, or 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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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; PtpLAA, 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.

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

<table>
<thead>
<tr>
<th></th>
<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>
<td>0.5080</td>
</tr>
<tr>
<td>Age, yr</td>
<td>67 (55–79)</td>
<td>61 (42–80)</td>
<td>0.3520</td>
</tr>
<tr>
<td>Height, cm</td>
<td>165 (161–169)</td>
<td>169 (164–174)</td>
<td>0.1631</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>26 (24–28)</td>
<td>27 (24–30)</td>
<td>0.3027</td>
</tr>
<tr>
<td>FEV₁, % of predicted</td>
<td>45 (33–57)</td>
<td>106 (98–114)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>FEV₁/VC, %</td>
<td>39 (32–46)</td>
<td>78 (74–82)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>FRC, % of predicted</td>
<td>147 (129–165)</td>
<td>98 (84–112)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>RV, % of predicted</td>
<td>161 (136–186)</td>
<td>97 (88–106)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>TLC, % of predicted</td>
<td>112 (105–119)</td>
<td>98 (92–104)</td>
<td>0.0028</td>
</tr>
<tr>
<td>DLCO, % of predicted</td>
<td>48 (34–62)</td>
<td>88 (80–96)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>PtpLAA, % predicted</td>
<td>69 (51–87)</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>LAA, %</td>
<td>26 (22–30)</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>D</td>
<td>1.71 (1.53–1.89)</td>
<td>NA</td>
<td></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; PtpLAA, 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. Insured 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 expiration. 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% CO, 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 E552, 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. Intrabreath 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 (Rrs) 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 Rrs (1/Rrs) at FRC and TLC to the simultaneous changes in VL as % TLC predicted (ΔGr/DVl) or to the difference in quasi-static Ptp between the two VL (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/ΔVl) and (ΔXrs/ΔPtp).
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 = 0.0180) (Fig. 1), without significant differences between upper and lower lung regions (P = 0.9240 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, ΔGrs/ΔVt was significantly different from zero (P < 0.001), thus confirming airflow distensibility with lung inflation. In contrast, ΔXrs/ΔVt was not significantly different from zero (P = 0.4607).

In COPD subjects, ΔGrs/ΔVt and ΔXrs/ΔVt 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.](http://jap.physiology.org/content/109/10/331D.full.pdf)

Table 2. Changes in lung mechanics after bronchodilator in COPD and healthy subjects

<table>
<thead>
<tr>
<th>Parameter</th>
<th>COPD</th>
<th>Healthy</th>
<th>ANOVA</th>
<th>Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Postalbuterol</td>
<td>Groups</td>
<td>Albuterol</td>
</tr>
<tr>
<td>FVC, liters</td>
<td>2.54 (2.20–2.88)</td>
<td>2.66 (2.30–3.02)</td>
<td>3.77 (3.37–4.17)</td>
<td>3.72 (3.36–4.08)</td>
</tr>
<tr>
<td>FEV₁, liters</td>
<td>1.23 (0.85–1.61)</td>
<td>1.39 (1.02–1.76)</td>
<td>2.05 (1.49–2.61)</td>
<td>2.14 (1.79–2.51)</td>
</tr>
<tr>
<td>sGrsFRC, cmH₂O/l</td>
<td>0.21 (0.17–0.25)</td>
<td>0.25 (0.21–0.30)</td>
<td>0.45 (0.33–0.57)</td>
<td>0.49 (0.36–0.61)</td>
</tr>
<tr>
<td>sXrsFRC, cmH₂O/l</td>
<td>0.32 (0.26–0.38)</td>
<td>0.45 (0.33–0.57)</td>
<td>0.85 (0.67–1.07)</td>
<td>0.93 (0.79–1.07)</td>
</tr>
<tr>
<td>GrsTLC, cmH₂O/l</td>
<td>1.30 (1.00–1.56)</td>
<td>1.45 (1.19–1.70)</td>
<td>2.51 (1.99–3.03)</td>
<td>2.83 (2.28–3.38)</td>
</tr>
<tr>
<td>XrsTLC, cmH₂O/l</td>
<td>0.61 (0.43–0.79)</td>
<td>0.78 (0.62–0.94)</td>
<td>1.52 (1.21–1.80)</td>
<td>1.80 (1.52–2.08)</td>
</tr>
<tr>
<td>Ptp, changes in Grs and Xrs with Ptp; changes in Grs and Xrs with lung volume as % TLC predicted. Values with * indicate significant differences compared to baseline.</td>
<td></td>
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</tbody>
</table>
both airway distensibility and volume recruitment with lung inflation were reduced in the former. \( \Delta \text{Grs}/\Delta V_L \), \( \Delta \text{Grs}/\Delta \text{Ptp} \), \( \Delta \text{Xrs}/\Delta V_L \), 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 \( \Delta \text{Grs}/\Delta \text{Ptp} \) (\( r = -0.2490, P = 0.5520 \)) (Fig. 3, top), \( \Delta \text{Grs}/\Delta V_L \) (\( r = -0.3919, P = 0.0280 \)) (Fig. 3, bottom), \( \Delta \text{Xrs}/\Delta \text{Ptp} \) (\( r = -0.0450, P = 0.9170 \)), or \( \Delta \text{Xrs}/\Delta V_L \) (\( r = 0.3770, P = 0.2260 \)). Also, no significant correlations were observed between the above indexes and \( D \) (\( \Delta \text{Grs}/\Delta \text{Ptp}: r = 0.3159, P = 0.4070 \); \( \Delta \text{Grs}/\Delta V_L : r = 0.3046, P = 0.3050 \); \( \Delta \text{Xrs}/\Delta \text{Ptp}: r = -0.1811, P = 0.6680 \); \( \Delta \text{Xrs}/\Delta V_L : r = -0.2950, P = 0.351 \)) or \( \text{Dlco}_\text{pred} \% \) pred (\( \Delta \text{Grs}/\Delta \text{Ptp}: r = -0.12, P = 0.784 \); \( \Delta \text{Grs}/\Delta V_L : r = -0.04, P = 0.907 \); \( \Delta \text{Xrs}/\Delta \text{Ptp}: r = 0.21, P = 0.686 \); \( \Delta \text{Xrs}/\Delta V_L : r = -0.19, P = 0.596 \)).

\( \Delta \text{Grs}/\Delta \text{Ptp} \) and \( \Delta \text{Xrs}/\Delta \text{Ptp} \) were correlated with \( \text{FEV}_1/\% \) pred (\( r = 0.7080, P = 0.0330 \) and \( r = -0.7130, P = 0.0470 \), respectively) (Fig. 4, top and bottom, respectively) and with \( \text{FEV}_1/\text{FVC} \) (0.875, \( P = 0.002 \); \(-0.7483, P = 0.033 \)) and inversely correlated with each other (\( r = -0.8440, P = 0.0080 \)), suggesting that airway distensibility but not volume recruitment with lung inflation is impaired in the more severely obstructed subjects.

**Postbronchodilator effects of lung inflation.** \( \Delta \text{Grs}/\Delta V_L \), \( \Delta \text{Grs}/\Delta \text{Ptp} \), \( \Delta \text{Xrs}/\Delta V_L \), and \( \Delta \text{Xrs}/\Delta \text{Ptp} \) of individual subjects after bronchodilator are shown in Fig. 2 (dashed lines). On average neither \( \Delta \text{Grs}/\Delta \text{Ptp} \) nor \( \Delta \text{Grs}/\Delta V_L \) changed significantly after albuterol (Table 2), but, at variance with prebronchodilator conditions, they became significantly and negatively correlated with LAA (\( r = -0.7870, P = 0.020 \) and \( r = -0.8190, P = 0.0010 \), respectively) (Fig. 3). By contrast, mean \( \Delta \text{Xrs}/\Delta \text{Ptp} \) and \( \Delta \text{Xrs}/\Delta V_L \) were significantly reduced after albuterol (\( P = 0.0241 \) and \( P = 0.0068 \), respectively) (Table 2) but once again unrelated to LAA (\( r = -0.2871, P = 0.4910 \) and \( r = 0.0332, P = 0.9190 \), respectively). Furthermore, \( \Delta \text{Grs}/\Delta \text{Ptp} \) and \( \Delta \text{Xrs}/\Delta \text{Ptp} \) were no longer correlated with each other (\( r = 0.2879, P = 0.4880 \)), 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 \( \text{FEV}_1 \) 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 (\( \text{FEV}_1 : r = -0.3000, P = 0.2980 \); \( \text{FVC}: r = -0.1679, P = 0.5660 \)). Mean Grs was not significantly increased at FRC or at TLC, and neither change was inversely correlated with LAA (\( r = -0.4710, P = 0.1220 \) 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 (\( \Delta \text{Xrs}_{\text{FRC}} : r = 0.1949, P = 0.5430 ; \Delta \text{Xrs}_{\text{TLC}} : r = 0.1208 , P = 0.7090 \)).

**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

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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.
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 Grs/VL instead of Grs/Ptp. Although a reduced Grs/VL 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 ΔGr /ΔPtp in COPD compared with control subjects indicates a reduced airway distensibility in the former. The lack of correlation between ΔGr /ΔPtp or ΔGr /ΔVl 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 ΔGr /ΔPtp 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). ΔGr /ΔVl before and after albuterol is shown in Fig. 5 for individual subjects. In two subjects, ΔGr /ΔVl was similar to control subjects and both ΔGr /ΔPtp and ΔGr /ΔVl 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 ΔGr /ΔPtp and ΔGr /ΔVl in COPD compared with healthy control subjects is not specific of irreversible intrinsic airway narrowing but may also be due to the coexistence of emphysema.

After bronchodilator, ΔGr /ΔPtp and ΔGr /ΔVl 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 ΔGr /ΔPtp 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 ΔGr /ΔPtp and ΔGr /ΔVl 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 ΔGr /ΔVl, ΔXrs /ΔVl in COPD was higher than in control subjects, and both ΔXrs /ΔVl and ΔXrs /ΔPtp 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 ΔGr /ΔVl and ΔGr /ΔPtp, however, both ΔXrs /ΔVl and ΔXrs /ΔPtp 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 ΔXrs /ΔVl and ΔXrs /ΔPtp. 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 ΔGr /ΔPtp or ΔXrs /ΔPtp before and after salbutamol and D, an index of cluster size of terminal air spaces. Even though D is related to LAA

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

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

Cstat, static lung compliance. Other abbreviations as in Tables 1 and 2.
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 \( \Delta \text{Grs}/\Delta \text{Ptp} \) or \( \Delta \text{Xrs}/\Delta \text{Ptp} \) 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 FEV\(_1\) or FEV\(_1\)/FVC would suggest a non-negligible 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 FEV\(_1\) 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 \( \Delta \text{Grs}/\Delta \text{Vt} \) or \( \Delta \text{Grs}/\Delta \text{Ptp} \) 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 \( \Delta \text{Grs}/\Delta \text{Vt} \) or \( \Delta \text{Grs}/\Delta \text{Ptp} \) allowed assessment of the role of airway smooth muscle in COPD as a function of LAA. Changes in FEV\(_1\) with albuterol were very small and well below the expected natural variability, and changes in Grs did not reach statistical significance. More importantly, neither FEV\(_1\) nor Grs changes at FRC correlated with LAA%. We believe that \( \Delta \text{Grs}/\Delta \text{Vt} \) and \( \Delta \text{Grs}/\Delta \text{Ptp} \) 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).

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29. Opazo Saez AM, Seow CY, Paré PD.

30. Opazo Saez AM, Seow CY, Paré PD.

31. Opazo Saez AM, Seow CY, Paré PD.

32. Opazo Saez AM, Seow CY, Paré PD.

33. Opazo Saez AM, Seow CY, Paré PD.

34. Opazo Saez AM, Seow CY, Paré PD.

35. Opazo Saez AM, Seow CY, Paré PD.

36. Opazo Saez AM, Seow CY, Paré PD.

37. Opazo Saez AM, Seow CY, Paré PD.

38. Opazo Saez AM, Seow CY, Paré PD.

39. Opazo Saez AM, Seow CY, Paré PD.

40. Opazo Saez AM, Seow CY, Paré PD.