

Lung Mechanics and Dyspnea during Exacerbations of Chronic Obstructive Pulmonary Disease

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Rationale: Exacerbation of chronic obstructive pulmonary disease commonly causes hospitalization. The change in lung mechanics during exacerbation and its relationship to symptoms in spontaneously breathing individuals has not been described.

Objective: We hypothesized that changes in both airflow and lung volumes would occur during an exacerbation, but that only volume change would relate to symptomatic improvement.

Methods: Lung mechanics and resting dyspnea were recorded in 22 hospitalized patients during recovery from exacerbation.

Measurements: Spirometry, inspiratory capacity, respiratory system resistance and reactance, tidal breathing patterns, and expiratory flow limitation were recorded after nebulized bronchodilator therapy on the first 3 d after admission, at discharge, and 6 wk postadmission (Day 42). Prebronchodilator measurements were taken on Day 2, at discharge, and on Day 42.

Main Results: Postbronchodilator inspiratory capacity increased 0.23 ± 0.07 L by discharge and 0.42 ± 0.1 L by Day 42, FEV₁ rose 0.09 ± 0.04 and 0.2 ± 0.05 L at discharge and Day 42, respectively, and FVC increased 0.21 ± 0.08 and 0.47 ± 0.09 L at discharge and Day 42 (all $p < 0.05$). Consistent reduction in dyspnea was seen as the exacerbation resolved. Respiratory system resistance, FEV₁/FVC, and expiratory flow limitation were unchanged throughout, indicating that changes in lung volume rather than airflow resistance predominated.

Conclusions: Improvement in operating lung volumes is the principal change seen as a chronic obstructive pulmonary disease exacerbation resolves and increase in inspiratory capacity is a useful guide to a reduction in dyspnea.

Keywords: breathlessness; inspiratory reserve volume; lung function; lung hyperinflation

Periodic exacerbations of symptoms are a major cause of morbidity, mortality, and health care costs in patients with chronic obstructive pulmonary disease (COPD) (1, 2). They are associated with a worse quality of life (3, 4) and a more rapid decline in both health status (4) and FEV₁ (5, 6). Most exacerbations are precipitated by either bacterial or viral infections (7, 8), but the resulting symptoms relate mainly to altered lung function. Increased cough, sputum production, and sputum purulence occur during exacerbations, but patients identify the most important symptom as being worsening breathlessness (9, 10). Although changes in lung mechanics are thought to be the major cause of dyspnea in COPD, we have few data about the time

course and nature of the change in lung mechanics during the resolution of an exacerbation in normocapnic patients.

Studies of patients in intensive care units have shown that the resistive and elastic work of breathing increases significantly during exacerbations, which leads to a marked increase in intrinsic positive end-expiratory pressure (11, 12). How these changes relate to more familiar measurements of flow and volume or to changes in symptom intensity in spontaneously breathing subjects has not been reported, but several mechanisms appear possible. Increased airway resistance, due to the release of mediators or the direct effect of inflammation reducing airway diameter, should lessen as the exacerbation resolves and be reflected by an increase in peak expiratory flow or FEV₁. However, the changes reported in these measures during an exacerbation of COPD are relatively small (13). Tidal expiratory flow limitation (EFL) is a better indicator of dyspnea severity than is the FEV₁ in stable COPD (14), and thus changes in EFL due to airway narrowing or closure during an exacerbation of COPD might relate to changes in symptom intensity. The relationship of EFL to other indices of lung mechanics during exacerbations has not been reported. However, the factor most likely to explain the change in symptoms during an exacerbation is a change in operating lung volume. An increase in end-expiratory lung volume (EELV) during exercise is the best predictor of symptom intensity and the degree of exercise limitation (15), and both improve after administration of a bronchodilator drug (16). During an exacerbation of COPD closure of small airways may occur because of mucus plugging, airway wall edema, or inflammation of lymph follicles, all of which may increase EELV even under resting conditions (17).

We hypothesized that during the resolution of an exacerbation of COPD there would be larger changes in lung volume than in expiratory flow–related measurements. It proved impractical to study the onset of an exacerbation and thus we prospectively studied patients on admission to hospital and monitored their subsequent clinical course. To compare patients we standardized treatment given and measurement timing as well as prior bronchodilator therapy. We recorded pre- and post-bronchodilator values for spirometry, dynamic lung volumes, oscillatory lung mechanics, and breathing pattern and tested for the presence of tidal expiratory flow limitation, relating these to changes in dyspnea and clinical improvement. Some of the results of these studies have previously been reported in the form of abstracts (18–20).

METHODS

Subject Recruitment

Patients were recruited within 24 h of hospitalization. An acute exacerbation was defined as an increase in at least two major symptoms: dyspnea, sputum purulence, or increased sputum volume, sufficient to require hospitalization (21). Patients were excluded if they had acute pneumonia, pneumothorax, atelectasis, or heart failure; had respiratory acidosis (pH < 7.32); had a coexisting illness that rendered them too ill to participate; or were unwilling to participate. All patients had a diagnosis of COPD defined both clinically and physiologically (22) with

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an FEV₁ less than 80% predicted and an FEV₁/FVC ratio less than 0.7 when enrolled (23). Any patient in whom the FEV₁ increased by more than 400 ml after administration of nebulized bronchodilator (24) or whose lung function improved to within normal values at any test session was excluded. Written informed consent was obtained from each patient. The local research ethics committee granted study approval (*see* the online supplement for further details).

Inpatient Management of Exacerbation

All patients were managed by a respiratory physician who determined the time of discharge on clinical grounds without knowledge of the study measurements. While hospitalized, patients received regular nebulized salbutamol and ipratropium bromide (5 mg and 0.5 mg per nebulization, respectively) and oral corticosteroids (30 mg daily for 1 wk), and most patients received antibiotics (usually a broad-spectrum penicillin) as directed by their clinician.

Study Design

Postbronchodilator assessments were made daily for the first 3 d (Days 1, 2, and 3), at discharge and, when possible, on Day 42 (6 wk postadmission). Additional prebronchodilator data were obtained on Day 2, at discharge, and, when possible, on Day 42. All prebronchodilator tests were performed in the morning with no bronchodilator therapy for 6 h beforehand. Patients subsequently received nebulized salbutamol (5 mg) and ipratropium bromide (0.5 mg). Forty-five minutes later, the tests were repeated. Tests were performed in the same sequence at each visit and comprised measurement of flow limitation, resting tidal breathing analysis, measurement of respiratory system resistance and reactance during tidal breathing, inspiratory capacity (IC), and spirometry (*see* the online supplement for further details).

Measurements

Spirometry and IC. Spirometry was measured to American Thoracic Society standards (23), using a pneumotachograph (Jaeger MasterScreen IOS; VIASYS Healthcare, Hoechst, Germany). IC was calculated indirectly by measuring the expiratory reserve volume (ERV) and VC, also using the same pneumotachograph. Testing was repeated until two reproducible values within 10% of each other were obtained; the best being recorded. Predicted IC was derived from combined total lung capacity (TLC) and FRC predictions. Inspiratory reserve volume (IRV) was calculated by subtracting V_T from IC.

Measurement of total respiratory system resistance and reactance. Respiratory system resistance at a frequency of 5 Hz (R_s) and reactance at 5 Hz (X_s) was measured by impulse oscillometry (Jaeger MasterScreen IOS); the apparatus deadspace was 120 ml. At least five tidal breaths of the same duration and volume were recorded and the analyzed data were averaged over this time period. Measurements were repeated until two values that were within 10% of each other were obtained. The mean value of these measurements was used for analysis (25).

Tidal breathing and resting expiratory flow limitation. Resting breathing was recorded with the pneumotachograph system for 3 min, with data analyzed during the final minute. Respiratory rate, V_T, inspiratory and expiratory times and their derivatives, mean inspiratory and expiratory flow (V_T/inspiratory time [T_i] and V_T/expiratory time [T_e], respectively), duty cycle (T_i/total cycle duration [T_{tot}]), and \dot{V}_E were calculated.

Negative expiratory pressure during tidal breathing was applied to detect expiratory flow limitation in the seated patient, as described previously (26). Breaths were considered flow limited when negative expiratory pressure did not increase expiratory flow relative to the preceding untested breath. Flow limitation was also expressed as the percentage of expired tidal volume affected (FL % V_T).

Assessment of Dyspnea

Before each testing sequence patients were asked to rate the intensity of their resting breathlessness on a modified Borg scale, in response to the question: "How breathless do you feel?" (27).

See the online supplement for additional detail on the methods used to make all these measurements.

Statistical Analysis

Data are expressed as means (SD) for group data or as means \pm SEM when time points or groups are compared. We used a Student *t* test

and repeated measures analysis of variance to compare differences in normally distributed data (SPSS version 10.0; SPSS, Chicago, IL), accepting *p* < 0.05 as significant. On the basis of the known test–test reproducibility of inspiratory capacity (26), we needed 14 patients to detect a 200-ml difference in IC from entry to study conclusion. We anticipated that we might have a 35% dropout with this protocol and planned to recruit at least 21 individuals.

RESULTS

Clinical Characteristics of the Study Population

Of 44 patients identified as being potentially eligible over an 18-mo period, 30 entered the study but 7 withdrew during the early stages because of clinical deterioration (*n* = 5) or technical difficulty in completing maneuvers (*n* = 2). One patient was excluded as that patient's lung function subsequently returned to normal. The admission characteristics of the remaining 22 patients are shown in Table 1.

All patients reported symptoms consistent with an acute exacerbation before admission to hospital. Four patients had received antibiotics and/or oral corticosteroids in the week before admission. No patient had been admitted with an exacerbation of COPD in the preceding 6 wk. Three patients received intravenous aminophylline and none required ventilation or died. The median length of hospital stay was 7 d (range, 3–10 d). Two patients were discharged on Day 3 and their measurements on Day 3 were also included in the discharge day data. *See* the online supplement for sputum microbiological data. Neither the presence of microorganisms in the sputum nor the treatment received before admission appeared to influence the changes in lung mechanics seen during recovery from the exacerbation.

Data for 6 of the 22 patients were not available for Day 42, either because of recurrent exacerbations of COPD (*n* = 5) or because the patient declined to attend for these follow-up studies (*n* = 1). Admission data for the 16 patients who returned on Day 42 are shown in Table 1. Admission characteristics of the subjects who returned on Day 42 did not differ from those who did not (Table 1), nor did the data at discharge (data not presented).

Changes in Lung Mechanics during the Exacerbation

Postbronchodilator spirometry and lung volume. Changes in post-bronchodilator spirometry and IC from admission to discharge and, when available, to Day 42 for all subjects are shown in Figure 1 and Table 2. Group mean postbronchodilator FEV₁ improved by 0.09 \pm 0.04 L at discharge (*n* = 22, *p* < 0.05) and by 0.20 \pm 0.05 L (*n* = 16, *p* < 0.01) by Day 42 relative to the Day 1 value. Postbronchodilator FVC improved by 0.2 \pm 0.08 L (*n* = 22, *p* < 0.05) on discharge and by Day 42 had increased 0.47 \pm 0.09 L from the admission value (*n* = 16, *p* < 0.001). There was no change in FEV₁/FVC ratio at any stage; for example, the ratio was 0.49 on admission and 0.48 on Day 42 (*p* = not significant). These data were not different if slow vital capacity data were substituted for the FVC.

IC increased from Day 1, when it was 62 \pm 4% predicted at admission, to 73 \pm 4% at discharge (*n* = 22, *p* < 0.05), and to 81 \pm 7% on Day 42 (*n* = 16, *p* < 0.01). These values correspond to an improvement of 0.23 \pm 0.07 L (*p* < 0.01) by discharge and 0.42 \pm 0.1 L (*p* < 0.01) by Day 42; *see also* Table 2. The change in IC from admission to discharge was related to the change in FVC (*r* = 0.47, *p* < 0.05) but not the change in FEV₁.

Respiratory system resistance and reactance. There was no significant change in respiratory system resistance, R_s, throughout the study. Thus the R_s fell from 0.65 \pm 0.04 to 0.59 \pm 0.04 kPa/L/s on discharge, whereas in those in whom it was recorded on Day 42 the R_s was 0.61 \pm 0.2 on admission and 0.58 \pm 0.04 on Day 42 (Tables 1 and 2 and Figure 2A).

TABLE 1. ADMISSION CHARACTERISTICS OF ALL SUBJECTS WHO WERE MONITORED TO DISCHARGE AND OF THE 16 SUBJECTS WHO COMPLETED 42 DAYS OF FOLLOW-UP

	All Subjects	Subjects Attending on Day 42
No. subjects (no. males)	22 (9)	16 (7)
Age, yr	70 (10.3)	69 (9.9)
Smoking, pack-yr	47 (22.5)	45 (15.5)
Body mass index, kg/m ²	21.9 (4.8)	22.3 (4.8)
White cell count, $\times 10^9/L$	11.50 (4.36)	11.42 (4.83)
Borg breathlessness score at rest on first assessment	3.7 (1.6)	3.9 (1.8)
pH	7.41 (0.05)	7.40 (0.05)
PaO ₂ , kPa	8.97 (1.40)	8.94 (1.51)
PaCO ₂ , kPa	5.02 (0.88)	5.04 (0.99)
FEV ₁ , L	1.03 (0.36)	1.06 (0.40)
FEV ₁ , %pred	46.7 (18.1)	46.8 (19.2)
FVC, L	2.15 (0.57)	2.08 (0.51)
IC, L	1.37 (0.43)	1.32 (0.39)
IC, %pred	62.2 (16.3)	59.3 (16.4)
Total respiratory system resistance		
R _s , kPa/L/s	0.65 (0.2)	0.61 (0.2)
X _s , kPa/L/s	-0.42 (0.16)	-0.40 (0.19)
No. subjects with resting EFL	9	7

Definition of abbreviations: EFL = tidal expiratory flow limitation assessed by negative expiratory pressure technique; IC = inspiratory capacity; R_s = total respiratory system resistance; X_s = total respiratory system reactance.

Values represent means (SD). No statistically significant differences were seen between the groups.

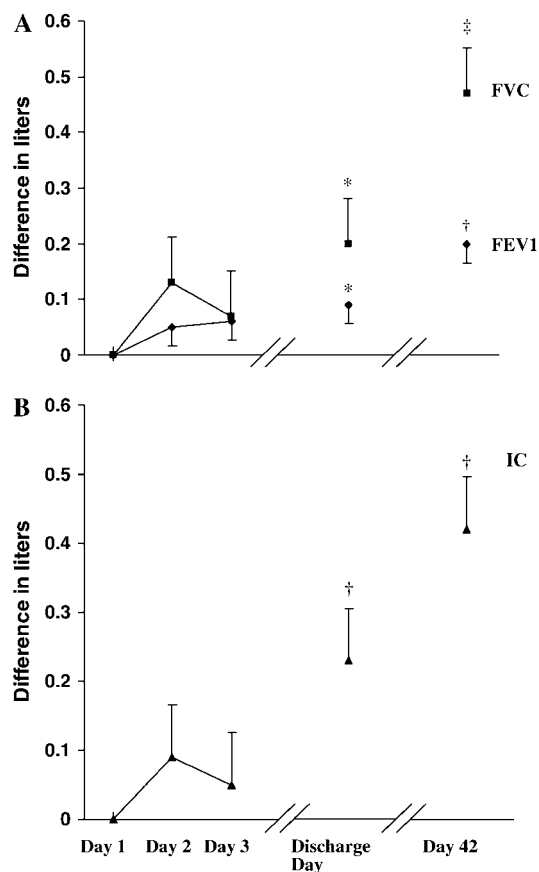


Figure 1. (A) Difference in FEV₁ and FVC over time from day of admission (Day 1) to discharge (median, Day 7) and postdischarge (Day 42). (B) Difference in inspiratory capacity (IC) over time from day of admission (Day 1) to discharge (median, Day 7) and postdischarge (Day 42). **p* < 0.05; †*p* < 0.01; ‡*p* < 0.001, discharge and Day 42 compared with Day 1. Note that data for Day 42 apply to 16 patients only (see Tables 1 and 2 for relevant baseline and Day 42 data).

The group mean respiratory system reactance measured at 5 Hz, X_s, improved from admission to discharge by 0.11 ± 0.02 kPa/L/s (*p* < 0.001) and was not significantly different on Day 42 (Table 2 and Figure 2B). From admission to discharge postbronchodilator X_s became less negative in 16 subjects (-0.45 ± 0.04 to -0.29 ± 0.04 kPa/L/s) and remained constant in the other 6 patients. There were no significant differences on admission between patients whose X_s improved over time and those for whom it did not. The “X_s improvers” had significant improvements in FEV₁ (mean change, 130 ml; *p* < 0.05) and IC (mean change, 270 ml; *p* < 0.01) whereas the “nonimprovers” did not show significant improvement (see Table E1 in the online supplement).

Breathing pattern. The postbronchodilator breathing pattern at rest did not change significantly during the recovery period (Table 3). Resting \dot{V}_E remained relatively high at each test session despite the improvement in other measurements of lung mechanics. A significant increase in IRV of 0.2 ± 0.1 L (*p* < 0.05) occurred during the in-hospital period. There was a further change in outpatient recovery period: on Day 42, IRV increasing from admission by 0.27 ± 0.64 L (*n* = 16, *p* = 0.05).

Tidal flow limitation during exacerbation. On admission, when seated, 9 of the 22 patients showed EFL, whereas 13 were not tidal flow limited. EFL resolved in four patients and appeared for the first time by discharge in two patients; the remaining 16 patients were unchanged. In EFL, subjects’ mean percentage of FL as a percentage of V_T (FL % V_T) was $44 \pm 3\%$ at baseline. There was no clear pattern of change or improvement in FL % V_T during recovery.

Bronchodilator Response during Exacerbation

Changes in lung mechanics, breathing pattern, and dyspnea after nebulized bronchodilators are presented in Table 4. There was a significant increase in FEV₁, FVC, IC, and X_s after bronchodilator administration, accompanied by a fall in dyspnea score and R_s. The increase in FEV₁ (*p* < 0.04) and fall in R_s (*p* < 0.01) immediately after bronchodilator administration was greater as the exacerbation resolved. The improvement in IC, FVC, and Borg score was similar irrespective of the time after admission that the test was performed.

Breathing pattern was little affected by the bronchodilator, with a small but significant increase in V_T occurring on Day 2

TABLE 2. CHANGE IN LUNG MECHANICS AND SYMPTOMS OVER THE COURSE OF THE FIRST 3 DAYS OF HOSPITALIZATION, AT THE TIME OF DISCHARGE, AND ON DAY 42

	Day 1	Day 2	Day 3	Discharge Day	Day 42
No. subjects	22	22	22	22	16
FEV ₁ , L	1.03 ± 0.08	1.08 ± 0.08*	1.08 ± 0.08	1.12 ± 0.09*	1.26 ± 0.10†
FEV ₁ , %pred	47.0 ± 3.9	49.2 ± 4.1*	49.4 ± 4.2	51.2 ± 4.6*	54.8 ± 4.2*
FVC, L	2.15 ± 0.12	2.28 ± 0.2	2.23 ± 0.14	2.36 ± 0.12*	2.54 ± 0.14‡
FVC, %pred	76.9 ± 4.8	80.2 ± 4.4	78.0 ± 4.3	83.5 ± 4.1*	86.3 ± 3.1†
FEV ₁ /FVC	0.49 ± 0.03	0.48 ± 0.03	0.50 ± 0.03	0.48 ± 0.03	0.49 ± 0.03
IC, L	1.37 ± 0.1	1.46 ± 0.1	1.43 ± 0.10	1.60 ± 0.10†	1.74 ± 0.13†
Borg score	3.73 ± 0.34	3.03 ± 0.34*	3.07 ± 0.30†	2.47 ± 0.24†	2.16 ± 0.30†
R _S , kPa/L/s	0.65 ± 0.04	0.60 ± 0.04	0.65 ± 0.04	0.59 ± 0.04	0.58 ± 0.04
X _S , kPa/L/s	-0.42 ± 0.03	-0.37 ± 0.04	-0.39 ± 0.04	-0.31 ± 0.03‡	-0.28 ± 0.04†

Definition of abbreviations: IC = inspiratory capacity; R_S = total respiratory system resistance; X_S = total respiratory system reactance. Values represent means ± SEM.

* $p < 0.05$, significant difference compared with Day 1.

† $p < 0.01$, significant difference compared with Day 1.

‡ $p < 0.001$, significant difference compared with Day 1.

(+80 ml) and Day 42 (+70 ml). Expressing the IC as a percentage of the FVC showed no acute change with bronchodilator administration, although the postbronchodilator IC/FVC ratio value rose from 64% on Day 2 to 68% at discharge. The acute change in IRV was small on Day 2 but increased by a mean of 120 ml ($p < 0.05$) on discharge and by 240 ml ($p < 0.05$) on Day 42.

Relative Change in Resting Breathlessness and Lung Mechanics

The median resting postbronchodilator Borg breathlessness score on admission was 4 (range, 0.5–7). There was a fall in postbronchodilator breathlessness score, relative to Day 1, of 1.7 ± 0.43 units at discharge ($p < 0.01$) and 2.16 ± 0.4 units on Day 42 ($p < 0.01$) with median scores of 2.5 (range, 0–4) and 2 (range, 0–5), respectively (Figure 2B).

Only 16 of 22 patients reported any reduction in resting dyspnea by discharge. These patients had a significantly lower IC on admission compared with patients not reporting a reduction in dyspnea ($p < 0.01$). Both FEV₁ and IRV were also lower in this group on admission (both $p = 0.05$). The degree of resting dyspnea these patients reported on discharge was similar to that on admission among the patients whose dyspnea did not improve over time (see Table E2).

In patients whose Borg score improved during hospitalization, mean FEV₁ increased by 0.20 ± 0.07 L ($p < 0.05$), mean IC by 0.54 ± 0.16 L ($p < 0.01$), and mean X_S by 0.15 ± 0.04 kPa/L/s ($p < 0.01$) by Day 42 ($n = 11$). In contrast, in those whose dyspnea was unchanged, neither FEV₁ nor IC increased significantly (see Table E2). Similar changes were seen in each of these variables at the time of discharge although these were generally of a smaller magnitude. By discharge, there was no significant difference in IC between patients who felt an improvement in breathlessness and those who did not. The magnitude of the change in dyspnea from admission to discharge or follow-up was unrelated to the change in IC or other measured variables.

DISCUSSION

Although exacerbations of COPD are a frequent cause of hospitalization, surprisingly little is known about the physiologic changes that accompany their resolution and what relationship these bear to the patient's symptoms. Hypoxia and hypercapnia have been carefully studied, with the latter relating directly to lung mechanics (28) and showing a variable resolution over time (29) and between episodes (30). Our data demonstrate that from admission to discharge and through the 6 wk after the exacerbation there was a small increase in FEV₁, no significant change in airway resistance or tidal FL, but a significant increase in both FVC and IC together with an improvement in reactance. In nonhypercapnic exacerbations, changes in operating lung volumes rather than either tidal or forced expiratory flow related to both the resolution of the exacerbation and the change in breathlessness reported by the patient.

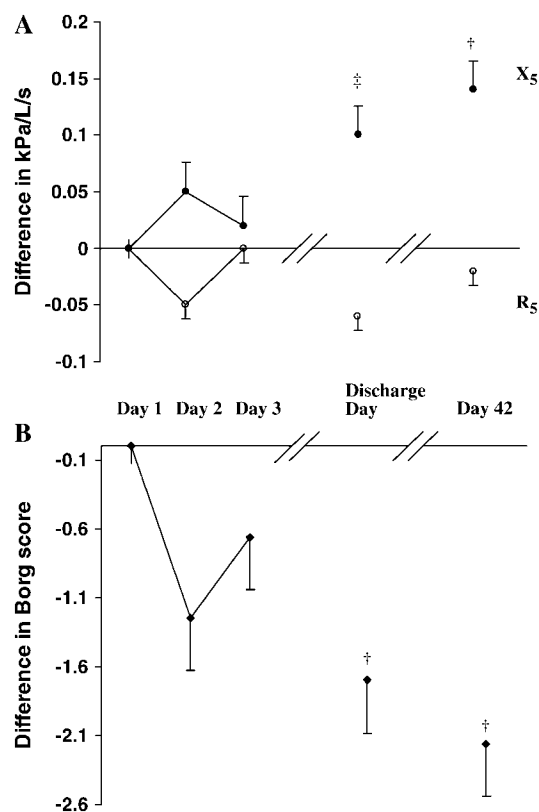


Figure 2. (A) Difference in total respiratory system resistance (R_S) and total respiratory system reactance (X_S) over time from day of admission (Day 1) to discharge (median, Day 7) and postdischarge (Day 42). (B) Difference in Borg breathlessness scores over time from day of admission (Day 1) to discharge (median, Day 7) and postdischarge (Day 42). † $p < 0.01$; ‡ $p < 0.001$, discharge and Day 42 compared with Day 1. Note that data for Day 42 apply to 16 patients only (see Tables 1 and 2 for relevant baseline and Day 42 data).

TABLE 3. BREATHING PATTERN DATA FOR ALL 22 SUBJECTS DURING THE FIRST 3 DAYS OF HOSPITALIZATION, ON THE DAY OF DISCHARGE, AND ON DAY 42

	Day 1	Day 2	Day 3	Discharge Day	Day 42
No. subjects	22	22	22	22	16
V _T , L	0.75 ± 0.05	0.76 ± 0.04	0.75 ± 0.04	0.78 ± 0.04	0.83 ± 0.06*
F, min ⁻¹	22.15 ± 0.9	23.05 ± 1.2	22.78 ± 1.4	21.93 ± 1.0	21.6 ± 0.9
Ṡ _E , L · min ⁻¹	16.8 ± 1.5	17.1 ± 0.8	16.71 ± 0.9	16.73 ± 0.9	16.1 ± 1.5
T _I , s	1.02 ± 0.05	0.99 ± 0.05	1.04 ± 0.07	1.05 ± 0.04	1.12 ± 0.04
T _E , s	1.77 ± 0.07	1.74 ± 0.08	1.83 ± 0.14	1.79 ± 0.09	1.75 ± 0.08
V _T /T _I	0.77 ± 0.06	0.80 ± 0.04	0.77 ± 0.04	0.75 ± 0.04	0.69 ± 0.06
V _T /T _E	0.45 ± 0.04	0.45 ± 0.02	0.44 ± 0.02	0.45 ± 0.03	0.45 ± 0.04
V _T /IC	0.57 ± 0.04	0.55 ± 0.03	0.59 ± 0.05	0.52 ± 0.03	0.49 ± 0.05
IRV, L	0.62 ± 0.08	0.71 ± 0.09	0.67 ± 0.08	0.82 ± 0.1*	0.97 ± 0.16*

Definition of abbreviations: F = breath frequency; IRV = inspiratory reserve volume; T_E = expiratory time; T_I = inspiratory time; V_T/T_E = mean expiratory flow; V_T/T_I = mean inspiratory flow; V_T/IC = ratio of V_T to IC.

Values represent means ± SEM. Statistically significant differences compared with Day 1 are shown.

* p < 0.05, significant difference compared with Day 1.

A particular strength of this study is the assessment of both flow- and volume-related measurements at standardized times and with standardized therapy as the exacerbation resolved. Treatment before or during admission, including theophylline use, did not influence lung mechanics, in keeping with another report (31). All measurements were made at rest and so we cannot assess the effect of dynamic changes in lung volume that are likely to occur on exercise in these patients (32). We did not measure TLC by body plethysmography as this was not possible in these sick patients. Nonetheless, we believe it unlikely that TLC increased during recovery and instead either remained constant or fell. Hence we believe it likely that the change in postbronchodilator FVC and IC reflects a fall in residual volume over time. Likewise, the calculated Ṡ_E was higher in our patients than in other studies, which may reflect disease severity of the patients we studied or the arduous nature of the protocol. However, Ṡ_E was unchanged with time and is unlikely to influence the other indices of lung mechanics.

Noninvasive measurements of total respiratory system resistance and reactance were easy to make, were well tolerated, and

provided information complementary to that obtained from the change in lung volumes. The accuracy of these data may be influenced in COPD by the presence of upper airway shunt compliance (33). This factor does not change acutely, and our data reported relative to the admission values are likely to be valid. We have reported data only at 5 Hz as this best reflects total respiratory system resistance rather than considering frequency dependence of resistance, a field in which the interpretation of oscillatory mechanics in COPD remains controversial. Tidal EFL was determined by the negative expiratory pressure technique in seated subjects. More information might have been obtained had the subjects been able to lie supine (34), although analysis of the percentage of each breath showing FL, a potentially more sensitive descriptor, did not change our results.

The small increase we observed in postbronchodilator FEV₁ from admission to discharge is similar to that reported previously (35). The changes in spirometry were due to an increase in volume rather than flow as judged by the static FEV₁/FVC ratio throughout the recovery period. This suggests that as the exacerbation resolved there was an opening of lung units with mechanical

TABLE 4. EFFECTS OF NEBULIZED BRONCHODILATORS ON LUNG MECHANICS, SYMPTOMS, AND BREATHING PATTERN DURING RECOVERY FROM EXACERBATION OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE

	Day 2		Discharge		Day 42	
	Pre	Post	Pre	Post	Pre	Post
FEV ₁ , L	0.99 ± 0.07	1.08 ± 0.08	0.98 ± 0.09	1.12 ± 0.10*	1.04 ± 0.10	1.26 ± 0.11*
FVC, L	2.04 ± 0.14	2.28 ± 0.15*	2.05 ± 0.12	2.36 ± 0.13*	2.18 ± 0.13	2.55 ± 0.15*
IC, L	1.34 ± 0.13	1.46 ± 0.11	1.44 ± 0.12	1.60 ± 0.11*	1.49 ± 0.10	1.74 ± 0.13†
IRV, L	0.65 ± 0.11	0.71 ± 0.09	0.70 ± 0.10	0.82 ± 0.10†	0.73 ± 0.09	0.97 ± 0.14†
Borg score	3.6 ± 0.4	3.0 ± 0.4†	2.8 ± 0.2	2.5 ± 0.25†	2.8 ± 0.3	2.15 ± 0.3*
R _S , kPa/L/s	0.71 ± 0.04	0.60 ± 0.04*	0.77 ± 0.06	0.59 ± 0.05*	0.79 ± 0.05	0.58 ± 0.05*
X _S , kPa/L/s	-0.45 ± 0.04	-0.37 ± 0.04†	-0.50 ± 0.05	-0.31 ± 0.03*	-0.51 ± 0.05	-0.28 ± 0.04*
V _T , L	0.68 ± 0.16	0.76 ± 0.16‡	0.74 ± 0.19	0.77 ± 0.21	0.72 ± 0.18	0.79 ± 0.24†
F, min ⁻¹	23.8 ± 5.8	23.0 ± 5.4	22.0 ± 5.2	22.6 ± 4.8	24.5 ± 6.1	22.0 ± 3.8†
T _I , s	0.97 ± 0.25	0.99 ± 0.24	1.07 ± 0.26	1.03 ± 0.20	0.99 ± 0.28	1.10 ± 0.21‡
T _E , s	1.67 ± 0.36	1.74 ± 0.39	1.82 ± 0.51	1.73 ± 0.40	1.60 ± 0.37	1.71 ± 0.35
Ṡ _E , L · min ⁻¹	16.2 ± 1.1	17.2 ± 0.8	16.3 ± 1.3	16.7 ± 0.9	16.9 ± 0.7	16.1 ± 1.3
V _T /T _I	0.75 ± 0.06	0.80 ± 0.04	0.72 ± 0.06	0.77 ± 0.04	0.74 ± 0.03	0.69 ± 0.06
V _T /T _E	0.43 ± 0.03	0.45 ± 0.02	0.43 ± 0.04	0.44 ± 0.03	0.46 ± 0.02	0.45 ± 0.04

Definition of abbreviations: F = breath frequency; IC = inspiratory capacity; IRV = inspiratory reserve volume; R_S = total respiratory system resistance; T_I = inspiratory time; T_E = expiratory time; V_T/IC = ratio of V_T to IC; V_T/T_E = mean expiratory flow; V_T/T_I = mean inspiratory flow; X_S = total respiratory system reactance. Values represent means ± SEM. Analysis using paired Student t test comparing pre- and post-bronchodilator values.

* p < 0.001, significant difference in comparing pre and post results for each day.

† p < 0.05, significant difference in comparing pre and post results for each day.

‡ p < 0.01, significant difference in comparing pre and post results for each day.

properties similar to the lung at admission, as the unchanged FEV₁/FVC ratio reflects the mechanical time constant of the respiratory system. The IC increase in proportion to the FVC during the course of the exacerbation is in keeping with this, as is the relatively constant R_s despite the fall in EELV. Respiratory frequency was also constant across the study days and did not seem to be an important determinant of the volume change at rest.

In our patients, we saw no consistent relationship between the presence of tidal EFL and the change in either IC or FVC over time. This might be due to breath-to-breath variation in the operating lung volume, as has been reported after administration of nebulized bronchodilators in stable COPD (26), but is more likely to reflect the change in residual volume over time. This contribution from a reduced static lung volume helps explain why the improvement in postbronchodilator inspiratory reserve volume occurred without any change in breathing pattern or respiratory timing.

Total respiratory system reactance became significantly less negative during recovery. This may in part result from the lower operating lung volume, but the magnitude of this change is larger than would be expected if this were the only operative factor. Taken together with the change in EELV and constant R_s, the data suggest that the “specific conductance” of the respiratory system was increasing as the patient improved but that individuals opt to reduce operating lung volume rather than to maintain a higher EELV with lower respiratory system resistance.

This is the first study of the response of patients with COPD to nebulized bronchodilators during and after an exacerbation. The large doses used are on the flat part of the dose–response curve for spirometry (36) and significantly improved FVC and Borg score at all time points support a relationship between operating lung volumes and breathlessness. In contrast, significant changes in FEV₁, IC, and reactance became apparent only on discharge, becoming larger in those monitored to 6 wk postadmission. These help explain why spirometric reversibility testing is unreliable soon after an exacerbation and why tests looking at FEV₁ change do not relate well to symptomatic response (37).

Increased breathlessness at rest is a common but not invariably accompaniment of COPD exacerbations (13). As in studies during exercise, Borg dyspnea scores were not normally distributed, but for comparison with other data in the literature we have reported them parametrically (15, 38, 39). Although these data can be indicative only of the direction of change, not its magnitude, we found that those patients reporting less breathlessness at the time of discharge and follow-up were the ones in whom IC and IRV improved significantly over this time, a change not seen in the smaller number of subjects in whom dyspnea remained constant. Patients reporting worse breathlessness at admission had significantly worse resting lung mechanics and larger studies will be needed to properly test the relationship between symptom change during exacerbation resolution and different measures of lung volume. Mechanically, the situation at rest during an exacerbation was comparable to that at maximal tolerated exercise when clinically stable, the change in postbronchodilator inspiratory capacity of 420 ml from Day 1 to Day 42 being comparable to the volume change reported during exercise (32, 40).

In summary, in normocapnic patients hospitalized with an exacerbation of COPD, improvement in operating lung volumes was related to reduction in dyspnea rather than any index of expiratory flow; however, it was measured. The impairment in resting lung mechanics resolved slowly and was not complete at the time of discharge as determined on the basis of clinical criteria. The relationship of resting lung mechanics on discharge to the dynamically regulated lung volume that usually deter-

mines exercise performance will require further study, as it may explain the variability in the subsequent clinical course postexacerbation.

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