Lung volumes and expiratory flow limitation during exercise in interstitial lung disease

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Marciniuk, D. D., G. Sridhar, R. E. Clemens, T. A. Zintel, and C. G. Gallagher. Lung volumes and expiratory flow limitation during exercise in interstitial lung disease. *J. Appl. Physiol.* 77(2): 963–973, 1994.—Lung volumes were measured at rest and during exercise by an open-circuit N_2-washout technique in patients with interstitial lung disease (ILD). Exercise tidal flow-volume (F-V) curves were also compared with maximal F-V curves to investigate whether these patients demonstrated flow limitation. Seven patients underwent 4 min of constant work rate bicycle ergometer exercise at 40, 70, and 90% of their previously determined maximal work rates. End-expiratory lung volume and total lung capacity were measured at rest and near the end of each period of exercise. There was no significant change in end-expiratory lung volume or total lung capacity when resting measurements were compared with measurements at 40, 70, and 90% work rates. During exercise, expiratory flow limitation was evident in four patients who reported stopping exercise because of dyspnea. In the remaining patients who discontinued exercise because of leg fatigue, no flow limitation was evident. In all patients, the mean ratio of maximal minute ventilation to maximal ventilatory capacity (calculated from maximal F-V curves) was 67%. We conclude that lung volumes during exercise do not significantly differ from those at rest in this population and that patients with ILD may demonstrate expiratory flow limitation during exercise. Furthermore, because most patients with ILD are not breathing near their maximal ventilatory capacity at the end of exercise, we suggest that respiratory mechanics are not the primary cause of their exercise limitation.

restrictive lung disease; end-expiratory lung volume; total lung capacity; mechanics; flow-volume curves

THE INCREASE in tidal volume (VT) that accompanies physical exercise in normal humans is due to an increase in end-inspiratory lung volume (EILV) and a decrease in end-expiratory lung volume (EELV). The fall in EELV causes the pressure generated by inspiratory muscles to be less and their pressure-generating capacity to be greater than would occur if the increase in VT was due to an increase in EILV alone (16, 22). The behavior of EELV may also effect the ability to increase expiratory flow rates during exercise, the body's CO_2 and O_2 storage capacity, pulmonary hemodynamics, and respiratory sensation. Whereas changes in EELV during exercise in normal humans (3, 16, 20) and patients with chronic airflow limitation (CAL) (2, 5, 15, 34) are well described, there is, to our knowledge, no information on EELV during exercise in patients with interstitial lung disease (ILD).

Because of their altered pulmonary mechanics (29, 35), patients with ILD have a reduced EELV at rest. This study tested the hypothesis that, because of their reduced resting EELV, there would be little or no change in EELV during exercise in patients with ILD. Because maximal expiratory flow rates are less at lower lung volumes, we hypothesized that the increase in ventilation during exercise in patients with ILD would result in expiratory flow limitation. We also examined tidal inspiratory and expiratory flow-volume (F-V) curves, which allowed us to assess whether patients with ILD are breathing near their maximal ventilatory capacity (MVC) at end exercise or whether significant ventilatory reserve exists at maximal exercise.

METHODS

Subjects

Seven patients with ILD were recruited from the outpatient clinics of the Division of Respiratory Medicine. Four patients had idiopathic pulmonary fibrosis, two had scleroderma, and one had sarcoidosis; four diagnoses were confirmed by lung biopsy. All patients were clinically stable for ≥2 mo before entering the protocol and had no rheumatologic, neuromuscular, cardiac, peripheral vascular, or any disease, apart from ILD, that might impair exercise tolerance. The project was approved by the Medical Ethics Committee of the University of Saskatchewan, and informed consent was obtained from all patients.

Baseline Measurements

Before the start of the study, pulmonary function was measured (SensorMedics 2200) in each patient. Forced expired volume in 1 s (FEV_1) and forced vital capacity (FVC) were measured using recommended methods (12); lung volumes were obtained using helium dilution, and the carbon monoxide diffusing capacity (DL_{CO}) was measured by the single-breath technique. Normal values of Morris et al. (27) were used for spirometry, the values of Goldman and Becklake (14) were used for lung volumes, and those of Burrows et al. (7) were used for DL_{CO}.

Protocol

Patients underwent two exercise tests on a cycle ergometer; each test was conducted on a separate day ≥3 days apart. Exercise testing was performed in an air-conditioned room, and patients had not performed strenuous activity on the day of testing, nor had they consumed food or caffeinated drink in the preceding 2 h. All patients were instructed in an identical fashion by the same person for all exercise tests.

Preliminary incremental test. Each patient underwent an initial incremental exercise study to determine maximal work rate (W_{max}). The initial exercise work rate of 20 W was increased by 15 W every minute of exercise until exhaustion. The patients were told that they should continue to exercise until they could exercise no more; no other type of encouragement was offered.

Lung volume and mechanics test. Patients performed maximal inspiratory and expiratory F-V loop maneuvers before exercising; data from at least three well-coordinated maximal efforts were obtained. The patient's body position was controlled so that it was the same as the position that would be assumed on the bicycle ergometer. Patients were then seated on the bicycle ergometer and, after being attached to the mouthpiece, rested quietly for 4 min while breathing room air. A noseclip was used for all experiments. Near the end of the 4-min period, patients were instructed to inhale maximally, for the determination of inspiratory capacity (IC), and then to resume tidal breathing. EELV was then measured as described below.

This procedure was repeated on three other occasions, which were identical in all respects, except the patients exercised at different work rates for the initial 4-min period of each measurement. Patients rested between the different work rates. These additional measurements involved exercising at work rates equivalent to 40, 70, and 90% of their previously determined W_{max} (preliminary incremental test) before the measurement of IC and EELV. For each exercise period, work rates were gradually increased over 30 s to achieve the necessary work rate for the remainder of the 4 min. Patients were instructed to raise their hand if they wished to discontinue exercise before completing each work rate. This enabled an IC maneuver and EELV measurement to be performed during exercise (not after patients stopped pedaling) in every instance where patients could not pedal for the full 4 min.

After the 90% W_{max} EELV measurement, maximal inspiratory and maximal expiratory F-V curves were again measured. Measurements were started immediately after the exhaled gas collection, and data were obtained on at least three well-coordinated maximal efforts.

Lung Volume Measurement

EELV was measured by an open-circuit N_2-washout system (17) similar to systems previously used during exercise (3, 38). The inspiratory line was connected to a three-way stopcock that permitted inhalation of room air or 100% O_2. The expiratory line was also connected to a three-way stopcock that enabled expired gas to exit into a 7-liter mixing chamber or into a Douglas bag. Immediately after the IC maneuver and with the use of a digital light-emitting diode (LED) system to identify inspiration and expiration, an attendant switched the inspiratory line to 100% O_2 during expiration, while during the subsequent inspiration, the expiratory line was switched so that expired gases were collected in the Douglas bag for later analysis. By use of this digital LED system and the same attendant, no technical errors were encountered in switching to the N_2-washout system.

The washout into the Douglas bag continued until expired N_2 was <0.5%, at which time measurements were halted and the patient came off the circuit. The patient was then allowed time for equilibration to room air, which was confirmed by the return of N_2 concentration at the mouth to previously measured levels and normalization of arterial O_2 saturation (Sa_{O_2}). During this time, the system plumbing was washed out with room air until measured gas concentrations returned to room air values. A fresh vacuum-emptied Douglas bag was also attached to the expiratory circuit.

Other Exercise Measurements

Electrocardiographic leads attached to the chest enabled continuous monitoring of the heart rate (HR) and electrocardiogram. Sa_{O_2} was monitored continuously by pulse oximetry (Nellcor 200). Patients breathed through a mouthpiece attached to a Hans Rudolph valve (model 2730, dead space 100.5 ml). Inspiratory and expiratory flow and volume were measured by separate inspiratory and expiratory pneumotachograph-transducer-demodulator-integrator systems we have used previously (23, 24). The response of the system was linear over the range of flows encountered in the study. The resistance of the inspired and expired limbs of the breathing circuit was <1.2 $cmH_2O \cdot l^{-1} \cdot s$ at flow rates ≤8 l/s. When the expired line was not diverted to the Douglas bag for collection, it was connected to a 7-liter mixing chamber with baffles. Mean expired and end-tidal O_2, CO_2, and N_2 gas concentrations were analyzed with a mass spectrometer (Airspec 2200). All equipment was calibrated before each exercise study; calibration was also rechecked after each experiment. Signals were continuously displayed in real time on a recorder (Gould) and also stored on computer for later analysis.

Data Analysis

Minute ventilation ($\dot{V}_I$), V_T, respiratory frequency (f), O_2 uptake ($\dot{V}O_2$), CO_2 output ($\dot{V}CO_2$), end-tidal P_{CO_2} ($P_{ET_{CO_2}}$), Sa_{O_2}, and HR were calculated over the last 30 s for each 1 min of exercise and at the end of exercise if a patient did not fully complete 4 min of pedaling. $\dot{V}_I$ and V_T were expressed at BTPS; $\dot{V}O_2$ and $\dot{V}CO_2$ were expressed at STPD. Predicted peak $\dot{V}O_2$ during exercise was calculated as follows (21)

$$\text{peak } \dot{V}O_2 = 0.83\text{Ht}^{2.7} \times (1 - 0.007 \text{ age}) \times (1 - 0.25S)$$

where height (Ht) is in meters and S is a factor that accounts for gender: $S = 0$ for males and $S = 1$ for females. Predicted peak HR was calculated as follows (21)

$$\text{peak HR} = 210 - 0.65 \text{ age (yr)}$$

IC was determined by drawing a line through the maximal IC maneuver and extending it through the stable end-expiratory points of the spontaneous breaths before the IC maneuver. Total lung capacity (TLC) was calculated by summing the measurements of EELV and IC at rest and at the end of each exercise work rate for each patient. Maximal F-V loops measured at rest before exercise were compared with those measured immediately after completion of the exercise lung volume measurements. The loops used in the analysis were a composite of the outer envelope derived from the three maximal F-V loop maneuvers performed in each case (4). In addition, tidal F-V loops at rest and at each exercise work rate were constructed by averaging the breaths during the 30 s preceding an IC maneuver.

The amount of N_2 washed out from the lungs during the collection period was calculated from the total amount of N_2 collected in the Douglas bag and the amounts of N_2 in the tubing (inspiratory, expiratory, and breathing valve) at the beginning and end of the washout period. This final N_2 volume was divided by alveolar N_2 concentration measured at the beginning of the washout period (minus alveolar N_2 concentration at the end, to account for this small amount of alveolar N_2). This gave lung volume (i.e., EELV) at the beginning of the washout period and was expressed at BTPS. Corrections were also made if the volume at the point of switching differed from the stable end-expiratory volume points observed before the switch in inhaled gases.

We ignored the very small amount of N_2 in the Douglas bag that resulted from N_2 excretion by the body (9, 17). Because the N_2 concentrations at the beginning and end of the washout were the same for the four tests (rest and 3 work rates), the small amounts of N_2 excreted should also be similar. Therefore, even if N_2 excretion was significantly greater than predicted (9, 17), this would not influence our ability to detect changes in EELV.

Calculation of MVC

MVC at maximal exercise was calculated from each patient's maximal expiratory and inspiratory F-V (MEFV and MIFV, respectively) curves (Fig. 1). MVC is defined here as the highest $\dot{V}_I$ that can be produced by a patient in a particular physiological situation (26). Because MVC varies with operating lung volume, MVC for each patient was calculated for the V_T and EELV that were used at maximal exercise. MVC was obtained by multiplying V_T by the respiratory frequency (f_{MVC}) that would be obtained if the patient breathed along the MEFV and

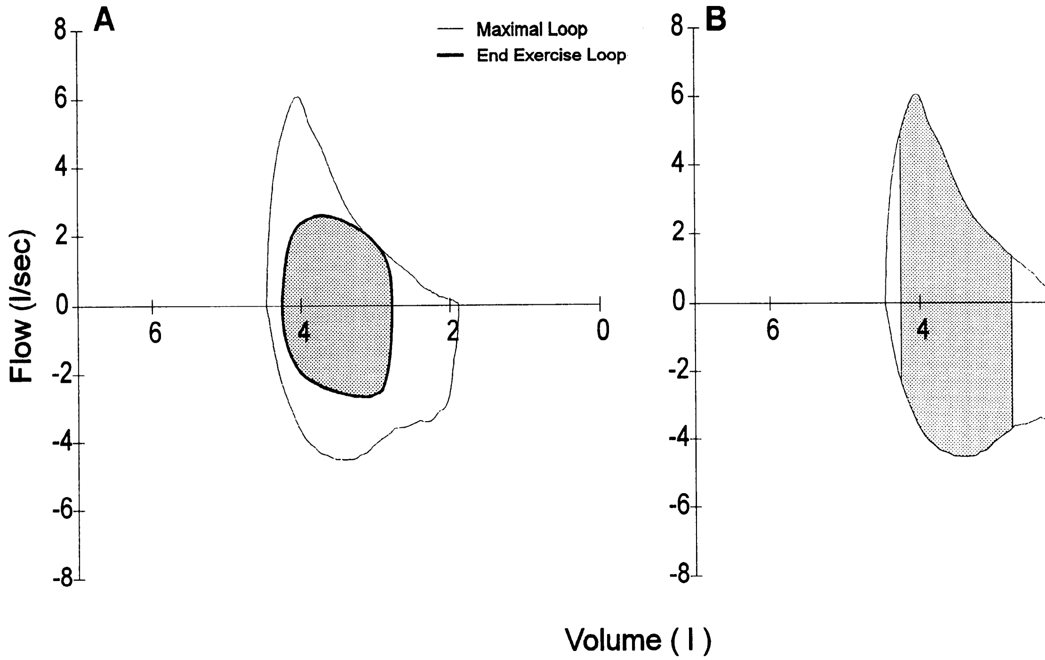

FIG. 1. Representative (*patient 6*) maximal and tidal flow-volume curve comparing measured maximal ventilation (*A*) with calculated maximal ventilatory capacity (*B*). Stippled area, flow used/available for maximal ventilation. Minute ventilations for *A* and *B* are 56.7 and 100.5 l/min, respectively.

MIFV curves over this lung volume range (Fig. 1). This was done by dividing V_T into 0.01-liter increments. Each volume increment was then divided by average maximal expiratory flow over that volume increment to derive the time of the volume increment. These times were then summed to provide total expiratory time (T_E). Similarly, inspiratory time (T_I) was calculated from the MIFV curve and the V_T and EELV that operated at maximal exercise. T_I and T_E were summed to provide total breath duration (T_T) and thus f_{MVC}. This is the f that would apply if patients could generate maximal inspiratory/expiratory flow immediately after the cessation of maximal expiratory/inspiratory flow, i.e., if patients could move instantaneously between their MEFV and MIFV curves. This is not possible because of the inertia of the respiratory system and because of the dynamic properties of respiratory muscles. Therefore, in keeping with the method of Babb and Rodarte (2, 4), we arbitrarily increased T_I and T_E by 11% (see DISCUSSION). This increase in T_I and T_E causes a 10% reduction in f_{MVC}, and therefore MVC is also reduced by 10%.

Statistical Analysis

Lung volume measurements at rest and during exercise at 40, 70, and 90% W_{max} were compared by analysis of variance with repeated measures. Pre- and postexercise data were compared by paired *t* test. Comparison of measurements from patients who discontinued exercise because of dyspnea and patients who discontinued exercise because of leg fatigue were made using unpaired *t* test. Significance for testing was set at $P < 0.05$. All results are presented as means ± SD.

RESULTS

Study Population

All patients demonstrated clinical, radiographic, and pulmonary function testing evidence of ILD but no evidence of pulmonary restriction secondary to chest wall disease, pleural disease, or respiratory muscle weakness. Four patients were receiving stable doses of oral corticosteroids (5–20 mg/day). Two patients were ex-smokers (*patient 1*: 20 pack/yr, quit 3 yr before study; *patient 6*: 15 pack/yr, quit 4 yr before study), and the remaining five patients had never regularly smoked. Five of the patients had exercised previously in our research laboratory.

Characteristics of the study population are shown in Table 1. Patients who reported discontinuing exercise because of dyspnea are compared with those who reported discontinuing exercise because of leg fatigue. Note that this is a posttesting comparison that was performed because of differences between the two groups of patients.

Exercise Performance

Table 2 compares data measured at the completion of the preliminary incremental exercise test with data obtained at the end of exercise in the lung volume test (90% W_{max}). All patients demonstrated a significant impairment in exercise performance (mean peak $\dot{V}O_2$ 57 ± 14% predicted) and a significant fall in arterial O_2 desatura-

TABLE 1. *Patient characteristics*

	Dyspnea (n = 4)	Leg Fatigue (n = 3)
Age, yr	46±8	47±23
Sex	3 M, 1 F	2 M, 1 F
TLC, %pred	67±8	66±8
VC, %pred	66±9	64±13
DL_{CO}, %pred	48±7	54±15
FEV_1/FVC, %	83±3	85±5
FRC, %pred	70±10	66±18

Values are means ± SD; n, no. of patients. TLC, total lung capacity; VC, vital capacity; FEV_1, forced expired volume in 1 s; FVC, forced vital capacity; DL_{CO}, diffusing capacity for CO; FRC, functional residual capacity. No significant differences were found between dyspnea and leg fatigue groups.

TABLE 2. *Comparison of data collected at end of incremental and lung volume tests*

	Incremental Test	Lung Volume Test
Peak $\dot{V}O_2$, l/min	1.36±0.39 (57% pred)	1.43±0.43
Peak $\dot{V}I$, l/min	67.4±26.0	67.8±31.3
Peak HR, min	143±14 (79% pred)	144±15
O_2 saturation, %	84±4	84±6

Values are means ± SD. $\dot{V}O_2$, O_2 uptake; $\dot{V}I$, minute ventilation; HR, heart rate. There was no significant difference in any variable between the 2 tests.

tion at end exercise (11 ± 6%). During the preliminary incremental exercise study, four patients stated that they discontinued exercise because of dyspnea (*patients 1* and *5–7*), and three patients stated that they stopped exercise because of leg fatigue (*patients 2–4*). There were no significant differences in peak $\dot{V}O_2$, peak $\dot{V}I$, peak HR, or degree of O_2 desaturation between the incremental test and the lung volume test. During the lung volume test, the ratio of $\dot{V}I$ at the completion of 90% W_{max} to FEV_1 was 29.9 ± 9.4 (range 16.4–43.2). The results show that measurements at the end of 90% W_{max} were comparable to those during the previous maximal incremental exercise test.

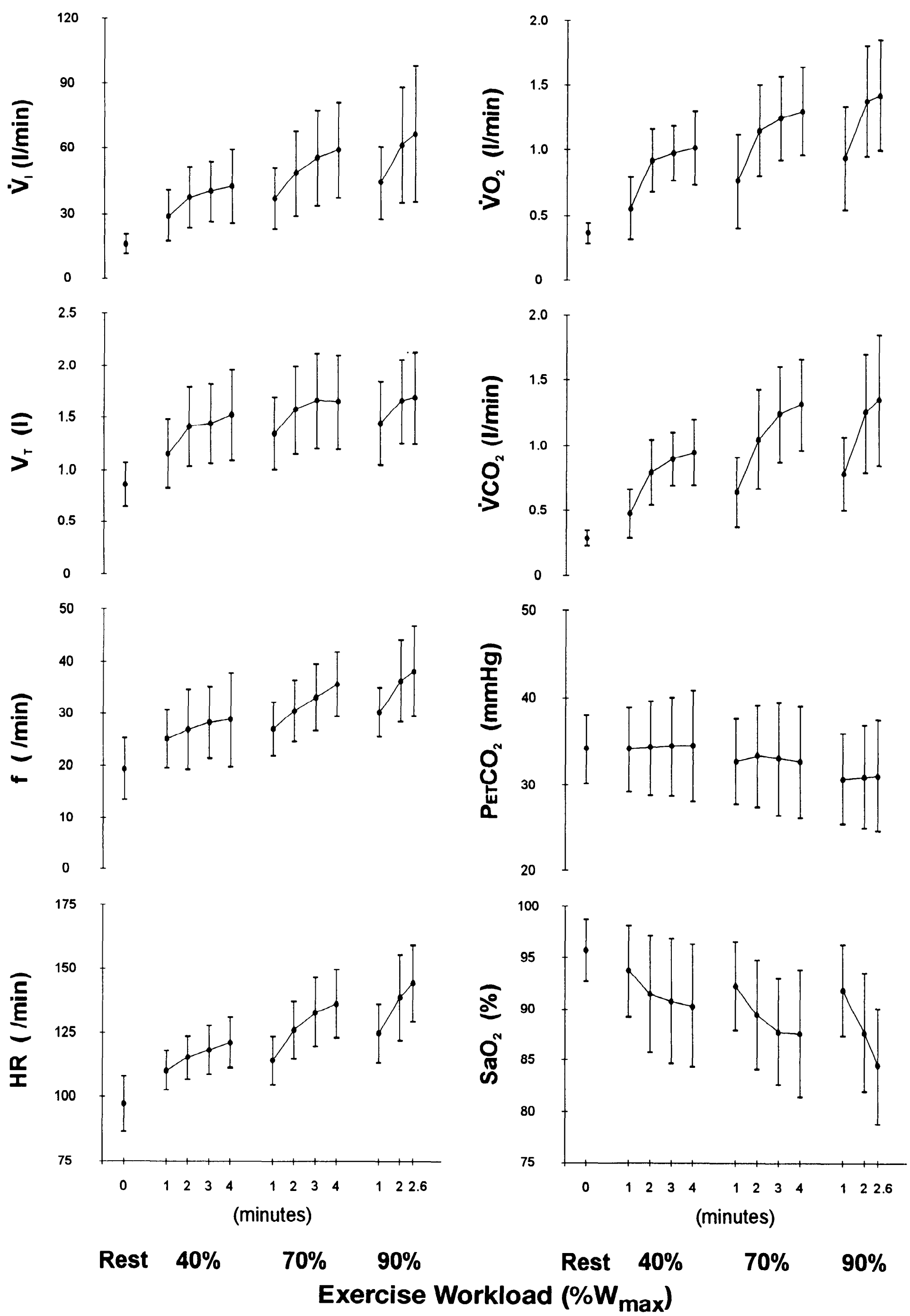

FIG. 2. Mean data collected at rest and at each minute of exercise for various exercise work rates. HR, heart rate; f, respiratory frequency; VT, tidal volume; $\dot{V}I$, minute ventilation; Sa_{O_2}, arterial O_2 saturation; PET_{CO_2}, end-tidal PCO_2; $\dot{V}CO_2$, CO_2 output; $\dot{V}O_2$, O_2 uptake.

TABLE 3. *Measured TLC at rest and at various exercise work rates*

Patient No.	Rest	Exercise		
		40% W_{max}	70% W_{max}	90% W_{max}
1	4.29	4.44	4.63	4.47
2	5.23	5.39	5.19	4.99
3	4.35		4.65	4.49
4	4.72	4.78	4.85	4.90
5	5.45	5.44	5.56	5.31
6	4.47	4.45	4.47	4.27
7	6.14	5.73	6.30	6.01
Mean ± SD	4.95±0.69	5.04±0.56	5.09±0.65	4.92±0.60

W_{max}, previously determined maximal work rate. No value is available for *patient 3* at 40% W_{max}, because of technical difficulties (see text). There were no significant differences between values measured during exercise and those measured at rest.

Figure 2 outlines group mean results measured at rest and at each minute of exercise during the three work rates. Group mean end-exercise results are displayed at 2.6 min of 90% W_{max}; this represents the mean exercise duration of all patients at this work rate. Only one patient completed the entire 4 min of exercise at this work rate. Because patients rested between work rates until they felt ready to proceed to the next work rate and also until gas concentrations returned to their baseline values, most variables returned toward their resting values between measurements. As shown in Fig. 2, $\dot{V}O_2$, $\dot{V}CO_2$, $\dot{V}I$, and HR rose with increasing work rate from rest to 90% W_{max}. The increase in $\dot{V}I$ was due to increases in VT and f. Sa_{O_2} fell progressively with increasing work rate and averaged 84% at the end of 90% W_{max}. PET_{CO_2} at 40% W_{max} remained the same as at that rest but fell with increasing levels of exercise.

Lung Volume Measurements

Table 3 summarizes individual and group mean measurements of TLC at rest and at the various exercise work rates. There were no significant differences in TLC between measurements at rest and during exercise. No data are available for *patient 3* during the 40% W_{max} test; he removed his noseclip during the exhaled gas collection phase of the test, resulting in inhalation of an indeterminate amount of room air. Analysis of our sample size revealed that it was sufficient to detect a 5% increase or decrease in TLC with a power of 94% (8).

F-V Curves

Figure 3 compares individual maximal F-V loops collected before exercise with those collected immediately after the completion of lung volume measurements. Except for *patient 3,* there are only slight differences between the pre- and postexercise curves. In *patient 3,* the postexercise measurement does not approximate the preexercise curve, and it was believed that this was due to suboptimal effort. For the group as a whole, there is no evidence of any postexercise increase or decrease in flows. When pre- and postexercise values were compared, there were also no significant differences in FEV_1, FVC, or FEV_1/FVC.

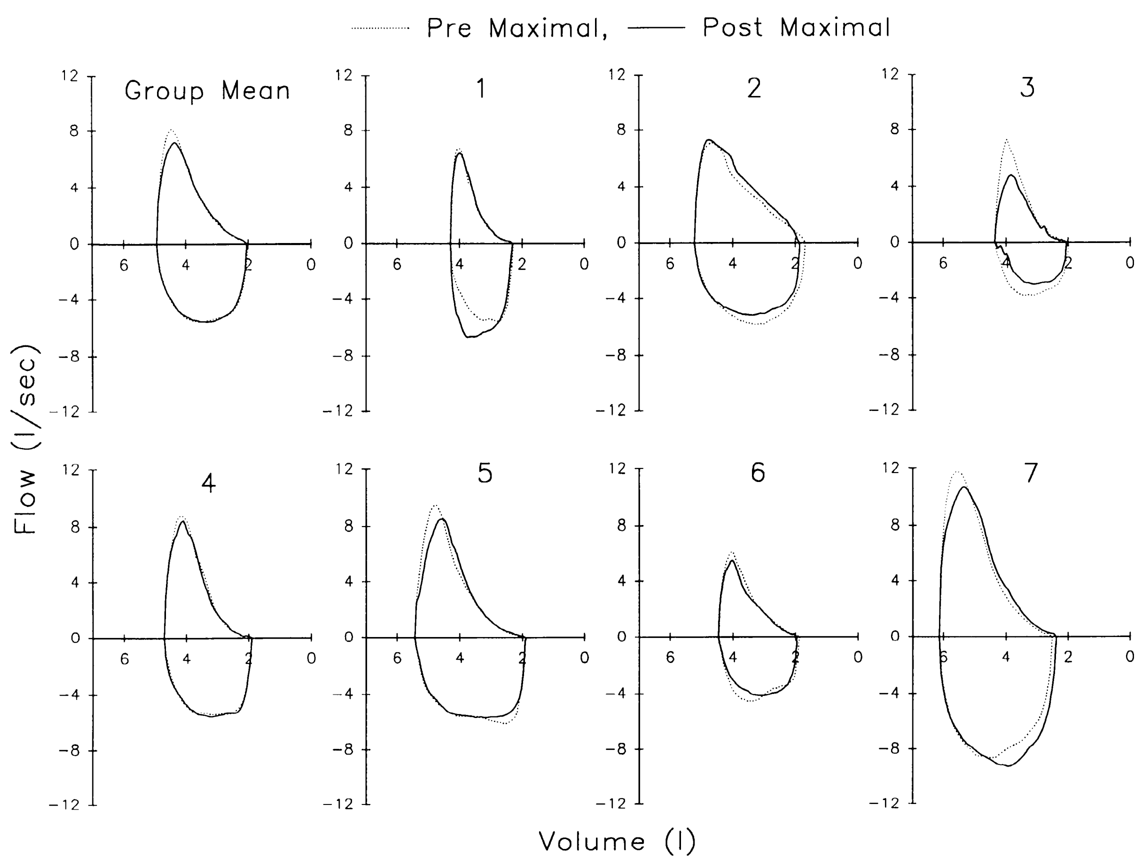

FIG. 3. Individual and group pre- and postexercise maximal flow-volumes loops.

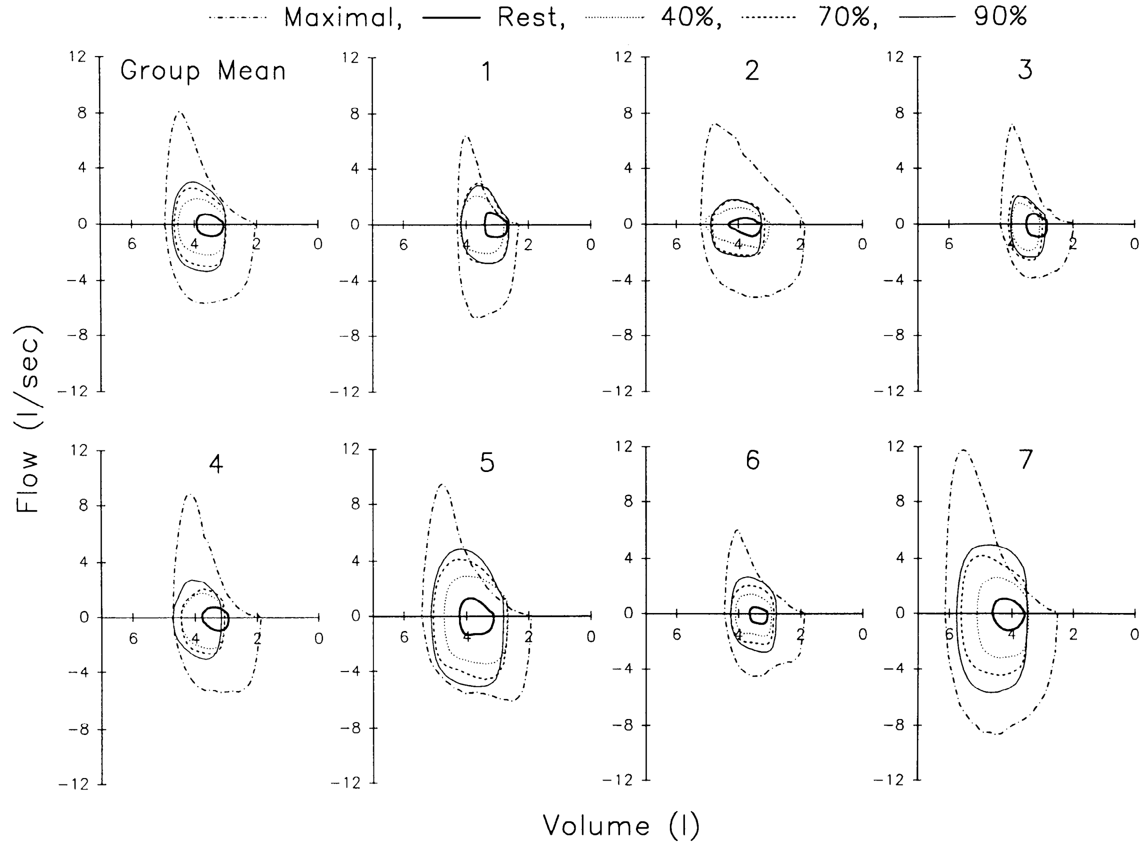

FIG. 4. Individual and group mean tidal flow-volume loops at rest and at various exercise work rates. Maximal flow-volume curve is plotted for comparison.

Figure 4 shows tidal F-V loops at rest and at each exercise work rate and the maximal F-V loop measured for each patient. At rest, none of the patients' tidal loops reached or exceeded their MEFV curve (*patient 1* approaches but does not reach the maximal curve). At 40% W_{max}, two patients were breathing on their maximal expiratory curves: 2.2 of tidal F-V curve in *patient 1* and 41.5% in *patient 5*. At 70% W_{max}, three patients were breathing on their maximal expiratory curves (*patient 1*, 55.1%; *patient 5*, 49.9%; *patient 7*, 28.2%), whereas at 90% W_{max} four patients were breathing on their maximal expiratory curves (*patient 1*, 55.7%; *patient 5*, 54.2%; *patient 6*, 1.7%; *patient 7*, 41.5%). Although individual variation is seen, mean EELV did not change during exercise when comparisons were made to the resting value. Interestingly, unlike patients with CAL, none of the patients who demonstrated expiratory flow limitation during exercise exhibited a major increase in EELV, although *patients 5* and *7* showed small increases near the very end of exercise. No patient reached his/her inspiratory maximal F-V curve at rest or during exercise, but *patient 5* came close at maximal exercise.

Ventilatory Measurements During Exercise

Figure 5 shows group mean EELV, EILV, and TLC, along with the corresponding $\dot{V}_I$, f, and duty cycle (T_I/T_T), for each exercise work rate. Group mean V_T increased 0.84 ± 0.30 liter during exercise; 92% (0.77 liter) of this change was due to an increase in EILV, whereas only 8% (0.07 liter) was due to a decrease in EELV. The mean $V_{T_{max}}$/IC(rest) at end exercise was 90 ± 11% (range 75–106%). No significant change was noted in T_I/T_T from rest to maximal exercise.

The mean peak $\dot{V}_I/FEV_1 \times 35$ was 82 ± 29%, and *patients 5* and *7* exceeded their maximal ventilation at end exercise, as predicted by the $FEV_1 \times 35$. This suggests that some of our patients were breathing near their ventilatory maximum at end exercise. However, their mean peak $\dot{V}_I$/MVC (see *Data Analysis*) was only 67 ± 26%, implying that our patients with ILD had the potential, on the basis of mechanical limits, to significantly further increase their ventilation during exercise. Figure 6 compares $FEV_1 \times 35$ for each patient with his/her MVC, as calculated from the patient's F-V curve. Figure 6 demonstrates that the $FEV_1 \times 35$ underestimates the potential maximal ventilation in all but one patient. Furthermore these results suggest that exercise performance in patients with ILD may not be limited solely by ventilatory factors, in view of their potential ventilatory reserve.

Relationship of Symptoms to Physiological Variables

Comparisons between patients who discontinued exercise because of dyspnea and those who discontinued exercise because of leg fatigue are shown in Table 4. A significant difference in mean V_T-to-vital capacity (VC) ratio was noted between the dyspnea and leg fatigue groups (70% W_{max}, 63.6 vs. 49.0%, $P < 0.05$; 90% W_{max}, 65.1 vs. 50.3%, $P < 0.05$). There was a trend toward a higher

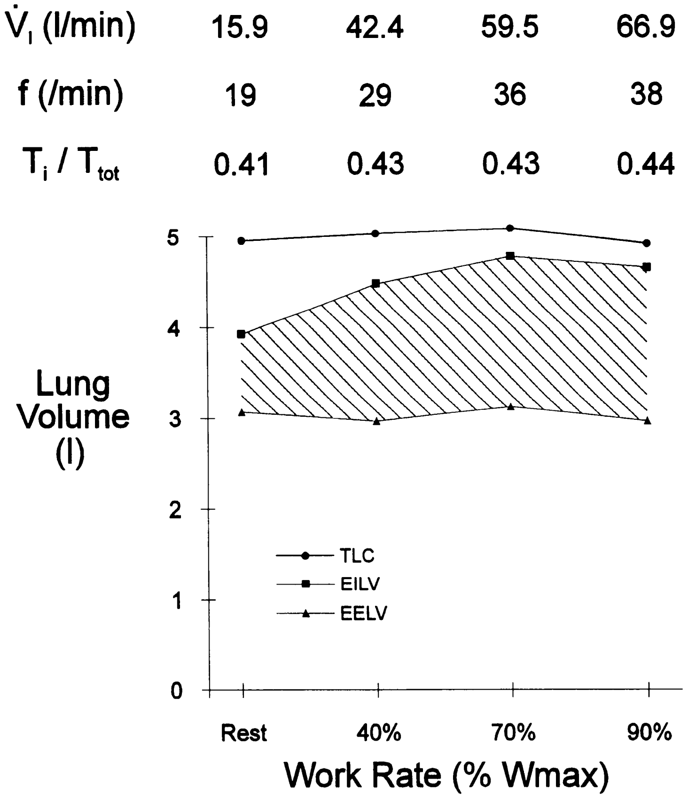

FIG. 5. Group mean end-expiratory lung volume (EELV), end-inspiratory lung volume (EILV), and total lung capacity (TLC) with corresponding $\dot{V}_I$, f, and duty cycle (T_I/T_T) for each exercise work rate.

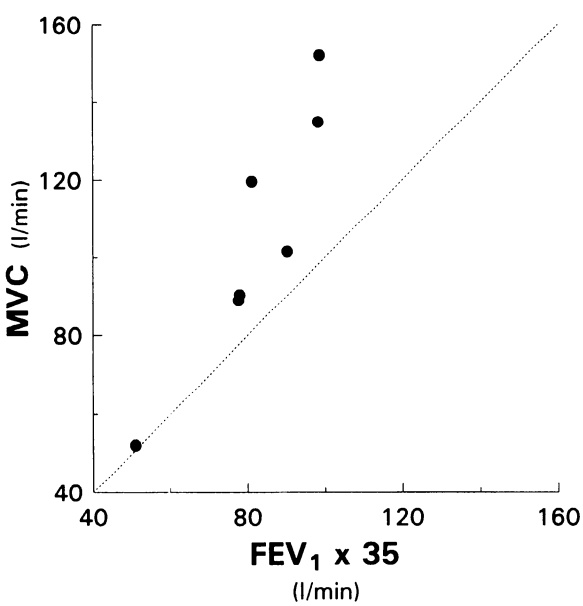

FIG. 6. Identity plot comparing maximal ventilatory capacity (MVC) with maximal ventilation calculated from forced expired volume in 1 s (FEV_1) × 35 in each individual.

ventilation for a given metabolic rate in the patients with dyspnea than in those with leg fatigue (mean $\dot{V}_I/\dot{V}_{O_2}$, 51 ± 6 vs. 38 ± 4; mean $\dot{V}_I/\dot{V}_{CO_2}$, 52 ± 5 vs. 44 ± 4, respectively), which may help explain why they discontinued exercise because of dyspnea. A significant difference was also noted in the mean $\dot{V}_I/FEV_1$ in dyspnea (36 ± 7%) vs. leg fatigue (22 ± 5%, $P < 0.05$) patients. Furthermore a large difference in peak $\dot{V}_I$ (dyspnea, 82.3 ± 34.9 liters, range 49.0–121.1; leg fatigue, 48.5 ± 5.2 liters, range 44.7–54.4) was also evident; however, this did not reach statistical significance. These results suggest that although patients could have achieved higher levels of ventilation (see *Ventilatory Measurements During Exercise*), those who discontinued exercise because of dyspnea were breathing closer to their ventilatory maximum than those who discontinued exercise because of leg fatigue.

TABLE 4. *Comparison of end-exercise measurements*

	Dyspnea (n = 4)	Leg Fatigue (n = 3)	P
$\dot{V}_{O_2}$, l/min	1.59±0.53	1.22±0.14	NS
$\dot{V}_I$, l/min	82.3±34.9	48.5±5.2	NS
$\dot{V}_I/\dot{V}_{O_2}$	51±6	38±4	NS
$\dot{V}_I/\dot{V}_{CO_2}$	52±5	44±4	NS
$\dot{V}_I$/MVC	85±17	43±8	<0.05
V_T/VC	65.1	50.3	<0.05
O_2 saturation, %	84±5	84±7	NS
HR, %pred	78±3	81±7	NS

Values are means ± SD; n, no. of patients. MVC, maximal ventilatory capacity (estimated from flow-volume curves, see text); V_T, tidal volume; $\dot{V}_{CO_2}$, CO_2 output.

This finding is also demonstrated in Fig. 7, which compares composite F-V curves from patients who stated that they discontinued exercise because of dyspnea with those from patients who stated that they discontinued exercise because of leg fatigue. As a group, patients who discontinued exercise because of dyspnea demonstrated expiratory flow limitation during a portion of their tidal F-V curve during submaximal exercise (70% W_{max}) and at the completion of maximal exercise. No evidence of expiratory flow limitation was noted in patients who stopped exercise because of leg fatigue.

No significant differences were noted in age or pulmonary function (FEV_1/FVC, %predicted TLC, %predicted VC, %predicted DL_{CO}) between the two groups of patients (not shown). Patients who reported stopping exercise because of leg fatigue desaturated by 15 ± 4% at end exercise compared with 9 ± 4% in those who reported stopping exercise because of dyspnea; however, this did not reach statistical significance.

DISCUSSION

TLC

We have shown that patients with ILD do not significantly change their TLC during exercise. Whereas the effects of exercise on lung volumes have not previously been addressed in this population, our results agree with previously published data examining this question in normal subjects and patients with other lung diseases. Younes and Kivinen (38), Babb and Rodarte (3), Stubbing et al. (33), and Maron et al. (25) found that TLC did not change in normal humans during exercise. Similar results have also been found in patients with CAL by Stubbing et al. (34). Therefore, although resting pulmonary mechanics and responses to exercise differ among these populations, the functional behavior of TLC remains unchanged.

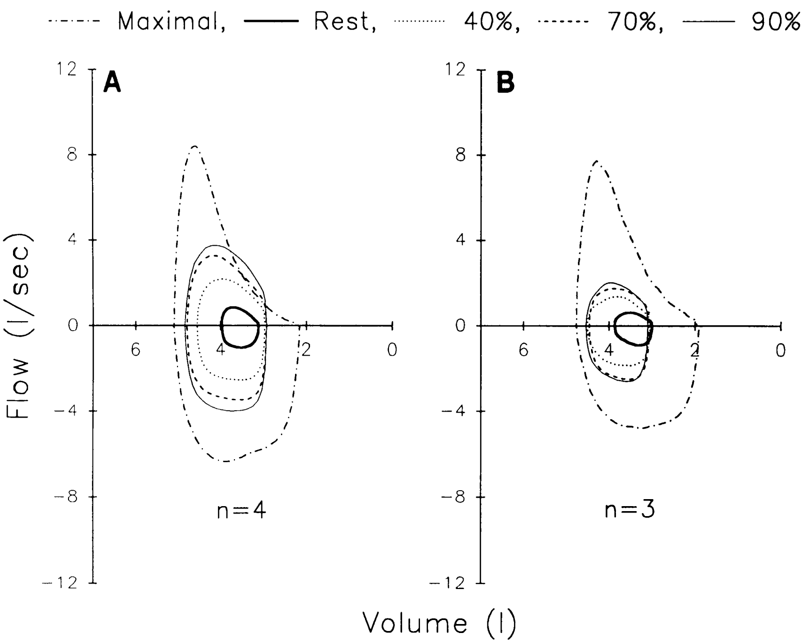

FIG. 7. Comparison of maximal and tidal flow-volume loops from patients who discontinued exercise because of dyspnea (*A*) and patients who discontinued exercise because of leg fatigue (*B*).

EELV

We did not demonstrate any significant change in EELV during exercise in patients with ILD. The behavior of EELV during exercise has been examined previously with different results. In normal subjects, Younes and Kivinen (38) found that EELV, while falling significantly during early exercise, was not significantly different from the preexercise value at maximal exercise. Stubbing et al. (33) assessed normal subjects in a body plethysmograph and found no significant change in EELV, although measurements were made only during submaximal exercise. More recently, Henke et al. (16), Johnson et al. (20), and Babb and Rodarte (3) measured EELV during exercise in normal subjects and found a significant fall in EELV during exercise. Johnson et al. (19) also measured a significant fall in EELV during heavy exercise in endurance athletes, although the EELV was increasing toward the end of maximal exercise. The fall in EELV during exercise in normal subjects is clearly due to expiratory muscle recruitment, but changes in thoracic blood volume may have a lesser role (6).

In contrast, a significant increase in EELV during exercise has been well documented in patients with CAL (2, 5, 15, 34) and in patients with cystic fibrosis (30). This increase is thought to occur because of expiratory flow limitation during exercise (28); by increasing EELV, these patients are therefore able to achieve greater expiratory flows to meet the increased ventilatory demands of exercise.

The behavior of EELV during exercise in patients with ILD has not been previously examined. Our results indicate that in patients with ILD EELV is quite different from that in normal subjects and also from patients with airflow limitation. A reduction of EELV during exercise would be an option in these patients with ILD, by sparing the inspiratory muscles, to compensate for the added ventilatory load of exercise (37). However, in previous work with moderately obese women with no evidence of lung disease but with reduced resting levels of FRC, Babb and Hodgson (1) found that EELV did not fall during exercise. They postulated that the obese women were already near their potential for decreasing EELV at rest without risking expiratory flow limitation and thus were unable to further decrease EELV during exercise.

Our results show that, in some patients with ILD, significant expiratory flow limitation occurs during exercise. These patients may therefore not be able to (or may choose not to) further reduce their EELV during exercise, because even at submaximal levels of exercise, further reducing EELV may worsen existing expiratory flow limitation. However, although this may help explain the behavior of EELV in these patients, it does not explain the pattern of EELV in those patients without expiratory flow limitation. *Patients 2–4* did not develop expiratory flow limitation with exercise. However, their EELV increased slightly for at least some of the three work rates (*patients 3* and *4*) or fell at the lowest work rate and later returned to the resting level (*patient 2*). These three patients had a greater arterial O_2 desaturation with exercise than the other four patients (15 ± 4 and 9 ± 4%, respectively). Hypoxia has been found to increase resting EELV in normal humans (13, 31). Such a hypoxia-induced increase (or lack of decrease) in EELV may be teleologically advantageous, because it increases the lung's "O_2 stores" (32), although the beneficial effects of increasing O_2 stores are most important when alveolar P_{O_2} is reduced, which is not the case in exercising ILD patients. A hypoxia-induced increase in EELV may also improve gas exchange by reducing airway closure and ventilation-perfusion mismatching. We therefore hypothesize that hypoxia promotes an increase in EELV during exercise in patients with ILD. However, whether EELV increases, decreases, or remains the same in an individual patient depends on the balance among a number of influences, including expiratory flow limitation, hypoxia, and the respiratory controller's desire to decrease EELV, thus reducing the load on the inspiratory muscles.

F-V Curves

Heavy exercise appears to cause bronchodilation in normal humans and patients with CAL (11, 18, 19). In contrast, our patients with ILD did not demonstrate a significant change in MEFV or MIFV curves after exercise (Fig. 3). However, we cannot exclude very mild bronchodilation, which resolved very rapidly with cessation of exercise.

Four of our patients developed expiratory flow limitation during exercise, and two of these had flow limitation at a work rate equivalent to 40% W_{max}. In three patients, expiratory flow rates during exercise exceeded their MEFV curve. As discussed elsewhere (11), expiratory flow rates may exceed the MEFV curve because of errors in measuring lung volume, thoracic gas compression during the MEFV maneuver, bronchodilation during exercise, airway narrowing during the MEFV curve, or nonuniform lung emptying. Errors in measuring lung volume are unlikely, because lung volume was measured at rest and during exercise. The higher expiratory flow rates during exercise (than during the MEFV maneuver) are probably not due to bronchodilation during exercise, because we measured MEFV curves shortly after exercise; however, this possibility cannot be completely excluded, because bronchodilation could have resolved by then. Thoracic gas compression is probably not a major factor in these patients, because the MEFV curves are the composite of at least three different curves and because thoracic gas compression is least in patients with small lung volumes, as in our patients. However, thoracic gas compression cannot be excluded at this time. Therefore, airway narrowing during the MEFV maneuver (due to inspiration to TLC), nonuniform lung emptying, and thoracic gas compression are the most likely reasons why expiratory flow rates exceed the MEFV curve in some patients with ILD. Previous studies showed that the MEFV curve may be exceeded during exercise in some patients with CAL (2, 5, 15) and in some normal humans (19).

Although expiratory flow limitation occurred during exercise in some patients, none of our patients reached their MIFV curve, even at maximal exercise. *Patient 5* approached his MIFV curve, but none of the other patients came close. Because MVC is determined by the MEFV and MIFV curves, this indicates that $\dot{V}_I$ at maximal exercise was significantly less than MVC in our patients. The ratio of $\dot{V}_I$ at maximal exercise to MVC averaged 67%, and the MVC determined from the MEFV and MIFV curves underestimates the true MVC in *patients 1, 5,* and *7,* because expiratory flow rates during exercise exceeded their MEFV curves. Regardless of the underlying mechanism for exceeding the MEFV curve, the MEFV curve clearly underestimates the capacity to generate expiratory flows, and, accordingly, true MVC is also underestimated. Therefore the above ratio (67%) slightly overestimates the actual ratio of peak $\dot{V}_I$ to MVC.

MVC

Previous studies of normal subjects and patients with pulmonary disease have tried to determine whether $\dot{V}_I$ at maximal exercise ($\dot{V}_{I_{max}}$) approaches or reaches MVC. These studies usually estimated MVC from the maximal voluntary ventilation (MVV). In some cases, MVV was measured directly over short periods of time (e.g., 12 s, 15 s, 4 min), whereas in others MVV was estimated from the FEV_1 (21, 36). Recently, FEV_1 and maximal inspiratory flow rate have been used to provide an improved estimate of MVV (10).

Whether it is measured or calculated, the MVV has significant limitations as a measure of MVC (11). Most importantly, MVC varies significantly with V_T and EELV. Therefore we calculated MVC in this study as the highest $\dot{V}_I$ that could be produced at the V_T and EELV that operated at maximal exercise. MVC is the $\dot{V}_I$ that would result if a patient breathed along the MEFV and MIFV curves over this lung volume range. Thus $\dot{V}_I$/MVC is essentially a (time-weighted) measure of how closely expiratory and inspiratory flow rates during maximal exercise approach the MEFV and MIFV curves.

Subjects cannot switch instantaneously between their MEFV and MIFV curves because of the inertia of the respiratory system and because of the dynamic properties of respiratory muscles. Therefore the f_{MVC} that would result if a subject breathed along the MEFV and MIFV curves should be slightly less than that calculated from the MEFV and MIFV curves alone; consequently MVC should also be slightly less. There is little information regarding the quantitative importance of such calculated "errors," although Babb and Rodarte (4) assessed these by analyzing the study of Jensen et al. (18). Because minimum T_I and T_E during exercise and during rebreathing were slightly greater than those predicted from MEFV and MIFV curves, Babb and Rodarte increased T_E (and therefore T_I) predicted from the MEFV curve by 11% (4; T. Babb, personnal communication). However, Jensen et al. (Fig. 3 in Ref. 18) showed that the minimum T_I and T_E (at a given V_T and EELV) predicted from the MEFV and MIFV curves could be achieved by their subjects during voluntary hyperventilation. Therefore the time needed to switch between MEFV and MIFV curves must be so small that it does not materially influence calculation of MVC. The 10% reduction in f_{MVC}, and thus MVC, in the study of Babb and Rodarte and in this study, results in underestimation of MVC. We adopted this correction because we preferred an underestimation of MVC to an overestimation. The calculated MVC further underestimates the true MVC in *patients 1, 5,* and *7,* because expiratory flow rates during exercise exceeded their MEFV curves. Regardless of the underlying mechanism, the MEFV curve clearly underestimates our patients' capacity to generate expiratory flows, and therefore true MVC is also underestimated.

Our method of calculating MVC is essentially identical to that of Jensen et al. (18), although they focus on the relationship between minimum T_I and T_E, and V_T. The method we use is identical to that used by Babb and Rodarte (2, 4), except we used MEFV and MIFV curves, whereas they used only the MEFV curve, and they derived the minimum T_I by use of the observed T_I/T_T at maximal exercise. The method used here assumes that subjects have the capacity to use maximal inspiratory, as well as maximal expiratory, flow rates. This assumption is supported by the observation that when ventilatory demands of exercise are high enough in fit normal subjects, the MIFV and the MEFV curves can be reached or approached during exercise (19).

Implications for Exercise Limitation

In our patients with ILD, maximal exercise capacity was significantly reduced. We previously used the addition of external dead space during exercise to selectively stress the respiratory system in patients with ILD (23). In this study, the addition of external dead space resulted in a reduction of exercise duration, maximal work rate, and peak $\dot{V}O_2$. However, compared with exercise without dead space (control), patients demonstrated a similar maximal ventilation and degree of arterial O_2 desaturation in both instances. The results from this earlier study suggested that exercise in patients with ILD was limited by ventilatory and/or gas exchange abnormalities.

The results in this study show that $\dot{V}I$ at maximal exercise is significantly less than MVC in patients with ILD. It is clear that, with the exception of *patient 5* (Fig. 4), our patients had a large ventilatory reserve at maximal exercise. This suggests that their exercise limitation is not primarily due to abnormal respiratory mechanics. It is possible that exercise is limited by breathlessness, related to abnormal respiratory mechanics, before a true ventilatory limitation occurs. This may have been the case for the four patients who stopped exercise because of dyspnea at an average $\dot{V}I$ of 82.3 l/min and an average $\dot{V}I$/MVC of 85%. However, it is unlikely that ventilatory mechanics or dyspnea was the primary mechanism of exercise limitation for the other three patients who stopped exercise at a lower $\dot{V}I$ (48.5 l/min) and a $\dot{V}I$/MVC of 43%. These patients had a greater, albeit nonsignificant, arterial O_2 desaturation (15% vs. 9%) than the patients who discontinued exercise because of dyspnea, and their exercise tolerance may be limited primarily by hypoxia. Further study is required to clarify mechanisms of exercise limitation in these patients.

In conclusion, patients with ILD showed no significant change in EELV during exercise. Some patients with ILD develop expiratory flow limitation during exercise, and this is dependent, in part, on a high ventilatory response to exercise. Because most patients with ILD are not breathing at or near their maximal ventilatory capacity at maximal exercise, we suggest that respiratory mechanics are not the primary cause of their exercise limitation.

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