Qualitative aspects of exertional dyspnea in patients with interstitial lung disease

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O’Donnell, Denis E., Laurence K. L. Chau, and Katherine A. Webb. Qualitative aspects of exertional dyspnea in patients with interstitial lung disease. J. Appl. Physiol. 84(6): 2000–2009, 1998.—We compared qualitative and quantitative aspects of perceived exertional dyspnea in patients with interstitial lung disease (ILD) and normal subjects and sought a physiological rationale for their differences. Twelve patients with ILD [forced vital capacity = 64 ± 4 (SE) %predicted] and 12 age-matched normal subjects performed symptom-limited incremental cycle exercise tests with measurements of dyspnea intensity (Borg scale), ventilation, breathing pattern, operational lung volumes, and esophageal pressures (Pes). Qualitative descriptors of dyspnea were selected at exercise cessation. Both groups described increased “work and/or effort” and “heaviness” of breathing; only patients with ILD described “unsatisfied inspiratory effort” (75%), “increased inspiratory difficulty” (67%), and “rapid breathing” (58%) (P < 0.05 patients with ILD vs. normal subjects). Borg-O2 uptake (VO2) and Borg-ventilation parameters selected by both groups at the end of symptom-limited exercise were similar; the distinct qualitative perceptions of dyspnea in patients with ILD were attributed to differences in dynamic ventilatory mechanics, i.e., reduced inspiratory capacity, heightened Pes-to-tidal volume ratio, and tachypnea. Factors contributing to dyspnea intensity in both groups were also different: the best correlate of the Borg-VO2 slope in patients with ILD was the resting tidal volume-to-inspiratory capacity ratio (r = 0.58, P < 0.05) and in normal subjects was the slope of Pes-to-maximal inspiratory pressure ratio over VO2 (r = 0.60, P < 0.05).

respiratory sensation; respiratory mechanics; exercise

DYSPNEA AND EXERCISE INTOLERANCE are common in interstitial lung disease (ILD) and often progress inexorably as the disease advances. The mechanisms of exertional dyspnea in this condition are not clearly understood and are likely multifactorial (19). Ratings of exertional dyspnea have been shown to correlate with the level of ventilation when expressed in absolute terms or as a fraction of the ventilatory capacity (19, 21). It is also known that exertional dyspnea in ILD may be aggravated by hypoxemia (5) or by concomitant expiratory flow limitation (21). As in other chronic cardiopulmonary disorders, dyspnea intensity in ILD correlates with increased inspiratory muscle force requirements (relative to the force reserve) and the duration of contraction (19). Accordingly, it is postulated that the amplitude of central motor command output to the inspiratory muscles is increased because of the elastic load in ILD and that this, in turn, is consciously perceived as the sense of heightened effort, an integral component of the subjective experience of breathing discomfort (19).

It has recently become clear that dyspnea encompasses a number of qualitatively distinct sensations that vary in intensity and may be different within various pulmonary disorders and in health (20, 24, 25). For example, we recently found that in the majority of patients with chronic airflow limitation (CAL), inspiratory difficulty and the awareness of “unsatisfied inspiratory effort” were important qualitative aspects of exertional dyspnea; this was in contrast to an age-matched normal group that did not report these sensations even at the peak of exhaustive exercise (26). We postulated that unsatisfied inspiratory effort had its mechanical basis in the disparity between the respiratory effort expended during exercise and the mechanical response of the system, which is seriously impaired in CAL (26).

In ILD, the mechanical response of the respiratory system is similarly restricted: inspiratory capacity (IC) is reduced, tidal volume (VT) expansion is thereby constrained, and during exercise VT must “cycle” close to total lung capacity (TLC) on the upper nonlinear extreme of the contracted pressure-volume (P-V) relationship of the respiratory system. We speculated that, as in CAL, this impaired mechanical response in the setting of increased ventilatory demand would give rise to distinguishable qualitative descriptions of exertional dyspnea in patients with ILD when compared with healthy normal subjects.

We hypothesized 1) that exertional dyspnea is qualitatively and quantitatively different in patients with ILD and in age-matched normal subjects, 2) that qualitative differences can be explained by differences in dynamic ventilatory mechanics, and 3) that the factors contributing to exertional dyspnea intensity are different in ILD than in normal subjects. To test these hypotheses, we first compared the qualitative descriptors selected by both groups at the end of symptom-limited exercise and evaluated the dynamic ventilatory parameters at this point of comparison. Second, we examined the relationships between dyspnea intensity and various physiological variables throughout exercise in each of the study groups. Finally, we used multiple-regression analysis to determine and contrast the physiological factors contributing to dyspnea intensity in patients with ILD and in normal subjects.

METHODS

Subjects

Subjects included 12 patients who had clinically stable ILD, were presently nonsmokers (2 exsmokers with 10 and 20 pack-yr histories had quit >10 and >20 yr before the study,
Table 1. Subject and patient characteristics

<table>
<thead>
<tr>
<th></th>
<th>Patients with ILD (n = 12)</th>
<th>Normal Subjects (n = 12)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men:women</td>
<td>7:5</td>
<td>6:6</td>
</tr>
<tr>
<td>Age, yr</td>
<td>64 ± 3</td>
<td>64 ± 2</td>
</tr>
<tr>
<td>Height, cm</td>
<td>166 ± 2</td>
<td>168 ± 4</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>76 ± 9</td>
<td>76 ± 5</td>
</tr>
<tr>
<td>Baseline dyspnea index</td>
<td>4.8 ± 0.3</td>
<td>11.8 ± 0.3</td>
</tr>
</tbody>
</table>

Pulmonary function

<table>
<thead>
<tr>
<th></th>
<th>ILD (n = 12)</th>
<th>Normal Subjects (n = 12)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEV1, liters</td>
<td>1.93 ± 0.15 (76)*</td>
<td>2.70 ± 0.27 (103)</td>
</tr>
<tr>
<td>FVC, liters</td>
<td>2.29 ± 0.17 (64)*</td>
<td>3.74 ± 0.41 (100)</td>
</tr>
<tr>
<td>FEF25-75, %</td>
<td>84 ± 1 (118)</td>
<td>73 ± 2 (103)</td>
</tr>
<tr>
<td>IC, liters</td>
<td>1.62 ± 0.17 (66)*</td>
<td>2.95 ± 0.38 (115)</td>
</tr>
<tr>
<td>TLC, liters</td>
<td>3.72 ± 0.24 (70)*</td>
<td></td>
</tr>
<tr>
<td>FRC, liters</td>
<td>2.11 ± 0.14 (73)*</td>
<td></td>
</tr>
<tr>
<td>RV, liters</td>
<td>1.43 ± 0.10 (72)*</td>
<td></td>
</tr>
<tr>
<td>PIm,m, cmH2O</td>
<td>70 ± 10 (89)</td>
<td>82 ± 13 (100)</td>
</tr>
<tr>
<td>Pir,m, cmH2O</td>
<td>97 ± 11 (104)</td>
<td>104 ± 15 (101)</td>
</tr>
<tr>
<td>DLCO, ml·min⁻¹·mmHg⁻¹</td>
<td>11.4 ± 0.9 (54)</td>
<td></td>
</tr>
</tbody>
</table>

Values are means ± SE (%predicted); n, no. of patients or subjects. ILD, interstitial lung disease; FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity; IC, inspiratory capacity; TLC, total lung capacity; FRC, functional residual capacity; RV, respiratory volume; 

Pulmonary Function Testing

Routine spirometry (6200 Autobox DL; SensorMedics, Yorba Linda, CA) was performed as recommended (13). Maximal inspiratory and expiratory mouth pressures measured at FRC and TLC, respectively, were assessed with a standard mouthpiece and a pressure manometer (Magnehelic; Dwyer Instruments, Michigan City, IN). In the patients with ILD, single-breath diffusing capacity for carbon monoxide (DLco) and plethysmographic thoracic gas volume were also measured (6200 Autobox DL). Predicted normal values for spirometry, lung volumes, DLCO, and mouth pressures were those of Morris et al. (23), Goldman and Becklake (14), Gaensler and Wright (11) and Hamilton and et al. (15), respectively.

Exercise Testing

Incremental symptom-limited cycle exercise tests were conducted as described previously (27). Esophageal pressure

Table 2. Modified descriptors of exertional dyspnea*

<table>
<thead>
<tr>
<th>Cluster Name</th>
<th>Descriptors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased work/effort</td>
<td>My breathing requires more work.</td>
</tr>
<tr>
<td></td>
<td>My breathing requires effort.</td>
</tr>
<tr>
<td>Unrewarded inspiration</td>
<td>My breath does not go in all the way.</td>
</tr>
<tr>
<td></td>
<td>I feel a need for more air.</td>
</tr>
<tr>
<td></td>
<td>I cannot get enough air in.</td>
</tr>
<tr>
<td>Inspiratory difficulty</td>
<td>My breath does not go in all the way.</td>
</tr>
<tr>
<td></td>
<td>I cannot take a deep breath in.</td>
</tr>
<tr>
<td>Heavy</td>
<td>My breathing is heavy.</td>
</tr>
<tr>
<td>Shallow</td>
<td>My breathing is shallow.</td>
</tr>
<tr>
<td>Rapid</td>
<td>I feel that my breathing is rapid.</td>
</tr>
<tr>
<td>Tight chest</td>
<td>My chest feels tight.</td>
</tr>
<tr>
<td></td>
<td>My chest feels constricted.</td>
</tr>
<tr>
<td>Exhpiratory difficulty</td>
<td>My breath does not go out all the way.</td>
</tr>
<tr>
<td>Suffocating</td>
<td>I feel that I am suffocating.</td>
</tr>
</tbody>
</table>

*Modified from Ref. 24.
Elastance ($E_{dyn}$) was calculated and expressed per minute by multiplying by breathing rate ($V_{\dot{E}}$) was compared with the maximal ventilatory capacity ($V_{\dot{T}O_2}$) derived solely from FEV$_1$. Values for $P_{\text{Imax}}$ at intermediate points during exercise were calculated at isovolume [i.e., at the concurrent dynamic end-expiratory lung volume ($EELV_{dyn}$) as estimated by IC measurements (see below)] by linear interpolation between simultaneous $P_{\text{Imax}}$ and EELV measurements taken at rest and at the end of exercise. All measurements of tidal $P_{\text{es}}$ were subsequently compared with $P_{\text{Imax}}$ at isovolume. The tension-time index for the inspiratory muscles ($TTI = \text{mean inspiratory } P_{\text{es}}/P_{\text{Imax}} \times T_{I}/T_{tot}$) (3), where $T_{I}$ and $T_{tot}$ are inspiratory time and total time, respectively, and the inspiratory pressure-time integral ($\int P_{\text{es}} \cdot dt$) (22) were calculated and expressed per minute by multiplying by breathing frequency ($f$). Tidal $P-V$ curves were examined, and dynamic elastance ($E_{dyn}$) was calculated as $\Delta P_{\text{es}}/V_{T}$ (i.e., the slope between points of 0 flow at the onset of inspiration and at end inspiration for each breath).

Assuming that TLC does not change during exercise in normal subjects (29) or in patients with ILD (21), changes in $EELV_{dyn}$ were estimated from IC measurements at rest, every 2 min during exercise, and at peak exercise. Satisfactory technique and reproducibility of IC maneuvers for each subject were established during an initial practice session at rest by evaluation of the consistency of volume and $P_{\text{es}}$ measurements. To verify that TLC was attained with each IC maneuver during exercise, we confirmed that the peak inspiratory $P_{\text{es}}$ during these maneuvers was similar to that at rest.

Flow, volume, $P_{\text{es}}$, and expiratory $CO_2$ and $O_2$ fraction signals were sampled continuously at a rate of 100 Hz by using computer data-acquisition software (CODAS; Datasol Instruments, Akron, OH) and stored for later analysis. Computer software was used to calculate timing [$f$, $T_{I}$, expiratory time ($T_{E}$), $T_{tot}$], $V_{T}$, and flow ($V_{T}/T_{I}$, $V_{T}/T_{E}$) parameters for each breath. Minute ventilation ($V_{E}$), $O_2$ uptake ($V_{O_2}$), and $CO_2$ output ($V_{CO_2}$) were calculated by using standard formulas (17) at rest, each minute during exercise, and at peak exercise for each subject. Exercise measurements were compared with the predicted maximum values from $J$ ones (17), and $V_{E}$ was compared with the maximal ventilatory capacity (MVC) calculated by using the method of Killian et al. (18).

The latter method of estimating MVC takes into account the individual's maximal $V_{T}$ and the maximum rates at which this volume can be inspired and expired; indirect estimates of MVC derived solely from $FEV_1$ are unreliable in this population. The $V$-slope method (2) was used to estimate an "anaerobic threshold" for each subject.

Tidal flow-volume curves were examined at a standardized $V_{O_2}$ ($V_{O_2_{sd}}$) during exercise for each subject and placed within their respective maximal envelopes according to coinciding IC measurements. Maximal flow-volume loops performed immediately before exercise were used for this analysis because they have been shown to be similar to those done immediately after exercise (21) and because the performance of maximal loops during exercise interferes with other measurements. Flow limitation was determined by measuring the percentage of $V_T$ that met or exceeded the maximal expiratory flow-volume boundary (16) and by comparing tidal expiratory flow at 50% of $V_T$ with that of the maximal envelope at isovolume. (Fig. 4)

Statistical Analysis

Results were expressed as means $\pm$ SE. A probability of $P < 0.05$ was accepted as significant for all analyses. Exercise-response slopes were expressed as means of slopes from linear regression analysis of individual subjects' data. Dyspnea "thresholds" were expressed as the x-intercepts of the relationships between Borg ratings and independent variables such as $V_{O_2}$ and $V_{E}$. Group data were compared by using unpaired $t$-tests. Fisher exact tests were used to compare the selection frequencies of dyspnea descriptor clusters between groups.

To illustrate group differences during exercise, we evaluated responses at a $V_{O_2_{sd}}$, i.e., 50% of the predicted maximum $V_{O_2}$ ($V_{O_{2\text{max}}}$) was chosen to represent a standardized metabolic load across groups because it 1) standardizes for age, gender, and body size and 2) represents an exercise stimulus of sufficient intensity to correspond with high ventilatory levels. Values for Borg ratings and cardiorespiratory parameters at 50% of the predicted $V_{O_{2\text{max}}}$ were calculated by linear interpolation between adjacent measurement points for each subject.

To standardize for stimulus intensity (i.e., metabolic load during exercise), the slope of Borg dyspnea ratings relative to $V_{O_2}$ was used as the index of exertional dyspnea. To determine the factors contributing to exertional dyspnea intensity in each group, Pearson's correlation coefficients were used to evaluate associations between the slope of Borg over $V_{O_2}$ (expressed as ml·kg$^{-1}$·min$^{-1}$) and independent variables that included exercise-response slopes [$V_{E}-V_{O_2}$, $V_{E}/MVC-V_{O_2}$, $V_{O_{2\text{max}}}$, arterial $O_2$ saturation ($SaO_2$)-$V_{O_2}$, heart rate-$V_{O_2}$, $P_{\text{es}}/P_{\text{Imax}}$-$V_{O_2}$, $P_{\text{es}}/P_{\text{Imax}}$-$V_{O_2}$, $P_{\text{es}}/V_{T}$-$V_{O_2}$]; breathing pattern slopes ($f-V_{E}$, $V_{T}/IC-V_{E}$, $f-V_{T}/IC$, $f-V_{T}$/predicted $VC$), where $VC$ is vital capacity; expiratory airflow limitation (extent of $V_T$ overlap on the maximal flow-volume curve); and resting parameters [$FEV_1$, $FVC$, IC, $DL_{CO}$, $f$, $V_{T}/IC$, end-inspiratory lung volume ($EELV$)/TLC]. In patients with ILD, the same analysis was performed by using the slope of Borg ratings of inspiratory difficulty over $V_{O_2}$ as the independent variable. In each of these analyses, significant variables were selected by stepwise multiple-regression analysis to form the best predictive equations for dyspnea intensity (i.e., Borg-$V_{O_2}$ slopes). A further analysis combining data from both groups was performed by using the same variables noted above; to avoid the possibility that group differences were responsible for the significance of any of these relationships (i.e., association due to two discrete clusters of points representing each group), each case was tested by adding "group" (normal subjects = 0, patients with ILD = 1) as a possible covariate. In this analysis, the group variable was tested as a possible covariate by forcing it into the model sentence before stepping or fitting of the model proceeded.

RESULTS

Exertional Dyspnea

The patients with ILD exhibited severe exercise curtailment and stopped exercise primarily because of dyspnea, alone or in combination with leg fatigue (Tables 3 and 4). In contrast, the normal subjects had average exercise tolerance and stopped exercise mainly because of leg fatigue (Tables 3 and 4). Selection...
Sensory Responses in Interstitial Lung Disease (ILD) (Table 4)

**Table 3. Exercise responses**

<table>
<thead>
<tr>
<th>Work rate, %pred max</th>
<th>Rest</th>
<th>VO2max</th>
<th>Peak</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with ILD (n = 12)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| Work rate, %pred max | 0 ± 0 | 24 ± 4 | 52 ± 9*$
| Heart rate, beats/min | 91 ± 3$ | 105 ± 4$ | 120 ± 5$
| SaO2, % | 95.9 ± 0.5 | 93.8 ± 1.0$ | 92.3 ± 1.2$*
| VO2, ml·kg⁻¹·min⁻¹ | 4.3 ± 0.2 | 9.3 ± 0.6 | 13.8 ± 2.2$*
| VE, l/min | 15.7 ± 1.3$ | 30.8 ± 3.2$ | 46.1 ± 4.9$*
| VE/MVC, % | 18 ± 2 | 35 ± 4 | 51 ± 5
| VT, liters | 0.71 ± 0.05 | 0.94 ± 0.10$ | 1.17 ± 0.13$*
| VT/IC, % | 43 ± 3$ | 55 ± 5$ | 69 ± 6$*
| f, breaths/min | 23.3 ± 2.2$ | 34.5 ± 2.8$ | 40.6 ± 3.1$*
| Ti/Ttot | 0.51 ± 0.02 | 0.46 ± 0.01 | 0.46 ± 0.01
| VT/TI | 0.60 ± 0.11 | 1.11 ± 0.11$ | 1.68 ± 0.20
| IC, liters | 1.71 ± 0.19$ | 1.78 ± 0.17$ | 1.73 ± 0.19$*
| EILVdyn, %TLC | 74 ± 3$ | 78 ± 3 | 85 ± 3
| Inspiratory Pes, %Pmax | 17 ± 3 | 27 ± 4$ | 37 ± 4
| Expiratory Pes, %PE, l | 5 ± 1$ | 8 ± 2$ | 9 ± 1
| Pes/VT, cmH2O l⁻¹ | 15.1 ± 2.0$ | 19.5 ± 1.9$ | 21.5 ± 2.2$*

**Table 4. Symptoms limiting exercise**

<table>
<thead>
<tr>
<th>Reasons for stopping exercise</th>
<th>Patients With ILD (n = 8)</th>
<th>Normal Subjects (n = 12)</th>
</tr>
</thead>
</table>
| Leg fatigue | 17% | 75%
| Dyspnea | 25% | 0%
| Dyspnea + leg fatigue | 5% | 29%

**Peak symptom ratings**

- Leg effort, Borg: 5.8 ± 0.4, 5.6 ± 0.7
- Overall dyspnea, Borg: 5.2 ± 0.5, 4.1 ± 0.7
- Inspiratory difficulty, Borg: 5.5 ± 0.6

**Dyspnea slopes**

- Borg-VO2: 0.55 ± 0.08*, 0.19 ± 0.03
- Borg-VE: 0.17 ± 0.02†, 0.09 ± 0.02
- Borg-VE/MVC: 0.16 ± 0.04†, 0.08 ± 0.01
- Borg-VE/IC: 0.20 ± 0.03*, 0.07 ± 0.01
- Borg-f: 0.28 ± 0.04, 0.37 ± 0.09
- Borg-Pes/Pmax: 0.25 ± 0.05, 0.16 ± 0.03

**Dyspnea thresholds (x-intercept)**

- VO2, ml·kg⁻¹·min⁻¹: 3.4 ± 0.8*, 10.0 ± 0.9
- VE, l/min: 13.3 ± 2.8, 20.4 ± 3.0
- VE/MVC, %: 13.4 ± 2.9†, 23.6 ± 2.5

**Values are means ± SE; n, no. of subjects.**

**Table 4.**

**Symptoms limiting exercise**

<table>
<thead>
<tr>
<th>Factors Limiting Exercise</th>
<th>Patients With ILD (n = 8)</th>
<th>Normal Subjects (n = 12)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Borg-VO2</td>
<td>0.55 ± 0.08*</td>
<td>0.19 ± 0.03</td>
</tr>
<tr>
<td>Borg-VE</td>
<td>0.17 ± 0.02†</td>
<td>0.09 ± 0.02</td>
</tr>
<tr>
<td>Borg-VE/MVC</td>
<td>0.16 ± 0.04†</td>
<td>0.08 ± 0.01</td>
</tr>
<tr>
<td>Borg-VE/IC</td>
<td>0.20 ± 0.03*</td>
<td>0.07 ± 0.01</td>
</tr>
<tr>
<td>Borg-f</td>
<td>0.28 ± 0.04</td>
<td>0.37 ± 0.09</td>
</tr>
<tr>
<td>Borg-Pes/Pmax</td>
<td>0.25 ± 0.05</td>
<td>0.16 ± 0.03</td>
</tr>
</tbody>
</table>

**Values are means ± SE; n, no. of subjects.**

**Fig. 1.** Selection frequency of descriptor clusters for exertional dyspnea in normal subjects and patients with interstitial lung disease (ILD). n, No. of subjects. *Significant difference between groups with use of Fisher exact test, P < 0.05.

**Figures:**

- Fig. 2A: Illustration of the relationship between VO2 and Borg ratings for patients and normal subjects.
- Fig. 2B: Comparison of inspiratory and expiratory Pes values between patients and normal subjects.

**Leg:** A noticeable level of respiratory difficulty (Borg < 0.5).

**Results:** Similar results were obtained between dyspnea and VO2 expressed as liters per minute or as %MVC (Table 4). In patients with ILD, slopes of “overall” dyspnea corresponded strongly with slopes of inspiratory difficulty...
Physiological Exercise Responses

All but one of the normal subjects reached VO₂max on the basis of criteria outlined by Jones (17); one overweight, deconditioned female subject achieved a peak VO₂ that was 98% of that predicted but had significant cardiac and ventilatory reserves and stopped exercise because of "moderate" leg fatigue only. In all patients with ILD, exercise studies were symptom limited and a "true" VO₂max was not attained (peak VO₂ = 76 ± 8% predicted).

Resting SaO₂ was normal in both groups, and there was no clinically significant desaturation in the normal group during exercise (Table 3). SaO₂ fell by 4% or more during exercise in six patients with ILD; however, SaO₂ fell below 90% (i.e., 83 and 87%, respectively) in only two of these patients. Compared with the normal group, the ILD group had a significantly (P < 0.01) heightened ventilatory response to exercise (Fig. 2B). Anaerobic thresholds were not significantly different between groups; a detectable anaerobic threshold could be determined with confidence in six patients with ILD at a VO₂ of 0.98 ± 0.05 l/min compared with 1.12 ± 0.08 l/min in the 12 normal subjects.

Breathing patterns and operational lung volumes. Patients with ILD had a significantly (P < 0.01) more rapid and shallow breathing pattern than did normal subjects (Fig. 2C). Although absolute VT at rest was comparable between groups (0.71 ± 0.05 and 0.75 ± 0.05 liter in patients with ILD and normal subjects, respectively), VT comprised a larger proportion of the significantly reduced IC in patients with ILD (43 ± 3%) compared with normal subjects (28 ± 2%; P < 0.001 between groups). With the increasing demands of exercise, increases in VT were progressively more truncated in patients with ILD such that increases in ventilation were achieved primarily by increasing f (Fig. 2C, Table 3): VT only increased by 0.46 ± 0.10 liter at peak exercise compared with the 1.54 ± 0.24-liter increase in VT in normal subjects.

The assumption that TLC did not change during exercise was supported by the fact that Pimax at the peak of symptom-limited exercise did not change significantly from rest in either group. In addition, peak values of inspiratory Pes (an estimate of effort) did not change during sequential IC maneuvers, thereby validating the use of IC measurements throughout exercise to estimate changes in EELVdyn. Because EELVdyn did not change significantly during exercise in either group, the increase in VT during exercise was accomplished by increasing dynamic end-inspiratory lung volume (EELVdyn) (EELVdyn-EELVdyn + VT) (Figs. 3 and 4). Accordingly, VT expansion during exercise correlated significantly with the constraints of baseline IC (n = 24, r = 0.72, P < 0.001).

Ventilatory mechanics. Inspiratory effort was greater during exercise in patients with ILD than in normal subjects, as shown by the elevated slope of the relationship between tidal Pes/Pimax and VO₂ (Fig. 2D) and the increased Pes/Pimax at VO₂std (Table 3); however, TTI and TTI/min in patients with ILD were not different from normal subjects at VO₂std. Throughout exercise, expiratory effort (Pes-to-maximal expiratory mouth pressure ratio) was also greater in patients with ILD than in normal subjects and was smaller than inspiratory effort in both groups (Table 3).
The mean change in inspiratory Pes (and Pes/Pmax) from rest to peak exercise in patients with ILD was similar to that in normal subjects, despite the much smaller increase in VT (and VT/IC) (Table 3). Therefore, the ratios of Pes to the resultant VT or of Pes/Pmax to VT/IC were greater in patients with ILD than in normal subjects both at rest and during all levels of exercise, reflective of the significantly elevated Edyn in patients with ILD. Dynamic elastance (Edyn) was 19.3 ± 2.2 cmH2O/l in patients with ILD vs. 6.0 ± 0.9 cmH2O/l in normal subjects at VO2std (P < 0.001); increased Edyn (or Pes/Pmax-VT/IC) correlated significantly with reduced IC (or increased EELVdyn/TLC) at VO2std (P < 0.01).

At VO2std, tidal flow-volume curves did not approach their respective maximal curves in five subjects from each of the normal and ILD groups. In the remaining seven subjects in each group, tidal expiratory flow-volume curves equaled or exceeded their maximal curves. In these latter subjects, impingement occurred near EELVdyn over a mean of 53 ± 11 and 33 ± 11% of the VT in normal subjects and patients with ILD, respectively. At 50% of VT, the degree to which tidal expiratory flow rates approached and/or impinged on their respective maximal loops at isovolume was not different between groups (82 ± 23 vs. 65 ± 14% in normal subjects and patients with ILD, respectively).

Correlates of Dyspnea

Within the ILD group, Borg-VO2 slopes failed to correlate significantly with any of the tested parameters except the resting VT/IC [Borg-VO2 = 1.63(VT/IC) − 0.16; r = 0.58, P < 0.05] or its inverse, IRV/IC (r = −0.58, P < 0.05), where IRV is inspiratory reserve volume. Similarly, Borg-time slopes were best predicted by the combination of resting VT/IC and exertional slopes of f-time (r = 0.82, P = 0.007). None of the Pes-derived measurements correlated significantly with dyspnea slopes in the eight patients with ILD with mechanical measurements. Similarly, the closest significant correlate of inspiratory difficulty-VO2 slopes in patients with ILD was the resting VT/IC (r = 0.52, P = 0.12).
In normal subjects, Borg-V̇O2 slopes correlated significantly with slopes of Pes/Pmax-V̇O2 [Borg-V̇O2 = 0.08 + 0.09 (Pes/Pmax-V̇O2); r = 0.60, P < 0.05] and Pes/Pmax-V̇E [Borg-V̇O2 = 0.09 + 0.18(Pes/Pmax-V̇E); r = 62, P < 0.05] but did not correlate with any other of the tested parameters. Stepwise multiple-regression analysis of the combined data from all subjects found that Borg-V̇O2 slopes correlated best with slopes of Pes/V̇T-V̇O2 (P < 0.015) after the group covariate, which alone predicted 42% of its variance: Borg-V̇O2 = 0.16 + 0.06 (Pes/V̇T-V̇O2) + 0.39(group), n = 20, r² = 0.60, P < 0.0005, was accounted for. None of the variables measured at end exercise, including VT/IC, correlated with any index of exertional dyspnea.

Interestingly, exercise capacity (V̇O2max expressed as %predicted) correlated best with resting IC (P = 0.002) and FVC (P = 0.002), both expressed as %predicted, after group was accounted for. By using stepwise multiple-regression analysis, the slope of Borg dyspnea ratings over V̇O2 was added to the baseline IC (%predicted) and the group covariate to form the best predictive equation for V̇O2max (r² = 0.70, P < 0.001).

DISCUSSION

Exertional dyspnea was qualitatively and quantitatively different in patients with ILD and normal subjects. Although descriptions of increased effort and/or work and heaviness of breathing were common to both groups, only patients with ILD consistently selected descriptors that alluded to unsatisfied inspiratory effort, inspiratory difficulty, and rapidity of breathing. Increased sense of effort is pervasive during exercise in health and across the spectrum of cardiopulmonary diseases; in qualitative terms, it is nondiscriminatory (20). Mahler and co-workers (20), in a similar qualitative analysis of dyspnea in various lung diseases, also found that the descriptors denoting increased work and/or effort and rapid breathing were commonly selected by patients with ILD. In their study, in contrast with our results, unsatisfied inspiratory effort was not specifically identified as being representative of ILD. Differences between results of the two studies may be explained by the fact that the three descriptors included under the cluster heading unsatisfied inspiratory effort in our study (Table 1) were subsumed under the work and/or effort and “inhalation” clusters in the study of Mahler et al. (20). Another important methodological difference that could account for differences in results was that our study subjects selected descriptors immediately after symptom-limited exercise, whereas patients relied on recall of more remote exertional symptoms in the other study.

The finding that awareness of inspiratory difficulty and, in particular, unsatisfied inspiratory effort, is characteristic of ILD implies that patients with ILD receive peripheral sensory information that indicates to them that the mechanical response of the ventilatory system is insufficient or inappropriate for the effort expended. It is noteworthy that in an earlier study by Simon et al. (25), normal subjects challenged with elastic mechanical loading selected similar descriptors of breathlessness to those selected by our ILD group.

Clearly, the mechanical response in our group of patients with moderate ILD is seriously impaired compared with that in normal subjects. The resting IC in patients with ILD was significantly diminished and represents the narrow operating limits for V̇T expansion because EELV dyn did not decrease from rest to peak exercise; the IC strongly predicted the extent of V̇T expansion during exercise in both groups and correlated significantly with exercise capacity. V̇T/IC and EILV/TLC at rest and during exercise were greater in patients with ILD than in normal subjects, thus indicating the serious mechanical constraints on V̇T expansion in the face of increased ventilatory demand during exercise (Fig. 3). Given the reduced IC, V̇T must encroach on the upper nonlinear extreme of the respiratory system’s P-V relationship. This contention is supported by our finding that the ratio of tidal Pes (effort) to V̇T (displacement) widened significantly from rest to peak exercise in patients with ILD. Although the sense of increased breathing effort was uniformly reported by all subjects at the breakpoint of exercise, the normal group rarely selected descriptors from the unsatisfied effort cluster to describe their breathing discomfort. In this group, V̇T expansion was not as restricted because the IC was considerably larger than in patients with ILD. Therefore, the relationship between effort and mechanical response remained harmonious throughout exercise: Pes/V̇T was unchanged, indicating that, unlike the ILD group, V̇T normally remains within the linear portion of the P-V relationship.

It is reasonable to assume that differences in the quality of dyspnea between patients with ILD and normal subjects fundamentally reflect differences in mechanical impedance and ventilatory demand. At the end of symptom-limited maximal exercise, when dyspnea intensity was similar in both groups, the qualitative differences that were evident could reasonably be attributed to differences in dynamic ventilatory mechanics. Thus the perceptions of inspiratory difficulty, unsatisfied inspiratory effort, and rapidity of breathing in patients with ILD were likely related to the significantly reduced IC, the heightened Pes/V̇T, and the tachypnea, respectively, that occurred at this point of comparison. Clearly, qualitative differences could not be attributed to differences in inspiratory effort (Pes/V̇T max), which was similar in both groups at end exercise.

Exertional dyspnea was quantitatively greater in patients with ILD than in normal subjects when Borg ratings were expressed as a function of V̇O2 or V̇E. Between-group differences in these relationships suggest that dyspnea may have different physiological contributors in the two groups. Thus the finding that dyspnea ratings were higher at a given V̇E in patients with ILD compared with normal subjects suggests that mechanical impedance is important in ILD. Moreover, multiple-regression analysis identified different contributing factors in each group. Pes-derived indexes correlated strongly with dyspnea in normal subjects, whereas
the resting Vt/IC was the main independent contributor to the intensity of dyspnea and inspiratory difficulty in patients with ILD. In other words, the mechanical constraints on volume expansion (determined at rest) correlated best with the rate of change of dyspnea during exercise in patients with ILD. Furthermore, resting mechanics (i.e., IC, FVC) and dyspnea intensity each contributed significantly to the variance in exercise capacity in patients with ILD. Although our contention is that restrictive mechanics shape exertional dyspnea intensity and that this leads to exercise curtailment, another explanation is that abnormal mechanics primarily limit exercise but do not directly give rise to dyspnea; increasing dyspnea in this scenario merely reflects increasing exercise intensity as it does in normal subjects. Given the strong statistical interrelationships among mechanical derangements, exercise capacity, and exertional dyspnea in patients with ILD, it is difficult, if not impossible, to examine these factors in isolation.

In normal healthy subjects, impedance is low and effort is used to increase the velocity of shortening and the extent of inspiratory muscle contraction to displace the thorax during respiration. In accordance with previous studies, it is not surprising that Pes/PImax (which directly reflects the amplitude of central motor command output) correlated well with dyspnea intensity in our normal group. By contrast, in our ILD group, impedance was increased, thoracic displacement was diminished, velocity of shortening was relatively increased at low work rates, and compensatory strategies were likely in place to minimize intrathoracic pressure perturbations and the associated breathing discomfort (see below).

In contrast to the situation in normal subjects, Pes-derived indexes of inspiratory effort did not correlate with exertional dyspnea intensity in the ILD group. This may be because of the smaller sample size of the ILD group (n = 8) in which Pes measurements were available. However, all of the variables that correlated with Borg dyspnea ratings in the larger group (n = 12) continued to correlate strongly in the smaller sample. Therefore, even if the sample size were increased and Pes-derived measurements correlated significantly with dyspnea intensity, they would still not correlate as strongly as other volume-derived measurements (i.e., resting Vt/IC).

Pes/PImax was significantly increased at any given V02 in patients with ILD compared with normal subjects; however, the magnitude of this increase was less than that reported in other pulmonary disorders (e.g., CAL): although impeded in their action by elastic loading, the inspiratory muscles were not working under a major mechanical disadvantage, as is the case, for example, in CAL. In accordance with a previous study (10), PImax was relatively well preserved in our ILD group. Thus, despite the increased tidal Pes excursions, and notwithstanding some reduction in functional muscle strength because of the increased Vt/Ti, Pes/PImax was only moderately increased and TTI, a measure of the oxygen cost of breathing, was comparable to normal at V02std because of the relatively reduced Ti. The adoption of a rapid shallow breathing pattern in patients with ILD served to minimize the work required to attain a given ventilation and was therefore an effective compensatory strategy for the elastic load (30, 31). Although this breathing pattern response to exercise in patients with ILD may, in part, be dictated by restrictive mechanics, there is also evidence to suggest that it may be behaviorally modulated to minimize breathing discomfort during elastic loading (30, 31).

Our finding that Pes/PImax did not correlate with exertional dyspnea in patients with ILD differs from that in a previous study by Leblanc et al. (19) that reported significant correlations between the intensity of dyspnea and Pes-to-maximal inspiratory mouth pressure ratio in 20 patients with various cardiopulmonary disorders, including ILD, and normal subjects. A separate analysis of the ILD subgroup was not provided in that study and would be required for accurate comparison with our results because different sensory and mechanical factors could have contributed to the intensity and quality of dyspnea across cardiopulmonary diseases and in normal subjects.

Exertional dyspnea in patients with ILD did not correlate with the extent of expiratory flow limitation at rest or during exercise. Resting SaO2, values were normal in all subjects, and SaO2 during exercise fell significantly (i.e., ≥4%) in only six patients with ILD and below 90% in only two of these patients. In addition, the resting SaO2 and the extent of oxygen desaturation during exercise did not contribute significantly to the variance in exertional dyspnea in our group of patients with moderately severe ILD; therefore, hypoxia was unlikely to have contributed to dyspnea causation in this group. However, our results are not generalizable to patients with ILD who have significant oxygen desaturation during exercise.

At peak exercise, when qualitative differences between groups were recorded, Pes/Vt was found to be almost three times higher in patients with ILD than in normal subjects, reflecting the increased elastic load. In the stepwise multiple-regression analysis including both groups, Pes/Vt emerged as the best predictor of exertional dyspnea; together with the group covariate, the slopes of Pes/Vt-V02 accounted for 60% of the variance in Borg-V02 slopes. The increased Pes/Vt provides a potential mechanical basis for some of its distinctive qualitative dimensions (e.g., unsatisfied inspiratory effort). Inspiratory difficulty and unsatisfied inspiratory effort in patients with ILD may have its physiological basis in the conscious awareness of a mismatch between expended effort and the mechanical response of the system that is conveyed to consciousness by afferent feedback from multiple mechanoreceptors (31). There is evidence that the sense of contractile effort is the sensory expression of motor command output that is conveyed to consciousness via central corollary discharge (8, 9, 12). Unsatisfied effort may therefore have its neurophysiological basis in altered afferent feedback from peripheral mechanoreceptors.
relative to the magnitude of coronary discharge. Of the receptors available, those in the ventilatory muscles (muscle spindles, Golgi tendon organs) represent a potential proximal source of sensory feedback (31) regarding effort-displacement mismatching. In this regard, Campbell et al. (6, 7) originally proposed that the ability of humans to detect imposed elastic loads depended on the perception of “length-tension inappropriateness”; this arises from the integration and central processing of signals conveying information about muscle lengthening (or volume change) via muscle spindles and joint receptors with those conveying information about muscle tension development (or pressure) via tendon organs. However, it is unlikely that the ventilatory muscles are the exclusive source of dyspneogenic afferent signals; feedback information concerning the extent of thoracic displacement for a given neural activation or effort could equally arise from proprioceptive mechanoreceptors in both the lung and chest wall (i.e., joint receptors) that ascend via vagal, autonomic, and spinal pathways.

The remarkable similarity in choices of qualitative descriptors (i.e., inspiratory difficulty, unsatisfied inspiratory effort) for exertional dyspnea in patients with ILD and a previously studied group of patients with CAL raises the intriguing possibility that they share some common underlying mechanisms. In both conditions, IC was diminished and VT/IC was increased early in exercise; thus movement of the thoracic cage and lung was greatly restricted despite patients mustering considerable inspiratory efforts during exercise. In patients with CAL, the intensity of inspiratory difficulty was strongly related to the ratio of Pes/PImax to VT/VC. This ratio, a measure of the disparity between respiratory effort and thoracic displacement, is increased in patients with CAL compared with normal subjects because of dynamic hyperinflation that results in VT being positioned at the upper, nonlinear extreme of the respiratory system's P-V curve.

In summary, the qualitative descriptors of dyspnea recorded at the termination of symptom-limited exercise were different in patients with ILD than in normal subjects. Significant differences in dynamic ventilatory mechanics and breathing pattern may explain the distinctive qualitative perceptions of inspiratory difficulty, unsatisfied inspiratory effort, and rapidity of breathing found in ILD. The relationship between exertional dyspnea and ventilation was different in patients with ILD than normal subjects, and the physiological factors contributing to dyspnea (and inspiratory difficulty) in patients with ILD were different from those contributing to dyspnea in normal subjects: the intensity of exertional dyspnea in patients with ILD was more closely linked to the mechanical constraints on volume expansion than to indexes of inspiratory effort per se.

D. E. O'Donnell holds a career scientist award from the Ontario Ministry of Health.

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