CHEST

Original Research

COPD

Decline of Resting Inspiratory Capacity in COPD

The Impact on Breathing Pattern, Dyspnea, and Ventilatory Capacity During Exercise

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Background: **To better understand the interrelationships among disease severity, inspiratory capacity (IC), breathing pattern, and dyspnea, we studied responses to symptom-limited cycle exercise in a large cohort with COPD.**

Methods: **Analysis was conducted on data from two previously published replicate clinical trials in 427 hyperinflated patients with COPD. Patients were divided into disease severity quartiles based on FEV_1 % predicted. Spirometry, plethysmographic lung volumes, and physiologic and perceptual responses to constant work rate (CWR) cycle exercise at 75% of the peak incremental work rate were compared.**

Results: **Age, body size, and COPD duration were similar across quartiles. As the FEV_1 quartile worsened (mean, 62%, 49%, 39%, and 27% predicted), functional residual capacity increased (144%, 151%, 164%, and 185% predicted), IC decreased (86%, 81%, 69%, and 60% predicted), and peak incremental cycle work rate decreased (66%, 55%, 50%, and 44% predicted); CWR endurance time was 9.7, 9.3, 8.2, and 7.3 min, respectively. During CWR exercise, as FEV_1 quartile worsened, peak minute ventilation ($\dot{V}_E$) and tidal volume (V_T) decreased, whereas an inflection or plateau of the V_T response occurred at a progressively lower $\dot{V}_E$ ($P < .0005$), similar percentage of peak $\dot{V}_E$ (82%-86%), and similar V_T/IC ratio (73%-77%). Dyspnea intensity at this inflection point was also similar across quartiles (3.1-3.7 Borg units) but accelerated steeply to intolerable levels thereafter.**

Conclusion: **Progressive reduction of the resting IC with increasing disease severity was associated with the appearance of critical constraints on V_T expansion and a sharp increase in dyspnea to intolerable levels at a progressively lower ventilation during exercise.**

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Abbreviations: CWR = constant work rate; FRC = functional residual capacity; IC = inspiratory capacity; ICdyn = dynamic inspiratory capacity measured during exercise testing; IRV = inspiratory reserve volume; TLC = total lung capacity; $\dot{V}_E$ = minute ventilation; $\dot{V}O_2$ = oxygen consumption; V_T = tidal volume

Exercise intolerance in patients with COPD is multifactorial, but respiratory mechanical abnormalities and the associated perceived respiratory discomfort undoubtedly contribute. Recent analytical approaches using measurement of operating lung volumes and breathing pattern have the potential to provide new insights into the evolution of these important sensorimechanical interactions as airway obstruction progressively worsens.

We have previously proposed that dynamic mechanical respiratory constraints are the primary influence on breathing pattern responses to exercise in severe COPD.[1-3] Thus, a low resting inspiratory capacity (IC), reflecting severe lung hyperinflation, limits the ability to increase ventilation in response to the increasing metabolic demands of exercise. In severe COPD, tidal volume (V_T) expands during exercise to quickly reach a critically low inspiratory reserve volume (IRV), or the V_T plateau.[3] This important mechanical event during exercise marks the onset of a progressively widening disparity between the contractile respiratory muscle effort expended (and central neural drive) and

volume displacement achieved; this increasing neuromechanical uncoupling contributes to both the intensity and the quality of dyspnea in COPD.[3,4] Previous studies that have examined the link between resting IC and exercise performance have used only small sample sizes of patients with advanced COPD.[1,5,6] Information is lacking on the impact of the natural decline in resting IC (as airflow limitation worsens) on dynamic operating lung volumes, breathing pattern, ventilatory capacity, and the evolution of dyspnea during physical exertion.

Therefore, the objective of the current study was to examine the interactions among resting IC, dynamic IC measured during exercise testing (ICdyn), breathing pattern responses, and the time course of change in dyspnea during cycle exercise in a COPD population with varying degrees of airway obstruction. Our hypothesis was that progressive reduction of the resting IC with increasing disease severity is associated with the appearance of critical constraints on V_T expansion (and the onset of tachypnea and severe dyspnea) at a progressively lower ventilation during exercise. Thus, we conducted a retrospective pooled analysis of two published multicenter clinical trials in a large cohort of patients with moderate to very severe COPD where detailed physiologic measurements were available during constant work rate (CWR) cycle exercise.[7,8] Using cross-sectional analysis of this unique data set, we compared ventilatory responses in the COPD cohort divided into quartiles by FEV_1 % predicted and examined their association with dyspnea intensity.

Materials and Methods

The data from two randomized, double-blind, placebo-controlled clinical trials that evaluated the effects of daily tiotropium on exercise tolerance, hyperinflation, and dyspnea in patients with COPD were retrospectively combined for this analysis.[7,8] There is no overlap between this independent analysis of the pretreatment data and previous analyses of the same data set.[7-10] The Queen's University and Affiliated Teaching Hospitals Research Ethics Board approved the use of these data and waived the need for additional patient informed consent (DMED-1398-11). A detailed methodology has been previously reported.[7,8]

Subjects

Subjects were aged 40 to 75 years, had a cigarette smoking history of > 10 pack-years, and were given a clinical diagnosis of COPD. Lung function requirements were prebronchodilator $FEV_1 \leq 65\%$ predicted, $FEV_1/FVC < 0.7$, and plethysmographic functional residual capacity (FRC) $\geq 120\%$ predicted. (Predicted values were based on North American[11,12] or European[13] normative equations, depending on site location.) Long-acting bronchodilators were not permitted throughout the study. Rescue salbutamol was withdrawn ≥ 6 h prior to study visits.

Study Design

Pulmonary function tests and symptom-limited incremental cycle exercise were performed at an initial screening visit. During two subsequent run-in visits, subjects performed pulmonary function tests followed by symptom-limited CWR cycle exercise at 75% of the maximum incremental work rate. Exercise data from the second run-in visit was defined as the baseline for treatment analysis. Both studies received approval from local ethics committees. Informed consent was obtained from all participants.

The current analysis included subjects from the intent-to-treat groups of both studies if they had baseline exercise test data available for preexercise rest and at least two exercise time points (ie, the first standardized data collection time between 1 and 2 min of loaded exercise and peak exercise). Exercise and pulmonary function data from this baseline visit were examined for primary analysis. Subjects were divided into quartiles of FEV_1 % predicted measured at the baseline visit. The upper through lower quartiles (Q1-Q4) represented the mildest to most severe groups, respectively. No postbronchodilator pulmonary function data were available.

Procedures

Spirometry and body plethysmography were performed according to recognized guidelines.[14,15] For the present analysis, values were expressed relative to the predicted values of Morris et al[11] and Crapo et al.[12] Procedures for conducting symptom-limited incremental and CWR exercise tests have been described previously.[7,8] Breath-by-breath data, intensity of dyspnea and leg discomfort (modified 10-point Borg scale),[16] and ICdyn were analyzed at steady-state rest, at every second minute during exercise, and at end exercise (peak). V_T/ICdyn ratios were calculated at each exercise time point. Exercise measurements were compared with the predicted normal values of Jones.[17] Maximum ventilatory capacity was estimated as $35 \times FEV_1$.[18] The inflection point of the V_T and minute ventilation ($\dot{V}_E$) relationship was determined for each subject by examining the averaged (30 s) data collected at each time point during exercise.[19]

Statistical Analysis

Data are expressed as mean ± SD, unless otherwise specified. Statistical significance was considered at $P < .05$. Nonparametric data were assessed using χ^2 analysis. All other between-group comparisons were assessed using analysis of variance; post hoc testing of significant variables was performed using t tests with Bonferroni adjustment for multiple comparisons. Simple regression was performed using Pearson correlations. To test the possibility that examined relationships were different across quartiles, multiple regression was used, and an interaction term (variable × quartile) was added to the model.

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Results

Subjects

Characteristics of the 427 evaluable subjects are shown in Table 1. Age, height, BMI, and COPD duration were similar across the FEV_1 quartiles. There was a larger percentage of current smokers in Q1 than in the other three quartiles. Pulmonary function data showed that lung hyperinflation worsened progressively as disease severity increased. Peak incremental cycle work rate and oxygen consumption ($\dot{V}O_2$) also decreased progressively from Q1 to Q4.

Physiologic Responses to Symptom-Limited CWR Exercise

Measurements at the peak of CWR exercise are reported in Table 2. Peak $\dot{V}O_2$ during CWR exercise was similar to that during incremental exercise. Although the duration of CWR exercise was not significantly different across the upper three quartiles, there was a mean difference of >2 min between Q1 and Q4 ($P = .004$). At any given time during this CWR protocol, subjects across quartiles worked at a similar proportion of their own peak $\dot{V}O_2$ (and $\dot{V}E$ [data not shown]), despite a progressive separation of absolute $\dot{V}O_2$, $\dot{V}E$, and VT measurements (Fig 1). The magnitude of oxygen desaturation during exercise was significantly greater in Q4, with 56 of 107 (52%) experiencing a fall in oxygen saturation as measured by pulse oximetry of $\geq 4\%$ vs 31%, 26%, and 13% of subjects in Q3, Q2, and Q1, respectively.

From Q1 to Q4, peak measurements of $\dot{V}E$, VT, and ICdyn all decreased incrementally (Table 2). ICdyn measurements at rest and at any given time during exercise also decreased progressively as the quartile worsened (Fig 1), reflective of progressive lung hyperinflation (Fig 2). Dynamic hyperinflation as defined by any decrease in ICdyn from rest to peak exercise was experienced by the majority in each group (ie, 93%, 89%, 88%, and 76% of subjects in Q4, Q3, Q2, and Q1, respectively) (Fig 3). The mean decrease in IC during exercise was similar in Q2 to Q4 but significantly less in Q1 than in Q4 (Table 2); however, the difference in magnitude disappeared if only those subjects who hyperinflated were evaluated. Based on resting pulmonary function measurements, the small proportion of subjects within each quartile who did not hyperinflate acutely during exercise could not be distinguished from those who did hyperinflate within the same quartile. However, the magnitude of absolute

Table 1—*Subject Characteristics and Baseline Pulmonary Function Across FEV_1 Quartiles*

	Q4 (n = 107)	Q3 (n = 107)	Q2 (n = 107)	Q1 (n = 106)	*P* Value
FEV_1 range, % predicted	16.5-34.9	34.9-43.6	43.8-54.1	54.5-85.1	
Male sex, %	84[a]	69	66	69	.015
Age, y	61 ± 7	63 ± 7	61 ± 8	61 ± 8	.281
Height, cm	169 ± 8	172 ± 9	171 ± 10	171 ± 9	.931
Mass, kg	76.1 ± 17.2	76.9 ± 14.7	78.8 ± 17.3	78.3 ± 16.1	.600
BMI, kg/m²	25.8 ± 5.1	26.2 ± 4.8	26.9 ± 5.0	26.8 ± 4.9	.358
COPD duration, y	10.2 ± 6.6	8.5 ± 0.9	8.0 ± 6.8	8.2 ± 6.9	.309
Smoking, pack-y	65 ± 35	48 ± 21	51 ± 26	52 ± 29	.053
Smoking status, % current	28	36	38	60[a]	< .0005
Peak incremental work rate, W	62 ± 25[A]	73 ± 24[B]	81 ± 31[B]	97 ± 32[C]	< .0005
Peak incremental work rate, % predicted maximum	44 ± 16[A]	50 ± 14[B]	55 ± 16[B]	66 ± 17[C]	< .0005
Peak incremental $\dot{V}O_2$, L/min	1.00 ± 0.33[A]	1.13 ± 0.37[A]	1.27 ± 0.44[B]	1.43 ± 0.45[C]	< .0005
Peak incremental $\dot{V}O_2$, % predicted maximum	50 ± 14[A]	68 ± 20[B]	75 ± 19[B]	84 ± 22[C]	< .0005
FEV_1, L	0.78 ± 0.19[A]	1.10 ± 0.20[B]	1.37 ± 0.29[C]	1.75 ± 0.37[D]	< .0005
FEV_1 % predicted	27 ± 5[A]	39 ± 3[B]	49 ± 3[C]	62 ± 5[D]	< .0005
FEV_1/FVC, %	36 ± 7[A]	43 ± 7[B]	47 ± 8[C]	54 ± 9[D]	< .0005
$FEF_{50\%}$ % predicted	7 ± 2[A]	11 ± 3[B]	13 ± 4[C]	22 ± 9[D]	< .0005
IC, L	1.91 ± 0.49[A]	2.03 ± 0.54[A]	2.35 ± 0.72[B]	2.50 ± 0.66[B]	< .0005
IC/TLC, %	23 ± 5[A]	27 ± 6[B]	32 ± 6[C]	35 ± 7[D]	< .0005
IC % predicted	60 ± 13[A]	69 ± 15[B]	81 ± 17[C]	86 ± 19[C]	< .0005
FRC % predicted	185 ± 33[A]	164 ± 28[B]	151 ± 24[C]	144 ± 29[C]	< .0005
RV % predicted	247 ± 51[A]	213 ± 45[B]	190 ± 38[C]	177 ± 40[C]	< .0005
TLC % predicted	125 ± 17[A]	120 ± 16[A,B]	119 ± 14[B]	117 ± 17[B]	.002
Raw % predicted	578 ± 270[A]	476 ± 214[B]	427 ± 169[B]	333 ± 139[C]	< .0005

Data are presented as mean ± SD, unless otherwise indicated. The letters A, B, C, and D indicate the following: means with the same letters are similar, and means with different letters are significantly different from each other after Bonferroni adjustment for multiple comparisons ($P < .05$).
$FEF_{50\%}$ = mid-volume forced expiratory flow; FRC = functional residual capacity; IC = inspiratory capacity; Raw = airway resistance; RV = residual volume; TLC = total lung capacity; $\dot{V}O_2$ = oxygen consumption.
[a]$P < .05$ different from the remaining subgroups by χ^2 analysis.

change in ICdyn during exercise in the group as a whole correlated with the FEV_1/FVC ($r = 0.275$, $P < .0005$), mid-volume forced expiratory flow % predicted ($r = 0.207$, $P < .0005$), and total lung capacity (TLC) % predicted ($r = -0.170$, $P < .0005$) and more weakly with the resting IC % predicted ($r = -0.134$, $P = .006$) and FEV_1 % predicted ($r = 0.116$, $P = .017$); the combination of FEV_1/FVC and the resting IC % predicted formed the best explanatory equation ($r = 0.338$, $P < .0005$).

A notable inflection of the $V_T/\dot{V}_E$ relationship during exercise occurred in the majority of subjects in each quartile (93%-95%) together with an inflection of IRV as it approached its lowest point (Fig 4). This point occurred at a lower $\dot{V}_E$ ($P < .0005$) but at a similar percentage of peak $\dot{V}_E$ (82%-86%), similar V_T/ICdyn (73%-77%), similar breathing frequency (25-26 breaths/min), and similar time frame (2.6-3.1 min) as disease severity worsened (Table 3). Dyspnea intensity at this inflection point was also similar across quartiles (3.1-3.7 Borg units, $P = .336$). Measurements of exercise time, dyspnea intensity, V_T/ICdyn, and $\dot{V}_E$ percent peak at the $V_T/\dot{V}_E$ inflection point were similar in the subgroup of patients who hyperinflated during exercise compared with those who did not.

Exertional Dyspnea

The distribution of reasons for stopping exercise was significantly different across quartiles ($P = .016$). Dyspnea as the primary reason was more frequent in Q4 ($P = .001$), but all groups stopped with an equal predominance (80%-86%) of dyspnea when it was considered both singly and in combination with leg discomfort. The peak intensity of dyspnea and leg discomfort was similar across quartile groups; however, peak ratings of dyspnea were significantly ($P < .05$) greater than leg discomfort in all but Q1 (Table 2).

Because the $\dot{V}_T/\dot{V}_E$ inflection point is an important mechanical event that occurred at a similar dyspnea intensity, V_T/ICdyn ratio, and $\dot{V}_E$ percent peak across all quartiles, interrelationships among these measurements were examined in more detail (Fig 5). Dyspnea increased linearly as V_T/ICdyn increased during exercise, reached an inflection point (coinciding with the $V_T/\dot{V}_E$ inflection point), then rose almost vertically to the symptom-limited end point of exercise; this relationship was similar across all quartiles. The dyspnea-$\dot{V}_E$ percent peak curves showed a tightly superimposed curvilinear relationship across all quartiles. Dyspnea-$\dot{V}_E$, dyspnea-V_T/ICdyn, and V_T/ICdyn-$\dot{V}_E$ relationships were also remarkably similar across the exercise hyperinflator and nonhyperinflator subgroups.

Correlates of Peak Exercise Capacity and Ventilation

When looking for resting indices, prognostic of exercise capacity in the group as a whole, the best correlates of peak incremental work rate (% predicted) were FEV_1 % predicted ($r = 0.458$, $P < .0005$) and IC % predicted ($r = 0.412$, $P < .0005$). Peak $\dot{V}O_2$ % predicted

Table 2—*Symptom-Limited Peak of Constant Work Rate Exercise at 75% of Wmax*

	Q4 (n = 107)	Q3 (n = 107)	Q2 (n = 107)	Q1 (n = 106)	ANOVA *P* Value
Work rate, W	48 ± 19^{A}	56 ± 18^{B}	62 ± 23^{B}	74 ± 24^{C}	< .0005
Endurance time, min	7.3 ± 4.8^{A}	$8.2 \pm 5.2^{A,B}$	9.3 ± 5.1^{B}	9.7 ± 5.4^{B}	.003
Dyspnea, Borg units	6.9 ± 2.3	6.7 ± 2.4	7.0 ± 2.2	6.9 ± 2.2	.764
Leg discomfort, Borg units	5.9 ± 3.1	6.3 ± 2.8	6.2 ± 2.9	6.8 ± 2.4	.361
$\dot{V}O_2$, L/min	0.99 ± 0.30^{A}	1.14 ± 0.36^{B}	1.25 ± 0.43^{B}	1.43 ± 0.44^{C}	< .0005
Heart rate, beats/min	124 ± 3	124 ± 4	124 ± 2	132 ± 2	.056
SpO_2, %	91.0 ± 4.9^{A}	93.1 ± 3.8^{B}	93.3 ± 3.9^{B}	94.9 ± 3.3^{C}	< .0005
ΔSpO_2 peak-rest, %	-4.6 ± 4.2^{A}	-2.7 ± 3.3^{B}	-2.6 ± 3.0^{B}	-1.5 ± 3.2^{B}	< .0005
$\dot{V}_E$, L/min	33.7 ± 8.9^{A}	38.6 ± 10.3^{B}	44.5 ± 13.0^{C}	52.6 ± 12.9^{D}	< .0005
$\dot{V}_E$, % estimated MVC	126 ± 33^{A}	101 ± 24^{B}	92 ± 13^{C}	$88 \pm 19^{C,D}$	< .0005
*F*b, breaths/min	30.4 ± 5.9^{A}	30.8 ± 6.4^{A}	$31.1 \pm 7.1^{A,B}$	33.2 ± 6.7^{B}	.007
V_T, L	1.13 ± 0.28^{A}	1.29 ± 0.34^{B}	1.48 ± 0.47^{C}	1.63 ± 0.42^{D}	< .0005
V_T/ICdyn, %	80 ± 15^{A}	$77 \pm 13^{A,B}$	$77 \pm 13^{A,B}$	73 ± 14^{B}	.005
ICdyn, L	1.45 ± 0.41^{A}	1.69 ± 0.44^{B}	1.93 ± 0.55^{C}	2.25 ± 0.56^{D}	< .0005
ΔICdyn peak-rest, L	-0.45 ± 0.32^{A}	-0.41 ± 0.36^{A}	-0.44 ± 0.36^{A}	-0.30 ± 0.39^{B}	.012
IRV, L	0.32 ± 0.27^{A}	$0.41 \pm 0.29^{A,B}$	0.45 ± 0.29^{B}	0.62 ± 0.35^{C}	< .0005
IRV, % TLC	4 ± 3^{A}	5 ± 4^{B}	6 ± 4^{B}	9 ± 5^{C}	< .0005
EELV, % predicted TLC	102 ± 18^{A}	93 ± 17^{B}	88 ± 15^{B}	81 ± 17^{C}	< .0005

Data are presented as mean ± SD. The letters A, B, C, and D indicate the following: means with the same letters are similar, and means with different letters are significantly different from each other after Bonferroni adjustment for multiple comparisons ($P < .05$). ANOVA = analysis of variance; EELV = end-expiratory lung volume; *F*b = breathing frequency; ICdyn = dynamic inspiratory capacity measured during exercise testing; IRV = inspiratory reserve volume; MVC = maximum ventilatory capacity; SpO_2 = oxygen saturation as measured by pulse oximetry; $\dot{V}_E$ = minute ventilation; V_T = tidal volume; Wmax = maximum incremental work rate. See Table 1 legend for expansion of other abbreviations.

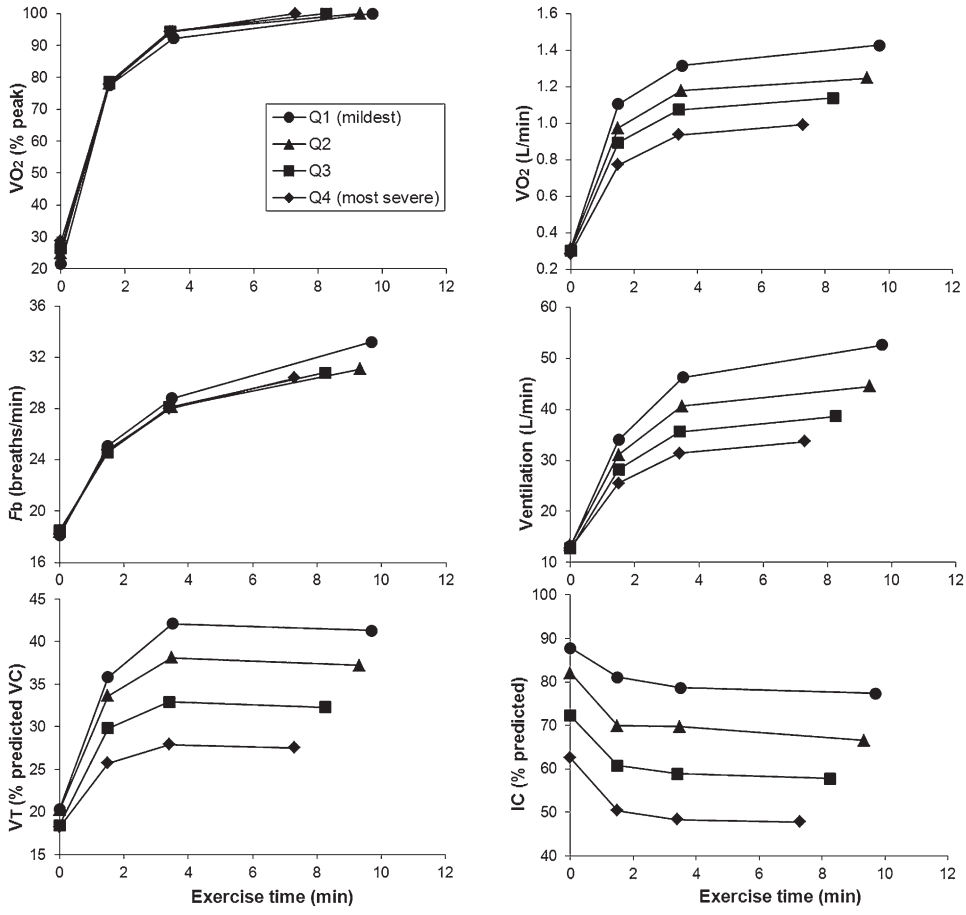

FIGURE 1. Measurements during constant work rate cycle exercise are shown against exercise time. With worsening FEV_1 quartile, subjects across quartiles worked at a similar proportion of their own peak V_{O_2} despite a progressive separation of absolute V_{O_2}, ventilation, VT, and dynamic IC. There was no difference in *F*b. Data plotted are mean values at steady-state rest, isotime (ie, 2 min, 4 min), and peak exercise. *F*b = breathing frequency; IC = inspiratory capacity; V_{O_2} = oxygen consumption; VT = tidal volume.

correlated best with FEV_1 % predicted ($r = 0.430$, $P < .0005$), FEV_1/FVC ($r = 0.328$, $P < .0005$), and IC % predicted ($r = 0.319$, $P < .0005$) and less strongly with the FVC % predicted ($r = 0.280$, $P < .0005$) and IC/TLC ratio ($r = 0.216$, $P < .0005$). To predict peak $\dot{V}_{O_2}$ in absolute terms, the best resting measurements were FEV_1 ($r = 0.626$, $P < .0005$) and IC ($r = 0.556$, $P < .0005$); both of these relationships were much stronger without the constant ($r = 0.959$ and $r = 0.957$, respectively).

In the group as a whole, the best equations for calculating peak $\dot{V}_E$ were $32.5 \times FEV_1$ ($r = 0.972$, $P < .0005$) and $18.9 \times IC$ ($r = 0.965$, $P < .0005$). Likewise, $\dot{V}_E$ at the VT inflection point was calculated as $15.4 \times IC$ ($r = 0.957$, $P < .0005$). Across all quartiles, the relationship between peak $\dot{V}_E$ and resting IC was more consistent (quartile × IC interaction term, $P = .342$) than the relationship between peak V_E and FEV_1 (quartile × FEV_1 interaction term, $P = .082$). Thus, peak $\dot{V}_E$ was calculated as 29.8, 32.5, 34.9, and $41.8 \times FEV_1$ or as 20.2, 18.3, 18.3, and $18.0 \times IC$ in Q1 through Q4, respectively.

The peak VT achieved during exercise correlated well with peak $\dot{V}_E$ ($r = 0.723$, $P < .0005$) and peak $\dot{V}_{O_2}$ ($r = 0.694$, $P < .0005$). In turn, peak VT was best determined by the concurrent peak ICdyn ($r = 0.837$, $P < .0005$) and less strongly by resting IC ($r = 0.694$, $P < .0005$).

DISCUSSION

The novel findings of this study were as follows: (1) the progressive erosion of resting IC with worsening airflow obstruction and hyperinflation was associated with the development of an increasingly shallow, rapid breathing pattern and worsening dyspnea at progressively lower levels of ventilation during exercise, and (2) despite significant interquartile differences in resting airflow obstruction, lung hyperinflation, and ventilatory capacity, exertional dyspnea intensity consistently increased steeply to intolerable levels after VT reached ~75% of the concurrent ICdyn. Individuals in each quartile were well matched for

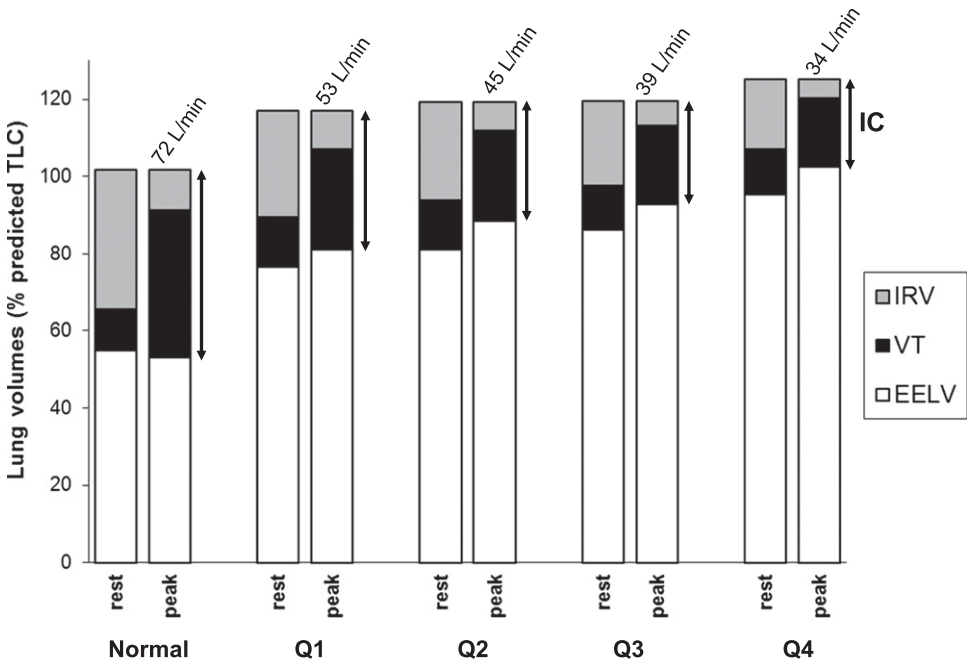

FIGURE 2. Progressive hyperinflation is shown, by increasing EELV, at rest and peak exercise as FEV_1 quartile worsens. Peak values of dynamic IC, VT, and ventilation (values shown above peak exercise bars) decreased with worsening severity, although similar peak ratings of dyspnea intensity were reached. Normative data are shown for comparison.[1,2] EELV = end-expiratory lung volume; IRV = inspiratory reserve volume; TLC = total lung capacity. See Figure 1 legend for expansion of other abbreviations.

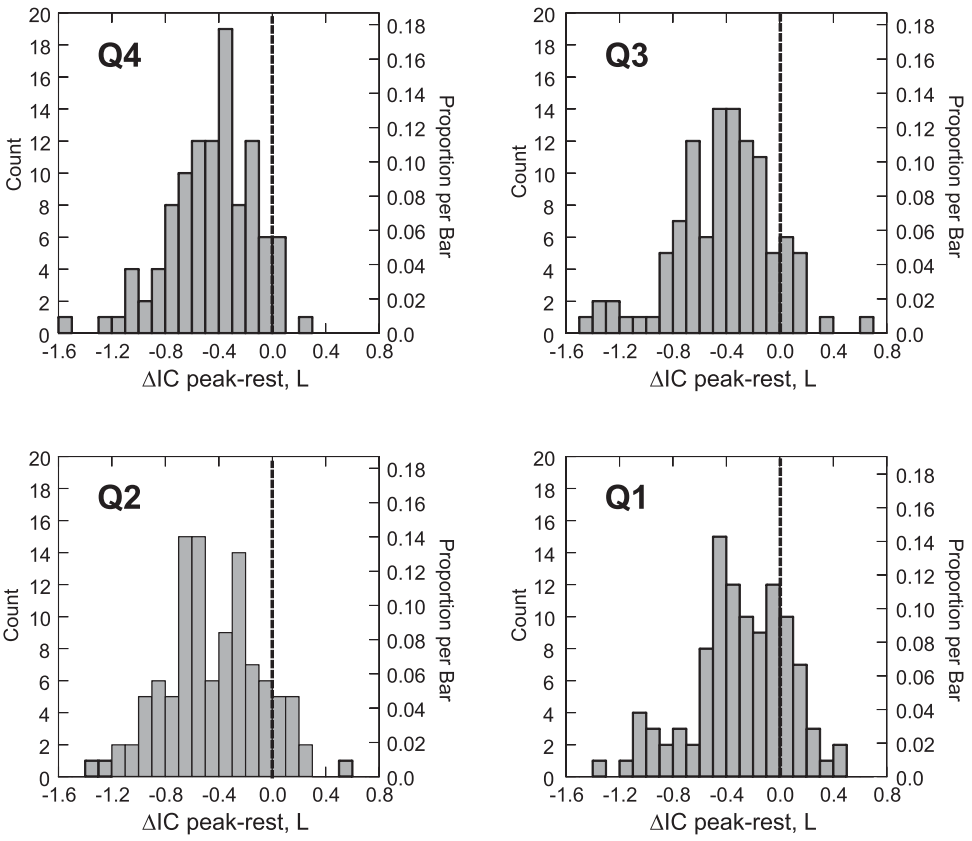

FIGURE 3. The distribution of change in dynamic IC during constant work rate exercise is shown for each FEV_1 quartile. Dynamic hyperinflation, as reflected by a decrease in dynamic IC from rest to peak exercise, is shown by the majority of each quartile. IC = inspiratory capacity.

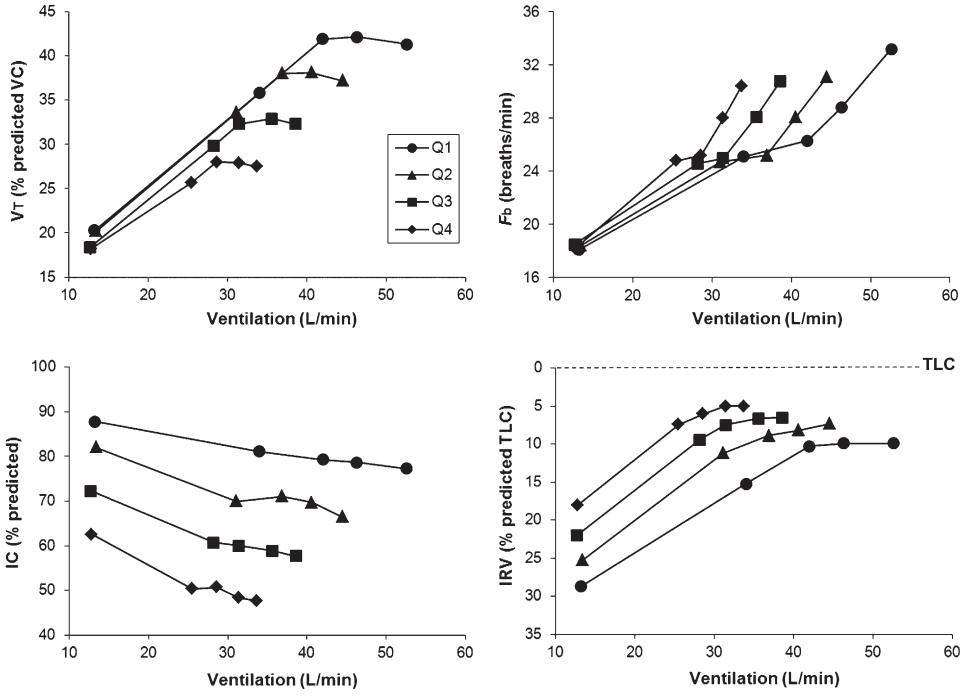

FIGURE 4. VT, *F*b, dynamic IC, and IRV are shown plotted against minute ventilation ($\dot{V}E$) during constant work rate exercise. Note the clear inflection (plateau) in the VT/$\dot{V}E$ relationship, which coincides with a simultaneous inflection in the IRV. After this point, further increases in $\dot{V}E$ are accomplished by accelerating *F*b. Data plotted are mean values at steady-state rest, isotime (ie, 2 min, 4 min), the VT/$\dot{V}E$ inflection point, and peak exercise. See Figure 1 and 2 legends for expansion of abbreviations.

age, height, BMI, sex, smoking history, and COPD duration. Cross-sectional comparisons of FRC and TLC showed that lung hyperinflation increased progressively and that IC correspondingly decreased from Q1 to Q4.

During the high-intensity CWR test, peak $\dot{V}E$ and peak $\dot{V}O_2$ progressively diminished as resting IC decreased. Interestingly, the pattern of change in $\dot{V}E$ and $\dot{V}O_2$ with time (relative to individual peak $\dot{V}E$ and peak $\dot{V}O_2$, respectively) was remarkably similar despite the considerable variation in resting pulmonary function tests across quartiles. Although exercise intolerance is multifactorial in COPD, this study confirms the central importance of respiratory mechanical factors.[1-5] In patients with expiratory flow limitation, the resting IC (and not vital capacity) dictates the operating limits for VT expansion during exercise. Thus, for the group as a whole and for patients within each quartile, the resting IC correlated well with the peak VT and $\dot{V}E$ achieved during CWR exercise. Predictive equations for peak $\dot{V}E$ derived from the resting IC ($18.9 \times IC$) and the FEV_1 ($32.5 \times FEV_1$) were comparable across quartiles, but the resting IC was more accurate in predicting peak $\dot{V}E$ in Q4.

Dynamic pulmonary hyperinflation was present in the majority of patients. The distribution of change in ICdyn was largely similar in each quartile (Fig 3); dynamic hyperinflation was present in 93%, 89%, 88%, and 76% of subjects in Q4, Q3, Q2, and Q1, respectively. Similar decreases in IC (from rest to peak) occurred over progressively smaller ranges of $\dot{V}E$ from Q4 to Q2. The extent of dynamic hyperinflation was significantly less in Q1 than in Q4, but the difference in magnitude disappeared only if those with measurable decreases in IC were evaluated. The combination of resting FEV_1/FVC and IC % predicted explained only a small part of the variance in the extent of dynamic hyperinflation during exercise. Our inability to accurately predict the magnitude of dynamic hyperinflation from resting pulmonary function parameters likely reflects the fact that these tests provide little information about the extent of expiratory flow limitation or heterogeneity in mechanical time constants and their interaction with breathing pattern.[20]

In tandem with the diminishing resting IC and its further reduction during exercise in the majority, breathing pattern became increasingly more shallow and rapid, and peak $\dot{V}E$ was increasingly curtailed from Q1 to Q4. Thus, in each quartile, VT expanded to reach a maximal value of ~75% of the concurrent ICdyn (or a minimal IRV of ~5% to 10% of the TLC) with attendant acceleration of breathing frequency. The submaximal $\dot{V}E$ at which the VT inflection or plateau occurs depended on the resting IC.

Table 3—*Measurements at the VT/V̇E Inflection Point During Exercise*

	Q4 (n = 99)	Q3 (n = 101)	Q2 (n = 102)	Q1 (n = 100)	ANOVA *P* Value
Exercise time, min	2.6 ± 1.5	2.6 ± 1.6	2.8 ± 1.5	3.1 ± 1.6	.042
Dyspnea, Borg units	3.6 ± 1.8	3.1 ± 1.6	3.2 ± 1.7	3.3 ± 1.9	.336
$\dot{V}O_2$, L/min	0.87 ± 0.27[A]	0.98 ± 0.32[A,B]	1.11 ± 0.36[B]	1.25 ± 0.40[C]	< .0005
V̇E, L/min	28.6 ± 7.7[A]	31.4 ± 8.9[A]	36.9 ± 10.8[B]	42.0 ± 11.2[C]	< .0005
V̇E, % peak	86 ± 12	84 ± 14	84 ± 14	82 ± 15	.274
*F*b, breaths/min	25.2 ± 4.8	25.0 ± 5.6	25.2 ± 6.5	26.3 ± 6.3	.371
VT, L	1.16 ± 0.30[A]	1.29 ± 0.35[A]	1.53 ± 0.49[B]	1.66 ± 0.48[B]	< .0005
VT/ICdyn, %	77 ± 15	74 ± 13	74 ± 12	73 ± 14	.192
ICdyn, L	1.55 ± 0.43[A]	1.77 ± 0.44[B]	2.09 ± 0.63[C]	2.29 ± 0.59[D]	< .0005
ΔICdyn inflection-rest, L	−0.37 ± 0.29	−0.35 ± 0.32	−0.31 ± 0.41	−0.25 ± 0.38	.065
IRV, L	0.39 ± 0.31[A]	0.48 ± 0.28[A,B]	0.56 ± 0.31[B,C]	0.63 ± 0.38[C]	< .0005
IRV, % TLC	5 ± 4[A]	6 ± 4[A,B]	7 ± 4[B,C]	9 ± 5[C]	< .0005
EELV, % predicted TLC	101 ± 18[A]	91 ± 17[B]	86 ± 15[B,C]	81 ± 17[C]	< .0005

Data are presented as mean ± SD. The letters A, B, C, and D indicate the following: means with the same letters are similar, and means with different letters are significantly different from each other after Bonferroni adjustment for multiple comparisons ($P < .05$). See Table 1 and 2 legends for expansion of abbreviations.

A minority (58 of 427) of our sample did not show any decrease in ICdyn during exercise. The small size of this group made any interquartile comparisons difficult. However, dyspnea-V̇E, dyspnea-VT/ICdyn and VT/ICdyn-V̇E relationships during exercise and measurements of dyspnea intensity, VT/ICdyn, and V̇E percent peak at the VT/V̇E inflection point were similar in nonhyperinflators to that of the majority who did demonstrate dynamic hyperinflation.

In keeping with worsening mechanical impairment (as indicated by diminishing resting IC), exertional dyspnea intensity ratings were higher at a given V̇E from Q1 to Q4 (Fig 5). These differences disappeared when the peak achievable V̇E was taken into account.

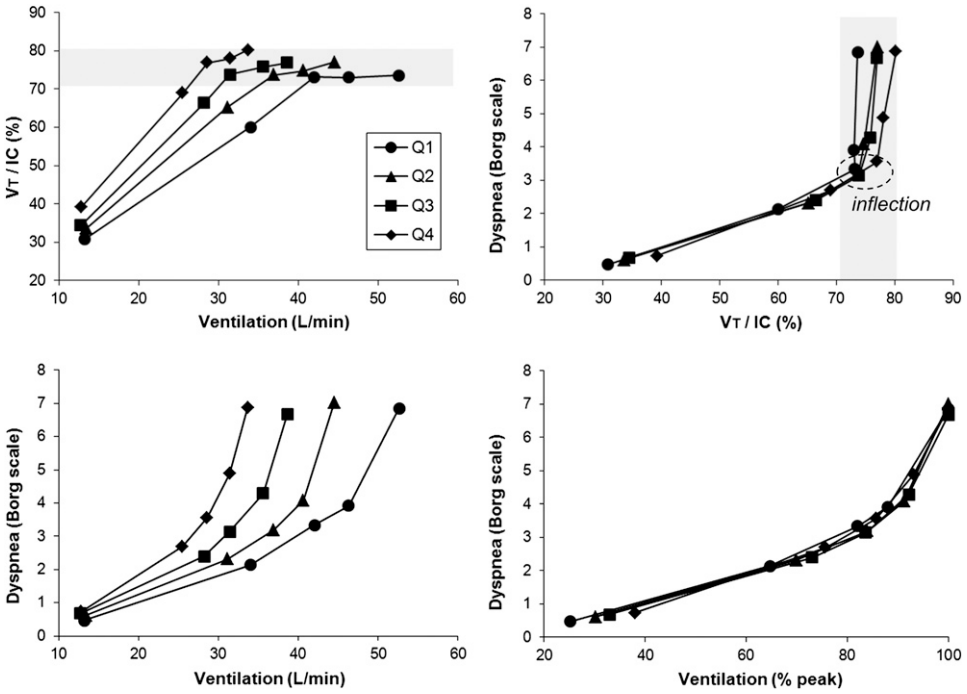

FIGURE 5. Interrelationships are shown among exertional dyspnea intensity, the VT/IC ratio, and ventilation. After the VT/IC ratio plateaus (ie, the VT inflection point), dyspnea rises steeply to intolerable levels. The progressive separation of dyspnea/V̇E plots with worsening quartile is abolished when ventilation is expressed as a percentage of the peak value. Data plotted are mean values at steady-state rest, isotime (ie, 2 min, 4 min), the VT/V̇E inflection point, and peak exercise. See Figure 1, 2, and 4 legends for expansion of abbreviations.

Regardless of baseline airway obstruction, dyspnea intensity increased sharply when V_T reached ~75% of the concurrent ICdyn, corresponding to a $\dot{V}_E$ of ~82% to 86% of the peak value. Thus, the relation between the increase in dyspnea and the increase in V_T/ICdyn was remarkably similar across all quartiles. This response appeared to be biphasic in each quartile; dyspnea rose linearly to moderate levels (3.1-3.7 Borg units) over the first 3 min (2.6-3.1 min) of exercise (phase 1) but increased sharply (phase 2) after the V_T inflection/plateau.

Why does dyspnea intensity rise more abruptly after V_T/ICdyn (and IRV) reaches a critically reduced value? At this point, V_T is positioned close to TLC where there is increased elastic/threshold loading of the functionally weakened inspiratory muscles. The accompanying tachypnea (and increased velocity of shortening) further weakens the overburdened respiratory muscles, and perceived effort rises in tandem. We have previously argued that in severe COPD, the inability to further expand V_T in the face of increasing central neural drive (neuromechanical uncoupling) contributes to the intensity and quality of dyspnea.[3,4] The current study suggests that similar mechanisms are at play across a range of COPD severity, the only difference being that the onset of this neuromechanical uncoupling occurs at a progressively lower $\dot{V}_E$ as resting IC declines.

The present study has limitations to note. The presence of lung hyperinflation (FRC ≥ 120% predicted) was an entry criterion; therefore, the results may not be generalizable to patients without lung hyperinflation. However, we believe that our study population was broadly representative. Based on recent cross-sectional analysis in a large COPD cohort,[21] resting lung hyperinflation was present in the majority of patients with moderate to severe COPD. We have few data on the severity of pulmonary gas exchange abnormalities (eg, exercise hypercapnia), which may further influence dyspnea perception in COPD.[22]

Conclusions

The resting IC importantly influences ventilatory capacity, breathing pattern responses, and the evolution of exertional dyspnea across the range of disease severity in patients with COPD who hyperinflate during exercise. Progressive reduction of the resting IC with increasing disease severity was associated with the appearance of critical constraints on V_T expansion and attendant increase in dyspnea at a progressively lower ventilation during exercise. Regardless of baseline differences in pulmonary function, there was a consistent steep rise in exertional dyspnea intensity to intolerable levels once V_T reached ~75% of the concurrent ICdyn.

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Dr O'Donnell: contributed to the study design and conduct as principal investigator of the original multicenter trials, the original idea for the current analysis and interpretation of the results, and the writing of the manuscript.

Dr Guenette: contributed to the data analysis and preparation for presentation and writing of the manuscript.

Dr Maltais: contributed to the study design and conduct as principal investigator of the original multicenter trials and the writing of the manuscript.

Ms Webb: contributed to the data analysis and preparation for presentation and writing of the manuscript.

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