Simplified Detection of Dynamic Hyperinflation*

Arthur F. Gelb, MD, FCCP; Carlos A. Gutierrez, MD, MSc; Idelle M. Weisman, MD; Randy Newsom, CPFT, RCP; Colleen Flynn Taylor, MA; and Noe Zamel, MD, FCCP

Study objective: To detect dynamic hyperinflation by comparing reduction in inspiratory capacity (IC) during both paced hyperventilation and cycle ergometry in patients with moderate-to-severe COPD, studied before and after acute bronchodilation.

Methods: IC and FEV₁ were measured before and after metronome-paced hyperventilation at twice the resting respiratory rate for 20 s in 16 patients with COPD before and after 54 μg aerosolized ipratropium bromide (IB). We also studied the same 16 patients before and after administration of 54 μg aerosolized IB during symptom-limited incremental cycle ergometry when the final respiratory rate was also twice the resting rate.

Results: Resting IC was 2.23 ± 0.53 L (mean ± SD), and the mean decrease in IC from baseline was 0.36 ± 0.25 L after exercise (p < 0.001), and not significantly different (p = 0.64) from mean decrease in IC of 0.40 ± 0.29 L following hyperventilation. Results following hyperventilation and exercise were similar after bronchodilator. The mean difference for decrease of IC between hyperventilation and exercise was 0.138 L (95% confidence interval, −0.347 to 0.622; r = 0.66, p = 0.006). The decrease in FEV₁ was 0.01 ± 0.13 L after exercise and 0.06 ± 0.18 L after hyperventilation. Separately, baseline and peak end-expiratory and end-inspiratory lung volumes were similar with hyperventilation vs exercise both before and after bronchodilator.

Conclusion: Both metronome-paced hyperventilation and incremental cycle ergometry, when resting respiratory rate was doubled, provoked similar significant decrease in IC, even after administration of 54 μg aerosolized IB. The noninvasive simplicity of hyperventilation for 20 s provides a clinically useful screening surrogate to monitor changes in IC following exercise.

Key words: COPD; dynamic hyperinflation; exercise; hyperventilation; lung function

Abbreviations: CI = confidence interval; EELV = end-expiratory lung volume; EILV = end-inspiratory lung volume; IB = ipratropium bromide; IC = inspiratory capacity; NS = not significant; TLC = total lung capacity

Measurements of FEV₁ have been widely accepted to classify the severity of COPD. Since FEV₁ may be a poor predictor of clinical symptoms, exercise tolerance, and response to bronchodilators, additional signals have been sought. Alternatively, exercise testing with repeated measurements of inspiratory capacity (IC) has been used to detect dynamic hyperinflation and evaluate the response to bronchodilators.

O’Donnell et al1 have provided confirmatory evidence that “Borg dyspneic ratings and measurements of inspiratory capacity (IC) and endurance time during submaximal cycle exercise testing are highly reproducible and responsive to changes in severe COPD.” Previous studies have demonstrated the utility of repeated measurements of IC during exercise to reflect changes in end-expiratory lung volume (EELV),2–4 since total lung capacity (TLC) remains constant after acute bronchodilation and during exercise.5,6 Progressive reduction in IC during exercise reflects dynamic hyperinflation, and is a good predictor of decreased exercise ability as well as increased exertional dyspnea.4 Additionally, peak values of inspiratory esophageal pressures used as a surrogate to estimate effort are relatively constant during multiple measurements of exercise IC.7,8
Changes in IC reflect dynamic hyperinflation and are correlated with breathing frequency in patients with COPD. We suspected increasing breathing frequency would produce changes in IC similar to the change in IC observed during exercise.

The present study was designed to compare metronome-paced hyperventilation, a relatively simple procedure, with incremental symptom-limited cycle ergometry to provoke respiratory rate-induced reduction of IC in patients with COPD. A similar comparison has not been previously reported. We also wanted to evaluate the role of inhaled ipratropium bromide (IB) to blunt the decrease in IC. O’Donnell et al have previously shown greater bronchodilation with IB when compared to inhaled albuterol sulfate in patients with COPD. In a preliminary study, we previously reported that hyperventilation in younger normal subjects resulted in insignificant changes in IC.

**Materials and Methods**

We selected 16 patients with smoking history > 20 pack-years with documented moderate-to-severe COPD, who were in clinically stable condition for at least 6 weeks prior to the present study and were not receiving oxygen. A history of wheezing and/or responsiveness to aerosolized albuterol were not specific inclusion criteria. Patients were instructed to continue all their usual medications, but to withhold short-acting β2-agonists and/or aerosolized IB for 6 h and long-acting β2-agonists for 24 h prior to testing.

After obtaining informed consent, patients underwent lung function studies before and after administration of 270 μg aerosolized albuterol sulfate using techniques and predictive values previously described in detail. We used a pressure-compensated flow plethysmograph (Model 6200; SensorMedics; Yorba Linda, CA).

Subsequently, on a separate day, metronome-paced hyperventilation was initiated in 16 patients with COPD to achieve a respiratory rate twice the baseline rate for 20 s, which was immediately followed by sequential measurement of IC and expiratory spirometry. Near-constant end-tidal carbon dioxide, patients were coached to maintain a respiratory rate synchronous with the metronome. Near-constant dynamic tidal volume during metronome-paced hyperventilation was achieved by having patients observe a graphic display of their breathing pattern. Patients were studied before and after administration of 54 μg aerosolized IB from a metered-dose inhaler. The technique for measuring IC has been previously described.

On a separate day, symptom-limited incremental exercise was initiated in all of the 16 patients with COPD after baseline values were achieved, using an electronically braked cycle ergometer (Ergometrics 800; SensorMedics) before and 15 min after administration of 270 μg aerosolized IB. Following unloading 2-min warm-up, a 10-W workload was increased at 1-min intervals during near-constant pedaling at 50 revolutions per minute. Immediately following symptom-limited peak exercise at constant workload for 1 min, measurements of IC and expiratory spirometry were obtained. During exercise, expired gases were collected and analyzed (Vmax 29; SensorMedics). The protocol is described in Table 1. We also studied 21 younger and 8 older nonsmoking healthy volunteers to evaluate the changes in IC during metronome-paced hyperventilation at twice the resting respiratory rate for 20 s.

**Statistical Analysis**

Repeated-measures analysis of variance was used. For the 16 patients, models with time (baseline and hyperventilation at twice the resting respiratory rate) and before and after bronchodilation were calculated for IC and FEV1. In the same 16 patients who performed both exercise and metronome-paced hyperventilation, repeated mixed-model analysis of variance was calculated for EELV, end-inspiratory lung volume (EILV), and FEV1, both before and after bronchodilation. The Bland-Altman method was used to measure the agreement between hyperventilation and exercise-induced changes in IC. Results are presented as mean ± SD. Analysis was done using statistical software (version 8.02 for Windows; SAS Institute; Cary, NC). Statistical significance was p < 0.05.

**Results**

In the 21 younger healthy volunteers (13 women) aged 37 ± 13 years, baseline IC was 2.98 ± 0.73 L. After 20 s of metronome-paced hyperventilation at twice the resting respiratory rate, IC was 2.90 ± 0.70 L. The mean decrease in IC was 2%. In the eight older healthy volunteers (five women) aged 60 ± 2 years, baseline IC was 2.58 ± 0.65 L. Following 20 s of metronome-paced hyperventilation at twice the resting respiratory rate, IC was 2.56 ± 0.71 L. The mean decrease in IC was 0.8%. In both groups,

**Table 1—Study Design for 16 Patients With Moderate-to-Severe COPD**

<table>
<thead>
<tr>
<th>Variables</th>
<th>Tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visit 1</td>
<td>Complete pulmonary function studies</td>
</tr>
<tr>
<td>Visit 2</td>
<td>Hyperventilation at twice the resting respiratory rate for 20 s; 16 patients before and after 54 μg aerosolized IB</td>
</tr>
<tr>
<td>Visit 3</td>
<td>Symptom-limited cycle ergometry; 16 patients before and after 54 μg IB</td>
</tr>
</tbody>
</table>

**Table 2—Results of Lung Function Studies in 16 Patients With Moderate-to-Severe COPD**

<table>
<thead>
<tr>
<th>Test</th>
<th>Observed</th>
<th>% Predicted</th>
</tr>
</thead>
<tbody>
<tr>
<td>FVC, L</td>
<td>2.90 ± 0.73</td>
<td>87 ± 11</td>
</tr>
<tr>
<td>FEV1, L</td>
<td>1.41 ± 0.42</td>
<td>52 ± 17</td>
</tr>
<tr>
<td>FEV1/FVC, %</td>
<td>49 ± 11</td>
<td></td>
</tr>
<tr>
<td>FRC, L</td>
<td>5.12 ± 1.42</td>
<td>162 ± 22</td>
</tr>
<tr>
<td>RV, L</td>
<td>4.21 ± 1.11</td>
<td>187 ± 34</td>
</tr>
<tr>
<td>TLC, L</td>
<td>7.42 ± 1.53</td>
<td>134 ± 11</td>
</tr>
<tr>
<td>DLCOsb, mL/min/mm Hg</td>
<td>16 ± 4.0</td>
<td>81 ± 19</td>
</tr>
</tbody>
</table>

*Data are presented as mean ± SD. FRC = functional residual capacity; RV = residual volume; DLCOsb = single-breath diffusing capacity of the lung for carbon monoxide.*
intraclass correlation for the two measurements was 0.94 (95% confidence interval [CI], 0.77 to 0.94).

We studied 16 patients with COPD (10 men) aged 69 ± 6 years with a smoking history of 50 ± 27 pack-years. Results of routine lung function studies described in Table 2 are consistent with moderate-to-severe COPD. Following administration of 270 μg aerosolized albuterol sulfate, FEV₁ increased 13 ± 12%.

**Hyperventilation and Dynamic Hyperinflation**

**IC After Metronome-Paced Hyperventilation:** In 16 patients, the metronome-paced respiratory rate at twice the resting rate for 20 s resulted in a significant decrease in IC from 2.23 ± 0.53 to 1.83 ± 0.53 L (p < 0.001). The resting respiratory rate was 16 ± 3 breaths/min, and the metronome-paced respiratory rate was 30 ± 5 breaths/min. The decrease in IC was 0.40 ± 0.29 L (Table 3).

Following administration of 54 μg aerosolized IB in the 16 patients, there was a significant increase in baseline IC of 0.15 ± 0.35 L (p = 0.03). FEV₁ increased from 1.42 ± 0.41 to 1.63 ± 0.53 L in the 16 patients with COPD who underwent both hyperventilation and exercise. However, with metronome-paced increased respiratory rate, the decrease in IC was similar to prebronchodilator decrease (p = 0.80) [Table 3; Fig 1].

**Hyperventilation vs Exercise and Dynamic Hyperinflation**

**IC After Exercise vs Hyperventilation:** In 16 patients, prebronchodilator symptom-limited cycle ergometry was achieved at 45 ± 6.0 W, with a respiratory rate of 29 ± 4 breaths/min, minute ventilation of 35 ± 4.5 L/min, and oxygen uptake of 1.1 ± 0.3 L/min. Following exercise, the decrease in IC was 0.36 ± 0.25 L from baseline, with an increase in respiratory rate 1.9 ± 0.3 times the resting respiratory rate. In these 16 patients, metronome-paced hyperventilation at twice the resting respiratory rate caused IC to decrease 0.40 ± 0.29 L similar to exercise (p = not significant [NS]) [Table 3, Fig 1].

After administration of 54 μg aerosolized IB, the decrease in IC was 0.32 ± 0.23 L following exercise to 43 ± 5 W, minute ventilation was 33 ± 4 L/min, respiratory rate was 30 ± 4 breaths/min, and oxygen uptake was 0.9 ± 0.3 L/min. This was similar to the decrease in IC of 0.39 ± 0.29 L following metronome-paced hyperventilation at twice the resting respiratory rate for 20 s (p = NS) [Table 3, Fig 1].

**Correlation Between Hyperventilation and Exercise:** Before bronchodilator, the mean difference between the peak change in IC comparing hyperventilation and exercise was 0.04 L (95% CI, -0.419 to 0.503).
to 0.619 L; \( r = 0.41, p = 0.115 \). After bronchodila-
tor, the mean difference between the peak change in
IC comparing hyperventilation and exercise was 0.07
L (95% CI, -0.347 to 0.622 L; \( r = 0.66, p = 0.006 \)).

Bland and Altman Method for Assessing Agree-
ment Between Hyperventilation vs Exercise

Results demonstrate bias for hyperventilation in-
duced greater decrease in IC both before (100 mL)
and after (130 mL) nebulized IB vs exercise (Fig 2).
Furthermore, with the exception of one outlier, all
values were within \( \pm 2 \) SD and the majority of
observations were within 1 SD of mean difference.

Effect of Hyperventilation and Exercise on \( \text{FEV}_1 \)

Prebronchodilator resting \( \text{FEV}_1 \) was 1.47 \( \pm 0.49 \)
L, and with hyperventilation there was an insignifi-
cant (p = NS) decrease in \( \text{FEV}_1 \) of 0.06 \( \pm 0.02 \) L.
Following cycle ergometry, the decrease in \( \text{FEV}_1 \)
was 0.01 \( \pm 0.10 \) L (p = NS).

\( \text{EELV and EILV} \)

Prebronchodilator baseline EELV equivalent to
functional residual capacity was 70 \( \pm 7 \)% of TLC in
16 patients, who underwent both hyperventilation
and cycle ergometry testing (Table 4; Fig 3). EILV
was 82 \( \pm 7 \)% of TLC. Following metronome-paced
hyperventilation, EELV was 76 \( \pm 6 \)% of TLC and
EILV was 88 \( \pm 5 \)% of TLC (p < 0.001). Following
the administration of 54 \( \mu \text{g} \) IB, baseline EELV was
69 \( \pm 6 \)% TLC and EILV was 82 \( \pm 6 \)% TLC; after
hyperventilation, EELV was 76 \( \pm 6 \)% TLC and
EILV was 88 \( \pm 6 \)% TLC. After bronchodilator ad-
ministration, these changes are similar to prebron-
chodilator changes (p = 0.37). Thus, acute bron-
chodilation failed to blunt the increase in EELV and
EILV percentage of TLC following hyperventilation.

Prebronchodilator and preexercise baseline EELV
and EILV were 71 \( \pm 6 \)% of TLC and 82 \( \pm 7 \)% of TLC,
respectively. Following exercise, EELV was 74 \( \pm 6 \)%
of TLC and EILV was 92 \( \pm 5 \)% of TLC (p = 0.03).
Following bronchodilation with 54 \( \mu \text{g} \) of IB, baseline
EELV and EILV were 69 \( \pm 6 \)% of TLC and 81 \( \pm 7 \)% of TLC, respectively; after exercise, EELV
and EILV were 73 \( \pm 6 \)% of TLC and 89 \( \pm 6 \)% of
TLC, respectively. The increase in EELV from
baseline was greater for hyperventilation compared
to exercise (p = 0.01), and was not blunted by
bronchodilation with 54 \( \mu \text{g} \) aerosolized IB (for
EELV, p = 0.4) [Table 4; Fig 3]. Increases in EILV
following hyperventilation vs exercise were similar
(p = 0.6), and were significantly greater than base-
line (p < 0.001) and not blunted by bronchodilator
(p = 0.5).

\[
\begin{array}{|c|c|c|c|}
\hline
& \text{Hyperventilation, % TLC} & \text{Exercise, % TLC} \\
\hline
& \text{Baseline} & \text{Peak} & \text{Baseline} & \text{Peak} \\
\hline
\text{Before 54 \( \mu \text{g} \) IB} & & & & \\
\hline
\text{EELV} & 70 \pm 7 & 76 \pm 6 & 71 \pm 6 & 74 \pm 6 \\
\text{EILV} & 82 \pm 7 & 88 \pm 5 & 82 \pm 7 & 92 \pm 5 \\
\hline
\text{After 54 \( \mu \text{g} \) IB} & & & & \\
\hline
\text{EELV} & 69 \pm 6 & 76 \pm 6 & 69 \pm 6 & 73 \pm 6 \\
\text{EILV} & 82 \pm 6 & 88 \pm 6 & 81 \pm 7 & 89 \pm 6 \\
\hline
\end{array}
\]

*Data are presented as mean \( \pm \) SD. There was a significant increase
in EELV and EILV from baseline that was similar following
hyperventilation and exercise, and was not blunted by 54 \( \mu \text{g} \) of
aerosolized IB.

\[
\text{Figure 2. Bland and Altman method plotting the net difference}
\text{in decrease in IC vs mean decrease in IC following hyperventi-
lation and cycle ergometry both before (top) and after (bottom)}
\text{aerosolized IB. There was a bias for greater decrease in IC}
\text{following hyperventilation, and the majority of observations fell}
\text{within 1 SD. BD = bronchodilator; see Figure 1 legend for}
\text{expansion of abbreviation.}
\]
Discussion

The present study in 16 patients with COPD with moderate-to-severe expiratory airflow limitation demonstrated the provocative ability of metronome-paced hyperventilation at twice the resting respiratory rate for 20 s to induce a significant decrease in IC. This was similar as a group to the decrease in IC following symptom-limited incremental cycle ergometry when the baseline respiratory rate was also doubled. The noninvasive simplicity of hyperventilation for 20 s provided a clinically useful screening surrogate to monitor changes in IC following exercise. Furthermore, the significant decrease in IC following hyperventilation and exercise was not blunted by acute bronchodilation with 54 μg aerosolized IB.

The correlation between the decrease in IC following cycle ergometry vs hyperventilation was strengthened after aerosolized IB with reduction in vagal tone. However, a high correlation is not a good test of agreement since it reflects only the relationship between two variables. Agreement is better tested using the Bland and Altman method (Fig 2). Results suggest hyperventilation is more sensitive than cycle ergometry to detect decrease in IC both before and after aerosolized IB.

Additionally, increases in EELV and EILV were similar with hyperventilation and exercise, and not blunted with acute bronchodilation with inhaled IB. IB is presumably but not clearly proven a greater bronchodilator than inhaled albuterol sulfate in patients with COPD. Increase EELV undergo symptom limited exercise, we and others have noted the increase in respiratory rate to approximately double baseline was primarily responsible for increased minute ventilation. Not surprisingly, O'Donnell et al reported respiratory frequency strongly correlated with Borg dyspnea scores, and dynamic hyperinflation strongly correlated with breathlessness during exercise in COPD.

It has been previously reported that following exercise, a decrease in EELV is associated with an improvement in breathlessness symptom score after acute bronchodilation in patients with COPD. During exercise and hyperventilation, EELV increases at the same rate; but since the starting point for EELV is lower after acute bronchodilation, the peak is also lower when the same load is reached. A similar phenomenon occurs with EILV. However, no interaction has been shown for the effect of bronchodilators on either EELV or EILV. The rationale to measure IC during exercise is that among all variables studied, changes in IC (baseline and peak exercise) not only showed good reproducibility, but correlated best with changes in Borg dyspnea scale.

In the present study, the failure to achieve reduction in EELV and EILV after administration of IB (or an equivalent increase in IC) at all levels (baseline and peak exercise and after hyperventilation) is in contrast to results previously reported. However, 500 μg nebulized IB was used, which is approximately 10 times the dose used in the present study.

Attempts have been made to find simpler and less expensive tests to objectively assess exercise limitation and response to bronchodilator therapy. Marin et al showed that IC decreased, using a standard 6-min walk test, as with standard exercise testing among patients with COPD. We are not aware of previously published studies using a standardized
method of hyperventilation and comparison with exercise in patients with COPD. Metronome-paced hyperventilation at twice the resting breathing frequency is a simple maneuver that can be carried out by almost any patient and can be done in any respiratory laboratory. If the decrease in IC following metronome-paced hyperventilation is as reproducible as that following exercise,\textsuperscript{1,14,17} it might be used as a screening surrogate for exercise-induced dynamic hyperinflation and to assess response to bronchodilators in patients with COPD. Normal age-matched control subjects in the present and previous study\textsuperscript{9} did not decrease IC with exercise, as do patients with COPD.\textsuperscript{17} Furthermore, since the extent of dynamic hyperinflation and decrease in IC with exercise is related to resting IC,\textsuperscript{17} hyperventilation testing should be provocative in patients with COPD with moderate-to-severe expiratory airflow limitation.

The response to bronchodilatation with 270 \( \mu \)g aerosolized albuterol sulfate and to that with 54 \( \mu \)g aerosolized IB was not considered an inclusion, and the median increase in FEV\(_1\) percentage of predicted was 5\%, and only 2 of 16 patients with COPD were responders according to American Thoracic Society criteria.\textsuperscript{18} In a previous study,\textsuperscript{14,16} of 29 patients with COPD (55\%) met the American Thoracic Society criteria\textsuperscript{18} for responders following administration of 500 \( \mu \)g aerosolized IB, yet there was poor correlation with exercise endurance time. Lack of response or poor reproducibility of FEV\(_1\) are among the reasons that prompted the search for other objective markers of abnormal lung function that correlate with symptoms and are responsive and reproducible in patients with COPD.\textsuperscript{1,2,14,16,19,20}

If confirmed by other investigators, we suspect the decrease in IC obtained during metronome-paced hyperventilation at twice the resting respiratory rate for 20 s may be used as a screening surrogate for exercise testing in the evaluation and response to dynamic hyperinflation before and after aerosolized bronchodilator in patients with COPD with moderate-to-severe expiratory airflow limitation. The goal of the present study was not to usurp standardized cardiopulmonary testing with its inherent merits, but rather to simply the detection of dynamic hyperinflation using metronome-paced hyperventilation as a screening surrogate.

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