Diaphragm efficiency estimated as power output relative to activation in chronic obstructive pulmonary disease

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Finucane KE, Singh B. Diaphragm efficiency estimated as power output relative to activation in chronic obstructive pulmonary disease. J Appl Physiol 113: 1567–1575, 2012. First published September 20, 2012; doi:10.1152/japplphysiol.01453.2011.—Muscle efficiency increases with fiber length and decreases with load. Diaphragm efficiency (Effdi) in healthy humans, measured as power output (Wdi) relative to the root mean square of diaphragm electromyogram (RMSdi), increases with hyperpnea due to phasic activity of abdominal muscles acting to increase diaphragm length at end expiration (Ldi ee) and decrease inspiratory load. In chronic obstructive pulmonary disease (COPD), hyperpnea may decrease Effdi if ln(Effdi) were negatively correlated (but not compared with controls; diaphragm radius of curvature at end inspiration and Rdi ee with hyperpnea). Flattening of the diaphragm during inspiration is reduced due to relaxation of expiratory muscles and the consequent decrease in Pg during inspiration (16). In healthy subjects, progressive hypercapnic hyperpnea to an end-tidal PCO2 (PETCO2) of ~60 Torr was associated with progressive increases in Effdi and Ldi ee and decreases in ΔPg (16). The latter changes, particularly the increase in Ldi ee, correlated with the increase of Effdi (16).

In our previous studies (15, 16), Effdi was estimated as the ratio of power output to the amount of electrical activity of the diaphragm, as follows:

\[
\text{Eff\textsubscript{di}} = \frac{\Delta P\text{dimean} \cdot \Delta V\text{di} \cdot T\text{i}^{-1} \cdot \text{RMS}^{1}_{\text{di}}}{1}
\]

where ΔPdimean is the mean increase in transdiaphragmatic pressure during inspiration, ΔVdi is the contribution of the diaphragm to inspiratory volume change, Ti is inspiratory duration, and RMSdi is the root mean square of the crural diaphragm electromyogram (EMG). This expression assumes that RMSdi is linearly related to the O2 consumption of the diaphragm (V\text{O2}\text{di}) up to ~75% maximum activation. The bases of this assumption have been examined previously (16).

In COPD, Ldi ee can be decreased (18, 43) and may decrease further with hyperpnea due to dynamic hyperinflation, i.e., an increase with hyperpnea in end-expiratory lung volume (EELV) attributed to airflow obstruction and a decreased expiratory time (Te) (32). Dynamic hyperinflation increases the threshold and elastic loads on the diaphragm during inspiration (27, 36, 46). Considering the effects of Ldi and diaphragm load on muscle efficiency, it is likely that, in subjects with COPD, Eff\textsubscript{di} may not increase normally with hyperpnea. Additionally, flattening of the diaphragm during inspiration (43) may decrease Eff\textsubscript{di} because a given level of ΔPdi and equivalently of ΔVdi·Ti\textsuperscript{-1} is likely to require an increased level of activation.

We hypothesized that, in COPD, Eff\textsubscript{di} may decrease with hyperpnea due to shortening and flattening of the diaphragm and to increased inspiratory loads. To examine this hypothesis, we measured Eff\textsubscript{di}, L\textsubscript{di}, and diaphragm radius of curvature (Rdi) in 6 subjects with COPD when breathing air and again at intervals during progressive hypercapnic hyperpnea. The results were compared with those of six healthy subjects measured under the same conditions and reported in part previously.
In the subjects with COPD, Eff_{di} and L_{di,ee} were constant, and R_{di} at end inspiration (R_{di,ei}) increased with hyperpnea.

**METHODS**

The study was approved by the Institutional Ethics Committee. The subjects were six ex-smokers with chronic airflow obstruction and a mean forced expiratory volume in 1 s (FEV_{1}) of 54% predicted. Informed, written consent was obtained from all subjects.

**Measurements.** The methods of measurement and data analysis have been described previously (14–16, 39, 43–45). Lung volumes for each breath, mean expiratory flow (V˙_E), tidal volume (VT), flow-volume relationships during tidal breathing, T_{I}, T_{E}, and breath duration, were measured with a pneumotachograph. Esophageal pressure (Pes), Pp, and RMS_{di} were measured with a single nylon catheter (Gaeltec) with two pressure transducers 20 cm apart, between which were 10 stainless steel electrodes, which were positioned across the gastroesophageal junction and wired as 8 overlapping bipolar pairs (16). Lateral fluoroscopic images of the diaphragm and adjacent chest wall were recorded digitally at a frame rate of 7.5 per second. Magnification and distortion of images in each subject were defined using fluoroscopic images of a radiopaque grid of precise squares (16, 44). Signals from a Geiger-Muller (GM) radiation counter were used to define onset and offset of fluoroscopy. Fluoroscopic images; pressures, flow, volume change, PCO₂, percent inspired O₂, and the GM signal; and diaphragm EMG signals, flow, and the GM signal were recorded continuously on three separate computers during each period of measurement (16).

**Protocol.** Subjects stood erect with arms elevated and hands resting on the head with the left chest wall touching the image intensifier while breathing through a pneumotachograph and low-resistance two-way valve open to either atmosphere or a bag containing oxygen while breathing through a pneumotachograph and low-resistance two-way valve open to either atmosphere or a bag containing oxygen. Images of the right hemidiaphragm were corrected for distortion and magnification (16). Lateral fluoroscopic images of the diaphragm and adjacent chest wall were recorded digitally at a frame rate of 7.5 per second. Magnification and distortion of images in each subject were defined using fluoroscopic images of a radiopaque grid of precise squares (16, 44). Signals from a Geiger-Muller (GM) radiation counter were used to define onset and offset of fluoroscopy. Fluoroscopic images; pressures, flow, volume change, PCO₂, percent inspired O₂, and the GM signal; and diaphragm EMG signals, flow, and the GM signal were recorded continuously on three separate computers during each period of measurement (16).

**Data analysis.** Data from each computer system was collated, and, for each breath, mean expiratory flow (V̇_e), tidal volume (V_t), flow-volume relationships during tidal breathing, T_i, T_e, and breath duration were measured. Minute ventilation was expressed as percent predicted maximum voluntary ventilation (% predicted MVV), calculated as 35 times predicted FEV_{1}. ∆P_{d_i}mean was computed as mean inspiratory ∆P_{d_i} corrected, in each subject, for the mean P_{d_i,ee} measured when breathing air. The end-expiratory values of P_g and Pdi were measured as the maximum values within 200 ms of end expiration. ∆P_{d_i} with maximum, static inspiratory efforts (∆P_{d_i,max}) was measured as previously described (16). The dynamic, positive end-expiratory pressure during tidal breathing (PEEP_{dyn}) was estimated as the ∆Pes between the maximum value of Pes near end expiration [P_{es,sec}(max)] and the value at onset of inspiratory flow (34). The contribution of expiratory muscle activity to PEEP_{dyn} was estimated from the rise in P_{g} during expiration (17, 34, 52). EMG segments of duration near the onset, middle, and end of each inspiration were analyzed using the methods of Beck et al. (4–6) and Sinderby et al. (40–42), and the average RMS_d of each inspiration was calculated. The RMS_d of any preinspiratory EMG was measured. The maximum value of RMS_d (RMS_{d,max}) was taken as the mean of the three to four highest values obtained during inspirations to TLC. Images of the right hemidiaphragm were corrected for distortion and magnification (16, 44) and L_{di,ee}, L_{di} at end inspiration (L_{di,ei}), ∆L_{di}, and ∆V_{di} were computed using the methods described previously (15, 16, 39, 43–45). Diaphragm muscle shortening with inspiration was estimated, assuming that the central tendon comprised 25% of L_{di,ee} measured at EELV when breathing air [functional residual capacity (FRC)] (9). R_{di} and the cross-sectional area of the abdominal rib cage (A_{ab,ab}) in the two groups were measured when breathing air and at maximum ventilation from images of the right hemidiaphragm corrected for distortion and magnification. The hemidiaphragm was assumed to be a segment of a circle subtending a central angle (θ) and bounded by an arc (S), the length of the lung-apposed diaphragm between the anterior and posterior costophrenic angles, and a chord (C), the distance between the costophrenic angles. R_{di} was calculated from S and C as follows:

\[ R_{di} = S/\theta \]

\[ S/C = \theta/2(\sin\theta/2) \]

where θ, in radians, is >0 and <π, and S and C are in cm. The right-hand term of Eq. 3 was solved numerically for all measured values of S/C. A_{ab,ab} was calculated as previously described (44) using C as the sagittal diameter of the abdominal rib cage.

**Statistical analysis.** In each subject, the measured and computed variables from each breath were normalized relative to the mean value of the variable measured when breathing air (16). The differences between mean values of variables within COPD and healthy subjects at different levels of ventilation were examined using one-way ANOVA or, where the data were not distributed normally, by ANOVA on ranks. Differences of variables between groups were examined by comparing the absolute values of particular variables using unpaired t-tests, or Mann-Whitney rank sum tests, where the data were not distributed normally. Relationships between variables within each group were examined using linear regression analysis with logarithmic transformation of data, which were not normally distributed; differences of these relationships between groups were examined by comparing regression coefficients using unpaired t-tests. In each subject, the linearity of RMS_{d} in P_{ETCO₂} was examined by measuring the mean RMS_{d} and P_{ETCO₂} of each breath during hypercapnia, excepting the first four to six and inspiratory capacity (IC) breaths and fitting these data with polynomial regressions. The data were not linear beyond P_{ETCO₂} values of 58 and 54 Torr in two of the subjects. Values of RMS_{d} beyond the linear range were corrected using the regression constants and coefficients fitted to data in the linear range in each subject. Results were analyzed using SigmaPlot statistical software (version 11) and are reported as means and SD, unless otherwise stated. Significance was defined as P < 0.05.

**RESULTS**

**Subjects.** Anthropometric data and lung volumes for the COPD and healthy subjects are shown in Table 1. Efficiency. The components of Eff_{di} in the COPD and healthy subjects and their change with ventilation are shown in Fig. 1. Mean minute ventilation when breathing air was 14.8 ± 2.3 (SD) and 11.8 ± 2.4% predicted MVV in the COPD and healthy subjects, respectively (P = 0.05). Maximum ventilation was similar in the two groups, approximating 42% predicted MVV. Relative to measurements when breathing air, diaphragm flow (∆Vdi·T_i), pressure (∆P_{d_i,mean}), and Wdi increased at a similar rate with hypercapnic hyperpnea in the COPD and healthy subjects (Fig. 1, A–C), and the absolute values at maximum ventilation were not different between groups (P = 0.86, 0.47, and 0.8, respectively). Normalized RMS_{d} increased more with ventilation in COPD subjects (P = 0.01) (Fig. 1D), and, at maximum ventilation, absolute mean RMS_{d} was greater than in the healthy subjects (P = 0.02).
absolute mean values of $\text{Eff}_{\text{di}}$ measured when breathing air were $18.7 \pm 10.7$ and $13.6 \pm 3.1 \text{cmH}_2\text{O}\cdot\text{l}\cdot\text{s}^{-1}\cdot\text{mV}^{-1}$ in COPD and healthy subjects, respectively ($P = 0.39$). $\text{Eff}_{\text{di}}$ did not change with ventilation in the COPD subjects, but increased linearly in the healthy subjects ($r^2 = 0.47$, $P < 0.001$) (Fig. 2). In the healthy subjects, there was a highly significant linear relationship between normalized $\text{Eff}_{\text{di}}$ and $\text{L}_{\text{di ee}}$ normalized with respect to $\text{L}_{\text{di ee}}$ at FRC ($r^2 = 0.62$, $P < 0.001$). Variability of measurements was greater in COPD than healthy subjects. For example, the coefficients of variation of $\text{Pdimean}$ and $\text{RMS}_{\text{di}}$ measured when breathing air were, respectively, 35 and 43% in COPD and 16 and 27% in healthy subjects.

Values are means ± SD; $n$, number of subjects. COPD, chronic obstructive pulmonary disease; BMI, body mass index; VC, vital capacity; FEV$_1$, forced expiratory volume in 1 s; TLC, total lung capacity; RV, residual volume; IC, inspiratory capacity; IC$_{\text{air}}$, IC breathing air; IC$_{\text{di air}}$, IC of the diaphragm breathing air; IC$_{\text{VEmax}}$, IC at maximum ventilation; IC$_{\text{di VEmax}}$, IC of the diaphragm at maximum ventilation. *$P < 0.05$ relative to healthy subjects. †$P < 0.05$ relative to breathing air. The data for healthy subjects are from Ref. 16.
Pdimean) expressed as a percentage of values during maximum, static
and the mean increase in transdiaphragmatic pressure during inspiration
rected for the effect of expiratory muscle activity was 3.0
inspiratory efforts at FRC (Pdimean %max; decreased, and
0.05 relative to baseline. The data for healthy subjects are from Ref. 16.
increased with hypercapnic hyperpnea (Fig. 4). PEEPdyn cor-
residual capacity (FRC) [Pgee(FRC)] in each group, which was set to zero (Pg)
relative to the mean value of Pg at end expiration at functional
shown between ventilation, %pred MVV, and the inspiratory change in gastric
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Pdimean was 17.6
subjects (Fig. 3). In COPD subjects at maximum ventilation,
hyperpnea to a similar degree in the COPD and healthy
loads. Pggee increased with hyperpnea and, in both groups,
was ~5 cmH2O higher at maximum ventilation relative to
when breathing air (P = 0.01 for both). Inspiratory ∆Pg
decreased, and ∆Pdimean %ΔPdimean increased with hypercapnic
hyperpnea to a similar degree in the COPD and healthy
subjects (Fig. 3). In COPD subjects at maximum ventilation,
∆Pdimean was 17.6 ± 11.6%ΔPdimean. In COPD subjects, mean
PEEPdyn %ΔPdimean and preinspiratory RMSdidi %RMSdidi max
increased with hypercapnic hyperpnea (Fig. 4). PEEPdyn cor-
rected for the effect of expiratory muscle activity was 3.0 ±
2.5%ΔPdimean at maximum ventilation and <1%ΔPdimean at all
other levels of ventilation. Preinspiratory RMSdidi %RMSdidi max
correlated with Pgee (P < 0.001) and with Pesee(max) (P =
0.003) (Fig. 5, A and B, respectively). These parameters reflect
the activity of the abdominal muscles. However, any preinspira-
tory activity of the diaphragm could have been associated with
diaphragm shortening and contributed to the end-expiratory
increase of Pgee potentially strengthening the correlation be-
 tween preinspiratory RMSdidi and Pgee. This is not the case with
Pesee(max), which occurred before the onset of preinspiratory
diaphragm activity. Together, these results suggest that dia-
phragm and abdominal muscle activity near end expiration increased proportionately with hyperpnea.

Ldi. Breathing air, average Ldi ee was 25.5 ± 1.8 cm in
COPD and 25.2 ± 2.3 cm in healthy subjects. Ldi ee did not
change with ventilation in COPD, but increased linearly in
healthy subjects (r² = 0.52, P < 0.001) (Fig. 6). Consistent
with these results, IC did not change with ventilation in COPD
and increased in healthy subjects (Table 1). At the two highest
levels of ventilation, Ldi ei was the same as that at TLC in each
group (Fig. 6). Ldi at TLC was similar in the two groups, while
Ldi at residual volume was decreased in COPD relative to
healthy subjects (P = 0.05) (Fig. 6). Estimated mean muscle
length at end inspiration with maximum hyperpnea relative to
muscle length at FRC was 0.69 ± 0.15 and 0.68 ± 0.10 in
COPD and healthy subjects, respectively.

Diaphragm and abdominal ribcage shape. In COPD, Rdi at
end expiration (Rdi ee) was similar to that of healthy subjects
and was independent of hyperpnea; at maximum ventilation,
Rdi ei was greater than Rdi ee (P = 0.03) and greater than in the
healthy subjects (P = 0.04) (Table 2). In healthy subjects,
Rdi ee and Rdi ei were independent of hyperpnea (Table 2). In
COPD, the Arc ab at end inspiration [Arc ab(ei)] was greater,
but not significantly greater, than that in healthy, both when
breathing air (0.36 ± 0.1 vs. 0.30 ± 0.05 m², P = 0.22) and at
maximum ventilation (0.39 ± 0.1 vs. 0.32 ± 0.06 m², P =
0.08). The combined data from the COPD and healthy subjects
for Rdi ei and Arc ab(ei) measured when breathing air and at
maximum ventilation showed a high positive correlation (r²
= 0.75) and a negative correlation between Rdi ei and ln(Effdi)
(r² = 0.22, P = 0.01).

Fig. 3. Diaphragm loads in COPD and healthy subjects. Relationships are
shown between ventilation, %pred MVV, and the inspiratory change in gastric
pressure (ΔPg) relative to the mean value of Pg at end expiration at functional
residual capacity (FRC) [Pggee(FRC)] in each group, which was set to zero (A),
and the mean increase in transdiaphragmatic pressure during inspiration
(ΔPdimean) expressed as a percentage of values during maximum, static
inspiratory efforts at FRC (ΔPdimean %max; B). Values are means ± SE. *P <
0.05 relative to baseline. The data for healthy subjects are from Ref. 16.

Fig. 4. Threshold load in COPD subjects. Relationships are shown between
ventilation, %pred MVV, and the decrease of esophageal pressure before the
onset of inspiratory flow (dynamic positive end-expiratory pressure (PEEPdyn)
%ΔPdimean (left ordinate) and preinspiratory RMSdidi (RMSdidi preinsp) expressed
as a percent of maximum RMSdidi (RMSdidi max) (right ordinate). Means ± SE are
shown. *P < 0.05 relative to baseline.
Respiratory flows and timing. During tidal breathing, expiratory flow limitation, evidenced by a monotonic decrease of expiratory flow with volume, was present in all COPD subjects at all levels of ventilation; however, with hyperpnea $V_E$ of tidal breaths increased (Fig. 7). This increase was negatively correlated with the decrease in $T_e$ ($r^2 = 0.65, P < 0.001$) (Fig. 7B). $T_e$ decreased more with hyperpnea in COPD than in healthy subjects: $1.8 \pm 0.8$ vs. $0.7 \pm 0.7$ s ($P = 0.04$). In COPD subjects, expiratory flows during hyperpnea were increased throughout expiration such that average expiratory flow near end expiration increased progressively (Fig. 7C).


\[
V_T \text{ values and } \Delta P_{d_{\text{max}}}.
\]

In COPD subjects, $V_T$ and $\Delta V_d$ increased from $1.3 \pm 0.4$ and $0.77 \pm 0.3$ liters, respectively, on air to $1.8 \pm 0.4$ and $1.0 \pm 0.3$ liters, respectively, at maximum hyperpnea ($P = 0.01$ and 0.26, respectively). In health, $\Delta V_d$ increased from $0.55 \pm 0.11$ liter when breathing air to $1.2 \pm 0.3$ liters at maximum hyperpnea ($P = 0.002$). $\Delta P_{d_{\text{max}}}$ was the same in the COPD and healthy subjects: $84 \pm 14$ and $82 \pm 27$ cmH$_2$O, respectively.

DISCUSSION

The $E_{d_{\text{i}}}$, estimated as power output relative to activation, has not previously been measured in subjects with COPD. The main findings of this study were that, in COPD subjects with moderate airflow obstruction, neither $E_{d_{\text{i}}}$ nor $L_{d_{\text{ei}}}$ increased normally with hyperpnea. In the following sections, we discuss some limitations of the methods and analyses and how $L_{d_{\text{ei}}}$, diaphragm load, and diaphragm shape may have contributed to the different response of $E_{d_{\text{i}}}$ to hyperpnea in COPD and healthy subjects.

Limitations. In this study, the amount of electrical activity of the diaphragm during inspiration, measured as the average $R_{d_{\text{i}}}$, was used as a surrogate for $V_{O_2{d_{\text{i}}}}$. Evidence from other studies (4, 7, 22, 38, 48), as discussed previously (16), suggest that $R_{d_{\text{i}}}$ is linearly related to and defines the change in $V_{O_2{d_{\text{i}}}}$, independent of length up to ~75% maximum activation. At high levels of activation, $R_{d_{\text{i}}}$ progressively underestimates the amount of electrical activity due to superposition of action potentials as firing frequencies and the numbers of motor units recruited increases (4). We found that $R_{d_{\text{i}}}$ was nonlinear in $P_{ET\text{CO}_2}$ during progressive hypercapnea in two COPD subjects; $R_{d_{\text{i}}}$ values in the nonlinear range were corrected (see METHODS). This correction assumes linearity of minute phrenic nerve activity in $P_{CO_2}$, which is the case for dogs up to an arterial $P_{CO_2}$ of 70 Torr (25).

Fig. 5. Diaphragm and abdominal muscle activity at end expiration in COPD. Relationship are shown between $P_{g_{ee}}$ (A) and the end-expiratory zenith of esophageal pressure $[P_{g_{ee \text{max}}}]$ (B) normalized to the mean values at FRC in each subject, and $R_{d_{\text{i}}}$ preinsp normalized to $R_{d_{\text{i}}}$ at baseline. Star = the different response of $E_{d_{\text{i}}}$ to hyperpnea in COPD and healthy subjects.

Fig. 6. Diaphragm lengths ($L_{d_{\text{i}}}$) with hyperpnea. Relationships are shown between ventilation, %pred MVV, and $L_{d_{\text{i}}}$ normalized to the length at FRC in each group, at residual volume (RV), end expiration (ee), end inspiration (ei), and total lung capacity (TLC) in healthy and COPD subjects. Means ± SE are shown. *$P < 0.05$ relative to FRC. #$P < 0.05, L_{d_{\text{ei}}}$ at baseline and at TLC. +$P < 0.05, L_{d_{\text{ee}}}$ COPD relative to healthy subjects. The data for healthy subjects are from Ref. 16.
Table 2. Diaphragm radii of curvature

<table>
<thead>
<tr>
<th>Condition of Measurement</th>
<th>Health</th>
<th>COPD</th>
</tr>
</thead>
<tbody>
<tr>
<td>$R_{\text{di ee}}$: V\text{E}max</td>
<td>11.1 ± 1.0</td>
<td>13.1 ± 3.6</td>
</tr>
<tr>
<td>$R_{\text{di ee}}$: V\text{E}air</td>
<td>11.4 ± 2.4</td>
<td>13.2 ± 4.1</td>
</tr>
<tr>
<td>$R_{\text{di e}}$: V\text{Emax}</td>
<td>11.5 ± 1.7</td>
<td>15.7 ± 7.1</td>
</tr>
<tr>
<td>$R_{\text{di e}}$: V\text{E}air</td>
<td>12.5 ± 3.0</td>
<td>20.3 ± 11.4*†</td>
</tr>
</tbody>
</table>

Values are means ± SD in cm. Radii of curvature of the diaphragm are given in healthy and COPD subjects at end expiration ($R_{\text{di ee}}$) and end inspiration ($R_{\text{di e}}$) measured when breathing air (V\text{E}air) and at maximum ventilation (V\text{Emax}). *P = 0.04, COPD vs. healthy subjects. †P = 0.03, COPD end-inspiration vs. end-expiration at V\text{Emax}.

Eff\text{di} when breathing air was 2.6, 1.7, and 1.7 times greater in three COPD subjects relative to the mean value when breathing air in healthy subjects (16). These values approximate the highest relative increases of Eff\text{di}, with maximum hyperpnea in healthy subjects questioning whether Eff\text{di} in these subjects was already maximal. The high values are unexplained; however, Eff\text{di} did not increase normally with hyperpnea in any of the COPD subjects, while the individual changes of Eff\text{di} at maximum hyperpnea were unrelated to baseline values (P = 0.5). Thus the lack of change of Eff\text{di} with hyperpnea in COPD subjects is not explained by the baseline values when breathing air. This conclusion is supported by the finding that $L_{\text{di ee}}$, the major determinant of Eff\text{di} (15, 16), was also independent of hyperpnea in COPD subjects (Fig. 6). The high values of Eff\text{di} in some COPD subjects may, in part, reflect a systematic variability in both pressure and RMS\text{di} values due to differences in the position of the distal pressure transducer relative to the gastric fluid level and to electrode orientation. This possibility is supported by an unusually low Pg\text{ee} in two of the three subjects and by the high coefficient of variation of Pdi\text{ee} and RMS\text{di} in the COPD subjects. Other factors that may contribute to an increased Eff\text{di} in COPD include an increase in the proportion of more efficient type 1 muscle fibers in the diaphragm (49), deletion of sarcomeres in series (50) with an increase in sarcomere length at FRC, and to phasic activity of expiratory muscles with inspiratory unloading of the diaphragm (16) when breathing air. However, the increase of type 1 fibers in COPD is inversely proportional to FEV\text{1} (49), and, in our subjects, FEV\text{1} was unrelated to Eff\text{di} measured when breathing air. Sarcomere remodeling is thought to be an adaptation to chronic hyperinflation, which, in these subjects, was of minor degree, while the similarity of ΔPg when breathing air relative to healthy subjects (Fig. 3) suggests that any phasic activity of expiratory muscles in the COPD subjects when breathing air was minimal.

In correcting PEEP\text{dyn} for activity of expiratory muscles, we followed the methods validated by others (17, 34, 52), except in two subjects, where the total rise of Pg during expiration exceeded PEEP\text{dyn}, and we assumed that factors other than activation of expiratory muscles, such as relaxation of intercostal-accessory muscles with caudad movement of the abdominal rib cage in early expiration, contributed to the initial increase of Pg. In these two subjects, we assumed that expiratory effort commenced with the onset of flow limitation and measured its contribution to PEEP\text{dyn} as the change in Pg between the onset of a monotonic decrease in expiratory flow and maximum Pg.

The $R_{\text{di}}$ was calculated assuming that the fluoroscopic silhouette of the lung-apposed diaphragm was a segment of a circle. Similar models have been used to define the costal $R_{\text{di}}$ in dogs (8, 11). To examine the error associated with this model, we calculated the area of the segment enclosed by the chord and arc $[\text{area} = R^2/2(\theta - \sin\theta)]$ at end expiration from six breaths in each of the 12 subjects when breathing air and compared these with the values of the same area measured by digital planimetry. The mean areas calculated from the estimated values of $R_{\text{di}}$ and measured by planimetry differed by <10% for both healthy and COPD subjects, suggesting that the estimated values of $R_{\text{di}}$ gave reasonable approximations of the shape of the diaphragm.

$L_{\text{di}}$. Mean Eff\text{di} and $L_{\text{di ee}}$ did not change with hyperpnea in COPD subjects. By contrast, in healthy subjects, both Eff\text{di} and

![Fig. 7. Expiratory flow and hyperpnea in COPD subjects. A: flow-volume loops during tidal ventilation when breathing air and at maximum hyperpnea in one subject. B: relationship between expiratory duration and mean expiratory flow of each breath measured when breathing air and at each level of hypercapnic hyperpnea in the six subjects. C: relationship between minute ventilation and expiratory flow at the onset of the sharp decrease of flow at end expiration. Shown are the mean values and SE at each condition of measurement in the healthy and COPD subjects. *P < 0.05 relative to baseline in each group. #P < 0.05, COPD vs. healthy subjects.](http://jap.physiology.org/doi/10.1152/japplphysiol.01453.2011)
increased with hyperpnea, and there was a highly significant linear relationship between them. The efficiency of muscle in vitro (21, 24, 51) and of the diaphragm in vivo (15) is linearly related to muscle length. Together, these data suggest that the major reason why Eff\textsubscript{di} did not increase with ventilation in COPD subjects was because \( L_{\text{di, ee}} \) did not change with hyperpnea. The results pose two questions. First, why, in these subjects with low ventilation during tidal breathing and an abnormal decrease of \( T_e \) with hyperpnea, did dynamic hyperinflation with a decreased \( L_{\text{di, ee}} \) not occur? Second, why did \( L_{\text{di, ee}} \) not increase with hyperpnea, given that \( P_{\text{GEE}} \) increased with hyperpnea to a similar degree in COPD and healthy subjects? Two changes observed during hyperpnea contributed to maintaining a constant EELV and \( L_{\text{di, ee}} \). First, during hyperpnea, the \( V_e \) of tidal breaths increased as \( T_e \) decreased (Fig. 7B), promoting deflation of the lung and maintenance of a constant EELV and \( L_{\text{di, ee}} \) during hyperpnea. Because flow was increased throughout expiration and IC did not change, the increased \( V_e \) was due both to the increased \( V_t \) with hyperpnea and to the effect of hypercapnea in decreasing airway smooth muscle tone and airway resistance (12). Second, the increased end-expiratory flow rates during hyperpnea relative to when breathing air (Fig. 7C) and the precipitate termination of expiration (Fig. 7A) suggest that the onset of inspiratory effort and not expiratory flow limitation terminated expiration. Near end expiration, there was an overlap of inspiratory and expiratory muscle activity. This activity, evidenced by preinspiratory RMS\textsubscript{di} and \( P_{\text{GEE}} \) or \( P_{\text{Ese(max)}} \), increased proportionately with hyperpnea (Fig. 5, A and B), thus promoting a constant \( L_{\text{di, ee}} \) with increasing ventilation. We suggest that inspiratory flow commenced when activation of inspiratory muscles was sufficient to reduce alveolar pressure below zero, despite continued activity of expiratory muscles. The overlap of expiratory and inspiratory muscle activity near end expiration in our subjects with COPD is consistent with observations in healthy subjects during imposed expiratory flow limitation, where transversus abdominis muscle and diaphragm electrical activity overlap in late expiration through early inspiration (34).

Previous studies demonstrate dynamic hyperinflation during progressive exercise in \( \sim 60\% \) of COPD subjects, including subjects with mild airflow obstruction (2, 23, 35). In these studies, dynamic hyperinflation was associated with flow limitation during tidal breathing; however, this was not invariable. The reasons for the difference between these studies and ours where none of the subjects developed dynamic hyperinflation are unclear. Expiratory flow rates increase with exercise in COPD, and this has been attributed to exercise-induced bronchodilatation (30). The magnitude of the increase of expiratory flow with maximum hyperpnea relative to baseline was greater in our study (126%) than reported with maximum exercise (\( \sim 30 \) and 50%; see Refs. 30 and 35, respectively), perhaps reflecting greater bronchodilatation with hypercapnea than with exercise-induced hyperpnea. Higher \( V_e \) values would be associated with a lower EELV at a given \( T_e \).

**Diaphragm loads.** Muscle efficiency in vitro is maximal at loads between 0.4 and 0.5 maximum isometric force (47). In the COPD subjects, the average load on the diaphragm at maximum ventilation as reflected by \( \Delta P_{\text{d,mean}} \) was \( <20\% \) of the maximum load (Fig. 3). 'Thus the inspiratory load on the diaphragm is unlikely to have limited Eff\textsubscript{di} during hyperpnea in the COPD subjects. In health, the decrease in \( \Delta P_g \) with hyperpnea was correlated with the increase in Eff\textsubscript{di} (16). Why Eff\textsubscript{di} did not increase to some degree with hyperpnea in COPD subjects, despite progressive inspiratory unloading of the diaphragm (Fig. 3A) and a \( \Delta P_{\text{d,mean}} < 0.4 \Delta P_{\text{d,max}} \), is unclear. A possible explanation is inspiratory flattening of the diaphragm.

**Diaphragm and abdominal rib cage shape.** The diaphragm flattened during inspiration at maximum hyperpnea in COPD subjects (Table 2). The negative correlation between \( R_{\text{di,ei}} \) and \( \ln(\text{Eff}_{\text{di}}) \) in the combined data from both groups suggests that inspiratory flattening of the diaphragm at high ventilations may have contributed to the constant Eff\textsubscript{di} with hyperpnea in COPD, perhaps offsetting any effect of inspiratory unloading of the diaphragm (Fig. 3A). Diaphragm flattening in the COPD subjects was not due to excessive muscle shortening as occurs in dogs with hyperinflation and phrenic nerve stimulation, where \( R_{\text{di,ei}} \) increases sharply when \( L_{\text{di,ei}} \) is \( <0.4 \) of the length at FRC (8, 11). In the COPD subjects at maximum hyperpnea, estimated muscle length at end-inspiration relative length at FRC was 0.69. An alternative explanation is the increased \( A_{\text{rc ab}(ei)} \) in the COPD subjects. The combined data from the two subject groups, measured when breathing air and at maximum ventilation, showed that \( R_{\text{di,ei}} \) increased with \( A_{\text{rc ab}(ei)} \) \( (r^2 = 0.75) \).

**Diaphragm muscle function.** In COPD, diaphragm muscle undergoes structural, functional, and metabolic changes, which have the potential to affect the Eff\textsubscript{di} (see Refs. 10 and 33 for reviews). In particular, the proportion of the more efficient type 1 fibers increases in the diaphragms of COPD relative to healthy subjects (26, 49), with the proportion increasing as FEV\textsubscript{1} decreases from 100 to \( \sim 25\% \) predicted (49). Thus our COPD subjects with a mean FEV\textsubscript{1} 54% predicted would have had an increased proportion of type 1 fibers acting to increase Eff\textsubscript{di} relative to healthy subjects. However, in the study of Stubbings et al. (49), the peak efficiency of diaphragm muscle fibers was not different between COPD and non-COPD subjects. Thus the effect of the changes in diaphragm muscle fiber type, as opposed to the effects of length, load, and shape on Eff\textsubscript{di} in COPD, is unclear.

Several studies suggest that the endurance of the diaphragm is increased in COPD (28, 31, 37), consistent with an increased proportion of type 1 fibers. Our finding that Eff\textsubscript{di} increased with hyperpnea in healthy (16), but not in COPD, subjects predicts the opposite. In the COPD subjects, all increases in diaphragm power output required proportional increases in activation and, therefore, energy consumption, whereas, in healthy subjects, \( \sim 50\% \) of the increase in diaphragm power at maximum hyperpnea was accounted for by an increased Eff\textsubscript{di} (16). These results suggest that diaphragm endurance would be less in COPD because endurance is determined by energy consumption and, therefore, by Eff\textsubscript{di} (29).

**Implications.** In this small group of subjects with COPD and moderate airflow obstruction, the diaphragm behaved normally with hyperpnea as a high-flow-low-pressure pump (Fig. 1, A and B) (1, 16). Nevertheless, Eff\textsubscript{di} did not increase normally with hyperpnea due mainly to a constant \( L_{\text{di, ee}} \) due, in turn, to a progressive increase of \( V_e \) during tidal breathing preventing dynamic hyperinflation, and to active termination of expiration determined by the balance between expiratory and inspiratory muscle forces at end expiration. The proportional increase of these forces with hyperpnea acts to prevent the normal increase of \( L_{\text{di, ee}} \) with increased expiratory muscle activity. Finally, the
results emphasize the importance of $L_{\text{te}}$ in determining $\text{Eff}_{\text{di}}$ and suggest that diaphragm flattening on inspiration may contribute to reducing the normal increase in $\text{Eff}_{\text{di}}$ at high levels of ventilation.

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AUTHOR CONTRIBUTIONS

Author contributions: K.E.F. and B.S. conception and design of research; K.E.F. and B.S. performed experiments; K.E.F. and B.S. analyzed data; K.E.F. and B.S. interpreted results of experiments; K.E.F. prepared figures; K.E.F. and B.S. edited and revised manuscript; K.E.F. and B.S. approved final version of manuscript.

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