Effects of respiratory muscle unloading on exercise-induced diaphragm fatigue

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Babcock, Mark A., David F. Pegelow, Craig A. Harms, and Jerome A. Dempsey. Effects of respiratory muscle unloading on exercise-induced diaphragm fatigue. J Appl Physiol 93: 201–206, 2002. First published February 22, 2002; 10.1152/japplphysiol.00612.2001.—We previously compared the effects of increased respiratory muscle work during whole body exercise and at rest on diaphragmatic fatigue and showed that the amount of diaphragmatic force output required to cause fatigue was reduced significantly during exercise (Babcock et al., J Appl Physiol 78: 1710, 1995). In this study, we use positive-pressure proportional assist ventilation (PAV) to unload the respiratory muscles during exercise to determine the effects of respiratory muscle work, per se, on exercise-induced diaphragmatic fatigue. After 8–13 min of exercise to exhaustion under control conditions at 80–85% maximal oxygen consumption, bilateral phrenic nerve stimulation using single-twitch stimuli (1 Hz) and paired stimuli (10–100 Hz) showed that diaphragmatic pressure was reduced by 20–30% for up to 60 min after exercise. Usage of PAV during heavy exercise reduced the work of breathing by 40–50% and oxygen consumption by 10–15% below control. PAV prevented exercise-induced diaphragmatic fatigue as determined by bilateral phrenic nerve stimulation at all frequencies and times postexercise. Our study has confirmed that high- and low-frequency diaphragmatic force output under resting conditions was not sufficient, by itself, to cause diaphragmatic fatigue, as tested in subjects who voluntarily increased diaphragmatic force output, as represented by the time integral of diaphragmatic pressure (Pdi) multiplied by breathing frequency (f), developed during high-intensity exercise, was not sufficient, by itself, to cause diaphragmatic fatigue, as tested in subjects who voluntarily increased diaphragmatic force output under resting conditions (2). So it was proposed that whole body exercise imposed extra stressors on the diaphragm that would hasten fatigue. We speculated that the increased sensitivity to diaphragm fatigue caused by whole body exercise was primarily due to the relative reduction in blood flow to the diaphragm under conditions in which the respiratory muscles would have to compete with the locomotor muscles for the available cardiac output. In this same study, we also showed that whole body exercise to exhaustion, which caused diaphragm fatigue, did not elicit fatigue in a minimally exercised muscle of the hand (2). Accordingly, we reasoned that the increased force output per se of the diaphragm, as required to produce hyperpnea during exercise, might also contribute significantly to exercise-induced diaphragm fatigue.

In the present study, we used proportional assist ventilation to partially unload the respiratory muscles during heavy endurance cycling exercise to determine the role of diaphragmatic force output per se on diaphragmatic fatigue caused by whole body exercise.

METHODS

Subjects. Seven male subjects with normal lung function and no signs of arterial hypoxemia (arterial oxygen saturation was above 92%) during the maximal oxygen uptake (V\textsubscript{O\text{\textsubscript{2}} max}) test were recruited to participate in this study. Informed consent was obtained in writing, and the Institutional Review Board of the University of Wisconsin-Madison approved all procedures. Physical characteristics of the subjects were as follows: age = 27.1 ± 2.5 yr; height = 177.3 ± 2.4 cm; weight = 72.0 ± 2.6 kg; V\textsubscript{O\text{\textsubscript{2}} max} = 55.4 ± 4.3 ml·kg\textsuperscript{-1}·min\textsuperscript{-1}, range = 33.3 to 72.5 ml·kg\textsuperscript{-1}·min\textsuperscript{-1}.

Inspiratory muscle unloading. A feedback-controlled proportional assist ventilator (PAV) was used to reduce the work of the inspiratory muscles during exercise (22). Briefly, subjects breathed through a Hans-Rudolph one-way breathing valve that was connected (on the inspiratory side) to the PAV. The PAV contains a linear motor that drives a piston of the inspiratory muscles during exercise (22).

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and flow assist (resistance). During inspiration, the PAV makes mouth pressure positive in proportion to volume and flow, such that the proportional assist (unloading) of the respiratory muscles occurs throughout the inspiratory cycle. In practice, we set the amount of flow and volume assist at the maximal levels each subject could tolerate during heavy exercise, as determined from practice sessions before testing. During these practice sessions and during testing sessions, subjects were verbally coached to “relax” and permit the PAV to assist each inspiration as much as possible (see Fig. 1).

**Paired-stimuli technique.** The paired-electrical stimuli technique and its reproducibility have been described in detail (3, 20). Subjects were seated in a semirecumbent position. A level of supramaximal bilateral phrenic nerve stimulation (BPNS) was determined by gradually increasing stimulus current until a plateau was reached in compound action potential (M wave) of the diaphragmatic electromyogram and diaphragmatic pressure (Pdi). During BPNS data collection, the M wave amplitude was checked to ensure that each stimulus resulted in supramaximal stimulation of the diaphragm. Two supramaximal electrical stimuli were delivered to both phrenic nerves at a constant current, and the time interval between stimuli was varied from 10 ms (100 Hz) to 100 ms (10 Hz) (20). For each stimulation protocol, five to eight repeated measures of twitch stimulation (at 1 Hz) and three to five repeated paired stimulations at 10, 20, 50, 70, and 100 Hz were obtained at functional residual capacity (FRC). The resultant esophageal pressure (Pes), gastric pressure, Pdi, and M waves from the left and right costal diaphragm were collected on computer, polygraph record (Gould Em2300) and magnetic tape (Hewlett Packard) for later analysis. Tidal and end-expiratory lung volumes were continuously monitored throughout the stimulation tests by connecting the subject to a wedge spirometer and providing the subject with visual feedback by using an oscilloscope display of lung volume.

**High-frequency response.** High-frequency stimulation effects are reflected in the response of the diaphragm to the second stimulus. It was assumed that the diaphragmatic response to the first stimulus was similar to a twitch response. Therefore, the single five to eight repeated twitch stimulations were ensemble averaged and then subtracted by computer from the ensemble-averaged paired responses at each frequency, and the amplitude of the resultant response (T2) was measured. High-frequency fatigue was considered to be present if T2 was different from preexercise values immediately after exercise but not different at 30 min postexercise, whereas the 10- and 20-Hz T2 were still different from control (3, 4).

**Exercise data collection.** During exercise, expired gases, flow rates, volumes, Pes, gastric pressure, Pdi, and mouth pressure were monitored continuously and stored on magnetic pressure-tidal volume (VT) loop (16). Wb multiplied by f and labeled the diaphragm force output and the inspiratory muscle force output, respectively. Work of breathing (Wb) was defined as the integrated area of the pressure-tidal volume (VT) loop (16). Wb multiplied by f represented the amount of work done per minute on the lungs. The use of the area within the Pes-volume loop underestimates the actual Wb by a variable amount (6). Thus our measurements provide only a conservative estimate of the total amount of work done by the respiratory muscles during exercise, with both no-assist and PAV exercise.

**Exercise test protocols.** The seven subjects exercised on an electromagnetically braked cycle ergometer (Elema). The first exercise test determined subjects’ VO2 max by using a progressive short-term test to volitional exhaustion, as outlined previously (11). Arterial blood O2 saturation was estimated throughout this exercise test by ear oximetry (Hewlett-Packard) to determine whether arterial hypoxemia occurred in any of our subjects.

Two endurance-exercise sessions were conducted on separate days. Various BPNS measurements were completed before exercise (baseline measures). Subjects warmed up briefly with light exercise and were then quickly brought up to a workload that required ~85% VO2 max, which was maintained until volitional exhaustion. Subjects breathed through the same breathing circuit setup during both endurance-exercise tests, and the assist was added only for the PAV test. Immediately after exercise, BPNS measures were repeated; this was also done 30 and 60 min postexercise. We completed all single twitches (five measures) and paired stimulations at different frequencies (3 measures per frequency) by 20 min postexercise because one major characteristic of high-frequency fatigue is that it recovers quickly, usually by 30 min postfatiguing effort (4). The procedure was the same for the inspiratory muscle-unloading test except that during the brief warm-up, the level of assist on the ventilator was gradually increased to the subjects’ predetermined values, and subjects were allowed to adjust to the ventilator. Exercise time during the PAV exercise was set to be isotime with the no-assist exercise time.

**Statistical analysis.** Statistical analyses were done by using the statistical program SigmaStat (Jandel). All data are reported as means ± SE. One-way ANOVA with repeated measures was used to determine differences in mean values over the duration of the exercise and recovery period. Two-way ANOVA was used to compare the no-assist exercise to the PAV exercise at the same time points. The level of significance was set at P < 0.05.
The relative contribution of $\dot{f}_{\text{Pdi}} \cdot f$ to $\dot{f}_{\text{Pes}} \cdot f$ during inspiration changed with both exercise duration and PAV (Fig. 2, bottom). In control conditions, $\dot{f}_{\text{Pdi}} \cdot f$ was 88–100% of $\dot{f}_{\text{Pes}} \cdot f$ early in the exercise trial and gradually fell to 80% of $\dot{f}_{\text{Pes}} \cdot f$ by the end of exercise. With PAV, $\dot{f}_{\text{Pdi}} \cdot f/\dot{f}_{\text{Pes}} \cdot f$ was reduced below control conditions throughout exercise, and $\dot{f}_{\text{Pdi}} \cdot f$ also remained relatively constant at 72–67% of $\dot{f}_{\text{Pes}} \cdot f$ throughout the exercise duration.

Figure 3 shows that Wb throughout exercise was substantially reduced relative to control throughout the entire PAV exercise period ($P < 0.05$). The decrease in Wb during PAV exercise was equally distributed between inspiration and expiration. For example, at 80% of total exercise time, Wb was decreased below control by 54 ± 7% during inspiration and by 53 ± 6% during expiration (see Fig. 1).

Oxygen uptake ($\dot{V}_{O_2}$) during the control-exercise trial rose throughout the exercise period and terminated at 88 ± 5% $\dot{V}_{O_2 \text{ max}}$ at exhaustion (range = 72–100%) (see Fig. 3). With PAV, $\dot{V}_{O_2}$ was reduced significantly less than control throughout exercise, averaging a reduction of 12–13% over the final half of the exercise period. Carbon dioxide consumption ($\dot{V}_{CO_2}$) during exercise with PAV was similarly reduced below control at most of the exercise time points (data not shown).

Ventilatory responses to exercise. Ventilatory responses to exercise and to PAV are shown in Figs. 4 and 5. In control, minute ventilation ($\dot{V}_{E}$) rose by an

- **RESULTS**

  Respiratory muscle force output and oxygen uptake. Exercise time to exhaustion during control and PAV conditions averaged 9.6 ± 0.6 min (range = 8.0–12.5 min), and these times were duplicated for each subject during the PAV trial. During exercise under control conditions, the force output of the diaphragm as represented by $\dot{f}_{\text{Pdi}} \cdot f$ increased from rest to 20% of total exercise time ($\text{rest} = 162 ± 0.7 \text{cmH}_2\text{O} \cdot \text{min}$; 20% total exercise time = 409.5 ± 68.2 cmH$_2$O·min) and thereafter leveled off or declined slightly (see Fig. 2). In contrast with during exercise with PAV, $\dot{f}_{\text{Pdi}} \cdot f$ increased by ~117% of the rest value ($\text{rest} = 160.1 ± 20 \text{cmH}_2\text{O} \cdot \text{min}$; 20% total exercise time = 191.0 ± 27 cmH$_2$O·min) and continued to slowly increase until ~60% of the exercise time was reached, and then it decreased slightly to the end of exercise (Fig. 2). Total inspiratory muscle force output (diaphragm plus accessory inspiratory muscles), as represented by $\dot{f}_{\text{Pes}} \cdot f$, increased progressively a total of almost 290% until 60% of total exercise time, when it leveled off over the remaining time. During PAV the $\dot{f}_{\text{Pes}} \cdot f$ increased to ~200% greater than rest during the initial 40% of exercise time and then leveled off over the remainder of the exercise time.

![Fig. 2. Diaphragmatic pressure force output ($\dot{f}_{\text{Pdi}} \cdot f$, top), all inspiratory muscles force output ($\dot{f}_{\text{Pes}} \cdot f$, middle), and the $\dot{f}_{\text{Pdi}}/\dot{f}_{\text{Pes}}$ ratio (bottom) during NA exercise (●) and PAV exercise (○). Absolute exercise time averaged 9.6 ± 0.6 min (range of 8–12.5 min). Mean $\dot{f}_{\text{Pdi}} \cdot f$ and $\dot{f}_{\text{Pes}} \cdot f$ were significantly reduced during exercise with PAV vs. NA ($P < 0.05$). Note that preexercise values in Figs. 2–5 were obtained after subjects completed warm-up exercise. Values are means ± SE.](http://jap.physiology.org/)

![Fig. 3. Group mean work of breathing ($\dot{W}_b$) and group mean oxygen consumption ($\dot{V}_{O_2}$) during the whole body endurance exercise with NA (●) and PAV (○). Both $\dot{V}_{O_2}$ and work of breathing were significantly reduced during PAV vs. NA ($P < 0.05$). Values are means ± SE.](http://jap.physiology.org/)
average of 35% from minute 3 to exhaustion entirely because of an increase in \( f \) as \( V_T \) peaked early and then fell slightly throughout the remainder of exercise. \( \dot{V}E/V\dot{O}_2 \) fell by 25% from beginning to end of exercise. With PAV, \( \dot{V}E \) was reduced to an average of 9.6 ± 3.4% less than control throughout exercise due solely to a reduction in \( f \) with no change in \( V_T \). Inspiratory time and mean inspiratory flow rate were also reduced during exercise with PAV. As shown in Fig. 4, the reduction in \( \dot{V}E \) during exercise with PAV paralleled the reductions in \( \dot{V}O_2 \) and \( \dot{V}CO_2 \); hence, PAV did not affect the degree of hyperventilation (i.e., \( \dot{V}E/V\dot{O}_2 \)) throughout exercise.

Diaphragmatic fatigue. Immediately after intense, whole body exercise with no assist, the Pdi response to supramaximal twitch stimulation decreased an average of 20.3 ± 3.1% compared with control values (range = -4.2 to -30.3%; \( P < 0.03 \); Fig. 6). Twitch Pdi was not significantly changed from preexercise control after PAV exercise. In the no-assist exercise, twitch Pdi was still decreased at 60 min of recovery (11.6%) but was no longer different from preexercise control values (\( P > 0.05 \)).

\( T_2 \). Immediately after the no-assist exercise, \( T_2 \) amplitude was significantly reduced at 10, 20, 50, 70, and 100 Hz (\( P < 0.05 \)) (Fig. 7A). Thirty minutes postexercise, 10- and 20-Hz values were still substantially reduced (-32.8 and -23.9%, respectively) compared with preexercise values, whereas 50-, 70-, and 100-Hz values were not different vs. control values. These data indicate the presence of high- and low-frequency fatigue in the diaphragm immediately after whole body endurance exercise with no assist. In contrast, at all times after exercise with PAV, \( T_2 \) amplitude at all frequencies was not reduced below preexercise control values (Fig. 7B).

DISCUSSION

Dual cause of exercise-induced diaphragmatic fatigue. Our present findings and those from our laboratory’s previous study (2) point to two general causes of exercise-induced diaphragmatic fatigue. First, the effects of whole body exercise per se on the threshold of diaphragmatic force output required for fatigue was previously shown to be significant and substantial (2). As mentioned above, this whole body exercise fatigue factor is likely due to less blood flow availability to the diaphragm during exercise (vs. voluntary hyperpnea at rest) in the face of high blood flow demands by the...
Locomotor muscles. Second, the combination of past and present findings shows that the work of the diaphragm incurred during high-intensity whole body exercise, although not sufficient to cause fatigue when mimicked voluntarily under resting conditions, was critical to causing diaphragmatic fatigue in the presence of whole body exercise. These findings are consistent with the additional observation that the effects of exhaustive high-intensity whole body exercise per se were not sufficient to elicit fatigue in nonexercising muscles of the hand (2, 14). Thus we postulate that the development of diaphragmatic fatigue during exercise is a function of the relationship between the magnitude of diaphragmatic work incurred and the adequacy of its blood supply; the less the latter is available to the diaphragm, the less work is required to produce its function of the relationship between the magnitude of diaphragmatic fatigue.

Consequences of exercise-induced diaphragmatic fatigue. By contrasting control and unloaded conditions during exercise, the present study speaks indirectly to the consequences of exercise-induced diaphragmatic fatigue on the regulation of ventilation and of respiratory muscle recruitment. First, f increases substantially over time during high-intensity exercise. Many mechanisms have been implicated, and some researchers have speculated that this tachypnea may be in part related to respiratory muscle fatigue (5). We observed VE and f to increase over time (at a fixed workload) in both control and unloaded conditions; however, f was reduced during the latter half of the unloaded trials, relative to control. The fact that the lower f occurred during the ventilator-assisted runs suggests that the prevention of diaphragmatic fatigue may have been involved. However, this lower f also occurs simultaneously with a reduced VE; when VT was examined at a given VE (21) over the entire time course of the exercise, we found no consistent effect of the unloading on VT or f. Second, we also found that exercise VE was significantly reduced during unloading, but this does not necessarily imply an effect of unloading and/or diaphragm fatigue on ventilatory control because the reduction in VE matched the reduction in VCO2 (and VCO2). Thus VE/VCO2 was unchanged. In addition to this metabolic effect of respiratory muscle unloading during heavy exercise, there is also the strong possibility of a behavioral effect on the regulation of breathing as a result of the foreign sensation of accompanying positive-pressure mechanical ventilation. These extraneous effects may explain at least part of the disparity in reported findings on ventilatory control with respiratory muscle unloading during exercise (5, 7, 8, 13). In short, we believe the multiple effects of mechanical unloading during heavy exercise preclude us from interpreting these data solely in terms of a consequence of diaphragmatic fatigue.

Third, fPdi has been shown to fall over the time course of constant-intensity exhaustive exercise, even in the face of rising VE and increasing negativity of Pes. We confirmed this effect during no-assist exercise (see Fig. 2). Furthermore, with ventilatory assist, we observed that fPdi and fPdi/Pes were substantially reduced below control; in addition, fPdi did not fall during almost the entire time course of exercise. These data suggest that ventilatory assist does prevent most of the reduction in Pdi over time during prolonged exercise and that this may, at least in part, be due to the prevention of exercise-induced diaphragmatic fatigue.

On the basis of our observed average fall in BPNS Pdi in the immediate postexercise period (i.e., 25% below preexercise Pdi at 1- to 20-Hz stimulation), we would speculate that peripheral diaphragm fatigue, by itself, is more than sufficient to account for the relative decrement in tidal Pdi from beginning to end of exercise. Of course we do not know at what time point of exercise peripheral diaphragm fatigue actually occurred, so it is feasible that so-called central fatigue (or feedback inhibition) could have contributed in part to the reduced tidal Pdi. Finally, as with the control of ventilation (see above), we cannot be sure that the behavioral response to positive-pressure mechanical ventilation did not influence the distribution of respiratory motor output to the respiratory musculature.

Summary and relevance. In summary, present findings have shown that the magnitude of force output required by the diaphragm during high-intensity whole body exercise is a significant determinant of exercise-induced diaphragmatic fatigue. The present data also suggest that most of the time-dependent fall...
in tidal $f_{Pdi}$, which occurs over the time course of heavy exercise, may be at least in part attributable to exercise-induced diaphragm fatigue.

Present findings might also have implications for interpreting recent evidence in humans that shows that mechanically reducing respiratory muscle work during high-intensity exercise resulted in 1) increased vascular conductance and blood flow to working limb locomotor muscles (7, 8) and 2) significant increases in endurance-exercise performance (9). Furthermore, simply mechanically unloading the respiratory muscles during moderate-intensity submaximal exercise (<75% VO$_2$max), in which diaphragm fatigue does not occur, had no effect on limb vascular conductance or blood flow (19). Because we presently found that ventilatory assist during heavy-intensity exercise also prevented diaphragmatic fatigue, these data imply (albeit indirectly) that fatigue of the diaphragm and likely of other respiratory muscles may be an important mechanism contributing to both the redistribution of blood flow and increased exercise tolerance. This concept of a role for exercise-induced diaphragm fatigue in cardiovascular regulation during exercise is also consistent with recent evidence showing that inspiratory muscle fatigue (i.e., as induced via voluntary inspiratory efforts in the resting subject) caused a sympathetically mediated vasoconstriction of the lower limb (17, 18). What remains to be experimentally determined is whether these sympathetic, vasoconstrictive influences induced specifically by fatiguing diaphragm contractions per se actually do influence blood flow distribution during whole body exercise.

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