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## Gas exchange during separate diaphragm and intercostal muscle breathing

A. F. DiMarco, A. F. Connors, Jr., and K. E. Kowalski

Rammelkamp Center for Education and Research, MetroHealth Medical Center, and Department of Physiology and Biophysics, Case Western Reserve University, Cleveland, Ohio 44109-1998

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**DiMarco, A. F., A. F. Connors, Jr., and K. E. Kowalski.** Gas exchange during separate diaphragm and intercostal muscle breathing. *J Appl Physiol* 96: 2120–2124, 2004;10.1152/jappphysiol.00628.2003.—In patients with diaphragm paralysis, ventilation to the basal lung zones is reduced, whereas in patients with paralysis of the rib cage muscles, ventilation to the upper lung zones is reduced. Inspiration produced by either rib cage muscle or diaphragm contraction alone, therefore, may result in mismatching of ventilation and perfusion and in gas-exchange impairment. To test this hypothesis, we assessed gas exchange in 11 anesthetized dogs during ventilation produced by either diaphragm or intercostal muscle contraction alone. Diaphragm activation was achieved by phrenic nerve stimulation. Intercostal muscle activation was accomplished by electrical stimulation by using electrodes positioned epidurally at the T<sub>2</sub> spinal cord level. Stimulation parameters were adjusted to provide a constant tidal volume and inspiratory flow rate. During diaphragm (D) and intercostal muscle breathing (IC), mean arterial PO<sub>2</sub> was 97.1 ± 2.1 and 88.1 ± 2.7 Torr, respectively ( $P < 0.01$ ). Arterial PCO<sub>2</sub> was lower during D than during IC (32.6 ± 1.4 and 36.6 ± 1.8 Torr, respectively;  $P < 0.05$ ). During IC, oxygen consumption was also higher than that during D (0.13 ± 0.01 and 0.09 ± 0.01 l/min, respectively;  $P < 0.05$ ). The alveolar-arterial oxygen difference was 11.3 ± 1.9 and 7.7 ± 1.0 Torr ( $P < 0.01$ ) during IC and D, respectively. These results indicate that diaphragm breathing is significantly more efficient than intercostal muscle breathing. However, despite marked differences in the pattern of inspiratory muscle contraction, the distribution of ventilation remains well matched to pulmonary perfusion resulting in preservation of normal gas exchange.

electrical stimulation; respiratory muscles; artificial respiration

DIAPHRAGM CONTRACTION ALONE, as occurs in patients with tetraplegia, causes preferential distribution of ventilation to the caudal regions of the lung, whereas intercostal muscle contraction alone, as occurs in patients with diaphragm paralysis, cause preferential distribution of ventilation to the cephalad lung regions (1, 26–28). Depending on the degree to which these changes in regional pulmonary ventilation are matched by coincident changes in the distribution of perfusion, gas-exchange impairment may result. In fact, patients with tetraplegia (3, 31), and more commonly patients with diaphragm paralysis, suffer from arterial hypoxemia (4, 12, 16, 19, 24, 29). Moreover, patients with diaphragm paralysis frequently suffer from variable degrees of hypercapnia (4, 12, 16, 19, 23, 29, 30). The precise contribution of alterations in the pattern of respiratory muscle contraction in the etiology of these gas-exchange abnormalities is not clear because these patients may

suffer from underlying lung disease, respiratory tract infections, mucus hypersecretion, and atelectasis, which also have adverse consequences on gas exchange (15, 25).

The purpose of the present study, therefore, was to investigate the effects of separate diaphragm and intercostal muscle contraction on gas exchange in anesthetized dogs. Diaphragm breathing was produced by bilateral phrenic nerve stimulation. Intercostal muscle breathing was produced by upper thoracic spinal cord stimulation after the phrenic nerves were severed. This methodology allowed the comparison of gas exchange during separate intercostal and diaphragm breathing at the same inspired volumes and flow rates.

### METHODS

Studies were performed on 11 adult mongrel dogs weighing between 12 and 16 kg (mean 14.6 ± 0.5 kg). All animal care and experimental procedures were according to National Institutes of Health guidelines and were approved by the Institutional Animal Care and Use Committee of Case Western Reserve University. Animals were anesthetized initially with 35 mg/kg pentobarbital sodium given intravenously and supplemented with 2–3 mg/kg. The level of anesthesia was monitored by the corneal reflex and the suppression of spontaneous respiration. Body temperature was maintained at 38 ± 0.5°C with a heating blanket (Harvard Apparatus, Cambridge, MA). Studies were performed with the animals in the supine posture while breathing room air. A cuffed endotracheal tube was inserted through the mouth; tidal volume was recorded by electrical integration of the flow signal from a pneumotachograph (Fleisch no. 1, OEM Medical, Richmond, VA). Animals were intermittently ventilated with a mechanical ventilator (Harvard Apparatus, Cambridge, MA). A catheter was placed in the femoral artery to monitor blood pressure (model P23 ID, Gould-Statham, Oxnard, CA) and obtain samples for arterial blood-gas analysis. A femoral venous line was placed to administer intravenous fluids and anesthetic. A Swan-Ganz catheter was placed in the pulmonary artery via the internal jugular vein. Cardiac output was measured via the thermodilution technique. Mixed venous blood samples were obtained from the pulmonary artery.

After a thoracic laminectomy, a flexible stainless steel stimulating electrode rubberized along its entire length, except for 2–3 mm at the distal tip, was introduced epidurally onto the ventral surface of the spinal cord. The electrode was advanced to the T<sub>2</sub>–T<sub>3</sub> spinal cord region and secured in position with sutures. Our laboratory has shown in previous studies (7) that this technique results in synchronized expansion of the rib cage and large inspired volumes in the post-phrenicotomy preparation. All cervical phrenic rootlets were exposed in the neck and cut bilaterally. The C<sub>5</sub> and C<sub>6</sub> phrenic rootlets were carefully positioned within stainless steel stimulating cuff electrodes

Address for reprint requests and other correspondence: A. F. DiMarco, Rammelkamp Center for Education, MetroHealth Medical, 2500 MetroHealth Dr., Cleveland, OH 44109-1998 (E-mail: afd3@po.cwru.edu).

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Table 1. Mean inspired volume and minute ventilation during separate intercostal muscle and diaphragm breathing

	Inspired Volume, ml	Minute Ventilation, l/min
Intercostal muscle breathing	174±6	5.66±0.31
Diaphragm breathing	170±6	5.47±0.25

Values are means ± SE; for 11 dogs.

bilaterally. The stimulator (Applied Neural Control Laboratory, Case Western Reserve University, Cleveland, OH) delivers a balanced charged biphasic stimulus and provides a pulse width-modulated impulse. Stimulus current and frequency could be varied between 0 and 20 mA and between 10 and 80 Hz, respectively. Individual stimuli could be applied independently through four separate channels.

Between trials, the animals were supported by mechanical ventilation, which was periodically discontinued in each animal to verify the absence of spontaneous respiration. Supplemental anesthesia was provided if the duration of apnea was <30 s.

**Protocol.** During separate diaphragm or intercostal muscle breathing, via bilateral phrenic nerve and spinal cord stimulation, respectively, ventilation was achieved with a constant tidal volume of 12 ml/kg, respiratory rate of 30 breaths/min, and inspiratory flow rate of 0.2 l/s. The desired tidal volume was achieved by adjusting stimulus current and frequency. After 10 min of each mode of ventilation, measurements of cardiac output and arterial and mixed venous blood gases were made during a 2-min collection of expired gas. From these data, oxygen consumption and carbon dioxide production, alveolar-arterial oxygen differences [(A-a)DO<sub>2</sub>], venous admixture, and dead space were calculated.

Statistical analysis was performed by using ANOVA and Student's *t*-test. A *P* value of <0.05 was accepted as statistically significant.

## RESULTS

The mean inspired volumes and total ventilation achieved by separate intercostal muscle and diaphragm breathing are shown in Table 1. Inspired volume of ~170 ml and minute ventilation of 5.5 l/min were achieved under each condition. Importantly, mean inspired volumes and minute ventilations were not significantly different between conditions. Arterial blood-gas tensions, dead space, oxygen consumption, and carbon dioxide production during separate intercostal muscle and diaphragm breathing are shown in Table 2. Intercostal muscle breathing resulted in a significantly lower arterial PCO<sub>2</sub> (88 compared with 97 Torr; *P* < 0.01) and higher arterial PO<sub>2</sub> (36.6 compared with 32.6 Torr; *P* < 0.05) compared with diaphragm breathing. These differences in arterial PCO<sub>2</sub> are not attributable to differences in dead space. In fact, dead space was higher during diaphragm breathing than during intercostal muscle breathing. The higher arterial PCO<sub>2</sub> with intercostal muscle breathing could be explained, in part, by the fact that carbon dioxide production was also significantly higher during intercostal muscle breathing compared with diaphragm breathing. During

intercostal muscle breathing, oxygen consumption was also higher than that during diaphragm breathing. (A-a)DO<sub>2</sub> and venous admixture during intercostal muscle and diaphragm breathing are shown for each animal in Figs. 1 and 2. The venous admixture and (A-a)DO<sub>2</sub> gradients were greater during intercostal muscle breathing compared with diaphragm breathing in 8 of the 11 animals. The mean (A-a)DO<sub>2</sub> was significantly greater during intercostal muscle breathing (11.3 ± 1.9 Torr) compared with diaphragm breathing (7.7 ± 1.0 Torr; *P* < 0.05). Similarly, venous admixture was also significantly higher during intercostal muscle breathing compared with diaphragm breathing (Fig. 2; *P* < 0.05). However, these values are within the normal range, indicating preservation of gas exchange under both conditions.

## DISCUSSION

This study demonstrates significant differences between intercostal and diaphragm breathing in that the (A-a)DO<sub>2</sub>, oxygen consumption, and carbon dioxide production are higher during intercostal muscle breathing. This suggests that diaphragm breathing is significantly more efficient than intercostal muscle breathing. However, despite markedly different patterns of inspiratory muscle engagement and resultant alterations in the distribution of ventilation, there are coincident alterations in the distribution of perfusion, resulting in normal gas exchange.

It is important to note that this investigation is unique in that gas exchange via intercostal muscle and diaphragm breathing were compared by utilizing very similar tidal volumes and inspired flow rates. This suggests that the pattern of inspiratory muscle contraction can alter the distribution of both ventilation and perfusion, independent of the effects of changes in airflow or gravitational effects.

We were concerned about the emergence of spontaneous respiratory activity during stimulated respiration, which would have interfered with our evaluation of separate breathing patterns. Because the phrenic nerve rootlets were severed bilaterally, spontaneous diaphragm activity was not a possibility. However, because the intercostal and accessory nerves were intact, it was necessary that spontaneous intercostal and accessory muscle activation be suppressed. To prevent activation of these muscle groups, sufficient anesthetic was administered to maintain apnea for at least 30 s after discontinuation of artificial respiration. In addition, it should be noted that ventilation provided during intercostal and diaphragm pacing maintained the animals in a hyperventilated state. It is unlikely, therefore, that spontaneous respiratory activity contributed to the observed responses.

Upper thoracic ventral root stimulation (VRS), which was used to selectively activate the intercostal muscles in this study, results in activation of the intercostal muscles in the

Table 2. Arterial PO<sub>2</sub>, PCO<sub>2</sub>, dead space, oxygen consumption, carbon dioxide production, and cardiac output during separate intercostal muscle and diaphragm breathing

	Arterial PO <sub>2</sub> , Torr	Arterial PCO <sub>2</sub> , Torr	Dead Space, %	Oxygen Consumption, l/min	Carbon Dioxide Production, l/min	Cardiac Output, l/min
Intercostal muscle breathing	88.1±2.7	36.6±1.8†	58.2±2.6	0.13±0.01‡	0.10±0.01‡	2.92±0.59
Diaphragm breathing	97.1±2.1*	32.6±1.4*	63.7±2.2*	0.09±0.01*	0.07±0.01*	2.88±0.39

Values are means ± SE for 11 dogs. \*Significantly greater than intercostal muscle breathing alone, *P* < 0.01. †Significantly greater than diaphragm breathing alone, *P* < 0.05. ‡Significantly greater than diaphragm breathing alone, *P* < 0.01.

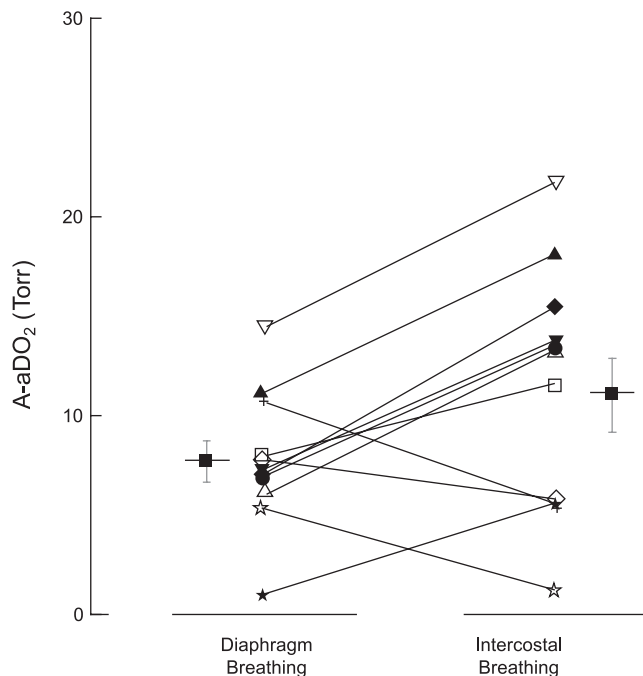


Fig. 1. Alveolar-arterial oxygen difference [(A-a)DO<sub>2</sub>] during stimulated breathing. Connected symbols represent values obtained in the same experiment. Unconnected symbols and squares with error bars at left and right represent mean values  $\pm$  SE obtained from 11 dogs.

upper fourth to fifth interspaces (7). This technique has been shown to result in the generation of large inspired volumes in both animals (7) and humans (8, 9). In fact, maximum VRS stimulation in combination with maximum bilateral phrenic nerve stimulation results in inspired volumes approximating the inspiratory capacity, suggesting maximum inspiratory intercostal muscle recruitment by this technique (7). Moreover, this technique, when used in conjunction with unilateral diaphragm stimulation, can maintain ventilatory support for prolonged time periods in ventilator-dependent tetraplegic individuals (8). Although VRS represents a valid method of simulating intercostal muscle breathing, this technique also results in the activation of nonrespiratory muscles (7–9), which may account for the observed higher oxygen consumption compared with diaphragm breathing (see below).

The fact that the (A-a)DO<sub>2</sub> and venous admixtures during both intercostal and diaphragm breathing were not abnormally elevated indicates that these different breathing patterns did not result in significant populations of low ventilation-to-perfusion ratio lung units. It is of interest, however, that the arterial PO<sub>2</sub> was significantly lower and the (A-a)DO<sub>2</sub> and venous admixture were significantly higher during intercostal compared with diaphragm breathing. This suggests either an increase in the proportion of low ventilation-to-perfusion ratio units or a reduction in the ventilation-to-perfusion ratio of existing units during intercostal muscle breathing.

Similarly, if either intercostal or diaphragm breathing resulted in significant populations of high ventilation-to-perfusion ratio lung units, this would have resulted in a significant increase in dead space and contribute to the development of hypercapnia. Although our animals were not hypercapnic, values for dead space with both intercostal and diaphragm breathing are quite high. This is attributable to the large

apparatus dead space in relation to the animals' inspired volume. The fact that the dead space-to-tidal volume ratio was consistently higher during diaphragm breathing suggests that there was either an increase in the proportion of high ventilation-to-perfusion ratio lung units or an increase in the ventilation-to-perfusion ratio of existing units during diaphragm breathing.

Consistent with the results of the present study, previous investigations have shown that inspired volumes achieved by voluntary preferential use of the diaphragm or intercostal muscles results in preferential distribution of inhaled gas to the dependent and nondependent zones of the lung, respectively (28). Although the mechanisms by which the pattern of respiratory muscle contraction alters the distribution of ventilation are not entirely clear, changes in the distribution of ventilation most likely relate to regional swings in pleural pressure. In support of this contention, previous studies in dogs have demonstrated that pleural pressure swings are more negative over the lower lobes during phrenic nerve stimulation and more negative over the upper lobes during spontaneous breathing after phrenicotomy (5, 21). It should be noted that other investigators (2) have not found significant differences in the distribution of ventilation with different patterns of inspiratory muscle engagement. The reason for the discrepancy between these studies is not clear but may relate to technique differences.

Also consistent with the results of present study, previous investigations have demonstrated redistribution of pulmonary perfusion from the base toward the apex in patients with diaphragm paralysis (1, 26). Changes in the pattern of respiratory muscle contraction may affect regional changes in the distribution of perfusion by several mechanisms. First, reductions in regional lung volume, as would occur at the base of the lung in patients with diaphragm paralysis and in the upper lung

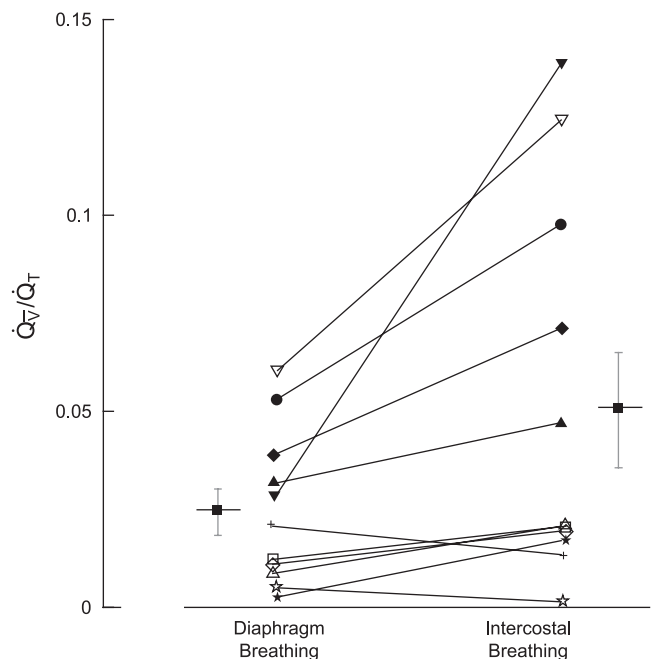


Fig. 2. Venous admixture during stimulated breathing.  $\dot{Q}_v/\dot{Q}_T$ , ratio of mixed venous to total flow. Connected points represent values obtained in the same experiment. Unconnected symbols and squares with error bars at left and right represent mean values  $\pm$  SE obtained from 11 dogs.

zones in patients with intercostal muscle paralysis, would increase local extra-alveolar vessel resistance, restricting local perfusion (14). Second, regional hypoxia, as would occur in poorly ventilated lung regions, results in local vasoconstriction, thereby restricting local perfusion (1). Finally, lung expansion is associated with increasing negative interstitial pressure. Regional decrements in interstitial pressure may reduce regional vascular resistance, resulting in expansion of extra-alveolar vessels and, thereby, increase regional pulmonary blood flow (14).

Clinical correlates of intercostal paralysis alone include patients with cervical spinal cord injury. Although patients with acute spinal cord injury often develop hypoxemia, this usually resolves as their condition stabilizes (18). These patients have an increased work of breathing due to a reduction in rib cage compliance and the paradoxical inward retraction of the rib cage. Despite these alterations, tetraplegic individuals with preserved diaphragm function generally remain eucapnic (11, 18, 20).

Clinical correlates of diaphragm paralysis include patients with damage or injury to the phrenic nerves, because of either trauma, tumor, various myopathies, or idiopathic disorders (4, 12, 16). These patients have a marked increase in the work of breathing secondary to reductions in pulmonary compliance and paradoxical movement of the diaphragm during inspiration (16, 22, 23). Moreover, these patients deteriorate further in the supine posture secondary to greater reductions in functional residual capacity (6). Tidal volumes produced by intercostal muscle contraction alone in the present study were, in fact, associated with a greater oxygen consumption and carbon dioxide production than comparable inspired volumes produced by diaphragm contraction alone. This suggests that the amount of inspiratory muscle work required to generate a given tidal volume is higher when achieved by intercostal muscle contraction alone. It should be mentioned, however, that the technique employed to activate the intercostal muscles in the present study also results in contraction of some back musculature and mild flexion of the forepaws (7, 9). It is quite possible that contraction of these nonrespiratory muscles may account for the increased oxygen consumption and carbon dioxide production observed during intercostal muscle breathing. Nevertheless our findings are consistent with those of Hart et al. (13), who demonstrated in humans with diaphragm paralysis that the ratio of peak oxygen uptake to minute ventilation was significantly higher in patients with diaphragm paralysis compared with controls. These data also suggest that intercostal muscle breathing is less efficient than diaphragm breathing.

In contrast to patients with intercostal paralysis, gas-exchange abnormalities, both hypoxemia and hypercapnia, are commonly described in patients with diaphragm paralysis (4, 12, 16, 23, 29, 30). The results of the present study would suggest that isolated bilateral diaphragm paralysis alone does not account for the frequently observed gas-exchange abnormalities in this patient population. Rather, these gas-exchange abnormalities in this population are secondary to the coexistence of atelectasis, respiratory secretions, underlying lung disease, or the presence of more diffuse respiratory muscle involvement (15, 22, 25). In support of this contention are the results of one report that analyzed patients with isolated bilateral diaphragm weakness and found only mild hypoxemia and normal  $P_{CO_2}$  values (17).

Finally, the results of this study also suggest that the inability of ventilator-dependent patients to tolerate artificial venti-

lation with intercostal muscle pacing alone for prolonged time periods (9) is not consequent to abnormalities in gas exchange but rather secondary to other factors such as reductions in lung (3) and/or rib cage compliance (10) that occur in chronic spinal cord injury.

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