Synergism between the canine left and right hemidiaphragms

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De Troyer, André, Matteo Cappello, Nathalie Meurant, and Pierre Scillia. Synergism between the canine left and right hemidiaphragms. J Appl Physiol 94: 1757–1765, 2003; 10.1152/japplphysiol.01013.2002—Expansion of the lung during inspiration results from the coordinated contraction of the diaphragm and several groups of rib cage muscles, and we have previously shown that the changes in intrathoracic pressure generated by the latter are essentially additive. In the present studies, we have assessed the interaction between the right and left hemidiaphragms in anesthetized dogs by comparing the changes in airway opening pressure (ΔPao) obtained during simultaneous stimulation of the two phrenic nerves (measured ΔPao) to the sum of the ΔPao values produced by their separate stimulation (predicted ΔPao). The measured ΔPao was invariably greater than the predicted ΔPao, and the ratio between these two values increased gradually as the stimulation frequency was increased; the ratio was 1.10 ± 0.01 (P < 0.05) for a frequency of 10 Hz, whereas for a frequency of 50 Hz it amounted to 1.49 ± 0.05 (P < 0.001). This interaction remained unchanged after the rib cage was stiffened and its compliance was made linear, thus indicating that the load against which the diaphragm works is not a major determinant. However, radiographic measurements showed that stimulation of one phrenic nerve extends the inactive hemidiaphragm toward the sagittal midplane and reduces the caudal displacement of the central portion of the diaphragmatic dome. As a result, the volume swept by the contracting hemidiaphragm is smaller than the volume it displaces when the contralateral hemidiaphragm also contracts. These observations indicate that 1) the left and right hemidiaphragms have a synergistic, rather than additive, interaction on the lung; 2) this synergism operates already during quiet breathing and increases in magnitude when respiratory drive is greater; and 3) this synergism is primarily related to the configuration of the muscle.

respiratory muscles; mechanics of breathing

THE INSPIRATORY PHASE OF THE breathing cycle is well known to involve coordinated contraction of the diaphragm, the internal intercostal muscles of the parasternal region (the so-called parasternal intercostals) (6, 7, 17), and the external intercostal muscles in the rostral interspaces (16, 18, 27). In humans, inspiration also involves contraction of the scalene muscles (6, 10, 23). However, the manner in which the changes in intrathoracic pressure produced by these various muscles add to each other remains largely unknown.

Otherwise stated, how does the pressure produced by a particular muscle during breathing, when the muscle acts in coordination with other muscles, compare with the pressure produced by this muscle during isolated contraction?

We have recently approached this question by stimulating electrically the parasternal intercostal and external intercostal muscles in dogs with the endotracheal tube occluded, first in two interspaces separately and then in the same two interspaces simultaneously (19). The change in airway opening pressure (ΔPao) measured during simultaneous stimulation of the muscles in two interspaces was, within 10%, equal to the sum of the ΔPao values produced by stimulation of the muscles in each individual interspace. The ΔPao produced by the simultaneous contraction of the parasternal intercostals in one interspace and either the scalenes or the sternomastoids was also found to be nearly equal to the sum of the ΔPao values produced by the two sets of muscles individually (19), and a similar finding was made for the parasternal intercostals and external intercostals situated on the left and right sides of the sternum (3). It was concluded, therefore, that the changes in intrathoracic pressure generated by the rib cage inspiratory muscles are essentially additive.

Earlier studies of the contractile properties of the diaphragm in dogs, cats, rabbits, and rats by Sant’Ambrogio and Saibene (26) have suggested that this principle of pressure superposition also applies to the left and right halves of the diaphragm. Specifically, these investigators reported that the ΔPao obtained during unilateral diaphragmatic stimulation was “about 50% of that obtained during bilateral stimulation.” However, subsequent studies by Minh et al. (22) noted that the ΔPao measured during tetanic stimulation of one phrenic nerve in dogs was only a third of the pressure produced by stimulation of the two phrenic nerves simultaneously. Bellemare et al. (1), stimulating the phrenic nerves with single twitches in normal humans, similarly reported that the peak transdiaphragmatic pressure (Pdi) obtained in response to bilateral stimulation was ~30% greater than the sum of the pressures obtained during separate left and right stimulation. When they applied asynchronous bilateral stimulation in two subjects, these investigators further
observed that the Pdi induced by stimulation on a given side increased gradually as the delay relative to the stimulation on the other side was shorter. It would appear, therefore, that the interaction between the left and right hemidiaphragms on the lung is fundamentally different from that between the rib cage inspiratory muscles, and this prompted us to reevaluate this interaction in dogs. The initial experiments indicated that the interaction between the left and right hemidiaphragms is indeed synergistic, rather than additive. We therefore set out to assess the mechanism of this synergism.

METHODS

Nineteen adult mongrel dogs (body wt 11–36 kg) anesthetized with pentobarbital sodium (initial dose 30 mg/kg iv) were studied as approved by the Animal Ethics and Welfare Committee of the Brussels School of Medicine. The animals were placed in the supine posture, intubated with auffed endotracheal tube, and connected to a mechanical ventilator (Harvard pump, Chicago, IL). A venous catheter was inserted in the forelimb to give maintenance doses of anesthetic, after which the neck was opened by a midline incision. The C5 and C6 phrenic nerve roots were then isolated bilaterally and laid over two pairs of insulated stainless steel stimulating electrodes, and a differential pressure transducer (Validyne, Northridge, CA) was connected to a side port of the endotracheal tube to measure Pao.

Fifteen minutes after instrumentation, the animal was made apneic by mechanical hyperventilation. After the ventilation was stopped, the endotracheal tube was occluded at functional residual capacity (FRC), and square pulses of 0.1-ms duration and supramaximal voltage were applied at a frequency of 50 impulses/s to the left C5 and C6 phrenic nerves. After this first data point collection, the animal was reconnected to the ventilator and hyperventilated, and the right C5 and C6 phrenic nerves were stimulated with similar pulses. The animal was then returned to the assisted ventilation, and the nerves on both sides of the neck were stimulated simultaneously. Two additional trials of unilateral and bilateral phrenic nerve stimulation were obtained, with different sequences, in each animal, after which four experimental protocols were followed.

Experiment 1. In six animals, we examined the influence of the stimulation frequency on the interaction between the right and left hemidiaphragms. In each animal, the left and right phrenic nerve roots were thus stimulated separately and simultaneously at 10, 20, 35, and 50 impulses/s.

Experiment 2. In six animals, we investigated the role played by rib cage compliance in determining the interaction (see DISCUSSION). The rib cage was exposed on both sides of the chest from the first through the tenth rib, and a pair of linearized magnetometers (Norman H. Peterson, Boston, MA) was attached to the external intercostal muscles in the fifth and sixth interspaces to measure the changes in rib cage diameter. The C5 and C6 phrenic nerve roots were then stimulated, separately and simultaneously, both on one and two sides of the neck so as to induce a wide range of ΔPao and to determine the relationship between ΔPao and the rib cage diameter; all stimulations were 0.1 ms in duration and 50 Hz in frequency. In each animal, the rib cage was subsequently stiffened by attaching clamps to adjacent bony ribs, as shown in Fig. 1. Two inverted V-shaped metallic bars were also firmly secured to the sternum and two pairs of ribs in the midaxillary line so as to prevent the sternum from moving relative to the ribs; one bar was positioned at the level of the second or third rib pair, and the other was positioned at the level of the sixth or seventh rib pair. The rib clamps were finally tethered, through metallic threads, to a rigid frame placed on both sides of the animal, and a second set of unilateral and bilateral C5–C6 phrenic nerve stimulation was performed. As in the control condition, all stimulations were applied at least three times in each animal. Bilateral C5–C6 stimulation with the rib cage stiffened, however, induced a pneumothorax in one animal; these data were not considered in the analysis.

Experiment 3. In six animals, we subsequently evaluated the magnitude of the (caudal) displacement of the diaphragm during simultaneous vs. separate stimulation of the left and right C5–C6 phrenic nerves. The abdomen in each animal was opened by a midline incision from the xiphisternum to the umbilicus, and a balloon-catheter system was positioned between the liver and the stomach to measure abdominal pressure (Pab); the balloon was filled with 1.0 ml of air. The abdomen was then closely sutured in two layers, after which unilateral and bilateral stimulation (50 Hz) of the C5–C6 phrenic nerves was repeated.

Experiment 4. Finally, six animals were studied to assess the changes in length of the diaphragmatic muscle fibers and the alterations in diaphragmatic silhouette during bilateral vs. unilateral contraction. Lead spheres, 4–5 mm in diameter with a small hole drilled through the center, were thus stitched to the peritoneal surface and superficial muscle fibers of the diaphragm through a midline laparotomy. Rows of five markers were attached to both the left and the right hemidiaphragm in the coronal midplane, as shown in Fig. 2A. The first marker in each row was placed at the junction of the muscle with the central tendon, and the last marker was placed at the costal insertion of the muscle. Typically, the markers attached to the cranial half of the muscle were spaced at ~2-cm intervals and those attached to the caudal half, in the zone of apposition of the diaphragm to the rib cage (21), were spaced at ~3-cm intervals. Consequently, the chord length between the successive markers closely approximated the arc length along the diaphragm. A balloon-catheter system filled with 1.0 ml of air was also inserted between
the liver and the stomach in each animal, and the abdomen was closely sutured. The animal was subsequently placed supine in a radiolucent fabric sling, and anteroposterior radiographs of the lower rib cage and upper abdomen were taken first during relaxation at FRC (Fig. 2B), then during separate stimulation of the right and left C5–C6 phrenic nerves, and finally during simultaneous stimulation of the right and left phrenic nerves. All stimulations in this experiment were also 50 Hz in frequency.

The animals in all experiments were maintained at a constant, rather deep level of anesthesia throughout. They had no pupillary light reflex, no corneal reflex, and no move-

ment of the fore- or hindlimbs, including during bilateral phrenic nerve stimulation. Rectal temperature was maintained constant between 36 and 38°C with infrared lamps. At the end of the study, the animal was given an overdose of anesthetic (30–40 mg/kg).

**Data analysis.** In each animal, the ΔPao values obtained during unilateral and bilateral 50-Hz stimulation of the C5–C6 phrenic nerves were averaged over the three trials. The ΔPao obtained during stimulation of the left side was then added to the ΔPao obtained during stimulation of the right side, and the value thus calculated (it will be referred to here as the predicted ΔPao) was compared with that measured during simultaneous stimulation of the right and left sides. The values of predicted and measured ΔPao were finally averaged for the animal group, and statistical comparison between these values was made by using a paired t-test; moreover, the linear regression of measured ΔPao on predicted ΔPao across the animal group was calculated by using the least squares method. The effects of rib cage stiffness on the predicted and measured ΔPao values (experiment 2) and the comparison between the measured and predicted ΔPao values (experiment 3) were also evaluated by using paired t-tests. However, because four stimulation frequencies were studied in experiment 1, comparison between predicted and measured ΔPao at the different frequencies was made by ANOVA with repeated measures, and multiple-comparison testing of the mean values was performed by using Student-Newman-Keuls tests.

The changes in diaphragmatic muscle length (experiment 4) were first quantified by measuring the linear distance between adjacent radiopaque markers and by summing the distances between markers in each row. To allow comparison between the different animals, the changes in muscle length during unilateral and bilateral stimulation were then expressed as percentage changes relative to the muscle length at FRC. In addition, the changes in diaphragmatic shape were examined by tracing the contour of the diaphragm in each condition and by superimposing the contours during the different stimulations on that at FRC. All contours were related to a metallic marker that was attached to the sling on the side of the animal and was, therefore, stationary. To quantify the changes in shape, the axial (craniocaudal) displacement of the dome in the sagittal midplane and in the two sagittal planes situated midway between the spinous processes of the vertebrae and the lateral rib cage margins was also measured. Stimulating the right or the left phrenic nerve alone produced identical changes in muscle length and identical changes in shape. These changes, therefore, were averaged for each individual animal, and they were then averaged across the animal group. Statistical comparisons between the changes in muscle length and the axial displacements of the dome during unilateral and bilateral stimulation were also made by using paired t-tests. The criterion for statistical significance was taken as *P* < 0.05.

**RESULTS**

Interaction between left and right hemidiaphragms on the lung. A representative example of the traces obtained during separate and simultaneous stimulation of the left and right phrenic nerve roots with a 50 Hz frequency is shown in Fig. 3. When the left C5–C6 nerve roots in this animal were stimulated alone (Fig. 3A), the fall in Pao was 16.5 cmH2O. Similarly, when the right C5–C6 nerve roots were subsequently stimulated (Fig. 3B), the fall in Pao was 18.0 cmH2O.
Therefore, the predicted $\Delta P_{ao}$ for the two sides was $-34.5$ cmH$_2$O. However, the $\Delta P_{ao}$ measured during combined stimulation of the left and right phrenic nerves amounted to $-51.0$ cmH$_2$O (Fig. 3C).

Although the predicted $\Delta P_{ao}$ showed a large variation among the 19 animals, ranging from $-15.8$ to $-48.7$ cmH$_2$O, similar results were obtained in all animals. The measured $\Delta P_{ao}$ for the group thus averaged (mean $\pm$ SE) $-44.4 \pm 3.3$ cmH$_2$O, whereas the predicted $\Delta P_{ao}$ was only $-30.5 \pm 2.1$ cmH$_2$O ($P < 0.001$). As shown in Fig. 4, the measured $\Delta P_{ao}$ was closely related to the predicted value (coefficient of correlation, $r = 0.922$), and the slope of the linear relationship ($\pm 95\%$ confidence interval) was $1.42 \pm 0.30$; this slope was significantly $>1$ ($P < 0.01$).

Influence of stimulation frequency. The values of predicted and measured $\Delta P_{ao}$ obtained at different stimulation frequencies in the six animals studied are shown in Fig. 5A. The measured $\Delta P_{ao}$ was greater than the predicted value at all stimulation frequencies in every animal ($P < 0.001$). However, the ratio between the measured and the predicted value increased progressively as the frequency was greater (Fig. 5B); whereas this ratio averaged $1.49 \pm 0.05$ ($P < 0.001$) for a frequency of 50 Hz, it was $1.10 \pm 0.01$ ($P < 0.05$) for a frequency of 10 Hz.

Role of rib cage compliance. The relationships between $\Delta P_{ao}$ and the rib cage transverse diameter obtained during phrenic nerve root stimulation before...
and after locking of the ribs and the sternum in the six animals are shown in Fig. 6. With the rib cage intact, the relationship was curvilinear in every animal, such that, for a given fall in Pao, the decrease in rib cage diameter was smaller as Pao was lower. As a result, the chord rib cage compliance corresponding to unilateral stimulation of the C5 and C6 nerve roots averaged 0.66 ± 0.05 mm/cmH₂O, but the compliance corresponding to bilateral C5–C6 stimulation was only 0.49 ± 0.05 mm/cmH₂O (P < 0.005).

When the ribs and the sternum were locked, the decrease in rib cage diameter associated with a given fall in Pao was markedly reduced. More importantly, the relationship between Pao and rib cage diameter was linear. Rib cage compliance during both bilateral and unilateral C5–C6 stimulation, therefore, amounted to only 0.12 ± 0.01 mm/cmH₂O (P < 0.005), and the predicted ΔPao was increased from −28.0 ± 3.4 to −41.5 ± 3.5 cmH₂O (P < 0.02). As shown in Fig. 7, however, the measured ΔPao concomitantly increased from −44.2 ± 5.5 to −59.4 ± 4.7 cmH₂O (P < 0.01), and the ratio between the measured and the predicted value remained unchanged.

Changes in abdominal pressure. The changes in Pab recorded during separate and combined stimulation of the left and right phrenic nerves in a representative animal are also shown in Fig. 3. As for ΔPao, the measured ΔPab was invariably and substantially greater than the predicted value. Whereas this value for the 12 animals averaged +6.6 ± 0.5 cmH₂O, the measured value amounted to +12.2 ± 1.0 cmH₂O (P < 0.001).

Length and shape of the diaphragm. The changes in diaphragmatic silhouette are reproduced for a representative animal in Fig. 8. As anticipated, stimulating the right and left phrenic nerves simultaneously caused a large shortening and a large caudal displacement of both hemidiaphragms. Also, stimulating the right (Fig. 8A) or the left (Fig. 8B) phrenic nerve alone elicited a large shortening and a marked caudal displacement of the ipsilateral hemidiaphragm.

Fig. 6. Relationships obtained in 6 animals (dogs 1–6 shown in A–F, respectively) between the fall in airway opening pressure (Pao) and the decrease in rib cage transverse diameter during isolated stimulation of the phrenic nerve roots with the rib cage intact (solid lines) and after locking of the ribs and the sternum (dashed lines). ○, Data obtained during unilateral and bilateral stimulation of the C5 roots alone; ●, data obtained during unilateral and bilateral stimulation of the C5 and C6 roots. Note that with the rib cage intact, the relationship is curvilinear such that a given fall in Pao is associated with a smaller decrease in rib cage diameter as Pao is more negative. When the ribs and the sternum are locked, however, the relationship is linear.

Fig. 7. Individual values of measured and predicted ΔPao obtained during 50-Hz stimulation of the C5 and C6 phrenic nerve roots on the left and right sides of the neck in 5 animals with the rib cage intact (○) and after locking of the ribs and the sternum (●). Solid line is the line of identity; dashed line is the linear relationship between the measured and predicted values shown in Fig. 4. This relationship fits all data well, including those obtained after locking of the ribs and sternum.
Table 1. Changes in diaphragmatic muscle length during unilateral and bilateral phrenic nerve stimulation

<table>
<thead>
<tr>
<th>Dog</th>
<th>Bilateral Stimulation</th>
<th>Unilateral Stimulation</th>
<th>ΔPao, measured/predicted</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-40.5</td>
<td>-42.2</td>
<td>+11.8</td>
</tr>
<tr>
<td>2</td>
<td>-42.9</td>
<td>-42.1</td>
<td>+7.3</td>
</tr>
<tr>
<td>3</td>
<td>-29.4</td>
<td>-42.6</td>
<td>+14.3</td>
</tr>
<tr>
<td>4</td>
<td>-31.5</td>
<td>-38.3</td>
<td>+13.1</td>
</tr>
<tr>
<td>5</td>
<td>-37.0</td>
<td>-40.1</td>
<td>+7.8</td>
</tr>
<tr>
<td>6</td>
<td>-35.0</td>
<td>-44.7</td>
<td>+7.3</td>
</tr>
</tbody>
</table>

Values are the individual changes in length for the right and left hemidiaphragms in 6 animals. These changes in length are expressed as percentage changes relative to muscle length during relaxation at resting end-expiration (Lr); negative changes indicate muscle shortening below Lr, and positive changes indicate muscle lengthening beyond Lr. ΔPao, change in airway opening pressure.

a shift and a tilt of the central tendon toward the stimulated side, and a significant lengthening of the muscle fibers in the contralateral (passive) hemidiaphragm. This hemidiaphragm, however, also moved invariably in the caudal direction; this displacement for the six animals averaged 14.6 ± 2.5 mm.

The shortening of the contracting muscle fibers during unilateral stimulation was similar in magnitude to that observed during bilateral stimulation in two animals (dogs 1 and 2 in Table 1). As a result, although four animals had a larger muscle shortening during unilateral stimulation, the difference for the group hardly reached the level of statistical significance (P = 0.05). However, there was a large difference in the caudal displacement of the diaphragmatic dome in the sagittal midplane; whereas this displacement during bilateral stimulation amounted to 59.9 ± 5.0 mm, with unilateral stimulation it was only 18.6 ± 2.3 mm (P < 0.001). Also, the caudal displacement of the stimulated hemidiaphragms averaged 70.6 ± 7.2 mm during bilateral stimulation but only 54.7 ± 5.8 mm during unilateral stimulation (P < 0.005).

DISCUSSION

The present studies have confirmed the earlier observation by Minh et al. (22) and Bellemare et al. (1) that the fall in airway opening (or pleural) pressure induced by simultaneous stimulation of the left and right phrenic nerves is greater than the sum of the pressure falls resulting from their separate stimulation. These studies have also demonstrated that the magnitude of the difference depends on the stimulation frequency; although this difference is only 10% for a frequency of 10 Hz, it amounts to 40–50% for frequencies of 35–50 Hz. Because each phrenic nerve in the dog supplies its own hemidiaphragm, including all the fibers in the crural segment on its own side of the esophageal hiatus (2, 4), it can therefore be concluded that the interaction between the left and right hemidiaphragms on the lung is synergistic. In addition, electrical recordings from phrenic motor axons in cats (14) and from the costal segment of the diaphragm in humans (8, 10) have shown that the firing rate of diaphragmatic motor units during resting inspiration is 10–11 Hz. Consequently, it can further be concluded that the synergism between the two hemidiaphragms operates already, albeit to a small extent, during resting breathing and that the synergism is amplified when respiratory neural drive is increased, such as during exercise.

To assess the mechanism of this synergism, we have considered the determinants of ΔPao. Thus the increase in lung volume (ΔVL) during breathing is related to the volume displaced by the diaphragm (Vdi) and the volume displaced by the rib cage (ΔVrc), such that

\[ \Delta V_L = V_{di} + V_{rc} \]  \hspace{1cm} (1)

When the endotracheal tube is occluded, \( \Delta V_L = 0 \) so

\[ \Delta V_{rc} = -V_{di} \]  \hspace{1cm} (2)

In addition, when the rib cage muscles are silent, ΔVrc is equal to the product of ΔPao and rib cage compliance.

Fig. 8. Contours of the diaphragm seen on anteroposterior radiographs in a representative animal during relaxation, during combined tetanic stimulation of the left and right phrenic nerves, during isolated stimulation of the right phrenic nerve (dashed line in A), and during isolated stimulation of the left phrenic nerve (dashed line in B). Stimulation frequency = 50 Hz. The 2 short bars on each contour correspond to the junctions of the muscle fibers with the central tendon. The hatched areas highlight the surface areas swept by the right hemidiaphragm during isolated contraction (A) and when the left hemidiaphragm is already active (B).
(Crc). Substituting for \( \Delta V_{\text{rc}} \) in Eq. 2 and rearranging thus yields

\[
\Delta P_{\text{ao}} = -\frac{V_{\text{di}}}{C_{\text{rc}}}
\]  

In other words, a greater \( \Delta P_{\text{ao}} \), as observed during simultaneous contraction of the left and right hemidiaphragms, could be the result of either a lower rib cage compliance, or a greater volume displaced by the diaphragm, or a combination of both changes.

Studies by D’Angelo and Sant’Ambrogio (5) have previously shown that, in the dog, the rib cage becomes less compliant when it contracts below its resting, end-expiratory volume. Because the fall in intrathoracic pressure during bilateral stimulation of the phrenic nerves is much greater than that during unilateral stimulation, it would therefore be expected that rib cage contraction would also be greater in the first instance and, hence, that rib cage compliance would be smaller. As shown in Fig. 6, this was indeed the case. On average, rib cage compliance during bilateral stimulation was only 75% of the compliance during unilateral stimulation. Consequently, the load placed on the diaphragm is greater during bilateral stimulation, and this should increase \( \Delta P_{\text{ao}} \) for a given muscle tension. However, when the ribs and sternum were locked such that rib cage compliance during bilateral stimulation was the same as that during unilateral stimulation, the synergism between the left and right hemidiaphragms remained unchanged (Fig. 7). The conclusion was drawn, therefore, that this interaction is primarily related to the volume “swept” by the diaphragm, rather than the load imposed on the diaphragm by the rib cage.

The finding that the measured \( \Delta P_{\text{ab}} \) was consistently greater than the predicted value (Fig. 3) is fully consistent with the idea that the volume displaced by the diaphragm during bilateral contraction exceeds the sum of the volume displacements induced by separate contraction of the two hemidiaphragms. However, two mechanisms working alone or in combination could theoretically operate to reduce the volume displacement and the \( \Delta P_{\text{ab}} \) during isolated contraction of one hemidiaphragm. First, diaphragmatic muscle fibers could shorten more during unilateral contraction than during bilateral contraction. In view of the length-tension characteristics of these fibers (15, 20), the force exerted during contraction would therefore be smaller in the first instance than in the second, and the displacement would be smaller as well. Second, the configuration of the diaphragm during unilateral and bilateral contraction could be sufficiently different that the mechanical effects of the forces exerted by the contracting muscle fibers would be different. Contraction of one hemidiaphragm in particular could induce, through the fall in intrathoracic pressure and the rise in Pab, a cranial displacement of the contralateral hemidiaphragm. Such a paradoxical displacement is a cardinal sign of hemidiaphragmatic paralysis in clinical practice (12, 24, 25), and, if present in our animals, it would reduce the volume displacement and the \( \Delta P_{\text{ab}} \) produced by the contracting hemidiaphragm.

The radiographic studies performed in the last experiment were designed to investigate these two mechanisms. Although the markers were placed in the coronal midplane, rather than along muscle bundles, and although the positions of these markers were assessed only in anteroposterior projections, these measurements confirmed that unilateral diaphragmatic contraction commonly leads to greater muscle shortening than bilateral contraction does. However, if this difference were the primary mechanism of the synergism, it would be expected that the ratio of the measured to the predicted \( \Delta P_{\text{ao}} \) would be greater as the ratio of muscle shortening during bilateral vs. unilateral contraction is smaller. As shown in Table 1, no such relationship was found in the six animals studied. In fact, two animals showed similar muscle shortening in the two conditions, yet they had measured \( \Delta P_{\text{ao}} \) values that were 41 and 52% greater than the predicted values. Also, the animal with the largest difference in the degree of muscle shortening (dog 3) was the one with the lowest ratio between the measured and the predicted \( \Delta P_{\text{ao}} \).

The radiographic studies also indicated that isolated stimulation of one phrenic nerve causes the contralateral hemidiaphragm to move caudally, rather than cranially. This contralateral motion tends to enhance the volume displaced by the contracting hemidiaphragm. The contralateral hemidiaphragm, however, is also stretched and extends medially; in many cases, the marker attached at the junction between the central tendon and the inactive muscle fibers even crossed the sagittal midplane (see for example Fig. 8A). Consequently, the caudal motion of the central portion of the diaphragmatic dome is reduced three to four times relative to that observed during bilateral contraction. Furthermore, because the contralateral hemidiaphragm is stretched, it develops passive tension and impedes the shortening of the contracting muscle fibers. As a result, the caudal motion of the contracting hemidiaphragm is also reduced, and this reduction, combined with the reduced caudal motion of the central portion of the dome, substantially limits the ability for the hemidiaphragm to displace volume. The hatched areas in Fig. 8, representing the surface areas swept by the contracting right hemidiaphragm when the left hemidiaphragm is inactive (Fig. 8A) and when the left hemidiaphragm is already active (Fig. 8B), highlight this difference. Indeed, planimetry indicates that the area in Fig. 8B is 92% greater than that in Fig. 8A; the surface area swept by the left hemidiaphragm in the presence of a right hemidiaphragmatic contraction is similarly 82% greater than that swept when the right hemidiaphragm is inactive. Thus, even though these figures refer to areas, rather than volumes, they support the concept that the synergism between the left and right hemidiaphragms is primarily related to the configuration of the muscle.

We have recently evaluated the respiratory effects of the external and internal intercostal muscles in dogs (9) and in humans (28) by applying to the respiratory system a standard theorem of mechanics, namely the
Maxwell reciprocity theorem. This theorem implies that the chest wall behaves as a linear elastic structure and, hence, that the resultant effect of different forces acting simultaneously is simply the sum of the effects of the individual forces. Because the \( \Delta P_{\text{a}} \) generated by the two hemidiaphragms contracting simultaneously is greater than the sum of the individual \( \Delta P_{\text{a}} \), one might therefore question the validity of this theorem in the respiratory context. In fact, the present findings point to the limits of such modeling. When the parasternal intercostal or the interosseous intercostal muscles contract in one or two interspaces on both sides of the sternum or contract in two interspaces on one side of the sternum, they distort the rib cage, but the magnitude of such distortions is relatively small. And indeed, in agreement with the model, the pressures generated by these muscles are essentially additive (3, 19). Similarly, when the phrenic nerves in our animals were stimulated with a frequency of 10 Hz, the difference between the pressure obtained during bilateral contraction and the sum of the pressures obtained during unilateral left and right contraction was only 10\% (Fig. 5). In other words, when muscle tension in the diaphragm is small, such that the configuration of the muscle is relatively preserved, the system remains within its linear range. However, because the diaphragm has less constraint on its configuration than the rib cage, large tensions in the muscle cause such a marked alteration in configuration that the system then departs from its linear range.

The findings of this study have a number of important physiological and pathophysiological implications. First, they indicate that the magnitude of the lung-expanding action of the diaphragm is not exclusively determined by the length of the muscle fibers as conventionally thought (13); the change in configuration of the muscle and, with it, the volume swept by the muscle during contraction plays a major role. Second, the configuration of the diaphragm during unilateral contraction (Fig. 8) is such that the mean radius of curvature on the contracting side is greater than that on the inactive side. Because tension in these muscle fibers is related to the product of pressure and radius of curvature (Laplace’s law), this difference implies that muscle tension in the contracting side is greater and, hence, that tension is incompletely transmitted across the central tendon. Third, as Bellemare et al. (1) have pointed out, the present findings imply that phrenic nerve stimulation as a tool to assess the pressure-generating ability of the diaphragm in clinical practice should be bilateral. Finally, these findings imply that, in subjects with hemidiaphragmatic paralysis, the loss in the pressure-generating ability of the inspiratory muscle pump is greater than anticipated on the basis of the pressure generated by one hemidiaphragm contracting alone. Although this additional pressure loss would be moderate during resting breathing, it should be prominent when an increased respiratory drive is needed.

However, the observation that isolated contraction of one hemidiaphragm in the dog causes caudal displace-


